

Annual surveillance mammography after early-stage breast cancer and breast cancer mortality

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ABSTRACT

Background After treatment for early-stage breast cancer (bca), annual surveillance mammography (asm) is recommended based on the assumption that early detection of an invasive ipsilateral breast tumour recurrence or subsequent invasive contralateral primary bca reduces bca mortality.

Methods We studied women with unilateral early-stage bca treated by breast-conserving surgery from 1994 to 1997 who subsequently developed an ipsilateral recurrence or contralateral primary more than 24 months after initial diagnosis, without prior regional or distant metastases. Annual surveillance mammography was defined as 2 episodes of bilateral mammography 11–18 months apart during the 2 years preceding the ipsilateral recurrence or contralateral primary. The association between asm and bca death was evaluated using a Cox proportional hazards model.

Results We identified 669 women who experienced invasive ipsilateral recurrence ($n = 455$) or a contralateral primary ($n = 214$) at a median interval of 53 months [interquartile range (iqr): 37–72 months] after initial diagnosis, 64.7% of whom had received asm during the preceding 2 years. The median interval between the 2 bilateral mammograms was 12.3 months (iqr: 11.9–13.0 months), and the median interval between the 2nd mammogram and histopathologic confirmation of ipsilateral recurrence or contralateral primary was 1.5 months (iqr: 0.8–3.9 months). Median follow-up after ipsilateral recurrence or contralateral primary was 7.76 years (iqr: 3.68–9.81 years). The adjusted hazard ratio for bca death associated with asm was 0.86 (95% confidence limits: 0.63, 1.16).

Conclusions Annual surveillance mammography was associated with a modestly lowered hazard ratio for bca death.

Key Words Breast cancer, contralateral breast cancer, local recurrence, surveillance mammography, mortality, proportional hazards regression, propensity score adjustment

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INTRODUCTION

The purpose of annual surveillance mammography (asm) is the early detection of an invasive ipsilateral breast tumour recurrence or a subsequent invasive contralateral primary breast cancer (bca) at a highly curable stage so as to reduce the risk of death from bca. Guidelines based on expert opinion and extrapolation of bca mortality reduction from trials of screening mammography recommend asm for women after treatment for early-stage primary bca^{1,2}.

The effectiveness of asm can be assessed only from retrospective studies because randomized trials have not been conducted. Many retrospective studies have examined the association of early asymptomatic detection

of ipsilateral recurrence or contralateral primary with bca mortality^{3–6}; however, those studies are biased in favour of a protective effect because they are actually examining the association between true positive asms (rather than all asms) and the outcome. Other studies have avoided that bias by examining the association of participation in asm (rather than early asymptomatic detection of ipsilateral recurrence or contralateral primary) with bca mortality^{7,8}. In other studies that count asm 1–2 years before the date of death from bca or date of censoring^{9,10}, it is unlikely that asm could reduce the risk during such a brief interval before death; however, asm among women without a recurrence by the date of censoring would bias the outcome in favour of a protective effect. It is also possible that the compliance

of women who participate in ASM is itself associated with improved survival independently of the effect of ASM^{11,12}. In addition, the selection of women for ASM in retrospective studies is biased and nonrandom, and the periodicity of ASM varies by physician and by woman.

To retrospectively study the effectiveness of a surveillance test to detect early, asymptomatic, and potentially curable recurrence of cancer, Weiss¹³ recommended that exposure to the surveillance test be measured during the detectable preclinical phase¹⁴ of the recurrence. That recommendation has two implications for the design of retrospective studies of the effectiveness of ASM. First, the study population should comprise individuals with ipsilateral recurrence or contralateral primary without prior regional or distant recurrence and should exclude those without such an event, who, by definition, do not have a detectable preclinical phase. Second, ASM should be measured during the period before ipsilateral recurrence or contralateral primary (rather than over many years or during the period shortly before bca death).

The goal of the present work was to evaluate the association between ASM and bca mortality in a population of women with unilateral early-stage bca treated by breast-conserving surgery who experienced ipsilateral recurrence or contralateral primary more than 24 months after initial diagnosis, without prior regional nodal or distant metastases. Participation in ASM was defined as 2 episodes of bilateral mammography 11–18 months apart during the 2 years before the ipsilateral recurrence or contralateral primary.

