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Special Issue Reprint

Advances in Cancer Data and Statistics

Edited by
Vesna Zadnik

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Guest Editor

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Preface

The reprint of this Special Issue, *Advances in Cancer Data and Statistics*, brings together 14 original peer-reviewed articles on the evolving and increasingly impactful role of cancer registries in cancer epidemiology, healthcare science, and public health. This collection focuses on the use of routinely collected cancer data—specifically from population-based and hospital registries—for advancing our understanding of cancer incidence and survival rates and outcomes and developing and applying novel statistical and epidemiological methods.

The scope of this Special Issue extends beyond the traditional use of cancer registry data for monitoring the cancer burden. It highlights innovative applications such as linkages with non-health data sources, the modeling of risk and prognostic factors, and the evaluation of cancer control efforts. Furthermore, it addresses the growing need to translate large-scale, routinely collected data into meaningful insights that can inform clinical practice, guide health policies, and improve patient outcomes.

This collection was motivated by the recognition that cancer registries worldwide have entered a new era: one characterized by enhanced data granularity, technological advances in data integration, and an increased demand for real-world evidence. This Special Issue aims to provide a platform for sharing methodological innovations, practical applications, and interdisciplinary collaborations that reflect this shift.

This work is intended for a broad audience of professionals engaged in cancer surveillance, epidemiology, biostatistics, public health, and health system research. It will be of particular interest to researchers and practitioners who seek to better understand the strengths and limitations of registry-based data and to apply them creatively to address pressing questions in cancer prevention and control.

The included articles were authored by a diverse and international community of experts working for cancer registry organizations, academic institutions, and public health agencies. Their contributions are methodologically rigorous and practically relevant, making this volume a valuable resource for advancing data-driven approaches in oncology.

I express sincere gratitude to all the contributing authors, reviewers, and the editorial team at the journal *Cancers* for their commitment and collaborative spirit throughout the preparation of this Special Issue. Their efforts have made it possible to share these cutting-edge insights with the broader scientific and public health community.

Finally, I should acknowledge the work of cancer registry professionals worldwide, whose meticulous data collection and long-standing dedication provide the foundation for much of the research presented in this volume.

Vesna Zadnik
Guest Editor

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Article

Population-Based Clinical Cancer Registration in Germany

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Simple Summary: Cancer registration has a long tradition in Germany. In 2013, new legislation obliged all German states to implement additional clinical cancer registration, including standardised documentation of all therapies, recurrences and further follow-up. The overall aim was to use cancer registry data to measure and improve the quality of cancer care. Now, 10 years later, the status of the extended cancer registration will be presented. In 2019, more than 500,000 new cancer cases were reported to the federal cancer registries. Age-standardised incidence has decreased slightly over the last decade. The five-year relative survival rate for all cancers was 67% for women and 63% for men. Therapy data show that an evidence-based assessment of quality of cancer care, including provider-based benchmarking, is feasible. Feedback of such results directly to healthcare providers should further improve cancer care. In conclusion, the introduction of population-based clinical cancer registration in Germany can be considered a success.

Abstract: Introduction: In 2013, a new federal law obligated all German federal states to collect additional clinical data in population-based cancer registries as an active tool for monitoring and improving the quality of cancer care, increasing transparency and promoting health research. Now, 10 years later, the current status of the expanded cancer registration is presented, including current figures on cancer in Germany. Methods: Reporting of cancer is mandatory for physicians, and about 5 to 10 reports from different healthcare providers are expected for each case. A uniform national dataset of about 130 items is used, and reports are usually sent electronically to the registry. We used the most recent data available from cancer registries up to the year of diagnosis in 2019. We calculated incidence rates and 5-year relative survival (5YRS) for common cancers. Data on clinical outcomes and benchmarking based on quality indicators (QIs) from guidelines were provided by the Cancer Registry Schleswig-Holstein (CR SH). Results: All federal state cancer registries met most of the previously defined national eligibility criteria. Approximately 505,000 cancer cases were

registered in 2019, with breast, prostate, colorectal and lung cancer being the most common cancers. The age-standardised cancer incidence has slightly decreased during the last decade. and spatial heterogeneity can be observed within Germany. 5YRS for all cancers was 67% and 63% for women and men, respectively. Therapy data for rectal cancer in 2019–2021 from the CR SH are shown as an example: 69% of the registered patients underwent surgery, mostly with curative intent (84%) and tumour-free resection (91%). Radiotherapy was given to 33% of the patients, and chemotherapy was given to 40%. Three selected QIs showed differences between involved healthcare providers. Discussion: The implementation of population-based clinical cancer registration can be considered a success. Comprehensive recording of diagnosis, treatment and disease progression and the use of registry data for quality assurance, benchmarking and feedback have been implemented.

Keywords: cancer registration; cancer; Germany; incidence; quality assurance; benchmarking

1. Introduction

Cancer registration has a long history in Germany. The first cancer report was published in 1902, showing the prevalence of cancer at a regional level in Germany in cartographic form [1]. In 1927, the Hamburg Cancer Registry was established, followed by other regions in the following decades. In 1980, the German Childhood Cancer Registry (GCCR) was formed. However, it was not until 1994 that a federal law was passed, requiring all German federal states to establish population-based cancer registries (CRs). The law stated the following overarching goal: "Cancer registries shall monitor and evaluate cancer incidence and trends, provide data for epidemiological research, including causal research, and contribute to the evaluation of preventive and curative interventions" [2]. The law was implemented fairly quickly by most of the federal states [3,4], and a cancer registration system according to international standards [5] was established in Germany. In the Eastern German federal states, and in Bavaria, the structure of pre-existing hospital-based cancer registries was used for that purpose. Their registries already collected additional clinical data and information on therapies and relapse [6]. As this type of cancer registration has been successfully used for the quality assessment of oncological care, hospital benchmarking and accreditation, the 2008 German National Cancer Plan recommended the implementation of additional population-based registration of clinical data as an active tool to monitor and improve cancer care in Germany. In 2013, a new federal cancer registration law came into force, which now obliges all federal states to implement the additional registration of clinical data [4]. The superordinate goals of this law can be summarised under the terms of oncological quality assurance, transparency in cancer care and oncology health service research. At the same time, the law intended to facilitate national standardisation of the data to be collected; to ensure the exchange and pooling of the collected data in the complex German federal healthcare system; and finally, to provide guidelines for adequate funding.

It is now 10 years since the law came into force. Has the goal of comprehensive clinical registration been achieved? The aim of this paper is to describe the current status of extended cancer registration in Germany; to present recent analyses of cancer in Germany based, for the first time, on data with clinical content; and to evaluate developments over the past decade.

2. Materials and Methods

2.1. Aims and Tasks of the New Clinical Cancer Registration

In addition to the usual tasks of cancer registries, such as describing incidence, survival and trends, the additional clinical cancer registration has the task of monitoring and improving oncological care. The corresponding federal law [4] mentions the following points, among others, for this purpose:

- Evaluation of the collected clinical data and the feedback of the evaluation results to the individual healthcare providers;
- The promotion of interdisciplinary, directly patient-related cooperation in cancer treatment;
- Participation in the Joint Federal Committee's inter-institutional and inter-sectoral quality assurance;
- Cooperation with centres in oncology;
- The provision of necessary data for the creation of transparency in care and for the purposes of healthcare research.

2.2. Structure of Cancer Registration

Germany currently has a population of 84 million inhabitants and consists of 16 federal states that are responsible for cancer registration (Table 1). The population size of the federal states varies between 680,000 and 18 million inhabitants. Each federal state has its own independent cancer registration structure, reflecting historical developments, with its own state law, budgetary sovereignty and registry topology. The exceptions are Berlin and Brandenburg, which form a geographical unit and operate a joint registry, and Saxony, which still has four separate regional sub-registries. The cancer registration laws of all federal states are comparable in content and aim to achieve uniform and interoperable cancer registration results throughout Germany. All federal and state laws on cancer registration have been aligned with the European General Data Protection Regulation (GDPR) [7]. In addition to the cancer registries of the federal states, two national institutions were established in the 1980s: The German Childhood Cancer Registry (GCCR), which records all cancers in persons younger than 18 years (the methods of the GCCR are described elsewhere [8]) and the German Centre for Cancer Registry Data at the Robert Koch Institute, which routinely collects data from the federal state registries to build a national cancer database [9]. Cancer registration is supported and harmonised at the national level by the following three associations: Association of Population-based Cancer Registries in Germany (GEKID, www.gekid.de (accessed on 5 June 2023)), Working Group of Tumour Centres (ADT, www.adt-netwerk.de (accessed on 5 June 2023) [8]) and the expert panel "Plattform 65c" for nationwide clinical cancer registration according to § 65c SGB V (www.plattform65c.de (accessed on 5 June 2023)).

Table 1. Federal state cancer registries (CR) in Germany and national cancer registry structures.

	Population (Mio)	**Founded**	**Clinical Data Since**
CR Baden-Wurttemberg	11.1	1994	2009
CR Bavaria	13.1	1998	2017
CR Berlin and Brandenburg	6.0 (3.7/2.3)	1953	1953
CR Bremen	0.7	1998	2015
Hamburg CR	1.9	1927	2014
CR Hesse	6.3	2001	2015
CR Lower Saxony	8.0	2000	2018
CR Mecklenburg-Western Pomerania	1.6	1953	1953
CR North Rhine-Westphalia	17.9	** 1986	2016
CR Rhineland-Palatinate	4.1	1997	2016
Saarland CR	1.0	1968	2016
CR Saxony	4.1	1953	1953
CR Saxony-Anhalt	2.2	2018	1993
CR Schleswig-Holstein	2.9	1997	2017
CR Thuringia	2.1	1953	1953
German Childhood Cancer Registry	13.5	1980	-
German centre of cancer registry data at the Robert Koch-Institute *	(84.0)	1983	2023

* data provided by federal state CRs; ** administrative district of Münster within North Rhine-Westphalia; since 2005 full coverage of North Rhine-Westphalia.

2.3. Notification of Cancer and Data Processing

The notification of cancer cases is mandatory for all physicians and healthcare providers involved in the diagnosis or treatment of cancer. Five major events along the disease trajectory were defined by law as events requiring notification to the registry: diagnosis, pathology report, specific cancer therapy, disease progression or unremarkable follow-up or death, and optional tumour conference. At least three sets of information (diagnosis, pathology and therapy) should be available for a tumour. In practice, however, there are usually about 5–10 reports per tumour, as typically more than one healthcare provider is involved. With few exceptions, reports are submitted electronically to the registries, either by entering individual cases in an online portal or by uploading multiple cases from the tumour documentation software implemented at the reporting institutions. The basis for reporting is the uniform national and legally binding oncology dataset (Table 2), which is continuously reviewed and updated. It contains approximately 130 items for all types of cancer and currently four tumour-specific modules (colorectal, breast, prostate and melanoma) with supplementary items. In addition, regular transmission of death information and/or death certificates from civil registries and an exchange of notifications between cancer registries have been established. Multiple reports for a patient are linked using the unique health insurance number, name and address, and date of birth. If there is multiple information from different physicians on the same issue, the best information is determined according to national rules. A harmonised set of validity and plausibility checks is applied to the reported data. In the case of conflicting or insufficient information, a query back to the reporting physician is possible.

Table 2. Simplified description of the mandatory German basic oncology dataset and its modules. Detail version available from https://basisdatensatz.de/basisdatensatz (accessed on 5 June 2023).

Item Class	Collected Information
Basic dataset	~130 item
Personal data patient	Health insurance numbers, names, address, date of birth and gender
Personal data notifying institution	Names, address, billing data
Cancer diagnosis	ICD-10, ICD-O topography, date, certainty, side
Histology	Date, ICD-O morphology, grading, lymph nodes examined and involved, if pathology report: name and address of physician sending in the sample
Tumour classification	TNM and other
Genetic variants	Type
Residual state	After surgery and total assessment
Performance status	ECOG (at diagnosis)
Surgery	Date, intention, OPS codes, complication
Radiotherapy	Date, intention, position to surgery, target area, begin, end, dose, boost, complication (CTCAE)
Systemic therapy	Date, intention, position to surgery, kind of therapy (including active surveillance), protocol, drug, begin, end
Tumour conference	Date, type
Follow-up	Date, total assessment of tumour, lymph nodes, metastases
Death	Date, cause
Organ specific modules	Specific items for quality assurance
Breast cancer module	10 items
Prostate cancer module	10 items
Colorectal cancer module	12 items
Melanoma of the skin module	4 items

2.4. Funding of Cancer Registration

The new federal law radically changed the financing of population-based cancer registration. Whereas in the past funding was mainly provided by the federal states, 90% the operating costs of clinical cancer registration are now covered by the statutory health insurance funds and 10% are covered by the federal state. To receive this funding, cancer registries must meet a defined set of 43 eligibility criteria, including comprehensive indicators on data quality, such as completeness of registration (>90% of expected cases), completeness of the information to be reported, timeliness of registration, and reporting and feedback.

In 2023, the national reimbursement scheme for cancer registries has been set at approximately EUR 120 per incident and continuously documented case (according to IARC rules [5]) but may vary from state to state. On top of this, notifying physicians are compensated with payments of EUR 5–18 per notification, depending on the reporting event.

2.5. Data and Analyses

We used the most recent dataset with data from all federal cancer registries in Germany, provided by the German Centre for Cancer Registry Data at the Robert Koch Institute, Berlin (ZfKD). Data were available up to the year of diagnosis 2019. Absolute numbers, crude rates and age-standardised rates were calculated using the Segi world standard. Regional comparisons of age-standardised rates (European Standard, 1976) [10] and relative age-standardised 5-year survival rates (method: period analysis using the Ederer II approach [11]) were provided by the Cancer Atlas of the German Association of Population-based Cancer Registries (GEKID) [12], which also uses the most recent ZfKD dataset. Mortality data were extracted from the German Federal Statistical Office [13]. Nationally defined quality indicators (QIs) from evidence-based (S3) guidelines were used to assess guideline-compliant care [14,15]. To give an example on this data usage, the CR Schleswig-Holstein provided exemplary evaluations of quality indicators for three tumour entities (breast (ICD10 C50), colon and rectum (ICD10 C18-20) and prostate (ICD10 C61)) from the regional quality conferences of the year 2023. The degree of compliance with the QIs is shown as a bar chart for anonymised healthcare providers involved in cancer care. In addition, treatment data for rectal cancer (ICD10 C20) were extracted from the interactive treatment report of the CR Schleswig-Holstein [16]. All data used were retrieved in June 2023. Analyses were performed using SPSS 22 and R version 4.1.3.

3. Results

After the new federal law on the implementation of clinical cancer registries in the German states had come into force in 2013, all states have built up population-based registries that now meet the national eligibility criteria of full clinical cancer registration for several years. As a result, complete cancer registration coverage in terms of incidence has been achieved for the whole of Germany. In 2019, 505,612 incident cancer cases (C00-96, excluding C44) were registered by the 15 CRs of the federal states (Table 3). A total of 236,218 cases (46.7%) occurred in women (crude rate: 561.2/100,000), and 269,394 cases (53.3%) occurred in men (657.0/100,000). The most common cancer sites in women are breast (73,279), colorectal (26,655) and lung cancer (22,892), while prostate (70,192), lung (34,572) and colorectal (33,440) cancer were the most common cancers in men. The overall 5-year relative survival (5YRS) was 67% and 63% in women and men, respectively. The highest 5-year relative survival was observed for melanoma of the skin (95%), testicular cancer (92%), prostate cancer (90%), Hodgkin lymphoma (women 89%, men 86%), breast cancer (women 87%) and thyroid cancer (92%, 86%). The lowest 5YRS was observed for pancreatic cancer (14%, 12%), lung cancer (25%, 21%) and brain cancer (28%, 24%). Age-standardised rates for common cancers from 2015 to 2019 showed stable incidence rates in the last five years (Supplementary Table S1).

Table 3. Most common cancer sites (ICD-10) in Germany in 2019: case numbers (N), crude rates per 100,000 (CR), age-standardised rates per 100,000 (ASR, World standard) and relative 5-year survival (5Y-RS) (period 2017–2019), percentage of all cancers (%) and ranking (place). Data source: common dataset of German cancer registries provided by the Centre for Cancer Registry Data at the Robert Koch-Institute, 2023.

	Women					Men				
Cancer Site	**N**	**CR**	**ASR**	**% (Place)**	**5Y-RS%**	**N**	**CR**	**ASR**	**Place-S**	**5Y-RS%**
Oral cavity, pharynx (C00–C14)	4357	10.4	4.6	1.8 (15)	61.3	9521	23.2	11.5	3.5 (9)	50.5
Oesophagus (C15)	1627	3.9	1.5	0.7 (19)	26.3	5694	13.9	6.3	2.1 (12)	26.4
Stomach (C16)	5650	13.4	4.8	2.4 (10)	39.1	9091	22.2	9.4	3.4 (10)	35.0
Colo-rectal (C18–C20)	26,655	63.3	22.1	11.3 (2)	68.2	33,440	81.6	34.3	12.4 (3)	64.8
Pancreas (C25)	9546	22.7	7.3	4.0 (7)	13.6	9614	23.4	9.6	3.6 (7)	12.4
Lung (C34)	22,892	54.4	22.5	9.7 (3)	25.0	34,572	84.3	36.0	12.8 (2)	20.6
Melanoma (C43)	11,038	26.2	14.1	4.7 (5)	95.3	12,527	30.6	14.4	4.7 (5)	94.0
Breast (C50)	73,279	174.1	86.2	31.0 (1)	86.5	721	1.8	0.8	0.3 (18)	78.8
Cervix uteri (C53)	4517	10.7	7.2	1.9 (14)	61.6	-	-	-	-	-
Corpus uteri (C54–C55)	11,221	26.7	11.6	4.8 (4)	78.4	-	-	-	-	-
Ovary (C56)	7128	16.9	7.6	3.0 (9)	41.3	-	-	-	-	-
Prostate (C61)	-	-	-	-	-	70,192	171.2	70.0	26.1 (1)	90.3
Testis (C62)	-	-	-	-	-	4113	10.0	9.3	1.5 (14)	92.4
Kidney (C64)	4912	11.7	4.6	2.1 (12)	79.2	9505	23.2	10.9	3.5 (8)	78.2
Bladder (C67)	4697	11.2	3.5	2.0 (13)	70.4	13,116	32.0	12.2	4.9 (4)	78.5
Brain (C70–C72)	3002	7.1	4.0	1.3 (18)	27.9	3909	9.5	5.5	1.5 (13)	24,3
Thyroid gland (C73)	4113	9.8	7.3	1.7 (16)	92.0	1816	4.4	3.0	0.7 (16)	86.3
Hodgkin lymphoma (C81)	1063	2.5	2.3	0.5 (20)	89.1	1386	3.4	2.7	0.5 (17)	86.0
Non-Hodgkin lym. (C82–C88)	8094	19.2	7.7	3.4 (8)	73.3	10,042	24.5	11.3	3.7 (6)	71.1
Multiple myeloma (C90)	3073	7.3	2.5	1.3 (17)	59.3	3835	9.4	3.9	1.4 (15)	57.8
Leukaemia (C91–C95)	5263	12.5	5.2	2.2 (11)	59.0	7467	18.2	8.5	2.8 (11)	60.7
All sites excluding C44	236,218	561.2	249.0	100.0	67.0	269,394	657.0	290.3	100.0	63.4

Regional differences in cancer incidence are present in Germany. For example, the age-standardised incidence of lung cancer in the region with the highest incidence is about twice that in the region with the lowest incidence (Figure 1). Other cancers with similarly large regional heterogeneity in incidence are cancers of the oral cavity and pharynx, liver, thyroid, and leukaemia and lymphoma. Common cancers like colorectal and prostate cancer show little heterogeneity. For breast cancer, lower rates are observed in the Eastern federal states (available online [12]).

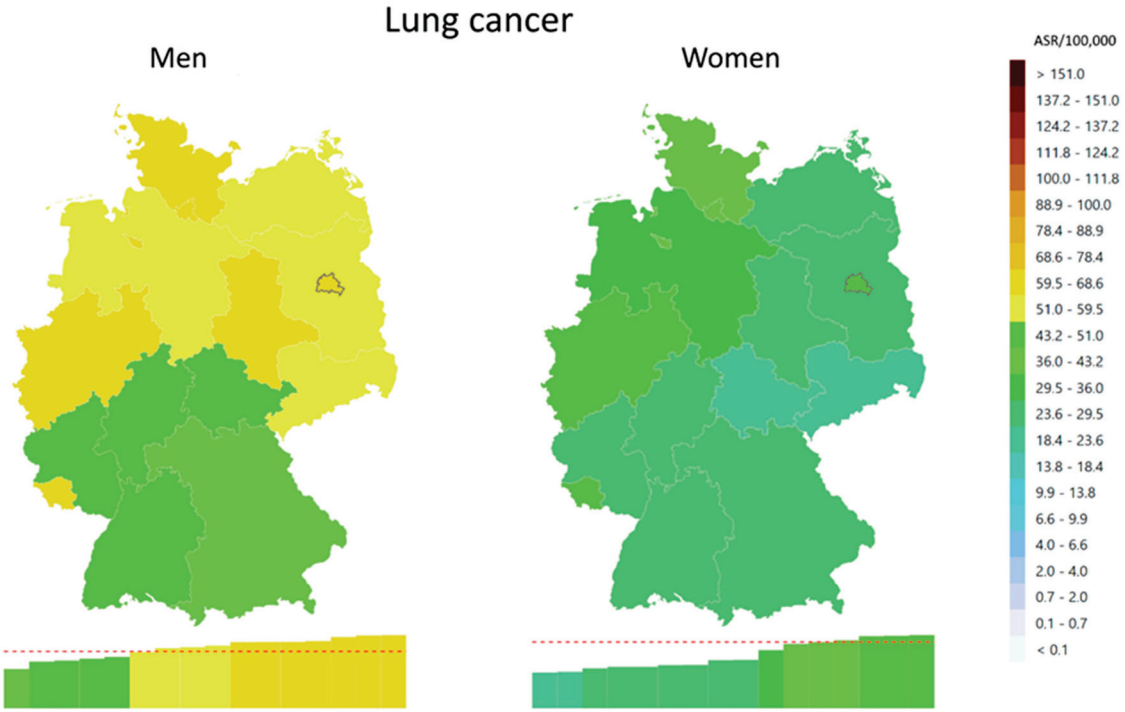


Figure 1. Geographical patterns of lung cancer incidence (ICD-10: C33-34) in 2019 in Germany on the level of federal states, age-standardised rates per 100,000 (ASR, European-Standard 1976). Data source: GEKID cancer atlas [12].

Long-term trends of age-standardised cancer incidence show stable (men) or slightly increasing incidence for all cancer sites from 1999 until around the year 2008 (Figure 2A), followed by a slight decrease in the last decade (women: 272.6 to 248.3 per 100,000 (−9%); men: 336.7 to 290.4 per 100,000 (−14%), both from 2008 to 2019). This decline is mainly driven by colorectal cancer (−23%), stomach cancer (−22%) and lung cancer among men (−17%), whereas an increase is observed in lung cancer among women (+22%). Prostate cancer incidence is on the rise in the most recent years, after a maximum was reached in 2007, followed by a decline until 2015 (−23%). Cancer mortality (Figure 2B) has been declining for decades, except for lung cancer in women. Compared with 1999, the total cancer mortality in 2019 is 18% lower among women and 28% lower among men.

For the purpose of evaluating oncological care, all relevant treatment information is recorded (Table 2). Table 4 shows an extract of routinely published registry data on therapy, in this case for rectal cancer (C20), stratified by stage, based on a report from Schleswig-Holstein. For the interpretation, it should be noted that if no information is available for an item (missing or probably not reported data), it is assumed that the corresponding therapy was not carried out (conservative approach). Approximately 69% of patients underwent surgery, mostly with curative intent (84%). In sano resection (R0) was achieved in 91% of the cases, with the proportion in stages III–IV decreasing to 79% (vs. 86% in stages I–II). Radiotherapy was applied to 33% of the patients, but 4% of these patients discontinued therapy before the planned end of treatment due to patient rejection (n = 4), side effects

(*n* = 12), progression (*n* = 1) or other reasons (*n* = 8). Chemotherapy was given to 40% of the patients, of which 44% received neoadjuvant chemotherapy therapy. The discontinuation rate was 22% (patient rejection (*n* = 9), side effects (*n* = 45), progression (*n* = 34) or other reasons (*n* = 73)). The most commonly used chemotherapeutic agents were antimetabolites (pyrimidine analogues as 5-FU, capecitabine, gemcitabine and cytarabine) (96%), platinum-based agents (48%) and topoisomerase inhibitors (16%). Immune/antibody therapy was administered to 12% of the patients.

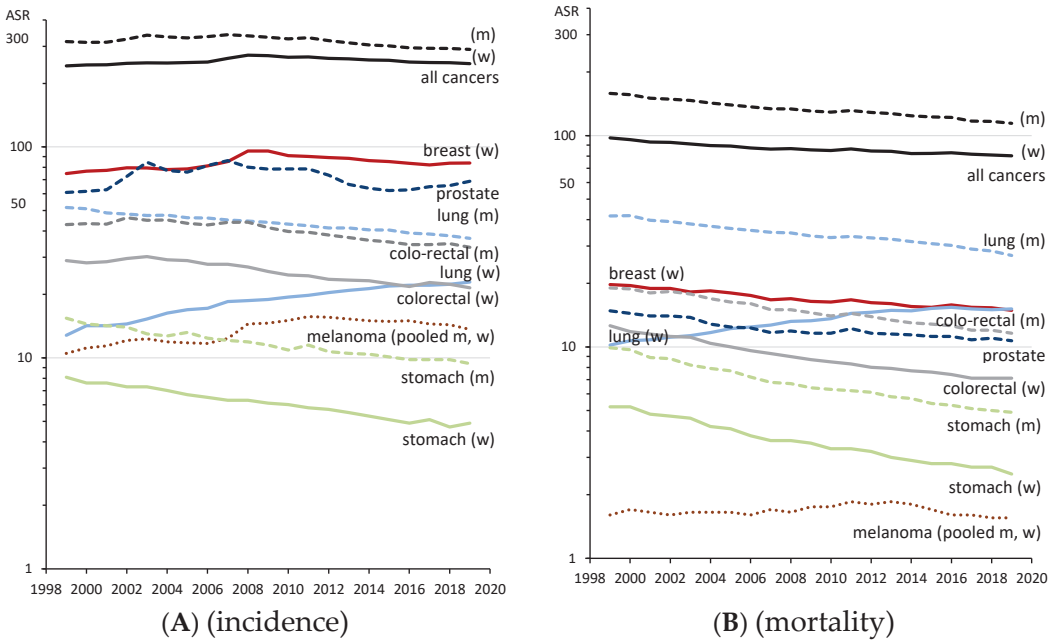


Figure 2. Incidence (**A**) and mortality (**B**) trends (1999–2019) of common cancers and all cancer sites (excluding C44), age-standardised rates per 100,000 (ASR, World). *Y*-axis logarithmic displayed. Data source: Centre for Cancer Registry Data at the Robert Koch-Institute [9].

Table 4. Treatment of rectal cancer (ICD-10 C20) patients, treated in 2019–2021 in Schleswig-Holstein, stratified by tumour stage. Data source: interactive cancer report CR Schleswig-Holstein [16].

	Patients Total N = 1734	**UICC Stages I–II N = 554**	**UICC Stages III–IV N = 792**	**UICC Stage Unknown N = 388**
Surgery	1200 (69%)	432 (78%)	591 (75%)	177 (46%)
Curative intention	1003 (84%)	372 (86%)	465 (79%)	166 (94%)
Resection R0 *	1047 (91%)	394 (95%)	496 (87%)	157 (92%)
Operation within 14 days after diagnosis	285 (24%)	128 (30%)	145 (25%)	12 (7%)
Radiation	850 (33%)	92 (17%)	286 (36%)	202 (52%)
Curative intention	552 (95%)	90 (98%)	268 (94%)	194 (96%)
Premature termination	25 (4%)	5 (5%)	11 (4%)	9 (4%)
Neoadjuvant	452 (78%)	67 (73%)	215 (75%)	170 (84%)
Chemotherapy	698 (40%)	87 (16%)	428 (54%)	183 (47%)
Curative intention	458 (69%)	68 (72%)	280 (69%)	110 (65%)
Premature termination	152 (22%)	10 (11%)	1127 (26%)	30 (16%)
Neoadjuvant	310 (44%)	41 (47%)	175 (41%)	94 (51%)
Immune/Antibody-therapy	99 (14%)	2 (2%)	79 (18%)	18 (10%)
cytostatic agents used:				
Antimetabolic	672 (96%)	85 (98%)	410 (96%)	177 (97%)
Platin-based	333 (48%)	29 (33%)	217 (51%)	110 (60%)
Topoisomerase inhibitors	115 (16%)	2 (2%)	90 (21%)	23 (13%)

* R0, no residual tumour/in sano, R-classification.

In addition to descriptive analyses of the therapeutic care provided to cancer patients, cancer registries are required to host regular regional quality conferences for healthcare

providers. Quality indicators (QIs) defined in evidence-based (S3) guidelines are used to assess cancer care. Currently, about 50% (94/188) of these have been operationalised using CR data, including standardised definitions for the nominator and denominator of the QIs. Figure 3 shows an example of selected QIs for three tumour types, including the operationalisation of each QI. Each bar in the figure represents a healthcare provider, usually a hospital or larger outpatient facility. For patients with breast cancer (Figure 3A), interoperative radiography or ultrasound should be used whenever possible. All providers complied with this QI in 96% or more of the cases. For prostate cancer surgery, a qualified report on lymph node involvement should be provided (Figure 3B). Four out of ten providers did not reach 90%. For patients undergoing surgery for colorectal cancer (Figure 3C), the quality of the total mesorectal excision (TME) should be as high as possible. Six out of twelve providers scored above 90%.



A Breast cancer

QI: Intraoperative specimen radio/sonography (%)

Numerator: operations with intraoperative preparative X-ray or intraoperative preparative ultrasonography

Denominator: operations with preoperative wire marking guided by mammography or sonography.

N= 2093

B Prostate cancer

QI: Report on lymph nodes (%)

Numerator: number of patients with reports of findings indicating the pN category and the number of affected in relation to removed lymph nodes.

Denominator: all patients with initial diagnosis of prostate cancer and lymphadenectomy.

N=684

C Colorectal cancer

QI: Quality of TME (%)

Numerator: number of patients with good or moderate TME quality (grade 1: mesorectal fascia preserved or grade 2: intramesorectal tears).

Denominator: all patients with radically operated rectal cancer.

N=503

Figure 3. Selected quality indicators (QI), based on German S3 therapy guideline for patients diagnosed and treated in 2020/2021. Each bar reflects a single healthcare provider, involved in treatment with more than 40 cases per year. Data source: Cancer Registry of Schleswig-Holstein (www.cancer-sh.de (accessed on 5 June 2023)).

4. Discussion

The introduction of clinical population-based cancer registration in Germany, initiated by a new law in 2013, can be considered a success. All major legal requirements have been implemented within the last 10 years. Although cancer registration for 84 million inhabitants is carried out by 15 independent cancer registries, decentralised registration is feasible and a high degree of standardisation in cancer registration has been achieved. Successful measures include not only uniform registration with a mandatory standardised dataset but also data exchange between registries, common standards for evaluation, and national availability of data for health monitoring and research. In this respect, cancer registration has now reached a level comparable with that of large international programmes such as SEER [17]. Such a major change in cancer registration from a dataset with only few recorded items, partly submitted as paper-based records, to full electronic recording with an extensive dataset, could have led to breaks in the epidemiological key figures. Luckily, this conversion to clinical cancer registration has not led to any breaks or temporal gaps in completeness or data quality. Time trends in incidence and other epidemiological indicators show stable values. On the contrary, the transition has improved the national completeness of cancer registration. In previous years, incidence had to be estimated for the whole of Germany due to regional registration gaps [18], but now, cancer incidence can be simply counted and reported on the basis of reported cancer cases. A comparison of cancer incidence in Germany with that of its northern neighbours, the Scandinavian countries, shows similar values and trends [19]. In both regions, the total cancer incidence (excluding non-melanoma skin cancer) decreased slightly in recent years. In 2019, the age-standardised incidence (world) in the Scandinavian countries was 288 and 311 per 100,000 for women and men, respectively, which is comparable with the figures for Germany (249/290 per 100,000 women/men). The same applies to the comparison with the western neighbour, the Netherlands, where the incidence in 2019 was 293/303 per 100,000 women/men [20]. Also, the European Cancer Observatory estimates for Germany (ECIS: 267/307 per 100,000 women/men) [21] are in concordance with our reported findings. Overall, the population-based approach of German cancer registration seems to provide reliable results on national level. Survival data are also in line with European results, as provided by ECIS. At this point it should be mentioned that the complete data of the cancer registries, partly going back to 1967, are accessible for research and have already been used intensively. The registry data are also regularly used for health reporting. There are interactive databases for incidence, mortality and survival at the federal and state levels up to small-area cancer reporting at the level of municipalities [22].

The most important advancement in cancer registration is the use of CR data for quality assurance and quality management. Treatment, progression and survival outcomes are now considered not only at the regional population level but also at the micro level of individual healthcare providers (HCPs). This includes not only feedback to individual HCPs on the quality of their own processes and outcomes but also benchmarking of the quality of care on a provider-by-provider basis. At present, such comparisons are mainly used to discuss the quality of cancer care with HCPs behind closed doors, without the public being present. However, the first countries have begun to publish quality parameters and name the institutions [23]. This is a big step towards transparency in oncology, and it is likely that this level of transparency will be introduced in other regions. In the long term, this may enable patients to choose their HCP on the basis of quality. It should be emphasised that the assessment of quality of care by cancer registries is not limited to selected hospitals but covers the entire oncological care landscape. This is particularly important for Germany with its strictly segmented healthcare system (strict separation of treatment in hospitals and outpatient/office-based care). The quality of care at cancer centres, which undergo voluntary annual certification by the German Cancer Society, is well known (see annual reports for different cancer types [24]). However, it is estimated that only 50% of all cancer patients are treated in these facilities (own calculation based on [24]), so that the quality of cancer care for all cancer cases is still unknown. Population-

based cancer registries, which record the care of cancer patients in all settings (inpatient and outpatient), allow a holistic assessment of cancer care. A recent publication by the European Network of Cancer Registries shows that about 50% of European cancer registries also collect clinical data, but the available data on therapy appear to be crude, such as surgery or chemotherapy yes/no [25], and few registries collect the clinical data needed to assess the quality of care [26]. There are several publications comparing accredited hospitals on the basis of quality indicators, for example for breast cancer [27] or renal cancer [28], but these reports are based on specific hospital-based data collection and not on routine cancer registration. However, recent publications indicate that the use of CR data for quality assessment at the HCP level is just beginning. In the Netherlands, hospital comparisons based on quality indicators have already been published for gynaecological cancers [29–31], lung cancer [32] or rectal cancer [33]. Such analyses, like ours, show that cancer care can be made measurable at the HCP level and that fair benchmarking of specific clinical aspects is possible. However, only the future will tell whether monitoring quality of care will ultimately lead to improved patient-relevant clinical outcomes. Do HCPs with well-documented quality produce better clinical outcomes than HCPs with poorly documented quality? Do recurrence rates decrease with increasing quality, do survival rates or quality of life improve? Cancer registry data will help answer such questions in the future.

It should be noted that all these efforts require a high financial input. In Germany, about EUR 160 is spent per registered case (EUR 120 for the CR + EUR 40 for five notifying physicians), or even more if relapse and additional therapies are reported, which is significantly higher than the European average of about EUR 50 per case, as reported by Zanetti et al. in 2014 [34]. A rough estimate—500,000 incident cancers per year, five notifications each—results in a sum of about 80 million EUR per year for Germany. 90% of these costs are covered directly by the health insurance funds. This has been facilitated by the fact that the new law makes cancer registration an integral part of public healthcare [35]. For the same reason, the use of registry data for quality assurance purposes became possible, independent of the consent of the institution. As a kind of return on investment, the healthcare system (and health insurance funds) obtains a comprehensive, evidence-based view of oncological care in order to initiate specific HCP-based measures for improvement, if necessary.

Limitations and outlook: Although much has been achieved in the last 10 years and cancer registration has undoubtedly reached a new level, major efforts are still needed to achieve all goals. For example, although it can be assumed that all incident cancers are currently fully recorded in cancer registries, data on treatment are not yet fully available. This is partly due to the sectoral structure of the German healthcare system, partly due to the fact that patients in Germany have complete freedom of choice of doctor or hospital, and partly due to the fact that the technical requirements for complex CR reporting and the corresponding software are still being developed. The latter limitation will be overcome in the next few years through increasing national efforts in digitisation and interoperability.

The national pooled dataset available for research purposes at the ZfKD will be expanded to include core clinical variables on treatment and disease progression based on the new federal law for data consolidation form the year 2021 [36]. The law paves the way to easier access to CR data for research, data linkage with other health data, identification of similar disease cases (digital twin) or long-term effects of cancer. In addition, the inclusion of patient-reported outcomes and patient-reported experience measures in cancer registries is being discussed as direct patient involvement in the registration process. In the near future, first results are expected to show whether the additional clinical cancer registration not only improves the process quality of oncological care but also leads to patient-relevant improvements regarding clinical outcome quality.

5. Conclusions

The implementation of clinical, population-based cancer registration can be considered a success. Basic features such as comprehensive recording of diagnosis, treatment and disease progression or the use of registry data for quality assurance, benchmarking and feedback have been implemented over the last 10 years. However, considerable efforts are still needed to achieve the goal of comprehensive and transparent assessment of oncological care in Germany.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers15153934/s1, Table S1: Most common cancer sites (ICD-10) in Germany 2015 to 2019: age-standardized rates per 100,000 (ASR World) Data source: common data set of German cancer registries provided by the Centre for Cancer Registry Data at the Robert Koch-Institute, 2023.

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The Population-Level Surveillance of Childhood and Adolescent Cancer and Its Late Effects in Europe with an Example of an Effective System at the Slovenian Cancer Registry †

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Simple Summary: The collection of detailed data, including on diseases that develop as a result of treatment later in life (i.e., late effects), on children and adolescents with cancer through cancer registries is important to provide exact, complete and clinically relevant results. Therefore, we surveyed European registries about their practices, revealing that collecting data on late effects is not widespread and that most registries collect only a basic set of data with little clinical detail. The approach of the Slovenian Cancer Registry is also presented, along with observations obtained through the setting up and testing processes, namely the lack of standardization in the variable sets, definitions and methods of collection and the poorer quality of results with retrospective registration. This research highlights the need for stronger collaboration between registries in order to harmonize collection practices, as this would facilitate the collection of more than just a basic dataset by population-based cancer registries.

Abstract: Background: The registry-based collection of detailed cancer and late effect (LE) data in childhood and adolescent cancer (CAC) is rarely explored. Aim: We aimed to provide an overview of CAC registration practices in Europe and share a Slovenian example. Methods: We distributed a questionnaire among European cancer registries on disease, treatment and LE registration and present the system at the Slovenian Cancer Registry along with an example of retrospectively collected LE data from a cohort of central nervous system tumour survivors from 1983 to 2000. Kaplan–Meier and Cox regression were used to calculate the LE incidence. Results: Out of 27 responding registries, over 80% registered cancer type, vital status, death and second primary cancer data. Less than 20% registered cumulative doses of radiation and systemic therapy or progressions. Only three registered LEs. The obstacles in setting up LE collection in registries are a lack of standardization in the variable sets, definitions and methods of collection. In the retrospective cohort, neurological and endocrine LEs were most common. Females had a higher risk of endocrine LEs (HR of 1.89; 95% CI of 1.08–3.31), while patients treated with radiotherapy had higher risks

of endocrine (3.47; 1.80–6.69), musculoskeletal and skin LEs (3.16; 1.60–6.26) and second primary cancers (2.85; 1.18–6.75). Conclusions: Standardization and harmonization are necessary to promote detailed CAC and LE registration.

Keywords: childhood and adolescent cancer; survivors; late effects; population-level surveillance; cancer registry

1. Introduction

Cancer in childhood and adolescence (defined here as occurring under the age of 20) has become a highly curable disease due to improvements in treatment [1–3]. While some data trends indicate a potential rise in the incidence of certain types of childhood and adolescent cancer, survival is improving and the mortality is decreasing in Europe and other high-income countries [4,5], leading to a growing and ageing cohort of childhood and adolescent cancer survivors (CACSs). However, this success comes with a burden of late sequelae in long-term survivors on account of the toxic effects of treatment on healthy tissues as well, especially as patients receive treatment while they are still growing and developing [6]. Additionally, there are reports of accelerated ageing in survivors as a pathological mechanism underlying some of the observed excess morbidity and mortality [7,8]. Large cohort studies [9–11] have provided a wealth of data on the type and frequency of late effects in survivors, such that overall follow-up guidelines [12,13] and specific internationally harmonized guidelines have been developed for the surveillance of breast cancer [14], cardiomyopathy [15], ototoxicity [16], premature ovarian insufficiency [17], gonadotoxicity [18] and thyroid cancer [19].

On the other hand, there are scarce data on the surveillance of late effects as part of population-based cancer registry (PBCR) activities. PBCRs have a rich history of continuous, systematic and harmonized data collection practices for the monitoring of standard cancer burden indicators [20]. While the primary aim of PBCRs is the complete registration of high-quality data, it is equally important to harmonize data across different countries. The European Network of Cancer Registries (ENCR) is an important institution in efforts to standardize datasets on an international level with the aim of better comparability and increased possibilities of pooled data analyses [21]. The standardization of practices in the estimation of the cancer incidence burden is at a high level, whereas the field of the late effects of cancer has not yet been improved in this regard. Having the necessary knowledge, technology, legal basis and other resources, PBCRs are the most appropriate setting for the prospective and routine monitoring of the population burden of late effects, which would bring several advantages in terms of complete estimates of the burden as well as more accurate time trends and the health system resources needed for its management. For late effects surveillance, very detailed treatment data are of the utmost importance. These are also vital in view of efforts to introduce a common European Survivorship Passport [22,23].

The first aim of our research was to provide an overview and comparison of population-level registration practices for childhood and adolescent cancers and the late sequelae of their treatment in Europe. Further, we present the effective system recently activated in the population-based Slovenian Cancer Registry (SCR): the structure of the database, along with the dataflow, is given for the newly established Slovenian Childhood Cancer Clinical Registry (SCCCR). Slovenia is a middle European country with one of the most developed cancer registration systems globally [19]. The establishment of the SCCCR was envisioned by the National Cancer Control Programme of Slovenia, with the aim of improving knowledge on the quality of treatment as well as detailed outcomes in terms

of late effects. For the illustration of the possible outputs of the SCCCR, an analysis of the late effects in a cohort of childhood and adolescent central nervous system cancer patients was prepared.

2. Materials and Methods

First, to map cancer registry practices, we sent out an online questionnaire-based survey to members of the ENCR. The survey was open to the members from 1 July 2022 to 31 August 2022 via the EUSurvey tool, emailed directly to 140 members (the majority of which, around 70%, were regional, and 30% were national) and advertised in the ENCR Newsflash for July 2022 with an additional reminder to boost the response rate. The complete questionnaire is available in Appendix A. It was divided into several sections, the first on the coverage of the registry (national/regional, the age range of pediatric patients, the malignant and non-malignant entities included), the second on whether PBCRs collect or are planning to collect detailed data (on the diagnosis, staging, treatment, progression, vital status follow-ups and other data) and the third on whether they register late effects data or are planning to, as well as how these data are or are going to be collected and coded. The survey results were analyzed using descriptive statistics; namely, we categorized questions addressing the availability of variables into categories (diagnosis, staging, follow-up, primary systemic therapy, surgery and radiotherapy) and reported the number and percentage of registries who answered either "yes", "no" or "planning to" to questions from each category regarding the collection of specific variables. Furthermore, individual registries were ranked according to their category and overall summary scores, which were calculated by summing answer-specific scores (0 points were allocated to answers of "no", 1 point for answers of "planning to" and 2 points for answers of "yes"). The data were presented in stacked bars and heat maps.

Second, we describe the elements of the SCCCR, the variable set, the sources of information and the methods of collection, in text and diagrams. For the illustration of the possible outputs of the SCCCR, an analysis of the late effects in the tested cancer patients' cohort was prepared. Adults older than 19 years with childhood and adolescent central nervous system (CNS) tumours were included in the testing cohort. CNS tumour patients were selected to ensure a large enough number of patients with a high number of expected events (late effects). We extracted from the SCR all cases of cancers with an ICD-O-3 topography of C70.0–C72.9 who were diagnosed with a first primary cancer at the age of 0–19 years between 1983 and 2000. We also extracted all second primary tumours (all malignant cases as well as melanoma in situ—ICD-10 D03 and non-malignant CNS tumours—as defined above) in these cases. We excluded patients who died before the age of 20, as well as those who died due to the protracted course of their primary tumour. By examining electronic patient files held at the Institute of Oncology Ljubljana, we then determined which patients had received a late sequelae follow-up at the Late Effects Clinic, which is a centralized service with national coverage for the surveillance of CACSs. We extracted information on late effects (as recorded by the end of February 2023), which we defined as early-onset but long-term or late-onset somatic health events. We adapted the Common Terminology Criteria for Adverse Events (CTCAE)-based classification developed by Hudson et al. [24] and classified late effects into organ systems (Table S2), recording the most accurate known date of onset of the first late effect according to the organ systems, as well as the number of all different known late effects recorded according to the by organ systems.

One of the major problems in preparing the classification was that we had difficulties in adapting it for use by Late Effects Clinic physicians as well as for cancer registries' purposes, where it might not be feasible to code every late effect to the highest level of detail. Therefore, unlike Hudson et al. [24], we included surgical procedures, because if the grading of organ failure was not possible, registering gross surgical procedures was deemed important. Similarly, some other surgery-related sequelae were also considered important, such as tissue defects, etc. Furthermore, we were unsure as to what detail certain events should be recorded with (for example, any valve defect or a specific valve defect) as well as how to include broader categories, if details were not available. We resolved this by adding broader and unspecific categories (not listed in the classification). During testing, we came across several barriers. As expected, grading was not possible to determine retroactively, because the level of detail in the electronic files was too low. The accuracy of dates was also poorer because of the retrospective approach. Furthermore, it was difficult to ascertain in which cases a medical condition was truly the result of cancer and its treatment; therefore, we collected all newly developed medical conditions recorded by the Late Effects Clinic. Additionally, since no specific classification existed, physicians were not systematically describing medical conditions in electronic patient files as late effects and the level of detail varied. Neurocognitive late effects in particular were often described only vaguely. Nevertheless, it was possible to at least count the number of different late effects (as classified in Table S2) according to the organ systems and record the most accurate known incidence date for each organ system.

The cohort characteristics were presented using descriptive methods. We determined the prevalence of late effects at the last follow-up in the Late Effects Clinic (as of the end of February 2023). In SPSS, Version 29.0, we calculated the cumulative incidence using the Kaplan–Meier method to ascertain the probabilities of developing second primary tumours and organ-specific late effects (cardiovascular, respiratory, gastrointestinal and hepatobiliary, renal and urinary, reproductive tract, endocrine, musculoskeletal and skin, neurological and neurocognitive, immunological and infectious, hematological, auditory, and visual). Psychosocial effects were not included. The time to event was defined as the time from the date of diagnosis to the date of onset of the first organ-specific late effect or the date of diagnosis of a second primary tumour. Patients were censored at the last known date of follow-up at the Late Effects Clinic (or 6 February 2023 for second tumour analysis). Patients without a known follow-up (those not invited/not responding to follow-up invitations) had zero follow-up time. Furthermore, we used Cox regression analyses to analyze the cumulative incidence of all late effects combined as well as late effects grouped according to the organ systems with the sex, the type of anticancer treatment received (surgery, yes/no; radiotherapy, yes/no; systemic therapy, yes/no) and the period (1983–1990 and 1991–2000) as covariables with significance at a p-value of less than 0.05.

3. Results

3.1. Survey on Cancer Registry Practices in Field of Late Effects of Childhood and Adolescent Cancers

We received responses from 27 European cancer registries (response rate of 19.3%; Table S1). Of these, there were 12 with national (Belgium, Croatia, Estonia, the Faroe Islands, Finland, Ireland, Luxembourg, Montenegro, Romania, Slovenia, Switzerland and the Netherlands) and 15 with regional coverage (from England, Germany, Italy, Romania and Spain). All in all, 16 different European countries provided responses. Six of the responding registries were childhood registries; others covered all ages. We searched online information on the registration systems of the non-respondents deemed important

for a better outline of the practices (especially childhood cancer-dedicated registries), which is presented in the discussion.

Regarding individual registries, according to the overall summary score, the top three were the Belgian and Swiss registries and the West Midlands tumour registry, United Kingdom (Table S1). Though a formal comparison of national versus regional registries was not feasible due to insufficient numbers, the results showed that among ten registries with the highest overall scores, two were national, while this number was only two among the bottom ten registries. All PBCRs registered all malignancies (i.e., they were not specific for, e.g., hematologic malignancies only). Only two registries (the Faroese Cancer Registry and the Cancer Registry of Friuli Venezia Giulia) did not and were not planning to register any non-malignant childhood and adolescent tumours. Of the remaining 25 registries, 24 already registered, at least to some degree, (and 1 was planning to) the non-malignant International Classification of Diseases for Oncology, 3rd Edition [25] (ICD-O-3), codes C70–C72 (meninges, brain and spinal cord, cranial nerves and other parts of the CNS), whereas 19 registered (3 were planning to) ICD-O-3 codes C75.1–C75.3 (pituitary gland, craniopharyngeal duct and pineal gland). The National Cancer Registry Ireland also registered in situ and uncertain behaviour tumours for all sites and the Belgian Cancer Registry all in situ locations, while several others included a wide variety of locations for in situ and uncertain behaviour tumours, most commonly bladder, ovary and skin melanoma.

Figure 1 presents the questionnaire results for the availability of data on the diagnosis, staging, therapy and follow-up. A high percentage of respondents (over 80%) collected data to classify childhood and adolescent tumours according to the International Childhood Cancer Classification (ICCC), third edition [26], and data on the vital status, the underlying cause of death and other primary tumours. On the other hand, few (less than 20%) registered the imaging diagnostics performed, cumulative doses of therapeutics, cumulative radiation doses, details of stem cell transplants, other treatments received and acute side effects of treatment, as well as data on the progression of the disease. Only three registries responded that they registered late effects (the Swiss Childhood Cancer Registry, the Belgian Cancer Registry and the West Midlands Regional Children's Tumour Registry), and only three expressed intent to introduce it (the Girona Cancer Registry, Romanian National Childhood Cancer Registry and the SCCCR of the Slovenian Cancer Registry). No responding registry currently collected non-stage prognostic indicators. Other items had between a 20 and 80% availability, with a notably high percent of the intention to introduce Toronto staging and expand the detail on systemic therapy and disease progression.

3.2. Development and Features of Slovenian Childhood Cancer Clinical Registry

The SCCCR was developed as an extension of the population-based SCR, with the collaboration of SCR staff, physicians working at the Late Effects Clinic and the Pediatric Clinic Ljubljana and IT experts. We also drew on good practice examples from abroad, such as the New Zealand Children's Cancer Registry and the Belgian Cancer Registry. It has in place the same internationally harmonized practices as the SCR, such as international coding rules, active registration, linkage with administrative databases and data protection measures, while at the same time building on these practices to vastly expand the number of collected variables (see Figure 2 to compare the SCR and the SCCCR variable sets).

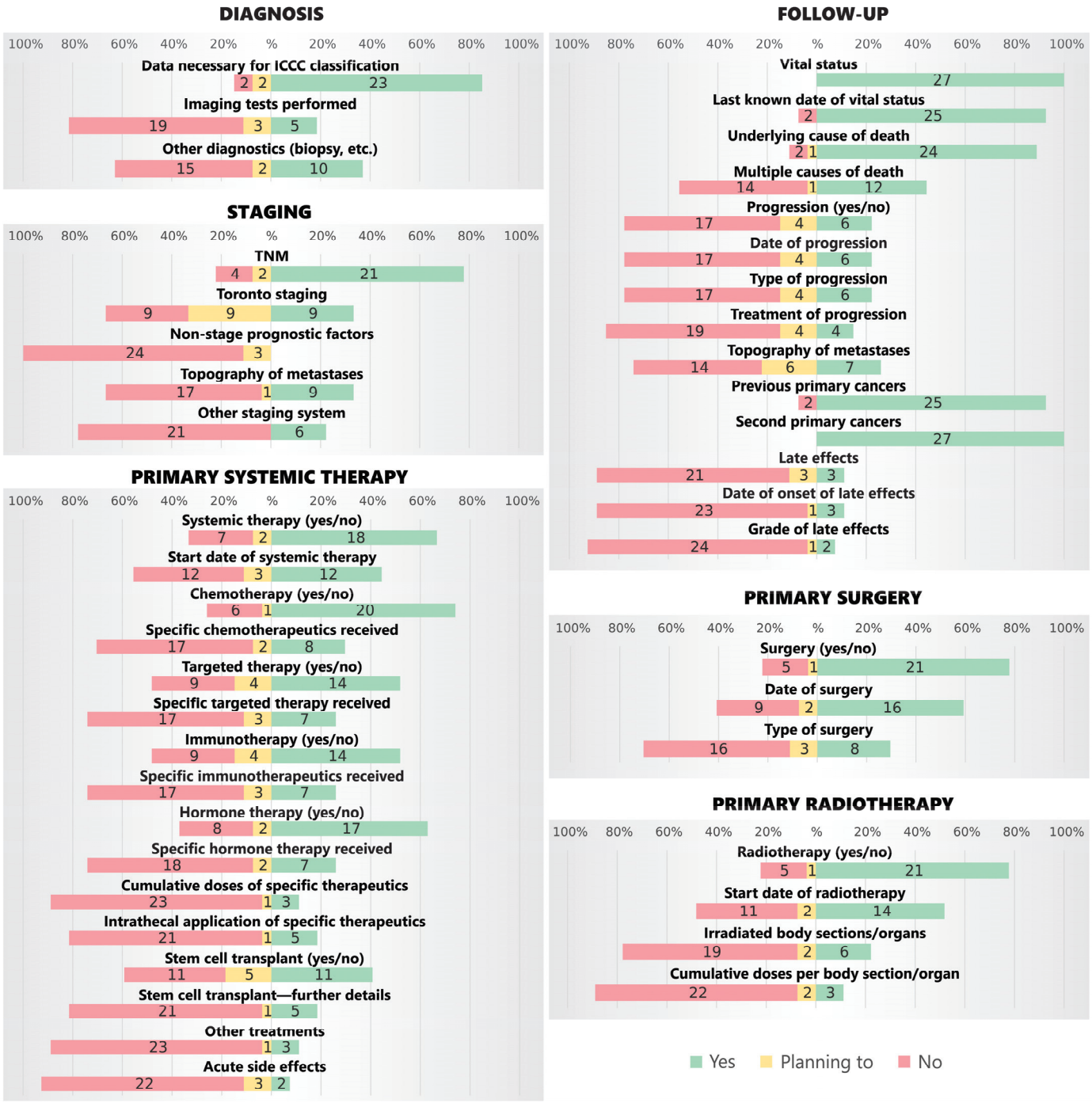


Figure 1. Number and percentage of all answers (n = 27) on data availability in cancer registries by type of data.

The SCR and SCCCR operate through two-way communication. All diseases registered within the special SCCCR platform are automatically transferred into the SCR (only the basic set of data on the disease, staging and treatment), and after the disease is also registered in the SCR, certain data available there are then transferred from the SCR to the SCCCR (such as personal data, the vital status, death data). Because the SCR is linked to the population registry, the personal data and vital status are very accurate and updated every 24 h.

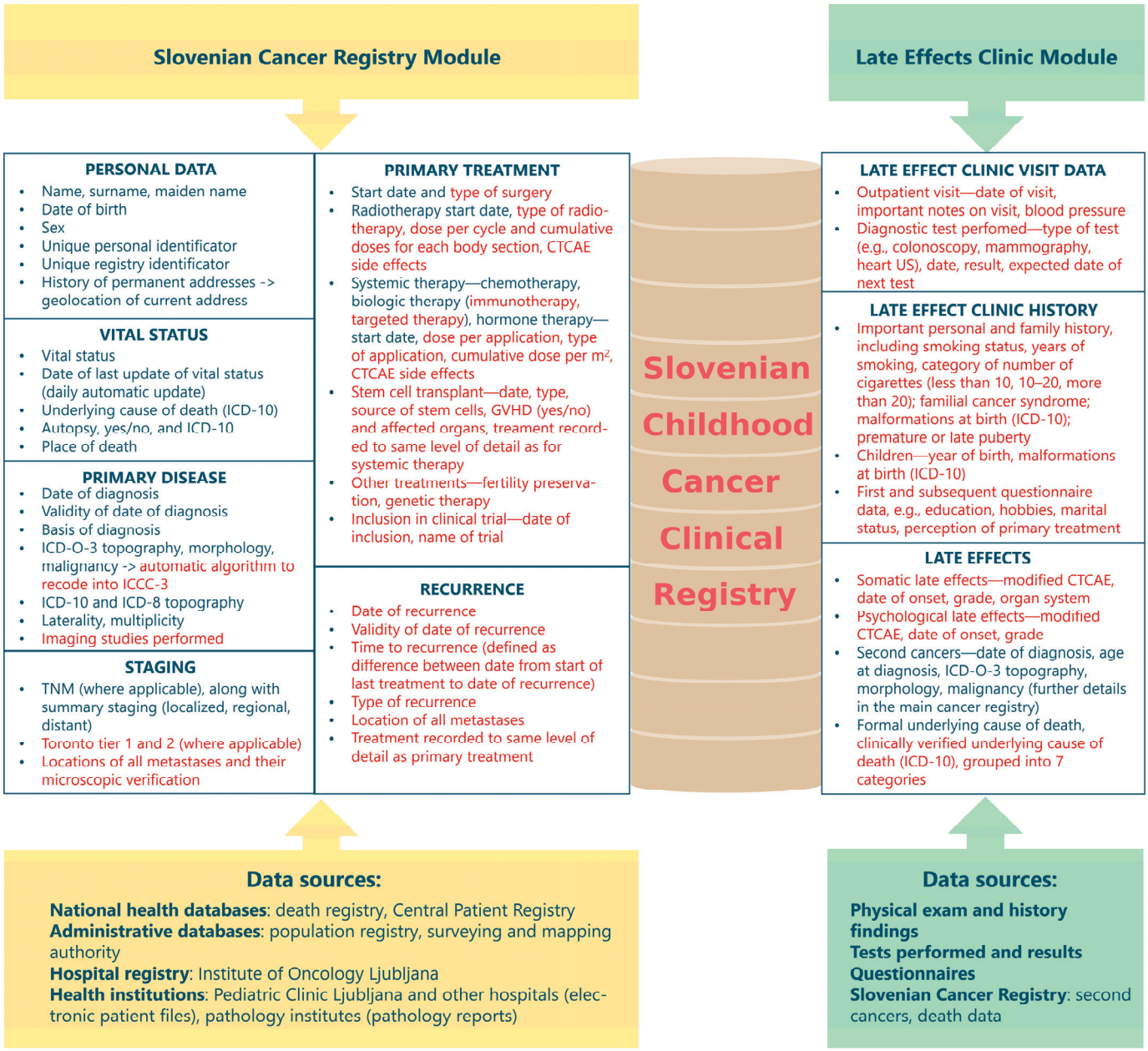


Figure 2. Data sources and variables of the Slovenian Childhood Cancer Clinical Registry (SCCCR). Red items represent the expanded set of variables in the SCCCR, whereas blue items were already in place in the Slovenian Cancer Registry before the introduction of the SCCCR.

The population covered by the SCCCR is all persons residing in Slovenia who were aged 0–19 years at diagnosis. We collect all malignant ICD-10 codes and non-malignant intracranial and intraspinal tumours (ICD-10 D32–D33, D35.2–D35.4, D42–D43, D44.3–D44.5), as well as certain other non-malignant codes (D03, D05, D06, D09.0, D39.1).

The SCCCR has two modules: (1) Since the primary aim was to create a platform that would enable the systematic registering and long-term monitoring of late effects (in terms of morbidity and mortality) in a population of CACSs, one module was designed for direct use by clinicians at the Late Effects Clinic at the Institute of Oncology Ljubljana, where entry is possible either retrospectively or prospectively, allowing them to access all historical data during patients' visits and the ongoing collection of clinical data from exams, questionnaires and other follow-up findings. This module does not have 100% population coverage, as patients eligible for follow-up are those treated for tumours at the Pediatric

Clinic (over 80% of all cases aged 0–14 years, fewer adolescents), aged 18 years or more and at least three years post treatment, but the coverage for the eligible population is almost complete. (2) For the proper evaluation of the burden of late effects in survivors, data on the primary cancer and treatment received are also of vital importance. Therefore, the secondary aim was to collect as much detailed data on disease and treatment as possible through a module managed by specially trained SCR staff, who extract the data manually directly from electronic patient records held at the Pediatric Clinic at the University Medical Centre Ljubljana, which treats the vast majority of children and adolescents with cancer, as well as other treating institutions. This module covers the whole childhood and adolescent cancer patient population and started collecting data since the incidence year of 2019. Of note, the cumulative doses per m^2 of the body surface of systemic therapy and cumulative radiation doses per organ are collected. This allows for analyses of the quality of treatment, as well as the short- or long-term outcomes.

3.3. Late Effects in Childhood and Adolescent Central Nervous System Cancer Patients

For the illustration of the possible outputs of the SCCCR, an analysis of the late effects in a cohort of childhood and adolescent central nervous system cancer patients was prepared. There were 240 cases of childhood and adolescent CNS tumours (0–19 years) diagnosed between 1983 and 2000. After eliminating cases who died before adulthood or due to protracted primary disease in early adulthood (Figure S1), there were 126 CACSs who were eligible for a late effects follow-up. Of those, the majority were male, and there were no observed differences between sexes in the age at diagnosis, malignancy, period of diagnosis, treatment and follow-up (Table 1). Of note, around 25% of eligible patients (32 out of 126) never received a late effects follow-up at the Late Effects Clinic. At least one late effect was observed in more than 90% of patients followed at the Late Effects Clinic. At the last known follow-up date for late effects, the prevalence was highest for neurologic (73.4%), endocrine (57.4%) and musculoskeletal and skin late effects (55.3%).

Table 1. Characteristics of the childhood and adolescent central nervous system tumour survivor cohort. SD—standard deviation; n—number; y—years.

Sex, n (%)	**Both Sexes**	**Male**	**Female**
Characteristic	n = 126 (100.0)	n = 79 (62.7)	n = 47 (37.3)
Age at diagnosis (y), mean ± SD	10.5 ± 5.3	10.4 ± 5.5	10.7 ± 5.0
Age at diagnosis group (y), n (%)			
0–4	26 (20.6)	18 (22.8)	8 (17.0)
5–9	34 (27.0)	20 (25.3)	14 (29.8)
10–14	33 (26.2)	21 (26.6)	12 (25.5)
15–19	33 (26.2)	20 (25.3)	13 (27.7)
ICD-10 code, n (%)			
C	99 (78.6)	65 (82.3)	34 (72.3)
D	27 (21.4)	14 (17.7)	13 (27.7)
Diagnosis period, n (%)			
1983–1990	61 (48.4)	38 (48.1)	23 (48.9)
1991–2000	65 (51.6)	41 (51.9)	24 (51.1)

Table 1. *Cont.*

Sex, n (%)	**Both Sexes**	**Male**	**Female**
Treatment, n (%)			
Surgery, yes; n (%)	111 (88.1)	72 (91.1)	39 (83.0)
Radiotherapy, yes; n (%)	56 (44.4)	34 (43.0)	22 (46.8)
Systemic therapy, yes; n (%)	22 (17.5)	15 (19.0)	7 (14.9)
Vital status (6.2.2023), n (%)			
Alive	114 (90.5)	73 (92.4)	41 (87.2)
Dead	12 (9.5)	6 (7.6)	6 (12.8)
No somatic late effects follow-up, n (%)	32 (25.4)	19 (24.1)	13 (27.7)
Somatic late effects follow-up, n (%)	94 (74.6)	60 (75.9)	34 (72.3)
Follow-up time for somatic late effects (y), mean ± SD	27.8 ± 7.2	27.0 ± 7.7	29.2 ± 6.1
Number of somatic late effects, mean ± SD	6.3 ± 4.5	5.8 ± 4.2	7.8 ± 5.1
At least one somatic late effect, n (%)	86 (91.5)	57 (95.0)	29 (85.3)
Reproductive organs, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, n (%)	2 (2.1)	1 (1.7)	1 (2.9)
Renal and urinary, n (%)	3 (3.2)	2 (3.3)	1 (2.9)
Gastrointestinal and hepatobiliary, n (%)	6 (6.4)	4 (6.7)	2 (5.9)
Hematological, n (%)	7 (7.4)	1 (1.7)	6 (17.6)
Immunological and infectious, n (%)	8 (8.5)	3 (5.0)	5 (14.7)
Auditory, n (%)	19 (20.2)	11 (18.3)	8 (23.5)
Visual, n (%)	34 (36.2)	22 (36.7)	12 (35.3)
Cardiovascular, n (%)	37 (39.4)	24 (40.0)	13 (38.2)
Musculoskeletal and skin, n (%)	52 (55.3)	31 (51.7)	21 (61.8)
Endocrine, n (%)	54 (57.4)	29 (48.3)	25 (73.5)
Neurological and neurocognitive, n (%)	69 (73.4)	43 (71.7)	26 (76.5)
Second primary cancers, n (%)	30 (23.8)	15 (19.0)	12 (25.5)

The results of Kaplan–Meier analyses (Figure 3) revealed that CACSs with CNS tumours in the cohort were at risk for developing a multitude of organ-specific late effects (with the exception of reproductive late effects, of which none were registered) and second primary tumours long after their primary treatment had finished, though, in general, there was a levelling off in the cumulative curves after around 20–30 years. For endocrine late effects in particular, the cumulative incidence curve did not level off.

The results of Cox regression analyses by the organ system and for second primary tumours are in Table S3. We report only on those organ systems with an event number of more than 10. In brief, females seemed to be at higher risk for endocrine late effects (HR of 1.89, CI of 1.08–3.31), while radiotherapy was a risk factor for endocrine (HR of 3.47, CI of 1.80–6.69) and musculoskeletal and skin late effects (HR of 3.16, CI of 1.60–6.26) as well as second primary cancers (HR of 2.85, CI of 1.18–6.75). The risk of second primary tumours did not differ among sexes. There was a higher risk for neurologic and neurocognitive effects in the later period (1991–2000; HR of 2.18, CI of 1.31–3.62). Although not significant, systemic therapy seemed associated with the risk of cardiovascular events (HR of 2.05, CI of 0.96–4.37).

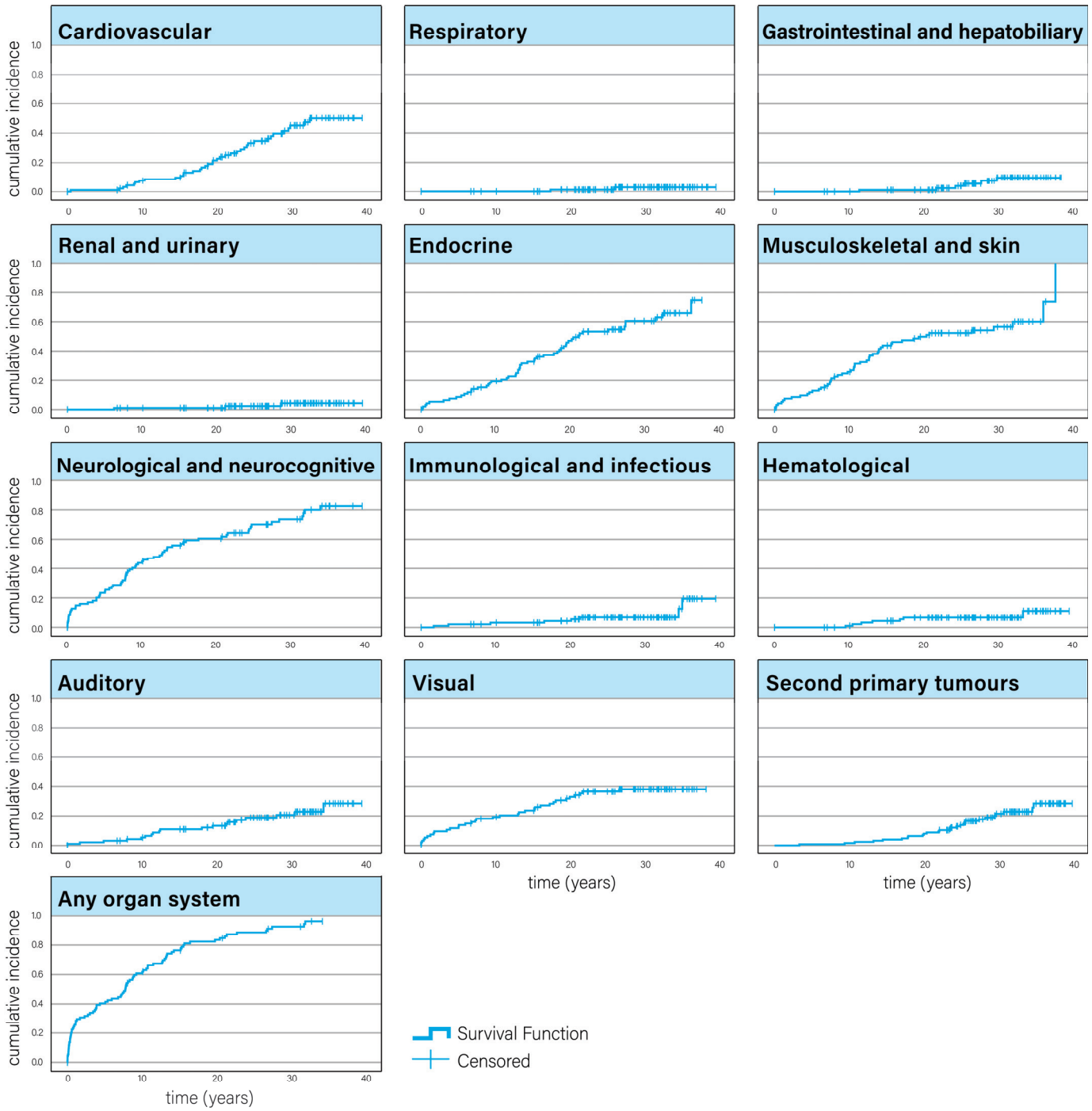


Figure 3. Cumulative incidence curves for somatic late effects and second primary cancers.

