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Systematic Review

Nipple-Sparing Mastectomy in BRCA1/2 Carriers: A Systematic Review and Meta-Analysis of Breast Cancer Occurrence After Risk-Reducing and Therapeutic Procedures

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Simple Summary

Women who carry a BRCA1 or BRCA2 mutation have a high lifetime risk of breast cancer, and many choose to have both breasts removed to prevent it. Keeping the nipple improves the cosmetic result but leaves a small amount of breast tissue behind, and it has been unclear whether this matters. We combined the published studies that reported outcomes in carriers. Among 1215 carriers who had a preventive nipple-sparing mastectomy, 7 developed breast cancer after the operation (about 1 in 170), over follow-up that ranged from about 3 to 11 years between studies. Among 363 carriers treated for breast cancer with a nipple-sparing mastectomy, 16 had the cancer come back in the chest-wall area or the armpit lymph nodes (about 4 in 100). These figures come from small studies with different follow-ups, and our confidence in them is very low. They show how often cancers were reported, not that nipple-sparing mastectomy is as safe as other operations. One international registry reported more cancers after nipple-sparing than after total mastectomy; this needs confirmation in longer studies.

Abstract

Background/Objectives: Nipple-sparing mastectomy (NSM) is increasingly performed in BRCA1/2 carriers, both for risk reduction and for treatment of breast cancer, but concern remains about glandular tissue left beneath the preserved nipple. We summarised the oncological outcomes of NSM in carriers. **Methods:** We searched PubMed/MEDLINE and Europe PubMed Central (Europe PMC) up to 30 September 2026, CENTRAL on 26 September 2026, and Embase on 7 November 2026 and screened the citations of relevant articles for series reporting outcomes of NSM in BRCA1/2 carriers. The outcomes were breast cancer diagnosed after risk-reducing NSM and locoregional recurrence after therapeutic NSM; cancers found at surgery were not counted. Proportions per woman were pooled with a binomial random-effects model (generalised linear mixed model, no continuity correction) and are reported as marginal (average-risk) and median-type (typical-study) proportions, with crude proportions, a beta-binomial model, follow-up strata, and approximate person-time analyses as checks. Two human reviewers went through all articles, with generative AI used only as an assistant, and the statistics were reviewed by a third author. Risk of bias was assessed with an adapted Joanna Briggs Institute checklist and certainty of evidence with GRADE. **Results:** Fifteen studies were included. After risk-reducing NSM, seven breast cancers occurred among 1215 women from eleven studies (crude proportion 0.58% (exact 95% CI 0.23–1.18%); model-based marginal proportion 0.60%, median-type 0.41% (95% CI 0.04–1.07%)); follow-up ranged from 33 to 129 months, and four of the seven cancers came

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from one international registry. After therapeutic NSM, locoregional recurrence occurred in 16 of 363 women from five studies (crude 4.4% (exact 95% CI 2.5–7.1%); model-based marginal proportion 4.3%, median-type 4.2% (95% CI 1.1–6.9%)); one study contributed 11 of the 16 events. Recurrence within the nipple–areolar complex was reported explicitly by only one study (none in 114 breasts). Sensitivity analyses yielded median-type proportions of 0.30% to 0.74% after risk-reducing NSM and 2.6% to 4.2% after therapeutic NSM. Risk of bias was moderate to high in most studies, and the certainty of the evidence was very low for both outcomes. **Conclusions:** In BRCA1/2 carriers, about 0.6% of women had breast cancer after risk-reducing NSM and about 4% had locoregional recurrence after therapeutic NSM, but follow-up was short and heterogeneous and the certainty of the evidence is very low. These data describe observed event frequencies and do not establish oncological safety or equivalence to other mastectomy techniques; longer prospective studies with time-to-event, gene-specific, and comparative reporting are needed.

Keywords: BRCA1; BRCA2; nipple-sparing mastectomy; risk-reducing mastectomy; locoregional recurrence; meta-analysis

1. Introduction

Bilateral risk-reducing mastectomy reduces breast cancer risk by approximately 90% [1,2] in carriers of a pathogenic BRCA1 or BRCA2 variant, whose cumulative risk to age 80 years is 72% and 69%, respectively [3]. In BRCA1 carriers, it has been associated with lower overall and breast cancer-specific mortality than surveillance [4]. In carriers who develop breast cancer, the risk of new ipsilateral and contralateral cancers is a reason to discuss mastectomy, including bilateral mastectomy [5].

Nipple-sparing mastectomy (NSM) preserves the skin envelope and the nipple–areolar complex (NAC) and improves the cosmetic result [6,7], but it deliberately leaves tissue beneath the nipple, and a risk-reducing operation is only as effective as the completeness of the glandular excision. Terminal duct lobular units, from which most breast cancers arise, are uncommon in the nipple papilla [8], and none of the prophylactic NAC specimens from BRCA carriers in one pathological series contained atypia, carcinoma in situ or invasive carcinoma [9]. Clinical outcome data, however, come from small single-institution series; a narrative review of nine studies in carriers concluded that NSM appeared oncologically safe, without a pooled estimate [10].