METHODS

Research Ethics

We obtained approval from the Research Ethics Board of Sunnybrook Health Sciences Centre and conducted the work at the Institute for Clinical Evaluative Sciences (ICES).

Data Sources

Data sources for this work are the electronic records held in linkable databases labelled with unique encoded identifiers, from which all personal identifiers have been removed.

Ontario Cancer Registry

The Ontario Cancer Registry (OCR) is a population-wide registry of invasive cancers ascertained by linkage of records from cancer centres, hospitals, pathology departments, and death certificates. During the study period, each record included the *International Classification of Diseases* version 9 (ICD9) diagnosis code, date of diagnosis, age at diagnosis, vital status, and ICD9 diagnosis code for cause of death, but no information about tumour markers, stage, treatment, recurrence, metastasis, or contralateral bca.

Archive of BCa Pathology Reports

The archive of bca pathology reports (ABCPR) consists of text files of histopathology reports concerning breast biopsies, lumpectomies, mastectomies, axillary surgery, and biopsies of distant metastases, dated during 1994–2003, for women with bca and other breast conditions, originally

received by Cancer Care Ontario from hospital-based and community-based laboratories throughout Ontario. Each report is identified by the unique encoded identifier.

Discharge Abstract Database

The Discharge Abstract Database (DAD) maintained by the Canadian Institute for Health Information contains information about hospital admissions in Ontario, including—to 31 March 2002—up to 16 discrete ICD9 diagnosis codes per admission, and thereafter up to 25 discrete diagnosis codes per admission, using the *International Classification of Diseases* version 10 (ICD10). Within the record of each admission, 1 diagnosis code is designated the “most responsible diagnosis.”

Ontario Health Insurance Plan Claims Database

The Ontario Health Insurance Plan Claims Database contains billing claims for physician services remunerated on a fee-for-service basis—for example, interpretation of bilateral mammography, prescription of intravenous chemotherapy, and radiation oncology consultation. Each record includes the unique encoded identifier of the patient, the code for the service, and the date on which the service was provided.

Registered Persons Database

The Registered Persons Database is a roster of all beneficiaries of the universal publicly funded Ontario Health Insurance Plan. Each record includes vital status, date of last contact, and postal and residential codes linkable to census-based data on socioeconomic status.

Definition of the Study Population

The study population consisted of women diagnosed with unilateral early-stage invasive bca between 1994 and 1997, who were treated with breast-conserving surgery, and who developed an ipsilateral recurrence or contralateral primary 24 or more months after initial diagnosis without prior appearance of distant metastases.

Identification of the Study Population

From the OCR, we identified women with a first diagnosis of invasive breast carcinoma (ICD9 174) between 1994 and 1997. We then searched the ABCPR to identify those who had histopathology reports at initial diagnosis and who also one or more histopathology reports dated during subsequent years.

Cases were manually abstracted from the ABCPR if the data satisfied these conditions:

- breast-conserving surgery for newly diagnosed unilateral invasive early-stage breast carcinoma resected with clear margins between 1994 and 1997, with reported laterality, reported tumour size less than 5.0 cm, and reported number of positive axillary lymph nodes if sampled; and
- histopathologic confirmation, with reported laterality, of invasive ipsilateral recurrence or contralateral primary 24 or more months after the initial diagnosis date of unilateral invasive early-stage breast carcinoma, up to the end of December 2003.

For any eligible case with both ipsilateral recurrence and contralateral primary confirmed on the same date, the case was categorized as ipsilateral recurrence. For any case with ipsilateral recurrence and contralateral primary confirmed on different dates, the lesion with the earliest date was included and that with the later date excluded. Cases were excluded in the presence of any histopathologic report of prophylactic mastectomy, of regional nodal or distant metastasis, or of diagnosis codes in DAD for distant metastasis (ICD9 197, 198, 199, or ICD10 C770–C772, C774–C778, C780–C788) before the date of histopathologic confirmation of ipsilateral recurrence or contralateral primary.

Definition of Participation in ASM

We defined participation in ASM (main exposure) as 2 billing claims for bilateral mammography between 11 and 18 months apart during the 24 months preceding the date of confirmation of ipsilateral recurrence or contralateral primary.