4. Discussion

4.1. Existing Practices in Pediatric Cancer and Late Effects Registration in Europe

With the use of the questionnaire, we sought to elicit information on current and possible future data collection systems among ENCR members. The survey results, although not comprehensive due to the relatively low number of respondents, provide an insight into which kinds of pediatric cancer data are available in Europe and to what degree. It seems that, according to the overall score, more national registries were higher ranked compared to regional ones, which might reflect differences in the available resources. Our primary aim was to evaluate late effects surveillance, and the results are not encouraging, since a very small percentage reported this type of monitoring or an intent to introduce

it, and one of those was Slovenia. A low number of PBCRs also collected more than basic (yes/no for the main modalities) treatment data. Detailed treatment data are vital when investigating long-term outcomes. The only areas with good coverage were the vital status and second primary tumours, which all general PBCRs already collected. Thus, the only possibility for widespread analyses of late effects using PBCR data are the mortality and incidence of second primary cancers. These robust indicators are of value and should be used more, especially in a standardized, internationally comparable fashion, such as within the CRICCS project for second primary tumours [27]. Nevertheless, they are insufficient for any in-depth studies looking into survivorship long-term health trends. A noteably high percentage of respondents already had or were planning to introduce Toronto staging. This is no doubt due to the good example of harmonization efforts within the BENCHISTA project, which aims to standardize and promote the collection of the endorsed registry-adapted pediatric-specific staging guidelines across the world [28,29].

Of the participating registries, three already had late effects registration in place. The Swiss Childhood Cancer Registry [30] had been collecting detailed data on treatment and outcomes (such as recurrences, late effects and second primary tumours) from treating institutions in yearly intervals. The late effects were classified according to the ICD-10 classification, meaning the grading was not recorded. The once-yearly update is also not optimal, although the data could still be very accurate if they are collected prospectively at the treating institutions. The Belgian Cancer Registry has been collecting data on late effects classified according to the CTCAE from hospital databases since 2004. Additionally, since 2017, the Belgian Cancer Registry has run an affiliated project called "Pediatrics—Late effects". The data are collected via online registration forms by the treating physicians, who send one primary and several follow-up registration forms after progression/relapse or a new primary tumour, as well as regularly every 5 years after diagnosis. Here, again, the 5-yearly update might be a small disadvantage in terms of the data availability and/or accuracy. The West Midlands Regional Children's Tumour Registry has been using CTCAE-based late effects registration, complete with grading, since 1997. It is part of an oncology department with regional coverage. Their data sources are hospital databases (the follow-up clinic), outpatient databases and primary health care institutions, which are actively contacted for data on patients not participating in the hospital follow-up [31].

A literature search for additional information on practices revealed a few further examples (Table S4). In France, the National Childhood Cancer Registry collects both detailed disease and treatment data. They also collect late effects data in a passive way from medical databases. Additionally, in 2013, they launched the French Childhood Cancer Observation Platform [32], which has data on all childhood cancers under 15 years. The platform receives core basic data from the national childhood registry, while also including geolocation and biobank data and collecting data on treatments (including cumulative doses) and late effects (relapses and second cancers in childhood) retrospectively every 5 years from medical records, linking yearly to the national health insurance information system (for morbidity, disabilities and care consumption) and adding online questionnaire data from childhood cancer survivors (CCSs). It is a good example of compiling diverse data from many sources through linkage as well, though a disadvantage is that the late effects are not ascertained clinically. The German Childhood Cancer Registry, while a PBCR, also has features of a clinical registry, receiving stage and follow-up data from clinical studies for over 40,000 CCSs [33,34]. Like the French example, it is well set up for the population-based surveillance of late effects, though it lacks therapy details because it has no direct access to hospital records. Having input from different clinical studies with different designs and inclusion criteria might also preclude it from recording late effects in a standardized way for all CCSs. In Greece, the Nationwide Registry of Childhood Hematological Malignancies

and Solid Tumors (NARECHEM-ST), in addition to basic disease data, collects information on death, relapse and bone marrow transplantations, as well as long-term sequelae, though the latter have not yet been sufficiently systematized [35]. The Hungarian Childhood Cancer Registry also collects some detailed data on treatment and disease as well as late effects, but the variable set and whether registration is systematic and continuous were hard to ascertain [36]. The regional Yorkshire Specialist Register of Cancer in Children and Young People [37] employs many modern data extraction and linkage practices with a variety of sources, including detailed treatment and late-outcome data (secondary care admissions). Of note, they include young adults and link with the National Pupil Database to obtain educational data. The Spanish Registry of Childhood Tumors (RETI-SEHOP) is a national registry compiling regional data primarily to investigate the incidence, causes of cancer and survival in Spain, whereas late effects do not seem to be prominently featured [38]. In southern Sweden [39], a similar approach to the one in Slovenia was undertaken in order to provide clinicians with reliable and complete PBCR data with the aim to facilitate efficient and appropriate medical follow-ups. Their PBCR, the clinical childhood cancer registry (BORISS) [40], although not part of the national PBCR, includes patients diagnosed at 0–18 years old from 1970 onwards and has detailed treatment data on 5-year survivors, retrospectively collected until 2016 and prospectively since. Furthermore, they annually import certain core data from the Swedish national PBCR as well as the national population registry. BORISS provides the late effects clinic in Skåne with a treatment summary for tailored surveillance. The Dutch Late Effects Registry (LATER) [41], which is also not part of a PBCR, is population-based as its design was based on an information model implemented in all Dutch oncology centres. It has a long tradition of use, and many studies have come about since its introduction, though it seems the studies are based on a closed cohort [42]. The PBCR approach, on the other hand, assumes an open cohort approach. The Swiss Young Survivors at KSA is another example of a registry not affiliated with a PBCR that has a very similar design to how the SCCCR was set up [43]. They collect detailed data on disease and treatment and late effects through follow-up visits, using Hudson et al.'s modified CTCAE classification [24]. Their advantage is that they start collecting follow-up data in a prospective manner immediately after patients enter follow-up care while still in childhood and adolescence, which closes the gap between diagnosis and adulthood. Furthermore, they register detailed data on physical, laboratory and imaging evaluations and other tests, which would allow for assessing the agreement between different assessors or reclassification using other classifications. They have retrospective data from 2016 to 2021 and prospective data onwards.

The main limitation related to the survey was the low response rate, though we endeavoured to overcome this by searching for good practice examples among childhood cancer-dedicated ENCR members. Nevertheless, important PBCRs were perhaps missed. Since we only contacted ENCR members, non-PBCR registries (who are also not part of the ENCR) that could have provided valuable information for PBCR-based surveillance were excluded. In searching for additional examples, we could have made mistakes in the interpretation of online findings as well.

4.2. Barriers to Registering Detailed Childhood Cancer Treatment and Outcomes

The main barriers to registration in PBCRs are likely similar to those that PBCRs usually encounter in their work—a lack of access to data (legal barriers, technical barriers, low-quality or incomplete data sources, no established follow-up services, etc.), a lack of human and financial resources and a lack of awareness of the importance of such surveillance, as well as methodological barriers. Specifically, access to electronic patient files through active registration is of paramount importance to be able to access high-resolution data,

which is hard for many registries. A vital aspect is also the age definition for childhood and adolescent cancer, as it varies among treating institutions and registries. Pediatric institutions across Europe have different upper age limits for the cancer patients they treat, which could affect registration as well [44]. The standardization of cancer treatment and recurrence coding is also lacking for now, but this might soon be made available through dedicated ENCR working groups [45]. In this regard, it would be important to also document any treatment deviations from established protocols, as these can be significant factors in survival and other outcomes [46]. Another important barrier to the standardized registration of late effects is that currently, the methods for assessing and defining long-term outcomes in childhood cancer survivors are not harmonized. A systematic review by Streefkerk et al. [47] found a large variability in the way researchers ascertain and classify health outcomes in survivors, stressing that we need global harmonization initiatives to improve survivorship research. Cancer registries in particular need to contribute to these efforts in order to achieve the same comparability and consistency level as that of standard cancer registry datasets. In order to improve the quality of cancer registry data on pediatric cancer treatment and outcomes, PBCRs need to form a data exchange agreement with clinical institutions or national/regional patient database administrative systems. A recent feasibility study from Switzerland [48] on the prospective registration of late effects by treating physicians used the modified CTCAE developed by Hudson et al. [24], and its results speak in favour of this type of approach to monitoring the late effects burden. The authors stress the importance of standardization in collection and confirm that this type of monitoring is feasible and provides a rich database for clinical as well as research purposes. During the development and testing of the SCCCR, we reached similar conclusions, which we describe below.

4.3. The Lessons Learned from the Slovenian Example

While we are aware that the example of Slovenia, a country of only 2 million inhabitants, might not be useful for countries that have vastly different legislation, management of CACSs (especially in terms of smaller countries with centralized services versus larger countries with many centres and registries), possibilities for the interinstitutional exchange of data or other established registry practices, it is important for registries to share practices and experiences. The main advantage of the Slovenian example is the exchange and enrichment of data between three institutions with national coverage: the Pediatric Clinic, SCR, and Late Effects Clinic. The SCCCR deepens the level of registry data, making them more useful for clinically important analyses, while also providing a platform to improve the follow-up at the Late Effects Clinic. The lack of the harmonized classification of late effects was a significant barrier, though, and we propose that it should entail several tiers based on the availability of clinical details to at least enable the registration of broader categories with suggestions for grading. We plan to promote this idea within the ENCR and International Association of Cancer Registries (IACR) community through conferences [49], expert meetings and international projects.

Through the exploratory study, we found that, at least in Slovenia, a retrospective approach based on searching for information in electronic medical files is not ideal and has many disadvantages in terms of the data quality, depth and completeness compared to prospective entries by treating physicians, which might be a better way for PBCRs to access very clinically complex data. Nevertheless, the CSN CACSs cohort late effects results were in line with many previous studies on late effects. We found a high prevalence of all previously reported common chronic health conditions, such as endocrine, neurological and neurocognitive sequelae and second primary tumours [50–53]. The higher risk of endocrine, musculoskeletal and skin sequelae and second tumours in irradiated patients is

in line with previous studies which guidelines have been based on [12,13,54]. The relevance of the higher risk of endocrine events in women and the higher risk of neurological and neurocognitive effects in the later period are difficult to ascertain. Given that treatment has improved in terms of toxicity and that neurocognitive effects can often manifest only years after treatment, we would have expected a reverse outcome. It is perhaps a phenomenon following temporal changes in the practices of registration by physicians or an effect of more patients with CNS tumours with a previously poor prognosis surviving recently due to improved treatment, while the finding of a higher risk of endocrine effects in women is in line with previous studies [55]. An additional finding from this study was the relatively high percentage of presumably eligible patients who never received a follow-up. This was attributed partly to patients "falling through the cracks" of the current referral system, where the Pediatric Clinic is the main referring institution and therefore patients treated there are more likely to be referred to an adult follow-up, but is in large part consequent to patients opting out. Having these types of data is useful in evaluations of the current follow-up systems.

4.4. Possible Advantages of Harmonization in Childhood Cancer Disease and Outcome Registration

As important as large childhood cohort studies are, introducing the systematic continuous and standardized surveillance of late effects within or as part of PBCRs has certain advantages. It would allow for more complete cancer burden estimates and determine the percentage of eligible patients receiving an appropriate follow-up. Compiling and endorsing a late effects classification would stimulate and improve the reporting on late effects by treating physicians, since their practices might differ between institutions, countries and across time. Psychosocial outcomes in particular are, though very impactful, unsystematically documented in our experience; therefore, we were unable to include them in this exploratory study of CNS CACSs. Harmonization would also improve the PBCR data quality in many countries and aid in pooling data across European countries, a useful approach in studying rare cancers, and provide more opportunities for high-resolution survivorship studies. Better data on cancer and outcomes could serve as a basis for advancing the initiative for the "right to be forgotten", namely that survivors face unjust financial obstacles, such as access to loans, after they have been cured of cancer, which has been increasingly recognized across Europe [56]. Detailed treatment data are also important with respect to international initiatives such as the Survivorship Passport (SurPass) [22], the aim of which is to provide a standardized childhood cancer treatment summary in Europe. Until now, the first version has been piloted in Italy, but its design is considered too time-consuming as each data item needs to be manually entered by hospital staff. Therefore, a new version is under development which will allow for semi-automatic data entry and has IT tools integrated for the automatic extraction of certain data, if they are available. Initially, six European countries will test the platform. The major barriers to this version of the SurPass [23] are access to clinical data sources and data harmonization between different institutions, such as hospitals and cancer registries, each of which hold data relevant for the SurPass. Therefore, embedding clinical registries within PBCRs offers a unique opportunity for enabling the adoption of the SurPass, as such registries have already addressed the most important obstacles by forming collaborations with clinicians and exchanging data between relevant institutions and can provide nationally relevant treatment reports to improve and tailor surveillance.

5. Conclusions

In order to improve the data quality and detail in pediatric cancer registration, access to electronic clinical patient data is an important option for cancer registries to explore

within the data availability and protection restraints. Applying the PBCR approach to clinically relevant data will lead to improved childhood and adolescent cancer burden estimates and trends, while allowing for analyses of risk stratification approaches for follow-ups. PBCRs should proactively seek for whether there are possibilities for such interinstitutional collaboration and most importantly collaborate at the European and international levels to develop harmonized treatment and late effects registration practices as well as publish examples of good practices. Recently, the most prominent experts in the field of childhood cancer and cancer registration held an event in Paris in 2023, where the case for the International Childhood Cancer Data Partnership was outlined along with important obstacles, including harmonization and standardization [57].

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cancers17040580/s1: Figure S1: Process of acquiring the final cohort of childhood and adolescent cancer survivors eligible for a late effects follow-up; Table S1: Basic characteristics and ranking of individual registry results, by questionnaire category and overall; Table S2: Classification of the late effects used in the exploratory study; Table S3: Cox hazard analyses for incidence of late effects by organ systems and second primary cancers; Table S4: Results of the online search for additional registries.

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Appendix A

Questionnaire for ENCR members about childhood cancer registrationpracticesand childhood cancer surveillance of late effects within cancer registries:

Dear cancer registry colleagues!

We are conducting a short survey with the aim to better understand the level of detail of data on registered paediatric cancer cases in Europe. The main purpose is to identify registries that have or are planning to have detailed data on paediatric cancer patients and

furthermore, if any registries have or are planning to have in place systematic registration of late effects of childhood cancer treatment for potential collaboration in the future.

We kindly ask you to fill out the questionnaire, which will take you about 5–10 min.
If you have any questions, please contact Ana Mihor at amihor@onko-i.si.
Thank you for your cooperation and kind regards,
Ana Mihor and Vesna Zadnik from the Slovenian Cancer Registry

1. Please, enter the cancer registry name

   _____ *(text, obligatory)*

2. Does your cancer registry include paediatric patients? *(not multiple choice, obligatory)*

   - Yes
   - No

     (a) If NO ---> 2.1 Can you provide name(s) of cancer registry(ies) that register paediatric patients in your country? _____ *(text, not obligatory)* ---> Thank you for your time.

     (b) If YES ---> *go to following questions*:

3. What is the extent of the registry coverage? *(not multiple choice, obligatory)*

   - National
   - Regional (Regional coverage refers to non-national coverage, for example: region, province, city, etc.) ---> 3.1 Please, specify the area covered by the cancer registry: _____ *(text, obligatory)*

4. What age range of childhood cancer cases is included in your registry? *(multiple choice, obligatory)*

   - 0–14 years
   - 0–19 years
   - Other ---> 4.1. Please, specify the range of age:_____ to age _____ *(numerical, obligatory)*

5. Which malignant cancer entities do you register? *(not multiple choice, obligatory)*

   - All
   - Specific entities only (such as solid tumours, haematological malignancies etc.) ---> 5.1. Please, specify:_____ *(text, obligatory)*

6. Do you also register non-malignant tumours? *(not multiple choice, obligatory)*

   - Yes
   - No
   - No, but we are planning to in the future

     (a) If no ---> 7.

     (b) If yes ---> 6.1

     (c) If no, but we are planning to in the future ---> 6.2

   6.1. Which non-malignant entities do you (or are planning to) register? (*table with several yes/no/we are planning to, obligatory)*

   - Central nervous system tumours (ICD-O-3: C70–C72)
   - Other intracranial tumours (pituitary, pineal, craniopharyngeal) (ICD-O-3: C75.1–C75.3)
   - Other tumours ---> 6.1.1. Please, specify _____ *(text, obligatory)*

   6.2. Which non-malignant tumours are you planning to register *(table with several yes/no, obligatory)*

   - Central nervous system tumours (ICD-O-3: C70–C72)

- Other intracranial tumours (pituitary, pineal, craniopharyngeal) (ICD-O-3: C75.1–C75.3)
- Other tumours ---> 6.2.1. Please, specify _____ *(text, obligatory)*

7. In addition to most basic data agreed for general/adult cancer registries (e.g., ENCR rules for coding), which detailed registry data do you or are planning to routinely collect on paediatric cancer patients (meaning the data can be extracted from the database with only basic manipulation for potential data calls)? *(tables with several yes/no/we are planning to, obligatory)*

7.1. Diagnosis

- Topography, morphology and behaviour for coding the tumour according to the International Childhood Cancer Classification, third edition (ICCC-3)
- Specific diagnostic imaging tests performed (with or without further details), for example MRI, CT, PET scan, ultrasound, etc.
- Other specific diagnostic procedures performed (with or without further details), for example tissue biopsy, bone marrow biopsy, cerebrospinal fluid examination.

7.2. Staging

- TNM stage (where applicable)
- Toronto stage tier I
- Toronto stage tier II
- Other staging system ---> 7.2.1 Please, specify other staging system(s): _____ *(text, obligatory)*
- Non-stage prognostic factors (i.e., Wingless/Sonic Hedgehog for medulloblastoma, FKHR-PAX3/7 rhabdomyosarcoma, N-myc for neuroblastoma etc.)
- Topography of metastases

7.3. Initial treatment of primary tumour

- Surgery yes/no
- Date of surgery
- Type of surgery
- Radiotherapy yes/no
- Date of start of radiotherapy
- Radiotherapy—body sections or organs irradiated
- Radiotherapy—cumulative doses per body sections or organs
- Systemic therapy yes/no
- Date of start of systemic therapy
- Chemotherapy yes/no
- Specific chemotherapeutics received
- Targeted therapy yes/no
- Specific targeted therapy drugs received
- Immunotherapy yes/no
- Specific immunotherapy drugs received
- Hormone therapy yes/no
- Specific hormone therapy drugs received
- Cumulative doses of specific therapeutics
- Intrathecal applications of specific therapeutics
- Stem cell and bone marrow transplantations yes/no
- Stem cell and bone marrow transplantations—further details (e.g., type of transplant, therapy received, GVHD disease)

- Other treatments received yes/no (with or without further details), for example solid organ transplantations, genetic treatments, fertility preservation
- Acute side effects of treatments

7.4. Disease progression

- 7.4.1 Presence/absence of progression/relapse/recurrence *(if yes/planning to selected, text appears)* ---> 7.4.1.1
  - ○ Please provide any comments on progression/relapse/recurrence definition that you use or are planning to use: _____ *(text, not obligatory)*
- 7.4.2 Date of progression/relapse/recurrence
- 7.4.3 Type of progression/relapse/recurrence
- 7.4.4 Treatment of progression/relapse/recurrence *(if yes/planning to selected, dropdown menu, not multiple choice)* ---> 7.4.1.2
  - ○ to same detail as primary treatment
  - ○ to lesser detail as primary treatment
  - ○ to greater detail as primary treatment
- 7.4.5 Topography of metastases

7.5. Follow-up

- Vital status
- Date of the last known vital status
- Underlying cause of death *(if yes/planning to selected, text appears)* ---> *7.5.1 Please, specify the classification(s) used for coding the cause of death:*
  - ○ Cause of death classification(s), please describe: _____ *(text, obligatory)*
- Multiple cause of death *(if yes/planning to selected, text appears)* ---> *7.5.2 Please, specify the classification(s) used for coding the cause of death:*
  - ○ Cause of death classification(s), please describe: _____ *(text, obligatory)*

7.6. Other data

- Previous primary cancers
- Second primary cancers
- Other ---> 7.6.1 Please, specify _____ *(text, obligatory)*

8. Do you or are you planning to routinely and systematically register late effects of childhood cancer treatment, other than secondary cancers (such as cardiovascular disease, endocrine dysfunction, cognitive deficits etc.)? *(not multiple choice, obligatory)*

- Yes
- No
- No, but we are planning to

(a) If NO ---> 8.1 Can you provide name(s) of cancer registries (or other institutions) that systematically register late effects in your country? _____ *(text, not obligatory)* ---> Thank you for your time.

(b) If YES ---> 8.2, then 9.1, 10.1, 11.1, 12.1 and 13.1

(c) If no, but we are planning to---> 8.3, then 9.2, 10.2, 11.2, 12.2 and 13.2

8.2. From which incidence year did you start registering late effects? *(not multiple choice, obligatory)*

- From incidence year _____ *(dropdown menu for year)*
- I do not know

8.3. From which incidence year will you start registering late effects? *(not multiple choice, obligatory)*

- From incidence year _____ (dropdown menu for year)
- I do not know yet

9

9.1. What is (are) the data source(s) for the collection of late effects data? *(multiple choice, obligatory)*

- National/regional patient database
- Hospital databases
- Outpatient databases
- Primary health care institutions
- Other ---> 9.1.1 Please, specify _____ *(text, obligatory)*

9.2. What will be the data source(s) for the collection of late effects data? (multiple choice, obligatory, if I do not know yet selected, then others not possible)

- National/regional patient database
- Hospital databases
- Outpatient databases
- Primary health care institutions
- Other ---> 9.2.1 Please, specify _____ *(text, obligatory)*
- I do not know yet

10

10.1. Which classification(s) of late effects do you use? *(multiple choice, obligatory)*

- CTCAE (Common Terminology Criteria for Adverse Events)
- Modified CTCAE
- ICD-10
- ICD-9
- Other ---> 10.1.1 Please, specify _____ *(text, obligatory)*

10.2. Which classification(s) of late effects will you use? (multiple choice, obligatory, if I do not know yet selected, then others not possible)

- CTCAE (Common Terminology Criteria for Adverse Events)
- Modified CTCAE
- ICD-10
- ICD-9
- Other ---> 10.2.1 Please, specify _____ *(text, obligatory)*
- I do not know yet

11.

11.1. Do you record the date of onset of late effects? *(not multiple choice, obligatory)*

- Yes
- No

11.2. Will you record the date of onset of late effects? *(not multiple choice, obligatory)*

- Yes
- No
- I do not know yet

12.

12.1. Do you record the grade/severity of late effects? *(not multiple choice, obligatory)*

- Yes

- No

12.2. Will you record the grade/severity of late effects? *(not multiple choice, obligatory)*

- Yes
- No
- I do not know yet

13. Can we contact you for further details on late effects registration practices? *(not multiple choice, obligatory)*

- Yes
- No

(a) If YES ---> 13.1
(b) If NO ---> 14

14.

14.1. Please, write your name and your email:

Name: _____ (text, obligatory)
E-mail: _____ (text, obligatory)

14.2. Do you have any additional comments/suggestions? _____ *(text, not obligatory)*

---> Thank you for your time

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Long-Term Projections of Cancer Incidence and Mortality in Japan and Decomposition Analysis of Changes in Cancer Burden, 2020–2054: An Empirical Validation Approach

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Simple Summary: This is the first comprehensive picture of cancer incidence and mortality projections in Japan, using the most up-to-date and nationally representative data to the best of our knowledge. We applied empirically validated statistical models to project cancer incidence and mortality from 2020 to 2054 for all 22 cancer sites and in both genders. Additionally, we provided the decomposition analysis of changes in cancer cases and deaths over 2020–2054 attributable to population aging, population decline, and changes in the population's risk of being diagnosed with or dying from cancer. We projected an increase in new cancer cases but a decrease in cancer deaths in both genders. Prostate and female breast cancers would be the leading cancer burdens among the Japanese population in 2050–2054, together with colorectal and lung cancers. Our findings warrant greater efforts in cancer control programs, specifically in enhancing cancer screening and controlling cancer risk factors in Japan.

Abstract: Purpose: The aim of this study was to project new cancer cases/deaths forward to 2054, and decompose changes in cancer cases/deaths to assess the impact of demographic transitions on cancer burden. Methods: We collected data on cancer cases/deaths up to 2019, empirically validated the projection performance of multiple statistical models, and selected optimal models by applying time series cross-validation. Results: We showed an increasing number of new cancer cases but decreasing number of cancer deaths in both genders, with a large burden attributed to population aging. We observed the increasing incidence rates in most cancer sites but reducing rates in some infection-associated cancers, including stomach and liver cancers. Colorectal and lung cancers were projected to remain as leading cancer burdens of both incidence and mortality in Japan over 2020–2054, while prostate and female breast cancers would be the leading incidence burdens among men and women, respectively. Conclusions: Findings from decomposition analysis require more supportive interventions for reducing mortality and improving the quality of life of Japanese elders. We emphasize the important role of governments and policymakers in reforming policies for controlling cancer risk factors, including oncogenic infections. The rapid increase and continued presence of those cancer burdens associated with modifiable risk factors warrant greater efforts in cancer control programs, specifically in enhancing cancer screening and controlling cancer risk factors in Japan.

Keywords: empirical validation; long-term projection; age–period–cohort; cancer burden; prostate; female breast; lung; colorectal

1. Introduction

Since cancer is the leading cause of death worldwide (accounting for 10 million deaths in 2020) [1], long-term projections of cancer burdens (incidence and mortality) are critical for allocating national healthcare resources, evaluating the interventions implemented, and planning future programs. As cancer occurs mainly in older adults (those aged ≥65 years), it is projected that a worldwide demographic transition (i.e., population aging and increasing) will lead to a substantial increase in the cancer burdens on public health in the future [2,3]. Specifically, the International Agency for Research on Cancer forecasted a global growth of 10.9 million cancer cases and 6.3 million cancer deaths by 2040 due to demographic changes [4]. Country-specific projections of cancer, however, should reflect both future changes in demographic components (i.e., population structure and population size) and epidemiological components (i.e., population risk of being diagnosed with or dying from cancer). This information has been in great demand as it can support policymakers and governments in demand-based resource allocations for patient-centered healthcare and evidence-based cancer policy transformation.

In Japan, cancer has been the number one cause of death since 1981 [5], accounting for one-third of total deaths in the country with the highest life expectancy among the Group of Seven nations [6]. Recent research has shown a leveling off of the age-standardized incidence rate (ASIR) and a decrease in the age-standardized mortality rate (ASMR) in all-site-combined cancers in Japan [7]. Nevertheless, these findings cannot suggest a reduction in the future cancer burden as age-standardized rates (ASR) adjust to a common standard population and do not factor in the influence of demographic changes. Notably, Japan has a super-aging society (proportion of older adults in 2020 of 28.8%) [8], but a decreasing population (as the fertility rate is lower than the death rate) [9] and uniquely short "baby booms" (only 1947–1949 and 1971–1974) [10]; thus, it has been challenged by complicated issues in economic, society, and healthcare sustainability. These demographic transitions, in combination with the complex mixture of reductions in cancer risk factor exposures (e.g., reduced smoking prevalence and infections) and improvements in cancer control (e.g., cancer diagnosis and treatment), require an investigation of long-term projections of cancer cases/deaths in Japan [11–13]. Additionally, the decomposition of changes in cancer cases/deaths attributable to demographic components (i.e., population aging and population decline) and epidemiological components (i.e., the shift in risk factor exposures, and improvements in cancer control, diagnosis, and treatment) further support evaluating the impact of demographic transitions on cancer burdens in Japan [14].

Among the different methods for projecting cancer burdens (e.g., microsimulation models, autoregression models, piece-wise linear regression models, generalized linear models, and Bayesian models), age–period–cohort (APC) models consider all components of age, calendar period, and birth cohort and allow for the incorporation of demographic transitions in population aging and growth [15,16]. APC models have been widely adopted for long-term cancer burden's projections of both common and rare cancers in numerous countries, including the US [17,18], UK [19,20], Canada [21], Australia [22], Switzerland [23], and the Nordic countries [24]. Nevertheless, the flexibility of the APC models, with dozens of different approaches, has posed difficulties in selecting the most appropriate model for a specific context, which usually requires an empirical comparison for decision-making [25]. Despite the important role of cancer burden's projections, none of the previous studies validated a statistical model and produced long-term projections for all cancer sites in Japan, although one model (age–period interaction model with spline smoothing) was validated for short-term cancer projections [26].

Here, we provide long-term projections of cancer incidence and mortality for all cancer sites in Japan based on empirically validated statistical models. We then present a decomposition analysis of changes in cancer cases and deaths over the study period to further assess the burden of population aging on cancer incidence and mortality in Japan.

2. Materials and Methods

Data sources: We collected the number of cases and deaths by gender for 22 cancer sites over the period 1975–2019 from the Cancer Statistics in Japan (CSJ) [27,28], and classified them into the major, sub-major, and other cancer groups based on leading cancers in Japan (either in incidence or mortality, and in males or females), similar to previous studies [7]. Detailed gender-specific information on the included cancer sites, classifications, and International Classification of Diseases codes are presented in Supplementary Table S1. In total, we gathered 39 gender–site combinations including 17 sites for males and females plus five gender-specific sites ($17 \times 2 + 5$). We used estimated population data (1975–2019), also from CSJ, and the projected population (2020–2054) from the Institute of Population and Social Security with the medium-fertility variant and medium-mortality rate assumptions [29]. The population data of Japan reveal an aging population with increasing proportions of older people, and a decreasing total population (Supplementary Figure S1).

Data processing: We aggregated data into 5-year age groups and 5-year calendar periods to have statistically sufficient numbers of cancer cases and deaths in younger age groups or rare cancer sites. Specifically, we generated 18 5-year age groups (0–5 up to 85+ years) in nine periods (from 1975–1979 to 2015–2019) for cancer cases and deaths, and in 16 periods (from 1975–1979 to 2020–2054) for population data. The numbers of breast cancer cases in 1975–2002 included carcinoma in situ (CIS), and they were incomparable with those excluding CIS in 2003–2019. We, thus, estimated the number of cases excluded CIS in 1975–2002 using the mean ratio of cases excluded CIS per case included CIS for each five-year age group in 2003–2019.

Projection models: In this study, we investigated APC models, including classical and several modified versions, for application to cancer projection. These models have been developed on the basis of 5-year age groups, 5-year periods, and birth cohorts (synthetically constructed by subtracting age from period), and they have been widely applied for projecting cancer incidence and mortality [17,20,24,30]. The generalized APC can be described as

$$\lambda_{ap} = f\left(A_a + D_p + P_p + C_c\right), \tag{1}$$

where λ_{ap} is the rate (incidence or mortality) in age group a and calendar period p, A_a is the age component of age group a, P_p is the nonlinear period component of period p, and C_c is the nonlinear cohort component of cohort $c = p - a$. The link function $f(x)$ is either an exponential function in the classical model [31] or a power function, e.g., $f(x) = x^w$, in modified models, presumedly aimed at leveling off exponential increasing/decreasing trends [32,33]. The drift parameter D is employed to deal with collinearity among age, period, and cohort (so-called identifiability problem) and estimate the common linear effect between birth cohort and calendar period [31]. Projections can be produced using either D as the average linear trend of the whole observed period, or

$$D_{last} = D - P_{p-2} \tag{2}$$

as the slope of the most recent two periods (where P_{p-2} is the last deviation from this), or an algorithm for automatically selecting D or D_{last} by testing whether the curvature in trends over time $\hat{S}$ is statistically significant [25], using the model

$$\lambda_{ap} = f\left(A_a + D_p + S_p^2 + C_c\right). \tag{3}$$

Additionally, some attenuation may be adopted to the drift according to the belief that observed trends would not indefinitely continue but eventually fade off [17,24,30], e.g., geometrically attenuating by k% every year using the formula

$$1 - (1 - k/100)^n, \tag{4}$$

where n is the number of calendar years [19,20]. In total, we generated 90 model variants from six potential link functions (Poisson, Power-3, Power-4, Power-5, Power-6, and Power-7), with three options of using a linear trend (D, D_{last}, and automatic selection) and five possible attenuating drift attenuations (k ranges from 6% to 10%).

Empirical validation approach: Previous work evaluated the performance of modified APC models (Power-5 and Poisson models) by empirically comparing retrospective projections of cancer incidence in Nordic countries [25]. The findings of that study cannot be directly applied to other countries with different characteristics of cancer epidemiology and control, but rather indicate that an empirical validation approach should be adopted to achieve optimal models for cancer projection. In our study, we empirically validated the performance of 7020 models (90 model variants × 39 gender–site combinations × 2 data) by applying fourfold time series cross-validation to the available data (1975–2019) to generate 15-year retrospective projections from four different projection bases (1975–1989, 1975–1994, 1975–1999, and 1975–2004). We then evaluated the projection performance by estimating and comparing absolute relative bias,

$$ARB = \frac{|Predicted - Observed|}{Observed} \times 100\%, \quad (5)$$

and then selected the optimal models on the basis of the lowest median ARB across the different projection bases and periods. The data-, gender-, and site-specific information of selected parameters are in Supplementary Table S1, with the median ARB range of 0% to 7.36%, suggesting the relatively good performance of the selected models.

Statistical analysis: We applied the validated models to incidence and mortality data in 1987–2019 to project cancer cases and deaths forward to 2020–2054 (Supplementary Table S1). We computed all-site and all-gender combined cancer cases/deaths by aggregating cancer cases/deaths of all cancer sites and genders, respectively. We estimated the annual average cancer cases/deaths as the arithmetic mean of each 5-year period, and then calculated the changes in cancer cases/deaths over 2020–2054 by subtracting the annual average of period 2015–2019 from 2050–2054, and dividing them by the period 2015–2019 to determine the percentage changes. We estimated the ASIR and ASMR values using the "Standard Japanese Population in 1985" to be consistent with earlier studies in Japan [7,34]. Additionally, we calculated age-specific rates for eight age groups including children (aged 0–14 years), adolescents (15–19 years), young adults (20–39 years), middle-aged subjects (40–64 years), youngest-old (65–74 years), middle-old (75–84 years), and oldest-old (85+ years). Lastly, we performed a sensitivity analysis of drift attenuation on long-term cancer projections by estimating ASIR and ASMR in 2020–2054 with different assumed drift attenuations (k% ranges from 4% to 12%).

Decomposition analysis: We decomposed changes in cancer cases/deaths into demographic components (i.e., population size and population aging) and epidemiological components (i.e., change in population's risk of being diagnosed with or dying from cancer due to a combination of changes in cancer risk and improvements in diagnostic or treatment practices; hereinafter, population risk) to evaluate the impact of demographic transition on the cancer burden in Japan [14,35]. We adopted a newly validated formula that proportionately allocates the three-way interaction term to all three components of changes in population age structure, population size, and population risk. This formula is superior to the previous ones as its decomposed results are stable and do not depend on the choice of reference year. All decomposition methods and formulas were presented in detail elsewhere [36].

3. Results

All-site combined incidence results, including new cancer cases, ASIR, and decomposition analysis of case changes between 2020 and 2054, are presented in Table 1. We observed an annual average of 936,570 new cancer cases (534,326 men, 402,244 women) in 2015–2019, and we projected an annual average of 1,097,567 new cases (571,065 men, 526,502 women)

in 2020–2054. An increase of 36,739 cases (+6.9%) among Japanese men was completely attributable to population aging (+194,657 cases, +36.4%), while the increase in 124,258 cases (+30.9%) among Japanese women was predominantly attributable to both population aging (+101,654 cases, +25.3%) and changes in population risk (+130,407 cases, +32.4%). Over the period 2020–2054, we predicted a slightly reduced ASIR of all ages and all sites combined among men (from 374.0 to 357.3), and an increased ASIR among women (from 353.5 to 487.6). In age-specific incidence rates, we projected the leveled-off trends in most age groups among men but momentous increases in most age groups among women (Figure 1A). The proportions of older patients among total cancer cases were projected to continue increasing over 2020–2054 along with population aging, with a notable increase in oldest-old cancer patients from 14.0% to 25.9% (Supplementary Table S2). Figure 1B illustrates the trends and projection of decomposed changes in all-site combined cases over 1985–2054 (the period 1985–1989 was used as the reference). In both genders, epidemiological (population risk) and demographic (population aging) components contributed to increased cancer cases in 1985–2019, but population size (population decline) contributed to reduced cancer cases in 2020–2054. Trends in age-specific incidence rates and decomposed case changes in all 22 cancer sites are in Supplementary Figures S2–S23, with population risk contributing to the increased cases in 2020–2054 in most cancer sites, except stomach, liver, cervix uteri, gallbladder, and larynx.

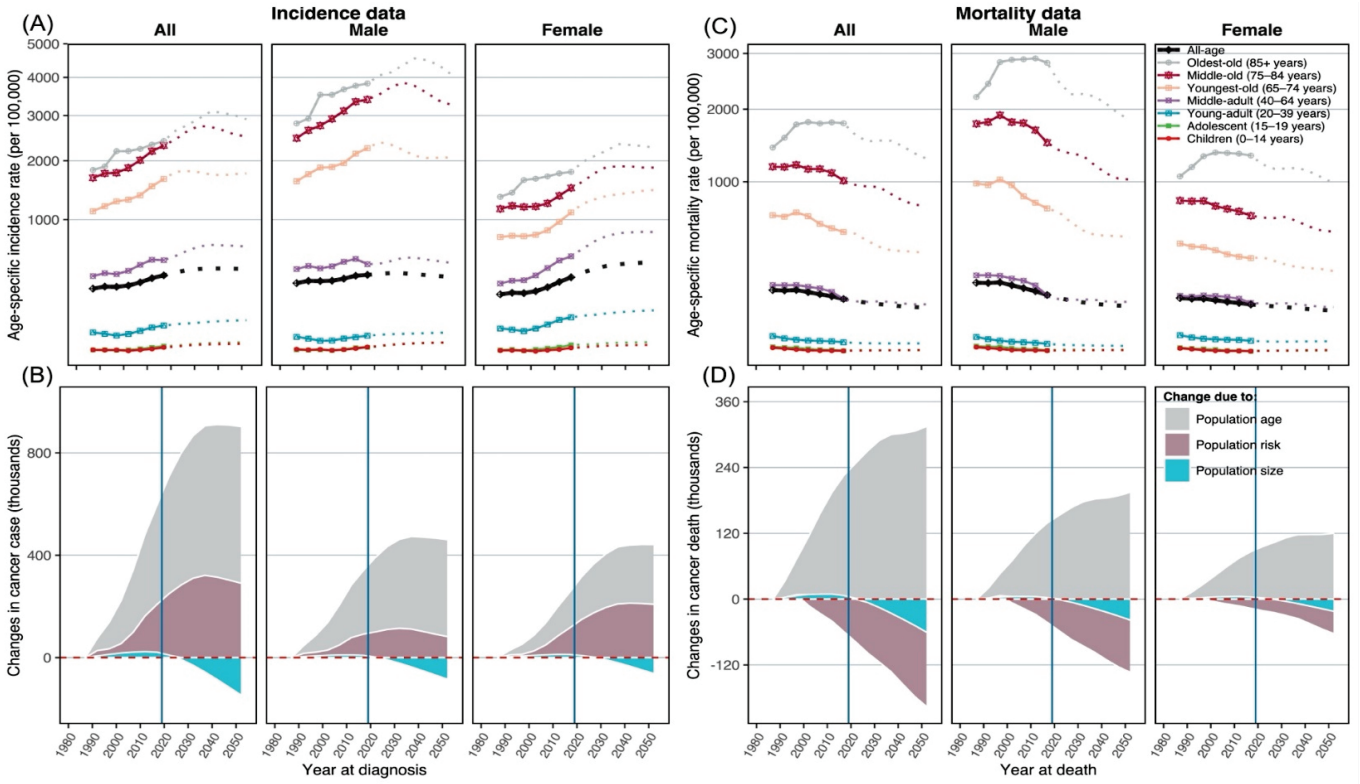


Figure 1. Projections of age-specific incidence rates (Panel (**A**)) and mortality rates (Panel (**C**)), and decomposed changes in new cancer cases (Panel (**B**)) and deaths (Panel (**D**)).

Notes: Log scales were applied to the Y-axis; in panels (**A, C**), solid lines describe the observed rates, and dotted lines describe the projected rates; in panels (**B, D**), period 1980–1985 was used as a reference.

Table 1. All-site and all-age combined cancer incidence and mortality by gender and decomposition of changes in new cancer case/death over 2020–2054.

Data	Gender	Period 2015–2019 [a]		Period 2020–2054 [a]		Case/Death Changes over Period 2020–2054			
		Case/Death	Rate [b]	Case/Death	Rate [b]	Total (%)	Population Risk (%) [c]	Population Age Structure (%) [d]	Population Size (%) [e]
Incidence	All-gender	936,570	369.8	1,097,567	427.0	+160,997 (+17.2%)	+108,160 (+11.5%)	+296,311 (+31.6%)	−243,474 (−26.0%)
	Male	534,326	374.0	571,065	357.3	+36,739 (+6.9%)	−22,247 (−4.2%)	+194,657 (+36.4%)	−135,671 (−25.4%)
	Female	402,244	353.5	526,502	487.6	+124,258 (+30.9%)	+130,407 (+32.4%)	+101,654 (+25.3%)	−107,803 (−26.8%)
Mortality	All-gender	355,070	109.9	307,840	79.9	−47,230 (−13.3%)	−120,244 (−33.9%)	+155,337 (+43.7%)	−82,323 (−23.2%)
	Male	210,654	125.5	175,797	85.1	−34,857 (−16.5%)	−81,941 (−38.9%)	+96,597 (+45.9%)	−49,513 (−23.5%)
	Female	144,416	90.0	132,043	70.3	−12,373 (−8.6%)	−38,303 (−26.5%)	+58,740 (+40.7%)	−32,810 (−22.7%)

[a] Estimated as annual average of 5-year periods; [b] age-standardized rate; [c] changes due to epidemiological factors (i.e., changes in population risks of being diagnosed with or dying from cancers, and improvements in diagnostic or treatment practices); [d] changes due to population age structure; [e] changes due to population size.

The site-specific incidence results, including new cancer cases, ASIR, rank of incidence burden, and decomposition analysis of case changes, of all major and sub-major cancer sites by gender are shown in Table 2 (other cancer sites are in Supplementary Table S3). Over the period 2020–2054, the majority of cancer sites showed increased new cases in both genders, predominantly attributed to population aging and population risk. Contrarily, some cancer sites had decreased cases including stomach (−53.3% among men, −36.5% among women), liver (−42.0%, −45.9%), and gallbladder (−8.0%, −42.9%), principally due to reduction in population risk. Specifically, decreasing ASIR was observed in cancers of the stomach, liver, and gallbladder in both genders. Demonstration of trends in and projections of site-specific ASIR by gender for major and sub-major cancer sites are shown in Figure 2A (ASIR of other cancer sites are in Supplementary Figure S24, and site-specific trends of cases are shown in Figure S25). The major cancer sites with a substantial increase in ASIR were colon/rectum (both men and women), prostate (men), and breast (women), while those in sub-major sites were malignant lymphoma (both genders), kidney (men), thyroid, and ovary (women). Our sensitivity analysis showed the modest impact of assumed drift attenuations (k% ranges from 4% to 12%) on ASIR in 2020–2054 in most cancer sites, except for male colon/rectum and female breast cancers (Supplementary Figure S26). The top three cancer incidence burdens by age group are in Table 3 (all-gender combined) and Supplementary Table S4 (by male and female). Generally, prostate and female breast cancers will be the highest incidence burdens in 2020–2054 among Japanese men and women (ahead of colon/rectum and lung cancers).

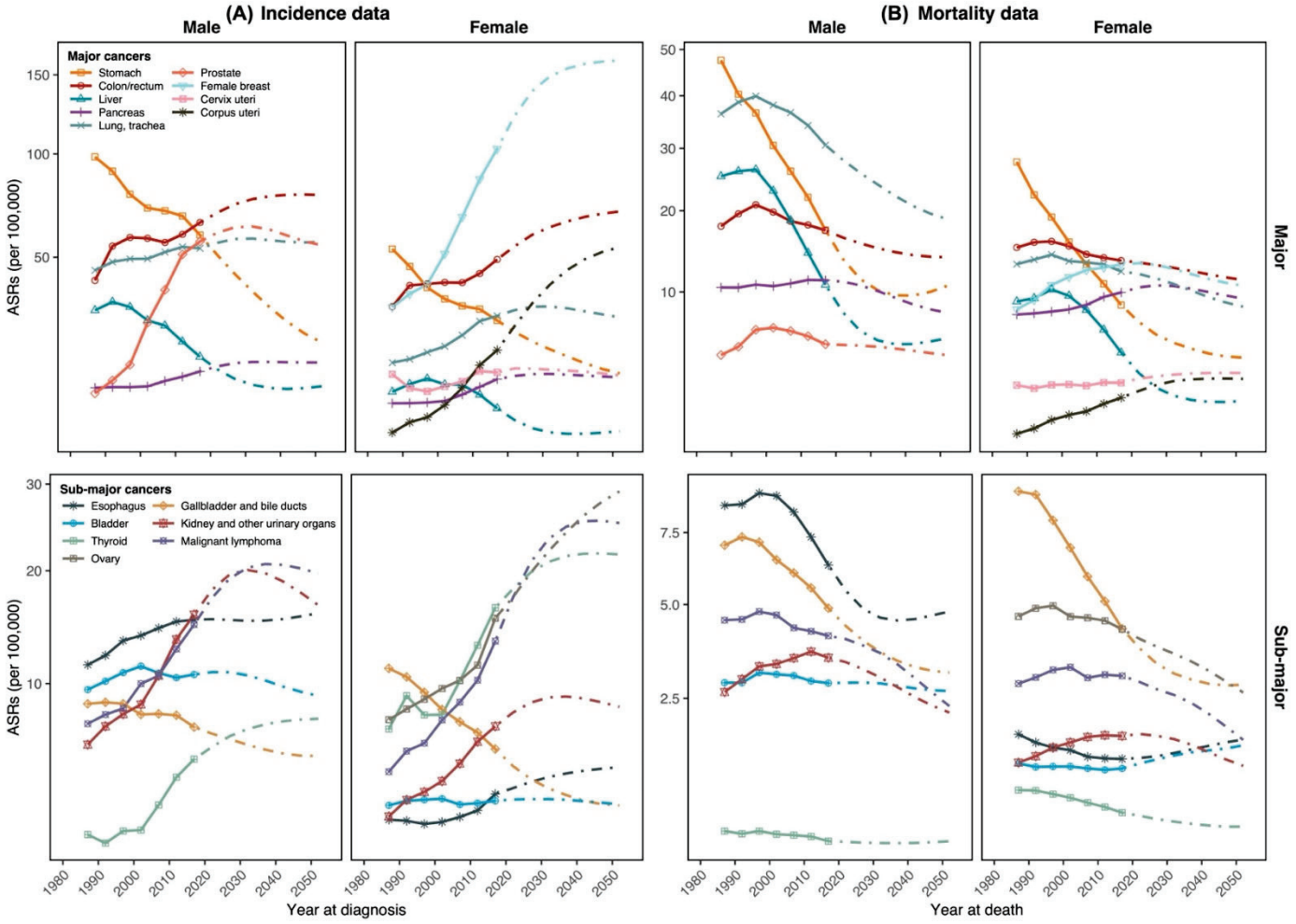


Figure 2. Projections of age-standardized incidence and mortality rates for major and sub-major cancer sites by gender, 1985–2054. (**A**) Incidence data and (**B**) Mortality data.

Notes: ASRs = age-standardized rates; log scales were applied to the *Y*-axis; trends in and projections of age-standardized incidence and mortality rates for other cancer sites are in Supplementary Figure S24.

Table 2. Site-specific cancer incidence by gender and decomposition of case changes 2020–2054 for major and sub-major cancers.

Gender	Cancer Group	Cancer Site	ICD-10	Period 2015–2019 [a]			Period 2050–2054 [a]			Case Changes over Period 2020–2054			
				Case	Rate [b]	Rank	Case	Rate [b]	Rank	Total (%)	Population Risk (%) [c]	Population Age Structure (%) [d]	Population Size (%) [e]
Male and female combined	Major	Stomach	C16	128,667	44.9	2	66,818	18.6	5	−61,849 (−48.1%)	−75,283 (−58.5%)	+36,870 (+28.7%)	−23,436 (−18.2%)
		Colon/rectum	C18–C20	151,904	58.0	1	207,435	75.1	1	+55,531 (+36.6%)	+45,279 (+29.8%)	+53,280 (+35.1%)	−43,028 (−28.3%)
		Liver	C22	39,532	13.3	7	22,438	8.4	14	−17,094 (−43.2%)	−20,969 (−53.0%)	+11,459 (+29.0%)	−7584 (−19.2%)
		Pancreas	C25	41,065	14.0	6	49,795	15.4	7	+8730 (+21.3%)	+3306 (+8.1%)	+16,287 (+39.7%)	−10,864 (−26.5%)
		Lung, trachea	C33–C34	123,105	42.5	3	146,149	44.5	2	+23,044 (+18.7%)	+7506 (+6.1%)	+47,977 (+39.0%)	−32,439 (−26.4%)
		Prostate	C61	89,466	30.3	5	114,306	30.6	4	+24,840 (+27.8%)	+10,420 (+11.6%)	+39,223 (+43.8%)	−24,804 (−27.7%)
		Breast (female)	C50	92,901	50.2	4	132,332	76.9	3	+39,431 (+42.4%)	+55,750 (+60.0%)	+9755 (+10.5%)	−26,073 (−28.1%)
		Cervix uteri	C53	10,986	7.1	19	10,036	6.6	20	−950 (−8.6%)	+1271 (+11.6%)	+173 (+1.6%)	−2394 (−21.8%)
		Corpus uteri	C54	16,581	9.6	16	38,482	25.9	9	+21,901 (+132.1%)	+27,799 (+167.7%)	+697 (+4.2%)	−6596 (−39.8%)
	Sub-major	Esophagus	C15	25,354	9.8	10	27,802	10.9	12	+2448 (+9.7%)	+1869 (+7.4%)	+7017 (+27.7%)	−6439 (−25.4%)
		Gallbladder and bile ducts	C23–C24	22,426	6.5	13	16,975	4.4	17	−5451 (−24.3%)	−9993 (−44.6%)	+9356 (+41.7%)	−4815 (−21.5%)
		Bladder	C67	22,743	7.2	12	25,737	6.5	13	+2994 (+13.2%)	−1995 (−8.8%)	+10,881 (+47.8%)	−5891 (−25.9%)
		Kidney and other urinary organs	C64–C66 C68	29,040	11.7	9	38,998	13.0	8	+9958 (+34.3%)	+7535 (+25.9%)	+10,561 (+36.4%)	−8138 (−28.0%)
		Thyroid	C73	17,954	10.7	15	22,408	14.4	15	+4454 (+24.8%)	+7834 (+43.6%)	+1362 (+7.6%)	−4742 (−26.4%)
		Malignant lymphoma	C81–C85 C96	34,265	14.2	8	57,875	22.5	6	+23,610 (+68.9%)	+21,577 (+63.0%)	+13,031 (+38.0%)	−10,998 (−32.1%)
		Ovary	C56	12,722	7.5	18	20,140	14.0	16	+7418 (+58.3%)	+10,682 (+84.0%)	+606 (+4.8%)	−3869 (−30.4%)
Male	Major	Stomach	C16	88,574	59.3	2	41,361	21.5	4	−47,213 (−53.3%)	−56,588 (−63.9%)	+25,272 (+28.5%)	−15,896 (−17.9%)
		Colon/rectum	C18–C20	86,247	64.9	3	109,737	78.0	2	+23,490 (+27.2%)	+17,888 (+20.7%)	+29,662 (+34.4%)	−24,060 (−27.9%)
		Liver	C22	26,664	18.0	5	15,471	11.6	11	−11193 (−42.0%)	−13,498 (−50.6%)	+7546 (+28.3%)	−5241 (−19.7%)
		Pancreas	C25	21,126	14.7	6	26,226	16.7	5	+5100 (+24.1%)	+2577 (+12.2%)	+8347 (+39.5%)	−5825 (−27.6%)
		Lung, trachea	C33–C34	82,290	53.6	4	97,615	56.4	3	+15,325 (+18.6%)	+3672 (+4.5%)	+33,836 (+41.1%)	−22,183 (−27.0%)
		Prostate	C61	89466	56.5	1	114,306	54.8	1	+24,840 (+27.8%)	+10,420 (+11.6%)	+39,223 (+43.8%)	−24,804 (−27.7%)
	Sub-major	Esophagus	C15	20,990	15.2	7	21,288	15.8	8	+298 (+1.4%)	−186 (−0.9%)	+5669 (+27.0%)	−5186 (−24.7%)
		Gallbladder and bile ducts	C23–C24	11,922	7.1	13	10,972	5.4	13	−950 (−8.0%)	−3568 (−29.9%)	+5472 (+45.9%)	−2854 (−23.9%)
		Bladder	C67	17,139	10.7	10	19,006	9.1	10	+1867 (+10.9%)	−1879 (−11.0%)	+8202 (+47.9%)	−4456 (−26.0%)
		Kidney and other urinary organs	C64–C66 C68	19,722	15.7	8	26,218	16.6	6	+6496 (+32.9%)	+4871 (+24.7%)	+7218 (+36.6%)	−5593 (−28.4%)
		Thyroid	C73	4663	5.2	16	6571	7.6	15	+1908 (+40.9%)	+2573 (+55.2%)	+716 (+15.4%)	−1380 (−29.6%)
		Malignant lymphoma	C81–C85 C96	18,331	14.8	9	25,718	19.7	7	+7387 (+40.3%)	+5831 (+31.8%)	+6972 (+38.0%)	−5415 (−29.5%)

Table 2. *Cont.*

Gender	Cancer Group	Cancer Site	ICD-10	Period 2015–2019 [a]			Period 2050–2054 [a]			Case Changes over Period 2020–2054			
				Case	Rate [b]	Rank	Case	Rate [b]	Rank	Total (%)	Population Risk (%) [c]	Population Age Structure (%) [d]	Population Size (%) [e]
Female	Major	Stomach	C16	40,093	27.8	4	25,457	14.3	6	−14,636 (−36.5%)	−18,694 (−46.6%)	+11,598 (+28.9%)	−7540 (−18.8%)
		Colon/rectum	C18–C20	65,657	49.1	2	97,698	70.0	2	+32,041 (+48.8%)	+27,391 (+41.7%)	+23,618 (+36.0%)	−18,968 (−28.9%)
		Liver	C22	12,867	7.7	9	6967	4.6	14	−5900 (−45.9%)	−7470 (−58.1%)	+3913 (+30.4%)	−2342 (−18.2%)
		Pancreas	C25	19,938	13.0	5	23,569	13.4	7	+3631 (+18.2%)	+729 (+3.7%)	+7940 (+39.8%)	−5038 (−25.3%)
		Lung, trachea	C33–C34	40,814	29.2	3	48,533	28.8	3	+7719 (+18.9%)	+3834 (+9.4%)	+14,141 (+34.6%)	−10,256 (−25.1%)
		Breast (female)	C50	92,901	103.0	1	132,332	160.2	1	+39,431 (+42.4%)	+55,750 (+60.0%)	+9755 (+10.5%)	−26,073 (−28.1%)
		Cervix uteri	C53	10,986	14.5	12	10,036	13.8	13	−950 (−8.6%)	+1271 (+11.6%)	+173 (+1.6%)	−2394 (−21.8%)
		Corpus uteri	C54	16,581	19.7	6	38,482	54.2	4	+21,901 (+132.1%)	+27,799 (+167.7%)	+697 (+4.2%)	−6596 (−39.8%)
	Sub-major	Esophagus	C15	4364	3.5	18	6513	4.8	17	+2149 (+49.2%)	+2055 (+47.1%)	+1348 (+30.9%)	−1253 (−28.7%)
		Gallbladder and bile ducts	C23–C24	10,504	5.8	13	6003	3.1	18	−4501 (−42.9%)	−6425 (−61.2%)	+3884 (+37.0%)	−1960 (−18.7%)
		Bladder	C67	5604	3.2	17	6732	3.1	16	+1128 (+20.1%)	−116 (−2.1%)	+2679 (+47.8%)	−1435 (−25.6%)
		Kidney and other urinary organs	C64–C66 C68	9318	7.1	14	12,780	8.4	11	+3462 (+37.2%)	+2664 (+28.6%)	+3343 (+35.9%)	−2545 (−27.3%)
		Thyroid	C73	13,291	16.3	8	15,837	21.7	10	+2546 (+19.2%)	+5261 (+39.6%)	+646 (+4.9%)	−3362 (−25.3%)
		Malignant lymphoma	C81–C85 C96	15,934	13.4	7	32,157	25.2	5	+16,223 (+101.8%)	+15,746 (+98.8%)	+6060 (+38.0%)	−5582 (−35.0%)
		Ovary	C56	12,722	15.4	10	20,140	29.1	8	+7418 (+58.3%)	+10,682 (+84.0%)	+606 (+4.8%)	−3869 (−30.4%)

[a] Estimated from 5-year periods; [b] age-standardized rate; [c] changes due to epidemiological factors (i.e., changes in population risks of being diagnosed with or dying from cancers, and improvements in diagnostic or treatment practices); [d] changes due to population age structure; [e] changes due to population size; %: proportion to the number of cases in 2015–2019.

Table 1 also presents all-site combined mortality results, with an annual average of 355,070 deaths (210,654 men, 144,416 women) observed in 2015–2019, decreasing to 307,870 deaths (175,797 men, 132,043 women) projected in 2020–2054. While population aging significantly added cancer deaths to both genders (+45.9% among men, +40.7% among women), the observed changes in overall deaths (−16.5%, −8.6%) were attributed to population decline (−23.5%, −22.7%) and population risk (−38.9%, −26.5%) among men and women, respectively. In the all-age and all-site combined age-standardized mortality rate (ASMR), there were substantial decreases in mortality rates among both men (from 125.5 to 85.1) and women (from 90.0 to 70.3). In age-specific mortality rates, we projected considerable reductions in mortality rates in most age groups in both genders over 2020–2054 (Figure 1C). In Figure 1D, population aging contributed to expanded cancer deaths across 1985–2054, while population risk and population decline jointly supported the diminished deaths in most of the study period. Similar visualizations of age-specific mortality rates and decomposed death changes of all 22 cancer sites are in Supplementary Figures S2–S23, with population risk contributing to the increased deaths in 2020–2054 in some cancer sites, including female breast, female pancreas, prostate, corpus uteri, bladder, and kidney cancers. Age-specific cancer deaths and proportion to all-age combined deaths are in Supplementary Table S2.

Table 4 presents cancer deaths, ASMR, ranks of mortality burden, and decomposition analysis of death changes by gender of all major and sub-major cancer sites (other cancer sites are in Supplementary Table S5). The majority of cancer sites showed reductions in deaths over the period 2020–2054 due to the decreased influence of population risk, while some had raised cancer deaths due to enormous contributions from population aging (e.g., bladder in both genders, prostate among men, colon/rectum, and pancreas among women). Visualizations of trends and projections of site-specific ASMR for major and sub-major cancer sites are in Figure 2B (ASMR of other cancer sites in Supplementary Figure S24; site-specific trends of deaths in Figure S27. The declining ASMR was observed in most cancer sites and both genders over 2020–2054, except cervix uteri (increased from 2.9 to 3.4), corpus uteri (from 2.1 to 3.1), and esophagus (1.3 to 1.7). Supplementary Figure S26 shows the minor impact of attenuation assumption on the projected ASMR in 2020–2054 in most cancer sites, except stomach and liver (both genders), male lung, and female breast cancers. While pancreas cancer will replace stomach cancer to be one of the three highest mortality burdens among the Japanese population in 2020–2054 (Table 3), the top three cancer mortality burdens will remain the same among men (lung, colon/rectum, and stomach cancers) and women (lung, colon/rectum, and pancreas cancers) across 2020–2054 (Supplementary Table S4).

Table 3. Top three cancer diagnoses in 2015–2019 and 2050–2054 by age group (both genders).

Data	Age Group	Burden Rank	Period 2015–2019 [a]			Period 2050–2054 [a]		
			Cancer Site	ICD-10	Case/Death (%)	Cancer Site	ICD-10	Case/Death (%)
Incidence	All age	1	Colon/rectum	C18–C20	151,904 (16.2%)	Colon/rectum	C18–C20	207,435 (18.9%)
		2	Stomach	C16	128,667 (13.7%)	Lung, trachea	C33–C34	146,149 (13.3%)
		3	Lung, trachea	C33–C34	123,105 (13.1%)	Female breast	C50	132,332 (12.1%)
	Oldest-old (85+ years)	1	Colon/rectum	C18–C20	22,521 (17.2%)	Colon/rectum	C18–C20	55,172 (19.4%)
		2	Stomach	C16	19,684 (15.0%)	Lung, trachea	C33–C34	41,747 (14.7%)
		3	Lung, trachea	C33–C34	19,300 (14.7%)	Prostate	C61	32,077 (11.3%)
	Middle-old (75–84 years)	1	Colon/rectum	C18–C20	44,914 (16.2%)	Colon/rectum	C18–C20	69,307 (18.9%)
		2	Stomach	C16	44,599 (16.1%)	Lung, trachea	C33–C34	55,801 (15.2%)
		3	Lung, trachea	C33–C34	41,414 (14.9%)	Prostate	C61	48,743 (13.3%)
	Youngest-old (65–74 years)	1	Colon/rectum	C18–C20	48,260 (16.6%)	Colon/rectum	C18–C20	47,693 (20.1%)
		2	Lung, trachea	C33–C34	42,430 (14.6%)	Lung, trachea	C33–C34	32,848 (13.8%)
		3	Stomach	C16	42,389 (14.6%)	Prostate	C61	27,218 (11.5%)
	Middle-adult (40–64 years)	1	Female breast	C50	45,392 (20.9%)	Female breast	C50	45,448 (23.7%)
		2	Colon/rectum	C18–C20	34,526 (15.9%)	Colon/rectum	C18–C20	33,667 (17.6%)
		3	Stomach	C16	21,156 (9.7%)	Corpus uteri	C54	18,232 (9.5%)
	Young-adult (20–39 years)	1	Female breast	C50	3967 (22.1%)	Female breast	C50	5047 (31.7%)
		2	Thyroid	C73	2390 (13.3%)	Thyroid	C73	1627 (10.2%)
		3	Cervix uteri	C53	1915 (10.7%)	Colon/rectum	C18–C20	1544 (9.7%)
	Adolescent (15–19 years)	1	Leukemia	C91–C95	180 (25.0%)	Malignant lymphoma	C81–C85 C96	202 (27.3%)
		2	Malignant lymphoma	C81–C85 C96	121 (16.8%)	Leukemia	C91–C95	179 (24.2%)
		3	Thyroid	C73	116 (16.1%)	Brain, nervous system	C70–C72	87 (11.8%)
	Children (0–14 years)	1	Leukemia	C91–C95	744 (46.8%)	Leukemia	C91–C95	681 (40.0%)
		2	Brain, nervous system	C70–C72	327 (20.6%)	Malignant lymphoma	C81–C85 C96	492 (28.9%)
		3	Malignant lymphoma	C81–C85 C96	237 (14.9%)	Brain, nervous system	C70–C72	334 (19.6%)

Table 3. *Cont.*

Data	Age Group	Burden Rank	Period 2015–2019 [a]			Period 2050–2054 [a]		
			Cancer Site	ICD-10	Case/Death (%)	Cancer Site	ICD-10	Case/Death (%)
Mortality	All age	1	Lung, trachea	C33–C34	74,407 (21.0%)	Lung, trachea	C33–C34	61,980 (20.1%)
		2	Colon/rectum	C18–C20	50,508 (14.2%)	Colon/rectum	C18–C20	50,737 (16.5%)
		3	Stomach	C16	44,910 (12.6%)	Pancreas	C25	34,741 (11.3%)
	Oldest-old (85+ years)	1	Lung, trachea	C33–C34	19,165 (19.8%)	Lung, trachea	C33–C34	24,317 (19.5%)
		2	Colon/rectum	C18–C20	14,892 (15.4%)	Colon/rectum	C18–C20	22,074 (17.7%)
		3	Stomach	C16	12,994 (13.4%)	Pancreas	C25	13,963 (11.2%)
	Middle-old (75–84 years)	1	Lung, trachea	C33–C34	26,988 (22.3%)	Lung, trachea	C33–C34	24675 (22.7%)
		2	Colon/rectum	C18–C20	15,797 (13.0%)	Colon/rectum	C18–C20	16,496 (15.2%)
		3	Stomach	C16	15,483 (12.8%)	Pancreas	C25	12,802 (11.8%)
	Youngest-old (65–74 years)	1	Lung, trachea	C33–C34	20,575 (23.1%)	Lung, trachea	C33–C34	9582 (20.3%)
		2	Colon/rectum	C18–C20	12,410 (13.9%)	Colon/rectum	C18–C20	7658 (16.2%)
		3	Stomach	C16	11,120 (12.5%)	Pancreas	C25	5095 (10.8%)
	Middle-adult (40–64 years)	1	Lung, trachea	C33–C34	7558 (16.4%)	Colon/rectum	C18–C20	4365 (16.9%)
		2	Colon/rectum	C18–C20	7146 (15.5%)	Lung, trachea	C33–C34	3348 (12.9%)
		3	Stomach	C16	5076 (11.0%)	Stomach	C16	2844 (11.0%)
	Young-adult (20–39 years)	1	Female breast	C50	268 (14.0%)	Female breast	C50	225 (21.3%)
		2	Colon/rectum	C18–C20	257 (13.4%)	Brain, nervous system	C70–C72	149 (14.1%)
		3	Stomach	C16	234 (12.2%)	Colon/rectum	C18–C20	141 (13.4%)
	Adolescent (15–19 years)	1	Leukemia	C91–C95	34 (44.2%)	Brain, nervous system	C70–C72	28 (45.9%)
		2	Brain, nervous system	C70–C72	21 (27.3%)	Leukemia	C91–C95	17 (27.9%)
		3	Malignant lymphoma	C81–C85 C96	7 (9.1%)	Malignant lymphoma	C81–C85 C96	6 (9.8%)
	Children (0–14 years)	1	Brain, nervous system	C70–C72	88 (45.1%)	Brain, nervous system	C70–C72	98 (58.7%)
		2	Leukemia	C91–C95	78 (40.0%)	Leukemia	C91–C95	48 (28.7%)
		3	Liver	C22	9 (4.6%)	Malignant lymphoma	C81–C85 C96	7 (4.2%)

[a] Estimated as annual average of 5-year periods.

Table 4. Site-specific cancer mortality by gender and decomposition of death changes in 2020–2054 for major and sub-major cancers.

Gender	Cancer Group	Cancer Site	ICD-10	Period 2015–2019 [a]			Period 2050–2054 [a]			Death Changes over Period 2020–2054			
				Death	Rate [b]	Rank	Death	Rate [b]	Rank	Total (%)	Population Risk (%) [c]	Population Age Structure (%) [d]	Population Size (%) [e]
Male and female combined	Major	Stomach	C16	44,910	13.4	3	29,123	7.9	4	−15,787 (−35.2%)	−24,870 (−55.4%)	+18,435 (+41.0%)	−9352 (−20.8%)
		Colon/rectum	C18–C20	50,508	15.6	2	50,737	12.9	2	+229 (+0.5%)	−10,571 (−20.9%)	+23,275 (+46.1%)	−12,474 (−24.7%)
		Liver	C22	27,143	8.0	5	13,014	4.1	7	−14,129 (−52.1%)	−18,662 (−68.8%)	+9649 (+35.5%)	−5116 (−18.8%)
		Pancreas	C25	34,261	10.7	4	34,741	8.7	3	+480 (+1.4%)	−5925 (−17.3%)	+14,812 (+43.2%)	−8408 (−24.5%)
		Lung, trachea	C33–C34	74,407	22.1	1	61,980	14.4	1	−12427 (−16.7%)	−28,935 (−38.9%)	+33,581 (+45.1%)	−17,074 (−22.9%)
		Prostate	C61	11,987	2.8	9	15,546	2.6	5	+3559 (+29.7%)	−2171 (−18.1%)	+9292 (+77.5%)	−3561 (−29.7%)
		Breast (female)	C50	14,275	6.3	7	12,804	5.1	8	−1471 (−10.3%)	−1617 (−11.3%)	+3276 (+22.9%)	−3130 (−21.9%)
		Cervix uteri	C53	2822	1.4	17	3287	1.6	18	+465 (+16.5%)	+649 (+23.0%)	+534 (+18.9%)	−717 (−25.4%)
		Corpus uteri	C54	2487	1.0	19	3791	1.5	16	+1304 (+52.4%)	+1296 (+52.1%)	+747 (+30.0%)	−738 (−29.7%)
	Sub-major	Esophagus	C15	11,550	4.0	10	10,193	3.4	11	−1357 (−11.7%)	−2543 (−22.0%)	+3900 (+33.8%)	−2714 (−23.5%)
		Gallbladder and bile ducts	C23–C24	18,091	4.7	6	14,621	3.0	6	−3470 (−19.2%)	−8521 (−47.1%)	+9161 (+50.6%)	−4110 (−22.7%)
		Bladder	C67	8577	2.1	13	11,550	2.2	9	+2973 (+34.7%)	−543 (−6.3%)	+6052 (+70.6%)	−2537 (−29.6%)
		Kidney and other urinary organs	C64-C66 C68	9340	2.7	11	7757	1.8	12	−1583 (−16.9%)	−3883 (−41.6%)	+4445 (+47.6%)	−2144 (−23.0%)
		Thyroid	C73	1785	0.5	20	1699	0.4	21	−86 (−4.8%)	−515 (−28.9%)	+858 (+48.1%)	−429 (−24.0%)
		Malignant lymphoma	C81–C85 C96	12,483	3.6	8	10,471	2.1	10	−2012 (−16.1%)	−5237 (−42.0%)	+6074 (+48.7%)	−2849 (−22.8%)
		Ovary	C56	4739	2.1	15	3801	1.2	15	−938 (−19.8%)	−1047 (−22.1%)	+1092 (+23.0%)	−983 (−20.7%)
Male	Major	Stomach	C16	29,457	17.3	2	19,634	10.6	3	−9823 (−33.3%)	−15,783 (−53.6%)	+12,312 (+41.8%)	−6352 (−21.6%)
		Colon/rectum	C18–C20	27135	17.3	3	26,083	13.9	2	−1052 (−3.9%)	−6420 (−23.7%)	+12,136 (+44.7%)	−6768 (−24.9%)
		Liver	C22	17,824	10.7	4	9100	5.8	6	−8724 (−48.9%)	−11,508 (−64.6%)	+6284 (+35.3%)	−3500 (−19.6%)
		Pancreas	C25	17,341	11.2	5	15,195	8.0	5	−2146 (−12.4%)	−5120 (−29.5%)	+7077 (+40.8%)	−4103 (−23.7%)
		Lung, trachea	C33–C34	52,872	30.6	1	42,325	18.8	1	−10,547 (−19.9%)	−22,530 (−42.6%)	+24,172 (+45.7%)	−12,189 (−23.1%)
		Prostate	C61	11,987	5.4	6	15,546	4.6	4	+3559 (+29.7%)	−2171 (−18.1%)	+9292 (+77.5%)	−3561 (−29.7%)
	Sub-major	Esophagus	C15	9562	6.3	7	7421	4.8	9	−2141 (−22.4%)	−3048 (−31.9%)	+3059 (+32.0%)	−2152 (−22.5%)
		Gallbladder and bile ducts	C23–C24	9199	4.9	8	7849	3.1	7	−1350 (−14.7%)	−4104 (−44.6%)	+4963 (+54.0%)	−2209 (−24.0%)
		Bladder	C67	5842	2.8	11	7457	2.7	8	+1615 (+27.6%)	−880 (−15.1%)	+4214 (+72.1%)	−1719 (−29.4%)
		Kidney and other urinary organs	C64–C66 C68	5955	3.5	10	4906	2.2	11	−1049 (−17.6%)	−2529 (−42.5%)	+2875 (+48.3%)	−1394 (−23.4%)
		Thyroid	C73	582	0.3	18	615	0.3	18	+33 (+5.7%)	−101 (−17.4%)	+288 (+49.5%)	−154 (−26.5%)
		Malignant lymphoma	C81–C85 C96	6964	4.1	9	5916	2.3	10	−1048 (−15.0%)	−2969 (−42.6%)	+3571 (+51.3%)	−1650 (−23.7%)

Table 4. *Cont.*

Gender	Cancer Group	Cancer Site	ICD-10	Period 2015–2019 [a]			Period 2050–2054 [a]			Death Changes over Period 2020–2054			
				Death	Rate [b]	Rank	Death	Rate [b]	Rank	Total (%)	Population Risk (%) [c]	Population Age Structure (%) [d]	Population Size (%) [e]
Female	Major	Stomach	C16	15,453	8.7	4	9488	4.4	5	−5965 (−38.6%)	−9088 (−58.8%)	+6123 (+39.6%)	−3000 (−19.4%)
		Colon/rectum	C18–C20	23,373	13.5	1	24,654	11.3	1	+1281 (+5.5%)	−4151 (−17.8%)	+11,139 (+47.7%)	−5707 (−24.4%)
		Liver	C22	9320	4.8	6	3915	2.0	9	−5405 (−58.0%)	−7154 (−76.8%)	+3365 (+36.1%)	−1616 (−17.3%)
		Pancreas	C25	16,920	10.0	3	19,545	9.3	3	+2625 (+15.5%)	−805 (−4.8%)	+7735 (+45.7%)	−4305 (−25.4%)
		Lung, trachea	C33–C34	21,535	12.2	2	19,655	8.6	2	−1880 (−8.7%)	−6405 (−29.7%)	+9410 (+43.7%)	−4885 (−22.7%)
		Breast (female)	C50	14,275	13.0	5	12,804	10.7	4	−1471 (−10.3%)	−1617 (−11.3%)	+3276 (+22.9%)	−3130 (−21.9%)
		Cervix uteri	C53	2822	2.9	12	3287	3.4	12	+465 (+16.5%)	+649 (+23.0%)	+534 (+18.9%)	−717 (−25.4%)
		Corpus uteri	C54	2487	2.1	14	3791	3.1	11	+1304 (+52.4%)	+1296 (+52.1%)	+747 (+30.0%)	−738 (−29.7%)
	Sub-major	Esophagus	C15	1988	1.3	17	2772	1.7	14	+784 (+39.4%)	+505 (+25.4%)	+841 (+42.3%)	−562 (−28.3%)
		Gallbladder and bile ducts	C23–C24	8892	4.3	7	6772	2.8	6	−2120 (−23.8%)	−4417 (−49.7%)	+4198 (+47.2%)	−1901 (−21.4%)
		Bladder	C67	2735	1.2	13	4093	1.6	8	+1358 (+49.7%)	+338 (+12.4%)	+1838 (+67.2%)	−818 (−29.9%)
		Kidney and other urinary organs	C64–C66 C68	3385	1.7	11	2851	1.2	13	−534 (−15.8%)	−1354 (−40.0%)	+1570 (+46.4%)	−750 (−22.2%)
		Thyroid	C73	1203	0.6	18	1084	0.5	19	−119 (−9.9%)	−414 (−34.4%)	+570 (+47.4%)	−275 (−22.9%)
		Malignant lymphoma	C81–C85 C96	5519	3.0	8	4555	1.7	7	−964 (−17.5%)	−2268 (−41.1%)	+2503 (+45.4%)	−1198 (−21.7%)
		Ovary	C56	4739	4.3	9	3801	2.6	10	−938 (−19.8%)	−1047 (−22.1%)	+1092 (+23.0%)	−983 (−20.7%)

[a] Estimated as annual average of 5-year periods; [b] age-standardized rate; [c] changes due to epidemiological factors (i.e., changes in population risks of being diagnosed with or dying from cancers, improvements in diagnostic or treatment practices); [d] changes due to population age structure; [e] changes due to population size. %: proportion to the number of deaths in 2015–2019.