The ASCO–ASTRO–SSO guideline considers NSM a reasonable approach for carriers eligible for mastectomy [5], and a Cochrane review of risk-reducing mastectomy could not pool outcomes because of heterogeneous designs and reporting [11]. Mastectomy is not obligatory in every carrier: in one series of 124 carriers with breast cancer, disease-free and overall survival did not differ between breast-conserving therapy and mastectomy [12]; this review concerns carriers who proceed to mastectomy. In PubMed (searched 12 November 2026), we found no systematic review or meta-analysis of cancer occurrence after NSM specifically in BRCA1/2 carriers: existing syntheses address NSM in general [13] or risk-reducing mastectomy without separating NSM [14,15]. This check covered PubMed only. We therefore pooled the published outcomes of NSM in BRCA1/2 carriers, analysing risk-reducing and therapeutic procedures separately and counting only cancers diagnosed after surgery. Our objectives were to estimate the proportion of BRCA1/2 carriers with breast cancer after risk-reducing NSM and with locoregional recurrence after therapeutic NSM and to examine how follow-up, overlap, and event definition affect these estimates.

2. Materials and Methods

2.1. Protocol, Reporting, and Search Strategy

This review followed the PRISMA 2020 statement [16] (checklist: Supplementary Table S1; flow diagram: Figure 1). The protocol was not registered, and the primary analysis set, outcome definitions, and pooling model were not pre-specified; they were refined after the first results and after peer review, and the earlier DerSimonian–Laird analysis [17] was kept for comparison (Supplementary Table S3). PubMed/MEDLINE (25 September 2026; ("nipple-sparing" OR "nipple sparing" OR "total skin-sparing") AND (BRCA OR BRCA1 OR BRCA2 OR "mutation carrier*" OR "pathogenic variant*"); English, from 2000, reviews and case reports excluded), Europe PMC, and CENTRAL (26 September) were searched, together with the bibliographies and Europe PMC citations of included studies. These database searches retrieved 11 of the 15 included studies (PubMed and Europe PMC, 10; CENTRAL, 1); 3 were found only by citation searching and 1 only in an unfiltered update of 30 September (PubMed and Europe PMC; no date, language, or publication-type limits). All search strings are in Supplementary Table S2. Embase (Embase.com) was searched on 7 November 2026 (301 records; 166 not indexed in MEDLINE; the 23 of these that were not conference records and matched a narrower title and abstract query were screened, and the remaining 143, conference records and records outside that query, were not screened individually and were not exported by record type). Scopus and Web of Science were not searched. The ten studies found by PubMed and Europe PMC that were used as seed articles for citation searching are listed in Supplementary Table S2.

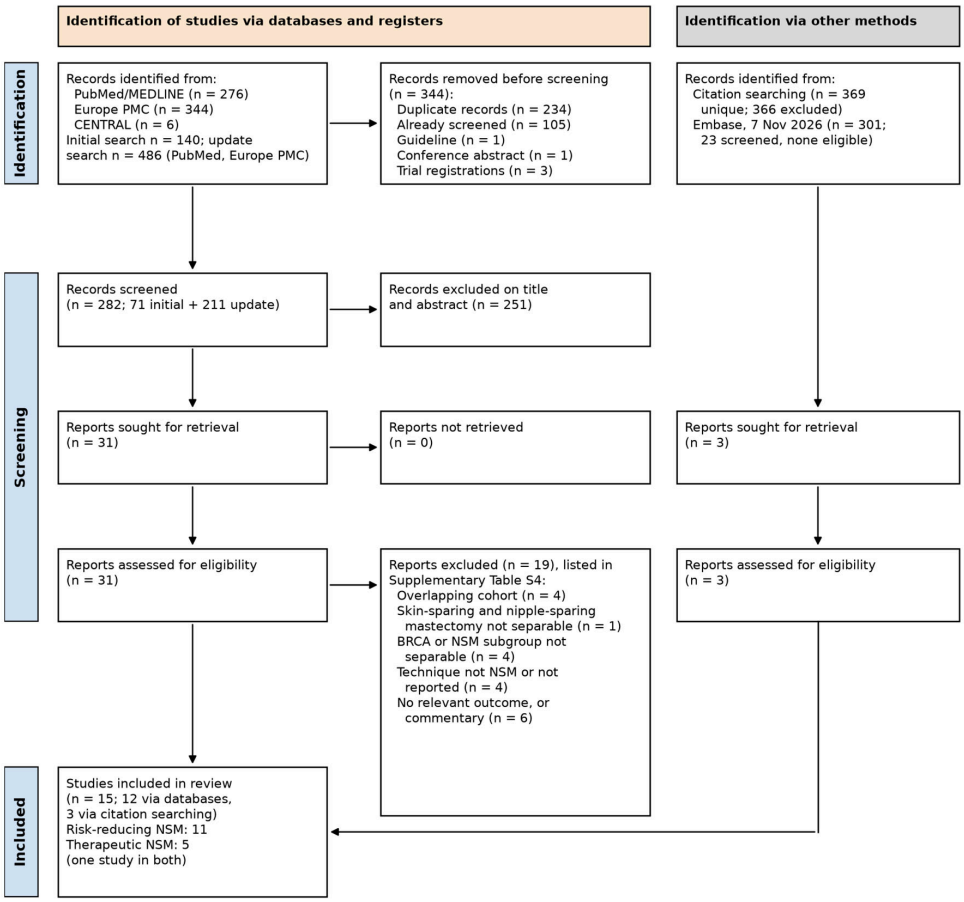


Figure 1. PRISMA 2020 flow diagram. Initial search: PubMed, Europe PMC, CENTRAL; update of 30 September 2026: PubMed and Europe PMC only. Duplicates: 64 initially and 170 between databases in the update. The Embase search of 7 November 2026 is described in the text.