Baseline Characteristics

Age at Initial Diagnosis: The age of each woman on the date of the initial diagnosis of unilateral early-stage bca was extracted from the ocr.

Tumour Size at Initial Diagnosis: The diameter of the primary invasive bca was abstracted from the ABCPR and categorized as T1 if 2 cm or less, and T2 if greater than 2 cm and less than 5 cm.

Positive Axillary Lymph Nodes at Initial Diagnosis: The number of positive axillary lymph nodes at initial diagnosis was abstracted from the ABCPR and categorized as N0 if that number was zero and N1 if it was 1 or more.

Adjuvant Chemotherapy at Initial Diagnosis: Receipt of adjuvant chemotherapy was operationalized as the presence of 1 or more billing claims for intravenous chemotherapy up to 6 months after the date of initial diagnosis.

Adjuvant Radiotherapy at Initial Diagnosis: Receipt of adjuvant radiotherapy (RT) was operationalized as the presence of a billing claim for radiation oncology consultation up to 12 months after the date of initial diagnosis.

Screening Mammography Before Initial Diagnosis: Participation in screening mammography before the initial diagnosis of unilateral early-stage bca was operationalized as the presence of a billing claim for bilateral mammography 7–36 months before the date of initial diagnosis.

Baseline Socioeconomic Status at Initial Diagnosis: The postal and residential codes in the Registered Persons Database were linked to census data to assign each woman to an urban quintile of median household income or to rural status as a measure of socioeconomic status at the time of initial diagnosis.

Baseline Score on the Adapted Charlson Comorbidity Index at Initial Diagnosis: We searched the DAD for admissions with ICD9 diagnosis codes mapping onto the Deyo

adaptation of the Charlson comorbidity index¹⁵ during the 5 years preceding the date of initial diagnosis of unilateral early-stage bca. The results were used to compute a baseline cumulative 5-year comorbidity score for each woman.

Interval Between Date of Initial Diagnosis of Unilateral Early Stage BCa and Date of Confirmation of Invasive Ipsilateral Recurrence or Contralateral Primary:

In the ocr, the date of histopathologic confirmation of invasive ipsilateral recurrence or contralateral primary was subtracted from the date of initial diagnosis of invasive unilateral early-stage bca to obtain the interval in months between the two events.

Outcome Definition

The outcome of interest was death from bca. We identified the date of death using the Registered Persons Database. We searched for the cause of death in the ocr, and if present, categorized the cause as bca (ICD9 174) or another cause. If the cause of death was missing in the ocr, we searched the DAD for a hospital admission ending in death, from which we extracted the diagnosis code for the most responsible diagnosis, treating it as the cause of death, and categorized it as bca death (ICD9 174 or ICD10 C50) or death from another cause. For individuals known to have died, but for whom a diagnosis code for cause of death in either source was lacking, the cause of death was categorized as “other cause.”

Analysis

We examined differences in the distributions of baseline characteristics and the distribution of the interval between initial diagnosis and confirmation of invasive ipsilateral recurrence or contralateral primary for women who did and did not participate in ASM. Chi-square tests were used to analyze differences between categorical variables, and t-tests were used to analyze differences between continuous variables.

We modelled the odds of participating in ASM using multivariable logistic regression. All baseline characteristics—and the interval between initial diagnosis and confirmation of invasive ipsilateral recurrence and contralateral primary—were incorporated as covariates. A logistic regression model was also used to calculate each woman's likelihood of participating in ASM, which was used to implement a propensity score adjustment approach as a way to reduce confounding of the association with bca mortality attributable to the nonrandom selection of cases for ASM¹⁶. The propensity score adjustment approach is one of four commonly implemented propensity score methods that aim to reduce the effects of confounding when estimating the association between exposures and outcomes^{17,18}. It consists in incorporating the estimated regression coefficient for the propensity score from the logistic regression model as an additional continuous covariate in a multivariate Cox proportional hazards regression model.