4. Discussion

We applied empirically validated statistical models to provide long-term projections of cancer incidence and mortality burden in Japan up to 2054. For cancer incidence, we projected a slight reduction in all-site combined ASIR among men over 2020–2054, which is comparable to recent studies in the US [18], the UK [20], Australia [22], and Switzerland [23]. In contrast, the projected substantial increase in all-site combined ASIR among women is unique to Japan, probably contributed to by the observed increasing female ASIR of some cancer sites (i.e., colorectal, ovary, and esophagus) in Japan versus decreasing or stabilizing rates in other developed countries. For cancer mortality, similar to global projections [2], we predicted reductions in all-site combined and most site-specific ASMR in both genders in Japan, which is possibly related to recent reductions in cancer risk factors (e.g., tobacco smoking, infections), improvements in cancer diagnosis, treatment, and disease management, as well as reported increases in cancer survival rates [37,38]. Despite the divergent trends in ASIR between genders, both genders showed increases in cancer cases (+6.9% among men, +30.9% among women), which were predominantly a consequence of population aging (among men) or a combination of population aging and population risk (among women). Furthermore, the overall number of cancer deaths was projected to decrease among both men (−16.5%) and women (−8.6%) due to the reduction effects of population decline and population risk. While colorectal and lung cancers were predicted to remain the leading causes of cancer incidence and mortality over 2020–2054 in both genders, female breast and prostate cancers were predicted to have the highest incidence burdens in 2020–2054 among Japanese women and men, respectively.

Our findings highlight the continuous presence of colorectal and lung cancers as the largest burdens in both genders (Table 3). Although the majority of lung cancer cases are caused by tobacco smoking (67.5% in Japan) [39], the attributable fractions and magnitudes of association of smoking behavior to incidence rates are divergent between histological types [40]. Specifically, the considerable reduction in smoking prevalence from 1965 to 2018 among both Japanese men (from 82.3% to 27.8%) and women (from 15.5% to 8.7%) might have contributed to the reported declines in lung squamous non-small-cell carcinoma and small-cell carcinoma [34,41]. However, our projected leveling-off trends of lung cancer ASIR in both genders could be explained by the substantial increases in localized and distant lung adenocarcinoma, which might be connected to the recent expansion and utilization of improved diagnostic and screening techniques [34]. In contrast, the increasing incidence rates of colorectal cancer in both genders could be explained by the spread of Westernized lifestyles [42] or the introduction of organized screening programs (fecal occult blood test) [43]. The Japanese government provides screening guidelines based on efficacy evaluation and recommends annual participation in population-based and/or workplace-based screening programs for lung, colorectal, breast, cervical, and gastric cancers. While participation rates in lung cancer screening are reported to have increased among both genders, those in colorectal cancer screening are relatively low for both fecal occult blood tests (47.8% among men, 40.9% among women) and follow-up examinations (69.8% in both genders) [44]. The current slow progress in achieving national targets for colorectal cancer screening (50% in fecal occult blood tests and 90% in follow-up examinations) may not secure further reductions in colorectal mortality rate shown in a microsimulation study [45]. Nevertheless, our decomposition analysis showed the large contribution of population risk to the increases in lung and colorectal cancer cases over 2020–2054 (Supplementary Figures S3 and S6), which were shown to be possibly reducible by effective cancer control measures, e.g., controlling risk factors (tobacco smoking and lifestyles) and improving diagnosis (cancer screening) [7]. Our findings warrant greater effort from the government and policymakers to promote primary and secondary preventive interventions aimed at reducing the incidence and mortality of lung and colorectal cancers in Japan.

Female breast and prostate cancers were predicted to be the highest incidence burdens in 2020–2054 among Japanese women and men, respectively. The increasing ASIR of female breast cancer was likely contributed to by the changing reproductive factors among

Japanese women (i.e., lower parity, older age at first parturition, or earlier menarche) [46], which also contributed to the increasing ASIR of other cancers that share common reproductive risk factors (i.e., ovary and corpus uteri). Another potential contributor was the increase in breast cancer screening rate (mammography) among Japanese women [44], which might be reflected in the reported increases in early-stage cancer and CIS of the breast [47]. Notably, female breast cancer will account for 25.1% and 12.1% of total new cancer cases in 2020–2054 among women and both genders combined, respectively (Supplementary Table S4 and Table 3), indicating the massive economic burden of treatment costs for breast cancer patients in the foreseeable future. Similarly, prostate cancer diagnosed by prostate-specific antigen (PSA) screening is projected to be the top burden in male cancer incidence in 2020–2054, accounting for one-fifth of new cases among men (Supplementary Table S4). The threefold increase in PSA screening in 2003 (widely adopted as an organized screening program in many municipalities) was subsequently reflected in the increasing localized prostate rate and decreasing distant prostate cancer rate in Japan after 2004, which included the possibility of overdiagnosis [48,49]. Generally, thyroid, prostate, and female breast cancers were considered to be subject to potential overdiagnosis in Japan, sharing the common factors of (1) wide adoption of minimally invasive tests (e.g., ultrasonography for thyroid, PSA for prostate, mammography for breast), and (2) a rapid increase in incidence without a corresponding change in mortality [50–52]. Our decomposition findings show that the majority of increasing cases of prostate and female breast cancers over 2020–2054 are attributable to population risk (Supplementary Figures S7 and S8), suggesting room for improving preventive interventions in the overdiagnosis context. Therefore, further studies using statistical or mathematical modeling approaches are needed to avoid overdiagnosis [53].

Among all cancer sites, only cancers of the stomach, liver, and gallbladder showed a substantial decrease in incidence and mortality (regarding both number of cancer cases/deaths and ASR) in both genders over 2020–2054. Our decomposition analysis showed the large contribution of population risk to the decreased number of cases of those infection-associated cancers over 2020–2054 (Supplementary Figures S2 and S4), emphasizing the necessity of controlling oncogenic infections. For example, Japan has included the eradication of *Helicobacter pylori* (*H. pylori*) in its universal health insurance for the treatment of chronic gastritis, gastric, and duodenal ulcers since 2013 [54]. Thus, the decreasing incidence of stomach cancer is mainly attributed to the tremendous decrease in *H. pylori* infection, in combination with improvements in diagnosis, diet, and food preservation techniques in Japan [55]. Similarly, reduction in risk factors for liver and gallbladder cancers (i.e., hepatitis B and C viruses, chronic infections, and obesity) was the predominant contributing factor to the decreasing incidence rates of these cancers among the Japanese population [56]. Our findings emphasize the important role of policymakers and governments in reforming cancer policies for controlling cancer risk factors, including oncogenic infections. However, the growing incidence of esophageal adenocarcinoma is believed to be related to the reduction in *H. pylori* infection, which plays a protective role in the presence of gastroesophageal reflux disease and Barrett's esophagus [57,58]. Thus, further investigations are required to summarize lessons learned for other low- and middle-income countries regarding health policies toward universal health coverage (e.g., improving communicable and noncommunicable disease management) to achieve better cancer control outcomes [59,60].

Notably, we projected neither age-standardized incidence nor mortality rates of cervical cancer significantly decreasing over 2020–2054, and only a modest contribution of population risk to the reduction of this infection-associated cancer burden in Japan (Supplementary Figure S9). As cervical cancer can be effectively prevented by nationwide organized screening [61], in combination with human papillomavirus (HPV) vaccination programs [62], our results suggest the currently modest effectiveness of cervical cancer control programs in Japan. Organized screening coverage in Japan is lower than in other developed countries (i.e., 43.7% in Japan compared with 51.9% in Korea, 72.6% in the US, and 74.4% in the UK), although Japan introduced (since the 1950s) and integrated (since

1982) cytology screening programs into its national system early on [63,64]. Additionally, Japan's HPV vaccination coverage is poor (<1%) [65], despite the fact that the Japanese government has recently confirmed the safety of this vaccination by ending the restriction on active recommendation and strengthening the support system for HPV vaccination [66]. Hence, our findings warrant greater efforts in improving the effectiveness of cervical cancer control programs in Japan, particularly the cervical cancer screening rate and HPV vaccination coverage, to better control cervical cancer burdens in the future [67].

We applied decomposition analysis of changes in cancer cases and deaths over 2020–2054 to further assess the burden of population aging on cancer incidence and mortality in Japan. Given the rapid escalation in the proportion of older people (≥65 years), we show that population aging is the major contributing factor to the increase in cancer cases (36.5% among men, 25.3% among women) and deaths (45.8% among men, 40.5% among women) over the study period (Table 1). We projected a dramatic escalation in the number of oldest-old cancer patients, from 14.0% in 2015–2019 to 25.9% in 2020–2054 (Supplementary Table S2). These older patients generally experience a combination of comorbidities, frailty, functional limitations, and other age-associated conditions, in addition to cancer. This situation, therefore, requires the development of tailored and supportive interventions which not only aim to reduce mortality but also to improve the quality of life for these elders [68]. Although the "Clinical practice guidelines of cancer drug therapies for the elderly", published in 2019, needs further improvement (e.g., the inclusion of more common carcinomas, higher levels of evidence, and more discussion on supportive and symptomatic therapies), it is the first and most qualified reference for the concept of elderly cancer pharmacotherapy in Japan [69]. Additionally, the ongoing reforms of social security systems in Japan (e.g., medical care, nursing care, and pensions) are expected to adapt to the complex challenges of population aging and decline, including the shortage of medical and human resources, and the decreasing sustainability of the finance and healthcare system [70]. Our projections of cancer burden will serve as qualified inputs and warrant further health economics and policy research in investigating future costs of cancer diagnosis and treatment, securing medical and human resources, and establishing evidence-based control programs [71].

This study provides the first comprehensive projections of cancer incidence and mortality for 22 cancer sites in both genders in Japan, using empirically validated APC models applied to the most up-to-date and nationally representative data. Additionally, it presents estimations and trends of decomposed changes in cancer cases and deaths over the period 2020–2054 using a newly proposed formula, which addresses limitations in the previous decomposition studies [36]. Nevertheless, several limitations of this study should be mentioned. First, we generated projections of cancer incidence/mortality on the basis of the projected population, which were forecast on the basis of prior assumptions of future migration, birth, and death rates, which in turn impact our cancer projections. Second, our APC models applied the widely accepted assumption that the last trends remained constant without substantial changes in policy nor significant improvements in human cancer control, such as new screening methods, novel vaccines, and advances in medical techniques. Thus, the presented projections may not reflect any newly implemented/future interventions/policies [72,73]; nevertheless, they still provide baseline projections against which the impact of future cancer interventions/policies or factors that appear after the study periods can be assessed (e.g., COVID-19-related delays in cancer screening and treatment) [22]. Nevertheless, a regular projection system in Japan with annual or biennial updates is recommended, as it could integrate the latest trends and provide the most stable and reliable cancer statistics for effective evidence-based cancer control. Furthermore, we did not incorporate covariates for projections of some specific cancers with potential overdiagnosis (e.g., PSA screening rate for prostate cancer and breast cancer screening rates for female breast cancer) as doing so would require further assumptions for projecting these covariates into the future, thereby risking more uncertainty. Nevertheless, future studies with different modeling approaches (e.g., microsimulation modeling studies) and

incorporating explanatory variables to predict cancers with potential overdiagnosis might be useful complements and comparisons to this work.

5. Conclusions

In conclusion, we project cancer incidence and mortality for 22 cancer sites and both genders in Japan, which may serve as baseline projections against which to assess the impact of future cancer interventions/policies, and qualified inputs for research into health economics investigating future costs of cancer diagnosis and treatment. The decomposition analyses show a relatively large cancer burden attributed to population aging in the future, requiring the development of tailored and supportive interventions for reducing mortality and improving the quality of life for the elders. We show the decreasing incidence and mortality for infection-associated cancers and emphasize the important role of policymakers and governments in reforming cancer policies aimed at controlling cancer risk factors, including oncogenic infections. Nevertheless, we project the continued presence and rapid increase in the burden of some cancers associated with modifiable risk factors in Japan. These findings warrant greater efforts in cancer control programs, specifically in enhancing cancer screening and controlling cancer risk factors, toward a vision for a healthier Japan [74].

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cancers14246076/s1., Table S1: Information of empirically selected models with data-, gender- and site-specific parameters; Table S2: Observed and projected new cancer cases and deaths in 2015–2019 and 2050–2054 by age groups and genders; Table S3: Cancer incidence by genders and decomposed changes in cases over 2020–2054 for other cancers; Table S4: Observed and projected top burden of cancer in Japan by genders and age groups; Table S5: Cancer mortality by genders and decomposed changes in deaths over 2020–2054 for other cancers; Figure S1: Trend in and projection of total population, proportions of people aged 65+ and 85+, and population pyramids in Japan, 1985–2055 10; Figure S2: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Stomach; Figure S3: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Colon/rectum; Figure S4: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Liver; Figure S5: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Pancreas; Figure S6: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Lung, trachea; Figure S7: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Prostate; Figure S8: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Female breast; Figure S9: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Cervix uteri; Figure S10: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Corpus uteri; Figure S11: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Esophagus; Figure S12: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Gallbladder and bile ducts; Figure S13: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Bladder; Figure S14: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Kidney and other urinary organs; Figure S15: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Thyroid; Figure S16: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Malignant lymphoma; Figure S17: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Ovary; Figure S18: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Oral cavity and pharynx; Figure S19: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Larynx; Figure S20: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Skin; Figure S21: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Brain, nervous system; Figure S22: Projections of age-specific incidence and mortality rates and decomposed changes

in new cases and deaths — Multiple myeloma; Figure S23: Projections of age-specific incidence and mortality rates and decomposed changes in new cases and deaths — Leukemia; Figure S24: Projections of age-standardized incidence and mortality rates by genders for other cancer sites Figure S25: Projections of new cancer cases by genders for all cancer sites Figure S26: Sensitivity analysis of drift attenuation in ASR in 2050–2054 Figure S27: Projections of new cancer deaths by genders for all cancer sites.

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cancers

MDPI

Article

Use Cases Requiring Privacy-Preserving Record Linkage in Paediatric Oncology

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Simple Summary: Large datasets concerning childhood cancers are rare. Therefore, it is important to fully exploit all available data, which are distributed over several resources, including biomaterials, images, clinical trials, and registries. With privacy-preserving record linkage (PPRL), datasets can be merged, without disclosing the patients' identities. Although PPRL is already implemented or described in various settings, use case descriptions are fragmented and incomplete. The present paper gives an overview of current and future use cases of PPRL in childhood cancer. We screened the literature, projects, and trial protocols, analysed a hypothetical patient journey, and discussed use cases with experts. All the identified use cases were structured along six key dimensions. We conclude that PPRL is a key concept in childhood cancer. Therefore, PPRL strategies should already be considered when starting research projects, to avoid distributed data silos, to maximise the knowledge derived from collected data, and, ultimately, to improve outcomes for children with cancer.

Abstract: Large datasets in paediatric oncology are inherently rare. Therefore, it is paramount to fully exploit all available data, which are distributed over several resources, including biomaterials, images, clinical trials, and registries. With privacy-preserving record linkage (PPRL), personalised or pseudonymised datasets can be merged, without disclosing the patients' identities. Although PPRL is implemented in various settings, use case descriptions are currently fragmented and incomplete. The present paper provides a comprehensive overview of current and future use cases for PPRL in paediatric oncology. We analysed the literature, projects, and trial protocols, identified use cases along a hypothetical patient journey, and discussed use cases with paediatric oncology experts. To structure PPRL use cases, we defined six key dimensions: distributed personalised records, pseudonymisation, distributed pseudonymised records, record linkage, linked data, and data analysis. Selected use cases were described (a) per dimension and (b) on a multi-dimensional level. While focusing on paediatric oncology, most aspects are also applicable to other (particularly rare) diseases. We conclude that PPRL is a key concept in paediatric oncology. Therefore, PPRL strategies should already be considered when starting research projects, to avoid distributed data silos, to maximise the knowledge derived from collected data, and, ultimately, to improve outcomes for children with cancer.

Keywords: privacy; record linkage; paediatric oncology; data management; secondary use; European Health Data Space (EHDS); General Data Protection Regulation (GDPR)

1. Introduction

Over half a century, consecutive clinical trials have improved survival rates across the spectrum of paediatric oncology (PO). Nevertheless, more than 6000 children die from cancer in Europe each year [1]. Since large datasets in PO are inherently rare, it is paramount to fully exploit all available data. Current PO research data are distributed over several resources holding biomaterials and their respective analysis, various image modalities, and clinical trial and registry data. In addition to clearly defined research goals in prospective settings, secondary use of data opens up important research and knowledge generation opportunities. However, secondary use is associated with various hurdles, including technical issues, legal barriers due to increasingly complex regulations, and ethical discussions about explicit informed consent for each analysis as compared to broad or even opt-out consent. Due to these and other reasons, most data are currently locked up in data silos.

The following levels of privacy can be distinguished:

- Personalised data, containing personal unique identifiers (IDs) or quasi-identifiers (QIDs), such as name, data of birth, and others, as defined by [2].
- Pseudonymised data, containing patient codes ("pseudonyms") that can be associated with related QIDs, if necessary.
- Anonymised data, which cannot be associated with related QIDs anymore.
- Aggregated data, e.g., statistical results as published in journals.

According to the General Data Protection Regulation (GDPR) [3], whenever possible, research data need to be collected in a pseudonymised way. As such, in general, different resources must generate different pseudonyms for one and the same patient. To overcome barriers due to distributed (pseudonymised) data, the European Joint Programme on Rare Diseases (EJP RD) is currently creating an effective rare diseases research ecosystem (https://www.ejprarediseases.org/ (accessed on 23 July 2024)). The EJP RD is based on the FAIR (Findable, Accessible, Interoperable, and Re-usable) principles [4], which are key to exploit existing data and support big data and artificial intelligence applications, as recently demanded by the European Society for Paediatric Oncology (SIOPE) [5,6].

Privacy-preserving record linkage (PPRL) concerns the linking of personalised or pseudonymised datasets, without disclosing the patients' identities. PPRL is a key concept for PO research [7]. During pseudonymisation, PPRL can avoid unintended double registration, which would lead to empty or fragmented pseudonymised records and—if followed by double randomisation—unbalanced cohorts.

PPRL is required for (a) merging patients from contexts with identical variables and/or (b) merging different data types from multiple sources holding the same patients (Figure 1).

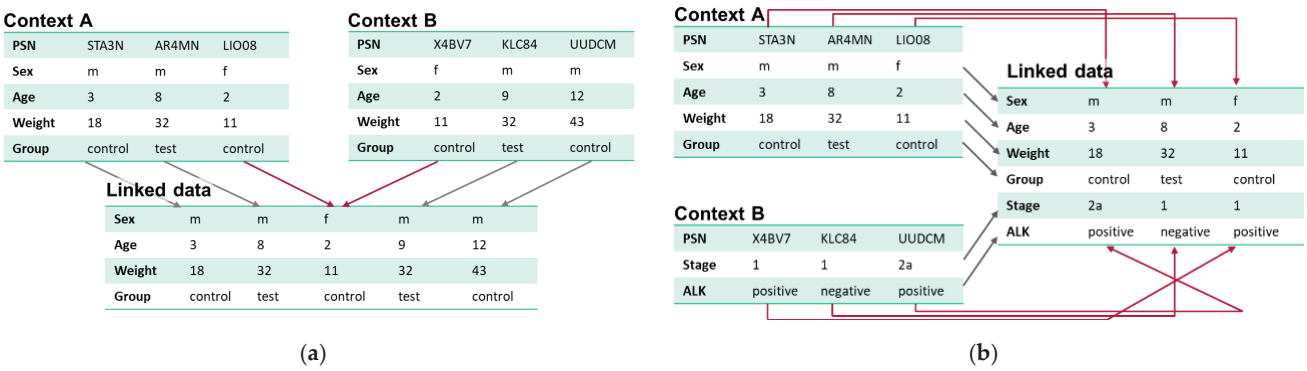


Figure 1. (**a**) Merging patients from contexts with identical variables mainly focuses on the identification of duplicate patient records in different contexts. (**b**) Merging different data types from multiple sources holding the same patients focuses on the identification of related patient records in different contexts.

Most PPRL publications focus on the technical implementation of PPRL algorithms. In general, PPRL algorithms can follow phonetic coding-based (e.g., [8,9]), hashing-based (e.g., [10,11]), reference-value-based (e.g., [12,13]), embedding-based (e.g., [14–16]), differential privacy-based (e.g., [17]), or secure multiparty computation-based techniques, which can either be applied on QIDs or on the clinical data themselves (e.g., [18–22]). Some solutions only support linkage in case of perfectly matching records. More comprehensive solutions can also link slightly differing records, e.g., in case of typing errors or missing data. Since both false positive as well as false negative linkage may have severe consequences, the optimal threshold of accordance must be chosen depending on the use case.

To compare PPRL solutions, Vatsalan et al. [23] and Gkoulalas-Divanis et al. [24] published PPRL overview papers, each with one out of many dimensions relating to application areas. A comprehensive overview of various aspects of PPRL was published by Christen et al. [25]. Their introduction summarises several aspects of why data should be linked at all and which sources of data might be linked, and they describe selected use cases. In particular, use cases focusing on health service research, national health insurance data in Germany, official statistics, and longitudinal studies are considered herein. In the conclusions of three recently published whitepapers [26–28], the European Union Agency for Cybersecurity (ENISA) highlights the importance of pseudonymisation and PPRL in distributed research environments as well as the need for cooperation in terms of implementation, development of application scenarios, regulatory support, and dissemination of best practice models. The use cases described especially in [26] represent a valuable resource for the present paper. PPRL is also expected to play a major role in the upcoming European Health Data Space (EHDS), which is supposed to provide a framework for structured and systematic secondary use of health data in the EU on a large scale [29].

For PO in Europe, there are mainly two PPRL services currently available: (1) SPIDER (https://eu-rd-platform.jrc.ec.europa.eu/spider/ (accessed on 23 July 2024)) focusses on PPRL between primary sources holding QIDs with perfect matches only (no typing errors, etc.). (2) The European Patient Identity (EUPID) Services [30] were designed to also link pseudonymised resources. EUPID further supports PPRL in case of typing errors based on phonetic hashing algorithms. The EJP RD virtual platform currently supports EUPID.

PPRL has been implemented in various PO settings. However, the related use cases have been described implicitly, based on the requirements of the respective projects. Use cases specified in the literature are fragmentary and spread over various publications. Therefore, the present paper provides a comprehensive overview of current and future use cases for PPRL in PO.

2. Materials and Methods

We followed three strategies to compile a comprehensive overview of PPRL use cases in PO.

First, we analysed the literature, existing PO projects, and trial protocols concerning how and why they implemented PPRL. For the literature search, we applied the following search terms in PubMed:

((((“record” OR “dataset” OR “registr”) AND (“link*” OR “merg*” OR “combin*”)) AND (“privacy” OR “GDPR” OR “data protection” OR “pseudonym*” OR “anonym*” OR “de-identif*” OR “deidentif*” OR “leak*”)) OR “PPRL”) AND ((“paediatr*” OR “pediatr*” OR “child*” OR “infant”) AND (“cancer” OR “oncolog*” OR “tumor” OR “tumour”)).*

Titles and abstracts and, in a second step, full-text publications were manually filtered to include only papers containing information concerning use cases of PPRL in PO, and the relevant use cases were extracted. The search terms revealed 85 articles, of which 23 articles containing use cases of PPRL in PO were considered.

Secondly, inspired by a recent paper by Ly et al. [31], we identified use cases along a hypothetical patient journey, as shown in Figure 2.

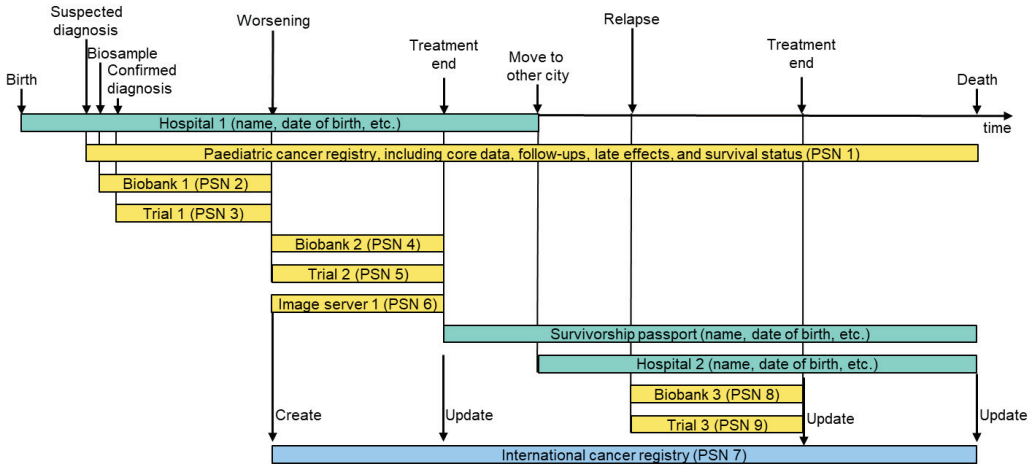


Figure 2. Hypothetical patient journey and related data sources. In this example, a patient is diagnosed with a primary tumour that worsens during treatment in trial 1. Treatment in a second trial 2 is successful. The cancer survivor suffers from a relapse a certain time after healing, which can again be treated successfully. In this patient journey, we end up with nine different pseudonyms (PSNs) for one patient. Green: personalised data; yellow: pseudonymised data; blue: linked data.

Finally, we discussed the identified use cases with stakeholders from (a) SIOPE and (b) the EJP RD to complement the list and to firm up the single use cases.

The identified use cases were then analysed and categorised along key dimensions.

3. Results

3.1. Overview of Dimensions in Privacy-Preserving Record Linkage

During our research, we found that a one-dimensional list of use cases is not feasible due to the variety of different PPRL applications in PO. Therefore, we categorised use cases along key dimensions, as illustrated in Figure 3.

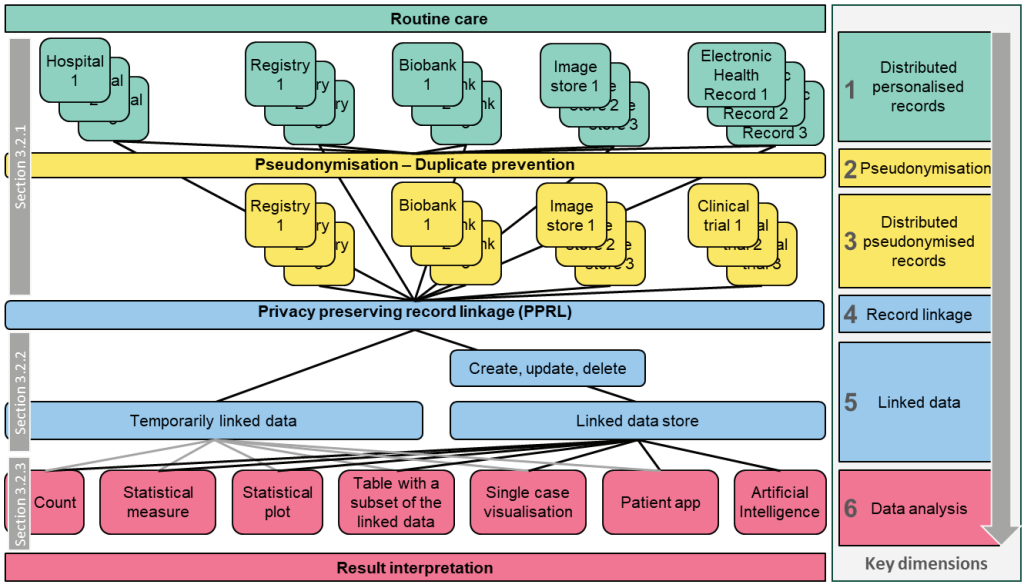


Figure 3. Overview of data residing in personalised routine care and different pseudonymised contexts, illustrating how data can be linked and how the linked data can be analysed to obtain new knowledge. On the right-hand side, the relation to the respective six key dimensions of record linkage is shown. Grey boxes reference chapters describing single-dimensional use cases.

Section 3.2 describes single dimensions of Figure 3 ("horizontal" slices), i.e., distributed personalised/pseudonymised data sources, record linkage/linked data, and data analysis, including PO examples.

Section 3.3 summarises multi-dimensional use cases ("vertical" paths through Figure 3), based on the EJP RD use case specification format: "As a <stakeholder>, I would like to <research focus> so that I can <objective> and visualise the result as a <output format>" (Terms between "<" and ">" were replaced by use-case-specific contents).

3.2. Single-Dimensional Use Cases

3.2.1. Distributed Personalised/Pseudonymised Data Sources

This chapter summarises the rationale for why PO data are distributed not only in routine care but also in research-related data environments.

Multiple Hospitals

Patients might be treated in more than one hospital over time, leading to distributed personalised records, thus increasing the risk of double registration.

PO example—Specialised and local hospitals: Patients with complex or rare diagnoses move from local to specialised hospitals. Vice versa, less complex cases are transferred from specialised to local hospitals.

PO example—Second opinion: Due to the severity of paediatric cancer, parents often seek a second opinion from another hospital.

Different Types of Data

Pseudonymised research data of different types are often distributed over different sources.

PO example—Data sources in neuroblastoma research: Neuroblastoma trial data are collected in several electronic data capture systems. Additionally, there are national and international registries (e.g., the French National Registry of Childhood Cancers [29]). Biosample data are stored in biobanks, some of which can be queried via BBMRI-ERIC [32]. Sequencing results can be stored in the RD-Connect Genome-Phenome Analysis Platform (GPAP) [33]. DICOM images are collected on a pseudonymised image management server.

Suspected Diagnosis

Eligibility criteria for clinical trials often require a confirmed diagnosis, although confirming a suspected diagnosis may already provide valuable research data (e.g., tumour samples in a biobank).

PO example—SIOPEN BIOPORTAL: SIOPE Neuroblastoma (SIOPEN) is currently establishing a "SIOPEN BIOPORTAL" (NCT05192980) (https://clinicaltrials.gov/study/NCT05192980 (accessed on 23 July 2024)), which supports registration and data collection based on suspected diagnoses with a specific BIOPORTAL pseudonym. This pseudonym can be used to send biological samples to reference laboratories. After confirmation of the diagnosis, the patient is registered to the corresponding trial (e.g., low/high risk) and a second trial-specific pseudonym is generated.

Multiple Subsequent Trials

Throughout their lifetime, patients can be included in one or more trials.

PO example—Poor response: If a high-risk neuroblastoma patient enrolled in an upfront treatment trial such as HR NBL2 (NCT04221035) (https://clinicaltrials.gov/study/NCT04221035 (accessed on 23 July 2024)) did not respond to the induction chemotherapy, the patient was transferred to an even more intensified treatment scheme, e.g., VERITAS (NCT03165292) (https://clinicaltrials.gov/study/NCT03165292 (accessed on 23 July 2024)).

PO example—Relapse: In case of a relapse, patients previously treated in a primary tumour study were frequently enrolled to relapse studies, such as BEACON (NCT02308527) (https://clinicaltrials.gov/study/NCT02308527 (accessed on 23 July 2024)). Subsequently,

patients could further be enrolled to national or international precision medicine programs or phase 1 or 2 Innovative Therapies for Children with Cancer (ITCC) trials like ESMART (NCT02813135) (https://clinicaltrials.gov/study/NCT02813135 (accessed on 23 July 2024)).

Multiple Concurrent Trials

There are trials that allow for or even foresee the participation in other trials at the same time.

PO example—OMS trial: The Opsoclonus Myoclonus Syndrome (OMS) trial (https://clinicaltrials.gov/study/NCT01868269 (accessed on 23 July 2024)) collects data concerning OMS, a rare syndrome in children that appears frequently in patients with neuroblastoma. Neuroblastoma patients may additionally be treated according to neuroblastoma trial protocols, where oncological data are collected. Therefore, the OMS infrastructure links OMS-specific trial data with oncological data from different neuroblastoma trials [34].

Transition from a Trial to Long-Term Follow-Up

Long-term follow-up data are essential but often not collected in trial databases or only for short periods.

PO example—Long-term follow-up: Since PO patients are frequently treated in more than one trial, long term follow-up data should be preserved for all trials, even for decades, without re-entering data in each context. The SIOPEN BIOPORTAL envisages reporting the long-term follow-up data within a neuroblastoma registry, which includes core, patient, tumour, and epidemiological data, with the aim to operate for longer periods.

Transition from Routine Care to Research (and Back)

For any trial patient, specific data are collected in routine care and others in research infrastructures, requiring transition from one to the other.

PO example—Continuity of care: With improving treatment options, continuity of care for PO survivors beyond cancer treatment is becoming increasingly important. SIOPE is working on guidelines dealing with the transition from paediatric patients to adolescent or adult survivors [35].

PO example—Late effects: The majority of the nearly 500,000 PO survivors in Europe experience late effects, with increasing incidence over the lifetime and impacts on their daily life [36]. Identification of late effects, even decades after the treatment, and development of long-term follow-up guidelines require transitions from research to routine care and back.

PO example—End-of-life treatment: Henson et al. used linked data to analyse prescriptions dispended in the community during end-of-life care of cancer patients [37].

3.2.2. Record Linkage/Linked Data

Temporarily Linked Data

Based on related pseudonyms of distributed contexts, data are temporarily linked in a central service, specific calculations are applied to the linked data, and the result is returned to the user.

PO example—Counting shared patients: Via the EJP RD virtual platform, users will be able to count patients that are registered in two different contexts, such as the HR-NBL1 trial and the International Neuroblastoma Risk Group (INRG) databases.

Linked Data Stores and Registries

Linked data can be stored in specific data stores, either to support subsequent tasks or to serve as a long-term data source (e.g., a linked registry). Therefore, regular updates must be supported, including the addition of new data, completion of previously missing data, or correction of data.

PO example—INRG database: Based on agreements between SIOPEN and other research organisations (e.g., US Children's Oncology Group, COG), core PO trial data are submitted to the INRG-DB [38] after publication. The HR-NBL1 trial [39] was amended

several times. Over the years, different randomisations were amended, and the corresponding results were successively published. Some patients were randomised more than once (e.g., pre-induction and pre-maintenance). Data of such patients were sent to the INRG-DB once per randomisation, and PPRL ensured that such patients were not registered twice.

PO example—The international diffuse intrinsic pontine glioma registry [40] provides an infrastructure for acquisition of biological specimens, imaging, and correlative clinical and genomics data to facilitate basic and translational research studies in diffuse intrinsic pontine glioma from 55 collaborating institutions in the United States, Canada, Australia, and New Zealand, including clinical, demographic, radiologic, and pathologic data.

3.2.3. Data Analysis

Counts, Statistical Measures, and Statistical Plots

Counting linked data without counting any patient twice and/or including filters (e.g., age < 3 years) requires PPRL. Statistical analyses can be applied on linked data, providing specific measures (e.g., mean value) or statistical plots (e.g., Kaplan–Meier curve).

PO example—Long-term toxicity: Calculate the rate of toxicity in patients who have been treated with a specific drug (e.g., cisplatin) and had a specific symptom thereafter (e.g., ototoxicity) in late-effect research scenarios. Or evaluate the effect of cancer treatment on paternity through use of assisted reproduction technology [41].

PO example—Large-scale statistics: Various studies applied PPRL to perform large-scale statistical analyses on cancer data, e.g., to analyse long-term survival after paediatric cancer [42] or after cancer in general (including PO) [43], to apply benchmarking on paediatric cancer survival [44], to develop a national resource of patient-level genomics laboratory records including PO patients [45], or to accelerate research on pontine glioma [40]. Walker et al. applied PPRL to analyse the prevalence of PO and other conditions increasing the risk of severe COVID-19 disease [46]. Finally, PPRL was applied to determine the incidence of melanoma [47] and of childhood cancer in general [48].

PO example—Effect of specific parameters on PO incidence: Analyse the effect of specific parameters from one dataset on the PO incidence as documented in another source (see, e.g., [49–54]).

PO example—Healthcare management: Use linked datasets for cost effectiveness analyses [55], data quality assessment [43], benchmarking [56], or capacity building [57].

Tables with Subsets of Linked Data

Subsets of linked data are provided to the user.

PO example—List of follow-ups of a patient: Provision of a table listing all follow-ups of a specific patient, documented in different data sources, including date of follow-up, originating data source, and the documented status of the patient.

Single Case Visualisation

Distributed data of a single patient are comprehensively visualised, either in a personalised (healthcare) or pseudonymised (research) context.

PO example—Tumour boards: Tumour boards enhance cancer treatment strategies. In the realm of PO, these boards are frequently conducted in a virtual setting, facilitating the collaboration of external experts with local physicians (see, e.g., [58]). Consequently, it is advisable to share only pseudonymised data that have emerged from both routine care (e.g., images) and research (e.g., randomisation arms).

Patient Apps and Digital Companions

Patient apps and digital companions represent a powerful way to provide outcomes of PPRL not only to researchers but also to patients.

PO example—Survivorship passport: The survivorship passport links core treatment data with follow-up recommendations based on guidelines [59]. It will closely be linked to electronic medical records and to national cancer and survivorship registries, supporting

regular updates and generation of care plans. The implementation of the survivorship passport is currently being piloted in six European countries [60].

Artificial Intelligence (AI)

To tap the full potential of AI, PPRL of distributed data sources is essential.

PO example—Image-defined risk factors: Image-defined risk factors (tumour size, anatomical regions, etc.) are key for risk-adjusted treatment of cancer. However, raw images either remain in the local centre's Picture Archiving and Communication System (PACS) or they are separately stored on specific image management servers. In the PRIMAGE project [61], DICOM-formatted raw image data from a PO image management server were integrated with clinical trial data and stored on the PRIMAGE platform. AI was applied to predict outcomes from the images.

3.3. Multi-Dimensional Use Cases

Table 1 presents a selection of identified high-priority use cases following specific "vertical" paths along the dimensions illustrated in Figure 2, represented in the format developed in the EJP RD project.

Table 1. Subset of possible use cases per stakeholder requiring privacy-preserving record linkage identified as potentially useful in paediatric oncology (PO). The use cases are displayed in the EJP RD use a case specification format, i.e., "As a <stakeholder>, I would like to <research focus> so that I can <objective> and visualise the result as a <output format>".

Stakeholder **"As a..."**	**Research Focus** **"...I Would Like to..."**	**Objective** **"...so That I Can..."**	**Output Format** **"...and Visualise the Results as..."**
clinician (corresponds to PO patient OR parent of a PO patient)	know if there have been patients in the past in any source who were similar to my patient, and their outcome	choose the optimal therapy for my patient	a table with key patient characteristics, data sources, and outcomes
	discuss my patient's case in a tumour board based on all the distributed data of my patient		comprehensive overview of my patient's case including tables, images, etc.
	compare the predicted survival rate of my patient, depending on the selection of treatment A or treatment B		two survival probabilities as derived from an AI algorithm (preferably including explanations)
paediatric cancer survivor	know which sources hold any data or samples of mine	have an overview of my data and samples	a table of data sources and types of data/samples they hold of mine
	receive life-long suggestions concerning screenings, etc., based on all my own data and recent study results	improve my life expectancy, health status, and quality of life	suggestions and summaries provided by a survivorship app
	make sure that my data are used for further research in the most valuable way	contribute to the improvement of paediatric cancer treatment	–
researcher in the field of PO	compare the outcome of treatment A with that of treatment B (taken from source A) in patients fulfilling a certain eligibility criterion (taken from source B)	see if the type of treatment is correlated with the outcome	a Kaplan–Meier-curve with two groups, for treatments A and B
	compare the outcome of study A with that of study B in patients fulfilling certain criteria	see if one of the studies' outcomes is superior	a Kaplan–Meier curve with two groups, for studies A and B
	know all follow-up results of one of the patients in my study, no matter within which context the follow-up was performed	use the most recent follow-up data for the analysis of my study	a table of all follow-ups including dates, sources, and results
researcher in the field of biology	know which biobanks have further samples on which I need to perform an additional experiment	contact these biobanks and ask for additional material	a table with the sample type and biobank including contact information
	know specific results, as stored in genome–phenome analysis platforms, which were achieved with the probes from my biobank	gain further insights into the properties of my samples	a table with platforms and results per probe in my biobank
	know which sources contain patients with a specific biomarker	contact these sources to perform further research on that biomarker	a table with the number of patients per source

Table 1. *Cont.*

Stakeholder "As a..."	Research Focus "...I Would Like to..."	Objective "...so That I Can..."	Output Format "...and Visualise the Results as..."
future principal investigator of a specific research activity	know how many cases fulfilling specific eligibility criteria are present in at least two data sources	estimate the number of cases for my study	a number of overall cases
	know which data sources contain cases fulfilling specific eligibility criteria (age, diagnosis, biomarker, treatment, etc.)	get in contact with these sources to consider them in my study	a table with cases per source
	correlate variables in patients from various sources, fulfilling my eligibility criteria, with one another	optimise stratification in my study	correlation between the variables
member of the SIOPE board	compare the survival rate of all neuroblastoma patients in all sources in 2001–2010 to the rate in 2011–2020	evaluate the improvements in neuroblastoma research in Europe	a boxplot
	compare the rate of severe adverse events per member state during immunotherapy with a certain biological in all sources	identify differences across Europe and improve potential shortfalls	a landscape, color-coded with the rate of severe adverse events
healthcare politician	know whether a specific type of PO treatment is cost-effective	optimise PO treatment based on outcomes and costs	table listing costs and outcomes of two different PO treatment options

4. Discussion

PO stands to benefit significantly from PPRL due to the scarcity and distribution of data, multimodal treatments, and complex patient journeys. This paper provides a comprehensive overview of potential use cases, emphasising that the list is not exhaustive and new dimensions may emerge in the future. While focusing on PO, most aspects discussed are also applicable to other conditions, rare diseases in particular.

Most identified use cases concern the analysis of clinical outcomes (long-term toxicities, event-free survival, overall survival) and the effect of certain parameters on the incidence/prevalence of PO. However, we identified a wide range of use cases, which require PPRL in PO care and/or PO research.

Many identified use cases concerned neuroblastoma research, where a European IT infrastructure supporting record linkage on clinical trial data, biological data from different samples, and imaging data has already been introduced in the FP5 project SIOPEN-R-NET. During the FP7 project ENCCA (2011–2015), the EUPID Services have been developed, which provide a more privacy-preserving approach for linking records. Since then, PPRL services have continuously supported collaborative European neuroblastoma research by providing large, linked datasets, which contribute to significantly improved survival rates as achieved in the past decade.

PPRL is a complex task, which is associated with various risks in terms of usability, costs, privacy preservation, potential misuse, the risk of breaking confidentiality, the risk of mismatched identities, etc. Different technical approaches for realising PPRL have different advantages and disadvantages in all these dimensions. Special care should be taken if PPRL is applied based on QIDs that can change over time (e.g., names in case of marriages, gender, etc.), especially if PPRL is to be supported in long-term settings, such as, e.g., the survivorship passport [59]. The present paper, however, concentrates on use cases, omitting technical details, privacy and security aspects, and consent considerations.

The use cases in this paper were identified in a three-step approach (screening of the literature, projects, and trials, hypothetical patient journey, and discussion with experts). On the one hand, the literature search was conducted by one researcher only. Therefore, use cases might have been overlooked that would have been identified if screening had been performed by more researchers. However, due to the multistep approach, such use cases were most likely identified in another step. On the other hand, even articles that did not cover PPRL and PO were considered, if use cases that are also applicable for PPRL in PO were described.

Selecting the right PPRL solution before starting data collection is crucial, especially for pseudonymised record linkage. The lack of standards for and interoperability between PPRL services is acknowledged, and efforts within EJP RD are underway to address this.

References to implementation projects are provided for some use cases, with varying stages of development. The evolution from project design to pseudonymisation and linked data analyses is noted. As applications progress, PPRL is recognised as a key concept of a broader privacy-preserving research landscape. Integration with other approaches like privacy-preserving artificial intelligence and federated/distributed learning is anticipated. For PO in Europe, currently, mainly SPIDER and the EUPID Services are implemented, which should be considered when setting up new projects. Choosing the appropriate privacy-preserving strategy will be a key consideration in future research across diverse fields, not limited to PO.

5. Conclusions

Research in PO has been at the forefront of PPRL implementations, making significant strides in realising tangible outcomes from linked records. As PPRL gains prominence across various application domains, both existing and new use cases are anticipated to evolve. The long-term nature of underlying diseases underlines the importance of adopting a robust PPRL strategy early on. By doing so, the benefits of linked data can be harnessed sooner, ensuring that datasets collected without a PPRL concept do not miss out on future applications and fall short of maximising patient benefits.

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Abbreviations

AI	Artificial Intelligence
COG	US Children's Oncology Group
EHDS	European Health Data Space
EJP-RD	European Joint Programme on Rare Diseases
ENISA	European Union Agency for Cybersecurity
EUPID	European Patient Identity
FAIR	Findable, Accessible, Interoperable, and Re-usable
GDPR	General Data Protection Regulation
GPAP	RD-Connect Genome Phenome Analysis Platform
INRG	International Neuroblastoma Risk Group
ITCC	Innovative Therapies for Children with Cancer
OMS	Opsoclonus Myoclonus Syndrome
PACS	Picture Archiving and Communication System

PO	Paediatric Oncology
PPRL	Privacy-Preserving Record Linkage
PSN	Pseudonym
QID	Quasi-Identifier
SIOPE	European Society for Paediatric Oncology
SIOPEN	SIOPE Neuroblastoma

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Impact of the COVID-19 Pandemic on Incidence and Observed Survival of Malignant Brain Tumors in Belgium

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Simple Summary: A decline in cancer diagnoses during the COVID-19 pandemic has been reported in many countries, including Belgium. Most of these reports focus on cancers with the highest incidence, while data for brain tumors are scarce. This study evaluates the impact of the COVID-19 pandemic on the incidence, treatment strategies, and observed survival of adults diagnosed with malignant brain tumors in Belgium in 2020. The results of this study, confirming a dramatic impact on incidence and survival, should be taken into account by policy makers when implementing measures during future disease outbreaks. Pathways for (neuro)-oncological care should be continued, and if necessary adapted, and physicians should pro-actively develop frameworks for shared and broadly informed decision making when capacity for care is reduced.

Abstract: (1) Background: This study evaluates the impact of the COVID-19 pandemic on the incidence, treatment, and survival of adults diagnosed with malignant brain tumors in Belgium in 2020. (2) Methods: We examined patients aged 20 and older with malignant brain tumors (2004–2020) from the Belgian Cancer Registry database, assessing incidence, WHO performance status, vital status, and treatment data. We compared 2020 incidence rates with projected rates and age-standardized rates to 2015–2019. The Kaplan–Meier method was used to assess observed survival (OS). (3) Results: In 2020, there was an 8% drop in age-specific incidence rates, particularly for those over 50. Incidence rates plunged by 37% in April 2020 during the first COVID-19 peak but partially recovered by July. For all malignant brain tumors together, the two-year OS decreased by four percentage points (p.p.) in 2020 and three p.p. in 2019, compared to that in 2015–2018. Fewer patients (−9 p.p.) with glioblastoma underwent surgery, and the proportion of patients not receiving surgery, radiotherapy, or systemic therapy increased by six percentage points in 2020. (4) Conclusions: The COVID-19 pandemic profoundly impacted the diagnosis, treatment strategies, and survival of brain tumor patients in Belgium during 2020. These findings should guide policymakers in future outbreak responses, emphasizing the need to maintain or adapt (neuro)-oncological care pathways and promote informed decision making when care capacity is limited.

Keywords: COVID-19; brain tumors; glioma; incidence; survival; pandemic

1. Introduction

A decline in cancer diagnoses during the COVID-19 pandemic has been reported in many countries, including Belgium [1–5]. Since healthcare facilities had to deviate much of their efforts and resources towards the care of COVID-19 patients, access to conventional healthcare, including oncological care, was significantly impaired. Therefore, healthcare services that were deemed non-essential, including cancer screening, were suspended in Belgium—and many other countries—for several weeks [6–9]. Most of these reports focus on cancers with the highest incidence, while data for brain tumors are scarce.

The most common brain tumor subtypes in Belgium are glioblastoma and hematolymphoid tumors involving the CNS, respectively representing 67% and 7% of all malignant brain tumors in adults in Belgium in 2015–2019, with a corresponding yearly average of 573 and 64 new diagnoses, respectively. Hematolymphoid tumors involving the CNS are mainly diffuse large B-cell lymphomas (DLBCL; 87%). Since glioblastoma and DLBCL of the brain have unfavorable prognoses, in combination with a steeply decreasing survival curve in the first few months after diagnosis, it is expected that short term delays in diagnosis and subsequent treatment, or divergence from recommended treatment strategies, might affect outcomes for these cancer types [10,11]. Here, we provide a nationwide analysis that aims to quantify and evaluate the impact of the COVID-19 pandemic on the incidence of malignant brain tumors in adults in Belgium, as well as on treatment strategies and observed survival (OS).

2. Materials and Methods

Since 2004, the Belgian Cancer Registry (BCR) has been legally responsible for the collection of data on all new oncological diagnoses. Its database is estimated to be more than 95% complete from 2004 onwards, thanks to mandatory cancer registration in Belgium [12,13]. The inclusion criteria for the selection of patients from the BCR database for this study were as follows: an age of 20 years or older at the time of diagnosis, Belgian residence at the time of diagnosis, International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) topography code C71 (brain), ICD-O-3 behavior code/3 (malignant, primary), and relevant ICD-O-3 morphology codes (see Supplementary Materials) [14]. The vital status of patients was updated until 31st December 2022.

Cancer incidence was described as the number of new diagnoses, age-specific (in 5-year-wide groups), and age-standardized incidence rates (WSR: World Standardized Incidence Rate). The observed survival probability was estimated using the Kaplan–Meier method [15]. The WHO performance status and treatment data were extracted from multidisciplinary oncological consult (MOC) forms. These forms contain information on planned and/or given treatment categories. In the context of this study, proportions of patients were calculated for each of the following treatment categories: surgery, radiotherapy, systemic therapy (which, in this study, refers to chemotherapy, targeted therapy, and immunotherapy), and patients who received none of these.

At the year level, the impact of the COVID-19 pandemic on cancer incidence was evaluated by comparing the observed incidence rates of 2020 with projected incidence rates for 2020. The latter were based on an extrapolation of the incidence trends over the period 2004–2019 [16]. At the month level, age-standardized incidence rates for 2020 were compared to the average incidence at the month level for 2015–2019. In all month-level comparisons, the months January and February 2020 were considered pre-COVID-19 baseline months. Besides results for all malignant brain tumors combined, more detailed analyses were added for the two most frequent subtypes of malignant brain tumors: glioblastoma and hematological malignancies. Two-sided z-tests, at a 5% significance level, were used for all statistical comparisons of incidence and survival between different months/years. Since the observed survival for patients diagnosed in 2019 might have been impacted by the COVID-19 pandemic in 2020, the OS in 2020 was compared to the OS in 2019 and 2015–2018, separately.

3. Results

3.1. Incidence of Malignant Brain Tumors

The observed age-specific incidence rates for malignant brain tumors in 2020 were similar compared to those in 2015–2019 for patients under 50 years of age, but were 8% lower for the age group 50+ (Figure 1). As such, this study further focused on the 50+ age group. The age-standardized incidence rate (WSR; Figure 2) in the 50+ age group for 2020 (13.0/100,000) was significantly lower than the projected incidence for 2020 (14.9/100,000) ($p < 0.005$), corresponding with an estimation of 70 missed diagnoses ($N_{Observed} = 640$; $N_{Projected} = 710$). Moreover, the observed incidence rate for malignant brain tumors in Belgium in 2020 was the lowest ever noted since the start of the registrations in 2004. After pre-COVID-19 baseline months (January–February 2020), the standardized incidence rates showed a significant decrease of −37% ($p < 0.005$) in April 2020 vs. April 2015–2019 (Figure 3A), which coincided with the peak of the first COVID-19 wave in Belgium. A subsequent recovery phase of delayed diagnoses can be noted, with a modest rebound in July 2020 (although the difference with July 2015–2019 was not significant; $p < 0.10$). In addition, the proportion of patients presenting with a WHO performance score of 2–4 (i.e., symptomatic and partially or fully bedbound) at diagnosis was 10 p.p. higher in 2020 compared to that in previous years (Figure 3B), and in April and November 2020—the first and second COVID-19 peaks—approximately 50% of all patients presented with a WHO performance score of 2–4.

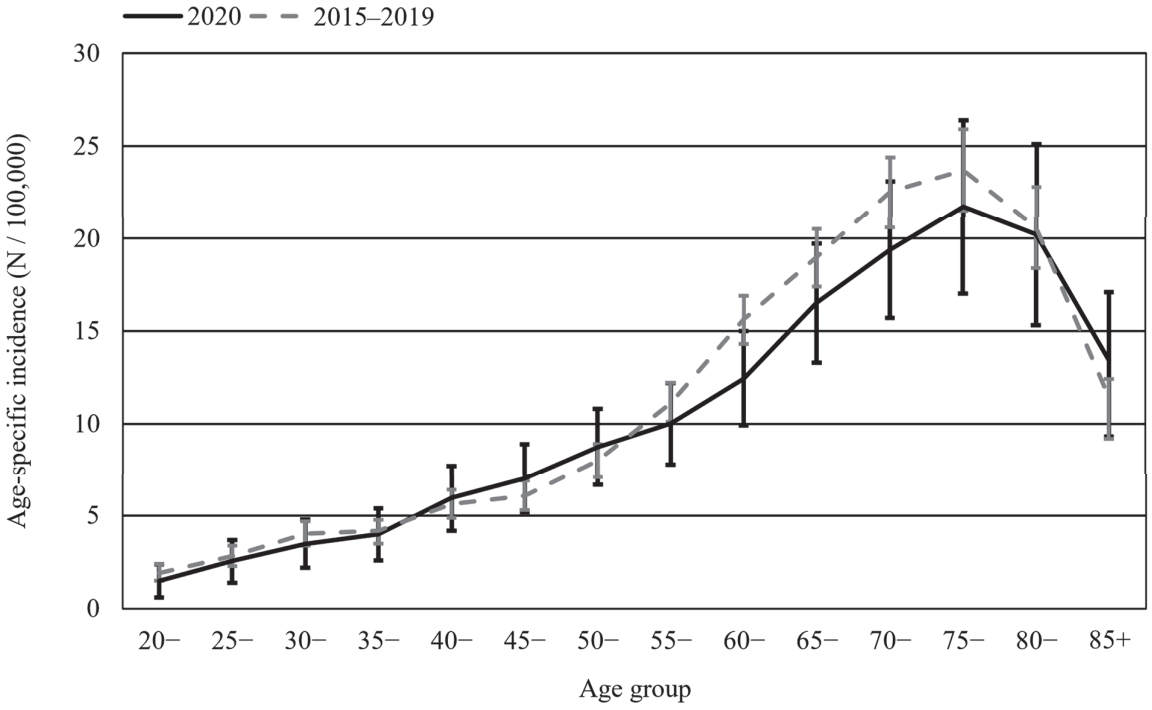


Figure 1. Age-specific incidence rates (N/100,000; 5-year age groups) with 95% confidence intervals for malignant brain tumors in adults (patients aged 20 years and older) for incidence years 2020 and 2015–2019.

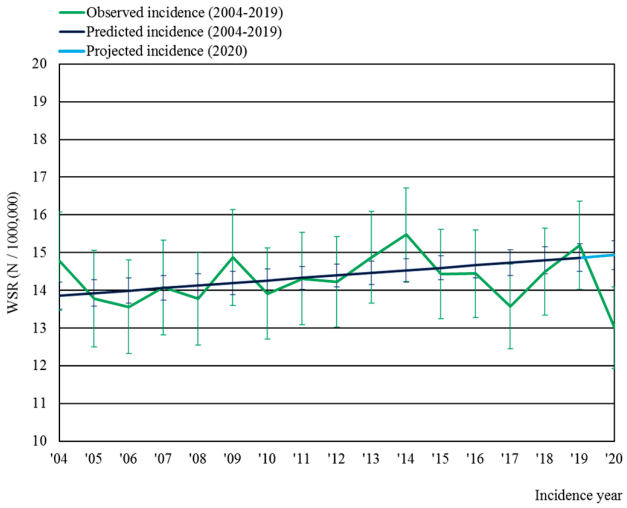


Figure 2. Observed age-standardized incidence rates (WSR, with corresponding 95% confidence intervals) versus predicted and projected incidence (WSR, with corresponding 95% confidence intervals) for malignant brain tumors in the age group 50+ in Belgium.

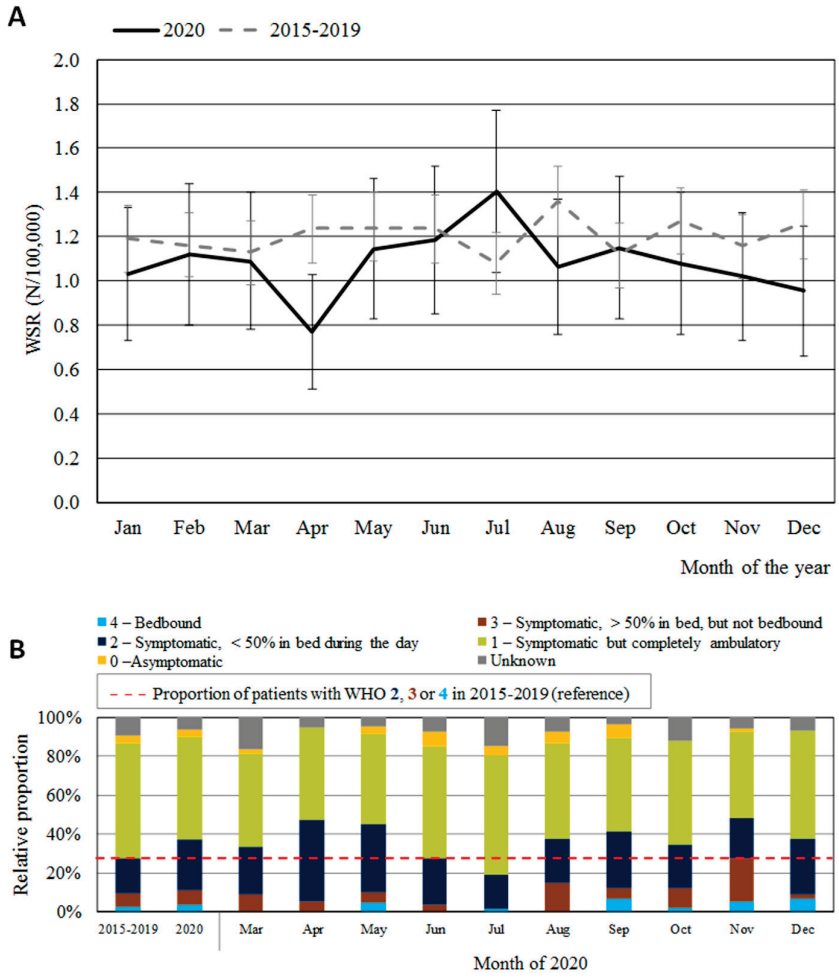


Figure 3. All malignant brain tumors, age group 50+. (**A**) Age-standardized incidence rates (WSR) and 95% confidence intervals by month for 2020, compared to the average month level for 2015–2019. January and February can be considered baseline months. (**B**) WHO performance status at diagnosis. Horizontal red dashed line indicates the proportion of patients presenting with a WHO status of 2–4 in the reference period 2015–2019.

3.2. Survival of Patients with Malignant Brain Tumors and Subtypes

OS for patients diagnosed with a malignant brain tumor by month in 2020 varied depending on the phase of the pandemic (Figure 4A). For patients diagnosed prior to the pandemic, in January–February 2020, and thus likely to have received at least part of their oncologic care during the first COVID-19 wave, the OS curve initially coincides with the curve of 2015–2018. However, at two years after diagnosis, the observed survival is reduced by 6 p.p. (17% for patients diagnosed in January–February 2020 vs. 23% for 2015–2018). For patients diagnosed with brain tumors in March–April 2020, during the first peak of the pandemic, the OS curve started to diverge from the 2015–2018 curve 5 months after diagnosis, to end with a difference of −10 p.p. at 2 years after diagnosis (13% for Apr–March 2020). During those two months of the first peak of the pandemic, the proportion of patients diagnosed with glioblastoma (78%) was higher compared to that in 2015–2018 (74%) and the other months of 2020 (Figure 4B). Patients diagnosed in July 2020, corresponding to the diagnostic recovery peak in the monthly incidence trend curve, had the lowest OS results in the first four months after diagnosis, but had more similar 2-year OS (19%) as compared to that in 2015–2018. Figure 5 presents OS at 0.5, 1, 1.5 and 2 years for patients diagnosed in 2020, 2019 and 2015–2018, by subgroups. For hematolymphoid malignancies (approximately 93% DLBCL in 2020), a strong impact of the COVID-19 pandemic on the OS in 2020 was marked relative to that in 2015–2018, with significant reductions of −16 p.p. by 6 months (47% vs. 63%), −18 p.p. at 1 year (36% vs. 54%), and −17 p.p. at 2 years after diagnosis (29% vs. 46%). For glioblastoma, there was a smaller but significantly lower 2-year OS (−3 p.p.) for patients diagnosed in 2019 when compared with that in 2015–2018. Also, for patients diagnosed in 2020, a decreasing trend was noted (−2 p.p.), although it was not significant. For all malignant brain tumors together, the 2-year OS significantly decreased in 2020 (−4 p.p.), as well as in 2019 (−3 p.p.), compared to that in 2015–2018.

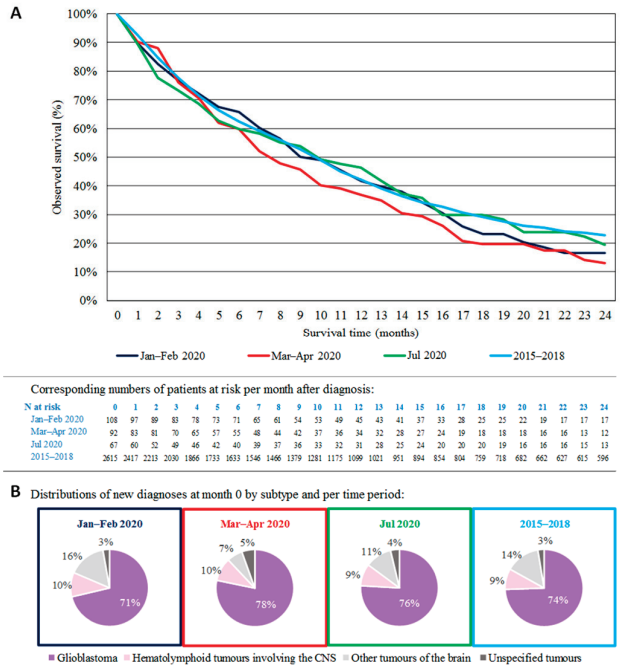
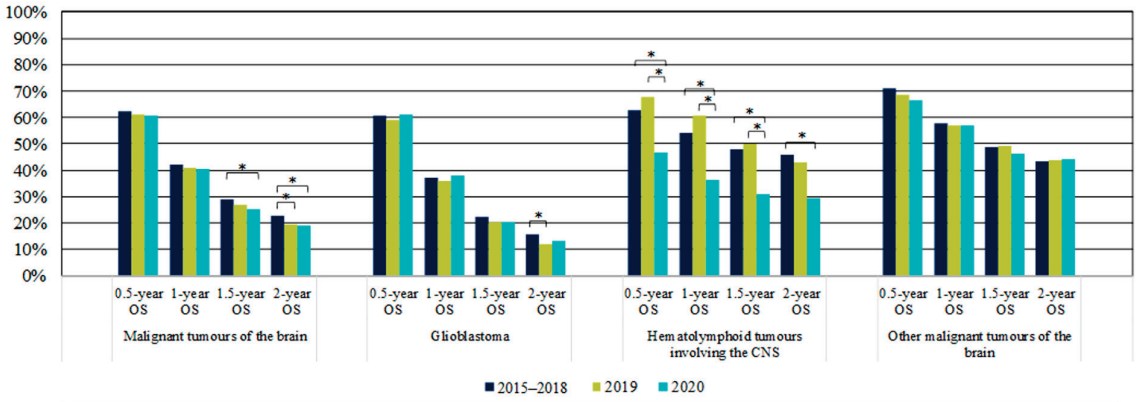


Figure 4. (**A**) Observed survival curves for malignant brain tumors in the age group 50+ during the year 2020 vs. that in 2015–2018 in Belgium and the corresponding numbers of patients (N) at risk. In this graph, OS results are calculated on the month level with the Kaplan–Meier method and the points obtained are connected with a line. (**B**) The corresponding distribution of tumor types during the year 2020 vs. that in 2015–2018.



		N at risk per year after diagnosis				
Histological subtype	**Incidence year(s)**	0	0.5	1	1.5	2
Malignant tumours of the brain	2015–2018	2614	1633	1099	759	596
	2019	735	450	302	199	143
	2020	639	384	258	160	121
Glioblastoma	2015–2018	1950	1181	724	438	303
	2019	565	334	203	115	69
	2020	486	294	183	98	62
Hematolymphoid tumours involving the CNS	2015–2018	226	142	122	108	104
	2019	56	38	34	28	24
	2020	58	27	21	18	17
Other malignant tumours of the brain	2015–2018	438	310	253	213	189
	2019	114	78	65	56	50
	2020	95	63	54	44	42

Figure 5. Diagram showing 0.5-, 1-, 1.5- and 2-year OS (observed survival) for subgroups of malignant brain tumors during 2020 vs. 2019 and 2015–2018. Significant differences ($p < 0.05$) are indicated with an asterisk (*).

3.3. Treatment for Glioblastoma and Hematolymphoid Tumors

Based on information on given and/or planned treatment from MOC registration files, for glioblastoma diagnosed in 2020, a decrease in the number of surgeries was noted when compared to that in 2015–2018 (−9 p.p.). For (radio)chemotherapy in glioblastoma (including radiotherapy with concomitant Temozolomide), no notable change was observed. In hematolymphoid malignancies (mainly DLBCL), the proportion of patients receiving systemic therapy increased by +8 p.p. for patients diagnosed in 2019 vs. 2015–2018, but decreased again by −10 p.p. in 2020. For all types of malignant brain tumors combined, the proportion of patients who received none of these three treatment categories (i.e., surgery, radiotherapy and systemic therapy) increased for patients diagnosed in 2020 (+6 p.p.) and 2019 (+3 p.p.) as compared to that in 2015–2018.

