

REVIEW ARTICLE **BREAST**

Timely access to risk-reducing bilateral mastectomy: a systematic review of uptake, predictors, surgical waiting times and barriers

Kathy Dempsey BBS, MA (Govt), PhD  0000-0003-4945-0857,^{1,a} Kylie L Snook BMed (Hons), FRACS  0000-0001-9972-0961,² Melanie Walker MBBS, FRACS  0000-0003-1405-6569,³ Meagan E Brennan FRACGP, FASBP, PhD  0000-0002-3281-7643⁴

¹ School of Public Health, The University of Sydney, Camperdown, New South Wales, AUSTRALIA. ² School of Medicine, The University of Sydney, Camperdown, New South Wales, AUSTRALIA. ³ Department of Surgery, The Alfred, Melbourne, Victoria, AUSTRALIA. ⁴ Westmead Clinical School, Faculty of Medicine and Health, The University of Sydney, New South Wales, AUSTRALIA.

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Abstract

Background: Women with genetic mutations predisposing them to breast cancer have a much higher risk of young-onset aggressive breast cancer than the average population. Risk-reducing bilateral mastectomy (RRBM) greatly reduces this risk. However, women who decide on RRBM are often faced with delays in accessing surgery.

Primary objectives: To document international data on uptake and predictors of RRBM, and time between identification of high-risk status and RRBM.

Secondary objective: To explore barriers to timely surgery.

Methods: MEDLINE, EMBASE, Scopus and PsycINFO were systematically searched for articles published between 1996 and 2024. Eligible abstracts (n = 433) were exported to an EndNote library for review. Discordance between reviewers was resolved by consensus. Ethics approval was not required for this systematic review of secondary data.

Results: Nineteen articles underwent full-text review with 12 meeting the selection criteria, comprising 9851 breast cancer unaffected, high-risk women. All were observational cohort studies, comprising data audit/review over varying periods of time. Three studies were based in England, two in the USA and two in France, with one each from North America and Europe combined, Slovenia, Canada, Denmark and the Czech Republic. Four of the 12 studies were fully prospective, with one using both retrospective and prospective data collection. Uptake of RRBM ranged from 3.6 per cent (France) to 50 per cent (Denmark), and time to RRBM ranged from five months (USA) to 92 months (Denmark). Predictors of RRBM uptake are described and barriers to timely access included planned delay strategies and clinician attitudes.

^a Corresponding author: Kathy Dempsey BBS, MA (Govt), PhD; kathy.dempsey@sydney.edu.au

Discussion: Results showed wide variation in median waiting times, partly reflecting cultural differences. Pre-genetic testing treatment intentions were generally followed. Denmark had both the highest uptake and longest median time to RRBm, suggesting timing of surgery was not hindered by resource limitations.

Conclusion: Reliable data about time between decision-making and surgery is lacking and could be improved with prospective national public databases.

Background

Women with a family history of breast cancer and/or a predisposition to breast cancer from a mutation in particular genes have an elevated risk of developing breast cancer. Approximately 5–10 per cent of breast cancers are due to germline mutations,¹ most commonly in the *BRCA1* and *BRCA2* genes.^{2,3} These mutations were first discovered in the mid-1990s.^{4,5} Since then, several other high-risk, but less common, breast cancer germline mutations have been identified, along with moderate- and low-risk mutations.^{3,6}

One option to manage the elevated risk of breast cancer is risk-reducing bilateral mastectomy (RRBM), which reduces the risk by at least 95 per cent.^{7–9} This benefit applies across all age ranges of *BRCA* mutation carriers. In 2014, Cancer Australia cited the average cumulative risk of developing breast cancer by age 70 years at 57 per cent (80% by age 80) for women with a *BRCA1* mutation and 49 per cent by age 70 (88% by age 80) for women with a *BRCA2* mutation.¹ This compares with a 14 per cent lifetime risk for women without a *BRCA* mutation in Australia.¹⁰ The latest Canadian study from Metcalfe and colleagues, published in 2023, concluded that women with *BRCA* pathogenic variants ‘have a high risk of cancer between the ages of 50 and 75 years and should be counselled appropriately’.^{11(p902)}

In addition to a higher incidence of breast cancer, *BRCA1/2* mutation carriers develop breast cancer earlier than non-carriers and tend to have more aggressive disease. Over half of women (57%) with *BRCA1* mutations and a quarter of women (28%) with *BRCA2* mutations are diagnosed with breast cancer before the age of 50 years.² In comparison, less than 25 per cent of non-*BRCA* mutation carriers in Australia are diagnosed below the age of 50.¹²

Another advantage of RRBm is detecting existing occult breast cancers that otherwise may have been diagnosed at a more advanced stage. Metcalfe and colleagues conducted a large, prospective, pseudo-randomised study with *BRCA* mutation carriers, published in 2024.¹³ Having

found 15 occult cancers at the time of RRBm, the authors reported that none of these women had died during follow-up. They concluded that RRBm had prevented 80 cancers and potentially another 15 breast-cancer-related deaths, through removal of these occult cancers.¹³

No international guidelines specify target waiting times for RRBm. Guidelines from the USA’s National Comprehensive Cancer Network (NCCN),¹⁴ Cancer Australia¹ and the UK’s National Institute for Health and Care Excellence (NICE)¹⁵ recommend that all women at high-risk should be offered a discussion about RRBm.

This systematic review has two aims: the primary aim is to document international data on uptake and predictors of RRBm and time between identification of high-risk status and RRBm; the secondary aim is to explore barriers to timely surgery.

