

Management of early breast cancer in women with an identified BRCA1 or BRCA2 gene mutation or at high risk of a gene mutation

A systematic review

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Contributors

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The *Management of breast cancer in women with an identified gene mutation or at high risk of a gene mutation: a systematic review* was developed with input from an expert multidisciplinary working group with the following members:

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See Appendix A for more information.

Executive summary

Understanding of the genetics of breast cancer susceptibility has increased substantially over the last 20 years.¹ Approximately 5-10% of breast cancers are due to germline mutations in high-penetrance genes including BRCA1 and BRCA2.^{2, 3} Other high risk genes in which mutations have been identified, but at lower frequency, include TP53 (Li-Fraumeni), PTEN (Cowden) and STK11 (Peutz-Jeghers).² More recently, moderate and low risk germline mutations have been identified in genes such as CHEK2, ATM, BRIP1, PALB2, and RAD51C.^{1,2}

BRCA1 and BRCA2 are genes in which germline mutations result in a greatly increased risk of developing breast cancer and ovarian/fallopian tube cancer. The average cumulative risk of developing breast cancer by age 70 years has been estimated to be 57% (80% by age 80) for women with a BRCA1 mutation and 49% (88%) for women with a BRCA2 mutation.^{4, 5} The average cumulative risk of developing ovarian/fallopian tube cancer by age 70 years has been estimated to be 40% (65% by age 80) for women with a BRCA1 mutation and 20% (37%) for women with a BRCA2 mutation.^{4, 5} Women with a BRCA1 mutation and, to a lesser extent, a BRCA2 mutation are often diagnosed with cancer at an early age compared to sporadic cancers. It has been reported that 58% of women with a BRCA1 mutation and 28% of women with a BRCA2 mutation are diagnosed with cancer before age 50.²

The aim of the present review was to systematically review the evidence related to the management of breast cancer in women with an identified gene mutation or at high risk of a gene mutation, to inform the development of clinical practice recommendations about the management of breast cancer in these women.

The systematic review addresses three research questions that were developed with input from a multidisciplinary working group. Following consultation with the working group, it was agreed that the search be limited to studies of the management of breast cancer in women diagnosed with non-metastatic breast cancer with a BRCA 1 or BRCA 2 (BRCA 1/2) gene mutation. Information identified on women with breast cancer who are suspected to have a gene fault due to a strong family history of breast and/or ovarian cancer, and on women with other gene faults (such as TP53, PTEN, STK11, RAD51C, CHEK2, ATM, BRIP1, and PALB2), was reported but not specifically searched for. Evidence for two additional issues of interest on outcomes for women with breast cancer and a BRCA1/2 mutation and on genetic testing to inform the management of breast cancer, was sourced using non-systematic methods.

A search of the literature published between January 2001 and April 2012 was undertaken using electronic databases. In total, 76 articles were included for the three research questions and for the two additional issues of interest. The studies identified included prospective and retrospective cohort studies and case-control studies. No randomised controlled trials or pseudo-randomised trials were identified for inclusion in the systematic review.

The key results for each research question are summarised below.

The level of evidence for each study is based on the National Health and Medical Research Council *Evidence Hierarchy Aetiology*.⁶

What is the optimal surgical management, with or without radiotherapy, of breast cancer for women with a BRCA1/2 mutation?

Survival outcomes

- In one Level III-2 retrospective cohort study,⁷ mastectomy resulted in similar overall and breast cancer-specific survival in women with breast cancer with a BRCA1/2 mutation in comparison to breast conserving treatment (breast conserving surgery and radiotherapy).
- There is evidence from one Level III-3 case-control study⁸ and two Level III-2 retrospective cohort studies^{9, 10} that breast conserving treatment has similar overall survival^{8, 10} and breast cancer specific survival⁹ for women with breast cancer with a BRCA1/2 mutation, in comparison to other women with breast cancer.*

Ipsilateral breast cancer (recurrence of the primary or a second primary)

- In one Level III-2 retrospective cohort study⁷ in women diagnosed with breast cancer with a BRCA1/2 mutation, breast conserving treatment was associated with a significant increase in the risk of ipsilateral breast cancer compared to a mastectomy (with and without radiotherapy). However, there was no significant difference in the risk of ipsilateral breast cancer between women who had breast conserving treatment and adjuvant chemotherapy, compared to all women treated with a mastectomy.
- There is evidence from one Level III-3 case-control study⁸ and four of six Level III-2 retrospective cohort studies⁹⁻¹² that breast conserving treatment is as effective in terms of the risk of ipsilateral breast cancer for women diagnosed with breast cancer with a BRCA1/2 mutation, as in other women with breast cancer.*
- In one Level III-2 retrospective cohort study¹³ in women diagnosed with breast cancer with a BRCA1/2 mutation, radiotherapy after breast conserving surgery significantly decreased the risk of ipsilateral breast cancer compared to no radiotherapy after breast conserving surgery.

* Other women with breast cancer refers to women with breast cancer not attributable to a BRCA1/2 mutation, that is, women with sporadic breast cancer or women who have not been proven to have a BRCA1/2 mutation with genetic testing

Are there particular neoadjuvant and adjuvant systemic therapies which are specifically effective for women diagnosed with breast cancer with a BRCA1/2 mutation?

Part A Chemotherapy

Survival outcomes

- In two Level III-2 retrospective cohort studies^{14, 15} in women diagnosed with breast cancer with a BRCA1/2 mutation, adjuvant chemotherapy did not significantly improve breast cancer-specific survival compared to no adjuvant chemotherapy.
- There is evidence from one Level II prospective cohort study¹⁶ and three Level III-2 retrospective cohort studies^{9, 14, 15} that, adjuvant chemotherapy shows similar overall survival and breast cancer specific survival for women with breast cancer with a BRCA1/2 mutation, in comparison to other women with breast cancer.*
- There is evidence from one Level II prospective cohort study¹⁶ and one Level III-2 retrospective cohort study⁹ of patients from four studies (one Level II prospective cohort study and three Level III-2 retrospective cohort studies) that women diagnosed with breast cancer with a BRCA1 mutation⁹ or a BRCA2 mutation¹⁶ who do not receive adjuvant chemotherapy have significantly poorer breast cancer-specific survival⁹ and significantly greater increased risk of death¹⁶ compared to women with breast cancer not attributable to a BRCA1/2 mutation* who do not receive chemotherapy.
- In one Level III-2 retrospective cohort study¹⁷, neoadjuvant chemotherapy shows similar breast cancer-specific survival and overall survival for women with breast cancer with a BRCA1/2 mutation, in comparison to other women with breast cancer.*

Response rate

- In one small Level III-2 retrospective cohort study,¹⁸ women diagnosed with breast cancer with a BRCA1 mutation had significantly better rates of pathological complete response (pCR) to platinum-based chemotherapy, compared to other types of neoadjuvant chemotherapy (such as cyclophosphamide, methotrexate and fluorouracil (CMF) or anthracycline-taxanes).
- There is inconsistent evidence on the effectiveness of taxane based chemotherapy compared to anthracyclines (without taxanes) or other non-taxane regimens, in women with a BRCA 1/2 mutation.^{17, 19}
- In one small Level III-2 retrospective cohort study²⁰ women diagnosed with breast cancer with a BRCA1/2 mutation had significantly better rates of complete clinical response to anthracyclines (without taxanes), compared to other women with breast cancer.*

* Women with sporadic breast cancer or women who have not been proven to have a BRCA1/2 mutation with genetic testing

Ipsilateral breast cancer (recurrence of the primary or a second primary)

- There is evidence from two large Level III-2 retrospective cohort studies^{7, 13} that adjuvant chemotherapy after breast conserving surgery significantly decreases the risk of ipsilateral breast cancer, compared to no adjuvant chemotherapy in women with a BRCA 1/2 mutation.

Contralateral breast cancer

- In one large Level III-3 case-control study²¹, adjuvant chemotherapy showed similar decreases in risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation, as in other women with breast cancer.*
- There is inconsistent evidence on the effectiveness of adjuvant chemotherapy compared to no adjuvant chemotherapy on the risk of contralateral breast cancer in women with breast cancer with a BRCA 1/2 mutation.^{12, 21-23}

Part B Endocrine therapy

Survival outcomes

- There was no evidence identified that investigated the effectiveness of endocrine therapies other than tamoxifen.
- There was no evidence identified that compared survival outcomes in women with breast cancer with a BRCA1/2 mutation treated with or without tamoxifen.
- There is evidence from one large Level II prospective cohort study¹⁶ and two small Level III-2 retrospective cohort studies^{9, 24} that tamoxifen is as effective in terms of the risk of death¹⁶, breast cancer-specific survival⁹ and the risk of death from breast cancer²⁴ for women diagnosed with breast cancer with a BRCA1 mutation^{9, 16} or a BRCA2 mutation,²⁴ as in other women with breast cancer.*
- There is evidence from two small Level III-2 retrospective cohort studies^{9, 24} that in women who did not receive tamoxifen, those with breast cancer with a BRCA1 mutation have a significantly higher relative risk of death from breast cancer²⁴, and a significantly poorer breast cancer-specific survival⁹ compared to other women with breast cancer.* However, in women who received tamoxifen, there was no significant difference in survival outcomes in women diagnosed with breast cancer with a BRCA1 mutation, compared to other women with breast cancer.*

Ipsilateral breast cancer (recurrence of the primary or a second primary)

- In three Level III-2 retrospective cohort studies^{7, 12, 13} in women diagnosed with breast cancer and a BRCA1/2 mutation, tamoxifen did not significantly reduce the risk of ipsilateral breast cancer compared to no tamoxifen.

* Women with sporadic breast cancer or women who have not been proven to have a BRCA1/2 mutation with genetic testing

Contralateral breast cancer

- The evidence on effectiveness of tamoxifen, compared to no tamoxifen, on risk of contralateral breast cancer in women with breast cancer and a BRCA1/2 mutation, is inconsistent.
- There is evidence from one Level III-3 case-control study²¹ that tamoxifen shows similar decreases in the risk of contralateral breast cancer for women diagnosed with breast cancer with a BRCA1/2 mutation, compared to other women with breast cancer.*

What is the effectiveness of the use of surgical risk-reducing strategies for women with a BRCA1/2 mutation subsequent to a diagnosis of breast cancer?

Part A Contralateral risk-reducing mastectomy

Survival outcomes

- In two Level III-2 retrospective cohort studies^{25,14} in women diagnosed with breast cancer with a BRCA1/2 mutation, contralateral risk-reducing mastectomy did not significantly improve overall survival²⁵ or breast cancer-specific survival,¹⁴ compared to no contralateral risk-reducing mastectomy.

Contralateral breast cancer

- There is evidence from one Level II prospective cohort study²⁶ and two Level III-2 retrospective cohort studies^{25, 27} that, in women diagnosed with breast cancer with a BRCA1/2 mutation, contralateral risk-reducing mastectomy substantially decreases (by more than 90%) the risk of contralateral breast cancer, compared to no contralateral risk-reducing mastectomy.