4. Discussion

The impact of the COVID-19 pandemic on both observed incidence and survival from malignant brain tumors in patients over 50 years in Belgium is clearly demonstrated in this study. The decreased incidence combined with the less favorable WHO performance (WHO 2–4) status at diagnosis in March–April 2020 vs. that in 2015–2019 suggests a delay in diagnosis, especially for patients with moderate to no symptoms. Unlike for some other malignancies, a delay in the diagnosis and treatment of brain tumors can be associated with a rapid deterioration of neurological function [17]. Castaño-Leon reported that one-quarter of patients experienced clinical or radiological deterioration while on a waiting list for surgery based on a multicenter study in Spain (size of study population: 680 patients) [18]. Single-center studies in Austria and China reported a larger-than-average tumor volume upon surgery during the COVID-19 pandemic, also suggesting a potential delay in diagnosis [19–21].

The worse WHO performance scores during March-April 2020 suggest that relatively more patients with severe symptoms were diagnosed during the first COVID-19 wave in Belgium. However, not only in March–April 2020, but also in most months during the pandemic, the proportion of patients with a weakened condition at diagnosis (a WHO performance score of 2–4) was higher compared to that in 2015–2019, suggesting that there has consistently been a small proportion of patients with delayed diagnosis since the start of the pandemic (Figure 3). From mid-March, all (deemed) non-essential healthcare services were temporarily halted in Belgium due to a governmental decision, limiting the accessibility of medical consultations and imaging [1]. One Belgian academic pathology department reported a reduction (although this was not statistically significant) in central nervous system (CNS) tissue samples received in March and April 2020 [1,22]. Moreover, the healthcare crisis also caused the reluctance of patients to seek medical care [4,23–26]. In addition, for patients already diagnosed, a delay in treatment and follow up amplifies the uncertainty that generally already comes with a cancer diagnosis in a normal pre-COVID-19 context [25]. As the first COVID-19 peak ended, access to healthcare was gradually restored—as in other countries—and in July 2020, a recovery phase took place [8].

The 2-year OS for malignant brain tumors diagnosed in 2020 is significantly lower compared to that in previous years (Figures 4 and 5). One factor could be that a proportion of the diagnoses were delayed [22,27]. The steep initial decrease in the OS curve in July 2020 suggests that there may be a relation between delayed diagnoses and impacted survival. Another likely factor is a change in treatment strategies, as reported by others, and as some of our results also indicate [18,28]. The observed decrease in the 2-year OS, not only for patients diagnosed in March–April 2020 (i.e., a higher proportion of patients with glioblastoma and more patients with severe symptoms as quantified via the WHO performance score), but also for those diagnosed in January-February 2020, supports this hypothesis. Moreover, for patients diagnosed with glioblastoma in 2019 (the year before the beginning of the pandemic and thus patients who were partially treated or followed up during the pandemic), we also note a significantly decreased OS of −3 p.p. compared to that in 2015–2018. In 2020, the proportion of patients treated with surgery for glioblastoma was 9 p.p. lower compared to that in 2015–2018. This can probably be explained by the reduced surgical and subsequent post-surgical intensive care capacity at the pinnacle of the pandemic. Furthermore, the fact that some patients were diagnosed with a delay, i.e., in a worse condition, may have shifted decisions towards more supportive care. A survey among 15 neuro-oncology centers in the U.K. illustrates that 9% of patients with high-grade glioma, who would have been offered surgery as standard pre-COVID-19 care by the multidisciplinary board, were given a different recommendation such as radiotherapy without biopsy (4%), or supportive care (5%), because of resource and capacity restrictions. Moreover, for newly diagnosed high-grade glioma patients to be treated with chemotherapy, 30% were offered best supportive care or a delay in treatment instead [29]. It is, however, not clear whether these deviations in standard care impacted survival rates in our cohort. Norman et al. reported significantly more delays in the care and use of telehealth in a single-center cohort of neuro-oncology patients in 2020 as compared to those in 2019, but noted no differences in outcome between 2020 and 2019 [30]. Ideally, those outcomes should have been compared with the outcomes in earlier years, since for some patients diagnosed in 2019, treatment plans and clinical decision making might have been impacted by the COVID-19 pandemic in spring 2020. In this context, Bernhardt et al. proposed a set of recommendations mainly focusing on adjuvant treatments for patients with high-grade gliomas to be treated with during the healthcare crisis, such as hypofractionated radiotherapy or withholding Temozolomide in unmethylated MGMT patients [31]. It is, however, not clear to what extent these recommendations were followed in Belgium during different phases of the pandemic. However, a final factor that might have influenced survival in brain tumor patients is an intercurrent COVID-19 infection causing a delay in or suspension of treatment, or even death [21,32].

In an earlier study of the Belgian Cancer Registry, we concluded that a substantial excess mortality was observed in the prevalent Belgian cancer cohort (diagnosed between 2013 and 2018 and alive on 1 January 2020) during the first wave of COVID-19, which, however, was not considerably different from the excess mortality in the general population [33]. Based on administrative information from reimbursement data, we found that at least 9.9% of our study population for 2020 suffered from a concomitant COVID-19 infection that was confirmed in a hospital setting during the follow up of our study. Such COVID-19 infections can have an impact on the treatment trajectories and observed survival of these patients, but we cannot draw strong causal conclusions since cause of death information obtained from death certificates was unavailable at the time of this study. Additionally, it could also be possible that some brain tumor diagnoses were not even registered due to the excess mortality caused by the COVID-19 pandemic in the general population. Based on a statistical approximation using the number of deaths of the general Belgian population in 2020, this impact was estimated to be negligible in our study population (<1 missing diagnoses) [34].

The OS of patients diagnosed with hematolymphoid malignancies involving the CNS (mainly DLBCL) in 2020 shows a substantial decrease already in the first few months after diagnosis (−16 p.p. at 6 months), and this decline grew larger in the months thereafter (to −18 p.p. at 1 year and −17 p.p. at 2 years). In addition, in 2020, the proportion of these patients receiving systemic therapy was 10% lower as compared with that in 2019. The larger decline in the OS of hematolymphoid malignancies involving the CNS (predominantly DLBCL) compared with glioblastoma could be explained by a typically higher number of hospital stays during the intensive treatment trajectory for patients diagnosed with DLBCL (treated with intravenous chemotherapy and sometimes requiring protective isolation, instead of oral Temozolomide for patients with glioblastoma). Treatments for DLBCL are thus more at risk to be affected by the immense pressure on the hospitals due to the COVID-19 outbreak. On the other hand, a subtle increase in 6-, 12-, and 18-month OS is noted for patients with DLBCL diagnosed in 2019 as compared to that in earlier years (Figure 5). This can probably be explained by scientific progress and the subsequent augmented availability of new (reimbursement) pharmaceuticals on the market [35].

A limitation of this study is the relatively small number of patients in some of the analyses, particularly for estimates of subtypes of brain malignancies and at the month level (e.g., the number of patients at risk of hematological malignancies was 58 in 2020). Secondly, information on treatment modalities is based on data extracted from the multidisciplinary oncological consult (MOC) forms. These forms allow the rapid evaluation of treatment modalities with a delay of about 6–18 months after diagnosis, yet they only provide information on treatment that is planned and/or given at the time of registration in the cancer registry, and analyses based on the data should therefore be considered as hypothesis-generating. Our results based on MOC data were, however, in line with preliminary results based on administrative information from reimbursement data. These comparisons confirmed the observed trends. However, these reimbursement data of therapeutic procedures were not fully complete at the time of analyses and no information on clinical trial treatment is available in these data. In many hospitals, inclusion in clinical trials was suspended during the pandemic, but on the other hand, very few clinical trials were open for brain tumor patients in that period. Another limitation of this study is that there are no other measures for the severity of disease (compared to other malignancies) than the diagnosed subtype and the WHO performance score. Based on our nationwide results and the limited data on neuro-oncological care access and strategies in the literature, it might be expected, however, that similar findings on survival will be observed by other cancer registries worldwide.

5. Conclusions

A clear impact on the incidence and survival of malignant brain tumors during the COVID-19 pandemic has been observed, including a significant drop in incidence rates in

April 2020 (−37%) compared to those in 2015–2019, and a significant decrease of −4 p.p. in the 2-year OS in 2020, as well as in 2019 (−3 p.p.), compared to that in 2015–2018. This should be taken into account by authorities when implementing measures during future infectious outbreaks or other crises with an impact on health care resources. Pathways for (neuro)-oncological care should be continued, and if necessary adapted, but complete suspension is not justifiable. Moreover, physicians should pro-actively develop skills, flows, and frameworks for shared and broadly informed decision making when the capacity for conventional care is impacted.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cancers16010063/s1. Table S1: Included ICD-0-3 codes for data extraction from the BCR database.

Author Contributions: Conceptualization, T.T., D.V. and L.V.E.; data curation, T.T., D.V., H.M.P., J.B., G.S., F.V. and C.D.G.; formal analysis, T.T. and D.V.; methodology, T.T., D.V., H.M.P., J.B., G.S., F.V. and C.D.G.; supervision, L.V.E.; validation, L.V.E.; visualization, T.T., H.M.P., J.B., G.S., F.V. and C.D.G.; writing—original draft, T.T. and D.V.; writing—review and editing, T.T., D.V., T.B., S.D.V., H.M.P., J.B., G.S., F.V., C.D.G. and L.V.E. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Ethical Committee approval for this study was not necessary, based on the following facts: This study was performed within the legal framework of the Belgian Cancer Registry (BCR). Based on the Coordinated Law of 10 May 2015 (art. 138); BCR has a legal task to collect data on cancer, subject it to quality control, process and analyze it, encrypt and store it, report on it, make it accessible for research, and protect it. Its activities are monitored and evaluated by the Advisory Committee of Users, an independent committee whose duly qualified members are appointed by law. 2. This retrospective study does not fall under the Belgian Law of 7 May 2004 regarding experiments on human persons (art. 3, §2). The research on human data for this study were obtained in compliance with the general principles of the Helsinki Declaration and applicable national guidelines.

Informed Consent Statement: The data controller shall be exempt from the obligation to disclose information to the persons whose data are processed (and to collect their consent) where a notification to the data subject is impossible or takes disproportionate effort, and in particular when data are processed for statistical purposes or for historical or scientific research (see. Art. 14.5, b. GDPR EU 2016/67).

Data Availability Statement: The cancer cohort data used and analyzed during the study are available upon reasonable request and those seeking them should be directed to info@kankerregister.org. The pseudonymized data can be provided within the secured environment of the Belgian Cancer Registry after having been guaranteed that the applicable GDPR regulations are applied.

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Conflicts of Interest: SDV is a certified Gliolan (Medac GmbH, Wedel, Germany) Trainer and has been involved in consultancy for Lamepro NV (currently Pharmanovia, CZ Breda, The Netherlands) (Gliolan), for which a fee was received. None of the other authors have any relevant financial or non-financial interests to disclose.

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Colorectal Cancer Survival in German–Danish Border Regions—A Registry-Based Cohort Study

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Simple Summary: This study reports updates on colon and rectum cancer survival differences in the German–Danish border region and investigates the effects of tumor stage at diagnosis and first-line treatment on cancer survival. Based on cancer registry data from 2004 to 2016, we estimated the risk of dying from all causes after a colon or rectum cancer diagnosis while also controlling for stage and treatment. We observed that colon and rectum cancer survival improved in the entire German–Danish border region, but much more in the Danish regions. At first, colon and rectal cancer survival was higher on the German side of the border, but the Danish regions caught up. In the end, colon cancer survival was similar across the border and rectal cancer survival was better in Denmark. Stage and treatment could not explain the observed survival differences. Health care reforms and early detection strategies may also contribute to the regional differences.

Abstract: The aim of this study was (i) to update the reporting of colorectal cancer survival differences over time in the German–Danish border region (Schleswig-Holstein, Southern Denmark, and Zealand) and (ii) to assess the extent to which it can be explained by stage and primary treatment. Incident invasive colorectal cancer cases diagnosed from 2004 to 2016 with a follow-up of vital status through 31 December 2017 were extracted from cancer registries. Analyses were conducted by anatomical subsite and for four consecutive periods. Kaplan–Meier curves and log-rank tests were computed. Cox regression models using data from Schleswig-Holstein from 2004 to 2007 as the reference category were run while controlling for age, sex, stage, and treatment. The cox regression models showed decreasing hazard ratios of death for all three regions over time for both anatomical subsites. The improvement was stronger in the Danish regions, and adjustment for age, sex, stage, and treatment attenuated the results only slightly. In 2014–2016, colon cancer survival was similar across regions, while rectal cancer survival was significantly superior in the Danish regions. Regional survival differences can only partially be explained by differing stage distribution and treatment and may be linked additionally to healthcare system reforms and screening efforts.

Keywords: colorectal neoplasm; radiotherapy; chemotherapy; surgery; neoplasm staging; Kaplan–Meier estimate; proportional hazard models; health care quality; benchmarking

1. Introduction

Colorectal cancer is the third most common cancer and the second most common cause of cancer death among men and women worldwide [1]. In Europe, diverse incidence and mortality trends were observed and linked to the varying implementation of screening programs [2], while survival has generally tended to improve [3]. Denmark was known for a lower colorectal cancer survival compared to the other Nordic countries and its neighboring country Germany, but remarkable improvements on the national level have been observed [3–6].

International population-based studies with data from cancer registries such as EUROCARE [7] and CONCORD [8] compared cancer survival across countries and continents

for the past decades [3,9–11]. The latest CONCORD-3 study included German and Danish cancer registry data and reported survival differences between the countries for colon cancer up until 2014 with a significantly higher relative survival in Germany. Rectal cancer relative survival was reported to be higher in Germany up until 2009. As of 2010–2014, a significantly higher relative survival was reported for rectal cancer in Denmark when compared to Germany. However, the study results are limited by the lack of information about tumor stage as TNM and treatment as major prognostic factors for cancer survival [3]. Within the CONCORD protocol, a high-resolution study on colorectal cancer survival was conducted and clinical data about Dukes' staging and treatment were successfully collected from seven US registries and nine European countries, but Danish and German data were not included [12].

Meaningful cancer survival comparisons based on German and Danish cancer registry data including tumor stage and treatment are, however, feasible as shown for colorectal cancer [13] and breast cancer [14] with data from 2004–2010 and 2004–2013, respectively. Both countries feature universal health care systems, but these differ substantially in terms of access to specialized care (gatekeeper function of Danish general practitioners versus free choice of physicians in Germany), the implementation of early detection programs, and treatment capacities [15]. It is crucial to take tumor stage (as indicator for early detection) and treatment into account when comparing cancer survival across different health care systems.

The cross-border collaboration in cancer research and care between the German federal state Schleswig-Holstein and the two bordering Danish regions, Southern Denmark and Zealand, was already established in 2007 [16] and has expanded since. The present study aims (i) to update the reporting of colorectal cancer survival differences over time in the German–Danish border region and (ii) to assess the extent to which they can be explained by tumor stage at diagnosis and type of primary treatment.

2. Materials and Methods

Incident invasive colorectal cancer cases (International Classification of Diseases (ICD)-10: C18-C20) from 2004 to 2016 with follow-up of vital status through 31 December 2017 were extracted from the population-based Schleswig-Holstein Cancer Registry and for the Danish regions of Southern Denmark and Zealand from the files created for the Nordic cancer statistics database NORDCAN [17] prior to de-identification. The Danish NORDCAN-data were supplemented with treatment information from the Danish Inpatient Hospital Register and death notifications were obtained from the National Population Register. The Danish databases used record linkage via unique personal identification numbers assigned to every resident in Denmark. In the Schleswig-Holstein cancer registry, probabilistic record linkage [18] is used for linking both death notifications from the residents' registration office and original death certificates to the cancer registry. Data were coded according to the ENCR-JRC 2015 data call protocol [19], and IACR/IARC-rules were applied in handling multiple primaries [20]. The data sets were merged, and a common database for analysis was constructed. The joint database contained information on diagnosis (ICD-10), month and year of birth, incidence, last known vital status, number of days of survival from incidence to death or end of follow-up by end of 2017 or last known vital status (death, immigration, or end of follow-up), sex, age at diagnosis, basis of diagnosis, topography, morphology, behavior, incidental finding of cancer at autopsy, TNM classification, TNM stage grouping, and primary treatment (surgery, radiotherapy, and systemic therapy (including chemotherapy, targeted therapy, immunotherapy, and hormone therapy) recorded as yes/no/unknown). The TNM classification and staging are based on both clinical and pathological information. In the Schleswig-Holstein Cancer Registry, pTNM is used whenever it is available, while cTNM is used only if pTNM is incomplete or not reported. In Denmark, the highest T, N, and M from either clinical or pathological TNM are chosen from the hospital records within the first 4 months after diagnosis. Information on the year of diagnosis was grouped into four periods (2004–2007, 2008–2010, 2011–2013,

2014–2016) to identify time trends in survival and increase the statistical power of regional estimates. All treatment variables were dichotomized, with categories "no" and "unknown" being pooled into one category. The German treatment variables contain information on the first-line treatments administered to patients, which is usually completed six to nine months after diagnosis. The Danish treatment variables contain treatment administered until six months after diagnosis as registered in the Danish Inpatient Hospital Register.

Cases notified by death certificates only (DCO), age at diagnosis of 90+ years, and incidental findings of cancer at autopsy were excluded from the analyses. DCO-cases and incidental findings of cancers at autopsy were excluded from survival analysis because a reliable incidence date and thus the length of survival was unknown for these cases. Moreover, stage and treatment were unknown for DCO-cases and incidental findings at autopsy. Individuals aged 90 years or older at diagnosis were excluded from analysis because it was expected that diagnostic and treatment rates were lower in this age group. Analyses were conducted for the anatomical subsites colon (ICD-10: C18) and rectum (IDC-10: C19-20) and for four consecutive periods (2004–2007, 2008–2010, 2011–2013, 2014–2016) separately. Frequencies and proportions of the main characteristics of the study population were used for descriptive analyses. Survival time was defined as the time interval between the date of incidence as the entry date and the date of death as the exit date. Patients with vital status alive at the end of follow-up on 31 December 2017 were censored at that date. The outcome of interest was all-cause mortality since diagnosis. The overall survival of colon and rectal cancer patients in the three project regions was calculated using the Kaplan–Meier method, and curves were plotted accordingly. Log-rank tests were conducted to test for significant survival differences between the regions. The regions were compared pairwise. Whether the underlying assumption of proportional hazards for Cox regression was met was assessed through visual inspection of the Kaplan–Meier curves. Multivariate Cox regression models using data from Schleswig-Holstein from 2004 to 2007 as the reference category were applied to calculate hazard ratios of death from all causes while controlling for age, sex, stage, and treatment for each region and period. Missing values in covariates were included as a separate category in all analyses and entered into the models. Results were considered statistically significant when $p < 0.05$. Analyses were conducted using IBM SPSS Statistics 22.

3. Results

In total, 35,279 colon cancer cases (Schleswig-Holstein (SH): n = 20,086; Southern Denmark (SD): n = 8638; Zealand (ZL): n = 6555) and 18,280 rectal cancer cases (SH: n = 10,455; SD: n = 4480; ZL: n = 3345) were reported to the cancer registries between 2004 and 2016. After exclusion of DCO-cases, incidental findings at autopsy, and patients aged 90 years and older at diagnosis, 32,067 colon (SH: n = 17,453; SD: n = 8290; ZL: n = 6324) and 17,172 rectal cancer cases (SH: n = 9554; SD: n = 4342; ZL: n = 3276) were included in the survival analysis. The proportion of DCO-cases was higher in Schleswig-Holstein (colon: 10.4%; rectum: 6.7%) than in the Danish regions (colon: 1.0%; rectum: 0.4%) (Table 1).

3.1. Stage Distribution

The stage distribution appeared to be more favorable in Schleswig-Holstein for both colon and rectum cancer. However, there was a shift toward earlier stages in the Danish regions in the latest observation period, 2014–2016. The majority of colorectal cancer cases with known stage were diagnosed in advanced stages III–IV in all three regions. In Schleswig-Holstein, the proportion with available stage information increased over time, while the inverse trend was observed in both Danish regions (Figure 1).

Table 1. Derivation of analytical sample based on registered colon cancer cases (C18) and rectal cancer cases (C19–C20) in Schleswig-Holstein and the Danish regions of Southern Denmark and Zealand, 2004–2016.

	Schleswig-Holstein		Southern Denmark		Zealand	
	Colon	Rectum	Colon	Rectum	Colon	Rectum
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
2004–2007						
Patients in cancer register	6192 (100.0)	3386 (100.0)	2280 (100.0)	1302 (100.0)	1698 (100.0)	987 (100.0)
Death certificates only (DCO)/incidental finding at autopsy *	537 (8.7)	191 (5.6)	30 (1.3)	9 (0.7)	20 (1.2)	8 (0.8)
Age 90+ at diagnosis *	305 (4.9)	125 (3.7)	75 (3.3)	38 (2.9)	40 (2.4)	19 (1.9)
Included in survival analysis	5475 (88.4)	3116 (92.0)	2178 (95.5)	1255 (96.4)	1639 (96.5)	960 (97.3)
2008–2010						
Patients in cancer register	4781 (100.0)	2423 (100.0)	1808 (100.0)	957 (100.0)	1494 (100.0)	751 (100.0)
Death certificates only (DCO)/incidental finding at autopsy *	549 (11.5)	173 (7.1)	12 (0.7)	5 (0.5)	14 (0.9)	0 (0.0)
Age 90+ at diagnosis *	208 (4.4)	59 (2.4)	67 (3.7)	25 (2.6)	34 (2.3)	7 (0.9)
Included in survival analysis	4134 (86.5)	2219 (91.6)	1730 (95.7)	928 (97.0)	1449 (97.0)	744 (99.1)
2011–2013						
Patients in cancer register	4532 (100.0)	2335 (100.0)	2025 (100.0)	1065 (100.0)	1486 (100.0)	706 (100.0)
Death certificates only (DCO)/incidental finding at autopsy *	508 (11.2)	171 (7.3)	17 (0.8)	4 (0.4)	14 (0.9)	2 (0.3)
Age 90+ at diagnosis *	234 (5.2)	91 (3.9)	57 (2.8)	28 (2.6)	43 (2.9)	12 (1.7)
Included in survival analysis	3909 (86.3)	2114 (90.5)	1952 (96.4)	1034 (97.1)	1433 (96.4)	692 (98.0)
2014–2016						
Patients in cancer register	4581 (100.0)	2311 (100.0)	2525 (100.0)	1156 (100.0)	1877 (100.0)	901 (100.0)
Death certificates only (DCO)/incidental finding at autopsy *	494 (10.8)	161 (7.0)	23 (0.9)	1 (0.1)	23 (1.2)	2 (0.2)
Age 90+ at diagnosis *	289 (6.3)	78 (3.4)	76 (3.0)	30 (2.6)	55 (2.9)	19 (2.1)
Included in survival analysis	3935 (85.9)	2105 (91.1)	2430 (96.2)	1125 (97.3)	1803 (96.1)	880 (97.7)
2004–2016						
Patients in cancer register	20,086 (100.0)	10,455 (100.0)	8638 (100.0)	4480 (100.0)	6555 (100.0)	3345 (100.0)
Death certificates only (DCO)/incidental finding at autopsy *	2088 (10.4)	696 (6.7)	82 (0.9)	19 (0.4)	71 (1.1)	12 (0.4)
Age 90+ at diagnosis *	1036 (5.2)	353 (3.4)	275 (3.2)	121 (2.7)	172 (2.6)	57 (1.7)
Included in survival analysis	17,453 (86.9)	9554 (91.4)	8290 (96.0)	4342 (96.9)	6324 (96.5)	3276 (97.9)

* Sources: Includes also 90+ DCO cases.

3.2. Treatment Patterns

In all regions, surgery was the most frequently performed therapy among colon cancer patients, while radiotherapy was fairly uncommon. The proportion of colon cancer patients receiving systemic therapy increased until 2013 and decreased thereafter. More colon cancer patients received systemic therapy in Southern Denmark (35.2%) and Zealand (43.3%) than in Schleswig-Holstein (25.2%). Among rectal cancer patients, surgery was also the most commonly performed therapy in all regions. Radiotherapy was given to roughly a quarter to one third of the rectal cancer patients. The administration of radiotherapy seemed to decline in the Danish regions, while the proportion of patients receiving systemic therapy increased. In Schleswig-Holstein, the proportion of rectal cancer patients receiving radiotherapy or systemic therapy remained constant (Table 2).

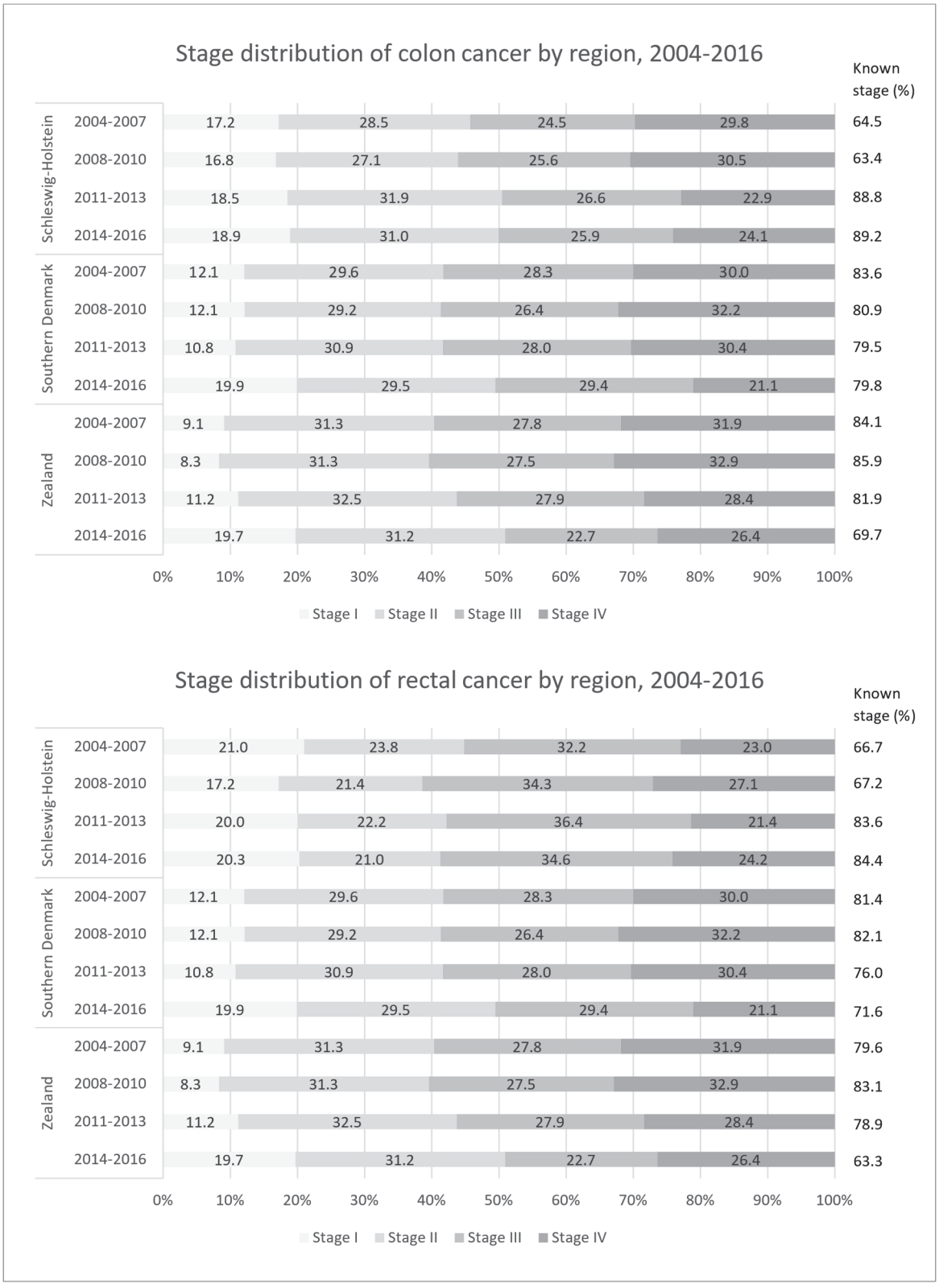


Figure 1. Stage distribution of the included colon and rectal cancer patients for the regions of Schleswig-Holstein, Southern Denmark, and Zealand in 2004–2016.

Table 2. Recorded treatment for colon cancer and rectal cancer for included patients in Schleswig-Holstein, Southern Denmark, and Zealand, 2004–2016.

	Schleswig-Holstein		Southern Denmark		Zealand	
	Colon	Rectum	Colon	Rectum	Colon	Rectum
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
2004–2007						
Surgery	4571 (83.5)	2417 (77.6)	1835 (84.3)	995 (79.3)	1295 (79.0)	735 (76.6)
Radiotherapy	115 (2.1)	1051 (33.7)	27 (1.2)	340 (27.1)	15 (0.9)	246 (25.6)
Systemic therapy	1330 (24.3)	1294 (41.5)	593 (27.2)	446 (35.5)	571 (34.8)	370 (38.5)
No treatment/Missing	859 (15.7)	560 (18.0)	232 (10.7)	114 (9.1)	219 (13.4)	113 (11.8)
2008–2010						
Surgery	3437 (83.1)	1725 (77.7)	1430 (82.7)	725 (78.1)	1099 (75.8)	535 (71.9)
Radiotherapy	62 (1.5)	730 (32.9)	22 (1.3)	313 (33.7)	22 (1.5)	207 (27.8)
Systemic therapy	1073 (26.0)	983 (44.3)	636 (36.8)	464 (50.0)	657 (45.3)	391 (52.6)
No treatment/Missing	649 (15.7)	357 (16.1)	173 (10.0)	66 (7.1)	168 (11.6)	59 (7.9)
2011–2013						
Surgery	3166 (81.0)	1607 (76.0)	1574 (80.6)	795 (76.9)	1142 (79.7)	517 (74.7)
Radiotherapy	49 (1.3)	697 (33.0)	30 (1.5)	335 (32.4)	24 (1.7)	165 (23.8)
Systemic therapy	1081 (27.7)	952 (45.0)	791 (40.5)	512 (49.5)	679 (47.4)	392 (56.6)
No treatment/Missing	667 (17.1)	400 (18.9)	191 (9.8)	75 (7.3)	138 (9.6)	51 (7.4)
2014–2016						
Surgery	3137 (79.7)	1496 (71.1)	1968 (81.0)	852 (75.7)	1488 (82.5)	671 (76.3)
Radiotherapy	49 (1.2)	680 (32.3)	27 (1.1)	270 (24.0)	27 (1.5)	177 (20.1)
Systemic therapy	916 (23.3)	864 (41.0)	902 (37.1)	487 (43.3)	771 (42.8)	425 (48.3)
No treatment/Missing	692 (17.6)	424 (20.1)	253 (10.4)	94 (8.4)	155 (8.6)	71 (8.1)
2004–2016						
Surgery	14,311 (82.0)	7245 (75.8)	6807 (82.1)	3367 (77.5)	5024 (79.4)	2458 (75.0)
Radiotherapy	275 (1.6)	3158 (33.1)	106 (1.3)	1258 (29.0)	88 (1.4)	795 (24.3)
Systemic therapy	4400 (25.2)	4093 (42.8)	2922 (35.2)	1909 (44.0)	2678 (42.3)	1578 (48.2)
No treatment/Missing	2867 (16.4)	1741 (18.2)	849 (10.2)	349 (8.0)	680 (10.8)	294 (9.0)

The stratification of administered treatment by stage showed that treatment for stage I colon cancer was similar in all regions. Among stage II and stage III colon cancers, an increased use of systemic therapies in the Danish regions was observed, while it decreased in Schleswig-Holstein. The treatment choices for stage IV colon cancers varied largely between regions. In Schleswig-Holstein, surgery was the most frequently performed procedure and less common in the Danish regions, while systemic therapies were frequently applied in the Danish region and were less common in Schleswig-Holstein. For rectal cancers, treatment choices were similar across regions for stage I cancers, but differences emerged with advancing stages. Radiotherapy was performed more frequently in Schleswig-Holstein than in the Danish regions among stage II and stage III rectal cancers. Among stage IV rectal cancers, surgery was more often performed in Schleswig-Holstein than in the Danish regions, while systemic therapies were administered more frequently in the Danish regions (Figure 2).

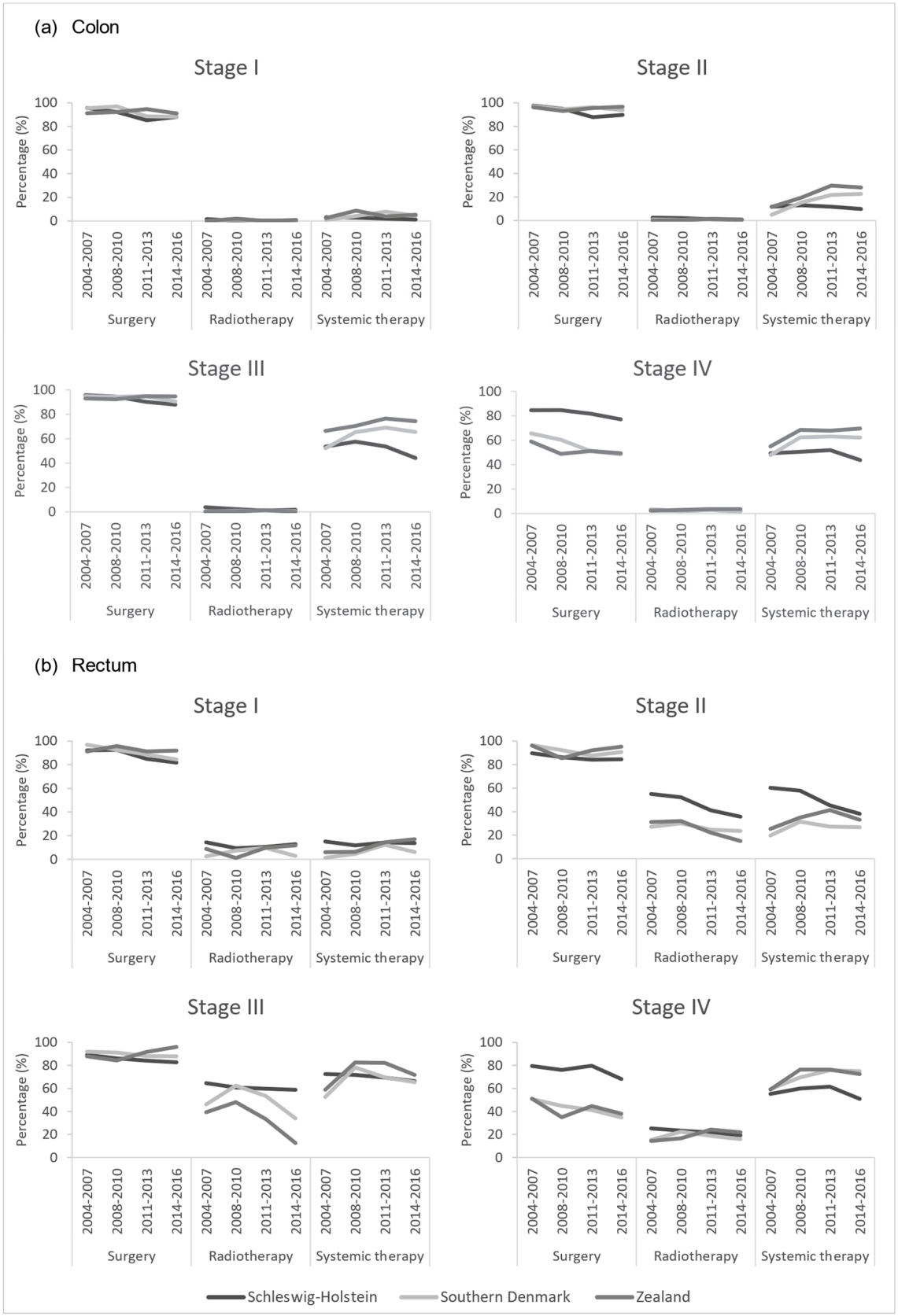
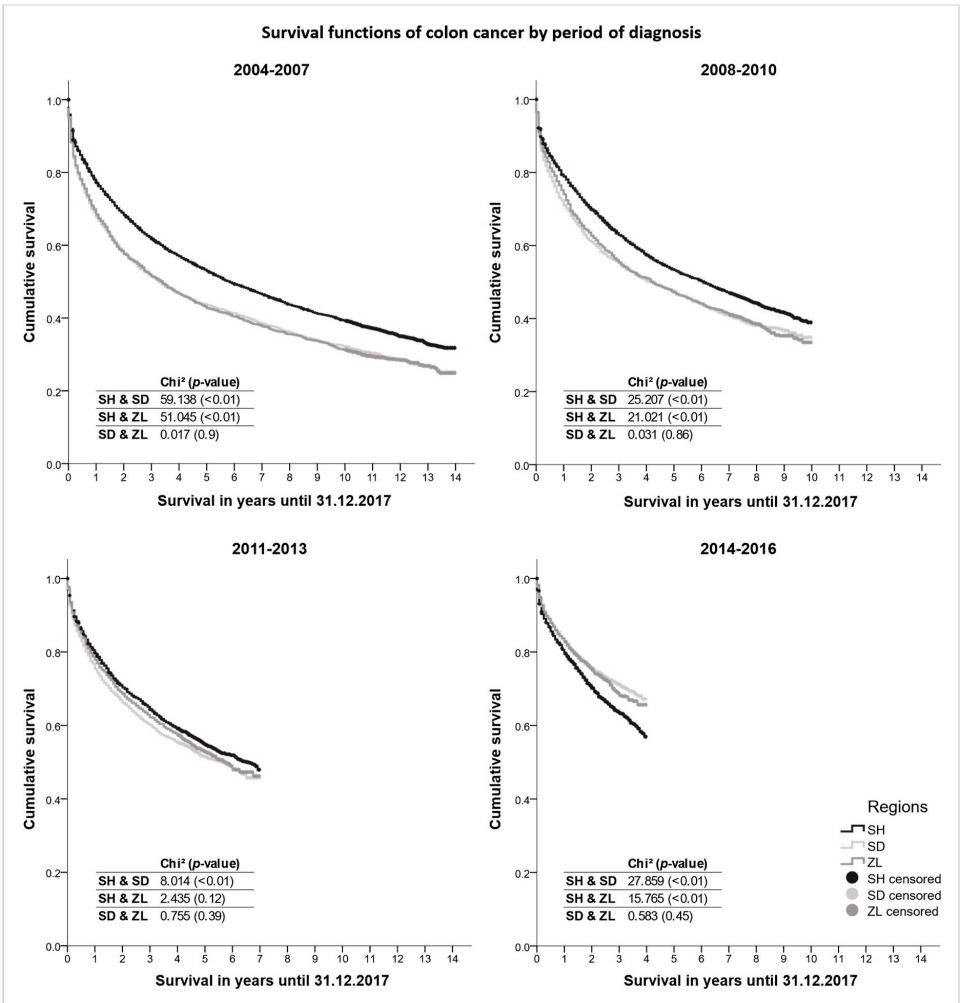


Figure 2. Cancer treatment stratified by stage for colon and rectal cancer in the project regions, 2004–2016.

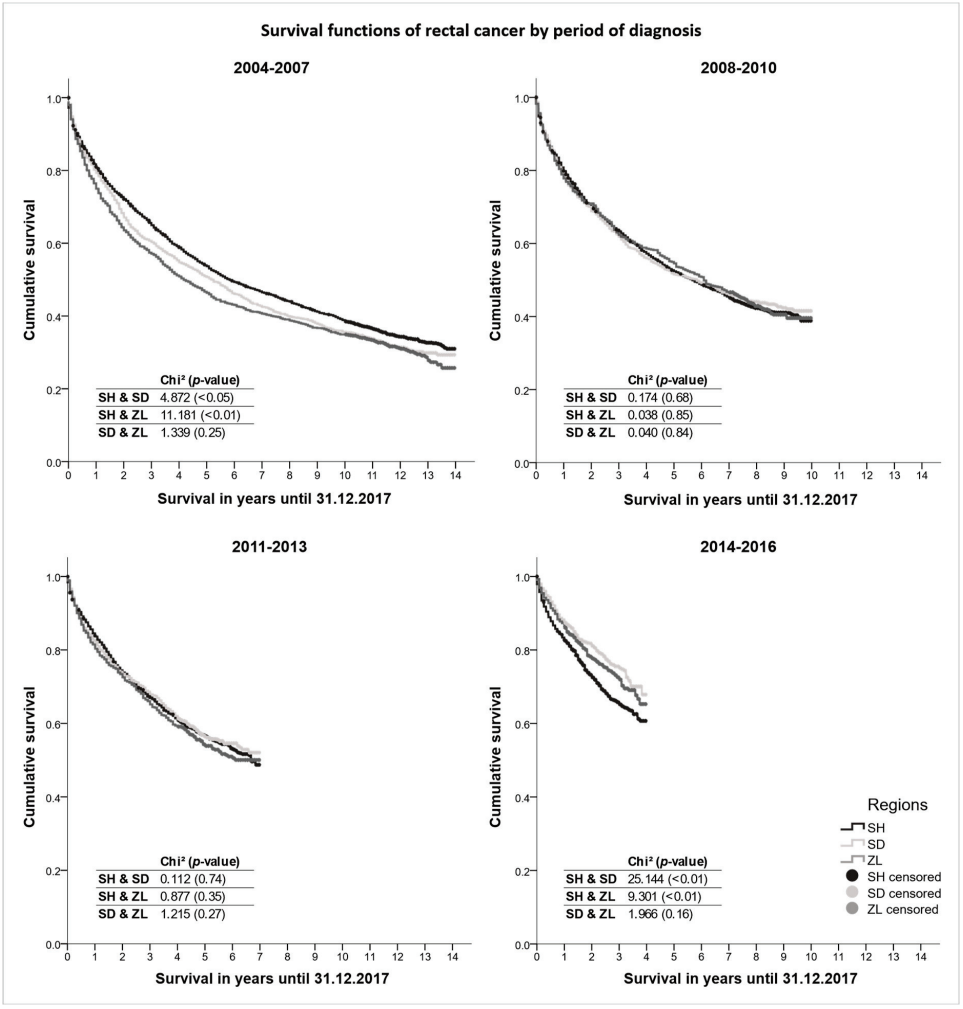
3.3. Survival Differences

The Kaplan–Meier survival functions and log rank tests showed, for both colon (Figure 3a) and rectal cancer (Figure 3b), a significantly higher absolute overall survival in Schleswig-Holstein at the beginning of the observation period (2004–2007, and 2008–2010 also for colon) compared to the Danish regions, diminishing survival differences between the three regions in the middle of the observation period, and significantly higher absolute overall survival in the Danish regions in the most recent period (2014–2016). Absolute overall survival improved rapidly in Southern Denmark and Zealand, but small improvements were also observed in Schleswig-Holstein. For colon cancer, the 1/5/10-year absolute survival probability improved in Southern Denmark from 0.68/0.44/0.32 for those diagnosed in 2004-07 to 0.83 (2014-16)/0.52 (2011-13)/0.35 (2008-10) and in Zealand from 0.69/0.43/0.31 in 2004-07 to 0.83 (2014-16)/0.53 (2011-13)/0.33 (2008-10), while it slowly increased in Schleswig-Holstein from 0.77/0.53/0.39 in 2004-07 to 0.80 (2014-16)/0.55 (2011-13)/0.39 (2008-10), respectively. For rectal cancer, very similar trends were observed. The 1/5/10-year absolute rectal cancer survival improved from 0.79/0.51/0.35 among cases diagnosed in 2004-07 to 0.88 (2014-16)/0.57 (2011-13)/0.42 (2008-10) in Southern Denmark and from 0.75/0.46/0.35 in 2004-07 to 0.80 (2014-16)/0.54 (2011-13)/0.40 (2008-10) in Zealand, while Schleswig-Holstein reported increases from 0.81/0.54/0.39 in 2004-07 to 0.83 (2014-16)/0.57 (2011-13)/0.40 (2008-10), respectively (Supplementary Table S1).



(**a**)

Figure 3. *Cont.*

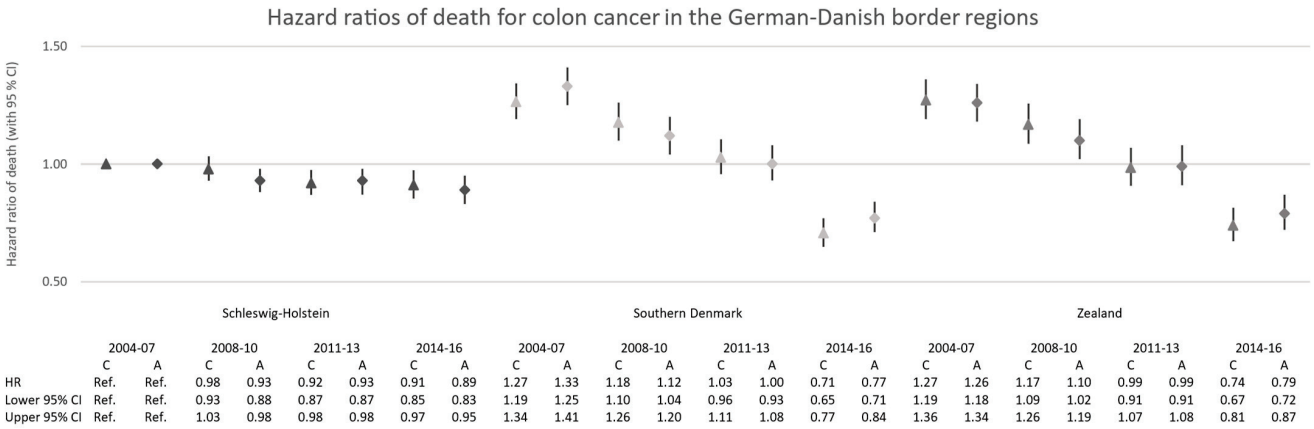


(**b**)

Figure 3. (**a**) Kaplan–Meier curves depicting the colon cancer survival in Schleswig-Holstein, Southern Denmark, and Zealand stratified by period of diagnosis. (**b**) Kaplan–Meier curves depicting the rectal cancer survival in Schleswig-Holstein, Southern Denmark, and Zealand stratified by period of diagnosis.

The cox regression models using Schleswig-Holstein's colon and rectal cancer cases from 2004 to 2007 as the reference category showed decreasing hazard ratios (HRs) of death for all three regions over time for both anatomical subsites (Figure 4).

For cancer patients from Schleswig-Holstein, the crude HR of death decreased to 0.91 (95% CI: 0.85; 0.97) for colon cancer and 0.93 (95% CI: 0.85; 1.02) for rectal cancer in 2014–2016 when compared to 2004–2007. The positive trend is much more prominent in the Danish regions. Though cancer patients residing in Southern Denmark experienced significantly higher crude HRs of death for colon cancer (HR: 1.27, 95% CI: 1.19; 1.34) and rectal cancer (HR: 1.09, 95% CI: 1.01; 1.19) after diagnosis in 2004–2007 when compared to Schleswig-Holstein in the same period, a decreasing trend was observed over the observation time, resulting in significantly lower crude HRs of death for colon cancer (HR: 0.71, 95% CI: 0.65; 0.77) and rectal cancer (HR: 0.64, 95% CI: 0.56; 0.73) in 2014–2016. Similar observations were made for Zealand, where the HR of death started significantly higher for both colon cancer (HR: 1.27, 95% CI: 1.19; 1.36) and rectal cancer (HR: 1.16, 95% CI: 1.06; 1.27) in 2004–2007 in comparison to Schleswig-Holstein and resulted in a significantly lower HR of death for colon cancer (HR: 0.74, 95% CI: 0.67; 0.81) and rectal cancer (HR: 0.73, 95% CI: 0.64; 0.84) in 2014-16.



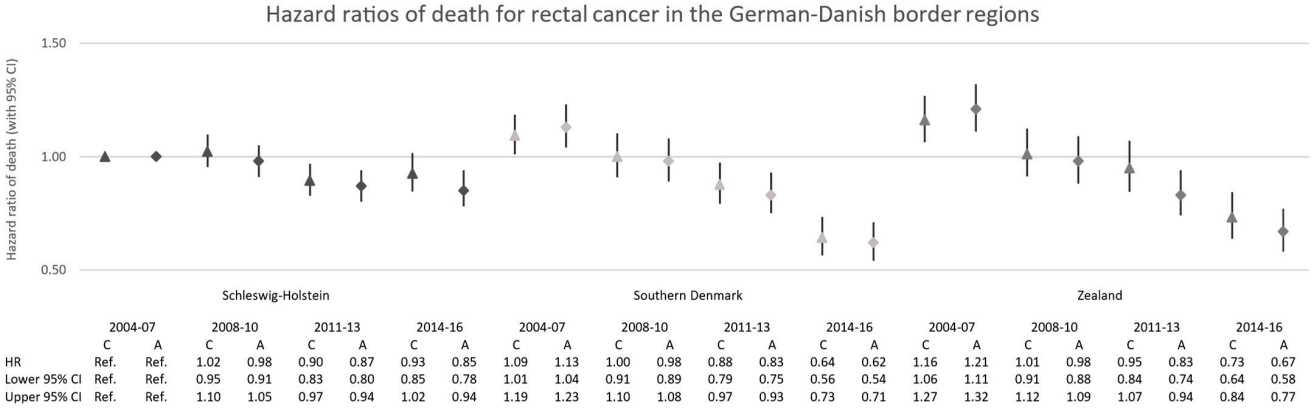


Figure 4. Crude (C) and fully adjusted (A) hazard ratios of death for colon cancer and rectal cancer in Schleswig-Holstein, Southern Denmark, and Zealand compared to cases diagnosed in 2004–2007 in Schleswig-Holstein.

After adjustment for age at diagnosis, sex, stage, surgery, radiotherapy, and systemic therapy, the observed regional differences between Schleswig-Holstein and the two Danish regions Southern Denmark and Zealand changed only slightly. The HR of death for colon cancer and rectal cancer patients in Southern Denmark and Zealand remained significantly higher after complete adjustment at the beginning of the observation period of 2004-07. In the latest observation period of 2014-16, all three regions showed a significantly lower fully adjusted HR of death for colon cancer (Schleswig-Holstein: HR: 0.89, 95% CI: 0.83; 0.95, Southern Denmark: HR: 0.77, 95% CI: 0.71; 0.84, Zealand: HR: 0.79, 95% CI: 0.72; 0.87) and rectal cancer (Schleswig-Holstein: HR: 0.85, 95% CI: 0.78; 0.94, Southern Denmark: HR: 0.62, 95% CI: 0.54; 0.71, Zealand: HR:0.67, 95% CI: 0.58; 0.77) when compared to Schleswig-Holstein in 2004-07. The regional comparison showed overlapping confidence intervals of the fully adjusted HR for colon cancer among the three regions in the most recent observation period, which indicated no significant survival differences after taking age, sex, stage, and treatment into account, while significantly better HRs were still reported for rectal cancer in the Danish regions after complete adjustment.

4. Discussion

This study is, to our knowledge, the first to examine colorectal cancer survival using additional clinical treatment information on the use of surgery, radiotherapy, and systemic therapy in the entire German–Danish border region including for the first time the Danish region of Southern Denmark.

We observed a more favorable stage distribution in Schleswig-Holstein than in Denmark for both cancer sites in 2004–2007, but the proportion of early-stage (TNM stage I + II) colorectal cancer cases increased in the Danish regions in the latest observation period, showing a similar stage distribution to Schleswig-Holstein (Figure 1). The treatment of early-stage colorectal cancer patients was similar across the regions. In the Danish regions, we observed an increase in the use of systemic therapies among colon cancer patients in stages II–IV, exceeding the proportions in Schleswig-Holstein. However, among Danish rectal cancer patients, radiotherapy appears to be less common for stage I–III. Regarding the treatment of stage IV colorectal cancer patients, considerable cross-border differences became apparent. Surgery was more commonly performed among advanced colorectal cancer patients in Schleswig-Holstein, while in the Danish regions, systemic therapies were given more commonly (Figure 2). Multivariate cox regression models showed decreasing hazard ratios of death for all regions in all periods for both colon and rectal. However, survival differences were observed. At the beginning of the observation period (2004–2007), a higher survival was observed in Schleswig-Holstein, but over the course of the observation period, the Danish regions overtook and, in the most recent period (2014–2016), the survival was higher in the Danish regions (Figure 3a,b). Age at diagnosis, sex, stage, surgery, radiotherapy, and systemic therapy could only explain the regional survival differences partially (Figure 4).

The continued positive trend of improving overall colorectal cancer survival in all German–Danish border regions is in line with previous studies. Improving (relative) survival and shrinking survival differences were reported for Germany and Denmark on the national level [3]. The magnitude of improvement was also indicated on the national level, showing steep increases in colorectal cancer survival in Denmark [3–6], while it stagnated in Germany [3]. A study by Storm et al. examined the relative survival on the regional level for Schleswig-Holstein and the Danish region of Zealand for the periods of 2004–2006 and 2007–2009 and reported superior relative colorectal cancer survival for Schleswig-Holstein, improvements in both regions, and diminishing survival differences especially for rectal cancer [13]. Our findings corroborated these trends on the regional level and seamlessly continued the positive development. The results confirmed the now-statistically significant, better rectal cancer survival after adjustment for various prognostic factors on the Danish side of the border and showed no significant survival differences among colon cancer patients in the German–Danish border region anymore.

The present study covers an observation period of more than a decade, during which scientific advances drove major innovation in clinical oncology and led to changes in health care policies. The exact causes for regional differences and trends in survival cannot be deduced from the present study data, but there are several possible explanations for the observed differences and trends, which may be linked to secondary prevention (early detection), novel therapies, and health care system reforms.

4.1. Secondary Prevention for Early Detection

Colorectal cancer screening is a proven public health strategy for early detection, which effectively reduces mortality [21]. A variety of screening tools is available covering stool-based tests (e.g., guaiac-based or immunochemical fecal occult blood test (gFOBT or iFOBT/FIT)) and visual inspection (e.g., computed tomography colonography (CTC), colonoscopy) [22]. While the gFOBT has nowadays been widely replaced by the improved iFOBT/FIT because of its higher sensitivity, visual inspection via colonoscopy remains the most effective tool for reducing colorectal cancer mortality [21,22].

In Germany, an opportunistic colonoscopy screening was introduced in 2002 and, ever since, mortality reductions of 2.6% for men and 3.1% for women were observed [2]. It probably had an impact on the slight but steady improvement in colorectal cancer survival on the German side of the border and might also explain the stage differences observed in 2004 to 2007 between Germany and Denmark. Denmark, however, caught up in terms of early detection and implemented an organized colorectal cancer screening based on

the fecal immunochemical test (FIT) in 2014, which led to a mortality reduction in older men with a colorectal cancer diagnosis [23]. We also observed a stage shift toward earlier stages in the latest observation period in 2014 to 2016 in the Danish regions and no relevant remaining stage differences in comparison to Schleswig-Holstein, which may be attributed to the FIT-screening.

4.2. Therapeutic Advances

Surgical resection of the malignant tumor and, in advanced stages, the combination with chemotherapy are the cornerstones of colorectal cancer treatment [24]. Over the past decades, existing chemotherapy regimens were improved by adding new agents to the scheme [25,26], or completely new treatment strategies such as gene therapy, targeted therapy or immunotherapy were developed [24]. These novel approaches significantly improved the survival time of colorectal cancer patients, especially among those with advanced stages [24–27].

Germany is known for a short time to patient access after European Medicines Agency (EMA) approval of new oncological drugs [28]. The fast adoption of novel treatment options may be reflected in the moderate survival improvement in Schleswig-Holstein. The significantly lower survival in the past reported for Denmark may be indicative of the delayed uptake of these new therapies and delayed patient access. Nowadays, however, Denmark is among the fastest adopting countries in Europe [29].

In addition to the accelerated uptake of new oncological drugs, the surgical management of colorectal cancer was improved in Denmark. Laparoscopic surgery was introduced in the early 2000s and, subsequently, the 30-day postoperative mortality after elective major surgery for colorectal cancer decreased significantly from 7.3% in 2001–2002 to 2.8% in 2011 [30].

4.3. Health Care System Reforms in Denmark

The steep improvements observed in the Danish regions most likely can be linked to a variety of health care reforms. So-called "National Cancer Plans" were implemented and regularly expanded since 2000 [31–35]. While the first National Cancer Plan focused on capacity building for more rapid diagnosis and surgical treatment [32], the second cancer plan introduced patient pathways to accelerate diagnosis and treatment start [33]. The cancer patient pathways were implemented in 2007-09 in order to reduce delays in diagnosis and speed up treatment start [31] and defined a maximum waiting time for initial treatment of 28 days upon the date of referral to the hospital for treatment [36], which was proven to speed-up the diagnostic and treatment processes successfully [31,37].

4.4. Strengths and Limitations

The results also have to be discussed in the light of strengths and limitations. The large study population retrieved from cancer registries with complete registration encompassing stage and treatment data is a major strength of the present study [38–45]. Moreover, cancer registry data on colorectal cancer, including stage and treatment information from Schleswig-Holstein and the Danish region South, were merged and jointly analyzed for the first time—now encompassing the entire German–Danish border region. A limitation is the relatively high DCO-rate in Schleswig-Holstein, which may introduce a bias toward better survival [46,47] in Schleswig-Holstein. However, excluding short-term survivors (of 30 and 90 days, respectively) for sensitivity analysis did not alter the results, suggesting minimal bias (Supplement Table S2). Additionally, the high proportion of missing stage information is a potential limitation. But since the Cox regression analysis is not presented on tumor stage level and patients with missing stage are included as a separate category, the overall survival estimates are not likely to be affected. Moreover, treatment is unknown for approximately 12% of the patients, which most probably might be caused by underreporting and may lead to incomplete adjustment. As the statistical adjustment for prognostic factors for cancer survival like age, sex, stage, and treatment attenuated the results, but did not

explain the observed survival differences completely, residual confounding is likely to occur. Within the scope of this study, it is not possible to determine the extent to which the various factors discussed (secondary prevention, therapeutic advances, and health care system reforms) contributed to the survival trends. More detailed data would be needed. Unfortunately, information on additional prognostic factors such as screening participation rates, agents and doses used for treatment, socio-economic status, or comorbidities was unavailable. Considering these strengths and limitations, we judge the comparisons made and trends observed to be only marginally biased and thus meaningful.

5. Conclusions

Our study shows that colorectal cancer survival improved over time in the entire German–Danish border region, but more so in the Danish regions of Southern Denmark and Zealand. The regional survival differences can only partially be explained by differing stage distribution and treatment and may be linked additionally to health care system reforms and screening efforts. We conclude that the survival improvements observed in all three regions are likely to be true.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cancers15184474/s1, Table S1: Number of patients at risk (NaR) and absolute survival (AS) after 1, 5, and 10 years in Schleswig-Holstein, Southern Denmark, and Zealand stratified by period of diagnosis; Table S2: Cox regression models of hazard ratio (HR) of death for cancer registry data of the German-Danish border regions excluding short-term survivors (crude and adjusted for various individual and prognostic factors).

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Institutional Review Board Statement: The study was based on anonymized registry data and no contact was made to patients or treating physicians. Therefore, no vote of an ethical review board was needed.

Informed Consent Statement: Patient consent was waived because the data used in this study are routinely collected data from registries that operate on a legally binding basis and their use does not require patient consent. The data were anonymized and no patient was contacted for study purposes.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available, due to privacy restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

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Evaluation of the Slovenian Breast Cancer Screening Programme: Years of Life Gained and Avoided Deaths

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Simple Summary: Public health interventions should evaluate their effect on the population. Measuring outcomes in organized cancer screenings is not straightforward, since expected reduction in mortality has drawbacks such as long observation time, quality of data, and the relationship between the intervention and the outcome. Researchers are exploring the use of survival, which is available sooner, but has limitations such as lead time bias, length time bias, and over-detection. Slovenian researchers have used a novel approach addressing the known biases comparing the survival between invited and not-invited women and providing estimations of years of life gained and deaths avoided for an easier interpretation for policy-makers. The results show that after 10 years the invited women have a 4.3 percentage points higher survival probability than the not invited, resulting in 22 avoided deaths per 100,000, amounting to a total of 114 years of life gained. The standardized results allow cross-country comparisons.

Abstract: Background: Most commonly, mortality is used for evaluation of organized breast cancer screening programmes. Survival analyses are also being employed to provide more timely assessment. A novel approach has been introduced for calculating survival using Slovenian data. **Methods**: Breast cancer cases from the Slovenian Cancer Registry between 2008–2021 in women aged 50 to 72 were included, supplemented by data on the screening history from the screening registry. The comparison was made in two scenarios—invited or not invited to the screening. Survival, years of life gained, and number of avoided deaths over 10 years were calculated and standardized. The comparison was adjusted for confounding covariates, and a biological tumour growth model was used to adjust the survival of the invited group for lead time bias and over-detection. **Results**: A total of 9392 breast cancer cases were included in the study. Estimated median lead time for screen-detected cases was 1.23 years. The survival probability accounting for lead time bias and covariates of cancers patients invited to the programme was 4.3 percentage points higher than the not invited (0.81 vs. 0.76). Standardized to 100,000 women in the 2-year period, this would result in 22 avoided deaths. On average, the invited cancer patient lived 0.22 years longer, which amounts to a total of 114 years of life gained. **Conclusions**: The results show the overall benefit of the breast cancer screening programme. The standardized results enable cross-country comparisons. The calculation of years of life gained and avoided deaths can provide additional opportunities for communicating the results to non-expert populations.

Keywords: breast cancer; organized screening; survival analysis; years of life gained; avoided deaths

1. Introduction

Breast cancer, which is the most common cancer in women worldwide, is one of the cancers where there is enough evidence of organized screening being beneficial for women attending it, and its introduction is thus recommended [1,2]. The primary aim of screening is early detection and treatment to reduce breast cancer mortality and improve quality of life [3,4].

All screening programmes need to monitor their quality and effectiveness to ensure that healthcare resources are allocated efficiently. Most commonly, mortality is used as the primary endpoint outcome. Its major drawback is that especially in cancers with good survival, which breast cancer is, the evaluation needs decades [5]. Additionally, there is uncertainty regarding how much of the observed improvement can be attributed to screening, improvements in treatment [6–9], or other health care interventions affecting mortality due to breast cancer, along with concerns about the quality of data on causes of death [10,11]. Therefore, in the effort to obtain more timely and relevant assessment of screening effectiveness, epidemiologists can instead turn to survival analysis. However, depending on the design of the study and the choice of comparison to be studied, there are at least three biases that have been described in relation to measurement of survival as the main outcome. Lead time bias refers to the phenomenon whereby the timing of diagnosis is shifted to an earlier date, resulting in an apparent increase in survival time measured from the point of diagnosis for cases detected by screening, even if total length of life remains unchanged [12]. Length bias arises when comparing patients diagnosed based on screening with any relevant control group. It occurs because screen-detected cases do not represent a random subsample of all cases; cases with a longer pre-clinical phase are more likely to be detected than those with faster-growing tumours [12]. Finally, there is a bias due to over-detection where due to the long natural trajectory of the disease some of the lesions detected by the screening programme would not cause any cancer symptoms in the course of the individual's lifetime or would not be observed during the study period. Thus, the true benefit of identifying such pre-clinical lesions through screening may be much smaller than is perceived [12]. Many approaches have already been suggested to correct for different biases [13–21]. Further possibilities of how to minimize the biases when comparing survival probabilities related to organized screening are being explored. Recently, Vratanar and Pohar Perme introduced a novel approach that helps in addressing all of the aforementioned biases and hence provides a more accurate and fair estimation of survival [22].

In Slovenia, the national organized breast cancer screening programme was launched in 2008, inviting women between 50 and 69 years old to digital mammography screening every two years, with all procedures established according to European guidelines for quality assurance in breast cancer screening and diagnosis. Initially, the organized breast cancer screening programme was limited to women in central Slovenia; by 2018, it was gradually extended to cover all municipalities [23,24]. This phased implementation constitutes a natural experiment, with invited women serving as the experimental group and uninvited women as the control group. In our previous study, we explored whether the implementation of the national screening programme is reflected in better survival of breast cancer cases diagnosed at screening. Stratification by stage was applied in that study to reduce the lead time bias and the survival probability was significantly higher in the

invited-to-screening group [25]. Still, the control group (not invited to screening) differed in many aspects to the screened group and further analysis which would allow us to make more robust causal statements is warranted.

This study aims to improve the previous evaluation of the Slovenian breast cancer screening programme in two aspects: first, by applying improved statistical methods to analyse the data more accurately; and second, by introducing new metrics that are more understandable and easier to interpret for the general public. In the analysis, we compare all cancer patients invited to the programme with those not invited, and employ a biological tumour growth model [21] to reduce lead time bias. Our approach ensures that the comparison is fair and bias-free. The endpoint outcomes include years of life gained and the number of avoidable deaths; both metrics are standardized to enable cross-country comparisons.

2. Materials and Methods

2.1. Dataset

For this epidemiological study with predictive modelling, the data on cancer cases were acquired from the population-based Slovenian Cancer Registry. The initial dataset consists of 9416 invasive breast cancers recorded in the cancer registry from 1 January 2008 to 1 January 2021 (code C50 according to ICD-10 classification; carcinoma in situ was not included in the analysis) diagnosed in women aged between 50 and 72. Of these, 21 were classified as death-certificate-only cases, which were excluded. Additionally, three screen-detected cases with missing tumour diameter values were also removed. This resulted in 9392 cancer cases that were included in the subsequent analysis. We included cases occurring in women with the upper age limit of 72 years, which is two years after the last inclusion in the screening programme; this is to observe the effect that screening has on the eligible population beyond the screening age due to the lead time and to include also the interval cases that would occur after the last screening round at the age 69 years. The acquired data for each case include the following variables: date of birth, date of cancer diagnosis, date of death, or date of last follow-up (last update on 1 October 2023), status at the end of the follow-up (alive, dead, lost to follow-up), cause of death, and socio-economic index. The socio-economic index was determined using the Slovenian version of the European Deprivation Index (SI-EDI) for the year 2011. The index was measured at the level of the National Assembly Polling Stations, which represents the smallest administrative geographic units with available population data [26]. The SI-EDI was categorized into quintiles, where each quintile represents a segment that includes 20% of the data, ordered from the most affluent (group 1) to the most deprived (group 5). Each cancer patient was assigned to a group based on their address at the time of diagnosis.

In addition, we collected data from the Slovenian national breast cancer screening registry [23]. These include invitation status, screening history, and tumour size at cancer diagnosis. Detection mode was determined from the data and categorized into three groups: screen-detected cases, interval cases, and cancers in non-attenders (never screened or diagnosed based on symptoms more than 2.5 years from the last screening). The definition of interval cancer has been adjusted to include a period up to 2.5 years, when more than 98% of eligible women should be re-invited to screening (instead of 2 years, which corresponds to the proposed length of a screening interval) [27] to accommodate possible slight delays in screening appointments (most often caused by women's request). Interval cancer patients were determined solely on the time interval from the last performed mammography, even in women who did not respond to the next invitation to screening mammography, which could be in the interval 20 to 30 months after previous mammography.

We also obtained background population data (counts) from the Statistical Office of the Republic of Slovenia for women aged 50 to 72, spanning each year from 2008 to 2021, for standardization purposes.

2.2. Statistical Analysis

2.2.1. Experimental and Projection Periods

The estimated effectiveness of cancer screening programmes in their initial stages is context-specific, influenced by fluctuating participation rates and a large pool of potentially screen-detectable cancers, which leads to an unstable ratio of screen-detected to interval cases compared to later periods. For our results to be more generalizable, we divided the study into two distinct periods: the Experimental period and the Projection period.

The Experimental period aligns with the initial phase of the programme (from 2008 to 2019), during which the programme gradually expanded to cover the entire country (the expansion rate is shown in Figure 1). During this period, we collected data on both cancer patients invited to the programme and those not invited, allowing for comparative analyses of survival probabilities between the two groups. Since our data come from a natural experiment, governed by the politics of breast cancer screening introduction, the two groups are not directly comparable. The programme initially prioritized older women and more urbanized regions (with higher socio-economic statuses), affecting the distribution of demographic variables.

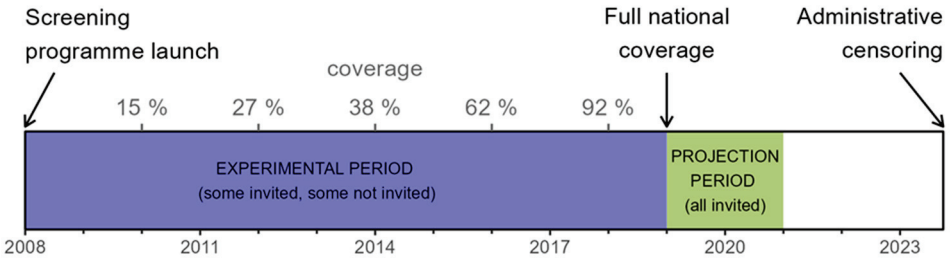


Figure 1. The Experimental and Projection periods, along with the coverage rate of the Slovenian breast cancer screening programme.

The Projection period takes place after the programme has expanded to the whole country (from 2019 to 2021; see also Figure 1). During this period, we have data for cancer patients invited to the programme, but not for non-invited cases, as the programme achieved nationwide coverage. This period is expected to be more representative of future screening effectiveness, as the programme had been well-established by this time.

2.2.2. Addressing the Lead Time Bias, Length Bias, and Over-Detection Biases

To adjust for lead time bias in our analysis, we estimated lead time values for each individual based on the biological tumour growth model [21]. We used model parameters estimated based on the Swedish dataset of a breast cancer screening programme as given in [21]. Following the approach proposed by Abrahamsson et al. [21], we sampled lead time for each Slovenian woman with cancer detected on a screening test based on her tumour size and screening history, leading to an individual lead time estimate that was used in further calculations. For interval cases and non-attenders, lead time was set to zero. Person-specific lead times were subsequently used to predict the age at hypothetical symptomatic detection.

The median lead time for screen-detected cases was estimated to be 1.23 years (1st quartile = 0.48 years, 3rd quartile = 2.53 years). Figure 2 presents the estimated distribution of lead time, calculated based on our covariates and Swedish parameters. The survival

time was computed by subtracting the age at predicted symptomatic detection from the age at death.

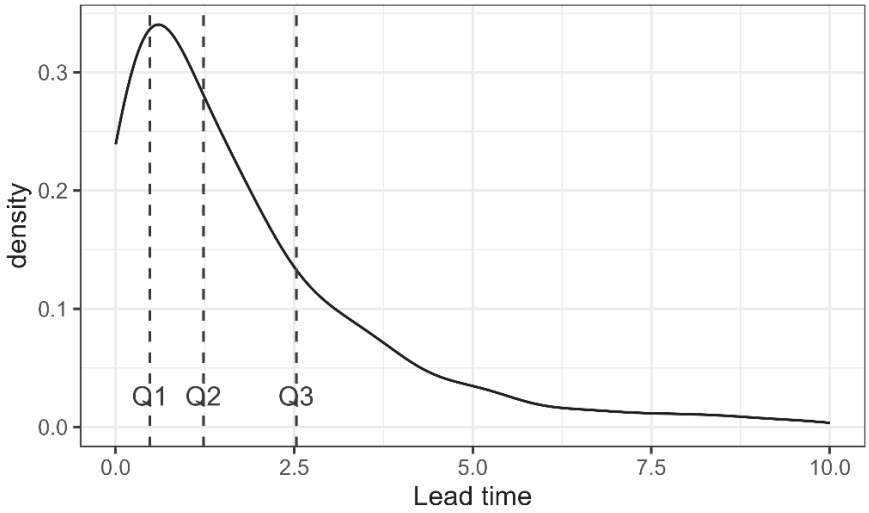


Figure 2. Distribution of lead time calculated on the data from the Experimental period (one run). The vertical lines represent 1st, 2nd, and 3rd quartile.