2.2. Eligibility Criteria

We included studies reporting, separately for BRCA1/2 carriers, new breast cancer diagnosed after risk-reducing NSM or locoregional recurrence after therapeutic NSM, with raw counts. Cancers found in the specimen at surgery (occult) were not counted. Series in which NSM could not be separated from skin-sparing or simple mastectomy, or carriers from non-carriers, conference abstracts, and trial registrations were excluded. For overlapping cohorts, the largest or most informative non-overlapping report was retained (Supplementary Table S5).

2.3. Data Extraction

This review was not performed by artificial intelligence alone. Two human reviewers (I.M. and E.S.) went through every article, so that all of the data and all of the work were reviewed by two people; the statistical analysis was reviewed by Y.N. Generative AI (Claude, Anthropic, San Francisco, CA, USA) was used only as an assistant for screening, data extraction, and statistical scripting. Every extracted value was checked against the original report. Agreement between the two reviewers was not quantified. We extracted the unit of analysis (women or breasts), BRCA1 and BRCA2 numbers where reported, follow-up (mean or median, and the group to which it refers), and for each event, whether it was an occult cancer found at surgery or a cancer diagnosed afterwards (the number of occult cancers found at surgery in each denominator was extracted only where an article reports it, Supplementary Table S6); items an article does not report are shown as not reported rather than estimated. All 15 studies were read in full for events, denominators, and follow-up, and other patient and treatment characteristics were extracted only as shown in Supplementary Table S8; abstract-only counts and actuarial estimates were not used. Locoregional recurrence was taken as each study defined it, which is why in-breast and nodal events could not be separated. The dataset and code are Supplementary Files.

2.4. Statistical Analysis

Counts were analysed per woman (Webster 2023 [18]: 105 women, 114 breasts). For each outcome we fitted a binomial–normal random-intercept mixed model (logit link, maximum likelihood) [19,20], which needs no continuity correction, and report the back-transformed intercept, the proportion for a study with a random effect of zero (the median-type proportion), with a profile-likelihood 95% CI and τ. Because this is the proportion in a typical study rather than the average risk across women, we also report the marginal (population-averaged) proportion, obtained by averaging the model-implied proportion over the fitted distribution of study effects (the general distinction between cluster-specific and population-averaged estimates is described in [21]), with its profile-likelihood interval in Supplementary Table S3; the marginal proportion is the primary summary of average risk. Cross-checks were the crude pooled proportion with an exact Clopper–Pearson CI and a beta-binomial mean [22]; the first version's DerSimonian–Laird model with Q, I^2, and τ^2 [23] and a Hartung–Knapp interval [24,25] is in Supplementary Table S3; Q, I^2, and τ are reported in Section 3. The mixed model reproduced the crude proportion with τ fixed at zero and the earlier results with the original method. We stratified studies by reported follow-up (under or at least 60 months) and approximated person-time (women × reported mean, else median, follow-up), pooling incidence per 1000 person-years with a Poisson mixed model [19,26,27] (the nearest published sources; none is specific to single-arm rates, nor is the beta-binomial reference [22] specific to single-arm proportions); this is approximate, and it assumes that the reported follow-up applies to the women analysed, which is not the case for 6 of 11 risk-reducing and 2 of 5 therapeutic studies (marked in Table 1). Time-to-event data were not available. Sensitivity analyses (Table 2) omitted each

study, the multicentre series (Jakub 2018 [28]), the registry (Metcalfe 2024 [29]), or all three series that could share centres (Jakub 2018 [28], Grobmyer 2019 [30], Metcalfe 2024 [29]: the set with least overlap); added a Swedish cohort (both attributions) and a probably overlapping Memorial Sloan Kettering subgroup (Amburn 2026 [31]); replaced Frasson 2020 [32] with Frasson 2023 [33]; omitted the two smallest series; and, for therapeutic NSM, omitted the largest study, counted only in-breast recurrence in Frasson 2023 [33], and analysed Webster 2023 [18] by breast. The analyses used Python 3.12.10 (NumPy 2.5.3, SciPy 1.18.1) scripts written with generative-AI assistance, and the statistical analysis was reviewed by Y.N.

Table 1. Characteristics of the included studies.

Study	Country	Setting	Women (n)	Follow-up	Follow-up Refers to	Outcome	Events
Peled 2014 [34]	USA	Therapeutic NSM	27	mean 37 mo	analysed women	LRR	0
Yao 2015 [35]	USA (2 centres)	Risk-reducing NSM	150	mean 32.6 mo	whole cohort (201 carriers)	New cancer	1
Manning 2015 [36]	USA	Therapeutic NSM	26	median 28 mo	analysed women	LRR	0
Jakub 2018 [28]	USA (9 centres)	Risk-reducing NSM	346	median 34/mean 56 mo	not stated (article provides both figures)	New cancer	0
Grobmyer 2019 [30]	USA	Risk-reducing NSM	97	mean 53 mo	whole cohort	New cancer	0
Frasson 2020 [32]	Brazil	Risk-reducing NSM	30	mean 50 mo	whole cohort (62 women)	New cancer	1
Stanek 2022 [37]	Czech Republic	Risk-reducing NSM	105	mean 50 mo	analysed women	New cancer	0
O'Connell 2022 [38]	UK	Risk-reducing NSM	37	median 129 mo	analysed women	New cancer	0
Boyd 2023 [39]	USA	Risk-reducing NSM	76	median 120.5 mo	analysed women	New cancer	0
Berkes 2023 [40]	Czech Republic	Risk-reducing NSM	86	median 60 mo	all 201 women, all techniques	New cancer	1
Webster 2023 [18]	USA	Therapeutic NSM	105 (114 breasts)	median 70 mo	whole cohort	LRR	3
Frasson 2023 [33]	Brazil (2 centres)	Therapeutic NSM	33	mean 45 mo	whole cohort (76 carriers; median 30 mo)	LRR	2
Metcalfe 2024 [29]	Interna-tional (9 countries)	Risk-reducing NSM	213	mean 75.6 mo	whole matched RRM arm (827 women; 6.3 y)	New cancer	4