To examine the association between ASM and the hazard of bca death, we used two approaches: a multivariable Cox proportional hazards regression model¹⁹ and a multivariable Cox proportional hazards regression model with propensity score adjustment^{16–18}. To avoid the introduction of survival bias and to be consistent with the underlying

assumptions of the Cox model, we calculated the time to bca death from the date of confirmation of invasive ipsilateral recurrence or contralateral primary rather than from the date of the initial diagnosis of bca. Women not dead from bca were censored on the date of last contact alive or the date of death from another cause. Independent variables in the Cox model included participation in ASM (binary variable), the interval in months between initial diagnosis and confirmation of invasive ipsilateral recurrence or contralateral primary (continuous variable), and baseline covariates from the initial diagnosis of unilateral early-stage bca. All analyses were performed using the SAS software application (version 9.3; SAS Institute, Cary, NC, U.S.A.).

RESULTS

We identified 669 women with histopathologic confirmation of invasive ipsilateral recurrence ($n = 455$, 68.0%) or contralateral primary ($n = 214$, 32.0%) and without prior evidence of regional nodal or distant metastasis 24 or more months [median: 53 months; interquartile range (IQR): 37–72 months] after the initial diagnosis of unilateral early-stage bca treated with breast-conserving surgery (Table I).

Stratified analysis demonstrated significant differences between the women who did and did not receive adjuvant RT after breast-conserving surgery at baseline. Compared with their counterparts who did not receive adjuvant RT at baseline, women who did receive RT were younger (mean age: 55 ± 12.21 years vs. 62.73 ± 15.79 years; $p < 0.001$), had a lower score on the adapted Charlson comorbidity index at baseline (mean: 0.07 ± 0.33 vs. 0.27 ± 0.67 ; $p < 0.001$), had a higher number of positive axillary lymph nodes (mean: 0.82 ± 2.21 vs. 0.40 ± 1.27 ; $p < 0.001$), were more likely to have received adjuvant chemotherapy (32.7% vs. 15.3%, $p < 0.001$), and were more likely to have previously undergone screening mammography before the initial diagnosis of bca (40.2% vs. 26.0%, $p < 0.001$).

Annual surveillance mammography had been received by 432 of the 669 women (64.6%) during the 24 months preceding confirmation of invasive ipsilateral recurrence ($n = 284$, 62.4%) or contralateral primary ($n = 148$, 69.1%). The median interval between the 2 required bilateral mammograms was 12.3 months (IQR: 11.9–13.0 months), and the median interval between the 2nd bilateral mammogram and the histopathologic confirmation of ipsilateral recurrence or contralateral primary was 1.5 months (IQR: 0.8–3.9 months). We observed significant differences in the distribution of age, score on the adapted Charlson comorbidity index, receipt of adjuvant RT, and receipt of screening mammography before the initial diagnosis, between women who did and did not participate in ASM (Table II). No differences in the distribution of baseline tumour stage were observed ($p = 0.99$). Of the 492 women who had received adjuvant RT, 358 (72.8%) participated in ASM; in the group of 177 women who had not received adjuvant RT, 74 participated (41.8%, $p < 0.001$). Adjusted logistic regression analysis of the likelihood of participating in ASM was remarkable mainly for the strong association with adjuvant RT at initial diagnosis with ASM [adjusted odds ratio:

TABLE I Baseline description of the 669 study subjects at time of initial diagnosis

Variable	Value
Mean age at initial Dx (years)	57.05±13.67
Age group at initial Dx [n (%)]	
<50 Years	226 (33.78)
50–59 Years	154 (23.02)
60–69 Years	157 (23.47)
≥70 Years	132 (19.73)
Year of initial Dx [n (%)]	
1994	184 (27.5)
1995	167 (24.96)
1996	171 (25.56)
1997	147 (21.97)
Socioeconomic status at initial Dx [n (%)]	
Urban income quintiles	
Q1 (lowest)	105 (15.7)
Q2	110 (16.44)
Q3	110 (16.44)
Q4	109 (16.29)
Q5 (highest)	157 (23.47)
Rural	78 (11.66)
Mean score on the adapted CCI at initial Dx	0.12±0.45
Adapted CCI score category at initial Dx [n (%)]	
0	614 (91.78)
1–2	48 (7.17)
≥3	7 (1.05)
Screening mammography before initial Dx [n (%)]	244 (36.47)
Mean primary tumour size at initial Dx (cm)	2.15±0.87
Mean positive lymph nodes at initial Dx (n)	0.71±2.01
Stage at initial Dx [n (%)]	
T1N0M0	326 (48.73)
T2N0M0	192 (28.7)
T1N1M0	72 (10.76)
T2N1M0	79 (11.81)
Adjuvant chemotherapy at initial Dx [n (%)]	188 (28.1)
Adjuvant radiotherapy at initial Dx [n (%)]	492 (73.54)
Mean interval between initial Dx and invasive ipsilateral recurrence or contralateral primary (months)	55.55±22.27

Dx = diagnosis; CCI = Charlson comorbidity index.