Women who died due to other causes prior to the predicted age of symptomatic detection were flagged as over-detected cases. The same was done if the predicted age of symptomatic detection was beyond 72 years as the study population was limited to cancer patients aged between 50 and 72 years. In our analysis, there were 10 cases of breast cancer that were over-detected per 100,000 women adjusted for covariates.

To avoid length time bias, we compared all cancer cases invited to the programme against all cancer cases not invited to the programme since similar case-mix of tumours is present in both populations.

2.2.3. Confounders and Scenarios

Because our data come from a natural experiment, the two groups—invited and not invited—observed during the Experimental period are not directly comparable (see Section 2.2.1). To address this issue, we used regression adjustment via a Cox proportional hazards model to align the covariate distributions of both groups to match the distribution observed in the Projection period. This approach estimates survival probabilities as if both groups had the same covariate distribution as in the Projection period. This alignment serves two purposes: first, it balances the two groups, making them directly comparable; and second, it enables predictions for the Projection period. A single Cox proportional hazards model was used to adjust the survival of each group with respect to confounding covariates. In this model, we included the following covariates: SI-EDI (groups from 1 to 5), detection mode (a new category "non-invited cancer" was created to describe cancer patients not invited to the programme), and lead-time-adjusted age and date of diagnosis. Both SI-EDI and detection mode were entered into the model as indicator variables (the reference category was 1 for SI-EDI and "non-invited cancer" for detection mode). The relationship between hazard and age, as well as the date of cancer diagnosis, was modelled using restricted cubic splines.

The parameters of the model were estimated based on the data (lead-time-adjusted) from both phases to reduce the variance of our estimates and to minimize extrapolation. This model was subsequently used to predict the survival of each (sub)group during the Projection period under two scenarios: Scenario A examines the situation where all cancer patients are invited to the programme, and Scenario B considers the situation where none

are invited. The survival of each subgroup in Scenario A (screen-detected, interval, and non-attenders) was predicted using the distribution of covariates, adjusted for lead time, specific to each subgroup from the Projection period. The survival for all cancer patients in Scenario A was estimated by weighting the survival of each subgroup based on their proportions observed during the Projection period (and adjusted for over-detection) and summing these values at each time point. For cancer patients in Scenario B, the survival was predicted based on the covariate distribution (adjusted for lead time) of invited cases during the Projection period, with detection mode indicators set to zero.

2.2.4. Calculations of Years Gained and Deaths Avoided in the Two Scenarios

Our final goal was to estimate the number of years gained and deaths avoided per 100,000 women invited to the programme (Scenario A) compared to a counterfactual scenario where they were not invited (Scenario B). The population at risk, as observed during the Projection period, was defined to represent our target population. The main results are presented in the form of flowchart and further visually represented in an infographic. Below, the calculations for each labelled step in the flowchart are explained in detail:

a. The attendance rate in Scenario A was estimated by dividing the total number of screenings by the total number of invitations in the Projection period;
b. The number of cancer patients in each subgroup (screen-detected cases, interval cases, and non-attenders) in Scenario A was estimated based on the data from the Projection period and normalizing the counts to a population size of 100,000. All other individuals who did not develop cancer are excluded from the flowchart to improve visibility;
c. The number of cancer patients in Scenario B was calculated by subtracting the number of over-detected cases from the total number of cases in Scenario A. The number of over-detected cases in the Projection period was estimated as described in Section 2.2.2. All other individuals who did not develop cancer are excluded from the flowchart to improve visibility;
d. Observed 10-years survival was estimated using the Kaplan–Meier estimator, and the corresponding 10-years restricted mean survival time (RMST) was estimated as the area under the survival curve from 0 to 10 years (measured in years).
e. The survival of screen-detected cases was adjusted for lead time (and over-detection) as described in Section 2.2.2;
f. The 10-year survival and RMST during the Projection period were adjusted for covariates (and lead time), and predicted;
g. The estimated 10-year survival probabilities and corresponding RMSTs for each subgroup (screen-detected cases, interval cases, and non-attenders) were weighted and aggregated. The weights, estimated as detailed in step (b), were adjusted for over-detection;
h. The survival benefit was estimated by subtracting the estimated 10-year survival in Scenario B from that in Scenario A. To estimate the number of avoidable deaths, we first estimated the number of deaths in each scenario by multiplying the proportion of individuals who died (1—survival) within 10 years of cancer diagnosis (lead time adjusted) by the total number of patients in Scenario B. The number of avoidable deaths was then calculated as the difference between the number of deaths in Scenario B and Scenario A;
i. The years of life gained (YLG) per cancer patient were calculated by subtracting the RMST of Scenario B from that of Scenario A. The total YLG was determined by multiplying the YLG per case by the number of cancer patients in Scenario B.

2.2.5. Addressing Statistical Uncertainty and Software Tools Used

Our analysis contains two levels of statistical uncertainty: the first arises from sampling, and the second from the stochastic generation of lead time values. To address the first source, 95% confidence intervals were calculated using bootstrap method. We generated 10,000 bootstrap samples, and the limits of the 95% confidence intervals were determined by approximating the resulting sampling distribution with a normal distribution. To address the second source, lead time was sampled 100 times for each individual within each bootstrapped sample and the results were averaged.

All statistical analyses were performed using the R programming language version 4.2.2 [28].

3. Results

3.1. Comparison of Study Populations in Two Periods

In total, there were 7733 cancer patients (1842 deaths) during the Experimental period, with 2702 (403 deaths) invited to the programme and 5031 (1439 deaths) not invited. During the Projection period, there were 1659 cancer patients (118 deaths) invited to the programme. In Figure 3, we compare the distribution of relevant confounding variables between cancer patients invited to the programme and those not invited during the Experimental period. As explained previously, the gradual and uneven implementation of the programme leads to significant differences in the distribution of these variables between the two groups. These discrepancies were adjusted for in the subsequent analysis to align with the distribution of cancer patients invited to the programme during the Projection period (indicated by the green line in Figure 3).

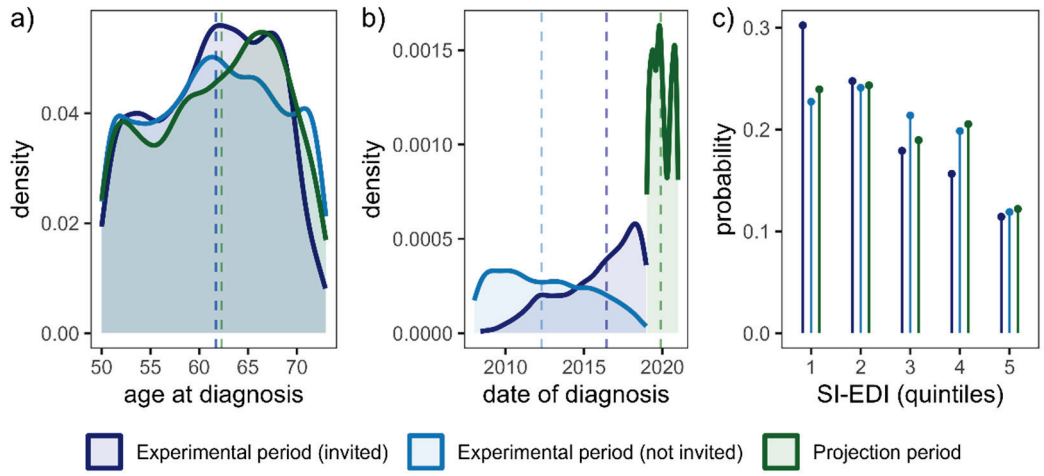


Figure 3. The distribution of confounders for cases invited to the programme and cases not invited to the programme during the Experimental period and for cases invited to the programme during the Projection period. The dashed vertical lines denote median values for each group. (**a**)—distribution of age at diagnosis, (**b**)—distribution of date of diagnosis, and (**c**)—distribution of socio-economic conditions represented by SI-EDI (Slovenian European Deprivation Index), which is segmented into quintiles, ordered from first quintile (most affluent) to fifth quintile (least affluent).

3.2. Survival Analysis

First, we estimated the survival for women diagnosed with breast cancer invited to the programme and for those not invited as observed during the Experimental period (see Figure 4, left). These estimates were not adjusted for lead time or relevant confounders; therefore, the comparison between the two groups does not allow for causal interpretation. The invited group is divided into subgroups of screen-detected, interval, and non-attenders,

where the screen-detected group has consistently the best survival, and non-attenders have consistently the worst survival.

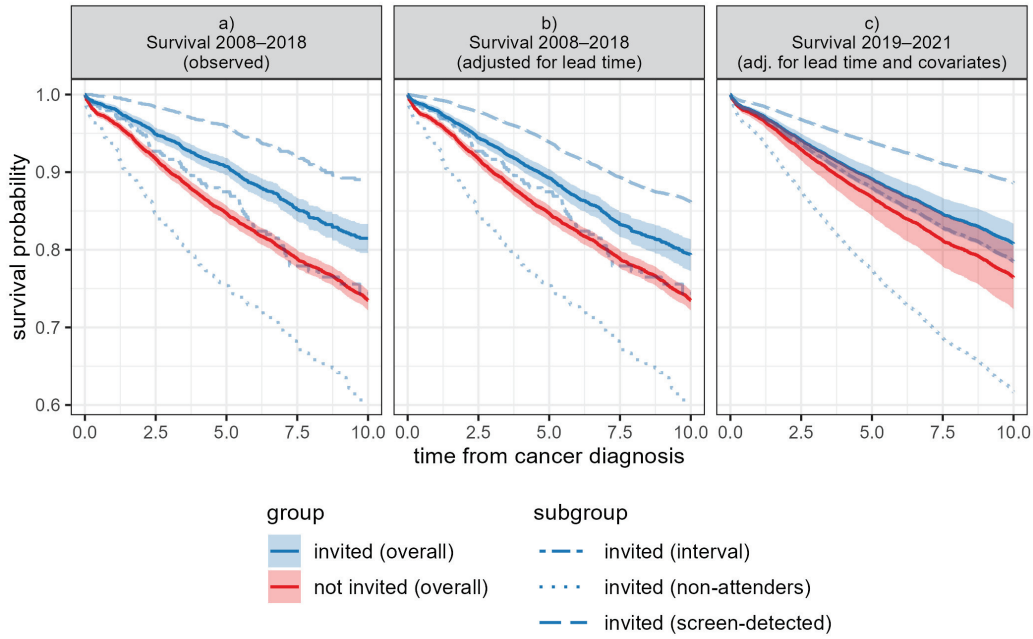


Figure 4. Comparison of survival of breast cancer patients between invited and not-invited groups in the Experimental and Projected periods, adjusted for lead time and covariates. Figure (**a**) presents observed survival in the Experimental period (2008–2018), Figure (**b**) presents survival in the Experimental period (2008–2018), adjusted for lead time, and Figure (**c**) depicts the predicted survival in the Projection period (2019–2021), adjusted for lead time and covariates. To improve visibility, only the 95% confidence intervals for overall survival are shown, indicated by the shaded area.

In the next step, we adjusted the survival of screen-detected cases for lead time bias, as shown in the central graph of Figure 4. This adjustment resulted in a lower estimate of survival for screen-detected cases and, consequently, also for all cancer patients invited to the programme. Despite these adjustments, the two groups—those invited and those not invited—remain incomparable due to differences in the distribution of confounding variables.

Lastly, a Cox model was used to predict the survival for each subgroup in the Projection period. The estimated coefficients for the Cox model are presented in Appendix A. The predicted survival curves are adjusted for lead time bias and relevant confounding variables, matching the distribution observed during the Projection period. These predictions are unbiased under the model's assumptions. As shown in Figure 4c, the survival rates for both cancer patients invited to the programme and those not invited have improved relative to the period from 2008 to 2018 (Figure 4a,b), reflecting advancements in cancer treatment and care. More importantly, the survival of cancer patients invited to the programme is higher compared to those not invited, indicating a general positive effect of cancer screening programmes on the whole population.

3.3. Years of Life Gained and Avoidable Deaths

Both years of life gained and avoidable deaths depend on the number of individuals invited to the programme. To ensure the results are generalizable, we standardized them to a population size of 100,000 individuals over the 2-year period from 2019 to 2021 (the Projection period). We investigated how reality unfolds for this population under two different scenarios: in Scenario A, individuals at risk are invited to the programme exactly once, and in Scenario B, they are not. In Figure 5, we compare the two scenarios

head-to-head. For transparency, we have included in the figure the observed survival (and RMST), as well as the lead time adjusted survival (and RMST). These metrics should not be directly compared between the two scenarios but are provided to illustrate how different sources of bias can affect the results. Only the results adjusted for both lead time and covariates provide a valid basis for comparing the two scenarios. Since we do not know which cancer patients in Scenario B would be screen-detected, we can only compare the survival of all cancer patients in Scenario A against the survival of all cancer patients in Scenario B. This comparison reveals that, after 10 years, cancer patients in Scenario A, being invited to the screening, have a 4.3 (95% CI 1.6, 7.1) percentage points higher survival probability (resulting in 22 (95% CI 8, 35) avoided deaths) and, on average, lived 0.22 (95% CI 0.07, 0.38) years longer per cancer case (which amounts to a total of 114 (95% CI 37, 191) years of life gained in population of 100,000 women) compared to those in Scenario B (women who are not invited). Note that the 95% confidence intervals do not include zero, meaning that the effect of the programme on 10-year survival is statistically significant at $\alpha = 0.05$.

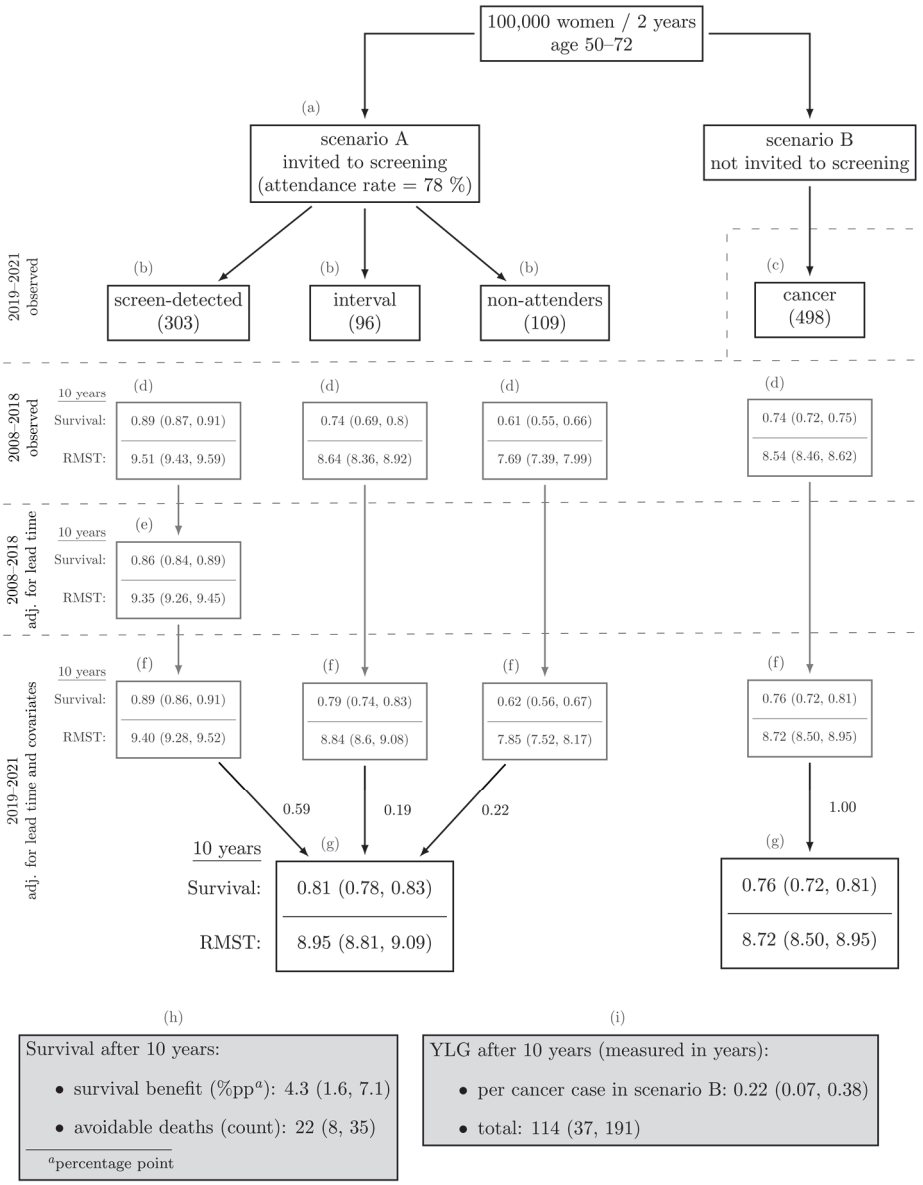


Figure 5. Flowchart comparing the survival probabilities and restricted mean survival times (RMSTs) of cancer patients between Scenario A and Scenario B (95% confidence intervals in the brackets). Each step is detailed in Section 2.2.4. (YLG—years of life gained.)

The results for Scenario A, as outlined in the flowchart (Figure 5), are visually depicted in an infographic (Figure 6). An additional simplification was made for the purpose of this illustration: specifically, all avoided deaths are assigned solely to the group of screen-detected cases. In our calculations, the avoidable deaths are calculated for Scenario A comparing to Scenario B, so in reality they cannot be attributed to a single subgroup of invited women.



Figure 6. Infographic depicting results from the flowchart for Scenario A—Cancer cases in 100,000 women invited to screening. For this illustration all avoided deaths are attributed solely to the group of screen-detected cases. One box in the upper infographic corresponds to 500 women; one human silhouette in the lower infographic corresponds to one woman.

4. Discussion

Evaluating outcomes of screening programmes represents quite some challenges [29–31]. One of the greatest challenges is using methodologically plausible and ethically acceptable methods which would enable comparisons of the outcomes between groups which would differ only by the intervention under study, that is, availability of breast cancer screening. In using survival as the measure of evaluating the benefits of cancer screening on the outcomes in the population, there are three main biases that strongly influence its use, namely lead time bias, length bias, and bias due to over-detection. Nevertheless, complex methodological approaches try to overcome the known biases by applying models to

estimate different biases imposed on a person exposed to screening [12], and only some models are trying to correct for more than one bias at once. Recently, Vratanar and Pohar Perme proposed a new non-parametric estimator that allows for estimating the survival of cancer patients that would be screen-detected among those not included in the screening programme by applying estimations of lead time bias using the tumour growth model [21], corrected for confounding variables, and thus importantly reducing all of the above-mentioned biases [22].

Our study assesses the effectiveness of the Slovenian breast cancer screening program by comparing survival between invited and non-invited individuals in a modelled situation, estimating life years gained and avoidable deaths within 10 years as standardized measures for cross-country comparisons. Our results confirm that implementation of organized screening has a positive effect on the eligible population; in 498 cancer patients selected from 100,000 eligible women, the invited have a 4.3 (95% CI 1.6, 7.1) percentage points higher survival probability than comparable not-invited cancer patients, resulting in 22 (95% CI 8, 35) avoided deaths. On average, the breast cancer patients in the invited population each lived 0.22 (95% CI 0.07, 0.38) years longer within a limited time period of 10 years, which amounts to a total of 114 (95% CI 37, 191) years of life gained in the pool of 100,000 eligible women. We believe that years of life gained (YLG) is a more comprehensive and understandable measure for the general public and decision-makers, making it particularly valuable for public health communication [32]. It also evaluates impact over a life-time horizon and has a real-world meaning. To further enhance understanding, we have included an infographic that visually represents three distinct groups, clearly illustrating the lives saved in breast cancer cases due to the implementation of organized screening [31]. Furthermore, by using correction for lead time bias and the confounding variables, our results are comparable to similar calculations that could be performed in other settings.

As seen in the results section, we have calculated the survival for three groups of women—screen-detected, interval cancers, and non-attenders—which all add to the overall benefit of introduction of screening in a population. As expected, the worst survival is in the group of non-attenders (0.62; 95% CI 0.56, 0.67), which is significantly worse than if screening had not been introduced (0.76; 95% CI 0.72, 0.81). As previously known, non-attenders are a special group of people, with a lower health awareness and lower health system use [33–35]. This encourages providers of organized screening to give special attention to groups of people who do not respond to breast cancer screening invitations. Reasons for not attending cancer screening programmes could be very different in different countries and even within countries, where differences in income, education, socio-economic status, cultural norms, health status and health perception, understanding of the provided information, social support, and many others are most commonly studied and mentioned [27,36]. Our study does not focus on possible circumstances contributing to non-attendance, but by using the socio-economic index SI-EDI in a Cox model, we have tried to counterbalance reasons that could be connected to socio-economic status [37]. The greatest survival is observed in screen-detected cases (0.89; 95% CI 0.86, 0.91), which is significantly higher than in case of the non-invited, which equates to a scenario of no breast cancer screening programme (0.76; 95% CI 0.72, 0.81). This result further supports the fact that cancers detected and treated in earlier stages provide better outcomes. This is one of the key rationales behind the introduction of cancer screenings [2,3,36], and is also supported by findings in other countries. In our previous work [25], we calculated survival differences between invited and non-invited women during the roll-out period, aiming to minimize lead time bias by comparing different stages of disease, recognizing that earlier stages are more frequently detected through screening. However, comparing

groups from different geographical areas, time periods of diagnosis, and varying age and socio-economic structures introduced selection bias, compounding the inherent biases of screening. In that study, the difference in 5-year net survival between attenders and non-attenders or non-invited women at localized and regional stages ranged from 4 to 10 percentage points [25].

One of the key strengths of our study is the availability of comprehensive nationwide real-world data, which serves as a robust foundation for calculating the parameters needed for modelling the benefits of organized cancer screening. The population-based data from our cancer and breast cancer screening registries are of high completeness and of excellent quality. This enables us to assess the impact of the phased implementation of screening across the entire population, as different segments were covered at varying times, providing valuable insights into its effectiveness. We have used the confounders that were readily available in the registry data. In further studies, additional confounding variables could be added (i.e., morphology), which could improve the modelling results.

In our study we have calculated parameters from the Experimental period to be used in a model for a control group in the Projection period from the real situation, which was possible due to the natural experiment of the 10-year roll out period of organized breast cancer screening in Slovenia. We have also considered the confounding variables that differed in the invited and not invited population in the Experimental period on real-world data. By using two total populations for comparison, we avoided the length time bias.

By applying the biological tumour growth model, we have calculated the lead time introduced into breast cancer patient data by screening. This enabled us to observe and compare groups of people from a common starting point to avoid lead time bias. For calculating the lead time bias, we used an approach based on Abrahamsson's model [21] applied to Slovenian cancer-screening data. We applied model parameters derived from the Swedish dataset of a breast cancer screening programme as we could not estimate the parameters from the Slovenian data due to the lack of tumour size measurements for interval cases. This is a key limitation of our study, as differences in tumour growth dynamics between populations could introduce bias. Obtaining the missing data would allow us to estimate these parameters directly, leading to more reliable lead time estimates. The calculated lead time was 1.23 years, which is slightly lower than the calculation on the Swedish screening data (the mean there was 1.9 years). This could be due to the fact that our Experimental period consisted of more women who were screened for the first time, no matter their age, since the screening programme had just been spreading out to the whole country. In the first round of screening, it is foreseen that more cancers are discovered and they are of greater size [27], compared to well-established screening programmes, such as the Swedish one, which has been operating nation-wide since 1986 [4], and thus invites mostly women that have already been screened in previous rounds. We expect that our lead time will eventually lengthen.

We have shown results for all steps of the process—adjustment for lead time bias alone and for lead time bias and confounding factors, where these metrics should not be directly compared between the two applied scenarios but are provided to illustrate how different sources of bias can affect the results. This adds to the pool of evidence how survival calculations could be improved and become more useful in the evaluation of screening programme implementation.

5. Conclusions

Comparison of screening outcomes is difficult in many aspects. Using survival, which needs less time to observe than mortality, the main concern is the selection of a control group and addressing the known biases, such as lead time bias, length bias, and over-

detection bias. In this study we have combined several well-established approaches that are usually used in different areas of epidemiological research, but not in monitoring cancer screening benefits. That means that we have applied a newer, more complex approach to calculate survival probabilities using real-world data for Slovenian women diagnosed with breast cancer. We have considered the biases, where the lead time bias was calculated individually taking into account the individual size of the tumour at the time of diagnosis, and also correcting for covariates between the comparison groups, to calculate the benefit of the introduction of an organized screening programme compared to a population in a hypothetical situation where no screening would have been available for the same population. We believe that such comparison of outcomes has a sounder ground, provides possibilities of evaluation of survival benefits of fully implemented screening programmes, and could be used in further studies of screening outcomes, also in the context of the introduction of more personalized approaches to screening. The calculation of years of life gained in the context of screening programme implementation provides additional opportunities for communicating the benefits of breast cancer screening to the non-expert community, since this measure is well established in other epidemiological studies, but also more understandable to policy-makers and other lay public.

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Institutional Review Board Statement: Not applicable since research using national cancer registry data and screening registry data has a legal background in Slovenia.

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Data Availability Statement: Detailed results are available from the corresponding authors upon reasonable request.

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Abbreviations

The following abbreviations are used in this manuscript:

SI-EDI	Slovenian version of the European Deprivation Index
RMST	restricted mean survival time
YLG	Years of life gained

Appendix A

In our work, we fitted the Cox proportional hazards model to the data from the Experimental period. The following covariates were included in the model: age at diagnosis (adjusted for lead time), date of diagnosis (adjusted for lead time), SI-EDI (entered into the model as a set of indicator variables with 1 being a reference category), and detection mode (entered into the model as a set of indicator variables with "non-invited cancer" being a reference category). The relationship between hazard and age, as well as the date of cancer diagnosis, was modelled using restricted cubic splines. The estimated coefficients in the Cox proportional hazards model are shown in Table A1.

Table A1. Summary of Cox proportional hazards model.

Variable	Coefficient	Std. Error	*p*-Value
Age at diagnosis	1.059×10^{-2}	1.038×10^{-2}	0.308
Age at diagnosis	3.227×10^{-2}	1.164×10^{-2}	0.006
Date of diagnosis	-9.368×10^{-3}	1.678×10^{-2}	0.577
Date of diagnosis	-1.509×10^{-2}	2.379×10^{-2}	0.526
SI-EDI	6.069×10^{-2}	1.830×10^{-2}	9.100×10^{-4}
Screen-detected	-0.670	0.094	8.179×10^{-13}
Interval	-0.044	0.117	0.710
Non-attenders	0.527	0.085	5.174×10^{-10}

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From Real-World Data to Causally Interpretable Models: A Bayesian Network to Predict Cardiovascular Diseases in Adolescents and Young Adults with Breast Cancer

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Simple Summary: Cardiovascular diseases are among the most frequent, although rare, long-term sequalae in adolescents and young adult survivors of breast cancer. However, no dedicated tool exists to help clinicians with planning personalized follow-up strategies for these patients. To make up for this lack, in this work, we developed a Bayesian network, an artificial intelligence model, to predict the 5-year risk for cardiovascular diseases in these patients, leveraging real-world data from two different cohorts. The model showed a very good ability to identify patients at risk and select those that should be prioritized because they are at higher risk, making it useful for guiding clinicians in everyday practice. Finally, the methodological approach proposed in this work is particularly interesting for all researchers who aim at developing causally interpretable tools, also dealing with real-world data and their biases.

Abstract: Background: In the last decades, the increasing number of adolescent and young adult (AYA) survivors of breast cancer (BC) has highlighted the cardiotoxic role of cancer therapies, making

cardiovascular diseases (CVDs) among the most frequent, although rare, long-term sequalae. Leveraging innovative artificial intelligence (AI) tools and real-world data (RWD), we aimed to develop a causally interpretable model to identify young BC survivors at risk of developing CVDs. **Methods**: We designed and trained a Bayesian network (BN), an AI model, making use of expert knowledge and data from population-based (1036 patients) and clinical (339 patient) cohorts of female AYA (i.e., aged 18 to 39 years) 1-year survivors of BC, diagnosed in 2009–2019. The performance achieved by the BN model was validated against standard classification metrics, and two clinical applications were proposed. **Results:** The model showed a very good classification performance and a clear causal semantic. According to the predictions made by the model, focusing on the 25% of AYA BC survivors at higher risk of developing CVDs, we could identify 81% of the patients who would actually develop it. Moreover, a desktop-based app was implemented to calculate the individual patient's risk. **Conclusions:** In this study, we developed the first causal model for predicting the CVD risk in AYA survivors of BC, also proposing an innovative AI approach that could be useful for all researchers dealing with RWD. The model could be pivotal for clinicians who aim to plan personalized follow-up strategies for AYA BC survivors.

Keywords: adolescents and young adults; survivorship; breast cancer; cardiotoxic treatments; risk prediction; personalized follow-up; artificial intelligence

1. Introduction

The increasing number of cancer survivors in recent decades has moved researchers' attention from cancer treatment to its long-term outcomes. In this context, artificial intelligence (AI) has achieved remarkable results in identifying cancer patients at risk of developing long-term outcomes, based on different types of data (such as omics and imaging data) [1,2]. Such results can be exploited to minimize therapy-related morbidity by offering tailored treatments and, at the same time, ensure the most appropriate management for high risk. However, AI models are known to be computationally intensive and to require large amounts of data to perform optimally. Moreover, real-world data (RWD) used to develop and train these models are often scarce, especially if the outcome of interest is rare or biased. Additionally, healthcare data are typically heterogeneous given the granularity of the information collected and are stored in silos which do not communicate with each other. In this framework, data fusion is needed to provide accurate predictions by combining heterogeneous data with expert knowledge.

Bayesian networks (BNs) are probabilistic graphical models which use graphical representations to describe conditional probability dependence relationships [3]. These AI models are well suited to prognostication and can be applied even when events are rare and some information is missing [4]. Moreover, BNs are able to merge information retrieved from different sets of data, handle the biases in RWD, and integrate domain knowledge coming from experts or the literature; all these properties make them an excellent candidate to build effective predictive models using RWD [5]. Moreover, besides the fact that the decision-making processes behind the most used AI tools are so complex as to make them perceived as black boxes by humans, BNs allow for the study of the cause–effect relationships of all the variables with one another and thereby resemble clinical reasoning [6].

Adolescents and young adults (AYAs) (15–39 years at first cancer diagnosis) are a heterogeneous group of cancer patients whose needs, expectations, and treatment deserve special consideration [7]. As in older women, breast cancer (BC) is the most common cancer in AYA females, with very high survival rates [8]. Compared to their older counterparts, however, female AYA patients present more aggressive forms of BC [9,10]. Cardiovascular diseases (CVDs) are the most common, although rare, long-term outcome in these patients. The main causes of CVDs in these survivors (as in older women) include not only intensive

cardiotoxic treatments [11–13] but also lifestyle and socioeconomic factors (e.g., smoking, obesity) and genetics [14,15].

Despite the large availability of data on older BC patients, no study has characterized the CVD risk in AYAs. Nevertheless, predictive AI tools developed for older patients are not directly transportable to this peculiar group of younger patients. Against this background, the project "*pRedicting cardiOvascular diSeAses iN adolescent and young breast caNcer pAtients*" (ROSANNA) is aimed at building a causally interpretable AI-based model to identify AYA BC survivors at higher risk of developing CVDs. In practice, we used a BN to estimate the CVD risk by solving a maximum a posteriori query via approximate inference. This allowed us to leverage the patient-specific conditions given by the observed covariates, mitigating the impact of the missing ones.

2. Materials and Methods

2.1. Population-Based Cohort (PBC)

A retrospective cohort of about 70,000 AYA patients was collected in the context of a previous project, named the Ada cohort [16]. To develop this cohort, 34 Italian population-based cancer registries (CRs) were asked to identify AYA cases and link several administrative datasets (i.e., hospital discharge records, outpatients, and drug flows) for long-term outcome identification. Among the Ada cohort, we identified 1036 BC patients, diagnosed between 2009 and 2014, with the following criteria:

- Female patients aged 18–39 years at first BC diagnosis;
- One primary tumor only;
- Malignant carcinomas only;
- 1-year survivors;
- No metastases at diagnosis;
- No CVD before cancer diagnosis.

We retrieved information on treatments, CVDs, and major cardiovascular risk factors from the administrative databases based on previously used, validated algorithms [17,18], described in the Supplementary Material, Table S1.

2.2. Clinic-Based Cohort (CBC)

The PBC had several advantages, such as the high number of patients and the possibility of tracking patients for long-term outcomes, but it lacked cancer prognostic factors and treatment details that are essential to drive causal interpretations. To overcome this limitation, we collected an additional retrospective single-institution (Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy) CBC of 339 AYA BC patients, diagnosed in 2011–2019. Patients were identified in the INT BC registry applying the same criteria as in the population-based cohort, and detailed clinical information on the BC treatment and BC prognostic factors was collected via the clinical charts. In contrast to the PBC, in the CBC, it was not possible to link the administrative datasets; thus, the information on the CVD follow-up is completely missing. Data from the two cohorts were not directly linkable because, even though some patients may overlap, privacy constraints made it impossible to de-identify the patients.

2.3. Variables Analyzed

As opposed to standard statistical techniques, the properties of the BN model make it possible to deal with data sparsity and low numbers of events; thus, no formal statistical restriction was made on the list of variables to be included in the model. The selection of the variables was made according to expert opinion to maximize the model's causal interpretability. All the variables selected for the analysis are described in Table 1.

Table 1. Variables used for the construction of the Bayesian network model.

Variable Type	Label in the Model	Description	Format	Values
Selection node				
	[cohort]	Cohort identification label	Discrete	Population-based cohort; clinic-based cohort
Cancer survival prognostic factors				
	[age35]	Patient aged 35 years or older at the date of breast cancer diagnosis	Dichotomous	Yes/No
	[histology]	Tumor morphology, according to ICD-O-3 [1] morphology codes	Discrete	Ductal and lobular neoplasm (ICD-O-3 M = 8500–8504, 8508, 8510, 8513, 8514, 8520–8523, 8530, 8540, 8541, 8543); epithelial neoplasms, NOS (ICD-O-3 M = 8010, 8015); adenocarcinomas (ICD-O-3 M = 8140, 8201, 8211, 8230); neoplasms, NOS (ICD-O-3 M = 8000, 8001, 8005); other histologies (ICD-O-3 M = 8050, 8070, 8575)
	[grade]	Tumor grading, according to ICD-O-3 codes	Discrete	Grade 1; Grade 2; Grade 3
	[vascular]	Tumor spread to the vascular system at the time of diagnosis	Dichotomous	Yes/No
	[ki67]	Ki67 index higher than 14%	Dichotomous	Yes/No
	[receptors]	Tumor receptor status	Discrete	Luminal; Luminal A; Luminal B; Luminal HER2; HER 2-enriched; triple-negative
	[pT]	Tumor size at the time of diagnosis (according to pathological stage)	Discrete	pT1 (<2 cm); pT2 (2–5 cm); pT3 (>5 cm); pt4 (spread to other organs)
	[pN]	Lymph nodes at the time of diagnosis (according to pathological stage)	Discrete	pN0 (no lymph node involvement); pN+ (lymph node involvement)
Cancer prognosis				
	[death_in_5y]	Death in the 5 years after cancer diagnosis	Dichotomous	Yes/No
Cancer treatments				
	[chemo_neo]	Neoadjuvant chemotherapy, i.e., the chemotherapy was administered within 6 months before the main surgical procedure	Dichotomous	Yes/No
	[radio_neo]	Neoadjuvant radiotherapy, i.e., the radiotherapy was administered within 6 months before the main surgical procedure	Dichotomous	Yes/No
	[target_neo]	Neoadjuvant target therapy, i.e., the targeted therapy was administered within 6 months before the main surgical procedure	Dichotomous	Yes/No

Table 1. *Cont.*

Variable Type	Label in the Model	Description	Format	Values
	[hormon_neo]	Neoadjuvant hormone therapy, i.e., hormone therapy was administered within 6 months before the main surgical procedure	Dichotomous	Yes/No
	[surgery]	Surgery type	Discrete	Conservative; radical (i.e., mastectomy)
	[chemo_adju]	Adjuvant chemotherapy, i.e., the chemotherapy was administered within 1 year after the main surgical procedure	Dichotomous	Yes/No
	[radio_adju]	Adjuvant radiotherapy, i.e., the radiotherapy was administered within 1 year after the main surgical procedure	Dichotomous	Yes/No
	[target_adju]	Adjuvant target therapy, i.e., the target therapy was administered within 1 year after the main surgical procedure	Dichotomous	Yes/No
	[hormons_adiu]	Adjuvant hormone therapy, i.e., the hormone therapy was administered within 1 year after the main surgical procedure	Dichotomous	Yes/No
Other cardiovascular risk factors				
	[dyslipidemia]	Diagnosis of dyslipidemia	Discrete	Pre (diagnosis of dyslipidemia within 1 year before the cancer diagnosis date); Post (diagnosis of dyslipidemia within 5 years after the cancer diagnosis date); No (no diagnosis of dyslipidemia)
	[hypertension]	Diagnosis of hypertension	Discrete	Pre (diagnosis of hypertension within 1 year before the cancer diagnosis date); Post (diagnosis of hypertension within 5 years after the cancer diagnosis date); No (no diagnosis of hypertension)
	[t2db]	Diagnosis of type 2 diabetes	Discrete	Pre (diagnosis of type 2 diabetes within 1 year before the cancer diagnosis date); Post (diagnosis of type 2 diabetes within 5 years after the cancer diagnosis date); No (no diagnosis of type 2 diabetes)
Target variables				
	[cardiotoxicity]	The patient showed any sign of cardiotoxicity (i.e., conduction disorders and arrhythmias or heart failure due to chemo-/radiotherapy) within 5 years after the cancer diagnosis	Dichotomous	Yes/No

Table 1. *Cont.*

Variable Type	Label in the Model	Description	Format	Values
	[ischemic_heart _disease]	Diagnosis of ischemic heart disease within 5 years after the cancer diagnosis	Dichotomous	Yes/No
	[cvds]	Diagnosis of any cardiovascular disease within 5 years after the cancer diagnosis	Dichotomous	Yes/No

[1] ICD-O-3: International Classification of Diseases for Oncology, 3rd edition.

Preoperative clinical and histopathological variables with prognostic value for the prediction of the 5-year survival of the tumor were identified according to standard treatment guidelines [19].

BC treatments (chemotherapy, radiotherapy, target therapy, and hormone therapy) were divided, according to the date of surgery, between neoadjuvant (i.e., pre-surgery) and adjuvant (i.e., post-surgery) treatments. All the treatments can, through different mechanisms, induce several types of cardiac events, which were further stratified as cardiac toxicities (i.e., conduction disorders, arrhythmias, or heart failure) and ischemic heart diseases (i.e., acute myocardial infarction or other forms of ischemic heart disease). In more detail, chemotherapy, radiotherapy, and targeted drugs exert a wide range of effects on the cardiac structure and function, with damage to cardiomyocytes and/or endothelial cells, resulting in various clinical alterations, including left-ventricular dysfunction, coronary artery diseases, pericarditis and pericardial effusion, cardiomyopathy, valvular disease and arrhythmias, and, in turn, heart failure in the most severe cases.

Hormone therapy blocks the body's ability to produce hormones, particularly estrogen, which has a cardioprotective effect in young females. Thus, the loss of estrogen during menopause is associated with an increased risk of ischemic heart disease either directly through vascular cells and cardiac myocytes or indirectly through systemic pathways, such as by altering lipid profiles and inducing major cardiovascular risk factors such as hypertension and dyslipidemia.

The distribution of the two cohorts' characteristics is illustrated in the Supplementary Material, Table S2. Missing data significantly impacted this analysis and depended strongly on the cohort of origin (missing not at random); thus, for example, cancer prognostic factors are completely missing in the PBC, and the same applies to the CVD follow-up in the CBC.

2.4. Model Development and Evaluation

The workflow for the model development is illustrated in the Supplementary Material, Figure S1. A BN consists of two parts: (i) a directed acyclic graph (DAG) and (ii) a set of conditional probability tables (CPTs) [20]. The DAG represents dependencies among the variables, and the conditional probability distributions quantify these dependencies. Our work focused on a discrete BN, such that all the included variables were dichotomous or discrete (as shown in Table 1). Given the limited follow-up period of the most recently diagnosed patients, we set a 5-year time span for the CVD follow-up. We split the overall combined dataset (PBC + CBC) into two subsets: 339 patients from the CBC + 623 patients from the PBC (approx. 70% of the overall sample) contributed to the training set, while the remaining 413 patients from the PBC (approx. 30% of the overall sample) contributed to the validation set. The CBC did not include CVD information, so it contributed to the training set only.

Learning the BN model only from training data was not advisable due to the rarity of the events. To overcome data scarcity, we firstly designed a basic structure of the DAG using prior knowledge taken from the domain literature and discussed with clinical experts. Secondly, we used the Structural Expectation–Maximization algorithm to handle

the missing-not-at-random issue. Structural Expectation–Maximization works when data are missing completely at random (MCAR) and missing at random (MAR) but can also be used when data are missing not at random (MNAR) if the missingness mechanism is modeled correctly, as in our case since the initial DAG was specified using prior knowledge. Then, the DAG was extended learning new causal relations directly from the training data (i.e., causal discovery) [21]. To ensure that the relationships identified in the RWD could be interpreted as causal, making it possible to leap from a probabilistic model to a causal BN, we subsequently validated them according to the existing literature before adding them as new arcs (i.e., arrows) to the model. We then estimated the CPTs using the training set. More technical details on the algorithms used to build the model are described in the work by Bernasconi et al. [22].

The validation set was used to validate the results and illustrate the possible model applications. To assess the model classification performance, i.e., its ability to correctly predict survivors not developing a CVD as not at risk and those developing a CVD as at risk, we used the standard classification metrics: the Area Under the Receiving Operator Characteristic Curve (AUC), True Positive Rate (TPR), True Negative Rate (TNR), Positive Predictive Value (PPV), Negative Predictive Value (NPV), Matthew's correlation coefficient (MCC), and accuracy. Accuracy, although popular, can generate overoptimistic results, especially if the dataset suffers from class imbalance (e.g., rare events, such as CVDs in AYAs with BC). Accordingly, we also assessed the accuracy rebalanced for the minority class (i.e., balanced accuracy, or BA). References to all the metric formulas can be found in the paper by Chicco et al. [23]. We used a normal approximation for proportions to calculate 95% confidence intervals (CIs).

We plotted a lift chart to illustrate how the model predictions could be used to sort patients by their risk. In the validation set, we placed survivors in descending order of the predicted probability of developing a CVD (x-axis), while we plotted the corresponding observed proportion of survivors who actually developed a CVD, namely, the TPR, on the y-axis. The faster the growth of the cumulative gain curve, the better the model is at prioritizing those patients at higher risk. Finally, to support clinicians in everyday practice, we developed an app-based tool which allows for an estimation of the probability of the 5-year CVD risk for individual AYA BC patients.

For the BN development, training, and validation phases, we used the "bnlearn" package freely available in R [24].

3. Results

3.1. Model Structure and Validity

The DAG of the final model is shown in Figure 1. All the probability distributions are displayed using frequency bars in the nodes (i.e., squares), and the dependencies are indicated by the arcs connecting the nodes. Nodes linked to each other, either directly (when one direct arc connects them) or indirectly (when the arc connecting two nodes passes through a third node, namely, a mediator), are assumed to be dependent. If no direct or indirect arcs connecting two nodes are present, the nodes are assumed to be independent. Arcs pointing from one node toward another one indicate that the first node is the cause of the second (e.g., neoadjuvant treatments-->surgery). The direction of the arcs represents the flow of causation. The cohort of origin ([cohort])—PBC or CBC—is a context variable (i.e., it represents the context in which the data were collected). By placing this variable as the root node (i.e., the first node, with no incoming arc), we can describe the missing mechanism arising from the data's different contexts of origin and allow the model to handle the selection bias; thus, patients in the CBC may differ from those in the PBC due to the selection mechanism. The node [death_in_5y], representing the patient's death within 5 years of diagnosis, is included in the model to take into consideration its competing role with CVDs. In the upper part of the DAG, we included by design all the nodes representing the prognostic factors that mainly impact it; these nodes were included to describe which factors directly or indirectly determined the choice of neoadjuvant treatment and show their

interplay, and how, in turn, they indirectly influenced the type of surgery and adjuvant treatment. The cardiotoxic role of chemotherapy, radiotherapy, and targeted drugs is illustrated in the left part of the DAG. On the opposite side, the hormone-induced risk of ischemic heart disease, hypertension, and dyslipidemia (which, together with type 2 diabetes, are among the major CVD risk factors) is described. The distribution of the latter may also depend on the cohort of origin, which accounts for the inclusion of the incoming arcs.

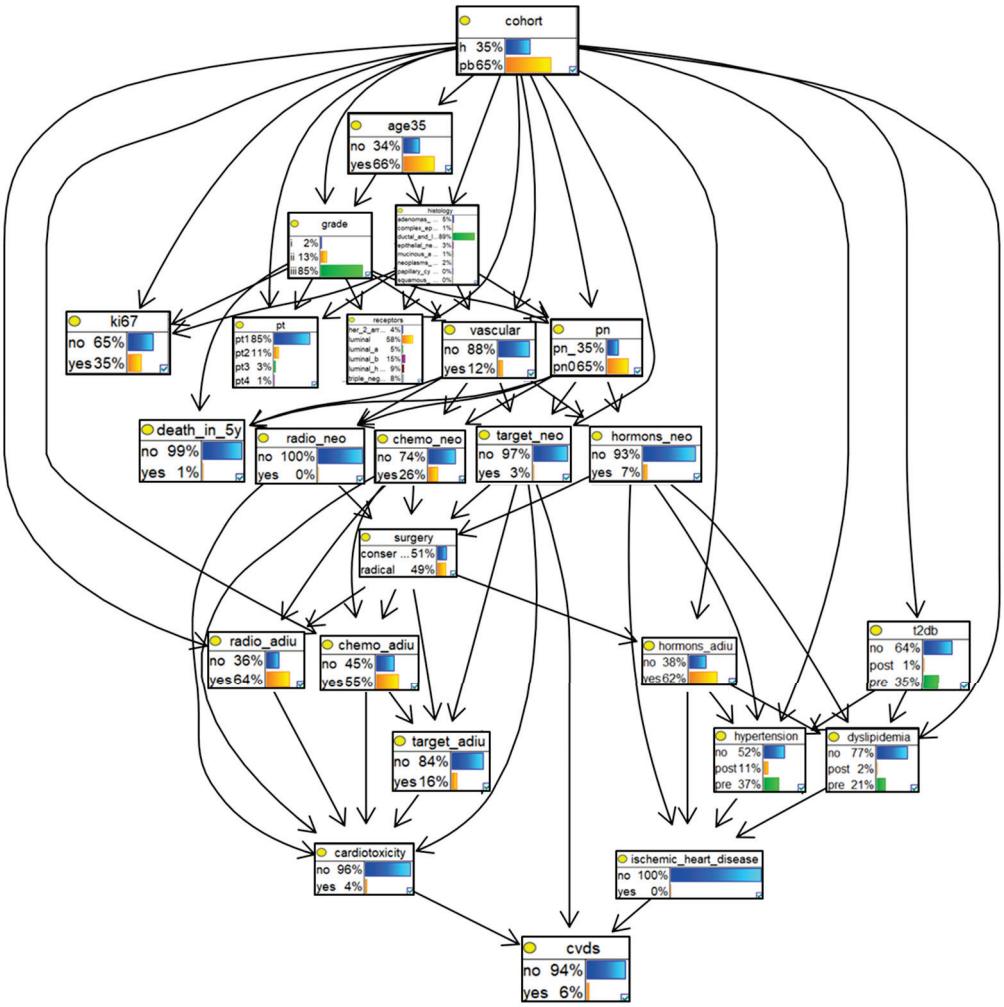


Figure 1. Final Bayesian network model structure. The figure illustrates the directed acyclic graph behind the model. Briefly, the cohort of origin is set as the root context node, followed by three subsequent lines that illustrate the cancer prognostic factors which affect both the 5-year survival and treatment decisions (neoadjuvant if pre-surgery, or adjuvant if post-surgery). Type 2 diabetes (t2db), dyslipidemia, and hypertension (bottom right in the figure) can already be present prior to the cancer diagnosis or can be induced by the cancer treatments. Finally, at the bottom of the model, the nodes can be seen describing cardiotoxicity induced by treatments and ischemic heart diseases, pointing to the target variable (i.e., cardiovascular diseases (CVDs)).

Figure 2 summarizes the overall performance of the BN. The BN model showed a high classification performance in the validation set, with an AUC, which is the measure of the model's ability to distinguish between survivors at risk of developing a CVD and those not at risk, very close to 90%. The high level of accuracy (i.e., the probability of a given survivor being correctly identified as at risk or not at risk by the model) is strongly influenced by the perfect TNR (i.e., the probability of a survivor without a CVD being identified correctly by the model), being the negative value of the most frequent class of the target variable

due to the rarity of the CVD event. In contrast, the model showed the lowest performance in terms of the TPR, which is the probability of a survivor with a CVD being identified correctly by the model, due to the low number of events the model was trained on. Thus, upon controlling for class imbalance and adjusting the accuracy accordingly (as it is for the balanced accuracy and MCC), the performances drop, even though they are maintained above 80%.

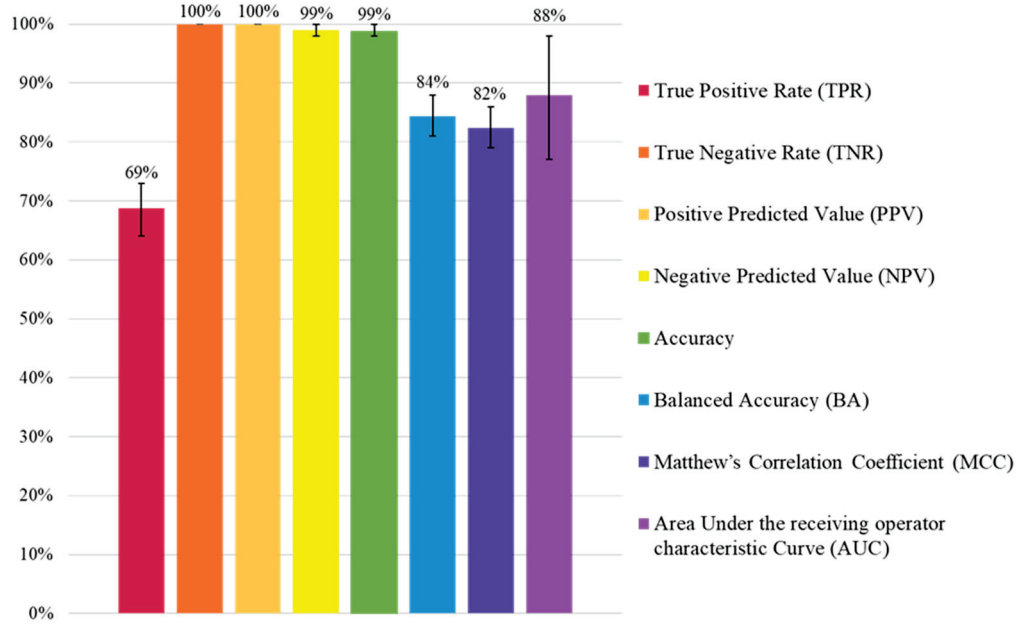


Figure 2. Bayesian network classification performances. Each classification metric is represented by a bar and the error bars are the 95% confidence intervals. Generally speaking, the model had good classification performances (AUC = 88% and accuracy = 99%). The model showed an almost perfect ability to correctly predict survivors not developing a CVD as not at risk (TNR, NPV), while identifying those developing a CVD as at risk is more complex due to the outcome rarity (TPR). When class imbalance is taken into consideration (BA and MCC), the performances decrease but remain very high (>80%).

3.2. Clinical Applications

The lift chart (Figure 3) illustrates how the probability values given by the model can be used to sort BC survivors according to their risk of developing a CVD in the 5 years following cancer diagnosis. As illustrated in the figure, the cumulative gain curve (depicted in bold black) suddenly increases. Thus, focusing on the 25% of patients predicted by the BN model to be at higher risk of developing a CVD enabled the identification of approximately 81% of patients who will actually develop it. The latter percentage rises to 88% when focusing on the first 50% of patients.

Moreover, if the evidence is set, i.e., if the BN model is provided with information about an individual patient (for example, information about the neoadjuvant and/or adjuvant treatments received), the probability distributions are automatically updated, and the model allows for a prediction of the individual probability of developing a CVD within five years from the cancer diagnosis. To support clinicians in everyday practice, we designed and developed an app-based tool which allows for an estimation of the probability of 5-year CVD risk for individual AYA BC patients (the user interface of the application is shown in Figure 4).

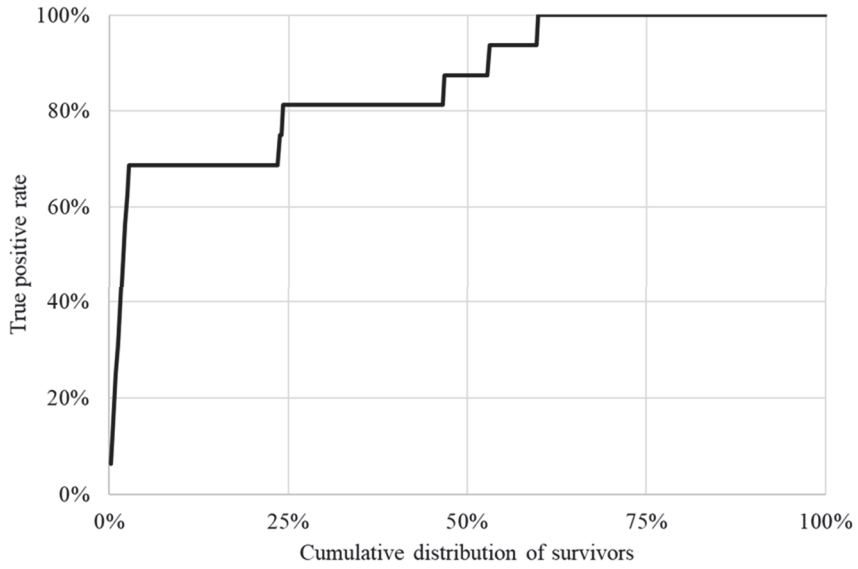


Figure 3. Lift chart obtained using Bayesian network model predictions. In this graph, survivors are sorted (*x*-axis), in decreasing order, according to their risk of developing a cardiovascular disease (CVD). While the cumulative distribution of the survivors increases, the corresponding True Positive Rate (i.e., the proportion of survivors in the validation set who actually developed a CVD within 5 years) is plotted on the *y*-axis. The sharp rise in the lift chart highlights the model's good ability to identify survivors who should be prioritized for CVD follow-up.

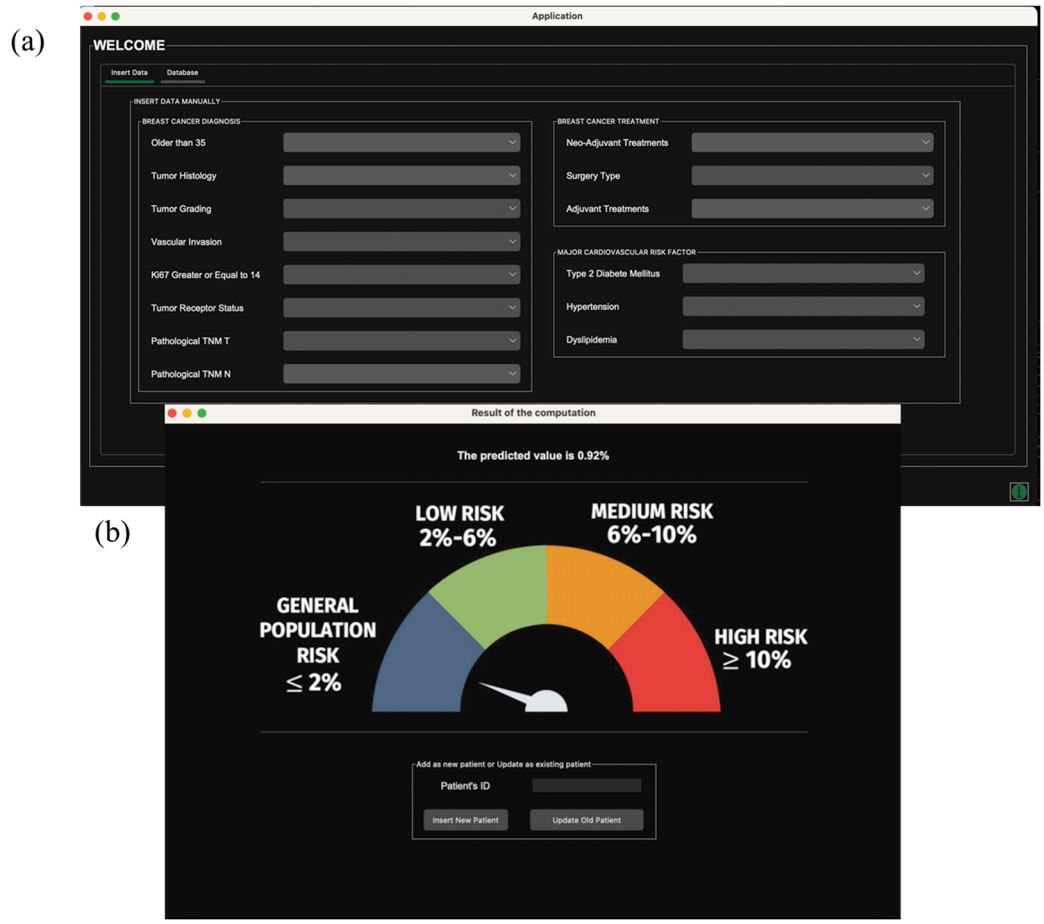


Figure 4. Concept draft of the interface (**a**) and the output (**b**) of the app-based tool. The figure illustrates the interface of the desktop-based app based on Bayesian network model probabilities.

When the user inputs the patient's information into the data entry window (**a**), the baseline model probability estimates for the 5-year cardiovascular disease risk are updated. Subsequently, in a new window (**b**), the user is provided with the individual predicted patient probability, together with an illustration that helps the user interpret the predicted value according to the risk classes.

4. Discussion

In this work, we developed and validated the first AI-based causal model for estimating the CVD risk in AYA females surviving BC. The model very accurately identified the patients who would develop CVDs (classification metrics), correctly ranking them by their risk probability (lift chart) and providing a causal interpretation of the variables involved. Moreover, using practical applications, we showed that the results obtained by our model could be pivotal for clinicians who aim at planning effective, tailored follow-up interventions for this particular group of patients.

4.1. Strengths

In the proposed BN, the context node accounted for the selection and missingness mechanism in the two cohorts, making it possible to combine them. Unfortunately, the same approach cannot be used for other machine learning (ML) techniques; therefore, standard ML models can only use multiple imputation approaches. Despite being very helpful, multiple imputation requires strong assumptions, such as data missing at random, which was not valid in this framework.

A crucial task for predictive models is to determine the minimal subset of variables needed to maximize the performance, which is what interests most clinicians and epidemiologists, especially when many variables are involved and the power set is limited. This can be easily performed in our model given its visual and interpretable causal structure, validated by medical knowledge [3].

Due to the AYA distinctive tumor case mix, biology, and treatments, it is not possible to identify, in the literature, any work that can be used for direct comparison. Despite this, the BN model proved very good at correctly prioritizing and classifying whether patients were at risk. In this setting, most classification metrics, such as the TNR and accuracy, are not informative, being biased by the rarity of CVDs in AYA BC survivors. The same also applies to the interpretation of the AUC, which is the classification metric most frequently presented in the scientific literature. Therefore, when dealing with rare events, preference should be given to metrics such as the balanced accuracy and MCC in view of their ability to summarize the classification performance while also considering the event prevalence [23].

Finally, classification is just one of the tasks that the BN model can accomplish. Indeed, we are currently working on applications of causal inference, such as the estimation of the causal effect of cancer treatments and counterfactual explanations [25].

4.2. Limitations

Like all AI models, the main limitations of this model are its assumptions.

First of all, the causal discovery algorithm used to train the BN has its own set of assumptions that must hold in order to obtain a sensible DAG. First, causal discovery assumes causal sufficiency. This assumption requires that all the causes related to the outcome of interest must be measured. In our case, being able to track adjuvant treatments, neoadjuvant treatments, type 2 diabetes, dyslipidemia, and hypertension allowed us to restrict the set of possible unobserved causes and investigate the potential impact of these variables on CVD. Nevertheless, this assumption is unlikely to hold in a real-world setting; hence, further methodological work is needed to extend the model to explicitly include latent confounders, like socioeconomic and lifestyle factors [26] and also genetic aspects [15,16] that can play an important role in the CVD risk of these patients. Moreover, it is not only important to include these quantities in the causal discovery process but

also to correctly codify them so that the causal relationships are still valid. However, the expert domain knowledge required to perform this is difficult to achieve, especially in new, emerging fields such as cardio-oncology. Finally, causal discovery is known to be affected by the discretization process; hence, deciding the discretization thresholds is challenging and arbitrary.

Another strong assumption is the "no-multiple-versions-of-treatment assumption", i.e., the definition of treatment is the same for all individuals. The BC treatments did not change during the considered period (diagnosis years 2009–2019); therefore, the treatments were not expected to be different in the CBC [19,27]. The same assumption may not be valid in the PBC, where different versions of treatment may be present, since the patients were treated in different hospitals. We do not expect major differences as national recommendations guide the treatment of BC patients and medical oncologists follow them not only for evidence-based standards but also for legal reasons. Nevertheless, attention should also be paid to the generalizability of the results to more recently diagnosed cases. Thus, the impact on the CVD risk profile of new schemes and therapies (e.g., immunotherapy) introduced in the 2020s needs to be further explored. In this regard, a new call for data collection on a more recent cohort of patients is envisioned in the next few years.

Finally, in advance of the validation performed internally in the data, the model needs external validation to confirm the transportability of the results to all AYAs with BC [28]. In this respect, work is already ongoing to externally validate the model in similar cohorts of AYA BC survivors in six different areas of Italy (Veneto, Friuli-Venezia-Giulia, Tuscany, the Apulia regions, and two Sicilian provinces). Moreover, the plan is to extend this work to four additional European countries thanks to a pilot study nested in an international Joint Action, namely, The Innovative Partnership for Action Against Cancer Joint Action and Joint Action PreventNCDs.

5. Conclusions

It is expected that further improvement in the interpretability of the BN model will be obtained while enriching it with more clinical and biological variables. Additional information on both treatments (e.g., drugs and doses) and lifestyle risk factors (i.e., body mass index, systolic pressure, cholesterol levels, and smoking) has already been collected for the CBC. In addition, in the ROSANNA project, a work package is analyzing preoperative circulating microRNAs to identify those associated with CVDs in patients treated in the NeoALTTO trial (NCT00553358) [29]. The circulating microRNA(s) identified in this dataset will be confirmed on independent case series collected in the prospective phase II NeoGENE trial (as the testing dataset), a multicenter, academic Italian study aimed at profiling HER2-positive tumor tissues before and after conventional trastuzumab-based therapy with the aim of studying tumor tissue and the plasma biomarkers of the response to treatment. Finally, the results will be validated using RWD extracted from a single-institution clinical cohort at the INT. The feasibility of the integration of microRNA results will also be assessed during the last year of the project (2025).

To conclude, in this paper, we propose an effective and innovative AI approach that makes it possible to compensate for data scarcity to overcome the missing-not-at-random and selection bias issues, also combining domain knowledge together with data gathered from different cohorts. This work could be a useful use case for all researchers dealing with RWD and rare events who aim at identifying and causally explaining the long-term outcomes in chronic patients.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cancers16213643/s1, Table S1: Algorithms used to retrieve patients' information in the administrative databases; Table S2: Absolute (N) and relative (%) distributions of the patients included in the analysis, by cohort type; Figure S1: Flow chart followed for the model development.

Author Contributions: Conceptualization, A.B. (Alice Bernasconi) and A.T.; data curation, A.B. (Alice Bernasconi), A.Z., M.C.D.S., E.L.R., P.B., I.C. and The Ada Working Group; formal analysis, A.B. (Alice Bernasconi); funding acquisition, S.D.C. and A.T.; investigation, A.B. (Alice Bernasconi) and A.T.; methodology, A.B. (Alice Bernasconi), A.Z., P.J.F.L., M.S. and F.S.; project administration, A.T.; resources, A.T.; software, A.Z., M.S. and F.S.; supervision, F.S.; writing—original draft, A.B. (Alice Bernasconi) and A.T.; writing—review and editing, A.B. (Alice Bernasconi), A.Z., P.J.F.L., M.S., S.D.C., M.C.D.S., E.L.R., P.B., I.C., P.V. (Paolo Verderio), C.M.C., S.P., A.B. (Adriana Blanda), P.P., P.V. (Paola Vallerio), F.S. and A.T. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Institutional Review Board (or Ethics Committee) of Fondazione IRCCS Istituto Nazionale dei Tumori, study protocol number INT 0083/21.

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study.

Data Availability Statement: Upon paper publication, a .net version of the model and the source code of the desktop application will be uploaded in a dedicated repository accessible via a web URL (https://github.com/madlabunimib/cardiovascular-diseases), together with a user manual, to allow readers to freely download them. Further requests for data sharing can be made to the corresponding author.

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Conflicts of Interest: Author Alessio Zanga was employed by the company F. Hoffmann—La Roche Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Article

Expert Judgment Supporting a Bayesian Network to Model the Survival of Pancreatic Cancer Patients †

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Simple Summary: A novel hybrid Bayesian network was created to predict pancreatic cancer survival, incorporating experts' opinions and best literature knowledge using the SHELF method. The hybrid Bayesian network model was developed using twelve clinically validated prognostic variables already available at diagnosis of pancreatic cancer. It aims at overcoming the limit of the lack of threshold values or categories for most clinical variables currently used to predict the survival of pancreatic cancer patients. A validation phase will validate its clinical applicability and reliability.

Abstract: Purpose: Pancreatic cancer is known for its poor prognosis. The most effective treatment combines surgery with peri-operative chemotherapy. Current prognostic tools are designed to predict patient outcomes and inform treatment decisions based on collected data. Bayesian networks (BNs) can integrate objective data with subjective clinical insights, such as expert opinions, or they can be independently based on either element. This pilot study is one of the first efforts to incorporate expert opinions into a prognostic model using a Bayesian framework. **Methods**: A clinical hybrid BN was selected to model the long-term overall survival of pancreatic cancer patients. The SHELF expert judgment method was employed to enhance the BN's effectiveness. This approach involved a two-phase protocol: an initial single-center pilot phase followed by a definitive international phase. **Results**: Experts generally agreed on the distribution shape among the 12 clinically relevant predictive variables identified for the BN. However, discrepancies were noted in the tumor size, age, and ASA score nodes. With regard to expert concordance for each node, tumor size, and ASA score exhibited absolute concordance, indicating a strong consensus among experts. Ca19.9 values and resectability status showed high concordance, reflecting a solid agreement among the experts. The remaining nodes showed acceptable concordance. **Conclusions***:* This project introduces a novel clinical hybrid Bayesian network (BN) that incorporates expert elicitation and clinical variables present at diagnosis to model the survival of pancreatic cancer patients. This model aims to provide research-based evidence for more reliable prognosis predictions and improved decision-making, addressing the limitations of existing survival prediction models. A validation process will be essential to evaluate the model's performance and clinical applicability.

Keywords: Bayesian network; prior elicitation; SHELF; pancreatic cancer; prognosis

1. Introduction

Pancreatic cancer is projected to become the second leading cause of cancer-related death [1]. The only chance for long-term survival in pancreatic cancer patients lies in the combination of chemotherapy and surgical resection, which is achievable in only 20% of cases. Prediction models focused on time-to-event outcomes after pancreatectomy—such as disease-free survival and overall survival—are essential for guiding treatment decisions and providing patient counseling. Current survival prediction tools primarily rely on inferential statistics and traditional regression techniques, such as the Cox proportional hazards model. However, these methods often do not capture the dynamic nature of the disease and the complexities of care processes. The literature suggests that advanced predictive models, which can incorporate perturbing events (like treatment complications) and time-dependent information, may enhance the predictive accuracy of survival models [2–4].

A Bayesian network (BN) implements Bayesian inference for conditional probabilities, allowing for the inclusion of expert opinions when data are limited or for a mixture of both data and opinions when available [5–8]. In a Bayesian framework, the "prior" represents the initial knowledge about the probability of an outcome and incorporating expert input can stabilize predictions when data are scarce or uncertain.

Thus, it is appropriate to derive priors (so-called "informative priors") in BN to compute posteriors adequately at the time of including any patient data for prediction. This process avoids biased estimation or difficult posterior computations (so-called "improper posteriors") [9]. Using "non-informative priors" may complicate model selection and hypothesis testing [10] in a clinical scenario. Therefore, it is essential to assign each node in the BN an informative prior and to connect the nodes using Bayes' theorem to create a robust model [9].

In pancreatic cancer care, many baseline variables guiding prognostic predictions (serum Ca 19-9 levels, tumor size, or tumor site) do not have a unique threshold or a definite category for reference. Parametrization of "informative priors" may be performed by converting clinical expertise and the best available literature into numerical values through the expert elicitation process, integrating these values into the BN. Expert elicitation is a well-established method for gathering and synthesizing unbiased expert judgments, providing valuable quantitative information when data lack a clear threshold or strong reference points in survival risk models [11]. This approach ensures process transparency and reduces biases [12–16]. The SHeffield ELicitation Framework (SHELF) is one of the most recognized methods [17,18].

This study represents the first effort to develop a hybrid BN clinical model for predicting survival in patients with pancreatic cancer. This was accomplished by converting expert insights into probability distributions and incorporating established prognostic indicators identified at diagnosis.

2. Materials and Methods

2.1. Pilot Eliciting Protocol

This study was approved by the local Ethics Committee (109CET). It serves as a pilot experiment in prior elicitation for constructing a BN to model survival outcomes in pancreatic cancer. Prior elicitation, the process of gathering expert opinions to define initial probability distributions, is an essential step for building reliable BNs, especially when clinical data are sparse or lack standardized thresholds. In this pilot phase, we aim to

establish a feasible and systematic framework for collecting expert insights that can later be validated and refined in more extensive studies. The results from this pilot will inform the structure and parameters of the BN, setting the basis for future iterations of the model that integrate both expert judgment and empirical data.