Methods

Selection criteria

Inclusion criteria:

- studies that present data of unaffected women (without a personal history of breast cancer) who have tested positive to *BRCA1/2* genetic mutations or have otherwise been defined as ‘high-risk’
- studies that define the time period to RRBm (with or without breast reconstruction)
- quantitative studies with original data
- studies published in English between 1996 and March 2024.

Exclusion criteria:

- studies with no original data (eg, systematic reviews, editorials, commentaries)
- studies that do not define ‘time to surgery’
- studies that report fewer than 10 unaffected women who have RRBm
- studies about men with breast cancer.

Definition of high risk

We have defined ‘high-risk’ women as those with a 30 per cent or higher risk of developing breast cancer in their lifetime, which corresponds to the NICE familial breast cancer guidance.¹⁵ These high-risk women have an 8 per cent or greater chance

of developing breast cancer between the ages of 40 and 50. All women who have a pathogenic mutation in the *BRCA1*, *BRCA2* or *TP53* genes are defined as high risk using this criterion.¹⁵

Literature search

Four electronic bibliographic databases were systematically searched between 16 February and 1 March 2024: MEDLINE, EMBASE, Scopus and PsycINFO. The search strategies included studies published from 1 January 1996 (because *BRCA1/2* mutation screening became available for clinical use in 1996).¹⁶ One author (KD) worked with a research librarian at the University of Sydney, to develop the search criteria. Detailed information on the search terms and results is available in **Supplementary material 1**.

All abstracts identified in the searches were exported to an EndNote (version 21, Clarivate)

library. Two authors (KD and MB) independently reviewed 433 abstracts. When exclusion criteria were applied and duplicates removed, this left a total of 206 abstracts for further review. Reference lists of each included article were searched and citation searching was also conducted to identify other relevant publications. Co-authors were consulted for additional relevant articles. Following this comprehensive review process, selection differences between reviewers were discussed and a consensus list developed. Nineteen articles underwent full-text review by KD and MB, with 12 of these meeting the selection criteria. The selection process is outlined in **Figure 1**. The methodology followed the PRISMA 2020 reporting guidelines for systematic reviews.¹⁷ Grey literature included Australian¹ and international guidelines.^{14–15} Ethics approval was not required for this systematic review of secondary data.