Table 1. *Cont.*

Study	Country	Setting	Women (n)	Follow-up	Follow-up Refers to	Outcome	Events
Kim 2025 [41]	Korea (19 centres)	Both	66/172	median 55.4 mo	184 carriers with cancer (whole cohort 787 women: 59.3 mo)	New cancer/LRR	0/11
Fu 2026 [42]	China	Risk-reducing NSM	9	median 45 mo	analysed women	New cancer	0

LRR, locoregional recurrence. Women are carriers (Webster 2023 [18]: 114 breasts in 105 women). Follow-up refers to a larger group than the carriers analysed (Supplementary Table S6). Kim 2025 [41] contributes 66 carriers to risk-reducing and 172 to therapeutic NSM.

Table 2. Sensitivity analyses.

Outcome and Scenario	Events/Women	Crude % (Exact 95% CI)	Median-Type % (Mixed Model, 95% CI)
A. Primary	7/1215	0.58 (0.23–1.18)	0.41 (0.04–1.07)
A. Without registry (Metcalfe 2024 [29])	3/1002	0.30 (0.06–0.87)	0.30 (0.02–0.80)
A. Without Jakub 2018 [28]	7/869	0.81 (0.32–1.65)	0.74 (0.12–1.55)
A. Least-overlap set †	3/559	0.54 (0.11–1.56)	0.54 (0.13–1.39)
A. Without two smallest series	6/1176	0.51 (0.19–1.11)	0.30 (0.03–0.95)
A. Adding Wiberg 2026 [43] (0/143)	7/1358	0.52 (0.21–1.06)	0.33 (0.03–0.92)
A. Adding Wiberg 2026 [43] (1/143)	8/1358	0.59 (0.25–1.16)	0.47 (0.09–1.07)
A. Adding Amburn 2026 [31] (2/333)	9/1548	0.58 (0.27–1.10)	0.49 (0.10–1.04)
A. Frasson 2023 [33] for 2020 (1/39)	7/1224	0.57 (0.23–1.17)	0.41 (0.04–1.06)
A. Without Berkes 2023 [40]	6/1129	0.53 (0.20–1.15)	0.30 (0.03–1.00)
B. Primary (per woman)	16/363	4.4 (2.5–7.1)	4.2 (1.1–6.9)
B. Without Kim 2025 [41]	5/191	2.6 (0.9–6.0)	2.6 (0.9–5.5)
B. Without Frasson 2023 [33]	14/330	4.2 (2.3–7.0)	3.6 (1.5–6.9)
B. Frasson 2023 [33] in-breast only (1/33)	15/363	4.1 (2.3–6.7)	3.6 (1.3–6.4)
B. Webster 2023 [18] by breast (3/114)	16/372	4.3 (2.5–6.9)	4.0 (1.4–6.8)

Median-type proportion: back-transformed intercept of a binomial random-intercept model (the proportion for a study with a random effect of zero) with profile-likelihood CI; the marginal (average-risk) proportions of the primary analyses are 0.60% (A) and 4.3% (B; Supplementary Table S3). † Set with least overlap: without Jakub 2018 [28], Grobmyer 2019 [30] and Metcalfe 2024 [29]. Wiberg 2026 [43]: only its NSM subgroup, with both attributions of its single event. Amburn 2026 [31]: BRCA subgroup of a Memorial Sloan Kettering series that probably overlaps Jakub 2018 [28]. Frasson 2023 [33]: recurrence in the same breast and/or ipsilateral axilla. Other scenarios are in Supplementary Table S3.

2.5. Risk of Bias and Certainty of Evidence

Risk of bias used the Joanna Briggs Institute checklist for prevalence studies [44], adapted to six domains (selection, sample size, germline confirmation, outcome ascertainment and completeness of follow-up, follow-up duration, crude counts; thresholds under Table 3). Checklists for case series exist, including the NIH and Institute of Health Economics tools [45,46]; we kept the adapted checklist because it was fixed before the data were extracted and was not re-applied with another tool, which is a limitation. It does not capture selection for NSM, era, technique, completeness of glandular excision, event definition or overlap, which are discussed as limitations. Publication bias could not be tested (five studies for the therapeutic outcome; seven of eleven studies for the risk-reducing outcome had no events). Certainty was rated with GRADE from low for observational data [47,48]; with no comparison group, it refers to how certain we are that the pooled proportion approximates the true proportion after NSM. Judgements were made by I.M. and verified by E.S.; agreement was not quantified.

Table 3. Risk of bias (adapted JBI checklist for prevalence studies).