3.21; 95% confidence limits (CL): 2.19, 4.70]; other factors were no longer significant after simultaneous adjustment for all other covariates (Table III).

Median follow-up after invasive ipsilateral recurrence or contralateral primary was 7.76 years (IQR: 3.68–9.81 years), and 198 of the 669 women died from bca (29.6%). The adjusted hazard ratio (HR) for bca death associated with ASM was 0.86 (95% CL: 0.63, 1.16) in the full multivariable Cox model (Table IV). The adjusted HR associated with each 1-cm increase in tumour diameter of the initial bca

TABLE II Participation by the 669 study subjects in annual surveillance mammography (ASM) during the 2 years before ipsilateral breast tumour recurrence or contralateral primary breast cancer

Variable	Participated in ASM		<i>p</i> Value
	Yes	No	
Women (<i>n</i>)	432	237	
Mean age (years)	55.91±12.09	59.12±15.97	0.004
Age group at initial Dx [<i>n</i> (%)]			
<50 Years	146 (33.8)	80 (33.8)	<0.001
50–59 Years	113 (26.2)	41 (17.3)	
60–69 Years	114 (26.4)	43 (18.1)	
≥70 Years	59 (13.6)	73 (30.8)	
Year of initial Dx [<i>n</i> (%)]			
1994	115 (26.6)	69 (29.1)	0.47
1995	105 (24.3)	62 (26.2)	
1996	109 (25.2)	62 (26.2)	
1997	103 (23.8)	44 (18.5)	
Socioeconomic status at initial Dx [<i>n</i> (%)]			
Urban income quintiles			
Q1 (lowest)	62 (14.4)	43 (18.1)	0.27
Q2	68 (15.7)	42 (17.7)	
Q3	69 (16.0)	41 (17.3)	
Q4	69 (16.0)	40 (16.9)	
Q5 (highest)	114 (26.4)	43 (18.1)	
Rural	50 (11.6)	28 (11.8)	
Mean score on the adapted CCI at Dx [<i>n</i> (%)]	0.07±0.31	0.21±0.62	<0.001
Adapted CCI score category at initial Dx [<i>n</i> (%)]			
0	408 (94.4)	206 (86.9)	<0.001
≥1	24 (5.6)	31 (13.1)	
Screening mammography before initial Dx [<i>n</i> (%)]			
Yes	175 (40.5)	69 (29.1)	0.003
No	257 (59.5)	168 (70.9)	
Mean tumour size at initial Dx (cm)	2.11±0.85	2.20±0.91	0.23
Positive nodes at initial Dx (<i>n</i>)	0.70±2.07	0.71±1.92	0.95
Stage at initial diagnosis [<i>n</i> (%)]			
T1N0M0	212 (49.1)	114 (48.1)	0.99
T2N0M0	123 (28.5)	69 (29.1)	
T1N1M0	47 (10.9)	25 (10.6)	
T2N1M0	50 (11.5)	29 (12.2)	
Adjuvant chemotherapy at initial Dx [<i>n</i> (%)]			
Yes	131 (30.3)	57 (24.1)	0.08
No	301 (69.7)	180 (75.9)	
Adjuvant radiotherapy at initial Dx [<i>n</i> (%)]			
Yes	358 (82.9)	134 (56.5)	<0.001
No	74 (17.1)	103 (43.5)	
Mean interval between initial Dx and invasive ipsilateral recurrence or contralateral primary (months)	56.47±21.76	53.87±23.11	0.15

Dx = diagnosis; CCI = Charlson comorbidity index.