Part B Risk-reducing salpingo-oophorectomy

Survival outcomes

- There is evidence from one Level II prospective cohort study²⁶ and one Level III-2 retrospective cohort study²⁵ that, in women diagnosed with breast cancer and a BRCA1/2 mutation, risk-reducing salpingo-oophorectomy significantly improves overall survival (two studies)^{25, 26} and breast cancer-specific survival (one study)²⁶ compared to no risk-reducing salpingo-oophorectomy.

Ipsilateral breast cancer (recurrence of the primary or a second primary)

- There is evidence from only one Level III-2 retrospective cohort study¹³ of patients from four studies^{7, 12, 13, 26} (one Level II prospective cohort study and three Level III-2 retrospective cohort studies) that, in women with breast cancer with a BRCA1/2 mutation, risk-reducing salpingo-oophorectomy significantly decreases the risk of ipsilateral breast cancer compared to no risk-reducing salpingo-oophorectomy.

Contralateral breast cancer

- In one Level III-2 retrospective cohort study²³ in women diagnosed with breast cancer with a BRCA1/2 mutation under 50 years of age, risk-reducing salpingo-oophorectomy significantly decreases the risk of contralateral breast cancer, compared to no risk-reducing salpingo-oophorectomy.

Ovarian cancer

- There is evidence from one Level II prospective cohort study²⁶ that, in women diagnosed with breast cancer with a BRCA1/2 mutation, risk-reducing salpingo-oophorectomy significantly decreased the risk of ovarian cancer, compared to no risk-reducing salpingo-oophorectomy.

1 Background

1.1 Germline gene mutations and breast cancer

Understanding of the genetics of breast cancer susceptibility has increased substantially over the last 20 years.¹ Approximately 5-10% of breast cancers are due to germline mutations in high-penetrance genes including BRCA1 and BRCA2.^{2, 3} Other high risk genes in which mutations have been identified, but at lower frequency include TP53 (Li-Fraumeni), PTEN (Cowden) and STK11 (Peutz-Jeghers).² More recently, moderate and low risk genes with mutations have been identified in genes such as CHEK2, ATM, BRIP1, PALB2, and RAD51C.^{1,2}

BRCA1 and BRCA2 are genes in which germline mutations result in a greatly increased risk of developing breast cancer and ovarian/fallopian tube cancer. The average cumulative risk of developing breast cancer by age 70 years has been estimated to be 57% (80% by age 80) for women with a BRCA1 mutation and 49% (88%) for women with a BRCA2 mutation.^{4, 5} The average cumulative risk of developing ovarian/fallopian tube cancer by age 70 years has been estimated to be 40% (65% by age 80) for women with a BRCA1 mutation and 20% (37%) for women with a BRCA2 mutation.^{4, 5}

BRCA1 and BRCA2 (BRCA1/2) mutation-associated breast cancers differ from sporadic tumours, particularly BRCA1 mutation-associated breast cancers. The majority of BRCA1 mutation-associated breast cancers are triple negative (oestrogen receptor-negative, progesterone receptor-negative, HER2- negative) and high grade.²⁸ The endocrine status of BRCA2 mutation-associated breast cancers are more often oestrogen receptor (ER) and progesterone receptor (PR) positive than BRCA1 mutation-associated breast cancers, similar to sporadic tumours, but BRCA2 mutation-associated breast cancers tend to be higher grade than sporadic tumours.²⁹ Women with a BRCA1 mutation and, to a lesser extent, a BRCA2 mutation are often diagnosed with cancer at an early age compared to sporadic cancers. Around 25% of breast cancer cases diagnosed are in women younger than 50 years.^{30, 31} However, it has been reported that 58% of women with a BRCA1 mutation and 28% of women with a BRCA2 mutation are diagnosed with cancer before the age of 50 years.²

1.2 Current clinical practice guidelines and guides

In 2010, National Breast and Ovarian Cancer Centre (NBOCC)⁺ published *Advice about familial aspects of breast cancer and epithelial ovarian cancer: a guide for health professionals*, which includes information about categories of risk, and the management of women at moderately increased or potentially high risk of developing breast cancer and ovarian cancer due to family history.³² Cancer Australia has also published *Recommendations for management of women at high risk of ovarian cancer* (2011).³³

⁺ In July 2011, NBOCC amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.

1.3 The present systematic review

The aim of this review was to systematically review the evidence related to the management of breast cancer in women with an identified gene mutation or at high risk of a gene mutation, to inform the development of recommendations about the management of breast cancer in these women. Following consultation with the multidisciplinary working group, it was agreed that the search be limited to studies of the management of breast cancer in women diagnosed with non-metastatic breast cancer (early breast cancer, with or without locally advanced breast cancer).

2 Methods

This systematic review addresses three research questions which were developed in consultation with a multidisciplinary working group. The questions addressed were:

- 1) What is the optimal surgical management, with or without radiotherapy, of breast cancer for women with a BRCA1/2 mutation?
- 2) Are there particular neoadjuvant and adjuvant systemic therapies which are specifically effective for women with breast cancer and a BRCA1/2 mutation?
- 3) What is the effectiveness of the use of surgical risk-reducing strategies for women with a BRCA1/2 mutation subsequent to diagnosis of breast cancer?

In consultation with the working group, it was agreed that the search was limited to studies of the management of breast cancer in women with a BRCA 1/2 gene mutation in women diagnosed with non-metastatic breast cancer (early breast cancer, with or without locally advanced breast cancer). Information identified on women with breast cancer who are suspected to have a gene fault due to a strong family history of breast and/or ovarian cancer, and on women with other gene faults (such as TP53, PTEN, STK11, RAD51C, CHEK2, ATM, BRIP1, and PALB2), was reported but not specifically searched for.

2.1 Inclusion criteria

2.1.1 Participants

Research Questions 1-3: Women diagnosed with non-metastatic breast cancer (early breast cancer with or without locally advanced breast cancer) with an identified germline BRCA1/2 gene mutation.

In addition, information was reported, but not specifically searched, for women diagnosed with non-metastatic breast cancer (early breast cancer, with or without locally advanced breast cancer) with either:

- a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation (including women who have not been proven to have a BRCA1/2 mutation with genetic testing and women who have not had genetic testing).
- non-BRCA germline mutations (such as TP53, PTEN, STK11, RAD51C, CHEK2, ATM, BRIP1, and PALB2).

2.1.2 Intervention/comparison

Research Question 1:

- Breast conserving treatment (breast conserving surgery with radiotherapy) compared to ipsilateral (therapeutic) mastectomy with or without

radiotherapy in women with a BRCA1/2 mutation or compared to other women with breast cancer;

- breast conserving treatment in women with a BRCA1/2 mutation compared to breast conserving treatment in women with sporadic breast cancer; and
- radiotherapy compared to no radiotherapy after breast surgery in women with a BRCA1/2 mutation or compared to other women with breast cancer.

Research Question 2: Systemic therapies (including neoadjuvant/adjuvant chemotherapy or endocrine therapy e.g. tamoxifen, endocrine replacement therapy after risk-reducing salpingo-oophorectomy) compared to no systemic therapy or other systemic therapies in women with a BRCA1/2 mutation.

Research Question 3: Contralateral risk-reducing mastectomy or risk-reducing salpingo-oophorectomy compared to no contralateral risk-reducing mastectomy or no risk-reducing salpingo-oophorectomy or other risk reducing strategies in women with a BRCA1/2 mutation.

2.1.3 Outcome measures

Outcome measures of interest were:

- overall survival/breast cancer-specific survival
- ipsilateral breast cancer (recurrence of the primary or a second primary)
- distant metastases
- contralateral breast cancer
- ovarian (and/or fallopian) cancer
- adverse events
- quality of life/psychosocial impact
- patient preferences.

2.1.4 Additional issues of interest

The following were identified as additional issues of interest. Information on these topics was sourced using non-systematic methods and is reported narratively in the review. There was no specific search for all key terms related to these areas and the evidence was not reviewed systematically:

- Survival outcomes, and risk of ipsilateral breast cancer and contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation.
- Issues related to genetic testing to inform the management of breast cancer.

2.2 Literature search

Literature search

A systematic literature search was conducted in April 2012 to identify relevant studies which addressed the inclusion criteria. The search was conducted using several databases including:

- Medline
- Embase
- Pubmed
- Cochrane library.

Additional papers identified from personal files and the reference lists of included papers were also sourced.

The search strategy, developed with input from the multidisciplinary working group, used combined key terms which described breast cancer and germline gene mutations/risk of germline gene mutations (see Appendix B).

The search was limited to papers published between January 2001 and April 2012 in the English language. The primary search was limited to studies of the management of breast cancer in women with a BRCA 1/2 gene mutation. Information identified on women with breast cancer and other gene faults (such as TP53, PTEN), or who are suspected to have a gene fault, was reported but not specifically searched for.

The titles and abstracts of these citations were assessed by two reviewers independently to determine eligibility for the current review, based on the criteria described previously. Ineligible studies were excluded based on the exclusion criteria below. For citations which provided insufficient information to assess eligibility, the full text was retrieved for assessment, by the same two reviewers.

In addition to the above databases, key oncology organisations, guidelines organisations and clinical trial websites were searched for relevant information (see Appendices C, E and F). The following conference websites which had an electronic search index for abstracts were also searched: American Society of Clinical Oncology (ASCO) Annual meeting and the International Gynecologic Cancer Society (IGCS) biennial meeting.

2.2.1 Exclusion criteria

Papers were excluded if they met any of the following criteria:

- Not an original research study - publications not reporting the findings of original research studies including non-systematic reviews, editorials, commentaries and letters.
- Inappropriate population - studies in a population other than as defined in the inclusion criteria. Studies were excluded if they investigated the outcomes in women with metastatic breast cancer. Studies were also excluded if they

investigated the outcomes in women with locally advanced breast cancer alone and did not include women with early breast cancer. Studies investigating women with a somatic gene mutation, that is, a mutation detected in the breast tissue were excluded.

- Inappropriate outcomes.
- Not published in the English language.
- Published prior to 2001.

2.2.2 Results of the literature search

From the search of the databases, 1307 abstracts were identified. On the basis of the title or abstract, 970 abstracts were excluded and 337 articles were retrieved for full text assessment. In total, 76 published articles were included in the review to address the research questions and the secondary issues.

See Appendix D for the flow-chart of the number of papers excluded and included in the present review.

The evidence identified in the present review that addressed the management of women diagnosed with breast cancer with a BRCA1/2 mutation included the following:

- Eight observational studies investigated the impact of the type of breast surgery (ipsilateral) on survival outcomes or ipsilateral breast cancer;
- Thirteen observational studies investigated the impact of neoadjuvant or adjuvant chemotherapy on survival outcomes, ipsilateral breast cancer or contralateral breast cancer;
- Nine observational studies investigated the impact of tamoxifen on survival outcomes, ipsilateral breast cancer or contralateral breast cancer;
- Four observational studies investigated the impact of contralateral risk-reducing mastectomy on survival outcomes or contralateral breast cancer; and
- Seven observational studies investigated the impact of risk-reducing salpingo-oophorectomy on survival outcomes, ipsilateral breast cancer, contralateral breast cancer or ovarian (and/or fallopian) cancer.