Study	Outcome	D1	D2	D3	D4	D5	D6	Overall
Jakub 2018 [28]	A	U	Y	Y	U	N	Y	Moderate
Grobmyer 2019 [30]	A	Y	U	Y	U	U	Y	Moderate
Stanek 2022 [37]	A	U	Y	Y	U	U	Y	Moderate
O'Connell 2022 [38]	A	N	N	Y	U	Y	Y	High
Boyd 2023 [39]	A	Y	U	Y	U	Y	Y	Low
Yao 2015 [35]	A	U	Y	Y	U	N	Y	Moderate
Metcalfe 2024 [29]	A	U	Y	Y	Y	Y	Y	Low
Frasson 2020 [32]	A	U	N	Y	U	U	Y	Moderate
Kim 2025 [41]	A	U	U	Y	Y	U	Y	Moderate
Berkes 2023 [40]	A	Y	U	U	N	U	Y	Moderate
Fu 2026 [42]	A	U	N	Y	U	U	Y	Moderate
Peled 2014 [34]	B	U	N	Y	U	U	Y	Moderate
Manning 2015 [36]	B	U	N	Y	U	N	Y	High
Frasson 2023 [33]	B	U	N	Y	U	U	Y	Moderate
Webster 2023 [18]	B	Y	Y	Y	U	Y	U	Low
Kim 2025 [41]	B	U	Y	Y	Y	U	Y	Low

A, new breast cancer after risk-reducing NSM; B, locoregional recurrence after therapeutic NSM. Adapted from the JBI checklist for prevalence studies. D1, sampling frame and selection; D2, sample size (at least 100 carriers = Y, 50–99 = U, fewer than 50 = N); D3, carrier status confirmed by germline testing; D4, outcome ascertainment and completeness of follow-up (U when follow-up was limited to visits at the treating centre or loss to follow-up was not reported); D5, follow-up duration (mean or median at least 60 months = Y, 36 to 59 = U, under 36 = N); D6, crude counts with denominators and appropriate analysis. Overall: High if D1 is N or at least two domains are N; Moderate if one domain is N or at least three are U; otherwise Low. Assessment by I.M., verified by E.S.

3. Results

3.1. Study Selection

The initial PubMed search yielded 69 records and Europe PMC 65 (64 duplicates; the remaining record was a guideline). Citation searching yielded 369 unique records and three eligible studies missed by the databases: a review [35], a case report [42], and a broader high-risk series [32]. CENTRAL returned six records, including one eligible study in which NSM was not named in the title or abstract [29].

An unfiltered update on 30 September 2026 returned 316 unique records (PubMed 207, Europe PMC 279; 170 in both): 105 already known, 211 new. In all, 626 records were identified, 344 removed before screening and 282 screened (Figure 1). Nine full texts were read; eight were excluded and one (Berkes 2023 [40], first seen as an abstract) was included (Supplementary Table S4). None of the 23 Embase-only records was eligible (Supplementary Table S4b): they were reviews, case reports, complication or reconstruction studies, duplicates of included studies, or series without a separable oncological outcome.

Of 31 reports assessed, 19 were excluded (Figure 1 and Supplementary Table S4). With 3 studies from citation searching, 15 studies were included: 11 for risk-reducing and 5 for therapeutic NSM, 1 in both (Table 1). Frasson 2023 [33] yielded 2 events among 33 carriers for therapeutic NSM; its risk-reducing arm (1/39) overlaps Frasson 2020 [32] and was used only in sensitivity analysis. Berkes 2023 [40] reported one cancer 2.4 years after subcutaneous mastectomy among 86 carriers; its second cancer was found in a skin-sparing specimen at surgery and not counted. The therapeutic arm of Yao 2015 [35] overlaps Webster 2023 [18] (both Massachusetts General Hospital) and was not used. A Swedish cohort (143 NSM [43]; its single event is not attributed to a technique) and the Memorial Sloan Kettering BRCA subgroup (Amburn 2026 [31]; 2 events among 333 carriers) entered only sensitivity analyses; a mixed Prague cohort [49] was not pooled. Institutions and overlaps are in Supplementary Table S5. Seven studies were from the USA, two each from the Czech Republic and Brazil, and one each from the UK, Korea, and China, plus one international registry; sample sizes ranged from 9 to 346 women.

3.2. Risk-Reducing NSM

Eleven studies reported seven breast cancers among 1215 women after risk-reducing NSM, all diagnosed after surgery. Four occurred among 213 women with NSM in an international registry, all in BRCA1 carriers, against one among 488 women with total mastectomy [29] (crude odds ratio 9.3, Fisher exact $p = 0.03$; unadjusted, from non-randomised groups, and best read as a signal rather than an estimate). The registry's risk-reducing arm also had fifteen occult cancers found at surgery, which were not counted; its five incident cancers arose a mean of 4.7 years after surgery, and its 15-year incidence (7.9% after NSM, 2.5% after total mastectomy) includes occult cancers [29]. The other three events were a new primary cancer in the inferior breast about 6 years after surgery, away from the NAC [35] (series mean follow-up 32.6 months), a cancer in a BRCA2 carrier at 18 months [32], and one at 2.4 years [40]. The crude proportion was 7/1215 (0.58% (exact 95% CI 0.23–1.18%)). The model-based marginal (average-risk) proportion was 0.60% and the median-type proportion for a typical study 0.41% (95% CI 0.04–1.07%) ($\tau = 0.89$; Figure 2A); the beta-binomial mean was 0.60%. Heterogeneity was not detectable but is uninformative with seven events ($Q = 6.6$, 10 degrees of freedom, $p = 0.76$; $I^2 = 0\%$). Excluding the registry yielded a median-type proportion of 0.30% (95% CI 0.02–0.80%). Approximate incidence was 0.82 per 1000 person-years from the Poisson mixed model (95% CI 0.08–2.09) and, crude, 1.11 (exact 95% CI 0.45–2.30): 0.60 with follow-up under 60 months and 1.70 with 60 months or more (four of its five events from the registry; Supplementary Table S7). Crude proportions were 0.25% (2/803) and 1.21% (5/412) in the two follow-up strata; without the

registry the incidence was 0.61 per 1000 person-years. These figures are approximate and are confounded by the registry.