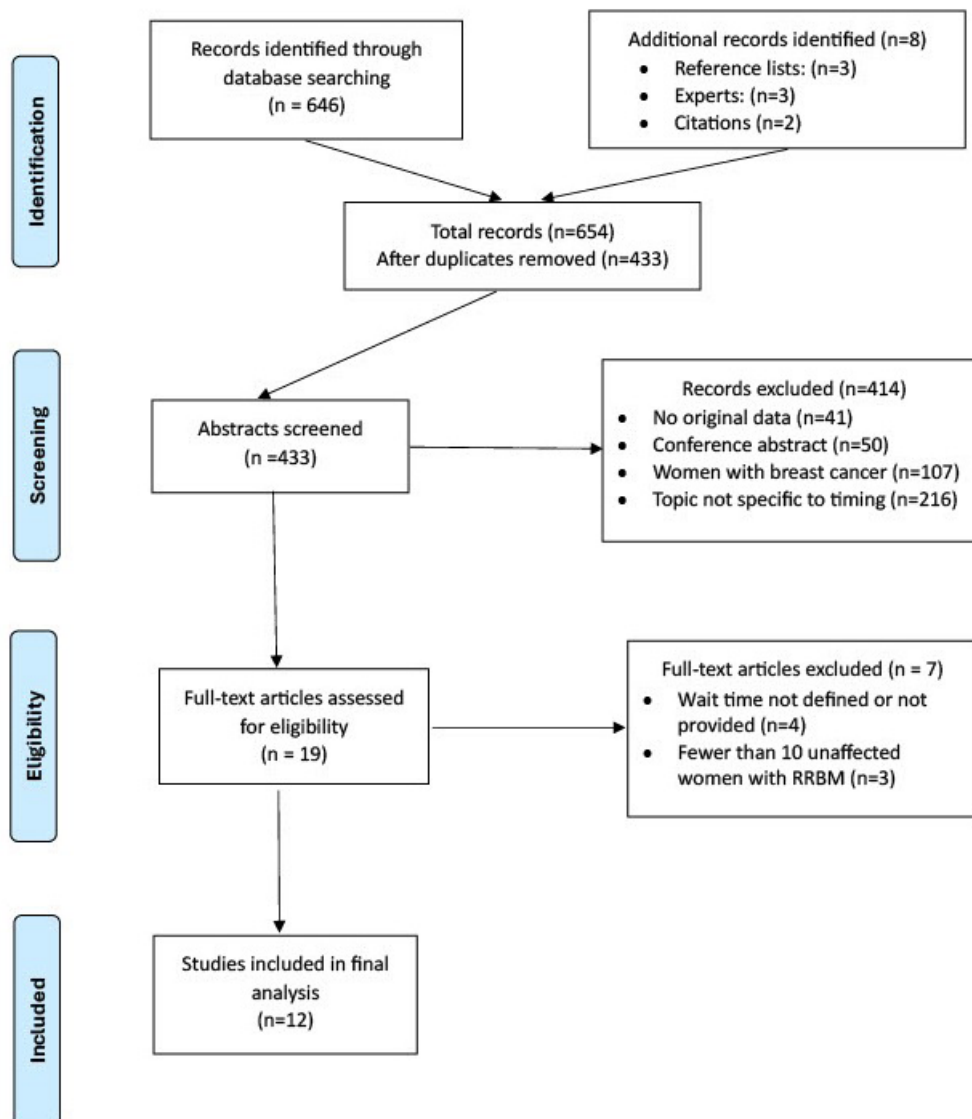


Fig 1. PRISMA 2009 flow diagram¹⁸

Table 1. Characteristics of included studies

First author, year, location, data source, study aim	Population, setting	Study design, time frame	Study outcome(s)
Beattie MS, 2009; ¹⁹ USA, Cancer Risk Program at University of California San Francisco, to assess uptake, time course and predictors of RRS in <i>BRCA</i> carriers	149 unaffected <i>BRCA</i> + mutation carriers from 3 affiliated cancer centres in San Francisco	Retrospective cohort study with data review Oct 1996–Oct 2006	Time to RRS; rate of RRS by age, prior BC, clinical site and calendar year of testing
Evans DGR, 2009; ²⁰ England, Breast Cancer Family History Clinic Manchester, to report on rate, timing and age of uptake of RRS in north-west England with 7 years follow-up	211 unaffected <i>BRCA</i> 1/2 mutation carriers	Retrospective cohort study with data review. Dates not stated. 7 years follow-up	RRBM uptake in <i>BRCA</i> carriers vs non- <i>BRCA</i> carriers and associated factors—risk, age and time
Evans DG, 2021; ²¹ as Evans 2009, to assess time trends and factors associated with RRBM uptake in women with <i>BRCA</i> 1/2 PV and other groups of high-risk women with no <i>BRCA</i> mutation	7195 women at $\geq 25\%$ lifetime breast cancer risk, including 479 <i>BRCA</i> 1/2 mutation carriers	Prospective cohort design, with data review over 32 years, to Jan 1, 2020	Factors associated with RRBM and their relative significance. Uptake rate and timing to RRBM
Filippo-Morton T, 2015; ²² USA, Carolinas Medical Center/ Levine Cancer Institute database, to document uptake and extent of surgery in <i>BRCA</i> + women and associated outcomes	87 unaffected <i>BRCA</i> mutation carriers screened over a 16-year period	Single-centre, retrospective data and literature review. Data from Jan 1996–Dec 2011. Median follow-up of 30.4 months	Choice of RRS vs surveillance, type of RRS chosen, time to cancer development, pathology and stage at time of cancer development
Friebel TM, 2007; ²³ 14 centres in USA, 2 centres in UK and 1 in Europe all collaborating on PROSE study, to examine uptake of RRBSO and RRBM among unaffected women with <i>BRCA</i> 1/2 mutations in 17 centres in North America and Europe	537 healthy women aged > 30 years, with no RRBM, RRBSO, BC or ovarian cancer before disclosure of genetic test results, and found to be <i>BRCA</i> 1/2 carriers	Prospective cohort review, 1994–2006. All completed demographic and medical history questionnaire; surgical interventions and cancer diagnoses confirmed by medical record review when available. Follow-up ≥ 6 months	Incidence of RRBSO and RRBM by <i>BRCA</i> 1 vs <i>BRCA</i> 2 carrier status and age. Predictors of RRBSO and RRBM. Time from genetic disclosure to surgery
Julian-Reynier C, 2010; ²⁴ France, French National Federation of Cancer Centres' cancer genetic network (GENEPSO), to investigate medical and psychosocial factors determining time to RRS of unaffected women carriers of <i>BRCA</i> 1/2; initial survey included perceived lifetime risk and intention to undergo RRS if positive	29 cancer genetic clinics, with 244 unaffected <i>BRCA</i> mutation carriers	Prospective cohort study, data review of unaffected <i>BRCA</i> 1/2 carriers between 2000 and 2006. Self-administered questionnaires pre-test results; and 15 days, 6, 12, 24 and 60 months after test disclosure. Follow-up to 6 years from <i>BRCA</i> 1/2+ disclosure (median follow-up 2.3 years)	Perceived risks, depression, impact of test disclosure; body image, TTS. Women who had already decided to have RRBM were operated on more quickly—related to psychological impact of test results
Ložar T, 2021; ²⁵ Slovenia, Cancer Genetics Clinic and Dept Molecular Diagnostics at Institute of Oncology Ljubljana, to assess rate, timing and dynamics of RRBM uptake in unaffected and likely <i>BRCA</i> + carriers	346 unaffected <i>BRCA</i> mutation carriers	Retrospective cohort study, with data review conducted Oct 1999–Dec 2019	Uptake of RRBM (rate and trend over time) and TTS
Macadam SH, 2021; ²⁶ Canada, British Columbia Hereditary Cancer Program's High Risk Clinic, to 1) determine incidence of <i>BRCA</i> carriers developing BC prior to surgery and 2) identify modifiable contributing factors	333 women with <i>BRCA</i> 1/2 mutation. 3 groups: RRBM only ($n = 7$); RRBM with IBR ($n = 132$); and surveillance ($n = 20$)	Retrospective cohort design, registry audit between Jan 2000 and Dec 2012. Patients choosing RRBM/IBR continued regular surveillance pre-surgery. Patient charts were reviewed until 2018	TTS from mutation disclosure; cancer incidence; strategies to facilitate decision-making and wait list prioritisation and dedicated operating time
Marcinkute R, 2022; ²⁷ England, Manchester Centre for Genomic Medicine, to summarise uptake, timing and effectiveness of RRS in unaffected mutation carriers	887 unaffected <i>BRCA</i> 1/2 mutation carriers	Prospective cohort design, with data review over 24 years, from Nov 1994–March 2019	Long-term uptake, timing and effectiveness of RRBM and RRBSO, by age and <i>BRCA</i> mutation type