2.3 Data extraction

Data extraction was performed by one reviewer and verified by a second reviewer to ensure accuracy. Descriptive data extracted from the studies included study characteristics (including author, year of publication, design, period of recruitment, study population, type/ number of women with BRCA1/2 mutation, median age, ethnicity, menopause status, and median follow-up) and study outcomes (including overall survival/breast cancer-specific survival, local/regional/distant breast cancer and contralateral breast cancer).

2.4 Quality assessment

The quality assessment of the studies included in the review was based on the criteria outlined in the *How to use the evidence: assessment and application of scientific evidence* (2000,)⁶ and include the following:

Cohort studies:

- How were subjects selected for the 'new intervention'?
- How were subjects selected for the comparison or control group?
- Does the study adequately control for demographic characteristics, clinical features and other potential confounding variables in the design or analysis?
- Was the measurement of outcomes unbiased (ie blinded to treatment group and comparable across groups)?
- Was follow-up long enough for outcomes to occur?
- Was follow-up complete and were there exclusions from the analysis?

Case/control studies:

- How were cases defined and selected?
- How were controls defined and selected?
- Does the study adequately control for demographic characteristics and important potential confounders in the design or analysis?
- Was measurement of exposure to the factor of interest (eg the new intervention) adequate and kept blinded to case/control status?
- Were all selected subjects included in the analysis?

Systematic reviews:

- Was an adequate search strategy used?
- Were the inclusion criteria appropriate and applied in an unbiased way?
- Was a quality assessment of included studies undertaken?
- Were the characteristics and results of the individual studies appropriately summarised?
- Were the methods for pooling the data appropriate?
- Were sources of heterogeneity explored?

3 Results

3.1 International guidelines and recommendations

Various international guidelines were identified either through the literature search or from health technology assessment and guidelines websites (see Appendix E). These included the following:

- New Zealand Guidelines Group *Management of Early Breast Cancer* (2009)³⁴
- European Society of Medical Oncology (ESMO) *Clinical Practice Guidelines* (2011)³⁵
- National Comprehensive Cancer Network (NCCN) *Guidelines on invasive breast cancer* (2012)³⁶
- NCCN *Guidelines on Breast and/or Ovarian Cancer Genetic Assessment* (2012)³⁶

3.2 Research Questions

3.2.1 Research Question 1: surgical management

What is the optimal surgical management, with or without radiotherapy, of breast cancer for women with a BRCA1/2 mutation?

Systematic reviews

Liebens et al (2007) systematically reviewed the evidence about the effectiveness of local and systemic therapies in women diagnosed with breast cancer with a BRCA1/2 mutation compared to women with sporadic breast cancer.³⁷ Studies were included if they were published between the period 1994 to 2006. Eight studies from the review included women exclusively treated by breast conserving treatment (breast conserving surgery and radiotherapy) and twelve studies included women treated by either breast conserving treatment or mastectomy.³⁷ Four studies^{9, 10, 12, 38} from the Liebens et al (2007) review were identified as relevant to the present review. The identified studies met the eligibility criteria of the present review and compared, either in the main analysis or in the subanalysis, the effectiveness of breast conserving treatment to mastectomy in women with a BRCA1/2 mutation, or compared the effectiveness of breast conserving treatment of women with a BRCA1/2 mutation to women with sporadic breast cancer. These studies^{9, 10, 12, 38} were included in the present review.

Intervention studies

No randomised controlled trials or pseudo-randomised trials or non-randomised trials were identified for inclusion in the review.

Observational studies

Eight observational studies were identified that investigated the impact of the type of breast surgery (ipsilateral) on survival or the risk of ipsilateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation. Seven studies were retrospective cohort studies and one study was a case-control study. One study compared the outcomes after breast conserving treatment to the outcomes after a mastectomy in women with a BRCA1/2 mutation,⁷ and seven studies compared the outcomes after breast conserving treatment in women with a BRCA1/2 mutation to the outcomes in women with sporadic breast cancer.^{8-12, 38, 39}

Study characteristics

The study characteristics are described in Table 1. The sample sizes of the studies included in the review ranged from 22 to 655 women with a BRCA1/2 mutation. Three studies^{7, 11, 12} included sample sizes greater than 100 women with a BRCA1/2 mutation. All the studies included women with non-metastatic breast cancer. Four studies included women with early breast cancer only^{8, 10, 12, 38} and four studies included women with early breast cancer and locally advanced breast cancer (Stage I-III).^{7, 9, 11, 39} (Note that Brekelmans et al (2007)¹¹ included 6% of women with metastatic breast cancer with a BRCA1/2 mutation and 3% of women with metastatic breast cancer in the sporadic control group.) The median follow-up of participants in the studies ranged from four to 13.4 years. Six studies^{7-10, 12, 38} had a median follow-up of greater than five years, including two studies^{8, 38} that had a median follow-up of greater than ten years.

Table 1 Study characteristics of observational studies that investigated the impact of the type of breast surgery (ipsilateral) in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Design, Period	Study population	Patients	Cases + treatment	Controls + treatment	Median age (range) yrs	Ethnicity	Menopause status	Median follow-up (years)
Pierce 2010 ⁷	Retrospective 2001	Multi-institutional: USA, Spain, Israel and Australia and New Zealand (kConFab)	BRCA1/2=655	BRCA1/2 + BCT=302	BRCA1/2 + M=353	BCT 40.5(20.1-85.0) M 41.9(23.6-81.5)	White: BCT=92.1% M=88.4%	Pre-menopausal: BCT=79.5% M=68 %	8.2-8.9 years Data projected to 15 years
Kirova 2010 ⁸	Retrospective 1981-2000 Matched for age and year of treatment	Family cancer clinic at the Institut Curie, France	BRCA1/2=27 Non-carriers familial=104 Sporadic=261	BRCA1/2 + BCT=27	Sporadic + BCT=261 Non-carriers familial + BCT=104	BRCA1/2 43(26-60) Sporadic 43(23-79) Non-carriers familial 43.5(24-78)	Not reported	Pre-menopausal: BRCA1/2=85% Non-carriers familial=70% Sporadic=76%	13.4 years
Garcia-Etienne 2009 ³⁹	Retrospective 1994-2007 Matched for age, tumour size, time of surgery	European Institute of Oncology (EIO), Italy	BRCA1/2=54 Sporadic=162	BRCA1/2 + BCT=54	Sporadic + BCT=162	BRCA1/2 36(22-53) Sporadic 37(23-55)	Not reported	Not reported	4 years Data projected to 10 years

Author Year	Design, Period	Study population	Patients	Cases + treatment	Controls + treatment	Median age (range) yrs	Ethnicity	Menopause status	Median follow-up (years)
Brekelmans 2007 ¹¹	Retrospective 1980-2004 Matched for age and year of diagnosis	Family Cancer Clinic, Rotterdam, Netherlands Note: Cases and controls had BCT or M	BRCA1/2=260 Non-carriers familial=238 Sporadic=759	BRCA1/2 + BCT=111	Sporadic controls + BCT=410 Non-carriers familial + BCT=111	BRCA1 Mean 42(23-82) BRCA2 Mean 44(27-85) Sporadic Mean 43(23-82) Non-carriers familial Mean 47(25-77)	Not reported	Not reported	4.3-5.1 years Data projected to 10 years
Pierce 2006 ¹²	Retrospective 1980-1987 Matched for age and year of diagnosis	Multi-institutional: USA, Canada, Israel	BRCA1/2 =160 Sporadic=445	BRCA1/2 + BCT=160	Sporadic + BCT=445	BRCA1/2 40.1(21.9-74.3) Sporadic 41.0(22.6-75.1)	White: BRCA1/2 =91% Sporadic =83%	Pre-menopausal: BRCA1/2=74% Sporadic=75%	6.7-7.9 years Data projected to 15 years
Seynaeve 2004 ¹⁰	Retrospective 1980-1995 Matched for age and year of diagnosis	Family Cancer Clinic, Rotterdam, Netherlands	BRCA1/2 =26 Sporadic=174 Non-specified HBC=61	BRCA1/2 + BCT=26	Sporadic + BCT =174 Non-specified HBC + BCT (Non-carriers and non-tested familial)=61	BRCA1/2 Mean 38.7 Sporadic Mean 46.1 HBC Mean 48.9	Not reported	Pre-menopausal: BRCA1/2 =80.8% Sporadic=60% HBC=47.5%	5.7-6.4 years
Robson 2004 ⁹	Retrospective 1980-1995	Multi-institutional: USA, Canada	BRCA1/2 =56 Sporadic=440	BRCA1/2 + BCT=56	Sporadic + BCT=440	BRCA1 70% <50 yrs BRCA2 29% <50 yrs Sporadic 31% <50 yrs	All Ashkenazi Jewish women	Not reported	9.7 years

Author Year	Design, Period	Study population	Patients	Cases + treatment	Controls + treatment	Median age (range) yrs	Ethnicity	Menopause status	Median follow-up (years)
Haffty 2002 ³⁸	Retrospective 1975-1998	Clinic, Yale University School of Medicine, USA	BRCA1/2 =22 Sporadic=105	BRCA1/2 + BCT=22	Sporadic + BCT=105	BRCA1/2 Mean 33.7 Sporadic Mean 37.3	White: BRCA1/2 =91% Sporadic =90%	Not reported	12.7 years

BCT Breast conserving treatment (breast conserving surgery and radiotherapy)
 BRCA1/2 Women with a mutation in BRCA1 or BRCA2
 M Mastectomy
 HBC Non-specified hereditary breast cancer (non-carriers and non-tested familial cases)

Quality of the studies

Many of the studies are limited by their retrospective design, small sample sizes, relatively short-follow-up, sampling biases and lack of control for important demographic characteristics, clinical features and treatment factors in the study design or analysis. Table 2 rates the overall quality of each study and describes the main attributes and limitations of each study.⁴⁰ Table 3 outlines the demographic characteristics, clinical features and treatment factors that were controlled in the design or analysis of each study.