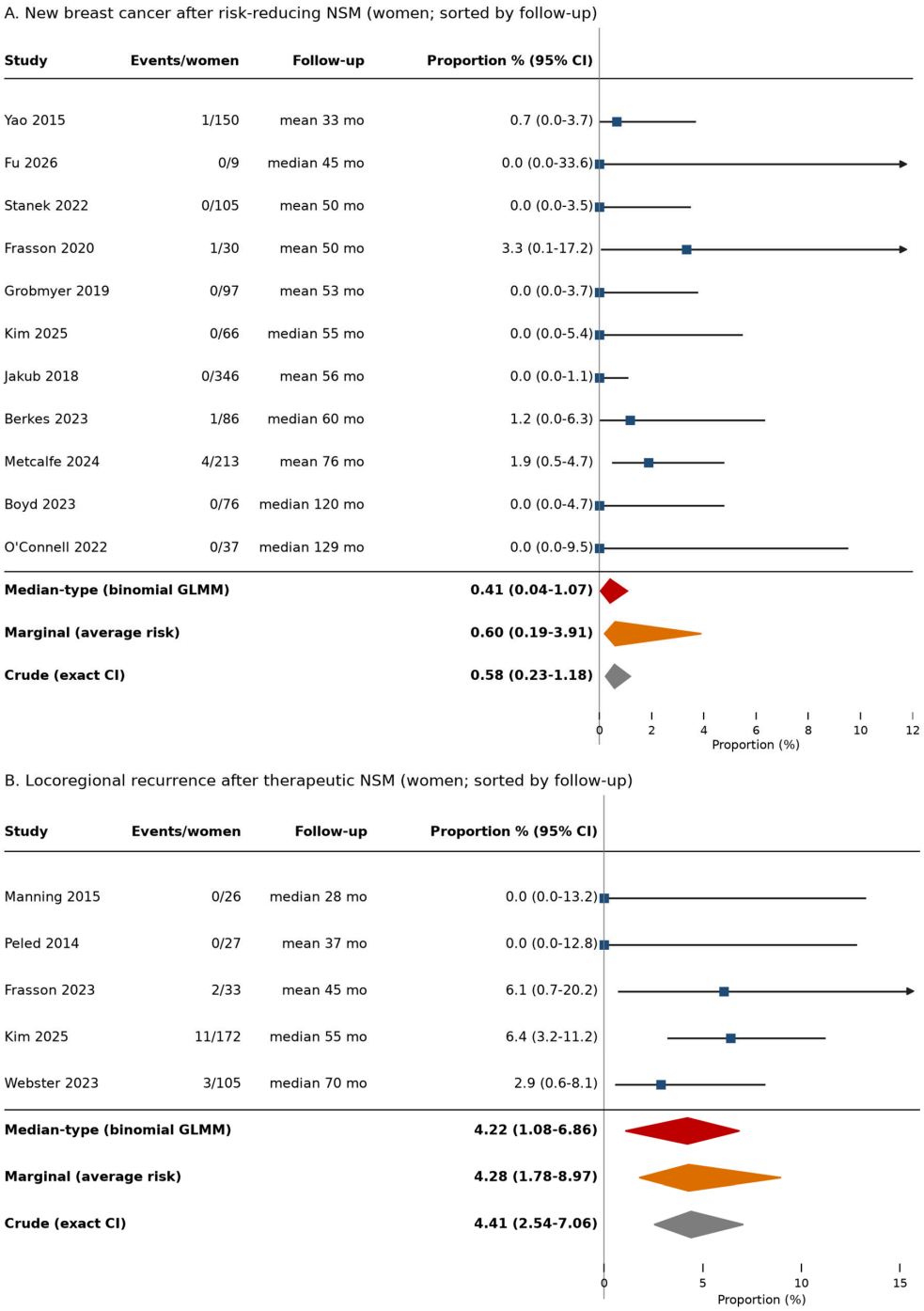


Figure 2. (**A**) Forest plot: new breast cancer after risk-reducing NSM (proportions per woman with exact 95% CIs, sorted by follow-up; pooled mixed-model and crude estimates). The horizontal scale differs from (**B**). (**B**) Forest plot: locoregional recurrence after therapeutic NSM (women; same conventions as (**A**)). (**A**) studies shown [28–30,32,35,37–42]; (**B**) studies shown [18,33,34,36,41]. Squares show study proportions and horizontal lines their exact 95% CIs (an arrow marks an interval that extends beyond the axis); the red diamond shows the pooled mixed-model estimate and the grey diamond the pooled crude estimate with exact 95% CI.