This manuscript focuses on developing an expert elicitation protocol to define the prior distributions and structure of a Bayesian network (BN) for predicting pancreatic cancer survival. The BN has not yet been implemented or validated with empirical data. Therefore, no data-driven feature selection or model training has been performed at this stage. Future phases of this research will include BN implementation, validation with real-world datasets, and testing of the model's predictive capabilities.

Future phases will include scenario testing and expert validation of BN structure to ensure model robustness and clinical relevance further.

2.2. Hybrid BN Design

The transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) checklist [19] is presented in Supplementary Materials S1. The clinical hybrid BN was selected to model the long-term overall survival of pancreatic cancer patients who underwent surgical resection, accommodating both continuous and discretized variables. This decision was based on specific prognostic variables available at the time of diagnosis. The hybrid BN effectively accommodates continuous and categorical variables, preserving important information. The selection of variables for the model was guided by clinical judgment, emphasizing their recognized prognostic relevance for overall survival.

A single-institution panel of 5 experts in pancreatic cancer care selected well-known and clinically relevant prognostic variables already present at diagnosis. To construct the clinical hybrid BN structure (Figure 1), we specified the Directed Acyclic Graph (DAG) based on clinical relevance and expert insights. The research team initially developed the qualitative structure of the BN, representing conditional dependencies among prognostic variables. This structure was guided by the literature on pancreatic cancer prognosis and refined through iterative consultations with a panel of five experts from the General and Pancreatic Surgery Unit at the Pancreas Institute, University of Verona, a globally recognized center for pancreatic cancer care. These experts have extensive experience and consensus regarding the clinical pathways and prognostic indicators relevant to pancreatic cancer, ensuring that the DAG structure accurately reflects real-world clinical relationships.

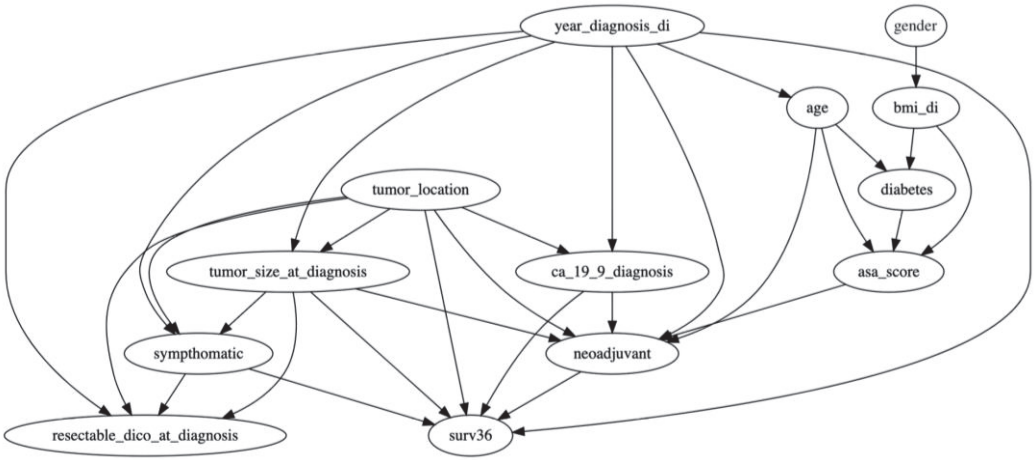


Figure 1. Proposed clinical hybrid Bayesian network.

Each node in the DAG is a clinically relevant factor, such as CA 19-9 serum levels, tumor size, and resectability status, which are known to impact survival outcomes. The experts validated the DAG's structure in two phases: first, through individual assessments where each expert reviewed the proposed relationships, and second, in a group session where the qualitative model was discussed and agreed upon. This approach enabled the expert panel to confirm that each connection in the BN represented a realistic clinical dependency, improving the network's face validity.

No automatic learning methods were used to analyze the available data (for more details, see Supplementary Materials S2). A thorough literature search was conducted to identify suitable variables, focusing on high-quality, peer-reviewed articles published in English.

The following 12 variables, already available at the time of diagnosis, were included in the model:

- CA19.9 serum levels at diagnosis (continuous; expressed as UI/mL);
- Gender (categorical dichotomous; male vs. female);
- Body mass index (BMI; categorical dichotomous; normal/overweight [BMI $\leq$ 30] vs. obesity [BMI > 30, Kg/m^2]);
- Year of diagnosis (categorical dichotomous; before 31 December 2014 vs. after 1 January 2015, given the introduction of FOLFIRINOX chemotherapy to clinical practice);
- Tumor location (categorical dichotomous; head vs. body/tail);
- Age (continuous; expressed in years);
- Diabetes (categorical dichotomous; presence vs. absence of diabetes);
- Tumor size (continuous; expressed in millimeters);
- Symptoms (categorical dichotomous; symptomatic vs. no symptoms);
- American Association of Anesthesiology (ASA) Score [20] (categorical dichotomous; ASA I–II vs. ASA III–IV);
- Resectability status (categorical dichotomous; resectable PDAC vs. borderline resectable/locally advanced PDAC according to NCCN criteria, version 2.2021) [21];
- Neoadjuvant treatment (categorical dichotomous; neoadjuvant treatment performed vs. non-performed).

To construct the clinical hybrid BN (Figure 1), the R software [22] (Version 1.3.959, "HydeNet" package) was used. Node-specific model classes were established based on the node class (binary factors, factors with any number of levels, factors with >3 levels, and numeric or integer) [23,24]. The process was manually executed by specifying only the network structure in the call to *HydeNetwork()* or, more specifically, through a list of arguments containing more model objects as elements. In this method, the network structure is automatically built using the names of the response and explanatory variables within each model in the list argument [23,24]. The advantage of this approach is that it increases flexibility in determining the model parametrization for each node. Permissible models include tabulation (*xtabs*), conditional probability table (*cpt*), ordinary least square (*lm*), logistic regression (*glm*), and multinomial logistic regression (*multinom*) [23,24]. After configuring the model's nodes, the package provides formula-like results of relationships defined in the model.

2.3. Elicitation Process—The SHELF Method

To render the BN informative, it was imperative to establish the probability distribution of each node, called the Quantity of Interest (QoI), a priori. When developing the BN, it was essential to establish both marginal and conditional probability distributions for each QoI to represent the dependencies between variables. For each node in the BN, conditional probabilities were elicited given its parent nodes. This approach reflects the BN's foun-

dational structure, where each variable's distribution depends on the values of its parent nodes, enabling the model to capture complex interdependencies within clinical variables.

This was achieved through expert judgment to generate a weighted linear pooled distribution using the SHELF method. The following steps were followed according to version 4 of the SHELF workflow: (i) definition of QoIs (where each QoI corresponds to a network variable); (ii) selection of experts (Figure 2 presents the host institutions of the experts involved); (iii) expert training in the QoI elicitation process; and (iv) workshop scheduling.



Figure 2. Experts host institutions.

In addition, we assembled a team that included a coordinator, a facilitator, a recorder, an analyst, and an impartial observer (RIO) [17]. To streamline the elicitation process and refine the survey and QoI, a two-stage protocol consisting of a pilot and definitive phase was implemented, as reported by Morgan [25].

2.4. Handling of QoIs

The QoI scores were subjected to an expert-like quartile method [17,26–28]. For continuous QoIs, experts were asked to provide credible intervals (ranges), along with the median and lower and upper quartiles. The QoIs were defined based on clinically plausible values. Credible intervals were established to indicate ranges within which the variable's actual value is expected to lie. However, experts considered it highly unlikely for the true value to fall outside these limits. To reduce overconfidence, these intervals were standardized. For categorical QoIs, experts provided the first, second, and third quartiles of distribution values, representing the "worst" and "best" clinical scenarios, respectively. Following recommendations from the literature, only two of the twelve nodes (year of diagnosis and BMI) were discretized from their original values.

2.5. Selection of Experts

During the pilot phase conducted at the General and Pancreatic Surgery Unit, Pancreas Institute, University of Verona, Verona, Italy, six expert academic surgeons, postdoctoral

fellows, and senior residents in surgery were involved, in line with suggestions in the literature [25]. After finalizing the survey and the semantic framework of the QoIs, nine of the initially invited twelve international academic experts in pancreatic cancer care (surgeons) agreed to participate in the project. Once their commitment was confirmed, the experts received an evidence dossier (composed of the initially selected 12 variables, proven by the literature and clinically relevant for prognostic purposes) that summarized contemporary scientific findings related to pancreatic cancer survival prediction and the specific QoIs for which their judgments were sought (the invitation letter can be found in Supplementary Materials S3). The experts then took part in a three-step elicitation process. First, they expressed individual judgments regarding the probability distribution for each QoI. Next, they engaged in a group discussion where anonymized responses were shared. Finally, they collaborated to reach collective decisions on the QoIs, fitting a "consensus" probability distribution to their judgments using SHELF software (https://jeremy-oakley.shinyapps.io/SHELF-multiple/, accessed on 13 January 2025). To enhance user experience, a deidentified web-based survey was employed throughout the process. Expert opinions were solicited to define the prior distributions and dependencies for a BN focused on predicting survival in pancreatic cancer. These questions aim to capture expert judgments regarding the impact of specific variables (e.g., age, gender) on survival probabilities, which are then used to inform the BN structure (see Figure 3; full data available in Supplementary Materials S4).

Variable #6: Age

***Description*: patient age (expressed as round years) at the time of diagnosis**
***Variable distribution*: continuous**

What would be, in your opinion, the **age cutoff** below which you are reasonably confident that the patient will be alive 36 months after pancreatectomy?

Given this cutoff, can you provide a **lower bound** of confidence (numeric value) based on your gut feeling?

Given this cutoff, can you provide an **upper bound** of confidence (numeric value) based on your gut feeling?

Variable #2: Gender

***Description*: patient gender**

***Variable distribution*: dichotomous (male vs. female)**

Which variable level, in your opinion, is associated with a **greater chance** of being alive 36 months after pancreatectomy?

- Male (patients alive at 36 months have a probability > 50% to be men)
- Female (patients alive at 36 months have a probability > 50% to be women)
- None (among patients alive at 36 months, 50% are men and 50% are women)

Considering the variable level you have selected (male or female), what is in your view the **positive deviation** of survival probability from the middle point (50%/50%)?

Example: selecting "female" and assuming a positive deviation of 15% indicates a probability of (50+15) = 65% that a patient alive at 36 months is female, as opposed to the probability of being male of (50-15) = 35%.

If you selected "none" this value will be 0

Could you specify a **lower bound** of confidence around this probability deviation (numeric value) based on your gut feeling?

Could you specify an **upper bound** of confidence around this probability deviation (numeric value) based on your gut feeling?

Figure 3. Example of the survey administered to the experts at the first step of the workshop (continuous variable, upper panel; categorical variable, lower panel; See Supplementary Materials S3).

2.6. Pooling Expert Opinions

The judgments were entered into R software, where distributions were fitted to each expert's input using the best statistical fit method following a complete case analysis as defined in SHELF protocol. The expert opinions were equally weighted, regardless of seniority or confidence, with respect to the node. This approach selected the distribution with the lowest sum of squared deviations between the specified quantiles and those fitted

by a least-squares algorithm. The candidate distributions included normal, T, shifted gamma, mirrorgamma, lognormal, log-T, mirrorlog-T, and shifted-scaled beta.

The experts' elicitation of QoIs was converted into numerical values, which were then interpolated across individual responses and aggregated. Linear mathematical aggregation was used to summarize the data from the expert pool. Visual representations of distribution graphs for each variable were shared with the experts to facilitate consensus on the optimal distributions.

The facilitator then presented the deidentified individual judgments of all experts to the group. The optimal fit distribution was computed as follows: for continuous nodes, the mean and standard deviation of the linear pooled distribution were used. For categorical values, the mean and standard deviation of the pooled distribution were transformed into shape (alpha) and scale (beta) parameters, as specified in Formula (S1) (see Supplementary Materials S5). Additionally, interpolating the beta-pooled distribution was applied to characterize the discrete data provided by experts in quantiles [29–33]. Beta distributions were bound between 0 and 1, aligning with the support of an event rate. Moreover, this distribution offered flexibility to support unimodal, multimodal, and uniform shapes [14]. For continuous nodes, the best-fitting distribution was determined by minimizing the sum of squared residuals.

3. Results

Figure 4 illustrates the linear pool distribution for each node of the clinical hybrid Bayesian network (BN) developed through the abovementioned process. It presents the elicited probability distributions for each predictor variable, serving as the prior probabilities for each node in the BN. These priors represent the initial beliefs about the possible values of each variable before observing any new patient data based on expert judgments and available demographic or clinical insights. The marginal probabilities are elicited and combined with conditional probabilities in a process explained in Supplementary Materials S6. Each prior distribution in Figure 4 is the starting point for calculating conditional probabilities within the BN. Examples include the following:

- For continuous variables like CA 19-9 serum levels or tumor size, the prior distribution provides a range of plausible values based on clinical experience. This influences the BN's estimation of survival outcomes for patients with varying CA 19-9 serum levels.
- For categorical variables such as gender, the prior distribution reflects the expected population proportion of male versus female patients, setting an initial baseline for the BN. For example, the probability distribution shown for gender, which lies mostly between 0.5 and 0.6, represents the experts' pooled estimate of the proportion of male patients among this model's total population of pancreatic cancer cases. In this case, a value of 0.5 to 0.6 indicates a slight prevalence of one gender over the other, with the probability reflecting the anticipated proportion based on clinical observations or available demographic data.

These prior distributions enable the BN to calculate the conditional survival probabilities by combining the base probabilities (priors) with evidence from related variables. As new data on a specific patient becomes available, the BN updates these probabilities by conditioning on observed values, dynamically refining predictions according to each variable's influence on survival outcomes (further details in Supplementary Materials S6).

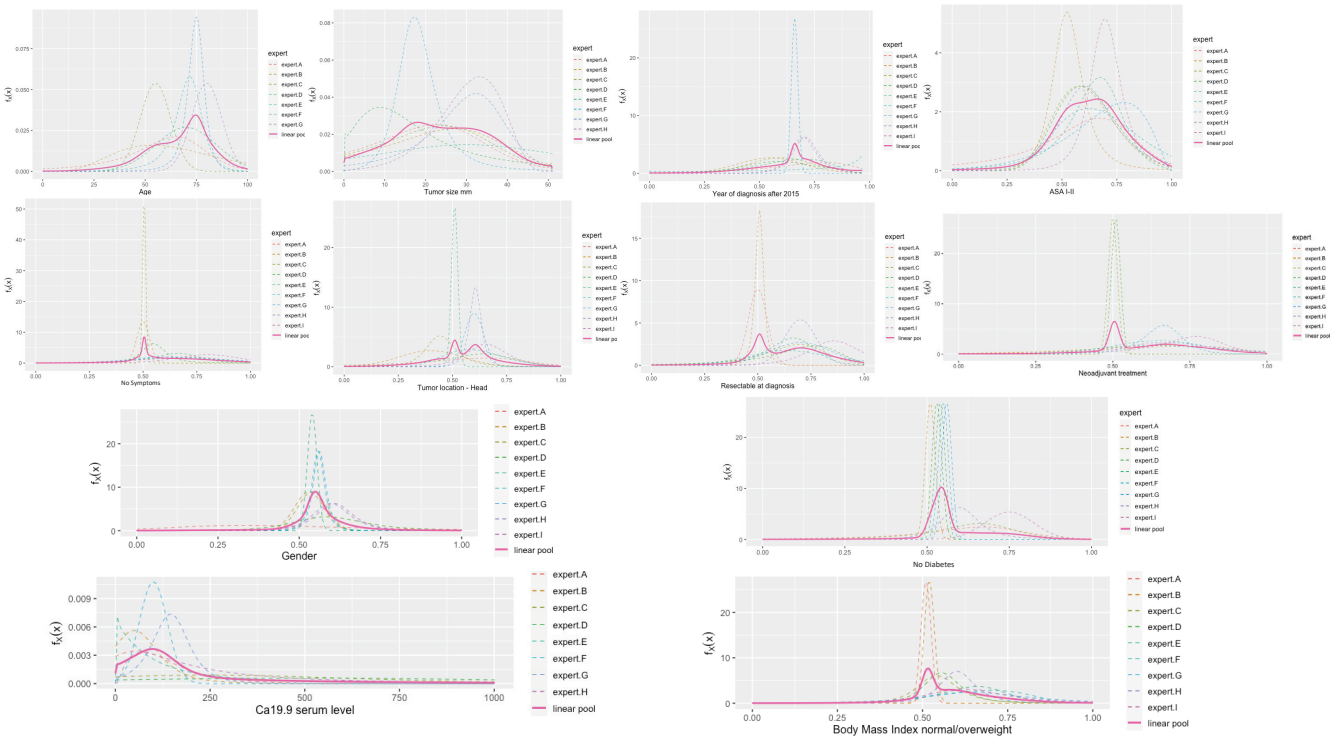


Figure 4. Pooled experts elicited distributions for each of the twelve nodes of the BN.

In this way, the priors established in Figure 4 enable the BN to perform probabilistic inference, producing predictions that adjust based on individual patient characteristics. This initial setup of priors is fundamental for model predictions, as it defines how each node relates to others and the likely values each variable may take, ultimately guiding the BN's predictive accuracy and relevance in clinical settings.

Figure 4 shows a general agreement in distribution shape among the individual experts, although specific disparities were noted in the nodes for tumor size, age, and ASA score.

The informative priors derived from the elicitation process are summarized in Tables 1 and 2, with details on each node including the pooled expert votes, the best-fit distribution, and the predominant distribution type. The right column indicates the level of expert concordance regarding the distributions of the nodes, represented as the proportion of prevalent distributions to the total distributions. Both tumor size and ASA score exhibit absolute concordance, reflecting the highest level of expert consensus. CA19.9 values and resectability status show a high degree of concordance, while the remaining nodes demonstrate acceptable levels of agreement.

Table 1. Mean and standard deviation of the linear pool distributions and best fit-derived prior.

Nodes	Mean	SD	Best-Fit Distribution
Ca 19.9 values	130.29	207.84	T (130.29, 207.84, df = 7 ***)
Age (years) *	69.49	15.69	MirrorlogT (69.49, 15.69, df = 6)
Tumor size (mm) **	23.86	11.42	MirrorlogT (23.74, 11.45, df = 7)
Gender	0.56	0.13	Beta (7.62, 5.76)
Body mass index (normal/overweight–obese)	0.59	0.11	Beta (10.07, 6.69)
Year of diagnosis (before 31 December 2014)	0.65	0.65	Beta (3.85, 2.08)

Table 1. *Cont.*

Nodes	Mean	SD	Best-Fit Distribution
Tumor location (head)	0.54	0.17	Beta (4.26, 3.63)
Diabetes (absence)	0.58	0.11	Beta (12.52, 10.00)
Symptoms (absence)	0.61	0.19	Beta (3.46, 2.15)
American Association of Anesthesiology (ASA) Score I–II	0.62	0.16	Beta (4.75, 2.94)
Resectability at diagnosis	0.64	0.18	Beta (3.83, 2.13)
Neoadjuvant treatment	0.61	0.19	Beta (3.46, 2.22)

* Two experts did not provide a complete response; one did not provide a lower limit and the other only gave null values. ** One expert did not provide the requested values. *** Degrees of freedom are the number of experts minus 1.

Table 2. Expert best-fit distribution and type of prevalent distribution of the expert pool.

Nodes	Expert Best-Fit Distribution		Type of Prevalent Distribution (Number of Experts with Prevalent Distribution/Number of Experts)
Ca 19.9 values	expert.A	t	T (6/8)
	expert.B	t	
	expert.C	t	
	expert.D	t	
	expert.E	logt	
	expert.F	normal	
	expert.G	mirrorlogt	
	expert.H	lognormal	
Age (years)	expert.A	mirrorlogt	MirrorlogT (4/7)
	expert.B	gamma	
	expert.C	normal	
	expert.D	normal	
	expert.E	mirrorlogt	
	expert.F	mirrorlogt	
	expert.G	normal	
Tumor size (mm)	expert.A	mirrorlogt	MirrorlogT (8/8)
	expert.B	mirrorlogt	
	expert.C	mirrorlogt	
	expert.D	logt	
	expert.E	t	
	expert.F	logt	
	expert.G	mirrorlogt	
	expert.H	mirrorgamma	
Gender	expert.A	logt	LogT (6/9)
	expert.B	normal	
	expert.C	normal	
	expert.D	logt	
	expert.E	normal	
	expert.F	mirrorlogt	
	expert.G	logt	
	expert.H	logt	
	expert.I	logt	

Table 2. *Cont.*

Nodes	Expert Best-Fit Distribution		Type of Prevalent Distribution (Number of Experts with Prevalent Distribution/Number of Experts)
Body mass index (normal/overweight–obese)	expert.A	normal	LogT (6/9)
	expert.B	normal	
	expert.C	logt	
	expert.D	logt	
	expert.E	mirrorlogt	
	expert.F	mirrorgamma	
	expert.G	logt	
	expert.H	logt	
	expert.I	logt	
Year of diagnosis (before 31 December 2014)	expert.A	mirrorlogt	LogT (5/9)
	expert.B	normal	
	expert.C	normal	
	expert.D	logt	
	expert.E	mirrorgamma	
	expert.F	beta	
	expert.G	normal	
	expert.H	logt	
	expert.I	logt	
Tumor location (head)	expert.A	mirrorlogt	MirrorlogT (6/9)
	expert.B	normal	
	expert.C	logt	
	expert.D	mirrorlogt	
	expert.E	normal	
	expert.F	gamma	
	expert.G	normal	
	expert.H	mirrorlogt	
	expert.I	logt	
Diabetes (absence)	expert.A	mirrorlogt	Normal (6/9)
	expert.B	normal	
	expert.C	mirrorlogt	
	expert.D	normal	
	expert.E	normal	
	expert.F	normal	
	expert.G	normal	
	expert.H	logt	
	expert.I	normal	
Symptoms (absence)	expert.A	mirrorlogt	MirrorlogT (5/9)
	expert.B	normal	
	expert.C	normal	
	expert.D	logt	
	expert.E	mirrorlogt	
	expert.F	normal	
	expert.G	gamma	
	expert.H	logt	
	expert.I	normal	
American Association of Anesthesiology (ASA) Score I–II	expert.A	mirrorlogt	LogT (9/9)
	expert.B	logt	
	expert.C	gamma	
	expert.D	gamma	
	expert.E	mirrorlogt	
	expert.F	gamma	
	expert.G	mirrorgamma	
	expert.H	logt	
	expert.I	logt	

Table 2. *Cont.*

Nodes	Expert Best-Fit Distribution		Type of Prevalent Distribution (Number of Experts with Prevalent Distribution/Number of Experts)
Resectability at diagnosis	expert.A	normal	MirrorlogT (7/9)
	expert.B	mirrorlogt	
	expert.C	mirrorlogt	
	expert.D	mirrorlogt	
	expert.E	mirrorlogt	
	expert.F	logt	
	expert.G	normal	
	expert.H	normal	
	expert.I	logt	
Neoadjuvant treatment	expert.A	mirrorlogt	MirrorlogT (6/9)
	expert.B	mirrorlogt	
	expert.C	normal	
	expert.D	normal	
	expert.E	logt	
	expert.F	normal	
	expert.G	mirrorlogt	
	expert.H	logt	
	expert.I	mirrorlogt	

4. Discussion

Despite ongoing research efforts, pancreatic cancer continues to have a poor prognosis. In many cases, the disease recurs with a fatal outcome even after surgical resection combined with neoadjuvant or adjuvant treatment [34]. Additionally, pancreatic cancer exhibits significant biological heterogeneity. Some cases display slow and localized growth, while others progress rapidly, highlighting the need for a personalized therapeutic approach [35].

In this context, it is crucial to allocate patients to personalized therapies based on the presumed biology of their disease. This includes decisions such as opting for aggressive surgery followed by chemotherapy versus total neoadjuvant chemotherapy followed by surgical resection. However, existing prognostic tools, such as nomograms, primarily rely on pathological variables—like tumor size and stage [36]—that are often unavailable at the time of diagnosis. Furthermore, these tools typically derive their data from single-center samples, which may limit their generalizability. These models can be classified as traditional or black boxes, both difficult to interpret. Traditional models rely on inferential statistics, drawing information solely from observed data, which makes their inferences highly dependent on the actual sample. However, a deep understanding of the relevant scientific domain suggests that not all scenarios are equally plausible; certain features should be considered a priori more likely than others. This knowledge becomes a valuable resource when available, highlighting the importance of capturing and leveraging it effectively [6]. BNs provide a flexible and unique predictive statistical approach that integrates objective data with subjective opinions, such as expert insights, which can be particularly valuable in a clinical setting. This study represents one of the few attempts to incorporate expert opinions into a prognostic Bayesian framework. The proposed clinical hybrid BN is both innovative and practical, as it enable to integrate existing knowledge regarding continuous and categorical variables within a single network.

In the context of pancreatic cancer management, this integration is especially relevant, as many clinical predictive variables available at diagnosis are continuous (e.g., CA 19-9 serum levels, tumor size from radiology, age), while others are categorical (e.g., gender, tumor location, presence of symptoms, or diabetes). Combining and integrating these heterogeneous variables enables the model to create a comprehensive BN that offers clinicians enhanced tools for accurately modeling long-term survival outcomes. Previous

applications of BN in pancreatic cancer did not include expert judgment [8,37]. The SHELF method effectively translates expert opinions into prior probability distributions and accommodates known distribution families. However, when expert consensus on a particular node is suboptimal, parametric methods may need to be more flexible to reflect that node's nature accurately. In such instances, a semi-parametric approach to prior elicitation should be considered, which offers greater flexibility [38].

The project is in its pilot phase, pertaining to implementing the elicitation process into a BN. Future steps will be developed to make the BN applicable to clinicians for prognostication at diagnosis. From a statistical standpoint, the concordance of the Markov chain algorithm will be tested. Using a real-world dataset including the 12 selected variables, possible clinical scenarios will be created. The sensitivity analysis of these scenarios will be compared and verified by implementing the BN with informative and non-informative priors (a sensitivity analysis plan is presented in Supplementary Materials S6). Further, a user-friendly, interactive application, Shiny, which will assist clinicians in using the developed BN for prognostication purposes, will be developed. Its engagement and ease of use will be measured to assess how well the tool can be integrated into clinical practice, whereas its clinical usability will be measured by assessing how it encourages clinicians to deviate from standard practice when the data suggest a better course of action. Finally, multicenter datasets will be employed to facilitate model validation.

The strengths of this project include its novelty, the intuitive graphical representation of pooled expert distributions, which aids in reaching consensus despite discordance, and the two-phase design that has improved the elicitation process, resulting in clear QoIs and surveys.

However, certain limitations should be acknowledged. First, while the experts were international and not geographically co-located, they all shared backgrounds as surgeons and academics. Despite this commonality, their regular involvement in pancreatic cancer care and research lends reliability to their opinions. Second, the COVID-19 pandemic prevented face-to-face elicitation, as suggested by the SHELF method [26]. Third, to effectively manage the elicitation results, the mean and standard deviation were used for symmetric and continuous variables, while a transformation was applied to derive a beta distribution for categorical variables. These processes may have caused a loss of information. Moreover, this study is an initial pilot phase. Future phases will focus on scenario testing with multicenter datasets and sensitivity analysis, followed by expert-validated scenario testing to ensure robust predictive accuracy for clinical applications.

Finally, some experts did not respond to the invitation, and two nodes did not receive complete responses.

5. Conclusions

This project introduces a clinical hybrid BN that integrates expert elicitation, utilizing clinical variables available at diagnosis to model the survival of pancreatic cancer patients. If further validated, this innovative approach can significantly inform clinical decision-making by providing reliably predicted survival outcomes.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers17020301/s1, Supplementary Materials S1: TRIPOD Checklist: Prediction Model Development; Supplementary Materials S2: Evidence Dossier (Version 1, June 2022); Supplementary Materials S3: Experts invitation letter; Supplementary Materials S4: Survey administered to experts at first step of workshop; Supplementary Materials S5: Formula (S1); Supplementary Materials S6: Technical Appendix.

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Conflicts of Interest: E.S., consultancy honoraria from AlphaTau; S.P., consultancy honoraria from AlphaTay and ClearNoteHealth, and speaker fees from Fresenius Kabi; G.M., consultancy honoraria from OncoSil. The remaining authors declare no conflict of interest.

Abbreviations

BN, Bayesian network; QoI: Quantity of Interest.

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Article

Drug Cost Avoidance Resulting from Participation in Clinical Trials: A 10-Year Retrospective Analysis of Cancer Patients with Solid Tumors

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Simple Summary: In the present framework of constraints on healthcare budgets, an assessment of costs of antineoplastic drugs is a crucial step in contributing to the sustainability of public-payer systems. This study evaluated the characteristics of cancer clinical trials and potential drug cost avoidance in a large population of adult cancer patients with solid tumors enrolled in clinical trials over a 10-year period (2010–2019). These trials were conducted at the Medical Oncology Department of Vall d'Hebron University Hospital in Barcelona (Spain), one of the largest tertiary care centers in the country. Based on the data of 2930 clinical trials with 10,488 participants, it was found that the total cost of antineoplastic drugs supplied by sponsors in the clinical trials setting was EUR 107,306,084, with a potential cost savings of EUR 92,662,609. Participation in sponsored clinical trials in which drugs are provided free of charge yields considerable cost savings, with benefits in clinical strategies to reduce drug expenditures.

Abstract: The objective of this single-center retrospective study was to describe the clinical characteristics of adult patients with solid tumors enrolled in cancer clinical trials over a 10-year period (2010–2019) and to assess drug cost avoidance (DCA) associated with sponsors' contributions. The sponsors' contribution to pharmaceutical expenditure was calculated according to the actual price (for each year) of pharmaceutical specialties that the Vall d'Hebron University Hospital (HUVH) would have had to bear in the absence of sponsorship. A total of 2930 clinical trials were conducted with 10,488 participants. There were 140 trials in 2010 and 459 in 2019 (228% increase). Clinical trials of high complexity phase I and basket trials accounted for 34.3% of all trials. There has been a large variation in the pattern of clinical research over the study period, whereas, in 2010, targeted therapy accounted for 79.4% of expenditure and cytotoxic drugs for 20.6%; in 2019, immunotherapy accounted for 68.4%, targeted therapy for 24.4%, and cytotoxic drugs for only 7.1%. A total of four hundred twenty-one different antineoplastic agents were used, the variability of which increased

from forty-seven agents in 2010, with only seven of them accounting for 92.8% of the overall pharmaceutical expenditure) to three hundred seventeen different antineoplastic agents in 2019, with thirty-three of them accounting for 90.6% of the overall expenditure. The overall expenditure on antineoplastic drugs in clinical care patients not included in clinical trials was EUR 120,396,096. The total cost of antineoplastic drugs supplied by sponsors in a clinical trial setting was EUR 107,306,084, with a potential DCA of EUR 92,662,609. Overall, clinical trials provide not only the best context for the progress of clinical research and healthcare but also create opportunities for reducing cancer care costs.

Keywords: clinical trial; solid cancer tumors; drug cost avoidance; pharmaceutical expenditure; sponsor; academic research

1. Introduction

Timely and accurate integration of scientific advances in evidence-based practice is a continuing challenge for the oncology clinician, given the increasing number of new drug approvals and expanded indications for previously approved drugs. All currently available antineoplastic therapies are developed through the clinical trial process led by the pharmaceutical industry and academic research [1]. Commercially sponsored clinical trials are responsible for the development of new anti-cancer drugs, although commercial interests and market expectations do not always coincide with clinical needs. Academic research optimizes the use of drugs in a clinical setting and develops new drug combinations with a strong focus on patients and their unmet needs. Based on clinical trials registered at 'ClinicalTrials.gov', 65% of trials are being supported by health systems, governmental funds, university bodies, and other research organizations [2]. Data from the European Clinical Trials Database (EudraCT) for the period 2005–2013 show that non-commercial sponsors conducted an important proportion (39%) of clinical trials [2]. However, recent statistics (2005–2022) have shown that the percentage of non-commercial trials has decreased to 20% [3], a dangerous trend that will ultimately prove detrimental to cancer care. Moreover, progress in other areas, such as radiation therapy and surgery, can only be achieved by research conducted almost exclusively in academic centers, so the overall contribution of non-commercial institutions to clinical research would be much higher.

Patients benefit from clinical trials due to access to experimental treatments when no other options exist, and to new therapies not yet available, while contributing to the advancement of medical research. In the framework of increasing concerns about the costs of cancer care, data on the cost savings derived from academic clinical trials is limited. Case–control comparisons have shown that participation in cancer clinical trials did not result in significant increases in the direct costs of medical care [4–9], but the provision of investigational drug services at academic institutions accounted for substantial drug cost avoidance (DCA) in different disease categories and therapeutic areas, including oncology [10–12].

In an analysis of 88 clinical trials with cancer patients in 11 hospitals in Germany from 2002 to 2005, an actual cost saving of EUR 1.5 million was reported [13]. In a lung cancer unit of the Italian National Institute for Cancer Research, the enrolment of 44 patients in 12 sponsored clinical trials allowed the saving of 30% of the pharmaceutical expenses for anti-neoplastic agents in 2010, with additional income from the grants received for each enrolled patient [14]. In a study of 17 phase III clinical trials and 3195 patients conducted by the NCIC Clinical Trials Group in Canada from 1999 to 2011, the total DCA was estimated at CAD 27,952,512, of which targeted therapy constituted 43% [15]. In a study of 357 oncology patients treated on 53 different trial protocols in 2009 and 2010 in a single UK institution, there was an average treatment cost saving of GBP 885,275, largely attributable to pharmaceutical company provision of free drug supplies [16]. In a

review of five phase III multicenter, international clinical trials with currently marketed drugs in 136 prostate cancer patients, a total cost avoidance of EUR 696,002 (EUR 5118 per patient) during the study period (1996–2013) was estimated [17]. In another study of 89 breast cancer patients included in 37 clinical trials between 2014 and 2016, the use of an investigational drug as compared to the best standard of care treatments was associated with a total cost avoidance of EUR 957,246 (EUR 10,756 per patient) [18]. In a single Spanish National Health System institution, the overall cost of treatment for 68 adult cancer patients enrolled in 20 different clinical trials was 79% lower in comparison to the routine standard of care, with an average treatment cost per patient and protocol ranging from an excess of EUR 8193 to a saving of EUR 59,770 [19].

However, real-world evidence of drug cost avoidance (DCA) from a large number of sponsored clinical trials in cancer patients is still lacking. Therefore, the objective of the study was to analyze the pharmaceutical antineoplastic expenditure and potential drug cost savings in a large cohort of adult cancer patients with solid tumors enrolled in sponsored clinical trials in a single institution over a 10-year period. The analysis of data by phases of the trials, pharmacological drug classes, tumor location, and active drugs is a differential contribution of the study. Assessment of drug cost savings in a very large cohort of patients with solid tumors will contribute to removing concerns regarding the additional costs of clinical trial settings.

2. Materials and Methods

2.1. Design and Patients

This was a single-center retrospective study of adult cancer patients with solid tumors enrolled in any ongoing clinical trial over a 10-year period (2010–2019) in the Medical Oncology Department of Vall d'Hebron University Hospital (HUVH) in Barcelona, Spain. Data on the pharmaceutical expenditure of adult cancer patients with solid tumors treated at HUVH during the same 10-year period in the health care setting, that is, outside the clinical trial setting, were previously reported [20].

The hospital is the largest tertiary care center in Catalonia and one of the largest in the country. It belongs to the network of medical centers of the national public health system, which provides healthcare services free of charge to all Spanish citizens independently of their demographic characteristics, socioeconomic status, or tax contribution level. In the case of oncological patients, antineoplastic treatments are reimbursed to the hospital by the public health authority. The HUVH has a reference population of 430,000 inhabitants and an annual budget of EUR 630 million [21]. The Medical Oncology Department develops extensive clinical and research activities in coordination with the Vall d'Hebron Institute of Oncology (VHIO). The Pharmacy Department provides services to the general, traumatology, and pediatric/maternal areas, and integrates the Outpatient Prescriptions Unit and the Pharmacy Oncology Unit with various subunits located at the different oncology day hospitals.

Inclusion criteria were: patients of both genders, aged 18 years or older, diagnosed with malignant solid tumors, enrolled in a clinical trial, and treated with any specific antineoplastic drug by the parenteral or oral routes. The parenteral route included intravenous, intramuscular, and subcutaneous drug delivery. Patients with solid tumors not enrolled in a clinical trial were excluded. Approval by the Clinical Research Ethics Committee was waived because of the quality of care nature of the study.

2.2. Study Variables

For each patient, the following variables were recorded: phase of the clinical trial including phase 0; phase I and basket trials; phase II (tumor-specific); phase III; post-authorization and rollover studies; cancer type, classified by body location/system following the National Cancer Institute classification [22]; and pharmacological classes of antineoplastic drugs categorized following the International Common Denomination of Drugs (ICD) or International Non-Proprietary Names (INN) or the Spanish Agency of

Medicines and Medical Devices [23], grouped into cytotoxic drugs, immunotherapy, targeted therapy, and other active drugs. For these subgroups, the number of patients and pharmaceutical expenditures for each natural year of the study period were recorded depending on the availability of data.

2.3. Pharmaceutical Expenditure, Sponsor Contribution, and Drug Cost Avoidance

The data for the sample of patients enrolled in clinical trials during the 2010–2019 study period were obtained from the Fundanet (Cantabria, Spain) CTMS (Clinical Trials Management) software (V.2020-13) (https://vhio.fundanetsuite.com/EstudiosClinicos/ (accessed 20 June 2020)) of the VHIO Center of Clinical Trials. Data extracted from this database were imported to the Microsoft Excel program to obtain the following information for each study year: number of clinical trials actively recruiting patients; number of clinical trials with actively recruited patients categorized by phases and cancer type; number of recruited patients by trial phases; and number of patients on active treatment by trial phases.

The costs of all pharmaceutical specialties provided by the sponsors were considered whenever they were marketed drugs at the time of prescription. In randomized double-blind clinical trials, in which the Pharmacy Service was masked regarding the identification of the investigational drug before opening the randomization code, the costs of the doses were calculated by applying the allocation ratio to the number of randomized arms of the protocol. Two types of economic analysis were performed:

(1) The economic contribution of the sponsor in the provision of drugs to carry out clinical trials was calculated according to the actual cost (for each year) of the pharmaceutical specialties that the Vall d'Hebron University Hospital would have had to purchase to carry out these clinical trials in the absence of sponsorship. Details of the calculation of pharmaceutical expenditure and the direct cost of acquiring the pharmaceutical specialties of antineoplastic drugs were previously reported [20].

(2) To obtain the estimated potential annual DCA in the total population of the clinical trials, the mean cost of antineoplastic treatment per patient and year, in each tumor location, of the population of patients treated in our center in the healthcare setting, that is, not included in clinical trials, in the same period (2010–2019), was previously calculated. For this calculation, data were used from the exhaustive analysis of pharmaceutical expenditure involved in antineoplastic treatment of the healthcare population previously reported in our previous study [20]. This mean cost obtained per patient in the healthcare setting outside of clinical trials (in each year and each tumor location) was applied to the number of participants in clinical trials to obtain an estimate of the pharmaceutical expenditure that these patients would have incurred with the treatment that would have been prescribed and used in these patients on the same dates if they had been treated in our healthcare population. The potential annual DCA by tumor location was calculated for clinical trial participants treated with intravenous antineoplastic medications only, as data on tumor locations in patients receiving oral antineoplastic medications in the clinical trial were not available in the anonymized database.

2.4. Statistical Analysis

The data are reported as descriptive statistics. Categorical variables are expressed as frequencies and percentages, and quantitative variables as the mean and standard deviation (SD) or the median and interquartile range (IQR) (25th–75th percentile) if non-normal distributions of data. Analyses were performed using the Pharmacy Analytics Manager (V.2022.1.0) (https://www.asserta.net (accessed on 20 July 2020)).

3. Results

3.1. Clinical Trials and Patient Population

A total of 2930 clinical trials with active recruitment were conducted at the Medical Oncology Department between 2010 and 2019 for solid tumor treatment. There were 140 in 2010 and 459 in 2019, an increase of 228%. As shown in Table 1, clinical trials of high

complexity phase I and basket trials accounted for 34.3% of all the trials. Also, clinical trials focused on a specific tumor type accounted for the largest percentage (76.5%), but trials not involving a specific tumor type increased markedly from 36 in 2010 to 103 in 2019, an increase of 186%.

Table 1. Number of clinical trials conducted at the Medical Oncology Department with active recruitment of patients at any time during the study period.

Study Year	Clinical Trials					
	Total	Phase 0 *n* (%)	Phase I and Basket *n* (%)	Phase II *n* (%)	Phase III *n* (%)	Post-Authorization and Rollovers *n* (%)
2010	140	0	37 (26.4)	54 (38,6)	49 (35.0)	0
2011	161	0	48 (29.8)	57 (35.4)	56 (34.8)	0
2012	219	0	66 (30.1)	85 (38.8)	68 (31.0)	0
2013	232	0	75 (32.3)	96 (41.4)	61 (26.3)	0
2014	251	0	83 (33.1)	99 (39,4)	64 (25.5)	5 (2.0)
2015	303	0	106 (35.0)	94 (31.0)	89 (29.4)	14 (4.6)
2016	370	0	129 (34.9)	117 (31.6)	108 (29.2)	16 (4.3)
2017	374	0	137 (36.6)	107 (28.6)	111 (29.7)	19 (5.1)
2018	421	0	161 (38.2)	131 (31.1)	107 (25.4)	22 (5.2)
2019	459	1 (0.2)	162 (35.3)	141 (30.7)	121 (26.4)	34 (7.4)
2010–2019	2930	1 (0.03)	1004 (34.3)	981 (33.5)	834 (28.5)	110 (3.7)

Between 2010 and 2019, specific antineoplastic treatment was delivered in the clinical trial setting to 10,488 patients, 4964 (47.3%) of whom were treated with intravenously administered drugs, and 5524 (52.7%) with oral drugs. The number of patients on active treatment in the different phases of the clinical trials between 2016 and 2019 is shown in Figure 1.

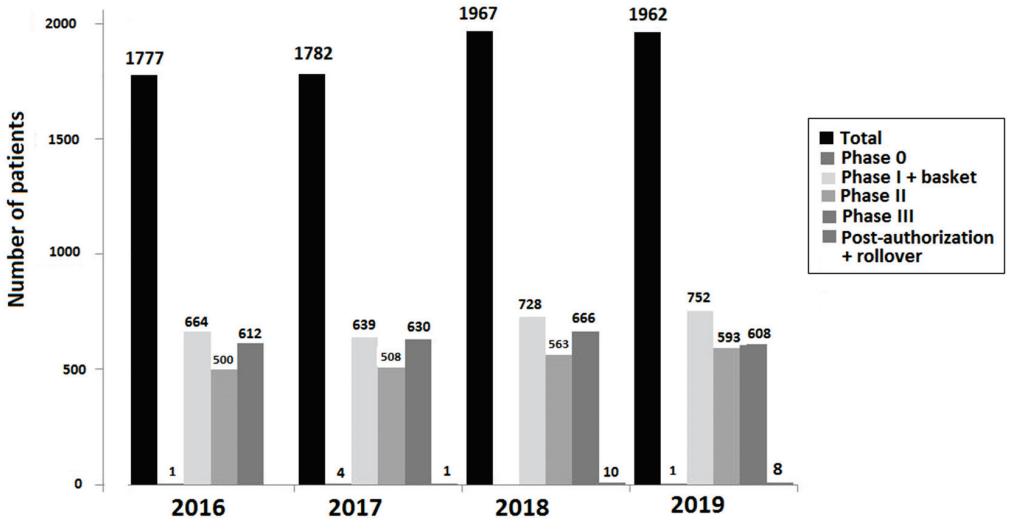


Figure 1. Distribution of 7488 patients on active treatment by phases of trials (2016–2019).

3.2. Pharmaceutical Expenditure on Cancer Treatment in Clinical Trials (Financial Contribution from the Sponsor)

The overall pharmaceutical expenditure during the study period (2010–2019) based on the contribution of the sponsor was EUR 107,306,084, divided into EUR 72,266,379 for treatment with intravenous antineoplastic drugs, and EUR 35,039,705 for oral drugs (Table 2).

Table 2. Pharmaceutical expenditure by type of antineoplastic drug in the period 2010–2019 in the clinical trial setting.

Study Years	Expenditures of Antineoplastic Drugs	
	Intravenous	Oral
2010	EUR 2,457,850	NR
2011	EUR 1,700,250	NR
2012	EUR 2,203,633	NR
2013	EUR 3,331,912	EUR 1,845,309
2014	EUR 4,636,490	EUR 2,022,064
2015	EUR 4,120,596	EUR 2,876,494
2016	EUR 6,220,320	EUR 3,545,183
2017	EUR 12,675,915	EUR 6,086,139
2018	EUR 17,844,749	EUR 8,166,853
2019	EUR 17,074,664	EUR 10,497,663
Total	EUR 72,266,379	EUR 35,039,705
Overall	EUR 107,306,084	

NR: not registered.

3.3. Expenditure by Pharmacological Classes

Expenditures by pharmacological classes and types of antineoplastic drugs were available for the period between 2013 and 2019. The overall use of intravenous and oral antineoplastic drugs accounted for 94% of the expenditures (EUR 100,944,351). As shown in Table 3, targeted therapy was associated with the largest expenditure (58%), followed by immunotherapy (35.3%), and cytotoxic drugs (6.7%). There was a marked increase in expenditures from a total of EUR 5,177,221 in 2013 to EUR 27,572,327 in 2019. However, annual increases varied from 5.1% (2014 to 2015) to 92.1% (2016–2017) and 6% (2018–2019).

Table 3. Pharmaceutical expenditure by pharmacological classes and study year (2013–2019) in the clinical trial setting.

	Cytotoxic Drugs	Immunotherapy	Targeted Therapy	Other Drugs	Total
Antineoplastic drugs					
Intravenous	EUR 6,322,282	EUR 35,623,961	EUR 23,958,403		EUR 65,904,646
Oral	EUR 424,306		EUR 34,609,333	EUR 6066	EUR 35,039,705
Total	EUR 6,746,588	EUR 35,623,961	EUR 58,567,736		EUR 100,944,351
Study year					
2013	EUR 957,915	EUR 590,250	EUR 3,629,056		EUR 5,177,221
2014	EUR 613,360	EUR 1,517,637	EUR 4,527,558		EUR 6,658,554
2015	EUR 796,317	EUR 222,342	EUR 5,978,431		EUR 6,997,090
2016	EUR 891,738	EUR 2,536,316	EUR 6,337,449		EUR 9,765,502
2017	EUR 1,175,345	EUR 6,900,964	EUR 10,685,745		EUR 18,762,054
2018	EUR 1,001,328	EUR 12,169,256	EUR 12,841,019		EUR 26,011,603
2019	EUR 1,310,587	EUR 11,687,195	EUR 14,568,479	EUR 6066	EUR 27,572,327

The data on pharmaceutical expenditure by pharmacological classes for the complete 10-year study period were available for intravenous antineoplastic agents (Table 4). There was a large variation in the pattern of clinical research over the study period: in 2010,

targeted therapy accounted for 79.4% of expenditure and cytotoxic drugs for 20.6%; in 2019, immunotherapy accounted for 68.4%, targeted therapy for 24.4%, and cytotoxic drugs for only 7.1%. Also, the percentages of patients treated with these pharmacological classes in 2010 and 2019 showed important changes, from 75.2% to 33.8% for cytotoxics, 0.8% to 67.2% for immunotherapy, and 54.2% to 28% for targeted therapy.

Table 4. Pharmaceutical expenditure by type of intravenous antineoplastic drug in the period 2010–2019 in the clinical trial setting.

Study Year	Cytotoxic Drugs	Immunotherapy	Targeted Therapy	Total Expenditure	Change vs. Previous Year, %
2010	EUR 506,138	-EUR	EUR 1,951,712	EUR 2,457,850	
2011	EUR 599,725	-EUR	EUR 1,100,526	EUR 1,700,250	−30.8%
2012	EUR 860,070	-EUR	EUR 1,343,563	EUR 2,203,633	29.6
2013	EUR 863,237	EUR 590,250	EUR 1,848,425	EUR 3,331,912	51.2
2014	EUR 568,777	EUR 1,517,637	EUR 2,550,076	EUR 4,636,490	39.1
2015	EUR 787,984	EUR 222,342	EUR 3,110,270	EUR 4,120,596	−11.1
2016	EUR 866,817	EUR 2,536,316	EUR 2,817,187	EUR 6,220,320	51.0
2017	EUR 1,047,329	EUR 6,900,964	EUR 4,727,621	EUR 12,675,915	103.8
2018	EUR 940,547	EUR 12,169,256	EUR 4,734,946	EUR 17,844,749	40.8
2019	EUR 1,217,591	EUR 11,687,195	EUR 4,169,878	EUR 17,074,664	−4.3

3.4. Expenditure by Antineoplastic Agent

The antineoplastic agents used for treating patients included in clinical trials between 2010 and 2019 are shown in Table S1 of the Supplementary Materials. A total of four hundred twenty-one different antineoplastic agents were used, the variability of which increased from forty-seven agents in 2010, with only seven of them accounting for 92.8% of the overall pharmaceutical expenditure) to three hundred seventeen different antineoplastic agents in 2019, with thirty-three of them accounting for 90.6% of the overall expenditure (Table 5).

Table 5. Antineoplastic agents used in patients treated in the clinical trial setting in 2010 and 2019.

2010			2019		
Antineoplastic Agent	**Expenditure**	**% of Total Expenditure**	**Antineoplastic Agent**	**Expenditure**	**% of Total Expenditure**
Trastuzumab	EUR 919,484	37.4	Pembrolizumab	EUR 3,590,128.10	13.0
Bevacizumab	EUR 449,063	18.3	Nivolumab	EUR 2,489,205.42	9.0
Aflibercept/placebo	EUR 301,600	12.3	Cabozantinib	EUR 2,392,934.10	8.7
Docetaxel	EUR 191,287	7.8	Atezolizumab	EUR 1,983,242.04	7.2
Pemetrexed	EUR 145,919	5.9	Bevacizumab	EUR 1,696,849.55	6.1
Cetuximab	EUR 145,079	5.9	Palbociclib	EUR 1,449,416.28	5.3
Panitumumab	EUR 129,287	5.3	Olaparib	EUR 1,338,767.04	4.9
Total		92.8	Lorlatinib	EUR 1,094,262.59	4.0
			Ipilumumab	EUR 786,563.46	2.8
			Pembrolizumab	EUR 670,891,67	2.4
			Pemetrexed	EUR 615,425.91	2.2
			Pertuzumab	EUR 581,406.00	2.1
			Avelumab	EUR 568,416.00	2.1
			Abiraterone	EUR 500,524.62	1.8

Table 5. *Cont.*

2010			2019		
Antineoplastic Agent	**Expenditure**	**% of Total Expenditure**	**Antineoplastic Agent**	**Expenditure**	**% of Total Expenditure**
			Pembrolizumab/placebo	EUR 405,841.74	1.5
			Cetuximab	EUR 393,887.10	1.4
			Lenvatinib	EUR 386,416.81	1.4
			Dinutuximab	EUR 348,727.07	1.3
			Atezolizumab/placebo	EUR 326,070.63	1.2
			Osimertinib	EUR 300,501.60	1.1
			Sunitinib	EUR 299,647.57	1.1
			BMS-986213/Nivolumab	EUR 289,906.56	1.0
			Axitinib	EUR 280,783.80	1.0
			Enzalutamide	EUR 274,394.96	1.0
			Trastuzumab s.c.	EUR 271,830.00	1.0
			Apalutamide	EUR 259,110.00	0.9
			Ipilimumab/placebo	EUR 222,314.53	0.8
			Trastuzumab	EUR 217,028.66	0.8
			Alectinib	EUR 204,001.91	0.7
			Panitumumab	EUR 183,674.66	0.7
			Nivolumab/placebo	EUR 183,520.80	0.7
			Niraparib	EUR 181,838.25	0.7
			Olaratumab/placebo	EUR 181,812.21	0.7
			Total		90.6

3.5. Expenditure by Tumor Location

In 2010, patients with 17 tumor locations received intravenous antineoplastic drugs, with five tumor sites (breast, colon, ovary, non-small cell lung cancer, and prostate) accounting for 90% of all cancer cost treatment, but this number increased to 30 tumor locations, with fifteen tumor sites, in particular non-small cell lung cancer, advanced solid tumors, breast, colon, and ovary accounting for 90% of expenditure in 2019 (Table 6). Also, the highest percentages of patients treated in 2019 corresponded to advanced solid tumors (20.2%) and non-small cell lung cancer (17.5%).

Table 6. Percentages of pharmaceutical expenditures and patients treated in the clinical trial setting with intravenous antineoplastic agents by tumor location in 2010 and 2019.

2010			2019		
Tumor Location	**% of Total Expenditure**	**% of Total Patients**	**Tumor Location**	**% of Total Expenditure**	**% of Total Patients**
Breast	46.4	34.8	Lung, non-small cell	27.0	17.5
Colon	18.0	19.1	Advanced solid tumor	10.1	20.2
Ovary	14.3	8.7	Breast	9.5	9.9
Lung, non-small cell	9.6	13.5	Colon	8.0	7.6
Prostate	5.8	3.0	Ovary	7.0	5.2
Pancreas endocrine	1.9	0.8	Melanoma	6.2	5.4

Table 6. *Cont.*

2010			2019		
Tumor Location	**% of Total Expenditure**	**% of Total Patients**	**Tumor Location**	**% of Total Expenditure**	**% of Total Patients**
Rectum	1.5	3.2	Kidney	5.2	3.7
Advanced solid tumors	1.3	8.4	Pancreas exocrine	2.9	4.3
Oral cavity and oropharynx	0.4	1.6	Uterine cervix	2.7	3.4
Stomach	0.3	1.6	Lung, small cell	2.6	2.7
Pancreas exocrine	0.2	2.4	Endometrium	2.3	3.2
Lung, small cell	0.2	0.5	Urinary bladder	2.2	2.7
Urinary bladder	0.04	2.2	Stomach	2.2	3.1
Kidney	0.02	0.5	Oral cavity and oropharynx	2.1	2.2
Soft tissue sarcoma	0.01	0.3	Mesothelioma	1.7	1.5
Endometrium	0.01	0.8	Esophagus	1.5	1.1
Extrahepatic bile duct	0.0	0.3	Soft tissue sarcoma	1.4	1.0
			Rhinopharynx/cavum	1.2	0.4
			Neuroendocrine	0.7	1.4
			Hepatic carcinoma	0.7	0.5
			Thymoma	0.7	0.5
			Brain	0.5	0.7
			Prostate	0.5	1.0
			Squamous cell skin cancer	0.4	0.3
			Larynx/hypopharynx	0.3	0.09
			Rectum	0.2	0.6
			Basal cell carcinoma	0.2	0.2
			Merkel carcinoma	0.07	0.2
			Extrahepatic bile duct	0.02	1.1
			Urothelial cancer	0.0	0.09
			Adrenal		0.09
			Anus		0.4
			Pancreas endocrine		0.5
			Thyroid		0.3
			Gallbladder		0.09

The pharmaceutical expenditures by tumor location for each study year in patients enrolled in clinical trials treated with intravenous antineoplastic agents are shown in Table S2 of the Supplementary Material.

3.6. Estimation of Potential Drug Cost Avoidance

The estimated potential drug cost of antineoplastic treatments avoided for patients included in clinical trials during the study period is shown in Table 7. The total pharmaceutical expenditure avoided was EUR 92,662,609, divided into EUR 34,463,891 for the use of antineoplastic agents administered intravenously, and EUR 58,198,718 for those given by the oral route.

Table 7. Estimated antineoplastic drug cost avoidance associated with patients included in clinical trials conducted between 2010 and 2019.

Study Years	Expenditures on Antineoplastic Drugs		
	Intravenous	Oral	Total
2010	EUR 1,650,750	EUR 4,541,111	EUR 6,191,865
2011	EUR 1,205,680	EUR 6,829,844	EUR 8,035,524
2012	EUR 1,322,395	EUR 4,141,530	EUR 5,463,925
2013	EUR 2,349,744	EUR 3,994,676	EUR 6,344,420
2014	EUR 2,157,533	EUR 4,933,760	EUR 7,091,293
2015	EUR 3,034,919	EUR 6,474,355	EUR 9,509,274
2016	EUR 4,087,619	EUR 6,370,112	EUR 10,457,731
2017	EUR 4,722,001	EUR 5,911,956	EUR 10,633,957
2018	EUR 7,266,822	EUR 7,196,238	EUR 14,463,060
2019	EUR 6,666,428	EUR 7,805,132	EUR 14,471,560
Total	EUR 34,463,891	EUR 58,198,718	EUR 92,662,609

The mean cost obtained per patient in the healthcare setting outside of clinical trials (in each year and each tumor location) is presented in Table S3 of the Supplementary Material. Applying this mean cost per patient to each patient included in a clinical trial allowed us to obtain a distribution of potential DCA by tumor location and study years, shown in Table S4 of the Supplementary Material (for intravenous drugs only). Breast cancer, rectal cancer, non-small cell lung cancer, and melanoma were the tumor locations in the upper rank of DCA.

To put into context what the savings in clinical trials have represented for our institution, previously reported data on pharmaceutical expenditure on antineoplastic drugs for patients with solid tumors treated in the healthcare setting (outside clinical trials) at our center are presented (EUR 120,396,096) for the same study period 2010–2019 [20]. The total cost of antineoplastic drugs supplied by sponsors in the clinical trials setting was EUR 107,306,084, with a potential DCA of EUR 92,662,609 (Table 8).

Table 8. Pharmaceutical expenditure for the treatment of patients with solid tumors during the study period (2010–2019).

Study Years	Pharmaceutical Expenditure of Antineoplastic Agents					
	Healthcare Setting		Clinical Trial Setting		Potential Drug Cost Avoidance	
	Intravenous	Oral	Intravenous	Oral	Intravenous	Oral
2010	EUR 6,565,263	EUR 2,579,163	EUR 2,457,850	NR	EUR 1,650,750	EUR 4,541,115
2011	EUR 4,464,740	EUR 3,271,684	EUR 1,700,250	NR	EUR 1,205,680	EUR 6,829,844
2012	EUR 4,695,722	EUR 2,853,205	EUR 2,203,633	NR	EUR 1,322,395	EUR 4,141,530
2013	EUR 4,436,132	EUR 2,437,685	EUR 3,331,912	EUR 1,845,309	EUR 2,349,744	EUR 3,994,676
2014	EUR 5,770,959	EUR 3,302,873	EUR 4,636,490	EUR 2,022,064	EUR 2,157,533	EUR 4,933,760
2015	EUR 7,596,964	EUR 4,346,928	EUR 4,120,596	EUR 2,876,494	EUR 3,034,919	EUR 6,474.355
2016	EUR 9,769,375	EUR 4,581,945	EUR 6,220,320	EUR 3,545,183	EUR 4,087,619	EUR 6,370,112
2017	EUR 9,475,022	EUR 4,990,955	EUR 12,675,915	EUR 6,086,139	EUR 4,722,001	EUR 5,911,956
2018	EUR 11,252,776	EUR 6,723,301	EUR 17,844,749	EUR 8,166,853	EUR 7,266,822	EUR 7,196,238

Table 8. *Cont.*

Study Years	Pharmaceutical Expenditure of Antineoplastic Agents					
	Healthcare Setting		Clinical Trial Setting		Potential Drug Cost Avoidance	
	Intravenous	Oral	Intravenous	Oral	Intravenous	Oral
2019	EUR 12,666,317	EUR 8,615,087	EUR 17,074,664	EUR 10,497,663	EUR 6,666,428	EUR 7,805,132
Total	EUR 76,693,270	EUR 43,702,826	EUR 72,266,379	EUR 35,039,705	EUR 34,463,891	EUR 58,198,718
Overall	EUR 120,396,096		EUR 107,306,084		EUR 92,662,609	

NR: not registered.

Figure 2 shows the percentages of pharmaceutical expenditure on antineoplastic drugs for the treatment of patients with solid cancers during the study period in the two populations of patients treated in the routine healthcare setting (mean cost 66%, range 41% to 82%) and participants in clinical trials with sponsor financing (mean cost 44%, range 18% to 59%). On the other hand, the economic contribution of the sponsors accounted for 89% of the expenditure incurred by HUVH for treating cancer patients with antineoplastic drugs in the routine healthcare setting.

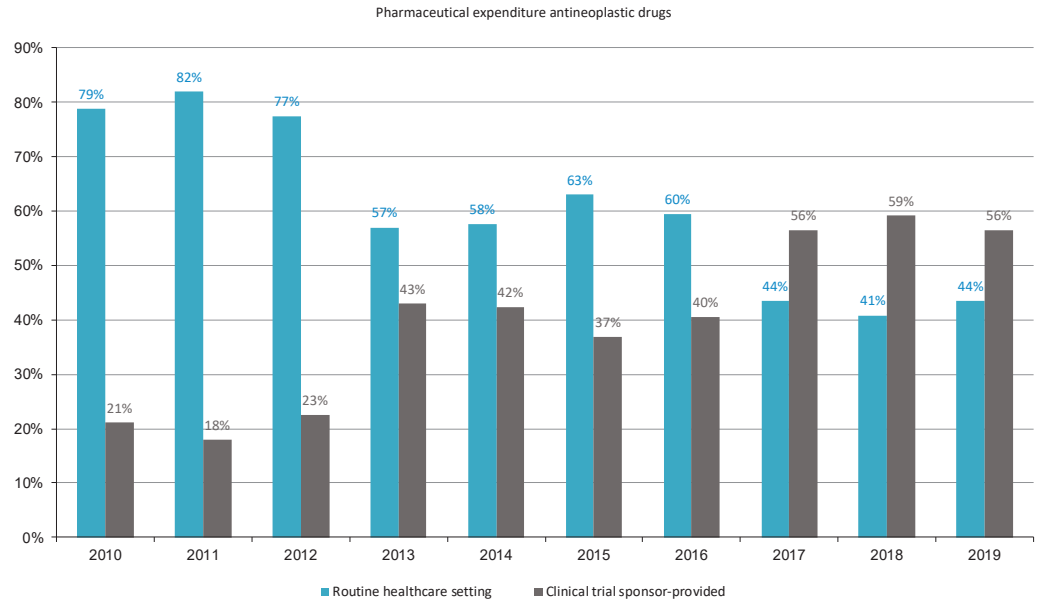


Figure 2. The proportion of pharmaceutical expenditure for antineoplastic drugs in the routine healthcare setting and in sponsor-supported clinical trials.

Figure 3 shows the percentages of pharmaceutical expenditure on antineoplastic drugs for solid cancers during the study period in the routine healthcare setting (mean cost 62%, range 49% to 60%) and the potentially avoided expenditure due to the performance of clinical trials (mean cost 48%, range 40% to 51%). Also, DCA accounted for 77% of the expenditure incurred by HUVH for treating cancer patients with antineoplastic drugs in the routine healthcare setting.

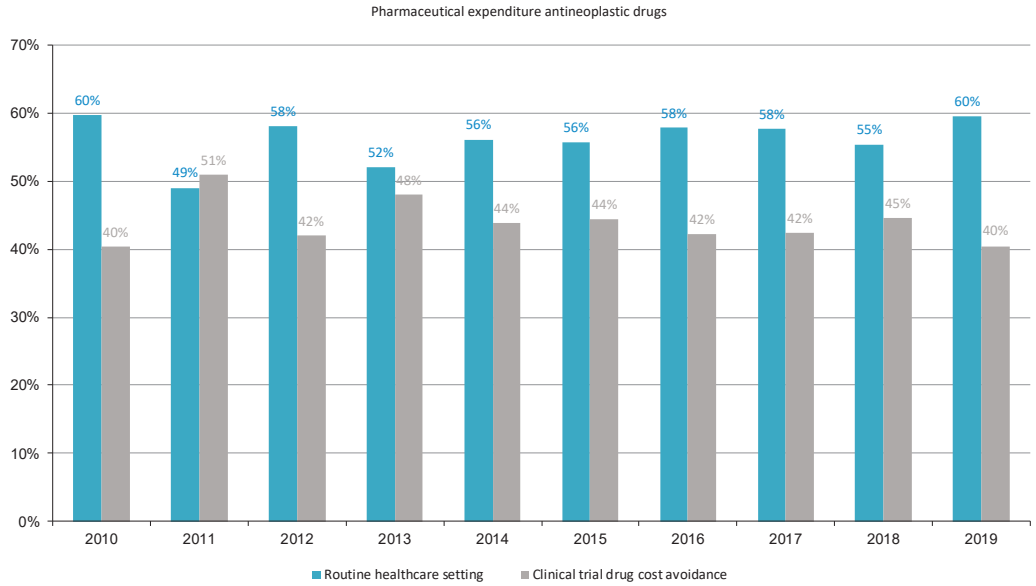


Figure 3. The proportion of pharmaceutical expenditure for antineoplastic drugs in the routine healthcare setting and potentially avoided due to sponsored financial contribution.

4. Discussion

The Vall d'Hebron Institute of Oncology (VHIO) is an oncology center of excellence and innovation, in which investigators and clinicians follow a translational research model working in multidisciplinary teams focused on advancing in the field of personalized and specific therapies against cancer. Scientific activity at the VHIO is based on three main programs, including preclinical research, translational research, and clinical research and transversal technologies. Each program incorporates high-level research teams dedicated to ensuring that research results can be implemented and translated into tangible benefits for patients (https://vhio.net). During the study period of 2010–2019, we identified a high number of clinical studies for the treatment of solid tumors with patients being recruited or actively participating in clinical trials. In 2019, there were 459 clinical trials with ongoing recruitment, 162 (35.3%) of which were phase I and basket trials. Also, in 2019, the total number of 1962 patients treated in clinical trials accounted for 41.4% of all cancer patients with solid tumors treated at the Medical Oncology Department, 38.4% participating in 162 phase I and basket trials. According to the Spanish Registry of Clinical Studies (REEC), in August 2020, 597 clinical cancer trials in adults with active recruitment were registered in this database, 188 (31.5%) of which were phase I trials [24]. These data show the leadership role of VHIO and HUVH in the overall and complex cancer clinical research landscape in Spain.

In the 2010–2019 study period, a total number of 10,488 patients were included in clinical trials, with treatments that resulted in drug contributions by sponsors for our center of EUR 107,306,084. The potential estimated DCA, according to our approximation, is EUR 92,662,609. In all the cases, the drug cost estimations were based on the same actual purchase price for the HUVH of the pharmaceutical specialties corresponding to the doses prescribed at the time of each prescription. The lower amount obtained from the calculation of the DCA is explained by the lower drug cost of antineoplastics used in routine healthcare conditions (used for the calculation of the DCA) as compared to innovative high-cost therapies in clinical trials (economic contribution of the sponsor). The distribution of expenses in each of the two populations clearly indicates greater use of innovative and high-cost therapies in the clinical trial population compared to the routine healthcare population; the expenses in targeted therapy plus immunotherapy were 93.31% compared to 81.37%, and in cytotoxic plus other drugs were 6.69% compared to 18.63%, respectively [20]. Also, the economic contribution of sponsors and DCA corresponded to 89% and 77%, respectively, of

the total pharmaceutical expenditure of HUVH in antineoplastic agents for treating cancer patients with solid tumors in the routine healthcare setting over the 10-year study period.

Academic research has been considered a source of sustainability of public healthcare systems [25,26], with trial sponsors providing tangible benefits [27,28]. However, quantification of DCA in cancer patients treated in clinical trials has not been consistently documented, particularly due to deficient infrastructure information systems of hospitals, and because trial drugs provided by sponsors are not systematically included in pharmacoeconomic analyses of cancer medications [29]. Previous studies addressing the cancer treatment costs of participants in cancer clinical trials have been carried out in the framework of healthcare systems in the USA, Canada, Germany, the UK, Italy, Taiwan, and Spain [10–18,30]. All of these studies have documented economic benefits for the medical center when patients participating in clinical trials receive drugs financed by external sources, although the results are difficult to compare due to differences in the design of the studies and methodological heterogeneity in the analysis of avoided costs, such as estimations of expenditures of commercialized or non-commercialized investigational drugs only, the regimen of the control arm, the standard of care treatment, and cost allocation of drugs with prices from different sources, etc.). Our study has made two estimates: that of the cost to the HUVH of the drugs provided by the promoter (which would coincide with the strategy of Calvin-Lamas et al. [17]) and would be interpreted as an avoided cost for the hospital if the center financed the studies carried out, and the cost avoided in the treatment of patients included in a clinical trial (DCA) if these patients were treated like routine healthcare patients. This strategy represents a more realistic approach to care practice than the consideration of theoretical costs of the standard alternative or the control arms of the trials [10,11,13,14,17,18]. Our study has other distinctive features compared with previous publications, including the 10-year study period, the large number of patients, the inclusion of different phases of the trials, and the analysis by pharmacological classes, route of administration, tumor location, and individual antineoplastic agents.

The pattern of clinical research by pharmacological classes showed an important variation over the 10-year study period, with the proportion of cytotoxic drugs decreasing from 20.6% in 2010 to 7.1% in 2019 and targeted therapy from 79.4% to 24.4%, whereas immunotherapy accounted for 68.4% in 2019. In the study by Shen et al. [12] conducted in 2008 at the most prominent medical center in Taiwan, targeted therapy accounted for 84.1% of the total cost avoidance of anti-cancer trials, with lapatinib as the most prominent drug. In the analysis of phase III trials between 1999 and 2011 by Tang et al. [15], targeted therapy constituted 43% of total DCA.

In patients treated with intravenous antineoplastic drugs, a total of 40 tumor locations were treated with 421 different antineoplastic drugs, which indicates the high representatively of the clinical trial setting in our clinical practice. A total of 15 cancer sites accounted for 90% of the economic contribution of sponsors, particularly non-small cell lung cancer, advanced solid tumors, and breast, colon, and ovarian cancer.

In fact, most of the previous studies on clinical trials analyzed a single tumor site, such as lung cancer and mesothelioma [14], prostate [17], breast [18], or cancer in general, without specification of the organ affected. Bredin et al. [30] evaluated 37 clinical trials grouped into five tumor groups (lung, gynecology, neurology, hematology, and genitourinary) and showed a large range of cost avoidance per patient due to a combination of factors, including the duration patients remain on the study (which varies widely among the tumor groups), the number of days in each cycle a drug is administrated, and the price of the drugs. Of the 17 clinical trials in the study by Tang et al. [15], most trials involved breast, lung, and ovarian tumors. In our study, in 2019, clinical trials with intravenous and oral antineoplastic agents were analyzed, with the inclusion of a total of 1122 different patients, which accounted for 25.8% of gastrointestinal tumors, 23.3% of lung cancer, 13% of breast tumors, 11.8% of gynecologic tumors, and 9.5% of genitourinary tumors. The antineoplastic agents representing 50% of the financial contribution of sponsors

were pembrolizumab (13%), nivolumab (9%), cabozantinib (8.7%), atezolizumab (7.2%), bevacizumab (6.2%), and palbociclib (5.3%).