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Table 1. Continued

First author, year, location, data source, study aim	Population, setting	Study design, time frame	Study outcome(s)
Skytte AB, 2010, ²⁸ Denmark, Danish Depts of Clinical Genetics and National Pathology Registry (patient data from all clinical genetic centres in Denmark), to 1) outline uptake of RRS in <i>BRCA</i> + women and 2) search for factors affecting this decision	306 unaffected <i>BRCA</i> mutation carriers with no personal history of ovarian cancer or BC	Retrospective population-based study, with data review conducted between 1998 and 2008	Estimated long-term uptake of RRB and RRSO and factors associated with uptake. Median time to RRB and RRSO
This P, 2012, ²⁹ France, Paris Institut Curie Paris, to report BC risk management patient choices and outcomes in a single centre cohort of 158 unaffected women with a <i>BRCA</i> /2 mutation	158 unaffected female carriers of <i>BRCA</i> /2 mutation	Systematic cohort study, with clinical data review from 2006 (retrospective 1998–2006 and prospective 2006 onwards); follow-up was prospective. Data extracted on 15 December 2010	Family history of cancer, clinical characteristics, RRS and their pathological results; RRSO and RRB or inclusion in the LIBER trial, development of breast and/or ovarian cancer
Zimovjanova M, 2023, ³⁰ Czech Republic, Onco-genetics Laboratory, General University Hospital Prague, to assess rate of RRSs, timing and longitudinal uptake of RRB and RRSO in healthy <i>BRCA</i> /2 carriers	496 unaffected female carriers of <i>BRCA</i> /2 mutation	Retrospective data review of two cohorts between 2000 and 2020. Median follow-up time of 6 years. Cohort 1 2005–2011; cohort 2 2013–2020	TTS in two time periods, age at genetic diagnosis, age at surgery, type of <i>BRCA</i> variant

BC = breast cancer; *IBR* = immediate breast reconstruction; *PV* = pathogenic variants; *RRBM* = risk-reducing bilateral mastectomy; *RRBSO* = risk-reducing bilateral salpingo-oophorectomy; *RRS* = risk reducing surgery; *TTS* = time to surgery

Data analysis

Relevant data were extracted from the 12 included studies and summarised in two tables. **Table 1** contains the characteristics of included studies, comprising first author, year and location of publication, data source and study aim, population, setting, study design, time frame and study outcomes. **Table 2** provides information on the main findings relating to uptake rates, timing and predictors of RRB.

Results

This systematic review has demonstrated a wide range of median waiting times from genetic testing and/or disclosure to RRB across 12 studies, comprising 9851 unaffected high-risk women. Furthermore, there tended to be wide variation around the median time within most studies. Only one study included information on specific waiting time from a woman's decision to have RRB to surgery.²⁶

All included articles were observational cohort studies, comprising data audit/review over varying periods of time. Within-study comparisons were made between women at different risk levels, age ranges, *BRCA1* or *BRCA2* mutation carrier status, or familial high-risk. One study used regularly administered questionnaires in addition to the data review.²⁴ Six articles were published between 2007 and 2012,^{19,20,23,24,28,29} and six between 2015 and 2023.^{21,22,25–27,30} Three articles were based on the same English dataset, at different timepoints and with different data subsets.^{20,21,27} We have assumed participant overlap between these publications which contributed 7195 (73%) of the total systematic review patients. Two studies were based in the USA^{19,22} and two in France,^{24,29} while one study came from each of the following countries: North America and Europe combined,²³ Slovenia,²⁵ Canada,²⁶ Denmark²⁸ and the Czech Republic.³⁰ Four of the 12 studies were fully prospective,^{21,23,24,27} with one using both retrospective and prospective data collection.²⁹

Primary aim: rate of RRB uptake

Reporting of uptake figures varied across studies. Some included uptake by gene mutation/risk level,^{21–23,25} individual centres,²³ age,^{25,27,30} or RRB with or without breast reconstruction,²⁶ and others considered whether participants had RRB only or also had risk-reducing bilateral salpingo-oophorectomy (RRBSO).^{24,25,30} Overall, for RRB only, uptake ranged from 3.6 per cent with medium follow-up of 2.33 years,²⁴ to 50 per cent with 10-year follow-up.²⁸