3.3. Therapeutic NSM

Five studies reported 16 locoregional recurrences among 363 women (Webster 2023 [18]: 105 women, 114 breasts); Kim 2025 [41] contributed 11 events (69%) and 172 women (47%). The crude proportion was 4.4% (exact 95% CI 2.5–7.1%), the model-based marginal proportion 4.3%, and the median-type proportion 4.2% (95% CI 1.1–6.9%) ($\tau = 0.18$; Figure 2B); heterogeneity was not detectable ($Q = 2.8$, 4 degrees of freedom, $p = 0.59$; $I^2 = 0\%$), which is uninformative with five studies. Approximate incidence was 9.0 per 1000 person-years from the Poisson mixed model (95% CI 2.9–16.2) and, crude, 9.6 (exact 95% CI 5.5–15.5), and 5.7 (crude) without Kim 2025 [41]; the crude proportion was 5.0% (13/258) in the four studies with follow-up under 60 months and 2.9% (3/105) in the one study with longer follow-up. NAC recurrence was reported explicitly by one study (none among 114 NSMs [18]), stated as not reported in another [33] and not separately reported in three; so, absent reports are not confirmed absence. In-breast and nodal recurrences and time-to-event data could not be pooled.

3.4. Sensitivity Analyses

After risk-reducing NSM, all sensitivity analyses yielded median-type proportions of 0.30% to 0.74% (Table 2), and 0.54% (95% CI 0.13–1.39%) in the set with least overlap (3/559; overlap among the remaining studies cannot be excluded, Supplementary Table S5). After therapeutic NSM, omitting the largest study yielded 2.6% (95% CI 0.9–5.5%) and the other scenarios 3.6% to 4.0%; leave-one-out estimates ranged from 2.6% to 5.0%. Leave-one-out results for risk-reducing NSM are in Supplementary Table S3. With Hartung–Knapp intervals the DerSimonian–Laird estimates were wider (Supplementary Table S3). Absent heterogeneity is not evidence of clinical homogeneity with so few events.

3.5. Risk of Bias

Risk of bias was rated high in 2, moderate in 10, and low in 4 of the 16 study–outcome pairs (Table 3); the two high-risk pairs were O'Connell 2022 [38] and Manning 2015 [36]. Berkes 2023 [40] was re-rated from low to moderate after peer review because the mutation is labelled inconsistently, follow-up is by questionnaire and registry linkage, and follow-up is reported for all 201 women, not the 86 carriers analysed. The main limitations were selective inclusion within institutions, small samples, follow-up under 5 years in most series, and follow-up limited to visits at the treating centre.

3.6. Certainty of the Evidence

Certainty was very low for both outcomes (Table 4): observational data started low, risk of bias and imprecision lowered both ratings, and indirectness lowered the therapeutic one. With no comparison group, comparative effectiveness cannot be graded.

Table 4. GRADE summary of findings.

Domain	A. Cancer After Risk-Reducing NSM	B. Locoregional Recurrence After Therapeutic NSM
Studies (women)	11 (1215)	5 (363)
Result	7 events; crude 0.58%; marginal 0.60%; median-type 0.41% (0.04–1.07%)	16 events; crude 4.4%; marginal 4.3%; median-type 4.2% (1.1–6.9%)

Table 4. *Cont.*

Domain	A. Cancer After Risk-Reducing NSM	B. Locoregional Recurrence After Therapeutic NSM
Risk of bias	Serious: retrospective, follow-up at the treating centre, median under 60 months in 7 of 11 (−1)	Serious: retrospective, 4 of 5 under 60 months (−1)
Inconsistency	Not serious; $\tau = 0.89$, $Q = 6.6$ ($p = 0.76$), $I^2 = 0\%$; uninformative with 7 events	Not serious; $\tau = 0.18$, $Q = 2.8$ ($p = 0.59$), $I^2 = 0\%$; uninformative with 5 studies
Indirectness	Not serious; follow-up shorter than the lifetime horizon (noted)	Serious: mixed stage and treatment; axilla included; one study 69% of events (−1)
Imprecision	Serious: 7 events (−1)	Serious: 16 events, wide interval, no decision threshold (−1)
Publication bias	Suspected, not testable; not downgraded again	Suspected, not testable; not downgraded again
Certainty	Very low	Very low

Observational data start at low certainty and were downgraded per domain; both outcomes are very low. Publication bias could not be assessed formally; selective reporting of favourable single-centre series cannot be excluded.

4. Discussion

Few cancers followed risk-reducing NSM (7 among 1215 women; marginal proportion 0.60%) and about 4% of women had locoregional recurrence after therapeutic NSM. Most series had no events: the multicentre series saw none where about 22 were expected [28], and none of 105 carriers after NSM developed cancer versus 9 of 105 under surveillance [37]. These are observed frequencies over follow-up of 28 to 129 months and do not establish oncological equivalence to other mastectomy techniques; no primary study had a powered comparison group.

These findings are consistent with the risk reduction of about 90% reported for bilateral risk-reducing mastectomy in carriers, not restricted to NSM [1,2]. Preserving the nipple is supported by the scarcity of terminal duct lobular units in the nipple papilla [8] and the absence of neoplastic change in prophylactic NAC specimens [9].