Table 2 Quality of the observational studies that investigated the impact of the type of breast surgery (ipsilateral) in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Overall quality rating	Main attributes	Main limitations
Pierce 2010 ⁷	High	<ul style="list-style-type: none"> • Large sample size (BRCA1/2 mutation=655) • Study design: compared women with a BRCA1/2 mutation after BCT and mastectomy • Long median follow-up (8.2-8.9 years) • Controlled for important demographic characteristics, clinical features and treatment factors 	<ul style="list-style-type: none"> • Retrospective • Longevity bias#
Kirova 2010 ⁸	Low	<ul style="list-style-type: none"> • Long median follow-up (13.4 years) 	<ul style="list-style-type: none"> • Retrospective • Longevity bias# • Small sample size (BRCA1/2 mutation =27) • Lack of control for treatment factors such as endocrine therapy and oophorectomy in the analysis
Garcia-Etienne 2009 ³⁹	Low		<ul style="list-style-type: none"> • Retrospective • Longevity bias# • Small sample size (BRCA1/2 mutation =54) • Sampling bias (most of the BRCA carriers who had IR had genetic testing after these events) • Short median follow-up (4 years) • Inadequate information about whether the study controlled for clinical factors such as ER positive and treatment factors such as oophorectomy, chemotherapy and endocrine therapy in the analysis

Author Year	Overall quality rating	Main attributes	Main limitations
Brekelmans 2007 ¹¹	Moderate	<ul style="list-style-type: none"> Exclusion of late-tested indexed patients to correct for longevity bias Moderately large sample size (BRCA1/2 mutation + BCT=111) Controlled for important demographic characteristics, clinical features and treatment factors 	<ul style="list-style-type: none"> Retrospective Short median follow-up (4.3-5.1 years)
Pierce 2006 ¹²	High	<ul style="list-style-type: none"> Large sample size (BRCA1/2 mutation=160) Medium median follow-up (6.7-7.9 years) Controlled for important demographic characteristics, clinical features and treatment factors 	<ul style="list-style-type: none"> Retrospective Longevity bias#
Seynaeve 2004 ¹⁰	Low		<ul style="list-style-type: none"> Retrospective Longevity bias# Small sample size (BRCA1/2 mutation =26) Short median follow-up (5.7-6.4 years)
Robson 2004 ⁹	Moderate	<ul style="list-style-type: none"> Long median follow-up (9.7 years) Addressed the issue of longevity bias by utilizing archival tissue for genetic analysis without regard for vital status 	<ul style="list-style-type: none"> Retrospective Small sample size (BRCA1/2 mutation =56) Lack of data about the number of women who had oophorectomy in the cases & control groups.
Haffty 2002 ³⁸	Low	<ul style="list-style-type: none"> Long median follow-up (12.7 years) 	<ul style="list-style-type: none"> Retrospective Longevity bias (66 women had died before genetic testing)# Small sample size (BRCA1/2 mutation =22) Lack of control for clinical factors such as ER positive and treatment factors such as endocrine therapy and oophorectomy in the analysis

Longevity bias: the preferential selection of longer-living cases

Table 3 Demographic characteristics, clinical features and treatment factors that were controlled in the design or analysis of each the observational studies that investigated the impact of the type of breast surgery (ipsilateral) in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Demographic characteristics, clinical features and treatment factors that were controlled in the design or analysis of each study									
	BRCA1 or 2	Age at diagnosis	Menopause status	Year of treatment	Tumour size/ T stage	Positive axillary nodes	ER positive	Endocrine therapy	Chemotherapy	Oophorectomy
Pierce 2010 ⁷	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Not reported	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis
Kirova 2010 ⁸	Reported Tested in multivariate analysis	Reported Matched and tested in multivariate analysis	Reported No Significant difference between groups	Reported Matched	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported	Reported No Significant difference between groups	Not reported
Garcia-Etienne 2009 ³⁹	Not reported	Reported Matched	Not reported	Reported Matched	Reported Matched	Reported No Significant difference between groups	Reported	Not reported	Not reported	Not reported
Brekelmans 2007 ¹¹	Reported Tested in multivariate analysis	Reported Matched and tested in multivariate analysis	Not reported	Reported Matched (year of diagnosis)	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis

Author Year	Demographic characteristics, clinical features and treatment factors that were controlled in the design or analysis of each study									
	BRCA1 or 2	Age at diagnosis	Menopause status	Year of treatment	Tumour size/ T stage	Positive axillary nodes	ER positive	Endocrine therapy	Chemotherapy	Oophorectomy
Pierce 2006 ¹²	Not reported	Reported Matched	Reported No Significant difference between groups	Reported Matched (year of diagnosis)	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis
Seynaeve 2004 ¹⁰ (BRCA mutations combined with familial BC)	Not reported	Reported Matched and tested in multivariate analysis	Not reported	Reported Matched (year of diagnosis)	Reported	Not reported	Not reported	Not reported	Not reported	Not reported
Robson 2004 ⁹	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Not reported	Not reported	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported No Significant difference between groups	Reported No Significant difference between groups	Not reported
Haffty 2002 ³⁸	Not reported	Reported Tested in multivariate analysis	Not reported	Not reported	Reported No Significant difference between groups	Reported No Significant difference between groups	Reported	Reported	Reported Not randomly assigned therefore not tested in multivariate analysis	Not reported

Outcomes

Impact of the type of breast surgery (ipsilateral) on survival outcomes in women with a BRCA1/2 mutation

Survival outcomes

Four studies were identified that investigated the impact of the type of breast surgery (ipsilateral) on survival in women diagnosed with breast cancer with a BRCA1/2 mutation.⁷⁻¹⁰ One study compared survival outcomes after breast conserving treatment (breast conserving surgery and radiotherapy) to survival outcomes after mastectomy in women diagnosed with breast cancer with a BRCA1/2 mutation.⁷ Three studies compared survival outcomes after breast conserving treatment in women diagnosed with breast cancer with a BRCA1/2 mutation to survival outcomes after breast conserving treatment in women with sporadic breast cancer.⁸⁻¹⁰ See Table 4 for the data relating to overall survival and Table 5 for the data relating to breast cancer-specific survival. See Table 3 for the demographic characteristics, clinical features and treatment factors that were controlled in the design or analysis of each study.

Pierce et al (2010) in a large retrospective study [BRCA1/2 n=655] compared survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation after breast conserving treatment to survival outcomes after a mastectomy (and radiotherapy in 29% of women).⁷ The study found no significant difference in breast cancer-specific survival or overall survival after breast conserving treatment compared to mastectomy, with a median follow-up of 8.2 to 8.9 years (data projected to 15 years: see Table 4 & 5 for data). The study also found no significant difference in distant failure (DF) after breast conserving treatment compared to mastectomy (7.1% vs 7.4% at 10 yrs; 11.1% vs 9.1% at 15 yr p=0.80). The study controlled for important demographic, clinical and treatment factors (see Table 3). Factors found to be significantly associated with distant failure were the presence of an infiltrating lobular cancer and a BRCA2 mutation. Factors found to be significantly associated with breast cancer-specific survival were the presence of an infiltrating lobular cancer and the development of a contralateral breast cancer. The only factor found to be significantly associated with overall survival (after adjustment for patient age at the time of diagnosis) was the development of ovarian cancer.

Three small studies found no significant difference in survival outcomes after breast conserving treatment in women diagnosed with breast cancer with a BRCA1/2 mutation compared to women with sporadic breast cancer (see Table 4 & 5 for data).⁸⁻¹⁰

Robson et al (2004), in a small retrospective cohort study of Ashkenazi Jewish women [BRCA1/2 mutation n=56], found no significant difference in breast cancer-specific survival after breast conserving treatment in women with a BRCA1/2 mutation at 10 years compared to women with sporadic breast cancer (after controlling for chemotherapy).⁹ The study controlled for important demographic, clinical and treatment factors apart from risk-reducing salpingo-oophorectomy (see Table 3).

Kirova et al (2010), in a small case-control study [BRCA1/2 mutation n=27], found no significant difference in overall survival after breast conserving treatment in women diagnosed with breast cancer with a BRCA1/2 mutation at 13.4 years compared to women with sporadic breast cancer.⁸ The study controlled for important demographic,

clinical and treatment factors apart from risk-reducing salpingo-oophorectomy and endocrine therapy (see Table 3).

Seynaeve et al (2004) in a small retrospective cohort study [BRCA1/2 mutation n=26], found no significant difference in overall survival after breast conserving treatment in women with a BRCA1 mutation (n=21) at 5.7 to 6 years compared to women with sporadic breast cancer.¹⁰ There were no data available for the outcomes in women with a BRCA2 mutation. There were also no data available about whether there were any significant differences in important clinical and treatment factors between women with a BRCA1/2 mutation, women with unspecified hereditary breast cancer (non-carriers and not tested familial cases) and sporadic controls as the data from women with a BRCA1/2 mutation and women with unspecified hereditary breast cancer were combined in the analysis (see Table 3).

Table 4 Observational studies that investigated the impact of the type of breast surgery (ipsilateral) in women diagnosed with breast cancer with a BRCA1/2 mutation on overall survival (OS)

Author Year	Cases Controls	Median follow-up (years)	OS significantly different between cases/ control	OS (%) Cases	OS (%) Controls	P value/HR
Pierce 2010 ⁷	BRCA1/2 + BCT =302 BRCA1/2 + M =353	8.2-8.9 years Data projected to 15 years	No significant difference	BCT 92.1%(10yrs) BCT 87.3%(15yrs)	M 91.8%(10yrs) M 89.8%(15yrs)	p=0.73
Kirova 2010 ⁸	BRCA1/2 + BCT =27 Non-carriers familial + BCT =104 Sporadic + BCT =261	13.4 years	No significant difference (between BRCA1/2 vs non- carriers vs sporadic)	No data	No data	No data
Seynaeve 2004 ¹⁰	BRCA1/2 + BCT =26 HBC + BCT =61 Sporadic + BCT =174	5.7-6.4 years	No significant difference (between BRCA1 & sporadic) No data for BRCA2 No significant difference (between HBC & sporadic)	No data	No data	HR 1.76, CI 95%[0.72-4.30], p=0.22 (BRCA1 vs sporadic) HR 0.88, CI 95%[0.42-1.87], p=0.74 (HBC vs sporadic)

BCT Breast conserving treatment (breast conserving surgery and radiotherapy)
M Mastectomy
HBC Non-specified hereditary breast cancer (Non-carriers and non-tested familial cases)
HR Hazard ratio
Cul Cumulative incidence
CI Confidence interval

Table 5 Observational studies that investigated the impact of the type of breast surgery (ipsilateral) in women diagnosed with breast cancer with a BRCA1/2 mutation on breast cancer-specific survival (BCSS)

Author Year	Cases Controls	Median follow-up (years)	BCSS significantly different between cases/ control	BCSS (%) Cases	BCSS (%) Controls	P value
Pierce 2010 ⁷	BRCA1/2 + BCT =302 BRCA1/2 + M =353	8.2-8.9 years Data projected to 15 years	No significant difference	BCT 93.6%(10yrs) BCT 91.7%(15yrs)	M 93.5%(10yrs) M 92.8%(15yrs)	p=0.85
Robson 2004 ⁹	BRCA1/2 + BCT =56 Sporadic + BCT =440	9.6 years	Yes (significantly worse in women with BRCA1 mutations compared to sporadic)	BRCA1 62%(10yrs) BRCA2 84%(10yrs)	Sporadic 86%(10yrs)	p <0.0001 (BRCA1 vs sporadic) p =0.76 (BRCA2 vs sporadic)

BCT Breast conserving treatment (breast conserving surgery and radiotherapy)
M Mastectomy

Ipsilateral breast cancer

Eight studies were identified that investigated the impact of the type of breast surgery (ipsilateral) on the risk of ipsilateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation.^{7-12, 38, 39} See Table 6 for the data relating to ipsilateral breast cancer from each study. See Table 3 for the demographic characteristics, clinical features and treatment factors that were controlled in the design or analysis of each study.