The fact that we have not considered the contribution, or costs avoided, of the supportive therapy is a limitation in the study. According to Bredin et al. [30], antiemetics and colony-stimulating growth factors account for 2.9% of costs regarding conventional cytotoxics, and anti-diarrheal and antihistamines for 0.28% regarding targeted therapy. In our previous study [20], supportive therapy (antiemetics, erythropoietins, colony-stimulating growth factors, and hypocalcemia medications) accounted for 4.6% of the total pharmaceutical expenditure for the treatment of solid tumors in patients treated in the routine healthcare setting, and although this percentage is low, it showed a decreasing trend along the years, with only 1.4% in 2019. Other aspects involved in the costs of the clinical trials, such as administrative or infrastructure variables, were not evaluated.

Regarding differences between commercial and non-commercial clinical trials, extrapolation of results from healthcare systems with different public or private financial structures is a complex issue. In an analysis of the financial sustainability of an oncology clinical trial unit from a Canadian medical center between 2007 and 2011, the authors describe the negative income of the trials promoted by cooperative groups due to not-funded or underfunded follow-up costs, so the unit accrued more patients in new clinical trials or existing industry-funded trials to offset that deficit, but as the number of patients on follow-up increased, the fiscal deficit grows larger each year, perpetuating the cycle [31]. Although patients included in clinical trials receive more frequent clinical visits, which translate into a higher number of tests and procedures, those receiving the routine healthcare standard of care (SOC) also receive costly therapies [8], and the differences disappear due to the free provision of antineoplastic drugs in clinical trials by the sponsors, which accounts for the largest difference in pharmaceutical expenditure between the two populations [9]. In a retrospective cost analysis of 68 adult cancer patients treated in 20 different clinical trials in a single Spanish institution, it was detected that although the load of procedures was 32% higher, the costs for the pharmacological treatment system were 79% lower in the cohort of clinical trial patients, and it was concluded that in the entirety of the clinical trial units, the most favorable scenario is a balanced portfolio of both commercial and non-commercial trials [19].

As a relevant limitation of our study, we do not assess the general costs of the administrative infrastructure for the execution of clinical trials, nor of the costs of all medical procedures (e.g., medical visits, management of adverse effects, lack of efficacy of treatments carried out, etc.). Also, other factors contributing to further analysis of the meaningfulness of cost savings from enrollment in clinical trials having access to free medications, such as patients' demographic characteristics or their socio-economic status, were not evaluated. These objectives were not in the scope of our work, which does not aim to evaluate the sustainability of the clinical trials unit (financed mostly by the private resources generated by the trials themselves) but aims to contribute knowledge to the expenditure contributed in drugs by the promoters and to the expenditure potentially avoided in the specific subject of pharmacological treatment from the perspective of reimbursement by the national health system. The study of the economic burden represented by clinical trials has been carried out from the payer's perspective, that is, the national public health administration because, in our country, all citizens regardless of their social, demographic, or economic status have universal free access to all funded oncological treatments through the Spanish national healthcare system. Overall, clinical trials provide not only the best context for the progress of clinical research and healthcare but also create opportunities for reducing public cancer-care costs [32].

In summary, the added value of the present analysis is based on its relevant differences compared with previous studies [4–19,30], that is, the assessment of all consecutive cancer patients enrolled in sponsored clinical trials, considering all tumor locations, and treated at the Medical Oncology Department of the largest hospital in Spain in which the largest number of oncological clinical trials are performed in the country. The analysis

of 2930 clinical trials with the enrollment of 10,488 patients with solid tumors located at 30 sites showed an impressive DCA of EUR 92,662,609. The detail of the data presented may be of interest for comparative purposes in studies by other authors.

5. Conclusions

The pattern of research through oncological clinical trials at the HUVH has allowed early access to innovation and a contribution to knowledge that reverts to clinical care practice. At the same time, it implies a lightening of the economic burden on the healthcare system by the impact of the free supply of investigational drugs and the potential avoided pharmaceutical expenditure from the perspective of reimbursement by the national health system, according to an approximation of the cost of treating patients in the trial setting with the actual clinical practice of the routine healthcare population.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers16081529/s1, Table S1: Pharmaceutical expenditure (EUR) by antineoplastic agent and study year (2010–2019) in patients treated in clinical trials. Table S2: Pharmaceutical expenditure (EUR) by tumor location and study year (2010–2019) in patients treated with intravenous antineoplastic agents in clinical trials. Table S3: Mean annual cost of antineoplastic treatment per patient (EUR) per tumor location and study year (2010–2019), in patients treated in the healthcare setting. Table S4: Potential drug cost (EUR) avoided, by tumor location and study year (2010–2019), in patients treated with intravenous antineoplastic agents in clinical trials.

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Article

Comparative Analysis of Three Predictive Models of Performance Indicators with Results-Based Management: Cancer Data Statistics in a National Institute of Health

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Simple Summary: Statistical predictive models using one of the most important strategies, known as results-based management (RBM), are relevant for improving the quality of medical services and could be used with cancer data statistics to monitor and evaluate children with cancer. We provided a comparative analysis of three predictive models that are considered robust in the literature. We also provided a tool to identify new medical cases that confirm a forecast increase or decrease in certain performance indicators and can convert data into useful information for decision-making; we propose to apply this approach to cancer data statistics at one of the National Institutes of Health in Mexico City. Our findings show that from an RBM-based perspective, predictive models are a valid and reliable instrument to forecast medical performance indicator results and can be applied to monitor and evaluate children with cancer.

Abstract: Predictive models play a crucial role in RBMs to analyze performance indicator results to manage unexpected events and make timely decisions to resolve them. Their use in Mexico is deficient, and monitoring and evaluation are among the weakest pillars of the model. In response to these needs, the aim of this study was to perform a comparative analysis of three predictive models to analyze 10 medical performance indicators and cancer data related to children with cancer. To accomplish these purposes, a comparative and retrospective study with nonprobabilistic convenience sampling was conducted. The predictive models were exponential smoothing, autoregressive integrated moving average, and linear regression. The lowest mean absolute error was used to identify the best model. Linear regression performed best regarding nine of the ten indicators, with seven showing $p < 0.05$. Three of their assumptions were checked using the Shapiro–Wilk, Cook's distance, and Breusch–Pagan tests. Predictive models with RBM are a valid and relevant instrument for monitoring and evaluating performance indicator results to support forecasting and decision-making based on evidence and must be promoted for use with cancer data statistics. The place numbers obtained by cancer disease inside the main causes of death, morbidity and hospital outpatients in a National Institute of Health were presented as evidence of the importance of implementing performance indicators associated with children with cancer.

Keywords: results-based management; performance indicators; predictive models; evidence-based decision making; cancer data statistics

1. Introduction

1.1. Results-Based Management to Address the Problem of Improving Public Health Services

Results-based management (RBM) is a public management strategy that aims to improve the efficiency and effectiveness of policies, programs and public services based on reliable information about the effects of governmental actions on society. RBM was introduced in response to the increasing demands and expectations of citizens, such as universal coverage of education and health services, the expansion of the rights of marginalized populations, and concerns about sustainable management of the environment. RBM provides a reference framework to facilitate public organizations in creating public value (results) [1].

The RBM model is used in Countries of the Organizations for Economic Cooperation and Development, the European Community, Latin America, the Middle East, Africa, and Asia. However, its use in Mexico is deficient or incorrect. Since the Paris Declaration in 2005, numerous governments and organizations worldwide have documented the effectiveness of the RBM approach in achieving significant changes by measuring the impact of public sector activity on people's quality of life. The literature shows how different agencies worldwide strive for greater effectiveness and efficiency in developing their countries [2].

According to Dwivedi et al. [3], the COVID-19 pandemic has challenged the capacity of health management to make timely decisions and effectively manage such events. The evaluation of an organization is based on performance indicators, and analyzing these indicators provides insight into the impact on the quality of services they provide [3].

1.2. Performance Indicators and Predictive Models for Measuring Healthcare Results with RBM

Performance indicators are mathematical expressions used to measure quantitative or qualitative variables that reflect changes linked to actions, enabling the monitoring and evaluation of results. These indicators are measured in units such as proportions, percentages, averages, rates, and indices [4].

An organization's results are measured in four dimensions with RBM: 1. Effectiveness; 2. Quality; 3. Economy; and 4. Efficiency. Effectiveness measures the level of achievement of objectives. Quality measures service attributes and compliance with requirements. Economy measures the capacity to adequately generate and allocate financial, human, and material resources to the goods or services provided. Efficiency measures the resources used compared to the results obtained [4].

Performance is a strategic concept in which the goals achieved are associated with the resources used to achieve them [5]. The Mexican government's entities and dependencies must demonstrate by law that public spending benefits society and promotes adequate accountability and transparency [6].

The hospital's performance is associated with the results of performance indicators, which can be analyzed and evaluated to assess their ability to achieve goals efficiently. This evaluation can be used to improve the positive impact of health services [7]. These findings agree with other research that found that performance indicators and statistical predictive models are important to measure a health system's quality [8].

There are two fundamental processes in performance indicator measurement: 1. Monitoring during the execution of activities and tasks carried out by organizations and 2. Performance evaluation at the end of public programs and projects. The first process involves follow-up on the achievement of objectives and goals [9]. Performance evaluation with RBM can be conducted in terms of design, processes, consistency, and results. Its function is to provide reliable information that helps to make better decisions for continuous improvement processes [10].

1.2.1. Predictive Models for Measuring Healthcare Results

Predictive models play a crucial role in public decision-making, particularly in the context of local and regional policies. Performance indicator values are typically arranged in time series data to generate accurate predictions that enable effective resource planning and optimization [11].

1.2.2. ARIMA Model

The ARIMA model was selected for this study due to its ability to predict results with autoregressive (AR) and moving average (MA) components when modeling changes in performance indicators over time. The ARIMA integration (I) component is added to determine the level of differentiation required to ensure data stationarity [12] and is effective in capturing linear patterns in time series data [13].

Sun et al. [14], Afilal et al. [15], and Milner [16] developed ARIMA forecasting models to predict patient attendance at hospital services and validated the model as an effective tool for predicting the number of expected annual patients in the Trent region of the United Kingdom, with a forecast error of only 3 percent. In a similar study, Sun et al. [14] were able to enhance their predictions of daily patient attendance at Singapore General Hospital by integrating other variables, including public holidays and frequency of appointments, into their ARIMA predictive model.

1.2.3. Exponential Smoothing (ES) Model

ES is the most common forecasting technique and is widely used by businesses of all kinds, including healthcare. ES techniques became widespread for six main reasons [17]:

1. Exponential models are surprisingly accurate.
2. Formulating an exponential model is relatively easy.
3. The user understands how the model works.
4. Very few calculations are required to use the model.
5. Computer storage requirements are low due to the limited use of historical data.
6. Accuracy tests related to model performance are easy to calculate.

ES forecast models are commonly used for time series forecasting due to their robustness, particularly for short periods with limited historical data. These models have been utilized in various fields to generate accurate predictions, with different studies highlighting their efficacy [18].

Kotillová [19] utilized performance indicator results to predict electricity demand in Australia and discovered that ES models produced highly accurate predictions with minimal errors. Similarly, Köppelová and Jindrová [20] found that ES performs well in terms of error and provides good results.

1.2.4. Linear Regression Model (LR)

LR is probably the most widely applied in both natural and social sciences research, as well as in daily life [21]. Regression analysis is defined as 'the study of dependency' or how a result depends on one or more predictors or independent variables [22].

LR and correlation are powerful statistical tools that can serve as effective predictive models when used properly. However, improper use can lead to meaningless results. Three examples of the inappropriate use of LR are as follows: 1. LR should not be used when the relationship between the dependent and independent variables is nonlinear. If the data exhibits a curved or nonlinear pattern, it may lead to inaccurate predictions and incorrect conclusions. To test the null hypothesis that a given dataset follows a normal distribution, the Shapiro–Wilk test could be used, if the p-value > 0.05 then we fail to reject the null hypothesis, suggesting that the data is normally distributed [23]. 2. LR should check the homoskedasticity assumption, which is a desirable property where the variability of the errors (residuals) is constant across all levels of the independent variable. One way to detect heteroskedasticity is by using the Breusch–Pagan test, the null hypothesis is that there is homoskedasticity in a LR model. If the p-value > 0.05, we fail to reject the null hypothesis, suggesting homoskedasticity. The problem with heteroskedasticity is that it may lead to incorrect estimates of the standard errors for the coefficients and, consequently obtain incorrect t values [24]. 3. Improperly handling outliers can unduly influence the regression line and impact the accuracy of the model. LR is sensitive to outliers, which are data points that deviate significantly from the overall pattern. Cook's distance (Di) can be used in regression analysis to identify influential outliers in a set of predictor variables.

Large values (usually greater than 1) indicate substantial influence by the case in affecting the estimated regression coefficients [25].

LR is applied in numerous areas: medicine, engineering, economics, and social sciences, among many others. It is an expansive field that has gained significant interest among researchers and administrators [26–28].

1.3. Other Management Models for Measuring Healthcare Performance

Different models have been developed in addition to RBM, such as data envelopment analysis (DEA) [29], Pabon lasso [30], analytical hierarchy process (AHP) [31], and balanced scorecards (BSC) [32].

The DEA model uses nonparametric deterministic analysis as an alternative to other efficiency measurement techniques, its complexity makes it difficult for many hospital managers [33,34].

The Pabon lasso model was introduced in 1984 for the identification of the state of a hospital in terms of resource utilization and performance trends.

The AHP model involves breaking down a complex decision into a hierarchy of smaller, more manageable subdecisions and then assigning relative weights criteria based on the importance [35]. The approach breaks down a complex decision problem suggested by Dolan et al. [36]: 1. Define the decision criteria and alternatives, 2. Rate the criteria by pairwise comparison, 3. Calculate the weights of priority, 4. Calculate the overall priority of the alternatives, 5. Check for inconsistencies and 6. Perform a sensitivity analysis [37].

The BSC model uses analysis of performance indicators associated with four perspectives: finance, internal processes, customers, development and research. Three studies suggest the use of many statistical methods, such as the mean, standard deviation, coefficients of variation, LR, Student's *t*-test, covariance analysis, analytic data, confirmatory factor analysis (CFA), and structural equation modeling (SEM). The latter two use the following indices: goodness-of-fit index (GFI), modified goodness-of-fit index (AGFI), comparative fit index (CFI), normalized fit index (NFI), index of relative fit (RFI), incremental fit index (IFI), Tucker Lewis index (TLI), residual root mean square (RMR), residual root mean square approximation (RMSEA), chi-square, and significance level [38–40]. To clarify some of the mentioned statistical methods, structural equation modeling (SEM) is a technique used in behavioral sciences that can be applied within the BSC model to comprehend and make decisions related to marketing and customer behavior. SEM focuses on theoretical constructs represented by latent factors, and the relationships between them are depicted through regression or path coefficients. It establishes a covariance structure among observed variables, providing an alternative modeling approach. Confirmatory factor analysis (CFA) is used to assess the fit of the model and determine whether the underlying structure of a scale aligns with the validity of self-report measures, such as surveys, questionnaires, interviews, and psychometric tests. The CFA process involves specifying a factor structure based on the theoretical construct and estimating factor loadings, which represent the correlations between the observed items and the underlying factors. Fit indices, such as the Comparative Fit Index (CFI), Tucker–Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR), are then used to evaluate how well the model fits the observed data. A well-fitting model will have CFI and TLI values close to 1 and low values for RMSEA and SRMR, thus enabling informed decision-making [41]. Importantly, statistical methods can be applied to any existing management model, not limited to the BSC.

Other Models with Statistical Methods to Measure Healthcare Results

Analytics data refer to different analyses that can be used with performance indicator values, including (i) descriptive analysis; (ii) operational analysis; (iii) online analytical processing (OLAP); (iv) statistical analysis; (v) data mining, predictive models; (vi) visual analytics, such as dashboards and statistical graphs; (vii) text mining as a natural language

process; (viii) big data analytics (BDA); (ix) network analysis (x) web mining; (xi) sentiment analysis; and (xii) analysis of social networks [42–45].

Business intelligence (BI) refers to the use of methods to support the decision-making process by transforming raw data into useful information [46,47]. The literature review revealed that the combination of business intelligence (BI) and data analytics is a promising technique for evaluating the management of hospital facilities. However, also identified certain limitations and recommended further research in this area [48].

Another study focused on data mining (DM), to generate useful information from databases. Ahmed et al. [49] and Fan et al. [50] stated that DM can be classified under supervised learning and unsupervised learning by learning machines. While supervised learning aims to produce predictions using data, unsupervised learning seeks to discover new insights from aggregated historical data. Ioannidis et al. [51] and Yafooz et al. [52] mentioned five categories of data mining: 1. anomaly detection or outlier detection; 2. association rule learning; 3. clustering analysis; 4. classification and analysis; and 5. regression analysis.

Hospitals are the most important cost factor in health systems worldwide. The health sector is associated with people's lives and with the highest levels of complexity in business models [53].

One limitation found was incorrect forecasting methods and a lack of understanding or confusion about the methodology. As a result, organizations often set goals and objectives without realistic forecasts to justify the probability of achieving them [54]. A Systematic Review of Financial Literacy Research in Latin America and The Caribbean mentioned that one of the most common problems is the lack of statistical test validity and reliability, it is necessary to improve the quality of these models [55]. The literature shows that the DEA model has deficiencies regarding the qualitative and methodological approaches used [29]. The Pabon lasso model showed no significant changes in its results in a performance evaluation of public general hospitals in Yugoslavia [30]. In the AHP model, as in the DEA model, performance indicator values are used less frequently compared to other models, and their use in the healthcare area is reported to be inconsistent. Finally, a systematic review of the BSC model found that articles mainly focus on its design process rather than its implementation, use and results [32].

One limitation of RBM in Latin America and the Caribbean is that monitoring and evaluation with predictive methods are among the weakest pillars of the model. In Mexico, studies have shown that monitoring and evaluating results using RBM and performance indicators associated with the National Institutes of Health lacked methodological rigor to be useful and credible [56]. Another study on RBM model implementation in Mexico City from 2018 to 2021 found a poor understanding of the methodology. No evidence of the use of predictive methods to analyze performance indicators for evidence-based decision-making and to enhance the quality of public services was found in the literature [57].

1.4. Problem Statement

Research regarding the impact of RBM supported by predictive models on healthcare performance indicators is promising, but one limitation is the availability of reliable measurement statistical methods and the fact that they must be validated and associated with cancer data statistics in a National Institute of Health. The comparative analysis of 3 predictive models can be useful for this purpose and has the advantage of having been developed in the Mexican cultural context. However, more complex models do not necessarily predict real values more accurately, and the model that fits the data best depends on the medical process context in which the results are obtained.

In response to these needs, the aim of this study was to perform a comparative analysis of three predictive models considered robust in the literature to analyze 10 medical performance indicators and cancer data statistics related to children with cancer. The predictive models used were ARIMA, LR and ES. We considered three objectives: (1) identify the predictive model that obtains the smallest error between the real and predictive values to be

used as RBM support; (2) describe how predictive models can be used as acceptable tools to analyze the results of performance indicators associated with RBMs; and (3) prove the validity of the RBM in relation to the performance indicator results analysis with predictive models in a National Institute of Health in Mexico City.

2. Materials and Methods

2.1. Design

A comparative and retrospective study with nonprobabilistic convenience sampling was conducted with 10 medical performance indicator results to evaluate the performance of the Hospital Infantil de Mexico Federico Gómez which is one of the National Institutes of Health in Mexico, and a number of patients and cancer diagnostics were included (Table 1). The inclusion criteria for performance indicators in this study were as follows: medical attention services; results obtained in the period from January 2014 to December 2018; and the existence of results in the analyzed period. Data were collected and analyzed by the authors of this paper from the quarterly historical reports used at the evaluation performance meeting that was held according to hospital procedures.

Table 1. Cause of death, cause of morbidity and cause of hospital outpatient for each cancer type of diagnosis.

Year	Cause of Death	Cause of Morbidity	Cause of Hospital Outpatient
2016 3798 patients	Tumors and neoplasm (2)/33.7%/64 patients	Acute Lymphoblastic Leukemia (1)/13.5%/1024 patients Malignant Tumor (3)/2.3%/176 patients	Tumors and neoplasm (1)/33.4%/2534 patients
2017 3768 patients	Tumors and neoplasm (1)/42.7%/73 patients	Acute Lymphoblastic Leukemia (1)/13%/1006 patients Malignant Tumor (2)/2.9%/108 patients	Tumors and neoplasm (1)/33.3%/2581 patients
2018 4130 patients	Tumors and neoplasm (2)/24.3%/43 patients	Acute Lymphoblastic Leukemia (1)/13.3%/1060 patients Malignant Tumor (2)/3.2%/399 patients	Tumors and neoplasm (1)/34%/2628 patients
2019 3591 patients	Tumors and neoplasm (1)/35%/62 patients	Acute Lymphoblastic Leukemia (1)/11.2%/915 patients Malignant Tumor (2)/2.8%/273 patients	Tumors and neoplasm (1)/32.1%/2341 patients
2021 2386 patients	Tumors and neoplasm (1)/34.2%/51 patients	Acute Lymphoblastic Leukemia (1)/12.5%/670 patients Malignant Tumor (2)/1.3%/68 patients	Tumors and neoplasm (1)/29.7%/1597 patients
Position among the main causes appear in parenthesis/Percentage from total/Number of patients			

2.2. Procedure for Measuring the Performance of Each Model

Time series containing at least 20 data points were used for prediction. We made quarterly forecasts of performance indicator results with four quarterly lagged results as a predictor. The fitting and forecasting performances of the 3 models were evaluated (ARIMA, LR and ES)

The performance criterion used to test the predictive accuracy was the mean absolute error (MAE) of the 3 statistical predictive methods. A low MAE indicates a good fit and was calculated as follows:

$$MAE = \frac{1}{n}\sum_{i=1}^{n}|Ei|,$$

where Ei is the error or difference between the real and predicted values.

2.3. Predictive Statistical Methods Used to Measure Performance Results

2.3.1. Linear Regression

The first step in LR is to determine the slope or inclination of the straight line, whose algebraic representation is as follows [21]:

$$E\,(Y/X) = a + bx,$$

where E is the estimated or predicted value of "Y" given a value of "X" that is equal to a + b multiplied by "x", assuming that the distribution of "Y" for a value of "x" follows a normal distribution and that the variances of both variables are homogeneous, a phenomenon known as homoscedasticity.

The most popular way to mathematically represent LR is as follows:

$$Y = \alpha + \beta\ X + e,$$

where:

Y is the explained or dependent variable that is the estimated or predicted value based on a sample.

α is the value at which the line intersects the *Y*-axis, equivalent to the value when x is equal to zero, also known as the regression constant.

β is the value that measures the influence that explanatory variable X has on the explained or dependent variable Y.

e is the error. When the equation is solved, it results in:

$$e = Y - (\alpha + \beta\ X),$$

Thus, e indicates the amount by which Y deviates from the obtained values.

2.3.2. ARIMA

Figure 1 shows the ARIMA(p,d,q) model; for nonstationary time series data, the mean and variance are unstable, and such data are generally converted to a stationary time series first by means of a differential operation [58].

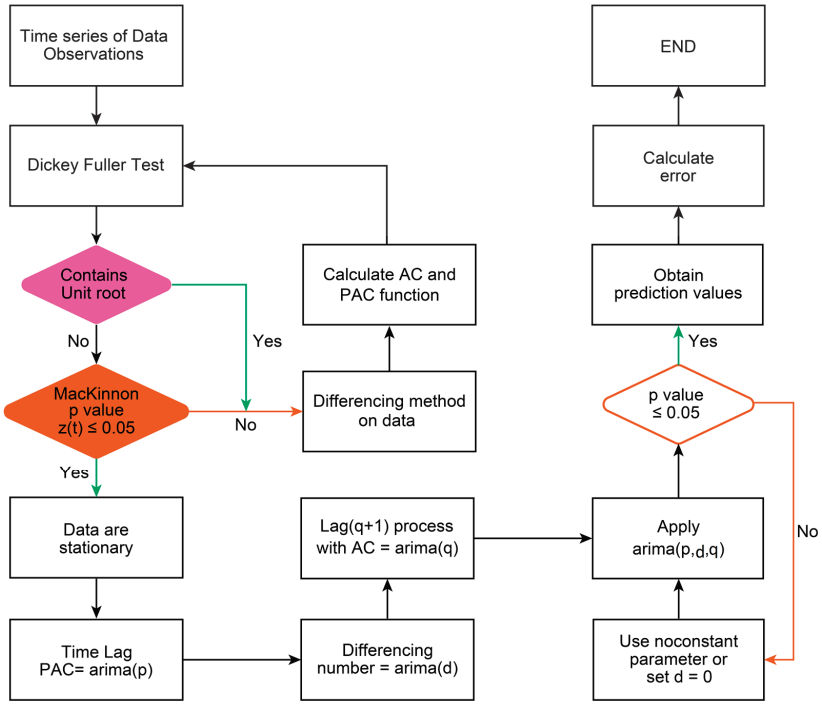


Figure 1. Box–Jenkins-Jenkins/ARIMA process.

The ARIMA model integrates autoregressive and moving average calculations. A basic requirement for predicting time series with ARIMA is that the time series is stationary or, at the very least, trend stationary [16,59]. ARIMA expects a stationary stochastic process as input; however, very few datasets are natively in such a format; thus, the use of differencing to "stationary" is performed in the model identification stage [60].

2.3.3. Stationary

A stationary time series is one whose properties do not depend on the time at which the series is observed. Time plots will show the series to be roughly horizontal (although some cyclic behavior is possible), with constant variance [61].

2.3.4. Differencing

Computing the differences between consecutive observations is known as differencing, which is one way to make a nonstationary time series stationary. Differencing can help stabilize the mean of a time series by removing changes and therefore eliminating (or reducing) trends and seasonality. For a stationary time series, the ACF will drop to zero relatively quickly, while the ACF of nonstationary data decreases slowly. Additionally, for nonstationary data, the value of r_1 is often large and positive (Figure 2).

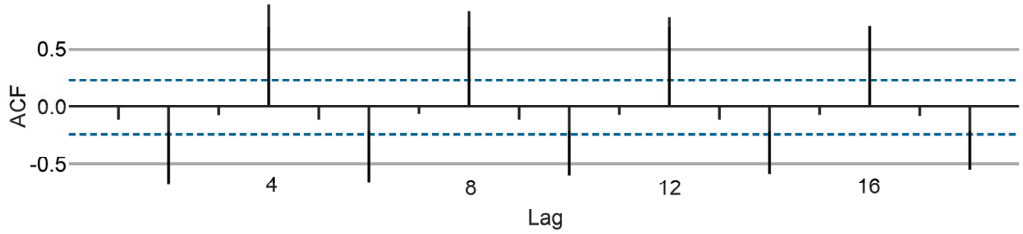


Figure 2. Correlogram of nine values or ACF.

2.3.5. Autocorrelation

Just as correlation measures the extent of a linear relationship between two variables, autocorrelation measures the linear relationship between lagged values of a time series. There are several autocorrelation coefficients corresponding to each panel in the lag plot. For example, r_1 measures the relationship between y_t and $y_t - 1$, r_2 measures the relationship between y_t and $y_t - 2$, and so on (Figure 2).

The value of rk can be written as

$$\frac{\sum_{t=k+1}^{T}(y_t - \hat{y})(y_{t-k} - \hat{y})}{\sum_{t=1}^{T}(y_t - \hat{y})^2},$$

where $\hat{y}$ is the mean of the historical data and T is the length of the time series. Figure 2 shows scatterplots of nine values. The autocorrelation coefficients are plotted to show the autocorrelation function or ACF. This plot is also known as a correlogram.

In this graph:

- r_4 is higher than the values for the other lags. This is due to the seasonal pattern in the data: the peaks tend to be four quarters apart, and the troughs tend to be two quarters apart.
- r_2 is more negative than the values for the other lags because troughs tend to be two quarters behind peaks.
- The dashed blue lines indicate whether the correlations are significantly different from zero.

2.3.6. White Noise

Time series that show no autocorrelation are called white noise. Figure 3 gives an example of a white noise series.

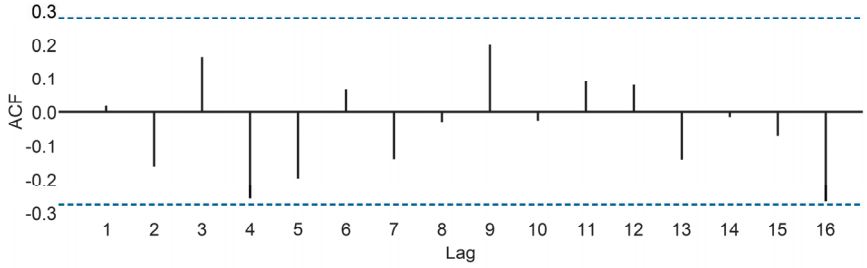


Figure 3. Autocorrelation function for the white noise series.

For the white noise series, we expect each autocorrelation to be close to zero, 95% of the spikes in the ACF should lie within $\pm 2/\sqrt{T}$ where T is the length of the time series. It is common to plot these bounds on an ACF graph (the blue dashed lines above). If one or more large spikes are outside these bounds or if substantially more than 5%, then the series is probably not white noise.

2.3.7. Autoregressive AR(p)

This component is a multiple regression that forecasts the variable of interest using a linear combination of its past values. It is called autoregression because it is a regression against the variable itself.

The model can be written as:

$$y_{t=} C + \Phi_1 y_{t-1} + \Phi_2 y_{t-2} + \ldots + \Phi_p y_{t-p} + \varepsilon_t,$$

where εt is white noise, and the AR(p) model is the autoregressive model of order p for multiple regression in period t with predictive values of yt.

2.3.8. Moving Average component MA(q)

Instead of using past values of the variable to be forecasted in a regression, the moving average uses past forecast errors in a model similar to regression.

$$y_{t=} C + \varepsilon_t + \theta_1 \varepsilon_{t-1} + \theta_2 \varepsilon_{t-2} + \ldots + \theta_q \varepsilon_{t-q},$$

where εt is white noise. We refer to this as an MA(q) or a moving average component of order q. Of course, we do not observe the values of εt, so it is not truly a regression in the usual sense. Moving average should not be confused with moving average smoothing. A moving average is used to forecast future values while moving average smoothing estimates the trend cycle of past values.

To define a series of values as nonstationary, the backward shift operator (B) is introduced. The time series yt is homogeneous if it is nonstationary and its first or dth difference produces a stationary time series, which means that $w_t = y_t - y_{t-1} = (1 - B)y_t$, o $w_t = (1 - B)^d y_t$. The model is known as ARIMA(p,d,q) if its d-th difference results in a stationary process and can be written as:

$$\Phi(\mathrm{B})(1 - \mathrm{B})^{\mathrm{d}} \mathrm{yt} = \delta + \Theta(\mathrm{B})^{\mathrm{d}} \varepsilon_{\mathrm{t}},$$

where

$$\Phi(\mathrm{B}) = 1 - \sum_{1=1}^{\mathrm{p}} \Phi \mathrm{i}\, \mathrm{B}^{\mathrm{i}}\ (1)\ \text{and},$$

$$\Theta(\mathrm{B}) = 1 - \sum_{1=1}^{\mathrm{q}} \theta \mathrm{i}\, \mathrm{B}^{\mathrm{i}}\ (2),$$

The lag terms in the autoregressive AR(p) and moving average MA(q) models are defined as follows:

$$\Phi(\mathrm{B})\ \mathrm{y_t} = \delta + \varepsilon_{\mathrm{t}},$$

$$\mathrm{y_t} = \mu + \Theta(\mathrm{B})\ \varepsilon_{\mathrm{t}}, \text{ con } \delta = \mu - \Phi\ \mu,$$

where μ is mean and ε_t is white noise, whose expected value is zero, $E(\varepsilon_t) = 0$. The orders of the model p and q are determined by the autocorrelation and partial autocorrelation functions using the Box and Jenkins method [14]. The best model is identified based on the Akaike information criterion (AIC), the Bayesian information criterion (BIC), and the Jarque–Bera normality test on the residual error series.

The Dickey–Fuller test is used to determine how many differences are needed for the time series to present stationary, if the null hypothesis of having a unit root can be rejected (i.e., if they are nonstationary), favoring the alternative hypothesis that the data have no unit root and are therefore stationary.

Often, the only value that does not achieve significance is the trend, in which case it is possible to use the ARIMA statistical function with the "noconstant" parameter, indicating that the value of the trend is not significant, if the function yields significant data for the number of autoregressive and moving average terms tested, the parameter d can be eliminated, and the model is used with only two components ARMA(p,q).

If the null hypothesis rejection cannot be supported with one difference, its value is increased by one, and the test is repeated until the difference produces significant data; there is a possibility of not finding stationarity, in which case the d value of the difference takes a value of zero and the model becomes ARMA because it lacks the integrating stationary component.

The number of autoregressive AR(p) values recommended for use is found via the graphical function of autocorrelation, the number of values observed outside the confidence interval or close to its limit are the ones to be tested to find the ARIMA function that generates significant statistical values.

2.3.9. Exponential Smoothing

This model searches for an optimal factor α in (0, 1) that best fits the actual results obtained. ES needs only three data points to forecast the future: the most recent forecast, the actual value in the forecast period, and a smoothing constant alpha (α). The smoothing constant determines the level of uniformity and the speed of reaction to differences between forecasted results and actual results. The equation for ES forecast is simply [17]:

$$Ft = Ft{-}1 + \alpha\ (At{-}1 - Ft{-}1),$$

where:

Ft = Exponentially smoothed forecast for period t

Ft−1 = Exponentially smoothed forecast for the previous period

At−1 = Actual demand in the previous period

α = Desired responsiveness index or smoothing constant.

In many cases, the most recent facts are more indicative of the future than are those from the more distant past. If this premise is valid (that the importance of data decreases as the past becomes more distant), it is likely that the most logical and easiest method is ES. The reason it is called exponential smoothing is that each increment in the past is reduced by a factor of $(1 - \alpha)$.

2.4. Ethical Considerations

This study was conducted in accordance with research protocol HIM-2018-053, which was approved by the Research, Ethics, and Biosafety committees at the Hospital Infantil de México Federico Gómez National Institute of Health. As noted, the subject studies are performance indicator results and correspond to public information according to Mexican transparency law [62].

2.5. Statistical Analysis

The database was built using Excel 2016, and statistical analysis was completed using STATA version 12 (Stata Corp; Lakeway, TX, USA) software. The number of patients and place numbers obtained by cancer disease inside the main causes of death, morbidity and

hospital outpatient and their percentage was presented as statistical evidence (Table 1), of the importance of implementing performance indicators associated with cancer to use RBM and predictive models in the monitoring and evaluation of children with cancer.

For the first specific objective, the MAE result for each model was used to identify the predictive model with the smallest error between the real and predictive values. The smallest standard deviation also was considered as an indication of data consistency and homogeneity, as it resulted in better predictive values in relation to the mean.

For the second specific objective to describe how predictive models can be used as acceptable tools to analyze the performance indicator results, statistical analysis for each model was conducted as follows:

A value of $p < 0.05$ is used to provide evidence to reject the null hypothesis in favor of the alternative hypothesis. For the ARIMA method, the Dickey–Fuller test was employed with the null hypothesis that time series data has a unit root equal to 1 or it is non-stationary. The alternative hypothesis asserts that the root differs from 1, signifying the absence of a unit root and ensuring that the data is stationary with a stable mean and variance. Additionally, the MacKinnon test was utilized for its enhanced precision in critical values, particularly for small sample sizes. This test represents an improved iteration of the Dickey–Fuller test and aligns with the aforementioned logic.

If the data were not stationary, autocorrelation (AC) and partial autocorrelation functions (PAC) were used to assess the difference until the data became stationary to be used as the AR(d) component. The lag number observed with the PAC function was used as the AR(p) component, and the number of values observed outside the confidence interval or close to its limit were the ones to be tested. The autoregressive number was calculated in an incremental process to establish the AR(q) component. Finally, the ARIMA model was applied based on the three components observed.

The second criterion to consider the ARIMA(p,d,q) model acceptable is to obtain a significance *p*-value for each parameter.

For the LR model the null hypothesis is that the coefficient of the independent variable (time) is equal to zero, meaning that it does not have a significant effect on the dependent variable (performance indicator results). The alternative hypothesis, in contrast, asserts that there is a significant linear relationship between the variables. A significant *p*-value in linear regression means that there is sufficient evidence to reject the null hypothesis and suggests that there is a relationship between the independent variable and the dependent variable.

For the ES model, the "desired responsiveness index or optimal factor α" was calculated to obtain the predicted values. ES is not directly associated with a *p*-value as in statistical hypothesis testing. Instead, exponential smoothing is a forecasting method that uses a weighted averaging approach to predict future values in a time series.

For the third specific objective to prove the validity of the RBM in relation to the performance indicator results analysis with predictive models, the best model can be used in order to calculate future expected values.

3. Results

3.1. Cancer Data Statistics

Table 1 shows the place number and percentage of cancer in terms of the cause of death, cause of morbidity and hospital outpatients in the period from 2016 to 2021. The year 2020 does not appear due to the activity alterations produced by the COVID-19 pandemic. Notably, the main causes of death in 2017, 2019 and 2021 were tumors and neoplasms. With respect to the main cause of morbidity, acute lymphoblastic leukemia was the most common disease in 2016, 2017, 2018 and 2021. Finally, the main cause of hospital outpatient visits in the five years was tumors and neoplasms.

3.2. The Best Predictive Model That Fit the Data with the Lowest Error

Table 2 shows summary statistics of the predictive models. The lowest MAE and standard deviation indicate the best fit of the data, and the *p*-value provides evidence of the significance reached.

Table 2. Summary statistics of predictive models.

Performance Indicator's Name	Predictive Model	MAE	Deviation Standard	*p* Value
Bed occupancy rate	ARIMA(2,0,1)	2.3117	2.2368	0.017 *
	LR	2.2453	1.5129	0.003
	ES	2.5845	1.8873	NA
Hospital admissions through emergency department	ARIMA(3,2,1) noconstant	0.1292	0.0789	0.252 *
	LR	1.1620	1.5129	0.000
	ES	1.1325	1.3363	NA
Bed turnover rate	ARIMA(1,0,1) noconstant	0.5129	0.6295	0.028 *
	LR	0.3320	0.2181	0.004
	ES	0.3841	0.2655	NA
Bed rotation index	ARIMA(1,0,1) noconstant	0.7388	1.6067	0.180 *
	LR	0.3012	0.1925	0.000
	ES	0.3447	0.2225	NA
Percentage of emergency Admissions	ARIMA(1,0,1) noconstant	2.2322	3.3174	0.025 *
	LR	1.3884	1.5952	0.025
	ES	1.4450	1.5600	NA
Major surgery index	ARIMA(1,0,1) noconstant	2.4514	1.8210	−2.756 *
	LR	1.8183	1.5148	0.001
	ES	1.8642	1.8720	NA
Mortality rate	ARIMA(1,0,0) noconstant	5.5113	6.5088	0.805 *
	LR	3.0747	2.2742	0.688
	ES	3.1302	2.2275	NA
Percentage of scheduled consults granted	ARIMA(1,0,0) noconstant	0.9754	2.0528	0.135 *
	LR	0.3594	0.2322	0.151
	ES	0.3887	0.2552	NA
First time consults index	ARIMA(3,0,1) noconstant	2.4413	5.3074	−1.589 *
	LR	1.5087	1.2620	0.483
	ES	1.5472	1.1538	NA
Proportion of subsequent consultants with relation to the first time	ARIMA(4,0,1)	1.5178	1.3511	−2.865 *
	LR	1.3400	1.3552	0.000
	ES	1.7370	1.6261	NA

Abbreviations: LR Linear regression, ES Exponential Smoothing, MAE: mean absolute error; NA: does not apply; $p < 0.05$ there is evidence to reject the null hypothesis. * If no constant parameter is included it is assumed that there is no constant in the trend.

3.3. Predictive Model Results

3.3.1. ARIMA

Table 3 for the ARIMA criteria results for each performance indicator's results indicates that none obtain significance for the three components of value, trend, and constant used to make the data stationary. The results of the indicators that best fit the ARIMA model are three that only obtain a nonsignificant value in their trend, and this can be corrected with the "noconstant" option of the ARIMA function: bed occupancy rate, bed turnover rate, and bed turnover index. The integration component or number of differences required to achieve stationary data was zero for the three mentioned indicators, which means that the models used were ARMA (autoregressive with moving averages without integration).

Table 3. ARIMA criteria results.

	Criteria ARIMA Used	Value/Type	*p* Value
Bed occupancy rate	dfuller CV z(t) 95% = −3.6	−3.5740	0.0321
	dfuller best difference	0	
	dfuller value, trend, constant (a,b,c)	0.1621 (b)	0.263 (b)
	ARIMA(2,0,1)/IC 95% (ar,ma)	Ma	0.017
Hospital admissions through emergency department	dfuller CV z(t) 95% = −3.6	−5.6590	0.0001
	dfuller best difference	2	
	dfuller value, trend, constant (a,b,c)	0.7877 (c)	0.375 (c)
	ARIMA(1,2,3)/IC 95%	Ma	0.002
Bed turnover rate	dfuller CV z(t) 95% = −3.6	−4.1860	0.0047
	dfuller best difference	0	
	dfuller value, trend, constant (a,b,c)	−0.0350 (b)	0.125 (b)
	ARIMA(1,0,1) noconstant/IC 95% (ar,ma)	Ma	0.028
Beds rotation index	dfuller CV z(t) 95% = −3.6	−4.5910	0.0011
	dfuller best difference	0	
	dfuller value, trend, constant (a,b,c) *	0.0239	0.180 (b)
	ARIMA(1,0,1) noconstant/IC 95% (ar,ma)	Ma	0.000
Percentage of emergency admissions	dfuller CV z(t) 95% = −3.6	−5.4260	0.000
	dfuller best difference	2	
	dfuller value, trend, constant (a,b,c) *	0.1703	0.197 (b)
	ARIMA(4,2,0) noconstant/IC 95% (ar,i)	Ar	0.042 (L2)
Major surgery index	dfuller CV z(t) 95% = −3.6	−4.0760	0.0068
	dfuller best difference	1	
	dfuller value, trend, constant (a,b,c) *	−0.0103	0.942 (b)
	ARIMA(1,1,1) noconstant/IC 95%	Ar	0.973
Mortality rate	dfuller CV z(t) 95% = −3.6	−4.8190	0.0004
	dfuller best difference	0	
	dfuller value, trend, constant (a,b,c) *	0.0405	0.805 (b)
	ARIMA(1,0,0) noconstant/IC 95% (ar)	Ar	0.000
Percentage of scheduled appointments granted	dfuller CV z(t) 95% = −3.6	−3.9990	0.0088
	dfuller best difference	0	
	dfuller value, trend, constant (a,b,c)*	0.0405	0.135 (b)
	ARIMA(1,0,0) noconstant/IC 95% (ar)	Ar	0.000
First time consults index	dfuller CV z(t) 95% = −3.6	−3.8820	0.0088
	dfuller best difference	1	
	dfuller value, trend, constant (a,b,c) *	1.1924	0.242 (c)
	ARIMA(2,1,1) noconstant/IC 95%	Ar	0.752 (L1)
Proportion of subsequent consults with relation to the first time	dfuller CV z(t) 95% = −3.6	−3.6460	0.0262
	dfuller best difference	1	
	dfuller value, trend, constant (a,b,c) *	−0.1540	0.902 (c)
	ARIMA(2,1,1) noconstant/IC 95%	Ar	0.646 (L1)

Abbreviations: a: dfuller value; CV: Critical value MacKInnon test; ar: autoregressive; b: trend; c: constant; dfuller: Dickey–Fuller to test unit root in stationary data; L1: first regression; L2: second regression; ma: moving average. * trend constant in the model means that it is assumed that the time series has a constant linear trend over time.

Table 3 shows that the models with the lowest MAE, resulting from the difference between the real value of the indicator and the estimated value, did not result in the lowest difference in any of the performance indicators' results for ARIMA. An exception is the indicator of hospital admissions through emergencies, where the predictive error and its standard deviation are minimal; however, the *p*-value did not reach significance.

3.3.2. Linear Regression

Seven indicators show better adjusted results with the LR model by showing lower predictive error and *p*-values < 0.05: 1. Bed Occupancy rate; 2. Hospital admissions through the emergency department; 3. Bed turnover rate; 4. Bed rotation index; 5. Percentage of emergency admissions; 6. Major surgery index; and 7. Proportion of subsequent consults with relation to the first time (Table 2).

Table 2 shows the remaining three indicators do not reach a *p*-value < 0.05 with the LR model; however, their predictive error is the lowest of the three models that were compared. The assumptions were checked as shown in Table 4.

Table 4. LR assumptions check (Normal, outlier and heteroscedasticity tests).

Performance Indicator	Shapiro Wilk *p*-Value (1)	Cook's Distance (2)	Breusch Pagan *p*-Value (3)
Bed occupancy rate	0.027	0 > 1	0.3976
Hospital admissions through emergency department	0.000	2 > 1	0.0001
Bed turnover rate	0.085	0 > 1	0.4146
Bed rotation index	0.409	0 > 1	0.5580
Percentage of emergency admissions	0.000	1 > 1	0.0000
Major surgery index	0.568	0 > 1	0.6507
Mortality rate	0.263	1 > 1	0.4861
Percentage of scheduled consults granted	0.999	0 > 1	0.7536
First time consults index	0.209	0 > 1	0.3049
Proportion of subsequent consultant with relation to the first time	0.899	1 > 1	0.5265

(1) Normality test. (2) The outlier test indicates the number of outliers among all 20 analyzed data values greater than one. (3) Heteroskedasticity test.

Seven performance indicators demonstrate normality as per the Shapiro–Wilk test. However, the first two indicators and the percentage of emergency admissions do not exhibit a normal distribution. It is important to note that since $p > 0.05$, we do not reject the null hypothesis suggesting that the data follows a normal distribution. We have effectively addressed outliers; within the 20 data points analyzed, three indicators have one or two data points exceeding the threshold. This indicates that the simple linear regression model is not significantly affected by unusual values. Lastly, the Breusch–Pagan test reveals that nine out of the ten indicators show homoskedasticity, confirming the accurate estimation of coefficient errors. Similarly, as with the Shapiro–Wilk test, the p-value > 0.05 supports that the null hypothesis could not be rejected suggesting homoskedasticity.

3.3.3. Exponential Smoothing (Table 2)

Three indicators show an acceptable fit to the ES model: 1. Mortality rate; 2. Percentage of scheduled consults granted; and 3. First-time consults index.

4. Discussion

The aim of the present study was to perform a comparative analysis of three predictive models considered robust in the literature to analyze 10 medical performance indicators and cancer data statistics related to children with cancer. The findings show that tumors and neoplasms were the main causes of death in 2017, 2019 and 2021; acute lymphoblastic leukemia was the most common disease in 2016, 2017, 2018 and 2021; and finally, the main causes of hospital outpatient visits in the five study years were tumors and neoplasms. These results justify the importance of implementing performance indicators associated with cancer to use RBM and predictive models in the monitoring and evaluation of children with cancer.

The first specific objective of this research was to identify the predictive model that achieves the smallest error between the real and predicted values. Three statistical predictive models were used and described to illustrate their use to help administrators, professionals, and decision-makers convert data into useful information for decision-making purposes [5] at the National Institute of Health. The performance indicator results could be analyzed with the statistical predictive models selected to help RBM identify which best fit the real values, so it could be used to address the goals and targets established during the planning process using values based on statistical evidence to obtain a realistic forecast to justify the probability of achieving them [54] and could also be used to analyze cancer data statistics.

The forecast values obtained with predictive methods are useful to monitor the results, to identify any value not expected to review what happened in the process and to take actions to correct errors or improve the effectiveness and quality of medical services delivered [53]. This approach increases the reliability of the monitoring and evaluation performance process, which was identified as one of the weakest pillars of the RBM model

in Latin America and the Caribbean. Furthermore, other National Institutes of Health in Mexico could promote its use to increase RBM methodological rigor and credibility [55].

The results show that more complex models do not necessarily predict real values more accurately and prove that RBM with statistical methods could be used as a demonstration tool for the effectiveness and efficiency of hospitals' performance [2] and their future trends.

The second specific objective of the study was to describe how predictive models can be used as acceptable tools to analyze the results of performance indicators associated with RBM. The expectation was described step by step for each predictive model and the criteria used to determine the acceptance of the predicted results. This research addressed such tasks and tried to provide an understanding and avoid confusion about the methodology used to search for accurate results regarding the hospital's performance. Moreover, guidelines could be formulated to encourage their use at the Hospital Infantil de Mexico Federico Gomez with an improved capacity for result management with RBM [55]. To check the method's assumptions of the LR model, we employed the Shapiro–Wilk, Cook's distance, and Breusch–Pagan tests. Our results demonstrate that the model fits appropriately for the majority of the performance indicators. The adequate quality of the predictive statistical methods to analyze performance indicator results is expected to improve RBM for use with cancer data statistics.

Our findings related to the second specific objective strengthen the predictive methods, consolidate them and overcome the limitations found in Latin America and the Caribbean and the lack of methodological rigor in the National Institutes of Health to ensure credibility and their usability to monitor performance indicator results and analyze statistics associated with children with cancer [56]. The set of criteria identified to accept a predictive model as a tool that can be used to analyze performance indicator values provides several factors to understand the methodology and help the National Institute of Health improve the knowledge of RBM and decision-making based on evidence about public spending to enhance the quality of healthcare [57]. All the previously mentioned results provide motivation that justifies the proposal to use predictive methods with RBM for the analysis of cancer data statistics, and importantly, performance indicators focused on cancer data statistics do not exist in the National Institute of Health, where the research was conducted. Therefore, this study notes the importance of designing and implementing such performance indicators to benefit children with cancer.

The results are congruent with the importance that Mexican government law assigns to increasing country development and ensuring accountability and transparency [6]. The four performance indicator dimensions are better understood and used to push effectiveness, quality, economy and efficiency [4]. Cancer data statistics must be included to evaluate the medical treatment of children with cancer and must be reflected in the place occupied by cancer as the main cause of death, morbidity and hospital outpatients.

The third objective of the study was to prove the validity of the RBM in relation to the performance indicator results analysis with predictive models in the National Institute of Health in Mexico City. The expectation was that the validity of a predictive model depends on statistical significance, which was demonstrated with error calculations and with the above step-by-step description. The study provides a better understanding of the methodology and strengthens the knowledge about the model. The use of predictive models to analyze performance indicators increases decision-making based on evidence and could be promoted to support cancer data statistics and public policies in Mexico's health sector [57].

The validated model can be used with financial performance indicators to associate the cost factor with medical treatment and with the highest levels of hospital complexity as a business model [53].

It is worth noting that the study has several limitations. Firstly, the absence of probabilistic sampling impacts the generalizability of findings. Secondly, the utilization of *p*-values for decision-making warrants caution due to their sensitivity to sample size; in large samples, *p*-values may appear small even when differences are absent, and vice versa.

Additionally, minor fluctuations in data or analytical methodologies can lead to substantial variations in *p*-values, influencing result interpretations.

Moreover, the tests chosen to assess LR assumptions (Shapiro–Wilk, Cook's distance, and Breusch–Pagan tests) might not be the most suitable options and could benefit from the inclusion of Q-Q plots. Tests relying on *p*-values can sometimes detect insignificant differences as significant in larger sample sizes, while the reverse problem arises for smaller samples. Notably, there are other statistical tests available that were not utilized to assess LR assumptions, such as assessing the independence of errors, detecting multicollinearity, identifying autocorrelation, and verifying constant variance. Additionally, the three statistical predictive models were designed to follow linear function data; consequently, the forecast values that were found are limited to the linear behavior of the statistical method used.

Future studies must include nonparametric methods to account for nonlinear function behavior; it is also important to consider the use of machine learning statistical methods and informatics tools to collect, analyze and present the performance indicator results to make decisions at the moment in which change results are not expected to occur. The limitations are similar to those in other studies related to management models that recommend further research in this area [48]. Additional predictive methods mentioned in other studies must be considered, for example, supervised learning and unsupervised learning by machines [51].

As a result of this study, the tool composed of predictive methods using RBM can help to address the following knowledge gaps: 1. To understand the methodology and predictive models; 2. To incorporate cancer data statistics to monitor and evaluate the medical treatment of children with cancer; 3. To identify new medical cases that confirm a forecast increase or decrease in certain performance indicators; 4. To verify that data can be converted into useful information for decision-making purposes; 5. To improve policies, programs and public services based on reliable information about the effects of governmental actions on society; 6. To strengthen the empirical practice of RBM in a National Institute of Health' and 7. To use financial performance indicators to associate the cost factor with medical treatment and with the highest levels of National Institutes of Health complexity.

The knowledge gaps not addressed in this study are as follows: 1. To use nonparametric statistics; 2. To use machine learning statistical methods; 3. To use a larger sample to increase statistical power; 4. To use an automated tool to collect, analyze and present performance indicators results such as Python or R which are programming languages that are versatile tools that go beyond statistical analysis, encompassing web development, automation, and machine learning capabilities. Additionally, they provide robust data visualization options through libraries, enhancing data exploration and presentation. Moreover, their open-source nature ensures widespread accessibility, making them cost-effective alternatives to STAT and 5. To use an artificial intelligence approach.

5. Conclusions

Our findings show that the predictive model that best fits real data depends on the process context in which medical services have been provided. LR was tested as a powerful statistical tool that can serve as an effective predictive model that produces meaningful results. The ARIMA model was confirmed as a systematic approach for the predictive modeling of both stationary time series and nonstationary time series data. For nonstationary time series data, the mean and variance are unstable, and they are generally converted to stationary time series by means of a differential operation. Then, stationary time series data are used to establish the ARMA mode [58]. Finally, ES was tested as the easiest forecasting technique and demonstrated that it can be used by businesses of all kinds [17].

The performance of healthcare services is related to their capacity to quickly respond to changes in indicator results; predictive statistical methods with RBM as a framework are fundamental tools to predict future behavior and detect changes as soon as possible to

find the reason for variations presented to support the decision-making process to solve problems or improve the quality of medical services by implementing suitable statistical methods and procedures.

Predictive models must be promoted to support RBM. Three predictive models: LR, ES and ARIMA, were compared in this paper: more complex models do not necessarily predict the real values more accurately.

The understanding and use of predictive models in hospital management should be disseminated to improve planning mechanisms and results provided to the served population.

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Association between Cholecystectomy and the Incidence of Pancreaticobiliary Cancer after Endoscopic Choledocholithiasis Management

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Simple Summary: The majority of the current evidence shows that people who have been accepted to receive cholecystectomy have higher hepatobiliary and pancreatic cancer risk. Meanwhile, strong evidence showed that cholecystectomy can reduce recurrent biliary events after endoscopic treatment for choledocholithiasis, and we suggest on-site or interval cholecystectomy in such patients. We need to explore the true risk of the pancreaticobiliary system after the endoscopic management of choledocholithiasis.

Abstract: (1) Background: Previous studies have raised concerns about a potential increase in pancreaticobiliary cancer risk after cholecystectomy, but few studies have focused on patients who undergo cholecystectomy after receiving endoscopic retrograde cholangiopancreatography (ERCP) for choledocholithiasis. This study aims to clarify cancer risks in these patients, who usually require cholecystectomy, to reduce recurrent biliary events. (2) Methods: We conducted a nationwide cohort study linked to the National Health Insurance Research Database, the Cancer Registry Database, and the Death Registry Records to evaluate the risk of pancreaticobiliary cancers. All patients who underwent first-time therapeutic ERCP for choledocholithiasis from 2011 to 2017 in Taiwan were included. We collected the data of 13,413 patients who received cholecystectomy after endoscopic retrograde cholangiopancreatography and used propensity score matching to obtain the data of 13,330 patients in both the cholecystectomy and non-cholecystectomy groups with similar age, gender, and known pancreaticobiliary cancer risk factors. Pancreaticobiliary cancer incidences were further compared. (3) Results: In the cholecystectomy group, 60 patients had cholangiocarcinoma, 61 patients had pancreatic cancer, and 15 patients had ampullary cancer. In the non-cholecystectomy group, 168 cases had cholangiocarcinoma, 101 patients had pancreatic cancer, and 49 patients had ampullary cancer. The incidence rates of cholangiocarcinoma, pancreatic cancer, and ampullary cancer were 1.19, 1.21, and 0.3 per 1000 person-years in the cholecystectomy group, all significantly lower than 3.52 ($p < 0.0001$), 2.11 ($p = 0.0007$), and 1.02 ($p < 0.0001$) per 1000 person-years, respectively, in the non-cholecystectomy group. (4) Conclusions: In patients receiving ERCP for choledocholithiasis, cholecystectomy is associated with a significantly lower risk of developing pancreaticobiliary cancer

Keywords: endoscopic retrograde cholangiopancreatography; cholecystectomy; pancreaticobiliary cancer; ampullary cancer; future cancer risk

1. Introduction

Cholecystectomy (CCY) is an important treatment [1] of choledocholithiasis after endoscopic treatment in different types of biliary events, including cholecystitis, cholangitis, and gallstone pancreatitis. This problem has become important due to obesity and is an important risk factor for cholelithiasis, which increases in prevalence in young-age people [2]. There is extensive evidence that CCY, after endoscopic retrograde cholangiopancreatography (ERCP) management for choledocholithiasis, can decrease future recurrent biliary events [3–6]. However, previous studies have shown that CCY might increase cancer risks in total liver cancers [7,8] hepatocellular carcinoma (HCC) [9,10], intra-hepatic cholangiocarcinoma (ICC) [9], extra-hepatic cholangiocarcinoma (ECC) [11], ampullary cancer (AVC) [11,12], and pancreatic duct adenocarcinoma (PDC) [7,11–13]. Because evidence of biliary tract malignancy could be caused by the condition of chronic inflammation resulting from cholestasis [14,15], CCY should be associated with a decreased incidence of bile duct cancers after patients undergo therapeutic ERCP for choledocholithiasis. However, conflicting results suggest a lack of direct association between CCY and hepatobiliary system cancers [16,17]. Meanwhile, laparoscopic cholecystectomy and common bile duct exploration (LCBDE) was shown to resolve this problem in one step without destroying the structure of Ampulla of Vater in the management of choledocholithiasis compared with CCY after ERCP [18]. The current evidence for the correlation between increased cancer risks in the pancreatic and hepatobiliary system and CCY or endoscopic sphincterotomy (ES) [19] is not completely clear. The problem in establishing a cause-and-effect relationship between PDAC, hepatobiliary system malignancy, and CCY is the procedure per se or the chronic inflammation environment caused by gallstone disease (i.e., the reason to perform CCY).

Biliary tract cancers, which can be divided into ICC, ECC, and AVC, are lethal diseases in the biliary system [20]. Our previous population-database cohort study showed that CCY was associated with a lower risk of cholangiocarcinoma in patients who underwent ERCP for bile duct stones management [21], but the evidence was not strong owing to the limited number of further cholangiocarcinoma cases. Therefore, we conducted a large-scale whole population-database cohort study in Taiwan and provided detailed confounding factor adjustments to clarify the association between CCY and the risk of pancreaticobiliary cancers after the ERCP management of choledocholithiasis and acute cholangitis.

2. Materials and Methods

We conducted a nationwide cohort study including whole population data, which comprised about 23 million beneficiaries who were enrolled in the Health Insurance Program in Taiwan from 1 January 2011 to 31 December 2018. The data were accessed from Taiwan's Health and Welfare Data Science Center (HWDSC). This center maintains many nationwide databases in Taiwan for the purpose of academic research [22]. We linked three nationwide databases, the National Health Insurance Research Database (NHIRD), the Cancer Registry Database, and the Death Registry Records, to evaluate the risk of pancreaticobiliary cancers, including ICC, ECC, AVC, and PDAC in choledocholithiasis patients after ES or endoscopic papillary balloon dilatation (EPBD). The information in the registry data of inpatient and outpatient visits was identified, including personal demographics, diagnosis of potential disease, prescriptions, and surgeries from the NHIRD. The Cancer Registry Database was established in 1979 (https://twcr.tw/), and it contains a high-quality database of the validated registry framework. We extracted data on the date of cancer diagnosis and the cancer site from the Cancer Registry Database. The Death Registry Records were used to check the survival status, date of death, and cause of death.

All study individuals were provided with a hashed and unique personal identification number to link the data between these nationwide databases. The primary outcome in this study is further biliary cancer risk, while the secondary outcome is PDAC risk after CCY in patients, whoever accepted ERCP choledocholithiasis management.

The Human Research Ethics Committee of the Institutional Review Board of Chung Shan Medical University Hospital approved our study (CS1-22080) on 27 June 2022. This study was sponsored by the Chung Shan Medical University Hospital Research Program (CSH-2021-C-006, CSH-2022-C-044).

2.1. Definition of Study Population

We identified patients hospitalized for the diagnosis of choledocholithiasis (ICD-9 codes: 574.3, 574.4, 574.5, 574.6, 574.7, 574.8, and 574.9), cholangitis (ICD-9 codes: 576.1 and 576.2), and treated with therapeutic ERCP (ES [procedure code: 56031B and 56033B] or EPBD [procedure code: 56032B]) for the first time, who were also identified by procedure codes of lithotripsy (28008B, 28035B) between 2011 and 2017 and followed the outcomes of these patients until 31 December 2018. Initially, 55,459 patients were selected, and the patients who had missing demographic data, were aged <18 years at admission, and had received CCY before admission were excluded. After the first exclusion, there were 14,068 patients who had received CCY within 2 months [23] after the first admission as the CCY group and 38,259 patients who did not have CCY throughout the study period as the comparison group. We defined the index date as the date 2 months after initial admission to avoid potential surveillance or detection bias. Furthermore, we excluded patients who died or had biliary tract malignancy before the index date. The 13,413 and 33,068 eligible cases were divided into CCY and non-CCY cohorts, respectively.

An additional analysis of propensity score matching (PSM) was performed to reduce the confounding bias after balancing the measured characteristics between the study groups [24]. We also provide the original baseline characteristics among study groups in Supplementary Table S1. The propensity score was estimated as the probability of the treatment of CCY by using logistic regression, and the covariates included were index year, baseline demographics (including sex, age, urbanization, and insured category), and pancreaticobiliary cancer risk factors (including chronic hepatitis B infections [CHB] [25], chronic hepatitis C [10] [CHC], Helicobacter pylori [HP] infection [26,27], diabetes mellitus [28,29] [DM], chronic kidney disease [CKD], choledochal cyst disease [30,31], inflammatory bowel diseases [IBD], and liver cirrhosis [LC] [8,32]). There were some rare diagnoses, which may increase biliary cancer risks, that were never recorded in our analysis, such as primary sclerosing cholangitis [33] and specific parasite infection [34]. We used the PSMATCH procedure in the SAS software version 9.4, the algorithm of greedy nearest neighbor matching, and non-replacement paired within 0.01 caliper widths [35]. Finally, 13,330 pairs of PSM CCY and non-CCY patients were selected for analysis (Figure 1).

2.2. Definition of Study Covariates

Baseline demographics, including age, sex, urbanization, and insured category, were identified based on the information at the index date. Age was calculated in years between the birth and index dates, and we classified patients into the age groups of 18 to <50, 50 to <60, 60 to <70, and ≥70 years. The risk factors of pancreaticobiliary cancers, including CHB, CHC, HP infection, DM, CKD, congenital cystic disease of the liver, IBD, and LC, were identified based on the ICD-9-CM codes listed in Supplementary Table S2. The baseline characteristics among study groups after PSM are shown in Table 1.

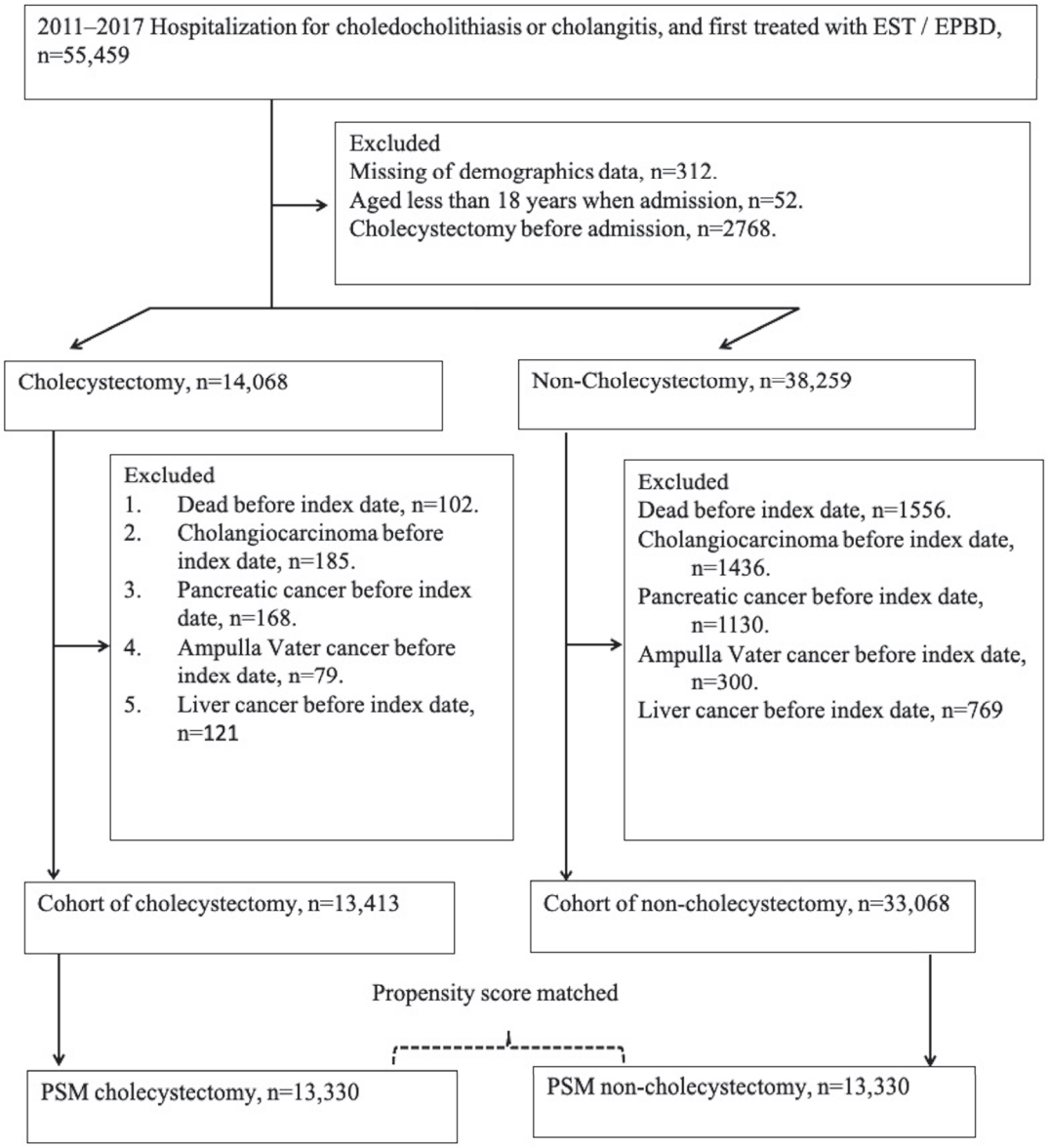


Figure 1. Flowchart of patient selection.

Table 1. Baseline characteristics among study groups after propensity score matching (PSM).

	Non-Cholecystectomy	Cholecystectomy	ASD
n	13,330	13,330	
Index year			0.000
2011, 2012	2932 (22.00%)	2911 (21.84%)	
2013, 2014	3615 (27.12%)	3585 (26.89%)	
2015, 2016	4144 (31.09%)	4189 (31.43%)	
2017, 2018	2639 (19.80%)	2645 (19.84%)	
Sex			0.004
Male	7111 (53.35%)	7047 (52.87%)	
Female	6219 (46.65%)	6283 (47.13%)	
Age			0.000
<50	3662 (27.47%)	3636 (27.28%)	
50–60	2516 (18.87%)	2510 (18.83%)	
60–70	2934 (22.01%)	2988 (22.42%)	
≥70	4218 (31.64%)	4196 (31.48%)	

Table 1. *Cont.*

	Non-Cholecystectomy	Cholecystectomy	ASD
Urbanization			0.000
High urbanization	3928 (29.47%)	3872 (29.05%)	
Moderate urbanization	4147 (31.11%)	4160 (31.21%)	
Developing town	2128 (15.96%)	2094 (15.71%)	
General town	1833 (13.75%)	1848 (13.86%)	
Aged town	368 (2.76%)	367 (2.75%)	
Agriculture town	605 (4.54%)	636 (4.77%)	
Village	321 (2.41%)	353 (2.65%)	
Insured category			0.083
Government	701 (5.26%)	721 (5.41%)	
Privately held company	7235 (54.28%)	7124 (53.44%)	
Agricultural organizations	2379 (17.85%)	2387 (17.91%)	
Low-income	90 (0.68%)	103 (0.77%)	
Non-labor force	2737 (20.53%)	2776 (20.83%)	
Others	188 (1.41%)	219 (1.64%)	
Co-morbidity			
Chronic hepatitis B	1029 (7.72%)	1134 (8.51%)	0.029
Chronic hepatitis C	406 (3.05%)	465 (3.49%)	0.025
Helicobacter infection	397 (2.98%)	466 (3.50%)	0.029
Diabetes mellitus	4222 (31.67%)	4210 (31.58%)	0.002
CKD	1276 (9.57%)	1270 (9.53%)	0.002
Congenital cystic disease of liver	93 (0.70%)	90 (0.68%)	0.003
Inflammatory bowel diseases	375 (2.81%)	427 (3.20%)	0.023
Liver cirrhosis	516 (3.87%)	510 (3.83%)	0.002

ASD, absolute standardized difference. CKD, chronic kidney disease.

2.3. Identification of Study Events

The subsequent pancreaticobiliary cancer was identified from the information in the Cancer Registry Database. The patients who were newly diagnosed with cholangiocarcinoma (ICC and ECC), PDAC, and AVC were ascertained using ICD-9 codes (Supplementary Table S2), while lung cancer was selected for potential bias detection.