TABLE III Factors associated with participation in annual surveillance mammography 2 years before ipsilateral breast tumour recurrence or contralateral primary breast cancer

Variable	Univariate analysis		Adjusted analysis	
	OR	95% CL	OR	95% CL
Age at initial Dx (per 1-year increase)	0.98	0.97, 0.99	1.00	0.98, 1.01
Year of initial Dx				
1994	Reference		Reference	
1995	1.02	0.66, 1.57	1.20	0.75, 1.90
1996	1.06	0.69, 1.62	1.09	0.69, 1.72
1997	1.41	0.89, 2.23	1.57	0.95, 2.59
Socioeconomic status at initial Dx				
Urban, lower 2 income quintiles	0.75	0.53, 1.07	0.87	0.60, 1.26
Urban, upper 3 income quintiles	Reference		Reference	
Rural	0.88	0.59, 1.46	0.99	0.57, 1.70
Score on the adapted CCI at initial Dx (per 1-unit increase)	0.51	0.35, 0.75	0.67	0.45, 1.00
Screening mammography before initial Dx	1.66	1.18, 2.33	1.43	0.99, 2.05
Tumour size at initial Dx (per 1-cm increase)	0.90	0.75, 1.07	0.93	0.76, 1.13
Positive nodes at initial Dx (per 1-node increase)	1.00	0.92, 1.08	0.97	0.89, 1.05
Adjuvant chemotherapy at initial Dx				
Yes	1.00		1.00	
No	1.37	0.96, 1.97	1.15	0.74, 1.80
Adjuvant radiotherapy at initial Dx				
Yes	1.00		1.00	
No	3.72	2.60, 5.32	3.21	2.19, 4.70
Interval between initial Dx and invasive ipsilateral recurrence or contralateral primary (per 1-month increase)	1.01	1.00, 1.01	1.00	1.00, 1.01

OR = odds ratio; CL = confidence limits; Dx = diagnosis; CCI = Charlson comorbidity index.

was 1.25 (95% CL: 1.07, 1.47); it was 1.08 (95% CL: 1.03, 1.14) for each 1-node increase in the number of positive lymph nodes at initial diagnosis. In the analysis of bca mortality, we tested for a statistical interaction between ASM and receipt of adjuvant RT, but found no evidence of an interaction; the interaction term in the adjusted model was not statistically significant ($p = 0.19$). The propensity-score-adjusted model produced similar results: the propensity-score-adjusted HR was 0.86 (95% CL: 0.63, 1.16).

DISCUSSION

Among women with unilateral early-stage bca who developed invasive ipsilateral recurrence or contralateral primary without prior regional nodal or distant metastases, participation in ASM during the 2 years before the ipsilateral recurrence or contralateral primary was associated with a modestly reduced risk of bca death, albeit not reaching statistical significance. The two most recent retrospective cohort studies examining the association between participation in ASM and bca mortality reported adjusted HRs (HR: 0.82; 95% CL: 0.56, 1.19⁸; and HR: 0.84; 95% CL: 0.78, 0.82⁹) similar to those in the present study (HR: 0.86; 95% CL: 0.63, 1.16).

The lower participation in ASM among women who did not receive adjuvant RT, among older women, among

women with higher scores on the adapted Charlson comorbidity index, and among women with a lower socioeconomic status was described in our work with an earlier cohort of women diagnosed with bca during 1991–1993^{20,21}. A practical implication of that observation might be that such women require more encouragement to participate in ASM. In addition, published variability in the periodicity of ASM might also warrant encouragement to physicians to adhere to annual periodicity^{22,23}.

The present study has several strengths. The population includes the entire age range of women with bca, rather than only those 65 years of age and older. Every woman in the study could potentially have benefited from a protective effect of ASM because each experienced an invasive ipsilateral recurrence or contralateral primary event without prior regional nodal or distant metastasis, the early detection of which would lie in the hypothesized causal pathway between ASM and reduction in the risk of bca death. The definition of ASM is appropriate for the study question because it requires consecutive annual bilateral mammograms and allows—but does not require—the most recent mammogram to detect the ipsilateral recurrence or contralateral primary. The median follow-up after ipsilateral recurrence or contralateral primary (7.76 years; IQR: 3.68–9.81 years) is appropriate for observation of bca death as the primary outcome. The