Of the eight studies, only one study compared the risk of ipsilateral breast cancer after breast conserving treatment (breast conserving surgery and radiotherapy) to the risk of ipsilateral breast cancer after mastectomy in women diagnosed with breast cancer with a BRCA1/2 mutation.⁷ Pierce et al (2010) in a large retrospective cohort study [BRCA1/2 n=655] found that breast conserving treatment in women diagnosed with breast cancer with a BRCA1/2 mutation was associated with a significant increase in the risk of ipsilateral breast cancer compared to a mastectomy (with and without radiotherapy).⁷ The study estimated that the cumulative risk of ipsilateral breast cancer in women with a BRCA1/2 mutation was 23.5% following breast conserving treatment compared to 5.5% following a mastectomy at 15 years (p<0.0001), with and without radiotherapy. However, the study found that the rates of ipsilateral breast cancer at 10 and 15 years in women with a BRCA1/2 mutation treated with breast conserving treatment *and* chemotherapy did not significantly differ from the rates following mastectomy. The study controlled for important demographic, clinical and treatment factors (see Table 3).

Pierce et al (2010) also reported that most ipsilateral breast cancers appeared to be second primary cancers rather than failure to control the primary tumour, due to the breast cancers largely being detected in different quadrants of the breast, the different

histology of the breast cancers to the primary cancers, and the long median time after the primary cancers to ipsilateral breast cancer.⁷ The study reported that the median time to ipsilateral breast cancer was 7.8 years for women who had breast conserving surgery and 9.4 years for women who had a mastectomy. Similarly, a large retrospective non-comparative study assessed the risk of ipsilateral breast cancer in 396 women diagnosed with breast cancer with a BRCA1/2 mutation and found that the average time between the first primary breast cancer and the ipsilateral breast cancer was 7.5 years.¹³

Seven studies, including six retrospective cohort studies and one case-control study, compared the risk of ipsilateral breast cancer after breast conserving treatment in women with a BRCA1/2 mutation to women with sporadic breast cancer.^{8-12, 38, 39} Only two small studies found a significantly increased risk of ipsilateral breast cancer after breast conserving treatment in women with a BRCA1/2 mutation compared to women with sporadic breast cancer.^{38, 39}

Garcia-Etienne et al (2009) in a small retrospective cohort study [BRCA1/2 mutation n=54] found a significantly increased risk of ipsilateral breast cancer after breast conserving treatment in women with a BRCA1/2 mutation compared to women with sporadic breast cancer.³⁹ The study had the following limitations: small sample size (and consequently the small number of events: 6 ipsilateral breast cancer in BRCA carriers and 4 ipsilateral breast cancer in controls); short median follow-up (n=4 years; data projected to 10 years); potential sampling bias with most of the women with a BRCA1/2 mutation who had ipsilateral breast cancer having genetic testing after these events (potentially overestimating the risk of ipsilateral breast cancer); and inadequate information about whether the study controlled for important clinical factors and treatment factors (see Table 3).

Haffty et al (2002) in a small retrospective cohort study [BRCA1/2 mutation n=22] with a median follow-up of 12.7 years also found a significantly increased risk of ipsilateral breast cancer after breast conserving treatment in women with a BRCA1/2 mutation compared to women with sporadic breast cancer.³⁸ The study did not find any significant difference in the risk of ipsilateral breast cancer at 5 years follow-up. The study had the following limitations: small sample size and lack of control for important clinical factors and treatment factors (see Table 3).

Five studies found that breast conserving treatment is as effective for women diagnosed with breast cancer with a BRCA1/2 mutation compared to women with sporadic breast cancer in terms of the risk of ipsilateral breast cancer.⁸⁻¹² Kirova et al (2010) in a small case-control study [BRCA1/2 mutation n=27] with a median follow-up of 13.4 years found no significant difference in the risk of ipsilateral breast cancer after breast conserving treatment in women with a BRCA1/2 mutation compared to women with sporadic breast cancer.⁸ The study controlled for important demographic, clinical and treatment factors apart from risk-reducing salpingo-oophorectomy and endocrine therapy (see Table 3). The study also found age to be the only significant predictor of ipsilateral breast cancer.

Brekelmans et al (2007) in a retrospective cohort study [BRCA1/2 mutation and breast conserving treatment n=111] also found no significant difference in the risk of ipsilateral breast cancer after breast conserving treatment in women with a BRCA1 or BRCA2 mutation compared to sporadic breast cancer in subgroup analysis (controlling for

important demographic, clinical and treatment factors: see Table 3).¹¹ The study had a short median follow-up of 4.3 to 5.1 years (and data was projected to 10 years).

Pierce et al (2006) in a retrospective cohort study [BRCA1/2 mutations n=160] also found no significant difference in the risk of ipsilateral breast cancer after breast conserving treatment in women with a BRCA1/2 mutation compared to sporadic breast cancer (controlling for important demographic, clinical and treatment factors: see Table 3).¹² The study had a median follow-up of 6.7 to 7.9 years (and data was projected to 15 years).

Robson et al (2004), in a small retrospective cohort study of Ashkenazi Jewish women [BRCA1/2 mutation n=56], also found no significant difference in the risk of ipsilateral breast cancer after breast conserving treatment in women with a BRCA1/2 mutation compared to sporadic breast cancer at 10 years (controlling for important demographic, clinical and treatment factors: see Table 3).⁹ The study did not investigate the number of women who had risk-reducing salpingo-oophorectomy.

Seynaeve et al (2004) in a small retrospective cohort study [BRCA1/2 mutation n=26], also found no significant difference in the risk of ipsilateral breast cancer after breast conserving treatment in women with a BRCA1 mutation (n=21) compared to sporadic breast cancer.¹⁰ The study had a short median follow-up of 5.7 to 6.4 years. There were no data available about outcomes in women with a BRCA2 mutation. There were also no data available about whether there were any significant differences in important clinical and treatment factors between women with a BRCA1/2 mutation, women with unspecified hereditary breast cancer (non-carriers and not tested familial cases) and sporadic controls as the data from women with a BRCA1/2 mutation and women with unspecified hereditary breast cancer were combined in the analysis (see Table 3).

Table 6 Observational studies that investigated the impact of the type of breast surgery (ipsilateral) in women diagnosed with breast cancer with a BRCA1/2 mutation on ipsilateral breast cancer (IBC)

Author Year	Cases Controls	Median follow-up (years)	IBC significantly different between cases/control	IBC (%) cases	IBC (%) controls	P value/ HR
Pierce 2010 ⁷	BRCA1/2 + BCT =302 BRCA1/2 + M =353	8.2-8.9 years Data projected to 15 years	Yes (significantly increased risk of IBC after BCT compared to mastectomy in women with a BRCA1/2 mutation)	4.1% (5yr Cul) 10.5% (10yr Cul) 23.5% (15yr Cul)	1.4% (5yr Cul) 3.5% (10yr Cul) 5.5% (15yr Cul)	p<0.0001
Kirova 2010 ⁸	BRCA1/2 + BCT =27 Non-carriers familial + BCT =104 Sporadic +BCT =261	13.4 years	No significant difference (between IBC in women with a BRCA1/2 mutation, non-carriers, and sporadic)	45% (BRCA1/2/ BCT) 31% (non-carrier familial/BCT) (at follow up)	24% (sporadic/ BCT) (at follow up)	p=0.43 (BRCA vs sporadic) p=0.13 (amongst groups)

Author Year	Cases Controls	Median follow-up (years)	IBC significantly different between cases/control	IBC (%) cases	IBC (%) controls	P value/ HR
Garcia-Etienne 2009 ³⁹	BRCA1/2 + BCT =54 Sporadic + BCT =162	4 years Data projected to 10 years	Yes (significantly increased risk of IBC after BCT in women with a BRCA1/2 mutation compared to sporadic controls)	15% (5yr Cul) 27% (10yr Cul)	4% (5yr Crude Cul) 4% (10yr Crude Cul)	p=0.03
Brekelmans 2007 ¹¹	BRCA1/2 + BCT=111 Sporadic +BCT=410 Non-carriers familial +BCT=111 Note: Cases and controls had BCT or M (IBC assessed after BCT in subgroup analysis)	4.3-5.1 years Data projected to 10 years	No significant difference (between IBC in women with a BRCA1/2 mutation, non-carriers and sporadic control in subgroup analysis)	BRCA1=12% (5yr Cul) BRCA1=16% (10yr Cul) BRCA2=17% (5yr Cul) BRCA2=17% (10yr Cul) Non-carriers=12% (5yr Cul) Non-carriers=15% (10yr Cul)	Sporadic=12% (5yr Cul) Sporadic=21% (10yr Cul)	HR=0.84, 95% CI, p=0.64 (BRCA1 vs sporadic) HR=0.85, 95% CI, p=0.79 (BRCA2 vs sporadic) HR=1.43, 95% CI, p=0.21 (non-carriers vs sporadic)
Robson 2004 ⁹	BRCA1/2 + BCT =56 Sporadic + BCT =440	9.7 years	No significant difference	12% (10yr Cul)	8% (10yr Cul)	p=0.68
Seynaeve 2004 ¹⁰	BRCA1/2 + BCT =26 Non-specified HBC + BCT=61 Sporadic +BCT =174	5.7-6.4 years	No significant difference (between IBC in women with a BRCA1/2 mutation compared to sporadic) Yes (between IBC in unspecified HBC and sporadic)	BRCA1/2 =15.4% HBC=24.6%	Sporadic =12.1%	HR=0.69, 95% CI, p=0.61 (BRCA1 vs sporadic) HR=2.31, 95% CI, p=0.02 (HBC vs sporadic)
Haffty 2002 ³⁸	BRCA1/2 + BCT =22 Sporadic + BCT =105	12.7 years	Yes (significantly increased risk of IBC after BCT in women with a BRCA1/2 mutation compared to sporadic)	22% (5yr Cul) 41% (10yr Cul)	15% (5yr Cul) 19% (10yr Cul)	p=NSD (5yrs) p=0.007 (10yrs)

BCT	Breast conserving treatment (breast conserving surgery and radiotherapy)
M	Mastectomy
IBC	Ipsilateral breast cancer
HBC	Non-specified hereditary breast cancer (Non-carriers and non-tested familial cases)
HR	Hazard ratio
Cul	Cumulative incidence
CI	Confidence interval
NSD	No significant difference

Radiotherapy

None of the studies included in previous section assessed the impact of radiotherapy after breast conserving surgery on the risk of ipsilateral breast cancer in women with a BRCA1/2 mutation.

A large retrospective cohort study by Metcalfe et al (2011) investigated the effectiveness of radiotherapy after breast conserving surgery in women diagnosed with breast cancer with a BRCA1/2 mutation.¹³ The study included 396 women, 91% of these women had a BRCA1/2 mutation and 8% of these women had not had genetic testing but were from families with a known BRCA1/2 mutation. The study had a mean follow-up of 10.5 years. The study found that radiotherapy (compared to no radiotherapy) after breast conserving surgery in women with breast cancer with a BRCA1 mutation significantly decreased the risk of ipsilateral breast cancer (controlling for important demographic, clinical and treatment factors) [RR 0.28, 95% CI [0.12-0.63], p=0.002]. Radiotherapy was found to be associated with a 72% reduction in the risk of ipsilateral breast cancer in women with a BRCA1 mutation. However, the decreased risk was not demonstrated in women with a BRCA2 mutation (perhaps due to small sample size).