The international registry is the exception: its four cancers after NSM were all in BRCA1 carriers, and its 15-year incidence including occult cancers was 7.9% after NSM versus 2.5% after total mastectomy; its authors thought the events too few to recommend against NSM [29]. Unadjusted, there were 4 cancers among 213 women after NSM and 1 among 488 after total mastectomy (operation unspecified in 126); the groups were not randomised, and selection, era, technique, flap thickness, or a previous cancer could explain a difference; so, we regard this as hypothesis-generating. In the registry, 15 of 827 women (1.8%) had an occult cancer at the time of risk-reducing surgery, a reminder that preoperative imaging and specimen pathology matter and that these cancers are not failures of nipple preservation. Its mean follow-up (6.3 years, whole arm) was shorter than that of two series without events (129 and 120.5 months [38,39]). No gene-specific denominators were available and events in other series occurred in BRCA2 carriers (Frasson 2020; the Memorial

Sloan Kettering subgroup [31,32]); so, we draw no gene-specific conclusion. Excluding the registry changed the median-type proportion from 0.41% to 0.30% (Table 2).

The therapeutic proportion of about 4% was driven by the largest multicentre cohort, where local recurrence was similar in carriers and non-carriers (6.4% vs. 7.4%) [41]; without it, the pooled proportion was 2.6%. The studies differ in stage, subtype, radiotherapy, systemic treatment, technique (one used robotic or endoscopic NSM [41]), and recurrence definition (one counts the axilla [33]), and recurrence including the axilla does not measure nipple preservation; the characteristics we could extract (stage, receptor status, radiotherapy) are in Supplementary Table S8, and margins and nipple-involvement criteria were not extracted. NAC recurrence was reported explicitly by one study [18], and in a further, probably overlapping, series all recurrences in carriers were outside the nipple [50]; for the other studies, the outcome is unknown, not zero.

Sensitivity analyses suggest the estimates are stable in order of magnitude (0.30% to 0.74% for risk-reducing and 2.6% to 4.2% for therapeutic NSM). Replacing the continuity-corrected analysis with a model that needs no correction lowered the risk-reducing estimate for a typical study from 1.25% to 0.41%, but the marginal (average-risk) proportion from the same model is 0.60%, close to the crude 0.58%; the fall therefore reflects the choice of target (a typical study rather than the average woman) more than any effect of removing the correction. For women who need or choose mastectomy, these data cannot say whether NSM carries a higher long-term risk than total mastectomy; the only direct comparison is the registry above. Breast-conserving therapy is an alternative for some carriers with early cancer [12]; so, counselling should set the residual risk after NSM, its uncertainty and the need for long-term follow-up beside the options of total mastectomy and, where suitable, breast conservation. Strengths of this review are the per-woman denominators, the separation of occult cancers from cancers diagnosed after surgery, a pooling model that needs no continuity correction, explicit overlap handling, and open data and code. The studies that would settle the question are prospective cohorts or registries of carriers with a defined start (the date of surgery), person-time or time-to-event reporting, separate counts of occult and incident cancers, gene-specific denominators, and a concurrent comparison group treated with total mastectomy.

Limitations: Most studies were retrospective, with follow-up shorter than the interval over which carriers accrue lifetime risk; so, pooled proportions have no defined time horizon and the person-time analysis is approximate. Overlap with the registry cannot be quantified. Follow-up refers to a wider group than the women analysed in 6 of 11 risk-reducing and 2 of 5 therapeutic studies, and Jakub 2018 [28] reports both a median (34 months) and a mean (56 months) without stating the group; so, person-time is approximate (using 34 months for Jakub 2018 [28] yields 1.24 instead of 1.11 per 1000 person-years, crude). The 143 Embase-only records not screened individually are a further limitation. Seven of eleven risk-reducing studies had no events; so, the pooled value depends on the model. Counts are per woman, but some series may count bilateral procedures in the same woman. Within-study comparisons by technique (for example, Berkes 2023 [40]) and whether risk-reducing series included women with a previous breast cancer were not extracted. We did not extract occult cancers at surgery for most denominators, retro-areolar margins, later NAC excision or NAC necrosis, or oophorectomy and tamoxifen use. One study contributes 69% of therapeutic events, and the populations differ. The search was not exhaustive (the database searches retrieved 11 of the 15 included studies; Scopus and Web of Science were not searched and Embase was screened only for records not indexed in MEDLINE and without conference records; no protocol was registered; the primary analysis set and model were fixed after seeing the data). Generative AI assisted screening, extraction, and scripting, but all articles were reviewed by two people. The adapted risk-of-bias tool is

not validated and was not re-applied with another tool, GRADE is limited by the lack of a comparison group, and one series used questionnaire follow-up and labels the mutation inconsistently [40].

5. Conclusions

In BRCA1/2 carriers, about 0.6% of women had breast cancer after risk-reducing NSM and about 4% had locoregional recurrence after therapeutic NSM, with nipple recurrence reported explicitly by only one study. Follow-up was short and heterogeneous and the certainty is very low; so, these data show an observed frequency of events, not oncological safety, equivalence, or long-term risk. NSM may be considered in selected carriers with counselling about this uncertainty. Prospective cohorts with time-to-event data, separate reporting of occult and incident cancers, gene-specific results and comparison with total mastectomy are needed.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers18223682/s1, Table S1: RISMA 2020 checklist—Oncological safety of nipple-sparing mastectomy in BRCA1/2 carriers; Table S2: Search strings; Table S3: Mixed model compared with the earlier DerSimonian–Laird analysis, and leave-one-out estimates; Table S4: Reports excluded at full-text stage (n = 19); Table S5: Institutions, periods and possible overlap of the included studies; Table S6: Study-level extracted data and event-level details; Table S7: Approximate person-time analysis; Table S8: Characteristics of the therapeutic studies, as reported in the articles we read; Supplementary files: screening ledger; dataset and analysis code.

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