TABLE IV Hazard ratios for breast cancer death after invasive ipsilateral breast tumour recurrence or contralateral primary breast cancer

Variable	Univariate analysis		Adjusted analysis	
	HR	95% CL	HR	95% CL
Participation in annual surveillance mammography during the 2 years before invasive ipsilateral recurrence or contralateral primary	0.82	0.62, 1.10	0.86	0.63, 1.16
Age at initial Dx (per 1-year increase)	1.01	1.00, 1.02	1.01	1.00, 1.02
Year of initial Dx				
1994		1.00		1.00
1995	0.75	0.50, 1.12	0.71	0.48, 1.07
1996	0.97	0.67, 1.41	0.87	0.59, 1.27
1997	1.10	0.75, 1.62	0.98	0.66, 1.48
Socioeconomic status at initial Dx				
Urban, lower 2 income quintiles	1.02	0.75, 1.62	0.85	0.62, 1.16
Urban, upper 3 income quintiles		1.00		1.00
Rural	0.82	0.50, 1.35	0.74	0.45, 1.24
Score on the adapted CCI at initial Dx (per 1-unit increase)	1.28	0.95, 1.71	1.28	0.94, 1.74
Screening mammography before original Dx	0.8	0.59, 1.08	0.84	0.62, 1.15
Tumour size at initial Dx (per 1-cm increase)	1.26	1.08, 1.46	1.25	1.07, 1.47
Positive nodes at initial Dx (per 1-node increase)	1.09	1.05, 1.14	1.08	1.03, 1.14
Adjuvant chemotherapy at initial Dx				
Yes	1.045	0.77, 1.42	0.92	0.63, 1.34
No		1.00		1.00
Adjuvant radiotherapy at initial Dx				
Yes	1.10	0.79, 1.53	1.28	0.89, 1.85
No		1.00		1.00
Interval between original Dx and invasive ipsilateral recurrence or contralateral primary (per 1-month increase)	0.99	0.98, 1.00	0.99	0.99, 1.00

HR = hazard ratio; CL = confidence limits; Dx = diagnosis; CCI = Charlson comorbidity index.

calculation of time to bca death from the date of histologic confirmation of ipsilateral recurrence or contralateral primary, rather than from the date of initial diagnosis, avoids the introduction of survival bias into the Cox model and complies with the model's underlying assumptions, while allowing for adjustment of baseline covariates and for the interval between initial diagnosis and ipsilateral recurrence or contralateral primary. Although the propensity-score-based adjustment did not change the estimated hazard ratio for the risk of bca death, the present analysis affirms that the adjustment of the HR for known confounders has been as thorough as possible.

The study has several limitations. Participation in ASM was nonrandom. The study population comprised women for whom baseline information was complete, rather than a representative sample of women or an entire population-wide cohort. Information on adjuvant endocrine therapy at baseline was not available. Mammography technology has improved since the era of ASM considered in the study²⁴, and those improvements might result in a greater effect on bca mortality than was observed here. Furthermore, because of the limitations of our data sources, we were unable to examine potential benefits of ASM other than reduction in bca mortality—for example, detection of invasive

ipsilateral recurrence or contralateral primary at an earlier stage (requiring less-intense therapeutic intervention) and longer recurrence-free survival after ipsilateral recurrence or contralateral primary^{25,26}. An additional limitation is that the study could not examine the potential combined effect of ASM, breast self-examination, and clinical breast examination on any of the beneficial outcomes of ASM²⁷. Finally, because the study was designed to examine the effect of ASM on bca mortality among women who had experienced invasive ipsilateral recurrence or contralateral primary, and because of the nature of the data sources available, we could not examine the nature and frequency of the harms of ASM.

CONCLUSIONS

Among women with unilateral early-stage bca who developed invasive ipsilateral recurrence or contralateral primary in the absence of prior regional nodal or distant metastasis, participation in ASM during the preceding 2 years was associated with a modestly reduced risk of bca death. The point estimate for mortality reduction is similar to those found in other recent studies that made use of different designs and methods.

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Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors and not necessarily those of CIHI.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interest: LFP received grants from the Canadian Institutes of Health Research during the conduct of the study. RS, SG, and ER have no conflicts to disclose.

AUTHOR AFFILIATIONS

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