Adverse Events

Two retrospective cohort studies investigated potential adverse effects from radiotherapy in women diagnosed with breast cancer with a BRCA1/2 mutation.^{41, 42} The studies found that there was no significant increase in clinically significant acute or late toxicity from radiotherapy in women diagnosed with breast cancer with a BRCA1/2 mutation compared to women with breast cancer not attributable to a BRCA1/2 mutation. Shanley (2006) found no increase in clinically significant acute or late toxicity (including breast erythema, moist desquamation, fatigue, rib fractures, lung and heart fibrosis, soft tissue and bone necrosis; and LENT-SOMA scores of oedema/lymphoedema, fibrosis, telangiectasia and atrophy) in women with a BRCA1/2 mutation (n=55) compared to women with sporadic breast cancer (controlling for important demographic, clinical and treatment factors).⁴² The study had a median follow-up of 6.75 to 7.75 years. Most of the participants in the study (including cases and controls) had radiotherapy after breast conserving surgery (16% of cases and controls had radiotherapy after mastectomy). Pierce et al (2000) also found no increase in acute or chronic morbidity in the skin, subcutaneous tissue, bone or lung in women diagnosed with breast cancer with a BRCA1/2 mutation, compared to women with sporadic breast cancer, undergoing radiotherapy after breast conserving surgery, with a median follow-up of 4.6 to 5.3 years.⁴¹

Although the evidence suggests that radiotherapy is not more harmful for women with a BRCA1/2 mutation, radiotherapy can cause fibrosis and vascular damage which can affect future wound healing in both these populations.⁴³ This may influence the success

of breast reconstruction following a mastectomy in the event of future ipsilateral breast cancer.

One retrospective cohort study investigated the possibility of radiation scatter by comparing the risk of contralateral breast cancer in women with a BRCA1/2 mutation who did and did not have radiotherapy.⁷ Pierce et al (2010) did not find any significant difference in the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation following breast conserving treatment and following a mastectomy (with or without radiotherapy), suggesting no increased risk of contralateral breast cancer due to radiation scatter.⁷

Patient preferences

Preliminary research indicates that genetic testing before definitive surgery may increase the uptake of a therapeutic (ipsilateral) mastectomy, with or without a contralateral risk-reducing mastectomy, rather than breast conserving treatment (breast conserving surgery and radiotherapy) in women found to carry a BRCA1/2 mutation.^{3, 44-49}

Quality of life

No evidence was identified that compared quality of life after breast conserving surgery and mastectomy on the ipsilateral side in women diagnosed with breast cancer with a BRCA1/2 mutation. However, Tercyak et al (2007) in a study of newly diagnosed women with breast cancer who had BRCA1/2 mutation testing at the time of their diagnosis found that women who chose mastectomy of the affected breast and contralateral risk-reducing mastectomy of the unaffected breast did not report diminished quality of life or elevated distress compared with women who chose breast conservation or unilateral mastectomy.⁵⁰ The study involved 149 women diagnosed with breast cancer with at least 10% risk of carrying a BRCA1/2 mutation. All women had genetic testing and 22 women were found to have a BRCA1/2 mutation.

Surgical management: outcomes in women with a strong family history but no identified BRCA1/2 mutation

Survival outcomes

Only three studies were identified that investigated the impact of the type of breast surgery (ipsilateral) on survival in women diagnosed with breast cancer with a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation (including women who have not been proven to have a BRCA1/2 mutation with genetic testing and women who have not had genetic testing).^{8, 10, 51}

Kirova et al (2010) in a small case-control study [BRCA1/2 mutation n=27] with a median follow-up of 13.4 years found no significant difference in overall survival between women with a BRCA1/2 mutation, familial non-BRCA1/2 mutation carriers and women with sporadic breast cancer after breast conserving treatment (although the actual rates were not reported) (see Table 4).⁸ The study controlled for important demographic, clinical and treatment factors apart from risk-reducing salpingo-oophorectomy and endocrine therapy (see Table 3).

Seynaeve et al (2004) in a small retrospective cohort study [BRCA1/2 mutation n=26], found no significant difference in overall survival after breast conserving treatment between women with a BRCA1/2 mutation, women with unspecified hereditary breast cancer (non-carriers and not tested familial cases) and women with sporadic breast cancer (see Table 4).¹⁰ The study had a short median follow-up period of 5.7 to 6.4 years. There were no data available about whether there were any significant differences in important clinical and treatment factors between women with a BRCA1/2 mutation, women with unspecified hereditary breast cancer and sporadic controls as the data from women with a BRCA1/2 mutation and women with unspecified hereditary breast cancer were combined in the analysis (see Table 3).

Vlastos et al (2002) in a retrospective cohort study compared breast-cancer specific survival after breast conserving treatment in women diagnosed with breast cancer with a positive family history of breast cancer (n=308) and women diagnosed with breast cancer without a positive family history of breast cancer (n=677).⁵¹ Women were considered to have a positive family history if they had a first degree relative who had been diagnosed with breast cancer (group 1) or any relative who had been diagnosed with breast cancer (group 2). The study found no significant difference in breast-cancer specific survival between women with a positive family history of breast cancer (group 1=76% at 20yr, group 2=87% at 20yr) compared to women without a positive family history (83% at 20yr), and between women with a first degree relative who had been diagnosed with breast cancer (group 1) and women who had any relative who had been diagnosed with breast cancer (group 2). The study had a median follow-up of 8.8 years (data projected to 20 years) and controlled for important demographic, clinical and treatment factors.

Ipsilateral breast cancer

Five studies were identified that investigated the impact of the type of breast surgery (ipsilateral) on the risk of ipsilateral breast cancer in women diagnosed with breast cancer with a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation (including women who have not been proven to have a BRCA1/2 mutation with genetic testing and women who have not had genetic testing).^{8, 10, 11, 51, 52}

Kirova et al (2010) in a small case-control study [BRCA1/2 mutation n=27] with a median follow-up of 13.4 years found no significant difference in the risk of ipsilateral breast cancer between women with a BRCA1/2 mutation, familial non-BRCA1/2 mutation carriers and women with sporadic breast cancer after breast conserving treatment (see Table 6).⁸ The study controlled for important demographic, clinical and treatment factors apart from risk-reducing salpingo-oophorectomy and endocrine therapy (see Table 3).

Brekelmans et al (2007) in a retrospective cohort study [BRCA1/2 mutation and breast conserving treatment n=111] found no significant difference in the risk of ipsilateral breast cancer after breast conserving treatment in women with breast cancer with a BRCA1/2 mutation, familial non-BRCA1/2 mutation carriers and women with sporadic breast cancer (see Table 6).¹¹ The study controlled for important demographic, clinical and treatment factors (see Table 3). The study had a short median follow-up of 4.3 to 5.1 years (and data was projected to 10 years).

Tilanus-Linthorst et al (2006) in a retrospective cohort study found no significant difference in the risk of ipsilateral breast cancer after breast conserving treatment in familial non-

BRCA1/2 mutation carriers (n=327, 17% at 10yr) and women with sporadic breast cancer (14.2% at 10yr, p=0.132). The study controlled for important demographic, clinical and treatment factors and had a mean follow-up of 6.5 to 7.3 years (data was projected to 10 years).⁵²

Seynaeve et al (2004) in a small retrospective cohort study [BRCA1/2 mutation n=26], found no significant difference in the risk of ipsilateral breast cancer after breast conserving treatment between women with a BRCA1/2 mutation and women with sporadic breast cancer (see Table 4).¹⁰ However, the study found a significant difference in the risk of ipsilateral breast cancer after breast conserving treatment between women with unspecified hereditary breast cancer and women with sporadic breast cancer. The authors suggest that increased radiosensitivity in women with a BRCA1/2 mutation may be one of the factors that explain why there was no significant difference in the risk of ipsilateral breast cancer in women with a BRCA1/2 mutation (compared to women with sporadic breast cancer). The study had a short median follow-up period of 5.7 to 6.4 years. There were no data available about whether there were any significant differences in important clinical and treatment factors between women with a BRCA1/2 mutation, women with unspecified hereditary breast cancer and women with sporadic breast cancer as the data from women with a BRCA1/2 mutation and women with unspecified hereditary breast cancer were combined in the analysis (see Table 3).

Vlastos et al (2002) in a retrospective cohort study compared the risk of ipsilateral breast cancer after breast conserving treatment in women diagnosed with breast cancer with a positive family history of breast cancer (n=308) and women diagnosed with breast cancer without a positive family history of breast cancer (n=677).⁵¹ Women were considered to have a positive family history if they had a first degree relative who had been diagnosed with breast cancer (group 1) or any relative who had been diagnosed with breast cancer (group 2). The study found no significant difference in the risk of ipsilateral breast cancer between women with a positive family history of breast cancer (group 1=10%, group 2=11%) compared to women without a positive family history (12%), and between women with a first degree relative who had been diagnosed with breast cancer (group 1) and women who had any relative who had been diagnosed with breast cancer (group 2). The study had a median follow-up of 8.8 years and controlled for important demographic, clinical and treatment factors. Age was found to be the only predictor of the risk of ipsilateral breast cancer.

Surgical management: outcomes in women with a non-BRCA germline mutation (TP53, CHEK etc)

Survival outcomes

Two studies were identified that investigated the impact of the type of breast surgery (ipsilateral) on survival in women diagnosed with breast cancer with non-BRCA germline mutation.^{53, 54}

Meyer et al (2007) investigated overall survival in women diagnosed with breast cancer with a germline CHEK2 mutation (n=25) and non-CHEK2 carriers (n=125) after breast conserving treatment.⁵³ The study found no significant difference in overall survival (OS) and breast cancer-specific survival (BCSS) after breast conserving treatment in women with a germline CHEK2 mutation and women without a germline CHEK2 mutation (OS

69% vs 78% $p=0.10$; BCSS 59% vs 78% $p=0.07$). However, a CHEK2 mutation was found to be a borderline significant discriminator for metastasis-free survival (64% vs 84% $p=0.048$). The study had a median follow-up of 7.25 years and controlled for important demographic, clinical and treatment factors.

Meyer et al (2004) investigated overall survival in women with breast cancer with an ATM mutation ($n=25$) and non-ATM carriers ($n=125$) after breast conserving treatment.⁵⁴ The study found no significant difference in overall survival (OS) and metastasis-free survival (MFS) after breast conserving treatment in women with a germline ATM mutation and women without a germline ATM mutation (OS 73% vs 89% $p=0.055$; MFS 63% vs 85% $p=0.068$ in multivariate analysis). The study had a median follow-up of 7.25 years and controlled for important demographic, clinical and treatment factors.

Ipsilateral breast cancer

No evidence was identified that investigated the impact of the type of breast surgery (ipsilateral) on the risk of ipsilateral breast cancer in women with a non-BRCA germline mutations (such as TP53, PTEN, STK11, RAD51C, CHEK2, ATM, BRIP1, and PALP2) diagnosed with breast cancer.