Table 2. Main findings of included studies

First author, year	Uptake of RRBM	Time to RRBM†	Predictors of RRBM
Beattie MS, 2009 ⁹	23% of 272 female carriers chose RRBM. However, 45.2% of cohort had previous breast cancer. Uptake not analysed separately for women with and without breast cancer. Median follow-up 3.7 years	A. Women who choose RRBM often do so within months of receiving <i>BRCA</i> + result. When TTS calculated in unaffected women only, median time was 154 days	Not stated separately for women with and without breast cancer. Age < 60; prior breast cancer; RRBSO
Evans DGR, 2009 ²⁰	Uptake highest in <i>BRCA1</i> (43%) and <i>BRCA2</i> (32%) carriers. Among non-mutation carriers at very high-risk (40%+), uptake was 6.4%; for those at high-risk (33–39%), uptake was 2.5%; and uptake was lowest in women at high-moderate risk (25–32% lifetime risk), only 1.8%	B. Majority of <i>BRCA1/2</i> mutation carriers (59% and 83%) had RRBM within 2 years of genetic test result, similar to very high-risk non-carriers with 43% uptake within the first 2 years ($p < 0.005$). Most high-moderate and high-risk women had surgery more than 2 years after initial discussion, and many beyond 4 years	Uptake proportional to risk ($p < 0.005$); and age. Majority of women opted for surgery between 35 and 45 years; also a non-significant trend for high-risk women to have surgery before 35 and lower risk to have surgery after the age of 45 ($p = 0.47$)
Evans DG, 2021 ²¹	Uptake clearly related to risk with only 1.95% of those at 26–29% risk, 3.6% of those at 30–39% risk and 6.9% of those at 40–49% risk having undergone RRBM ($p < 0.0001$). Of 7195 women at $\geq 25\%$ lifetime breast cancer risk followed for up to 32 years, 451 (6.2%) underwent pre-symptomatic RRBM. Of those eligible in different risk groups, 20-year uptake of RRBM was 47.7% (95% CI = 42.4–53.2%) in 479 <i>BRCA1/2</i> carriers; 9.0% (95% CI = 7.26–11.24%) in 1261 women at $\geq 40\%$ lifetime risk (non- <i>BRCA</i>); 4.8% (95% CI = 3.98–5.73%) in 3561 women at 30–39% risk and 2.9% (95% CI = 2.09–4.09%) in 1783 women at 25–29% lifetime risk	C. <i>BRCA1/2</i> PV carriers opted for surgery much sooner than other risk categories (median 1.5 years). For non-carriers, median time to RRBM was 2.97 years (range 0.14–22.3 years; IQR = 1.3–6.7 years) from clinic entry. 154 (34.1%) had surgery > 5 years after clinic entry. 47 (10.4%) > 10 years, and 3 more than 20 years after entry. Uptake continued to rise to 20 years from initial risk assessment	Death of a sister with breast cancer, aged < 50 (OR = 2.4; 95% CI = 1.7–3.4); death of a mother with breast cancer, aged < 60 (OR = 1.9; 95% CI = 1.5–2.3); having children (OR = 1.4; 95% CI = 1.1–1.8); and having a recent benign breast biopsy (OR = 1.4; 95% CI = 1.0–1.8) were all independently associated with RRBM uptake. Being aged > 50 at assessment was less likely to be associated with RRBM (OR = 0.26, 95% CI = 0.17–0.41)
Flippo-Morton T, 2015 ²²	Of the 87 unaffected patients, 36 (41%) chose surveillance and 51 (59%) elected RRS, with a median follow-up of 30.4 months. Within the RRS group, 38 (75%) chose RRBM and 27 (71%) of these women also underwent RRBSO in one or more operations	D. Median time to RRBM was 7.5 months	No significant differences in age among unaffected patients who received RRBM alone, RRBSO alone or both surgeries. Potential additional predictors relate to speed and availability of testing, cultural differences, and coordination with reconstructive surgery
Friebel TM, 2007 ²³	No difference in RRBM ($p = 0.83$) in <i>BRCA1</i> vs <i>BRCA2</i> carriers. Eligible women had to be aged > 30 years with at least six months of follow-up after disclosure of positive result. Mean follow-up time was 39.6 months (median, 36 months). Overall frequency of RRBM was 20% in the US centres and 31% in the UK centres ($p = 0.02$); and 13% in the single European centre, not significantly less than in the US centres ($p = 0.42$), but significantly less frequent than the UK centre ($p = 0.03$). The overall frequency of RRBM (20% vs 25%; $p = 0.22$) use not significantly different in US and non-US centres	D. Mean time to RRBM: 13.6 months; range < 1 to 104.4 months	No difference in RRBM uptake in <i>BRCA1</i> and <i>BRCA2</i> carriers ($p = 0.83$). Multivariate models identified parity (OR = 2.7; 95% CI = 0.101–7.14) and breast cancer family history (OR = 0.41; 95% CI = 0.21–0.78) as a predictor of RRBM in <i>BRCA1</i> carriers; and smoking (OR = 2.26; 95% CI = 1.04–4.88) and ovarian cancer family history (OR = 0.28; 95% CI = 0.09–0.84) in <i>BRCA2</i> carriers. Mean age at RRBM was 41.3 years (range 30.8–64.6 years). Three women (3%) were aged > 60 years at the time they elected to have a RRBM. In women aged > 40 years at the time of test disclosure, 19% had a RRBM, and 24% of women aged < 40 years had a RRBM ($p = 0.17$)