2.4. Statistical Analysis

We used the absolute standardized difference (ASD) [36] to compare the baseline covariates between the groups in this large-sample observational study. The characteristics were balanced when the ASD was <0.1. We conducted survival models to evaluate the association between CCY and the risk of pancreaticobiliary cancers. The incidence rate and 95% confidence interval (CI) were calculated by considering the Poisson distribution. All study individuals were followed from the index date until the occurrence of the study event. The censoring point included the death of patients or the end of the study (31 December 2018). Kaplan–Meier survival curves were plotted to compare the 7-year cumulative probability of developing cholangiocarcinoma (including ICC and ECC), PDAC, AVC, or lung cancer among the CCY and non-CCY cohorts, with a median follow-up period of 3.9 years. A log-rank test was performed to determine the overall homogeneity of the hazard rate functions among the study groups. After the proportional hazard assumption was tested, univariate and multivariable Cox proportional hazards regressions were used to estimate the hazard ratio (HR) of the exposure to CCY on the risk of cholangiocarcinoma, PDAC, AVC, and lung cancer (Table 2). We considered the covariates, including index year, baseline demographics, and known pancreaticobiliary cancer risks, which were described in the definition of the study population in the multivariable regression. The competing HR was estimated using the sub-distribution Fine–Gray regression approach, wherein mortality was considered a competing event. A subgroup analysis and an interaction effect test were performed to evaluate the effects of sex and age in different stratifications using multivariate Cox regression. When considering the possible incubation period from exposure to the

diagnosis of cancer, we performed the sensitivity analysis using the landmark time at 24 months after the index date. We excluded individuals who were followed for less than 24 months in the landmark analysis. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). A significance level of 0.05 was used for the hypothesis test.

Table 2. Risks of cancer incidence among patients with EST/EPBD after PSM.

	Non-Cholecystectomy	Cholecystectomy	*p* Value
Cholangiocarcinoma			
Observed person-years	47,718.8	50,262.1	
Incident cases	168	60	
Incidence rate †	3.52 (3.03–4.1)	1.19 (0.93–1.54)	
Crude HR (95% CI)	Reference	0.34 (0.26–0.46)	<0.0001
Adjusted HR (95% CI)	Reference	0.34 (0.25–0.46)	<0.0001
ICC			
Observed person-years	47,768.3	50,276.6	
Incident cases	117	46	
Incidence rate †	2.45 (2.04–2.94)	0.91 (0.69–1.22)	
Crude HR (95% CI)	Reference	0.38 (0.27–0.53)	<0.0001
Adjusted HR (95% CI)	Reference	0.37 (0.26–0.52)	<0.0001
ECC			
Observed person-years	47,825.8	50,286.9	
Incident cases	52	24	
Incidence rate †	1.09 (0.83–1.43)	0.48 (0.32–0.71)	
Crude HR (95% CI)	Reference	0.45 (0.28–0.73)	0.0011
Adjusted HR (95% CI)	Reference	0.44 (0.27–0.72)	0.0010
Pancreatic cancer			
Observed person-years	47,785.9	50,273.8	
Incident cases	101	61	
Incidence rate †	2.11 (1.74–2.57)	1.21 (0.94–1.56)	
Crude HR (95% CI)	Reference	0.58 (0.43–0.80)	0.0009
Adjusted HR (95% CI)	Reference	0.58 (0.42–0.79)	0.0007
Ampulla Vater cancer			
Observed person-years	47,829.0	50,289.0	
Incident cases	49	15	
Incidence rate †	1.02 (0.77–1.36)	0.3 (0.18–0.49)	
Crude HR (95% CI)	Reference	0.30 (0.17–0.53)	<0.0001
Adjusted HR (95% CI)	Reference	0.30 (0.17–0.53)	<0.0001
Lung cancer			
Observed person-years	47,765.7	50,171.8	
Incident cases	135	96	
Incidence rate †	2.83 (2.39–3.35)	1.91 (1.57–2.34)	
Crude HR (95% CI)	Reference	0.88 (0.63–1.24)	0.4753
Adjusted HR (95% CI)	Reference	0.86 (0.61–1.21)	0.3737

† per 100 person-years. ICC, Intrahepatic cholangiocarcinoma. ECC, Extra-hepatic cholangiocarcinoma. aHR, adjusted hazard ratio, the covariates included index year, sex, age, urbanization, unit type of insured, and co-morbidities. Competing aHR, competing adjusted hazard ratio was estimated by the Fine and Gray sub-distribution hazard function.

3. Results

We collected 13,330 cases who received CCY after ES or EPBD for choledocholithiasis or cholangitis management. We provided another 13,330 cases without CCY after PSM under similar clinical conditions as the control group (Figure 1). In the baseline covariates, the ASD in the index year, gender, age, urbanization, and insured category, which were all less than 0.1, means balanced baseline characters between the CCY and non-CCY groups. Meanwhile, there were no statistically significant differences in the known risk factors for pancreaticobiliary cancer, such as CHB, CHC, Helicobacter infection, diabetes mellitus, CKD, congenital cystic disease of the liver, IBD, and LC, between the CCY and non-CCY cohorts. Detailed information is shown in Table 1.

The results showed that 168 patients had cholangiocarcinoma in the non-CCY group, while 60 cases had cholangiocarcinoma in the CCY group. There were 3.52, 2.45, and 1.09 cases per 1000 person-years of cholangiocarcinoma, ICC, and ECC in the non-CCY group and 1.19, 0.91, and 0.48 cases per 1000 person-years of cholangiocarcinoma, ICC, and ECC, respectively, in the CCY group. The competing HR in the multivariable regression, considering the covariates, including index year, baseline demographics (including sex, age, urbanization, and insured category), and risk factors for pancreaticobiliary cancers (including CHB, CHC, HP infection, DM, CKD, congenital cystic disease of the liver, IBD, and LC), revealed an adjusted HR of the CCY group of 0.34 (0.25–0.46), 0.37 (0.26–0.52), 0.44 (0.27–0.72) in cholangiocarcinoma, ICC, and ECC, respectively, compared with the risks of the non-CCY group.

There were 101 cases of PDAC in the follow-up period, which resulted in an incidence rate of 2.11 (1.74–2.57) per 1000 person-years in the non-CCY group, while there were 61 cases of PDAC with an incidence rate of 1.21 (0.94–1.56) per 1000 person-years in the CCY group. The adjusted HR of PDAC in the CCY group compared with the non-CCY group was 0.58 (0.42–0.79), with a p value of 0.0007. Similar results were noticed in the AVC, which showed that the adjusted HR of the AVC in the CCY group compared with the non-CCY group was 0.30 (0.17–0.53), with a p value of <0.0001. For potential bias detection, we chose lung cancer, which is supposed to have no relationship with CCY, to calculate the adjusted HR between the CCY and non-CCY cohorts. The adjusted HR of lung cancer was 0.86 (0.61–1.21) in the CCY group compared with the non-CCY group, which showed a non-significant difference, with a p value of 0.3737. Detailed information is provided in Table 2. We provided the pancreaticobiliary cancer risk in the study groups before PSM in Supplementary Table S3.

Kaplan–Meier curves were plotted to compare the 7-year cumulative probability of developing cholangiocarcinoma, ICC, ECC, and lung cancer in Figure 2. The cumulative incidence probability of cholangiocarcinoma, ECC, and ICC was significantly higher in the non-CCY group than in the CCY group, with p values of $p < 0.0001$, $p = 0.0002$, and $p < 0.0001$, respectively. The Kaplan–Meier curve of lung cancer incidence probability was similar ($p = 0.4750$) between the non-CCY and CCY groups in Panel D, Figure 2. The cumulative incidence probability of PDAC, which is demonstrated in Panel A, Figure 3, is significantly higher in the non-CCY group ($p = 0.0003$), while the AVC risk is also higher ($p < 0.0001$) in the non-CCY group (Panel B, Figure 3).

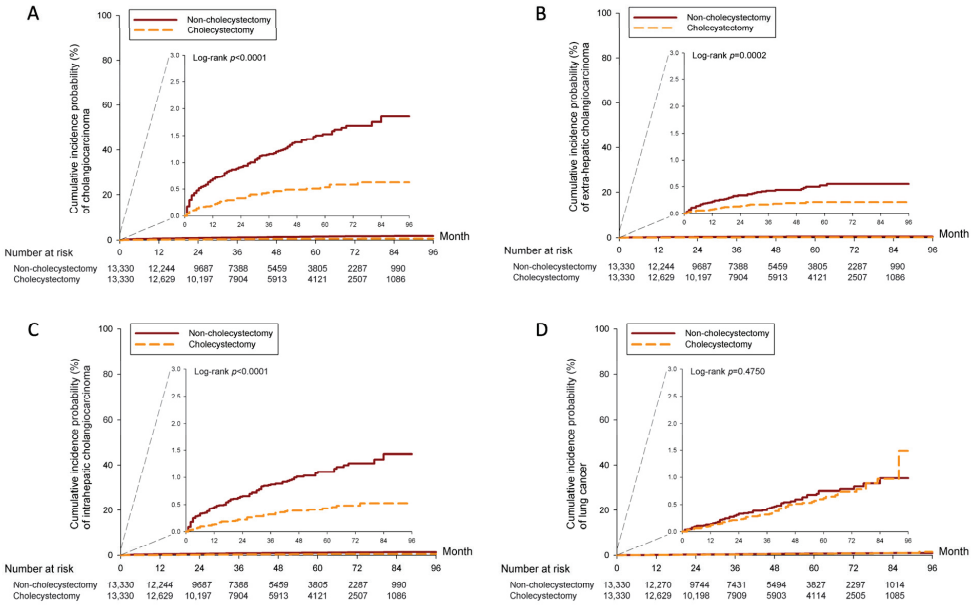


Figure 2. KM curves of incidence probability of (**A**) cholangiocarcinoma, (**B**) extra-hepatic cholangiocarcinoma, (**C**) intrahepatic cholangiocarcinoma, and (**D**) lung cancer.

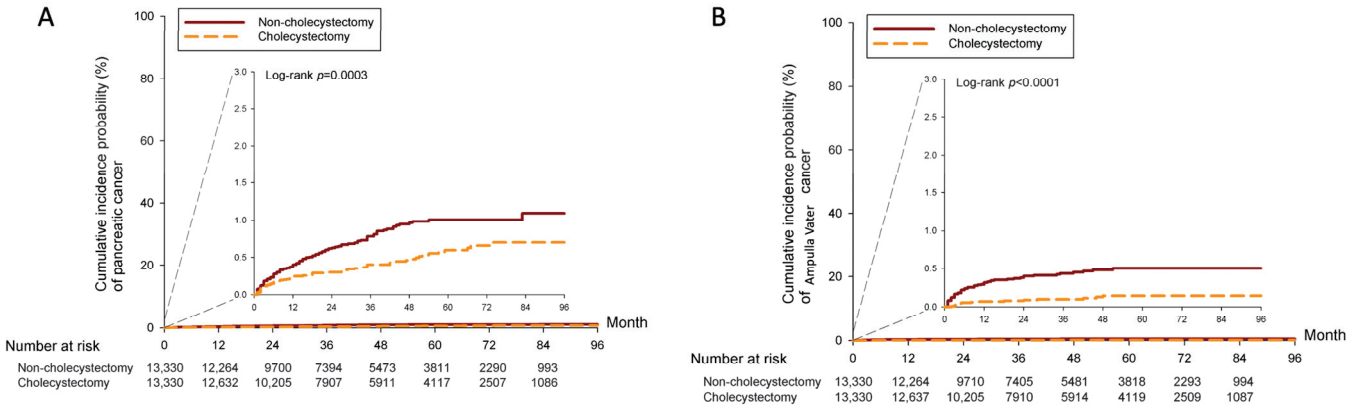


Figure 3. KM curves of incidence probability of (**A**) pancreatic cancer and (**B**) ampullary cancer.

We performed the sensitivity analysis using the landmark time at 24 months after the index date by excluding individuals who were followed for less than 24 months in the landmark analysis. The competing adjusted hazard ratios of the CCY group compared with that of the non-CCY group were 0.30 (0.17–0.51) in cholangiocarcinoma, 0.44 (0.25–0.75) in ICC, 0.46 (0.18–1.14) in ECC, 0.84 (0.47–1.48) in PDAC, 0.48 (0.16–1.40) in AVC, and 1.05 (0.65–1.68) in lung cancer when individuals who were followed for less than 24 months were excluded. Detailed information is presented in Table 3. The original results before PSM showed similar conditions in Supplementary Table S4.

Table 3. Sensitivity analysis by moving the time 0 as +24 from index date.

	Cholecystectomy aHR (95% CI)
	Excluded Patients Followed <24 months
Incidence rate	
Cholangiocarcinoma	0.30 (0.17–0.51)
ICC	0.44 (0.25–0.75)
ECC	0.46 (0.18–1.14)
Pancreatic cancer	0.84 (0.47–1.48)
Ampulla Vater cancer	0.48 (0.16–1.40)
Lung cancer	1.05 (0.65–1.68)

ICC, Intrahepatic cholangiocarcinoma. ECC, Extra-hepatic cholangiocarcinoma. aHR, adjusted hazard ratio. The covariates included index year, sex, age, urbanization, unit type of insured, and co-morbidities.

4. Discussion

This is the first nationwide whole-population study to evaluate the cancer risk of CCY in patients after choledocholithiasis or cholangitis managed with therapeutic ERCP. The inclusion criteria used both the diagnosis code and procedure code of ES or EPBD combined with lithotripsy to ensure disease accuracy and balance the heterogeneous condition of choledocholithiasis in both CCY and non-CCY groups in order to minimize the limitations inherent to retrospective research. These patients usually need CCY to reduce recurrent biliary events in the rest of their lifetimes, but the decision becomes more difficult because of prior studies reporting that CCY could possibly increase cancer risk. In our study, we found that the competing adjusted hazard ratios in the CCY group were 0.34 (95% CI, 0.25–0.46), 0.37 (95% CI, 0.26–0.52), 0.44 (95% CI, 0.27–0.72), 0.58 (95% CI, 0.42–0.79), and 0.30 (95% CI, 0.17–0.53) for cholangiocarcinoma, ICC, ECC, PDAC, and AVC, respectively, compared with the risk in the non-CCY group. Instead of increasing cancer risk, CCY was associated with a significantly lower risk of pancreaticobiliary cancer by 42–70% (ICC 63% reduction, ECC 56%, PDAC 42%, and AVC 70%). These results remained consistent in the sensitivity tests, including the landmark analysis. Across multiple analytical methods, no evidence was found to suggest that CCY was associated with elevated risks of ECC, PDAC, or AVC.

There is very limited clinical evidence focusing on cancer risks after CCY in patients with choledocholithiasis, which was previously managed by therapeutic ERCP. In pancreatic and hepatobiliary systems, previous cohort studies demonstrated that patients who received CCY had higher cancer risks of overall liver cancers [7], HCC [9,10], ICC [9], ECC [11], AVC [11,12], and PDAC [7,11,12]. Meta-analysis studies also supported the increased risk of liver cancer [37,38] and PDAC [13] in patients with gallstone disease after CCY. Only one review showed no association between CCY and cancer risk in the hepatobiliary system after a strict quality checkup [17]. In contrast, our study exhibits opposite results: the incidence of cholangiocarcinoma, ICC, ECC, AVC, and PDAC were all significantly lower and reduced in crude, adjusted, and competing adjusted hazard ratios after CCY subsequent to therapeutic ERCP choledocholithiasis treatment. There might be some major issues in previous literature, such as earlier studies using historical comparisons [11,12] and case-control study designs [7]. Although other studies [9,39] have performed the adjustment of gallstone disease, the disease severity of cholelithiasis in patients who received CCY and in patients who need no intervention is still different from the background inflammation situation.

While we focused on cholangiocarcinoma risk, a previous large-scale Swedish database study [40] showed increased ICC and ECC risks in the CCY group compared with the non-CCY group, while the risk of these tumors is reduced back to the level of the background population more than 10 years after CCY. However, this study used patients with non-symptomatic gallstone disease as a control group, which may be confounded by the disease severity of gallstone disease. A recent systemic review [41] showed that CCY was associated with a significant 54% increase in the risk of cholangiocarcinoma, especially in the ECC, in comparison with healthy controls. The updated study, which focused on complicated gallstone disease patients, showed that CCY slightly decreased cholangiocarcinoma risk [42], but this study still used age-matched and sex-matched controls without further detailed confounding factors adjustments. The problems of heterogenous disease severity and inflammatory conditions due to cholelithiasis in the CCY group and in the pure gallstone disease group/normal population existed in almost all previous articles. Our study design directly discussed the future cancer risk in patients who received therapeutic ERCP intervention for choledocholithiasis in both patients who received CCY or chose not to receive CCY. We believe this study design can help clarify the truest risk of CCY for pancreaticobiliary cancer incidence in patients who have undergone ES or EPBD for choledocholithiasis and need CCY to reduce recurrent biliary events in the rest of their lifetime.

Limitations

There are some limitations to our study. First, our study, like most retrospective database studies, had some confounding factors, such as environmental risk exposure, personal habits, and exact family history, which cannot be corrected and may lead to some clinical bias. Second, although the longest follow-up period is 7.6 years, the mean follow-up time in our cohort study is 3.9 years, which is relatively short. However, we cannot expand the observational period due to all the data being kept in HWDSC in accordance with our regulations in Taiwan. Third, the general characteristics of the CCY and non-CCY groups were less homogenous in the original data, which required PSM to balance the background parameters. However, the PSM process itself led to a loss of study samples and may have reduced statistical power, especially in the sensitivity analysis, with the exclusion of patients followed up for less than 2 years. Fourth, we didn't evaluate further the cancer risk in patients who accepted LCBDE because we seldom performed this procedure routinely in Taiwan. As a result, our results should be applied with caution to the patients who underwent LCBDE.

5. Conclusions

In patients who underwent therapeutic ERCP for choledocholithiasis or cholangitis, CCY was not associated with an excessive risk of pancreaticobiliary cancer. Instead, the relationship between CCY and the subsequent development of pancreaticobiliary cancer post-ERCP appeared to be protective.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cancers16050977/s1. Table S1: Baseline characteristics among original study groups (before propensity score matching); Table S2: definition of co-morbidities and study outcome; Table S3: Risks of cancer incidence among patients with EST/EPBD before propensity score matching; Table S4: Sensitivity analysis by moving the time 0 as +24 from index date before propensity score matching.

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Institutional Review Board Statement: All study individuals were provided with a hashed and unique personal identification number to link the data between these nationwide databases. The study was conducted in accordance with the Declaration of Helsinki, and the Human Research Ethics Committee of the Institutional Review Board of Chung Shan Medical University Hospital approved our study (CS1-22080).

Informed Consent Statement: This is a retrospective national database study that obtained waiver 1 for informed consent.

Data Availability Statement: Datasets from the National Health Insurance Research Database are available through a request to the Health and Welfare Data Science Center (HWDSC). However, the data are not publicly available due to the privacy of research participants. We are unable to share the data sets and code lists on request. For this study, the application number is H111231, which was registered in HWDSC.

Conflicts of Interest: The authors declare no conflicts of interest.

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Article

Lung Cancer and Air Quality in a Large Urban County in the United States

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Simple Summary: Lung cancer incidence varies geographically for several reasons, including environmental exposures. The incidence of lung cancer and corresponding air quality was examined over three decades in one large urban county in the United States. There were specific clusters of lung cancer cases that were found over that period. The most intense clusters corresponded to the areas of the county with the worst pollution. Sulfur dioxide, particulate matter < 10 µm, nitrogen dioxide, volatile organic compounds and ozone levels had significant relationships with lung cancer incidence. Different pollutants had different lag times between exposure level and lung cancer development.

Abstract: Lung cancer is the leading cancer-related killer in the United States. The incidence varies geographically and may be affected by environmental pollutants. Our goal was to determine associations within time series for specific air pollutants and lung cancer cases over a 33-year period in Wayne County, Michigan, controlling for population change. Lung cancer data for Wayne County were queried from the Michigan Cancer Registry from 1985 to 2018. Air pollutant data were obtained from the United States Environmental Protection Agency from 1980 to 2018. Autoregressive distributed lag (ARDL) models were estimated to investigate time lags in years between specific air pollution levels and lung cancer development. A total of 58,866 cases of lung cancer were identified. The mean age was 67.8 years. Females accounted for 53 percent of all cases in 2018 compared to 44 percent in 1985. Three major clusters of lung cancer incidence were detected with the most intense clusters in downtown Detroit and the heavily industrialized downriver area. Sulfur dioxide (SO_2) had the strongest statistically significant relationship with lung cancer, showing both short- and long-term effects (lag range, 1–15 years). Particulate matter ($PM_{2.5}$) (lag range, 1–3 years) and nitrogen dioxide (NO_2) (lag range, 2–4 years) had more immediate effects on lung cancer development compared to carbon monoxide (CO) (lag range, 5–6 years), hazardous air pollutants (HAPs) (lag range, 9 years) and lead (Pb) (lag range, 10–12 years), which had more long-term effects on lung cancer development. Areas with poor air quality may benefit from targeted interventions for lung cancer screening and reductions in environmental pollution.

Keywords: air pollution; lung cancer; lung cancer screening; autoregressive distributed lag models (ARDLs); Michigan, USA

1. Introduction

Lung cancer is the most common cause of cancer-related death in the United States [1]. In 2024, there were an estimated 234,580 new cases and 125,070 deaths due to lung cancer [2]. Lung cancer is also the leading cause of death among patients with cancer, accounting for

about one in five of all cancer deaths in the U.S. [3]. One of the main reasons for the poor outcomes is that lung cancer is largely asymptomatic in the early stages of disease. As such, early detection is one of the strategies by which the medical community can reduce mortality from lung cancer. Although cigarette smoking remains the main risk factor for lung cancer development, the importance of environmental factors such as air pollution and poor air quality is becoming more recognized [4,5].

Air pollution appears to be a particularly important factor contributing to lung cancer, as evident by an estimated 25,000 annual deaths from lung cancer in non-smokers in the U.S. [6]. Other factors that contribute to the increased risk of developing lung cancer in non-smokers include secondhand smoke from cigarettes, occupational exposures and genetic susceptibility [7–10]. Several studies have indicated that exposure to air pollution, including fine particulates, nitrogen dioxide, sulfur dioxide, ozone, radon and asbestos, are associated with lung cancer [11–13]. Long-term exposure to air pollution may increase lung cancer risk through oxidative damage, which occurs via inflammatory injury and the production of reactive oxygen species [14,15]. Oxidative stress and inflammation can induce cellular damage and lead to the promotion of metaplastic cell survival.

Elevated levels of air pollutants in the U.S. can be found in the Midwest and Southeast regions of the country. In the Midwest, there are economically declining urban areas such as Detroit, Michigan [16]. Also referred to as the Rust Belt, these urban areas were historically manufacturing hubs for important industries, such as the automobile industry. With economic restructuring in the early 1970s, there was the movement of industries to the South and overseas. As residential areas were rezoned to industrial areas, low property values provided an incentive for new industries to move in. This movement led to a shift in air-borne lead-polluting industries from the suburbs to urban areas [17,18]. Several industrial plants and automobile factories are currently major sources of pollution and have led to seasonal trends in elevated air pollution levels [19].

The goal of this study was to investigate associations in the time series of specific air pollutants and lung cancer cases over three decades in Wayne County, Michigan. The spatial distribution and clusters of high lung cancer relative risk were mapped at the zip code level, and temporal trends in lung cancer incidence and air pollutants were graphed. Finally, the associations in the time series of specific air pollutants and lung cancer cases were explored for statistically significant time period(s) and lag time(s) in years, controlling for population changes, to inform future air pollutant and lung cancer studies. The findings from this study are also intended to inform the Michigan Department of Environment, Great Lakes and Energy, Wayne County Health Department, and highlight the need for improved lung cancer screening in areas of high air pollution.

2. Materials and Methods

2.1. Patients

Approval for the study was obtained from the Henry Ford Health Institutional Review Board prior to conducting the study (IRB-15286). The Michigan Cancer Surveillance Program (MCSP) is a state government-funded surveillance program that collects healthcare data for all patients in the state diagnosed with cancer at a participating treating institution. Every patient who developed lung cancer in the state from 1985 to 2018 was included in the database.

2.2. Study Area

The study was conducted in the city of Detroit and Wayne County, Michigan. It consists of urban and suburban regions. Detroit is the largest city in Wayne County. Wayne County is the most populous county in the state of Michigan, with a population of 1.8 million people in 2020. In the county, 48 percent of people are White Americans, 38 percent are Black Americans, 7 percent are Hispanic Americans and 7 percent are other races [20].

2.3. Study Design and Settings

A retrospective cross-sectional study design was implemented utilizing the MSCP database queried from 1985 to 2018 for all lung cancer cases in Wayne County using the 'county of diagnosis' (FIPS code = 163) (n = 58,866). Patient demographics (sex, age and race), stage of cancer (extent of disease) and survival were recorded overall and at the patients' zip code level. Stage was categorized in the database as early, regional and distant. Regional or distant disease was considered to be advanced stage. Age was considered to be the patient's age at the time of diagnosis. Although smoking history was a variable in the MCSP database, roughly 85 percent of patients had missing data for this variable. Furthermore, no zip-code-level smoking rates were available for Wayne County during the study period.

2.4. Air Quality

Daily air quality–pollution data from 1980 to 2021 were obtained from the United States Environmental Protection Agency (EPA) AirData website for Michigan. A total of nine pollutants and their levels were collected from monitoring stations, including carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), particulate matter < 2.5 microns ($PM_{2.5}$), particulate matter < 10 microns (PM_{10}), lead (Pb), hazardous air pollutants (HAPs) and volatile organic compounds (VOCs). CO and O_3 were measured in parts per million. NO_2 and SO_2 were measured in parts per billion. Lead, HAP, $PM_{2.5}$ and PM_{10} were measured in micrograms per cubic meter. VOCs were measured in parts per billion carbon. While the levels of air pollutants were available at each air monitoring station, an empirical Bayesian Kriging model was used to interpolate (estimate) values between monitoring stations, thereby resulting in a continuous surface of annual average air pollution estimates for each air pollutant in Wayne County [21].

2.5. Statistical Analysis

Firstly, descriptive statistics of the lung cancer patients were generated. Secondly, the cumulative relative risk (RR) of lung cancer incidence across the study time period was calculated at the zip code level using the 2010 American Community Survey 2018 5-year population estimates in SaTScan (v9.7) software [22]. The observed number of lung cancer cases was divided by the expected number estimated using a Poisson model to obtain the RR for each zip code and also to identify areas where the observed numbers were significantly higher than expected. These areas in which observed incidence was significantly higher were referred to as lung cancer clusters. Lung cancer clusters were optimized using the Gini coefficient to detect smaller non-overlapping clusters instead of overly large clusters in the study area [23]. The Gini coefficient is a measure to describe how closely the expected number of cases is to the observed number of cases in different areas. As such, within one overly large cluster, there may be additional smaller clusters that a high Gini coefficient would detect. The temporal patterns of lung cancer incidence and pollutant levels were also presented graphically over the study time period.

Thirdly, the time series of specific air pollutants and lung cancer cases were investigated by estimating autoregressive distributed lag (ARDL) models. The ARDL model utilizes a linear regression model to find significant time period(s) and lag time(s) in years within those time periods between an air pollution level (independent variable) and lung cancer cases (dependent variable), controlling for trends in varying population size. For this study, a maximum of 15 years' lag or less was studied to assess each air pollutant's relationship with lung cancer cases. Using this method, a "significant" lag would represent the number of years from a pollutant's levels and the magnitude of lung cancer cases [24].

3. Results

3.1. Lung Cancer Statistics

A total of 58,866 new cases of lung cancer were identified in Wayne County. The demographics are listed in Table 1. The mean age was 67.8 years. Thirty-seven percent of patients

identified as African American. The largest proportion of lung cancer diagnoses presented in advanced stages, with 20 percent of patients presenting with regional metastases and 48 percent of patients presenting with distant metastases.

Table 1. Lung cancer patient demographics in Wayne County, Michigan, from 1985 to 2018.

N	**58,866**
Age, years (mean)	67.8 ± 11.14
Men	56.8%
Race	
Caucasian	62.0%
African American	37.2%
Other	0.8%
Extent of disease	
Localized	10,197 (17.3%)
Regional	11,761 (20.0%)
Distant	28,494 (48.4%)
Unknown	8404 (14.3%)

More men (56.8%) than women were diagnosed with lung cancer. The gender differences narrowed over time, however. In 1985, men were 2.2 times more likely to develop lung cancer than women, with men representing 66 percent of all lung cancers in 1985. By 2018, the incidences of lung cancer for men and women were relatively similar, with women representing 53 percent of all lung cancers (Figure 1).

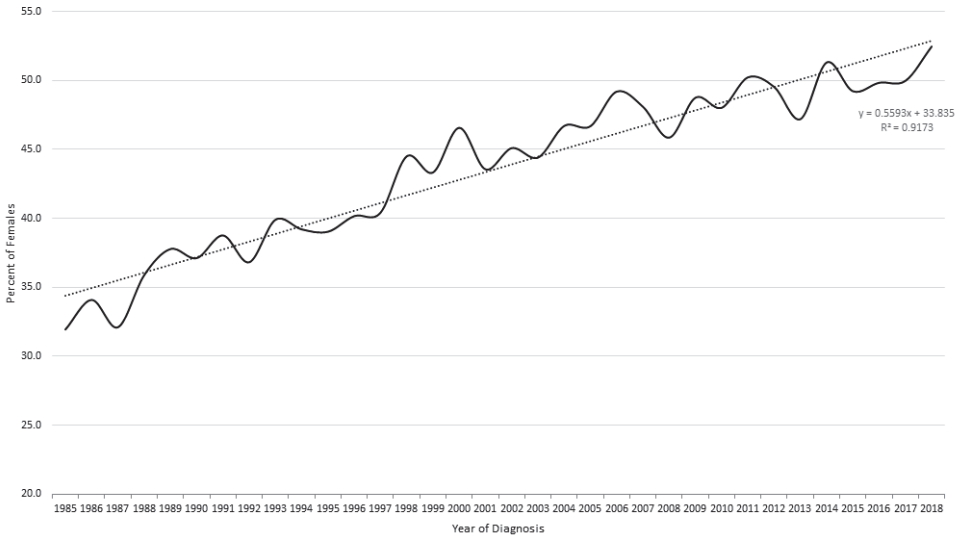


Figure 1. Gender ratio of lung cancer cases over time.

3.2. Spatial Distribution

Figure 2 shows the spatial distribution of lung cancer relative risk (RR) at the zip code level in Wayne County (RR range, 0.17 to 2.1). There were three significant clusters of lung cancer RR found (a) in downtown Detroit (RR range, 0.86–2.02), (b) in the downriver Detroit area (RR range, 1.11–2.02) and (c) the western suburbs of Detroit (RR range, 1.11–1.47).

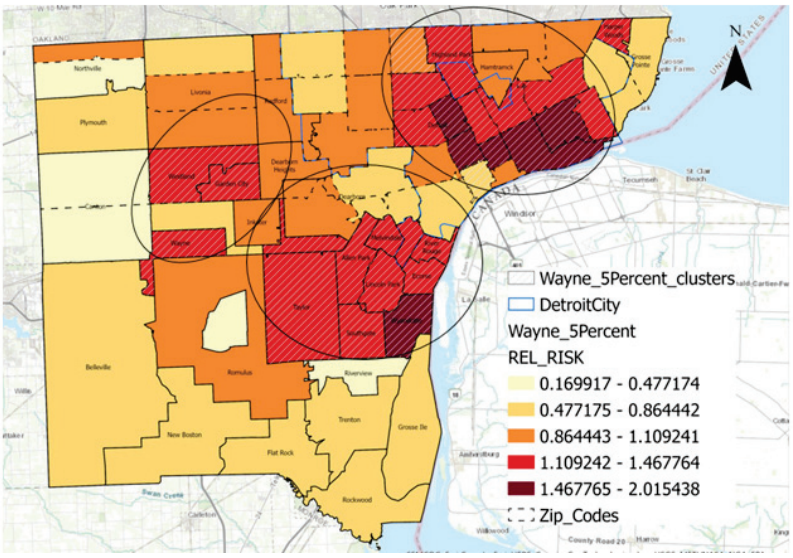


Figure 2. Geographic distribution of lung camcer cases over time.

3.3. Temporal Trends in Lung Cancer Incidence and Air Quality

Figure 3 shows the temporal trends of lung cancer incidence across the study time period. There was a declining trend beginning in the mid-1990s and particularly after 2005.

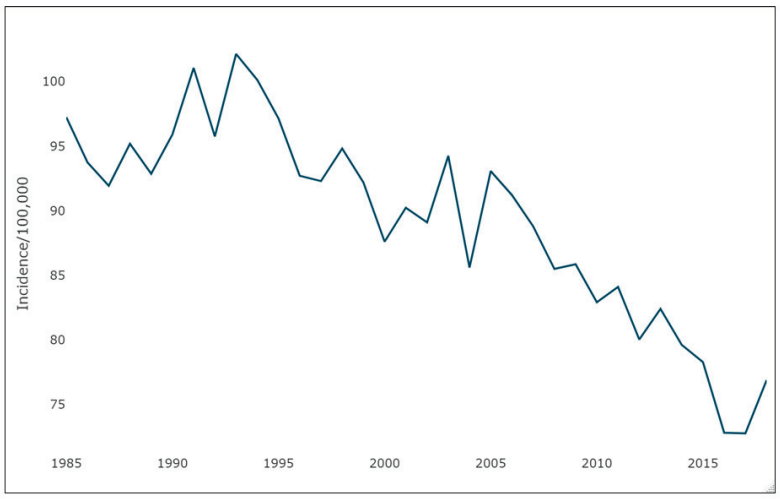


Figure 3. Trends in incidence of lung cancer over time.

Figure 4 shows the temporal trends in the nine air pollutants studied. While most pollutant levels decreased over time, the levels of $PM_{2.5}$ increased in Wayne County in the last 5 years.

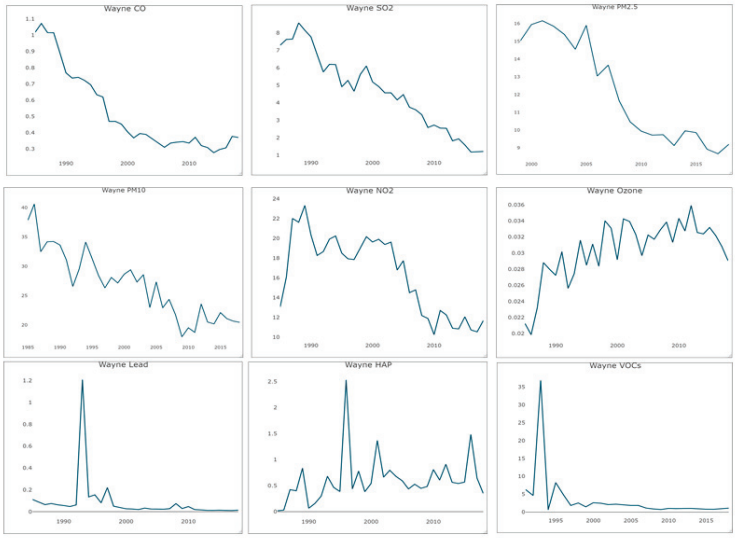


Figure 4. Pollutant levels over time.

3.4. Associations between Air Pollutants and Lung Cancer

The results of the ARDL model also showed that multiple air pollutants had a significant impact on the trend of lung cancer incidence after controlling for population variability. Figure 5 provides the results of comparative analyses of those air pollutants, time periods and lag time(s) in years in which specific air pollutants had a statistically significant effect on lung cancer cases. All air pollutants demonstrated a significant relationship with lung cancer cases between the time periods within which air pollution data were collected (1985–2018). Within these time periods, the pollutant with the widest range in significant lag times was SO_2 (lag range 1–15 years). There was also a large range in lags for PM_{10} (lag range 2–8 years) and O_3 (lag range 1–8 years). There were more immediate effects of $PM_{2.5}$ (lag range 1–3 years) and NO_2 (lag range 2–4 years). In contrast, there were more delayed effects of other air pollutants on lung cancer development, including HAP (lag range 9 years) and Pb (lag range 10–12 years). VOCs were not a good fit in the ARDL models due to the lack of temporal changes, as the VOC pollutant levels were quite stable from 1996 to 2018 (Figure 4). As such, a generalized linear regression model was applied to study the concurrent relationship between VOCs and lung cancer cases. The results showed a significant relationship between VOCs and lung cancer from 1991 to 2018 ($p < 0.01$).

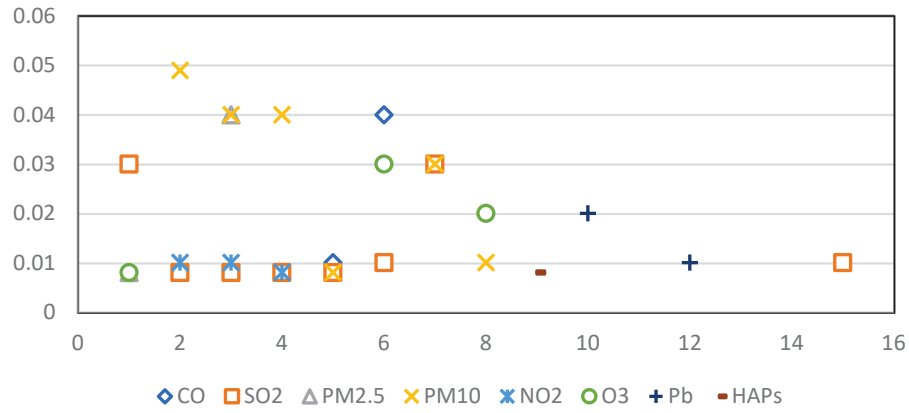


Figure 5. Temporal trends in lag time for the nine air pollutants studied.

4. Discussion

This study found that air pollution had a significant association with lung cancer development in Wayne County, Michigan, with varying lag times. These relationships have been seen in multiple studies that have linked air quality to the development of lung cancer, although these studies did not provide evidence of lag time(s) between potential exposure to air pollution levels and lung cancer [25–29]. Ambient particulate matter exposure was previously demonstrated to contribute to lung cancer development in males and older patients as the cumulative dose increased [30]. Additionally, the ESCAPE study conducted in Europe demonstrated a statistically significant relationship between PM_{10} and $PM_{2.5}$ exposure and the development of lung disease, in addition to distance to heavy road traffic areas [31]. Our study is novel in that it shows that different pollutants have different lag times between pollutant levels and lung cancer. Previous work has demonstrated how cumulative exposure to highly pollutant regions can increase risk for the development of lung cancer. Further work is needed to fully understand the significance of short lag times on lung cancer incidence.

When evaluating the incidence of lung cancer in Wayne County during our study period, we observed that men initially presented with higher rates of lung cancer than women. By the end of our study period, however, men and women developed lung cancer at nearly equal rates. This is likely due to multiple factors, including the overall decreasing rate of smoking in the United States. While smoking has decreased overall, the rate of smoking has decreased more dramatically in men than in women. Overall, the rates of lung cancer have declined over time in the United States. In 1999, the age-adjusted new lung cancer diagnosis rate was 70.7 per 100,000 people. In 2020, that rate dropped to 47.1 per 100,000 people [32]. The falling rates of lung cancer over time, in addition to decreasing smoking rates, likely contributes to the trend we see in our lung cancer dataset.

Although our study was only performed in Wayne County, it is expected that these results should be applicable to other urban areas with similar levels of air pollution. By identifying high-risk areas, hospitals and public health groups can better engage with the most at-risk populations to address disease prevention.

The rise in industrialization, traffic density and population density has led to changes in air quality over the last 100 years [29,33]. It is important for the medical community to understand these relationships as we seek to lower mortality from lung cancer. Currently, most caregivers ask for patient information such as age, smoking history and occupational history to determine risk factors for lung cancer development. In the future, it will be important to understand a patient's residential history as well. If it can be determined that a patient has lived in an area of poor air quality for a prolonged period, increased surveillance may be warranted.

In our study, SO_2 appeared to have the strongest lag relationships with lung cancer cases. SO_2 pollution has been linked to respiratory diseases in multiple studies [34–36]. Most studies, however, have focused on benign disease. Our study is among the very few to show strong immediate and delayed relationships between SO_2 and lung cancer. Our study was aided by two important factors. Firstly, we utilized pollution data from the EPA over a very long time period. We hypothesized that any relationship between pollution and cancer would potentially take decades to be revealed. Secondly, Michigan has had a comprehensive cancer database since 1985. In this database, every patient who developed lung cancer was recorded. Utilizing these two factors, we were able to show a significant relationship between SO_2 and lung cancer time series. As a major manufacturing hub since the 1880s, Detroit and Wayne County have had some of the highest SO_2 levels in the country for decades. In 2013, Detroit was one of several cities that failed to meet the 2010 air quality standard set by the Clean Air Act. As a result, the EPA in 2022 released a Federal Implementation Plan to improve air quality in this area [37]. We feel that other cities across the country and world with high SO_2 levels should implement similar plans in their regions. Lower SO_2 levels should reduce incidence of both benign and malignant lung-related illnesses.

We also saw that environmental VOC levels correlated with lung cancer incidence in our study. There is significant ongoing research about the use of inhaled VOC levels to encourage screening or detect lung cancer at early stages [38]. Although the compounds and assays are different, it is worthwhile to study any associations between exhaled lung biomarker assays and environmental pollutant levels. By identifying areas which are high risk for the development of disease, interventions like lung cancer screening and air quality improvement can be targeted and potentially have greater yield. By linking local businesses, government agencies, medical institutions, and community partners, we can use the information gained in this study to intervene at the patient level to reduce mortality from lung cancer.

This study has limitations. One major incomplete variable was individual or zip-code-level smoking history. It is possible that more industrialized areas have residents who are more likely to smoke. In addition, there have been changes in smoking rates over time. From 1965 to 2006, the rate of smoking in adults nationally decreased from 44 percent to 21 percent [39]. Unfortunately, long-term data do not exist concerning smoking rates at a local level. Despite this limitation, it is still important to investigate potential associations between environmental pollutants and lung cancer incidence. Additionally, the only publicly available air quality data were over the 30-year study period from the EPA, and the density of air quality sensors was relatively low in Wayne County, Michigan. The length of data availability limited the number of time lags that could be tested from a statistical perspective. Lung cancers and other solid tumors generally have latency periods of 20 to 30 years [40]. Furthermore, establishing a higher density of air sensors will allow for better data collection and the ability to make precise measurements. The establishment of a local air quality network using consumer-level instruments is one method to increase data collection and better understand the relationship between air quality and lung cancer. Finally, this study was unable to capture any migration patterns in patients. The large number of lung cancer cases, however, likely mitigates any migration bias to a large degree.

5. Conclusions

Our study revealed associations between air pollutants and lung cancer incidence over a 33-year period. Lag times between pollutant levels and lung cancer cases ranged and varied for different pollutants. Medical institutions can utilize this information by querying patients about their residential histories in addition to other information such as smoking and occupational exposure. In addition, the business community can work with government officials to improve air quality over time.

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Informed Consent Statement: The institutional review board waived consent, as all data were de-identified.

Data Availability Statement: Data were obtained from the Michigan Cancer Surveillance Program and the United States Environmental Protection Agency. Data from the Michigan Cancer Surveillance Program are unable to be shared secondary to a binding agreement through this program. All data

are available directly through the Michigan Cancer Surveillance Program upon request and the completion of application for data. Data from the United States Environmental Protection Agency are also available upon request.

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Impact of Indoor Radon Exposure on Lung Cancer Incidence in Slovenia

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Simple Summary: Lung cancer is one of the most frequently diagnosed cancers worldwide. Radon is a radioactive gas whose concentrations can accumulate indoors. The long-term exposure to radon is considered carcinogenic to humans and is an important risk factor for lung cancer. Our epidemiological study investigated the impact of indoor radon exposure on the incidence of lung cancer in Slovenia over a period of 40 years. Around 60 newly diagnosed cases of lung cancer per year (out of a population of around 2 million) can be attributed to radon exposure in residential environments in the period 1978–2017, which corresponds to 5.5% of all lung cancer cases. The most important information that needs to be communicated to the Slovenian public and decision-makers about the health risk and about support for preventive measures is that living in areas with elevated radon levels is associated with a higher risk of lung cancer.

Abstract: Indoor radon is an important risk factor for lung cancer, as 3–14% of lung cancer cases can be attributed to radon. The aim of our study was to estimate the impact of indoor radon exposure on lung cancer incidence over the last 40 years in Slovenia. We analyzed the distribution of lung cancer incidence across 212 municipalities and 6032 settlements in Slovenia. The standardized incidence ratios were smoothed with the Besag–York–Mollie model and fitted with the integrated nested Laplace approximation. A categorical explanatory variable, the risk of indoor radon exposure with low, moderate and high risk values, was added to the models. We also calculated the population attributable fraction. Between 2.8% and 6.5% of the lung cancer cases in Slovenia were attributable to indoor radon exposure, with values varying by time period. The relative risk of developing lung cancer was significantly higher among the residents of areas with a moderate and high risk of radon exposure. Indoor radon exposure is an important risk factor for lung cancer in Slovenia in areas with high natural radon radiation (especially in the southern and south-eastern parts of the country).

Keywords: indoor radon exposure; lung cancer; Bayesian hierarchical model; population attributable fraction

1. Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths in men worldwide. In women, lung cancer is the second type of cancer both in newly diagnosed cancers and as the cause of cancer-related deaths [1]. In Slovenia, a Central European country with a population of around 2 million, lung cancer is the third most commonly diagnosed cancer. In 2020, 1554 new cases of lung cancer were diagnosed, which corresponds to 12.5% of all cancer cases in both sexes combined [2]. Smoking is the most important risk factor for lung cancer in the general population [3], and it is estimated that 85–90% of lung cancer cases are attributable to smoking [4].

Radon is a radioactive gas without smell, color, or taste, which is produced by the radioactive decay of uranium and radium in the earth's crust. Uranium and its decay

product radium are found in soil, rock, water, and building materials. The radon concentration in the outdoor air is low and not harmful to health, but the radon concentration can increase indoors [5]. The main source of indoor radon is the infiltration of radon from the soil through cracks and structural gaps in buildings [6]. The concentration of radon and its decay products depends on the structure of the earth's crust, the soil parameters, and the weather conditions; indoors, it also depends on the construction and ventilation of buildings [7]—all of which influence the risk of lung cancer.

Radon and its decay products are deposited in the respiratory tract and emit ionizing radiation, which directly and indirectly damages the DNA in the epithelium of the respiratory tract and can lead to lung diseases and lung cancer [6,8]. The relation between the dose of radon radiation and the health effects appears to be linear and has no threshold value [9]. The International Agency for Research on Cancer has evaluated the evidence for the carcinogenicity of radon and classified radon as carcinogenic to humans in 1988 [10]. It is estimated that 3–14% of lung cancer cases can be attributed to radon [3]. To date, not many studies have been conducted on the geographical distribution of lung cancer incidence in Slovenia. In the 1980s, an epidemiological study was conducted using data from the Slovenian Cancer Registry to investigate the relation between the incidence of lung cancer and the Žirovski vrh uranium mine. Between 1981 and 1985, an increased incidence was found in men and women in settlements near the uranium mine, but a causal relationship could not be confirmed (it could not be determined whether this was due to exposure to radon, tobacco smoke, or chance) [11,12].

The Jožef Stefan Institute carried out the first radon measurements in Slovenia in 1969, at the Žirovski vrh uranium mine [13]. The Slovenian radon program was launched in 1990, and, since then, measurements have been carried out in kindergartens, schools, homes, and workplaces [13,14]. Since 2010, radon measurements have also been carried out in the soil near buildings with high indoor radon concentrations [15]. The results of the measurements of radon concentration and soil properties were used to create the Slovenian radon map [15,16], in which settlements and municipalities were categorized into areas of a low, moderate, and high risk of indoor radon exposure, with a threshold value of 200 Bq/m^3 for a moderate risk and 300 Bq/m^3 for a high risk [15]. High radon concentrations are mainly found in the Karst region in the south and south-east of Slovenia. Out of the 6032 settlements, the risk of indoor radon exposure is high in 1235 (21%) and moderate in 611 (10%) settlements. Out of 212 Slovenian municipalities, the risk of indoor radon exposure is high in 24 (11%) and moderate in 27 (13%) municipalities [15].

As the high risk of radon exposure has been demonstrated in some parts of Slovenia, the aim of our study was to investigate the association between indoor radon exposure and lung cancer incidence at the national level over a 40-year period and to find out how many lung cancer cases per year are attributable to radon exposure.

2. Materials and Methods

In our geographical descriptive correlational epidemiological study, four consecutive 10-year periods from 1978 to 2017 were analyzed. Two levels of geographical division were applied. To reduce heterogeneity, the smallest possible geographical areas were selected for the principal analysis—6032 settlements in Slovenia according to the 2017 definition. As several settlements have been renamed, changed their boundaries, or split into two new settlements over time, all older addresses had to be correctly reclassified into the settlements valid in 2017. Analyses by settlement were only possible for the 30-year period 1988–2017. In order to include the data for the period 1978–1987, for which only municipality-level data was available, all analyses were also repeated at the municipality level.

Three datasets were linked in the study at the level of the settlements: the risk of indoor radon exposure, the lung cancer incidence, and the background population. The information on radon exposure was provided by the Slovenian Radiation Protection Administration. As reported by Vaupotič and Gregorič [15], the indoor radon spatial activity concentration was measured in residential and working environments and averaged over

the same lithological units (areas with the same physical properties of the rock) and settlements with more than two measurement points. The average radon concentration in the lithological units and settlements was divided into five radon concentration categories. The first category contained the units/settlements with an average radon concentration below 100 Bq/m^3, the second those with a concentration between 100–200 Bq/m^3, the third 200–300 Bq/m^3, the fourth 300–600 Bq/m^3, and the fifth category contained units/settlements with an average radon concentration above 600 Bq/m^3. The polygons of the settlements were divided into a 50 m $\times$ 50 m grid, and each cell was assigned a lithological unit with a corresponding category. The average category across all the cells in the settlement was calculated. In this way, the average category of the settlement was calculated based on the lithological properties of the settlement. If there were two or more measurement points for the radon concentration in the settlement, the radon concentration category was determined based on the category of an average radon concentration in the settlements. The final radon concentration category of the settlement was the average of the average category based on the lithological properties and the category based on the average radon concentration in the settlement. Based on the categories, the settlements were categorized into three groups for the risk of indoor radon exposure—low (category of an average radon concentration 1 to 3), moderate (category 3 to 3.5), and high (category 3.5 to 5). The polygons of the municipalities were also divided into a 50 m $\times$ 50 m grid, where each cell was assigned the corresponding average category of radon concentration in the respective settlement, and the average category was calculated over all cells of the municipality. The average category was used to categorize the municipalities into three groups for indoor radon exposure risk, which were used for the analysis.

From the Slovenian Cancer Registry, we obtained data on lung cancer cases defined as C33–C34 according to the tenth revision of the International Classification of Diseases. The data on lung cancer cases were reported by sex, 5-year age groups, and place of residence at the time of diagnosis. The data on the population size in the settlements by sex and 5-year age groups were obtained from the Slovenian Statistical Office. We used data from the 1981, 1991, and 2002 censuses. For the period 2008–2017, data was available for each calendar year.

The number of new cancer cases depends heavily on the size and age structure of the population, which varies over time and space. To overcome this variation, the indirect method of standardization was applied, and the standardized incidence ratios (SIRs) were calculated by dividing the observed and expected cases [17]. A SIR of 1 means that the incidence in the geographical area being studied is the same as expected based on the incidence in the reference population, i.e., the Slovenian population in the same calendar period. A SIR above 1 is interpreted as the relative risk of developing lung cancer. The Slovenian national age-specific incidence rates were used to calculate the expected number of lung cancer cases. Analyses based on small geographical areas could lead to unreliable observations, as cancer is a rare disease and there are only a few or even zero cases in several units. To smooth the observed values and to account for spatial correlation and sampling variability, we used one of the Bayesian hierarchical spatial models, the Besag–York–Mollie (BYM) model fitted by the integrated nested Laplace approximation (INLA). The model proposed by Besage et al. [18–20] is as follows:

$$\ln \frac{O_i}{E_i} = \ln E_i + a + H_i + S_i, \quad (1)$$

where O_i and E_i represent the observed and expected number of the lung cancer cases in the i-th geographic area and a is the baseline relative risk of lung cancer in the entire analyzed area. The model also contains two types of random effects. H_i represents the geographically independent heterogeneous component and has a normal distribution with mean zero and precision τ_h. S_i represents the spatial autocorrelation component. We evaluated the clustering of the smoothed SIRs across the Slovenian municipalities and settlements based on the ratio between the precision of the spatial autocorrelation component (τ_s) and the

precision of the heterogeneous component (τ_h). If the τ_s/τ_h ratio is less than 1, it indicates that the spatial autocorrelation component is more important than the heterogeneous component, as the variability of the spatial autocorrelation component is smaller than the variability of the heterogeneous component.

We included the risk of indoor radon exposure as an explanatory variable in the BYM model and thus excluded the effect of radon exposure in the smoothed SIRs. We calculated the proportion of cancer cases attributable to indoor radon exposure, the so-called Population Attributable Fraction (*PAF*) [21,22], as follows:

$$PAF = 1 - \frac{1}{\sum_1^3 p_i * SIR_i}, \quad (2)$$

where p_i is the proportion of the population in the i-th category of risk of indoor radon exposure and SIR_i is the smoothed relative risk of lung cancer in each of the three i-categories of risk of indoor radon exposure.

We combined the areas with a moderate and high risk of indoor radon exposure and analyzed the relative risk of lung cancer in the areas with a low and moderate/high risk of indoor radon exposure. We calculated the SIRs and interpreted the results as the relative risk of lung cancer.

The analysis was conducted using the cancer incidence mapping tool CanMapTool (version 1.1) [20] and Rstudio (version 4.0.2; Posit Software, PBC, Boston, MA, USA) with the R package dplyr (version 1.0.2) for the data preparation. The shape files of the municipalities and settlements were provided by the Slovenian Surveying and Mapping Authority.

3. Results

3.1. The Burden of Lung Cancer in Slovenia

In the 40-year period 1978–2017, 8.1% of the Slovenian population lived in settlements with a high risk of indoor radon exposure and 7.3% with a moderate risk, making 15.4% of the population in total living in areas with a moderate or high risk of indoor radon exposure (Table 1).

Table 1. Incidence of lung cancer, average annual incidence of lung cancer, average annual population size, and the percentage of the population living in settlements with a moderate or high risk of indoor radon exposure over four consecutive 10-year periods.

10-Year Period	Incidence	Average Annual Incidence	Average Annual Population	% of Population Living in Areas with a Moderate or High Risk of Indoor Radon Exposure
1978–1987	7201	720	1,891,864	15.1% *
1988–1997	9426	943	1,965,986	15.1%
1998–2007	11,324	1132	1,978,897	15.5%
2008–2017	13,304	1330	2,052,376	15.9%
1978–2017	41,255	1031	1,972,281	15.4%

* Calculated for municipalities since data on settlement level is not available for period 1978–1987.

In the 40-year period 1978–2017, there were 41,255 cases of lung cancer in Slovenia (Table 1). The place of residence at the time of the diagnosis was known for all lung cancer patients in the 40-year period analyzed, but the quality of this information is better for the period 1998–2017 than for earlier years.

The relative risk of developing lung cancer was higher for the residents of the coastal (in the south-west), the south-east, the central, and the north-west regions of Slovenia, as well as on the northern border from Koroška to Maribor and on the eastern border around Murska Sobota. In the period 2008–2017, the relative risk of lung cancer was statistically significantly higher than the Slovenian average for the residents of eleven settlements and six municipalities (Figure 1). The values of the ratio τ_s/τ_h were below 1 for all four 10-year

periods analyzed (between 0.0004 and 0.43 for the analysis by settlement and between 0.001 and 0.026 for the analysis by municipality), indicating that the random spatial component has a greater influence on the smoothed SIR distribution than the random heterogeneous component, i.e., maps of the smoothed SIRs of lung cancer across settlements (Figure 1) and municipalities show a geographical clustering.

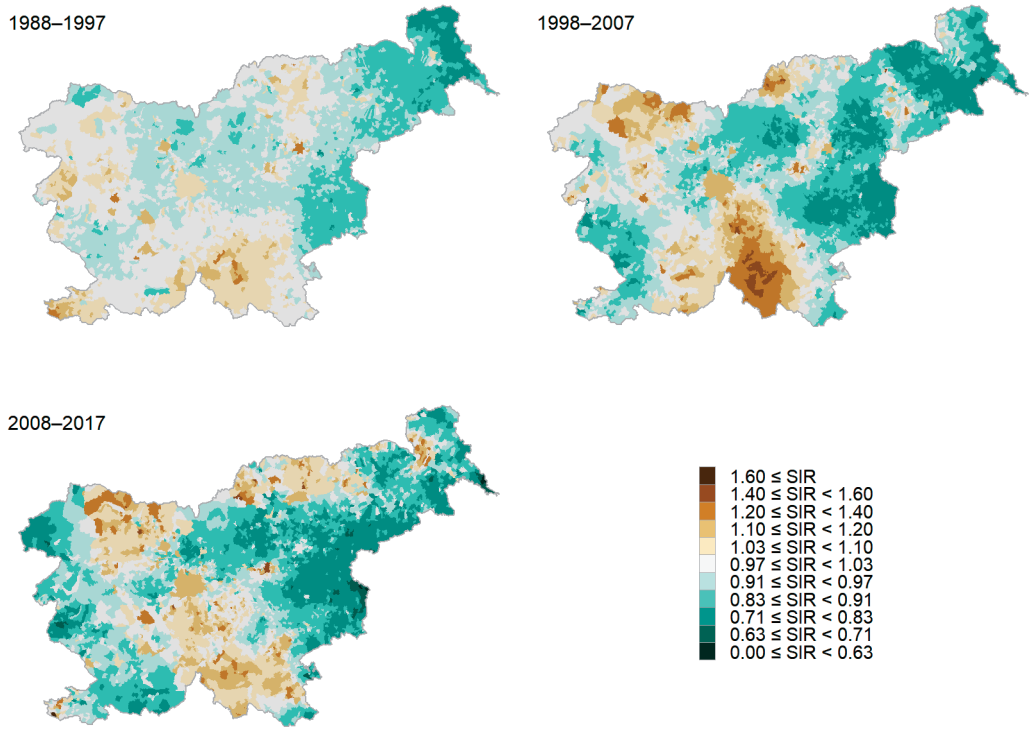


Figure 1. Smoothed standardized incidence ratio (SIR) of lung cancer by settlement in three consecutive 10-year periods.

3.2. The Burden of Lung Cancer in Slovenia and Indoor Radon Exposure

In the BYM models, we included the risk of indoor radon exposure as an explanatory variable. The smoothed SIRs remained geographically clustered, as the value of the τ_s / τ_h ratio in the analyses at the level of settlements and municipalities was less than 1 (between 0.001 and 0.06) in all four 10-year periods analyzed. The relative risk remained higher for the residents in the northern, central, and south-eastern parts of the country, even when we excluded the effect of radon exposure (Figure 2), confirming that radon exposure is not the main risk factor for lung cancer.

Depending on the time period, between 1.2% and 5.6% of the lung cancer cases in Slovenia could be attributed to exposure to radon in the residential environment when analyzed by settlement and between 2.8% and 6.5% when analyzed by municipality (Table 2). According to municipality-level analysis, 2278 lung cancer cases in Slovenia during the entire 40-year period were attributable to indoor radon exposure, which accounted for 5.5% of all lung cancer cases in Slovenia during this period.

The relative risk of developing lung cancer was higher among the residents of the areas with a moderate or high risk of indoor radiation exposure in all 10-year periods analyzed from 1978 to 2017 (Table 3). More specifically, the relative risk was 5% (95% confidence interval (CI): 0–11%) higher in the period 1978–1987, 7% (95% CI: 2–12%) higher in the periods 1988–1997 and 1998–2007, and 5% (95% CI: 0–9%) higher in the period 2008–2017.

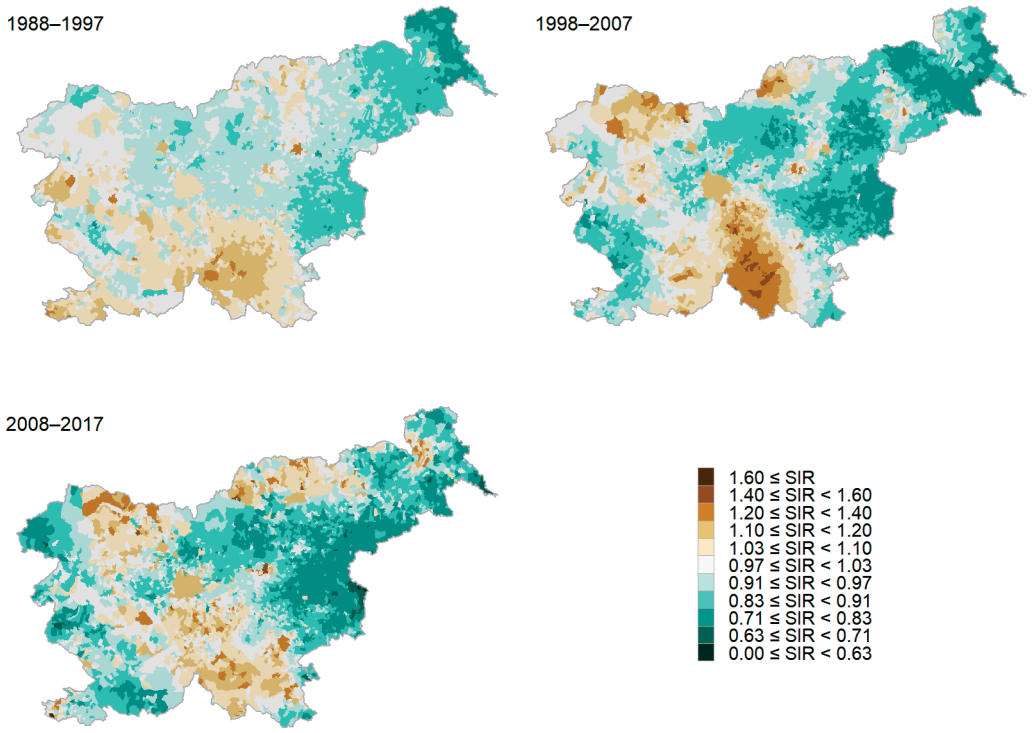


Figure 2. Smoothed standardized incidence ratio (SIR) of lung cancer by settlement in three consecutive 10-year periods. The effect of radon exposure is excluded.

Table 2. Incidence of lung cancer for consecutive 10-year periods from 1978 to 2017 and the population attributable fraction (PAF) to radon exposure according to the analysis by settlement and municipalities.

		Settlements		Municipalities	
	Incidence	**PAF**	**Attributable Incidence**	**PAF**	**Attributable Incidence**
2008−2017	13,304	4.3%	572	6.5%	865
1998−2007	11,324	5.6%	634	6.2%	702
1988−1997	9426	1.2%	113	2.8%	264
1978−1987	7201	/ *	/ *	6.2%	447

* Data not available on settlement level.

In men living in the areas with a moderate or high risk of indoor radon exposure, the relative risk was statistically significantly higher in all periods analyzed. The relative risk was 7% (95% CI: 1–13%) higher in the period 1978–1987, 9% (95% CI: 3–15%) higher in the period 1988–1997, 8% (95% CI: 3–14%) higher in the period 1998–2007, and 5% (95% CI: 0–13%) higher in the period 2008–2017. Among women, the relative risk of developing lung cancer was not statistically significantly increased in areas with a moderate or high risk of indoor radon exposure in the 10-year periods 1978–1987, 1988–1997, and 1998–2007, but an increased relative risk of developing lung cancer could not be excluded, as shown by the upper limits of the 95% CI, which were above one.

Table 3. Standardized incidence ratio (SIR) with a 95% confidence interval for lung cancer by sex and by areas for indoor radon exposure in consecutive 10-year periods from 1978 to 2017 in Slovenia.

		Males	Females	Males and Females
2008–2017				
Risk of radon exposure	low	0.99 [0.97–1.01]	1.00 [0.97–1.03]	0.99 [0.97–1.01]
	moderate or high	**1.05 [1.00–1.13]**	1.01 [0.94–1.09]	**1.05 [1.00–1.09]**
1998–2007				
Risk of radon exposure	low	0.98 [0.96–1.01]	1.00 [0.96–1.04]	0.99 [0.97–1.01]
	moderate or high	**1.08 [1.03–1.14]**	0.98 [0.89–1.09]	**1.07 [1.02–1.12]**
1988–1997				
Risk of radon exposure	low	0.98 [0.96–1.01]	1.01 [0.95–1.06]	0.99 [0.97–1.01]
	moderate or high	**1.09 [1.03–1.15]**	0.97 [0.85–1.10]	**1.07 [1.02–1.12]**
1978–1987				
Risk of radon exposure	low	0.98 [0.95–1.01]	1.00 [0.94–1.07]	0.98 [0.96–1.01]
	moderate or high	**1.07 [1.01–1.13]**	0.99 [0.86–1.12]	**1.05 [1.00–1.11]**

The results in bold are statistically significant-the lower limit of the 95% confidence interval was above one.

4. Discussion

The aim of our study was to assess to what extent indoor radon exposure influences lung cancer incidence. The results showed that in Slovenia, for all four analyzed 10-year periods between 1978 and 2017, the map of the smoothed SIR of lung cancer is geographically clustered across municipalities and settlements and remains similarly distributed even when we had excluded the effects of indoor radon exposure in the models. The risk of lung cancer is higher in the northern, central, south-eastern, and coastal parts of the country.

Although indoor radon exposure is not the main risk factor in the general population, it is a significant health risk for people who live, work, or go to school in regions with a high risk of indoor radon exposure [3,10]. According to our analysis by municipality, almost 2300 lung cancer cases in Slovenia in the 40-year period 1978–2017 could be attributed to living in an area with a moderate or high risk of indoor radon exposure, which corresponds to 5.5% of lung cancer cases. In the most recent 10-year period 2008–2017, 4.3% of the lung cancer cases in Slovenia can be attributed to living in an area with a moderate or high risk of indoor radon exposure, as a more detailed analysis by settlement shows, which corresponds to about 570 cases. Our PAF results are in line with the WHO estimates of 3–14% of lung cancer cases being attributable to indoor radon exposure [3]. The percentage varies depending on geological properties and how governments and people respond to the increased risk of indoor radon exposure. For example, it is estimated that 8% and 5% of the lung cancer cases in Switzerland and Germany [23], as well as 4.7% of the lung cancer cases in 2010 in the UK, are attributable to radon exposure. In the UK, it is additionally estimated that 6% of lung cancer deaths per year are due to indoor radon exposure [24].

In order to reduce the health risks to individuals and populations, the World Health Organization has recommended a national reference level for radon concentrations in residential buildings of 100 Bq/m^3, which must not exceed 300 Bq/m^3 [25]. Researchers are not entirely in agreement about the threshold level of radon concentration in the air at which the risk of radon-induced lung cancer is lowest [26]. One of the assumptions is that the relationship between radon concentration and risk of radon-induced lung cancer is

linear and that there is no threshold, meaning that the risk of radon-induced lung cancer is lowest at 0 Bq/m^3 [9]. Some research results indicate that the radon-induced risk of lung cancer is lowest at a minimally elevated radon concentration of around 50 Bq/m^3 [26,27]. In our study, the lowest exposure category was defined as 0–100 Bq/m^3, which meant that it was not possible to distinguish between the two views.

A higher risk of lung cancer due to indoor radon exposure was found in a meta-analysis of seventeen case-control studies, in which the pooled odds ratio at an indoor radon concentration of 150 Bq/m^3 was 1.24 (95% CI: 1.11–1.38) [28]. Another meta-analysis of case-control studies showed that the pooled relative risk for lung cancer at an indoor radon concentration of 150 Bq/m^3 was 1.14 (95% CI: 1.0–1.3) [29]. In the case-control study in eastern Germany, an odds ratio of 1.30 (95% CI: 0.88–1.93) was reported for indoor radon concentrations greater than 140 Bq/m^3, compared with indoor radon exposure up to 50 Bq/m^3 [30]. In the presented investigation, the indoor radon concentration on an individual level was not available. However, in our additional analysis of the relative risk of developing lung cancer by settlements (1988–2017) and municipalities (1978–1987), which were divided into two categories according to the risk of indoor radon exposure, we showed that the relative risk of developing lung cancer in the 40-year period 1978–2017 was 5% to 7% higher among the residents of the areas with a moderate or high risk of indoor radon exposure. A sub-analysis of our dataset where the moderate and high risk areas were distinguished has been performed as well. There was no significant difference in the relative risk of high or moderately exposed settlements. Our study showed that, from a public health perspective, ongoing efforts are needed in Slovenia in order to further reduce lung cancer incidence attributable to radon exposure.

We should also emphasize that our analysis is most reliable for the more recent 20-year period 1998–2017 at the settlement level due to the reliability of the information on residence at the time of diagnosis and the availability of data on the population. Another limitation of descriptive epidemiological geographical studies is using a person's place of residence as a surrogate indicator of exposure in a study, since it might be a source of potential biases. In our research, it was not possible to account for daily mobility or migration, so using the residential address as an indicator of exposure is not an exact measure of exposure, especially if exposure occurs at the place of work or in educational institutions [31]. In addition, individuals can be exposed to environmental factors in various locations throughout the day, and some patients may have a reported residence that is different from where they actually live.

A probable risk factor is living near the uranium mine in Žirovski vrh (a settlement in the western part of Slovenia). For the period 1981–1985, an increased incidence was found in men and women in the settlements near the uranium mine [11,12]. In our analyses, we found no clusters corresponding to the uranium mine in Žirovski vrh. The most important confounding factor is smoking. It is estimated that 84% of lung cancer deaths per year in Slovenia are attributable to tobacco [32]. As an improvement to this presented study, information on smoking could be included in the analysis, because it is reported that the risk of lung cancer increases significantly with the joint effect of two risk factors: radon exposure and smoking [33–36]. In this present analysis, it is not possible to determine to what extent our results exclusively reflect the risk of indoor radon exposure and to what extent they rather reflect smoking behavior, as indoor radon exposure and smoking behavior are not geographically independent and also influence each other [33–35]. However, no data on smoking are available for Slovenia on a small geographical level, which imposes a severe limitation on our study. We have tried to include information on smoking by including indirect information that is available. For this reason, we have conducted an additional analysis using the SI-EDI (Slovenian version of the Socio-Economic Deprivation Index [37]) as an explanatory variable in the models to adjust the results for socioeconomic status. But the results did not provide additional insight into the topic under study, so we did not include them in the reporting of the results. This supports our earlier findings that social segregation and stratification in Slovenia is low, meaning there are no strong and

extended areas where only affluent or deprived inhabitants would live [37]. The World Factbook [38] ranks Slovenia 153rd out of 157 countries, which means that the country's income distribution is almost equal.

5. Conclusions

Indoor radon exposure is an important risk factor for lung cancer in Slovenia in areas with high natural radon radiation (especially in the southern and south-eastern parts of the country). In the 40-year period 1978–2017, the relative risk for lung cancer was 5–7% higher in areas with a moderate or high risk of indoor radon exposure. This resulted in 60 lung cancer cases per year on average attributable to the risk of indoor radon exposure in the residential environment, which corresponds to 4.9% of lung cancer cases (according to the analysis by settlement).

It is known that the geology in some parts of Slovenia is the cause for the increased risk of indoor radon exposure. In recent decades, many measures have been implemented in building regulations and in efforts to educate people about the hazards and about preventive behavior. Nevertheless, our study showed that, from a public health perspective, ongoing efforts are needed in Slovenia in order to further reduce lung cancer incidence attributable to radon exposure.

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