Radiotherapy

Two studies, including one small case series and one case study, investigated potential adverse effects from radiotherapy in women diagnosed with breast cancer with a germline TP53 mutation.^{55, 56}

Heymann et al (2010) in a small case series ($n=8$) assessed the incidence of radiation-induced malignancies in women with a germline TP53 mutations who had been treated for breast cancer (DCIS=3; invasive breast cancer=3, phyllodes tumour=1) as a first event.⁵⁵ The study had a median follow-up of six years. The study found that of the six women who had received radiotherapy (after breast conserving treatment=3 and after mastectomy=3), the following events occurred: three cases of ipsilateral breast cancer, three cases of contralateral breast cancer, two cases of radiation-induced cancer (one chest wall angiosarcoma, one breast histiocytofibrosarcoma), and three cases of new primary (thyroid cancer) compared to only one case of contralateral breast cancer in a woman who did not receive radiotherapy.

Salmon et al (2007) reported on a rapid development of post-radiotherapy sarcoma and a second breast cancer in a young woman (age 27 years) diagnosed with breast cancer with a germline TP53 mutation.⁵⁶

Summary

What is the optimal surgical management, with or without radiotherapy, of breast cancer for women with a BRCA1/2 mutation?

Survival outcomes

- In one Level III-2 retrospective cohort study,⁷ mastectomy resulted in similar overall and breast cancer-specific survival in women with breast cancer with a BRCA1/2 mutation in comparison to breast conserving treatment (breast conserving surgery and radiotherapy).

- There is evidence from one Level III-3 case-control study⁸ and two Level III-2 retrospective cohort studies^{9, 10} that breast conserving treatment has similar overall survival^{8, 10} and breast cancer specific survival⁹ for women with breast cancer with a BRCA1/2 mutation, in comparison to other women with breast cancer.*

Ipsilateral breast cancer (recurrence of the primary or a second primary)

- In one Level III-2 retrospective cohort study⁷ in women diagnosed with breast cancer with a BRCA1/2 mutation, breast conserving treatment was associated with a significant increase in the risk of ipsilateral breast cancer compared to a mastectomy (with and without radiotherapy). However, there was no significant difference in the risk of ipsilateral breast cancer between women who had breast conserving treatment and adjuvant chemotherapy, compared to all women treated with a mastectomy.
- There is evidence from one Level III-3 case-control study⁸ and four of six Level III-2 retrospective cohort studies⁹⁻¹² that breast conserving treatment is as effective in terms of the risk of ipsilateral breast cancer for women diagnosed with breast cancer with a BRCA1/2 mutation, as in other women with breast cancer.*
- In one Level III-2 retrospective cohort study¹³ in women diagnosed with breast cancer with a BRCA1/2 mutation, radiotherapy after breast conserving surgery significantly decreased the risk of ipsilateral breast cancer compared to no radiotherapy after breast conserving surgery.

Adverse effects

- There is evidence from two Level III-2 retrospective cohort studies^{41, 42} that there is no significant increase in clinically significant acute or late toxicity from radiotherapy in women with a BRCA1/2 mutation compared to women with breast cancer not attributable to a BRCA1/2 mutation.*
- There is limited evidence from one case series⁵⁵ and one case study⁵⁶ that, in women with a germline TP53 mutation, radiotherapy after breast surgery is associated with an increased risk of radiation induced malignancies.

* Other women with breast cancer refers to women with breast cancer not attributable to a BRCA1/2 mutation, that is, women with sporadic breast cancer or women who have not been proven to have a BRCA1/2 mutation with genetic testing

3.2.2 Research Question 2: neoadjuvant and adjuvant systemic therapies

Are there particular systemic therapies (neoadjuvant/adjuvant) which are specifically effective for women with breast cancer and a BRCA1/2 mutation?

Systematic reviews

No systematic reviews were identified for inclusion in the review.

Intervention studies

No randomised controlled trials or pseudo-randomised trials or non-randomised trials were identified for inclusion in the review.

Observational studies

Thirteen observational studies were identified that investigated the impact of neoadjuvant or adjuvant chemotherapy on survival outcomes, ipsilateral or contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation. The studies included retrospective and prospective cohort studies and a case-control study. Four small retrospective cohort studies investigated the type of neoadjuvant chemotherapy on the rates of pathological complete response (pCR) in women diagnosed with breast cancer with a BRCA1/2 mutation.

Nine observational studies investigated the impact of endocrine therapy on survival outcomes, ipsilateral or contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation. The studies included retrospective and prospective cohort studies and a case-control study. There was no studies identified that investigated the effectiveness of endocrine therapies other than tamoxifen.

Study characteristics and quality rating

Table 7 summarises the study characteristics and a quality rating for each included study.⁴⁰ Many of the studies are limited by their retrospective design, small sample sizes, relatively short-follow-up, sampling biases and lack of control for important demographic characteristics, clinical features and treatment factors in the study design or analysis. Table 8 outlines the demographic characteristics, clinical features and treatment factors that were controlled in the design or analysis of each study.

Table 7 Study characteristics and quality of observational studies that investigated the impact of (neoadjuvant/adjvant) systemic therapies in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Design, Period	Study population	Patients	Adjuvant systemic therapy details	Median Age (range) yrs Overall	Ethnicity	Menopause status	Median follow-up (range) years	Quality Rating Limitations Attributes
Arun 2011 ¹⁷	Retrospective cohort study 1997-2009	University of Texas MD Anderson Cancer Center USA	BRCA1/2=80 Non-carriers=237	Chemotherapy	BRCA1 38(21-61) BRCA2 37(22-53) Non-carrier 40(21-73)	White Black Hispanic NS	Not reported	3.2 (0.5-21.6) years	Moderate Limit: retrospective, moderate follow up, small population of BRCA2, non-carriers not representative of sporadic population, patient selection of treatment Attrib: multivariate analysis adjusted for age, clinical tumour stage, ER status, nuclear grade, and use of trastuzumab with NST
Metcalfe, Gershman 2011 ²³	Retrospective cohort study 1975-2008	10 participating cancer genetics clinics in Nth America	BRCA1/2=810	Chemotherapy Endocrine therapy	Mean at diagnosis 42.2(21-65)	Not reported	Not reported	Mean 11.5(0.3-33.1) years	Moderate Limit: retrospective, BRCA1/2 mutation confirmed in family not subject Attrib: large cohort, long follow up, inclusion of deceased cases so no survivorship bias
Metcalfe, Lynch 2011 ¹³	Retrospective cohort study 1975-2008	10 cancer genetics clinics, North America	BRCA1/2=396	Chemotherapy Endocrine therapy Radiotherapy	Mean at diagnosis 42.4(21-65)	Not reported	Not reported	Mean 10.5(0.9-27.1) years	Moderate Limit: retrospective, no control/non carriers, untested women (BRCA1/2 mutation confirmed in family no subject) Attrib: large cohort, long follow up, inclusion of deceased cases so no survivorship bias

Author Year	Design, Period	Study population	Patients	Adjuvant systemic therapy details	Median Age (range) yrs Overall	Ethnicity	Menopause status	Median follow-up (range) years	Quality Rating Limitations Attributes
Goodwin 2012 ¹⁶	Prospective cohort study 1995-2000	Population-based cancer registries (Ontario, northern California, Australia)	BRCA1=93 BRCA2=71 Sporadic =1550	Chemotherapy Endocrine therapy	Mean at diagnosis 45.3(39.9-45.7)	Not reported	Reported	Mean 7.9 years	Moderate Limit: relatively small number of BRCA1/2 mutation carriers and small number of events Attrib: prospective cohort study, international, controlled for important demographic characteristics, clinical features and treatment factors; mean follow-up 7.9 years
Bryski 2010 ¹⁸	Retrospective cohort study 1996-2009	Poland 18 hospitals	BRCA1=102	Neoadjuvant chemotherapy	Mean 42.1 (26-50)	Not reported	Not reported	Not reported	Low Limit: retrospective, small population, no median follow up reported, not all cases matched to control, missing data, no survival analysis Attrib: data given on each regimen
Pierce 2010 ⁷	Retrospective cohort study 2001-	Multi-institutional : USA, Spain, Israel and Australia and New Zealand (kConFab)	BRCA1/2=655	Chemotherapy Endocrine therapy	BCT 40.5(20.1-85.0) M 41.9(23.6-81.5)	Reported	Pre-Menopause: BCT=79.5% M=68 %	8.2-8.9 years Data projected to 15 years	High Limit: retrospective, longevity bias Attrib: Large sample size, good study design — compared women with a BRCA1/2 mutation after BCT and mastectomy, long median follow-up, controlled for important demographic characteristics, clinical features and treatment factors

Author Year	Design, Period	Study population	Patients	Adjuvant systemic therapy details	Median Age (range) yrs Overall	Ethnicity	Menopause status	Median follow-up (range) years	Quality Rating Limitations Attributes
Reding 2010 ²¹	Matched (1:2) case-control study 1985-2000	5 cancer registries (4 USA, 1 Denmark)	BRCA1/2=181 Non-carriers=1992	Chemotherapy Endocrine therapy	Mean at diagnosis 38.3-46.5	White Hispanic Black Asian	Not reported	4.2-5.1 years	Moderate Limit: retrospective, no follow up time (but not survival analysis) Attribute: large cohort, matched case-control (birth, year of diagnosis, registry region, and race), controlled for multiple variables
Bryski 2008 ¹⁹	Retrospective cohort study 1997	Poland, 18 hospitals	BRCA1=44 Non-carriers =41	Neoadjuvant chemotherapy	BRCA1 Mean 42.3 Non-carriers Mean 42.0	Not reported	Not reported	Not reported	Low. Limit: retrospective, small population, no median follow up reported, not all cases matched to control, missing data, no survival analysis Attrib: treatment/regimen, tumour, response data for each patient presented individually
Fourquet 2009 ²⁰	Retrospective cohort study Jan 1991-Jul 1998	Institut Curie, Paris, France	BRCA1=28 BRCA2=9 Non-carrier=53	Chemotherapy Radiotherapy	BRCA1 37.5(25-74) BRCA2 36(29-58) Non-carriers 44(27-68)	Not reported	BRCA1 Pre 86% Post 11% HRT 3% BRCA2 Pre 67% Post 22% HRT 11% Non-carrier Pre 79% Post 15% HRT 6%	Not reported	Moderate Limit: small cohort, retrospective, Attrib: BRCA1 and 2, clinical response to chemo/RT

Author Year	Design, Period	Study population	Patients	Adjuvant systemic therapy details	Median Age (range) yrs Overall	Ethnicity	Menopause status	Median follow-up (range) years	Quality Rating Limitations Attributes
Rennert 2007 ¹⁵	Retrospective cohort study 1987-1988	Israel National Cancer Registry	BRCA1 =78 BRCA2 =53 BRCA1/2 =4 Non-carriers =1659	Chemotherapy	Jews 58.8(± 14.0) Non-Jews 49.7(± 9.9)	Jews (Ashkenazi, Sephardi, Iraqi Jews, Israeli Jews, 'other') and non-Jews	Not reported	All subjects were followed for a minimum of 10 years	High Limit: retrospective, only 3 Ashkenazi Jewish Founder mutations tested, cohort from Israel only, tumour grade and estrogen receptor status not routinely recorded. Attrib: moderately large sample size, controlled for demographic characteristics, clinical features and treatment factors, long follow-up
Brekelmans 2006 ¹⁴	Retrospective cohort study 1980-2001 Matched for age and year of treatment	Family Cancer Clinic, Rotterdam, Netherlands	BRCA1-unselected =170 BRCA-late-tested index =53 Sporadic=446	Chemotherapy	39(23-82)	Not reported	Not reported	5.1 (0.1-21.9) years	Moderate Limit: retrospective, median-long follow up Attrib: separation of late-tested patients to correct for longevity bias, moderately large sample size, controlled for important demographic characteristics, clinical features and treatment factors