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Table 2. Continued

First author, year	Uptake of RRBm	Time to RRBm†	Predictors of RRBm
Julian-Reynier C, 2010 ²⁴	Of 244 unaffected carriers, only 8 (3.3%) had RRBm alone; and 12 (4.9%) had both RRBm and RRBso (8% in total). Not 'surprising in French context' given different attitudes to prophylactic surgery. No impact of age on uptake of RRBm was observed	A. Median time between results and RRBm was 2.05 years (n=20); (25–75%: IQR = 0.48–2.54 years). Latest expert committee advice was RRBm should not be recommended before the age of 30. After multivariate adjustment, women who decided before disclosure that they would have RRBso/RRBm were operated on more quickly than the others. TTS was shorter when the psychological impact of <i>BRCA1/2</i> result disclosure was stated to be higher ($p \leq 0.01$)	Predictors of RRBm Median age of RRBm women 38.8 years (25–75%: IQR = 31.8–46.8; range 28.3–51.7). After multivariate adjustment, rate of RRBm significantly associated with having children < 15 years at time of testing ($p = 0.006$), occurrence of breast cancer in a first-degree relative before 50 ($p = 0.024$), intending before disclosure to have RRBm ($p = 0.037$), and immediate psychological effects of disclosure, as measured 15 days after the disclosure in terms of the individual's score on the Impact of Events Scale ($p = 0.016$)
Ložar T, 2021 ²⁵	87 (25.1%) unaffected <i>BRCA</i> PV/LPV carriers (74.7% <i>BRCA1</i> carriers and 25.3% <i>BRCA2</i> carriers) had RRBm (age range 35–50 years; median age at surgery 38 years). Of those, 67 (77.9%) had RRBm only (median age 38), and 20 (23.3%) had combined RRBm and RRBso procedure (median age 42)	A. Median time from testing to disclosure of results = 2.1 months; overall median time from testing to RRBm = 22.6 months for women who had RRBm only and 8.7 months for women who had RRBm with RRBso ($p = 0.0009$). Shortest time in 2011 (8.6 months) and longest in 2013 (36.8 months)	Angelina Jolie effect in 2013; high percentage of women referred for genetic counselling through a relative (78%) rather than other specialists
Macadam SH, 2021 ²⁶	132/340 (38.8%) unaffected carriers chose RRBm with IBR; 7/340 (2.1%) chose RRBm only (and were excluded from analysis due to small numbers)	A. Median time from mutation diagnosis to surgery in the RRBm/IBR group was 31 months; range 5.3–75.7 months. Time from positive test to decision for surgery (median 8.5 months; range 1.9–74.3); time from decision to surgical consultation (median 3.5 months; range 1.1–14.4); and time from consultation to surgery (median 7.7 months; range 1.5–26.6). 40% of patients made decision to proceed within 3 months of mutation disclosure; 70% had their surgical consultation within 6 months; 62% had surgery within 1 year of their surgical consultation	Predictors of delay to RRBm include long surgical wait lists, the patient being undecided after consultation, the patient requesting a second opinion and patient health issues
Marcinkute R, 2022 ²⁷	306/887 (34.5%) women had RRBm. Mean age at RRBm = 39.2 years. 165 <i>BRCA1</i> mutation carriers had RRBm compared with 141 <i>BRCA2</i> ($p = 0.04$). 296/306 women (87.9%) had RRBm before age 50, 29 of whom (9.5%) were under 30 years old	A. Mean time is 28.4 months; median 18.4 months; range 0.2–177.6 months. 20 (7%) had RRBm within 6 months	RRBm associated with statistically significant decreased breast cancer risk (HR = 0.061; 95% CI = 0.02–0.20, $p < 0.001$) but not with overall mortality (HR = 0.32; 95% CI = 0.09–1.17, $p = 0.09$)
Skytte AB, 2010 ²⁸	Estimated long-term uptake of RRBm was 50% at 10 years of follow-up (50% of <i>BRCA1</i> and 65% of <i>BRCA2</i> mutation carriers)	A. 11% had RRBm within 6 months of receiving test result (range 2–93 months). Median time to RRBm is 92 months overall. In women aged under 40, median time to RRBm was 67 months and long-term uptake is 70%	Younger women 30–40 years chose RRBm more often than older. Women with children had significantly higher uptake of RRBm than women without ($p = 0.003$). Uptake rate not changed significantly over the last decade. RRS widely acceptable among Danish <i>BRCA+</i> women and uptake (50%) higher than most other countries. Possible reasons: RRBm at no cost within the National Health Care System; national guidelines; limited size of Denmark; close relationship between genetic departments with regular clinical discussions about management of <i>BRCA</i> families

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Table 2. Continued

First author, year	Uptake of RRBM	Time to RRBM†	Predictors of RRBM
This P, 2012 ²⁹	RRBM was performed in 14 (8.9%) of the 156 unaffected women who systematically received information about RRBM. Overall, 5.3% (95% CI, 1.7–8.9%) of women underwent RRBM during the follow-up (median 54 months, range 13–148)	A. 9 (64%) of the 14 women who had RRBM did so within 36 months after inclusion in the study	<i>BRCA1</i> mutation, at least 2 relatives with breast cancer, including one relative affected before the age of 41, and women with young children
Zimovjanova M, 2023 ³⁰	Statistically significant difference in rate of uptake between 2005 and 2020 ($p < 0.001$). 156 (31.5%) participants had RRBM (mean age 39.3 years); 53 had RRBM only (mean age 32.9 years); 103 had RRBM and RRBSO. 111/348 (31.9%) of <i>BRCA1</i> and 45/148 (48.6%) of <i>BRCA2</i> carriers had RRBM	E. Time to RRBM was 2.3 years between 2005 and 2012 (RRBM: $n = 23$, 12%) and 1.8 years from 2013–2020 (RRBM: $n = 96$, 31.6%).	All costs covered in Czech Republic. More sophisticated methods of reconstruction

† Time to RRBM defined as time from: (A) disclosure of positive *BRCA* mutation test; (B) date of genetic testing/advice; (C) clinic entry; (D) not specifically stated—either time from diagnosis of mutation OR time from disclosure of mutation; (E) entering surveillance program

CI = confidence interval; HR = hazard ratio; IBR = immediate breast reconstruction; IQR = interquartile range; LPV = likely pathogenic variant; OR = odds ratio; PV = pathogenic variant; RRBM = risk-reducing bilateral mastectomy; RRBSO = risk-reducing bilateral salpingo-oophorectomy; RRS = risk-reducing surgery; TTS = time to surgery

Primary aim: predictors of RRBM

Table 2 provides information on factors found to be independently and significantly associated with RRBM uptake. Findings about age and RRBM varied. One study reported age was not associated with RRBM uptake,²² one found a decreased association in women aged over 50²¹ while another reported an increased association for women aged under 60.¹⁹ Results reported at two-year follow-up stated women in their 50s had a lower RRBM uptake rate than women aged in their 30s.²⁷ Several other studies supported the finding that uptake was highest in women aged between 30 and 45 years of age, with a median/mean age around 40.^{20,23,24,27}

Primary aim: time to RRBM surgery

Seven of the 12 studies defined time to RRBM as the time from disclosure of a positive genetic mutation test result to date of RRBM (see **Table 2**).^{19,24–29} Overall, median time to RRBM ranged from five months¹⁹ to 92 months.²⁸ Julian-Reynier and colleagues found the time to surgery was shorter when the psychological impact of *BRCA1/2* result disclosure was stated to be higher and when the patient had made the decision pre-testing.²⁴ Macadam and colleagues reported Canadian data from 333 women using three different time spans and 40 per cent of these patients made the decision to proceed within three months of mutation disclosure.²⁶

Secondary aim: to explore barriers to timely surgery

Barriers to accessing timely RRBM were specifically identified in two studies. This and colleagues noted that in France, guidelines recommend women considering RRBM undergo a mandatory psycho-oncology consultation prior to surgery, which is organised for them, followed by a four-month period of reflection before they undertake RRBM.²⁹ The authors commented that such attitudes towards a woman's ability to make her own informed decision 'probably partially explains why so few patients in our cohort [5.3%] have chosen RRBM.^{29(p479)} The role of clinician attitudes was also raised by Evans and colleagues, who stated that international differences in RRBM uptake are likely to reflect 'not only cultural differences, but also clinician attitudes and potentially the way in which [RRBM] is discussed, if at all, as a preventative option'.^{21(p50)}

Discussion

This systematic review has demonstrated a wide range of median waiting times from disclosure of genetic testing results to RRBm across 12 studies, comprising 9851 unaffected high-risk women. Furthermore, there tended to be wide variation around the median time within most studies. Only one study included specific information on the waiting time from a woman's decision to have RRBm to the actual surgery and on the reasons for choice of treatment.²⁶ Such information is important for two reasons: first, there is growing anecdotal evidence from Australia that delay following decision-making can lead to poorer psychological and oncological outcomes for this relatively small number of high-risk women;³¹ and second, uptake rates of RRBm are rising over time.^{19,22,25,27,30} A 2023 review of UK guidelines for risk-reducing surgery noted the role of RRBm 'has become widely accepted, and rates have increased in recent years, due to improved genetic testing and significant media attention with consequent increased awareness'.^{32(p385)}

McCarthy and colleagues also commented that because NICE guidelines take several years to develop, guidance for the management of healthy carriers of germline mutations, including risk-reducing surgery, may not be keeping pace with advances in testing.³² Macadam and colleagues commented on the lack of studies that considered the proportion of breast cancers that develop while women who have made the decision to have RRBm wait for surgery.²⁶ They reported five cancers had developed in this time in their patient cohort, with a further three found at surgery (6% of the total RRBm/immediate breast reconstruction group), but noted in all cases that the decision-making component was the main reason for the delay.²⁶

A highly influential decision analysis published in 1997 concluded the benefit received from RRBm declined with age, with little gain obtained after the age of 60.³³ More recent studies do not support this decrease in the likelihood of breast cancer with increasing age.^{1,11} Three studies included in this review provided further support for the need for all *BRCA*+ women, regardless of their age, to be informed about both surveillance and surgical options. This noted '*BRCA* 1/2-related tumors, especially *BRCA1*, often occur in young women and are generally triple-negative, and these features are independent predictors of poor outcome'.^{29(p480)} In contrast, Beattie and colleagues reported *BRCA* carriers aged 60 years and over were least likely to choose RRBm or RRBSO 'despite their high and increasing risks for breast and ovarian cancers

with age'.^{19(p55)} They concluded that discussions about surgical options for gene mutation carriers should include women over 60 years of age.¹⁹ Similarly, Ložar and colleagues stated *BRCA1* carriers had an estimated lifetime risk of breast cancer of 60–65 per cent by age 70, and 72 per cent by age 80, while *BRCA2* carriers' estimated risk of breast cancer was 45–55 per cent by age 70, and 69 per cent by age 80.²⁵

International differences in RRBm uptake are likely to reflect cultural differences. In Denmark, where 50 per cent of unaffected carriers chose RRBm, risk-reducing surgeries are widely acceptable.²⁸ In contrast, Israel has only a 13 per cent uptake of RRBm.³⁴ The Laitman and colleagues study reported that, even with physician recommendation for RRBm, only 18.5 per cent (20 of 108 cancer-free carriers) opted for RRBm.³⁴ This is despite the higher frequency of *BRCA1/2* mutations in the Israeli population than in almost all other countries, and the formation of a not-for-profit organisation to support *BRCA1/2* carriers, which encourages them, among other things, to 'actively pursue risk-reducing surgery'.^{34(p70)} The authors did not explain this finding.

Several barriers to prompt access to RRBm were identified in the results section. In addition, Head and colleagues noted that in Canada, national cancer databases do not collect information on healthy women without breast cancer, making it difficult to accurately assess RRBm trends.³⁵ This is presumably true in most countries, with Denmark being a notable exception.²⁸ Although Denmark had the highest known uptake of RRBm, it also has the longest median time to RRBm (92 months), although 11 per cent had RRBm within six months of receiving their test result.²⁸

The link between pre-genetic testing intentions and the subsequent choice of risk management options, identified by Julian-Reynier and colleagues,²⁴ is supported by a 2010 Dutch study which compared risk management preferences of individual women shortly after genetic test disclosure and matched this with choice of RRBm or surveillance around two years later.³⁶ They found that almost all *BRCA* mutation carriers follow their first preference for breast cancer surveillance or risk-reducing mastectomy and reported strong predictors for RRBm within two years as younger age and prior preference for mastectomy ($R^2 = 0.57$). Strong attendance at an educational support group made adherence to their original intention more likely (OR 4.8, $p = 0.04$).³⁶ The stability of women's preferences

was discussed in another Dutch study by van Dijk and colleagues, who reported that 90 per cent of 338 women who opted for *BRCA* testing had already indicated a preference regarding risk management at baseline and, for most women, these preferences remained stable.³⁷

The study by Julian-Reynier and colleagues also highlighted a crucial factor in determining RRBm uptake rates, that is, the importance of long-term follow-up. They noted that even when women were undecided or opposed to RRBm, a 'nonnegligible proportion of the women opted for surgery in the long run'.^{24(p805)} Evans and colleagues also found that uptake of RRBm continued to rise up to 20 years from initial risk assessment.²¹ A report on 24 years of follow-up of the same prospective, large-scale cohort confirmed that while around 50 per cent of RRBm is undertaken within the first two years, later uptake may be driven by several factors.²⁷ These include previously identified issues such as false positive screens, new breast cancer diagnoses in the family or breast cancer-related deaths.²⁰

Three studies have suggested alterations to surgical coordination and timetabling to provide a rapid access model of care. Macadam and colleagues proposed unaffected carriers who have made the decision to proceed with RRBm should be 'clearly prioritized on a surgeon wait list for consultation and surgery with a guaranteed maximum wait program for the delivery of service'.^{26(p712)} They also suggested a dedicated block of operative time should be allocated to allow surgical oncology and plastic surgery specialists to coordinate RRBm and reconstruction concurrently in adjacent operating theatres.²⁶ A similar approach trialled in an Australian hospital in 2024 was found to significantly increase the number of high-risk gene carriers' risk-reducing procedures (5–26%, $p = 0.001$), although waiting time for RRBm did not significantly change (and actually increased) after the intervention (55.0 to 61.1 weeks, $p = 1.000$).³⁸ An earlier, smaller Canadian study by Head and colleagues developed a rapid access risk-reducing mastectomy and immediate reconstruction (RAPMIR) program, which involved RRBm patients having a separate waiting list to women with breast cancer.³⁵ Although mean wait time from referral to surgery for RAPMIR patients was significantly shorter than for the traditional model (165.4 vs 309.2 days, $p = 0.027$), women still waited over five months for RRBm.³⁵

Strengths and limitations

This systematic review has several important strengths. The methodology was rigorous, and

followed the PRISMA 2020 reporting guidelines for systematic reviews (**Supplementary material 2**). Reviewed studies covered almost 10,000 women from Europe, Scandinavia, the USA and Canada. Great care was taken to ensure that the findings from included studies were only cited in relation to breast cancer and RRBm; data relevant to ovarian cancer and RRBSO were excluded. However, choice of RRBSO was shown to influence the choice of RRBm in some studies and this may be a confounder.

The main limitation reflects the observational methods used within the included studies. Only four of the 12 reviewed studies were fully prospective, which is considered a superior methodology because inclusion of all relevant variables can be planned, accurately measured and recorded.³⁹ However, an advantage of retrospective studies is that they may have larger, established databases to draw data from. Other limitations include potential selection bias from observational cohort studies on uptake and efficacy of risk-reducing surgeries,⁴⁰ and the relatively short length of follow-up of most study cohorts, which did not allow for the calculation of accurate RRBm uptake rates over time.^{21,24,28} Other limitations, due to non-reporting in most publications, include whether RRBm was always discussed or encouraged as an option for newly-diagnosed *BRCA* mutation carriers,²¹ and how long women took to make a decision for or against RRBm following genetic testing disclosure.²⁶

Conclusion

There appears to be no clear international or national models that have successfully shortened the waiting time to access RRBm for women who have chosen that option. Furthermore, the literature has documented cases of breast cancer developing while women are waiting for this surgery²⁶ and the case study evidence on the adverse psychological impact of waiting time continues to grow.³¹

In Australia, surgical wait time is also impacted by choice of breast reconstruction, with the wait often shortest for simple mastectomy without reconstruction and longest for mastectomy with autologous reconstruction. This latter option requires longer theatre times and coordination between breast oncoplastic and plastic reconstructive surgeons, often leading to scheduling delays. Unfortunately, reliable, quantitative data on the time between decision-making and RRBm is lacking for this cohort of

women. The creation of a prospective, national and publicly accessible database for women with genetic predispositions for breast cancer would represent an important first step in this process.

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Conflict of interest

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