Author Year	Design, Period	Study population	Patients	Adjuvant systemic therapy details	Median Age (range) yrs Overall	Ethnicity	Menopause status	Median follow-up (range) years	Quality Rating Limitations Attributes
Gronwald 2006 ²²	Case-Control study Cancer diagnosis 1971-2000	49 centres, 10 countries	BRCA1/2=285	Endocrine therapy	Age of 1st breast cancer: Risk-reducing 40.1 (mean)± 7.5 Unilateral 41.0± 7.5 Age of 2nd breast cancer: Risk-reducing 45.8±8.0	Country of residence reported	Reported	7.4 years [controls (matched to case)]	Good Limit: moderate follow-up (but 1971-2000), no ER status, tamoxifen use by patient recall Attrib: case-control, large cohort, long follow up, controlled for other treatments received (radiotherapy and chemotherapy), smoking (ever/never), parity and oral contraceptive use (ever/never), place of residence,
Pierce 2006 ¹²	Retrospective cohort study 1980-1987	Multi-institutional : USA, Canada, Israel	BRCA1/2=160 Sporadic =445	Chemotherapy Endocrine therapy	BRCA1/2 40.1 (21.9-74.3) Sporadic 41.0 (22.6-75.1)	White: BRCA1/2 =91% Sporadic =83%	Pre-Menopause: BRCA1/2 =74% Sporadic =75%	6.7-7.9 years Data projected to 15 years	High Limit: retrospective, longevity bias Attrib: large sample size, medium follow-up, controlled for important demographic characteristics, clinical features and treatment factors

Author Year	Design, Period	Study population	Patients	Adjuvant systemic therapy details	Median Age (range) yrs Overall	Ethnicity	Menopause status	Median follow-up (range) years	Quality Rating Limitations Attributes
Robson 2004 ⁹	Retrospective cohort study 1980-1995	Two databases Memorial Sloan-Kettering Cancer Center Sir Mortimer B. Davis-Jewish General Hospital USA	BRCA1/2=56 Non-carriers =440	Chemotherapy Endocrine therapy	Control 31%<50yr BRCA1 70%<50yr BRCA2 29%<50yr	Ashkenazi Jewish	Not reported	9.6 years	Moderate Limits: retrospective combined cohorts, non-randomised Attrib: moderate size cohort of Ashkenazi, Moderate-long follow up, multivariate analysis accounts for most variables
Foulkes 2002 ²⁴	Retrospective cohort study 1980-1995	Not reported	BRCA1=31	Endocrine therapy	Not reported	Ashkenazi Jewish	Not reported	8.9 years	Low-Moderate Limit: correspondence (not full paper), retrospective, small cohort Attrib: multivariate survival analysis, proportional hazards model, moderate-long follow up.

BCT Breast conserving treatment (breast conserving surgery and radiotherapy)
M Mastectomy
HBC Non-specified hereditary breast cancer (Non-carriers and non-tested familial cases)
NST Neoadjuvant systemic chemotherapy
NS no statistically significant difference

Table 8 Demographic characteristics, clinical features and treatment factors that were controlled in the design or analysis of each observational studies that investigated the impact of (neoadjuvant/adjvant) systemic therapies in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Demographic characteristics, clinical features and treatment factors that were controlled in the design or analysis of each study									
	BRCA1 or 2	Age at diagnosis	Menopause status	Year of treatment	Tumour size/ T stage	Positive axillary nodes	ER positive	Endocrine therapy	Chemotherapy	RRSO
Reding 2010 ²¹	Reported	Reported Matched and included in regression analysis	Reported No significant difference between groups	Reported Matched	Reported No significant difference between groups	Not reported	Reported No significant difference between groups	Reported No significant difference between groups	Reported No significant difference between groups	Not reported
Goodwin 2012 ¹⁶	Reported	Reported Tested in multivariate analysis	Reported	Reported Tested in multivariate analysis (year of diagnosis)	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Not reported
Arun 2011 ¹⁷	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Not reported	Not reported	Reported Tested in multivariate analysis	Reported	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Study pre-surgery
Metcalfe, Gershman 2011 ²³	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Not reported	Not reported	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis

Author Year	Demographic characteristics, clinical features and treatment factors that were controlled in the design or analysis of each study									
	BRCA1 or 2	Age at diagnosis	Menopause status	Year of treatment	Tumour size/ T stage	Positive axillary nodes	ER positive	Endocrine therapy	Chemotherapy	RRSO
Metcalfe, Lynch 2011 ¹³	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Not reported	Not reported	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis				
Pierce 2010 ⁷	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Not reported	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis				
Fourquet 2009 ²⁰	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Not reported	Not reported	Reported Tested in multivariate analysis	Not reported	Reported Tested in multivariate analysis	Not reported	Reported Clinical response to chemotherapy tested	Not reported
Bryski 2008 ¹⁹	Reported	Reported Matched	Not reported	Reported Matched	Not reported	Not reported	Not reported	Not reported	Reported Testing with Fishers Exact	Not reported
Rennert 2007 ¹⁵	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Not reported	Not reported	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported	Not reported	Reported Tested in multivariate analysis	Not reported

Author Year	Demographic characteristics, clinical features and treatment factors that were controlled in the design or analysis of each study									
	BRCA1 or 2	Age at diagnosis	Menopause status	Year of treatment	Tumour size/ T stage	Positive axillary nodes	ER positive	Endocrine therapy	Chemotherapy	RRSO
Brekelmans 2006 ¹⁴	Reported Tested in multivariate analysis	Reported Matched	Not reported	Reported Matched (year of diagnosis)	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis			
Gronwald 2006 ²²	Reported Tested in multivariate analysis	Reported Matched	Reported Tested in multivariate analysis	Reported Matched	Not reported	Not reported	Not reported	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis
Pierce 2006 ¹²	Not reported	Reported Matched	Reported No Significance between groups	Reported Matched (year of diagnosis)	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis			
Robson 2004 ⁹	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Not reported	Not reported	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Reported No Significant difference between groups	Reported No Significant difference between groups	Not reported
Foulkes 2002 ²⁴	Reported Tested in multivariate analysis	Not reported	Not reported	Not reported	Reported Tested in multivariate analysis	Reported Tested in multivariate analysis	Not reported			

Outcomes

Tables 9-14 outline the data about the impact of systemic therapies on outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation.

Part A Chemotherapy: women with a BRCA1/2 mutation

Adjuvant chemotherapy and survival outcomes

Four studies investigated the impact of adjuvant chemotherapy on survival in women diagnosed with breast cancer with a BRCA1/2 mutation (see Table 9).^{9, 14-16}

Goodwin et al (2012) in a large prospective cohort study [BRCA1 mutation n=93; BRCA2 mutation n=71] found that the risk of distant recurrence and death in women with a BRCA1 mutation, with and without adjuvant chemotherapy, did not differ significantly to women with sporadic breast cancer.¹⁶ (Distant recurrence BRCA1 vs sporadic with chemotherapy: Multivariate HR 0.80 [0.48-1.33], p=0.39; Death BRCA1 vs sporadic with chemotherapy: HR 0.96 [0.57-1.6], p=0.86). In women with a BRCA2 mutation who received adjuvant chemotherapy, the risk of distant recurrence and death did not significantly differ compared to women with sporadic breast cancer. However, Goodwin et al (2012) found that in women with a BRCA2 mutation who did not receive adjuvant chemotherapy, the risk of death was significantly increased compared with women with sporadic breast cancer who did not receive adjuvant chemotherapy (multivariate HR 3.62, 95% CI [1.46 to 8.99]). In contrast, risk of death was found to be similar in women with a BRCA2 mutation and women with sporadic disease when adjuvant chemotherapy was administered (HR 0.94, 95% CI [0.54 -1.65]). The study had a mean follow-up of 7.9 years.

Brekelmans et al (2006) in a retrospective cohort study [BRCA1 mutation n=170] found no significant difference in breast cancer-specific survival in women diagnosed with breast cancer with a BRCA1 mutation with and without adjuvant chemotherapy.¹⁴ However, there was a trend towards improvement in breast cancer-specific survival with adjuvant chemotherapy (multivariate HR 0.36 [0.12-1.03], p=0.06). The study also found that there was no significant difference in breast cancer-specific survival, in women who received adjuvant chemotherapy and women who did not receive adjuvant chemotherapy, between women with a BRCA1 mutation and women with sporadic breast cancer. The study had a median follow-up of 5.1 years.

Rennert et al (2007) in a retrospective cohort study (BRCA1 mutation n=67; BRCA2 mutation n=46) found no significant difference in breast cancer-specific survival at 10 years in Jewish women diagnosed with breast cancer with a BRCA1 mutation or women with a BRCA2 mutation, with and without adjuvant chemotherapy.¹⁵ The study also found no significant difference in 10-year breast cancer-specific survival between women with a BRCA1 mutation, or a BRCA2 mutation, *and women without a BRCA mutation*, with adjuvant chemotherapy (BRCA1 mutation to non-carriers with chemotherapy= multivariate HR 0.48 [0.19-1.21], p=0.12; BRCA2 mutation-no HR data shown) and without adjuvant chemotherapy (BRCA1 to non-carriers without chemotherapy= multivariate HR 0.93 [0.43-2.02], p=0.86; BRCA2 mutation-no HR data shown).

Robson et al (2004) in a small retrospective cohort study [BRCA1/2 mutation n=56] of Ashkenazi Jewish women found that women with a BRCA1 mutation (n=42) who received adjuvant chemotherapy did not have worse breast cancer-specific survival after breast

conserving treatment at 10 years compared to women with sporadic breast cancer.⁹ However, the study found that Ashkenazi Jewish women with a BRCA1 mutation *who did not receive* adjuvant chemotherapy had worse breast cancer-specific survival after breast conserving treatment at 10 years compared to women with sporadic breast cancer (multivariate HR 4.8, 95% CI [2.0–11.7], p=0.001).

Neoadjuvant chemotherapy and survival outcomes

One small retrospective cohort study [BRCA1/2 mutation n=80] investigated the effectiveness of neoadjuvant chemotherapy (including anthracycline-taxanes, anthracycline-non taxane or taxane) on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation.¹⁷ Arun et al (2011) found no significant difference in breast cancer-specific survival or overall survival at five years in women diagnosed with breast cancer with a BRCA1/2 mutation who received neoadjuvant chemotherapy compared to women without a BRCA1/2 mutation.¹⁷ In addition, the study found that women with a BRCA1 mutation who had a pathological complete response (pCR) were found to have a better overall survival and five year relapse-free survival than women who did not have a pCR. The study was limited by a short median follow-up period of 3.2 years.

Table 9 Impact of adjuvant chemotherapy on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Patients	Median follow-up (years)	Survival outcomes: Breast cancer-specific survival (BCSS) Risk of death	Cases	Controls	P value/ HR Multivariate
Goodwin 2012 ¹⁶	BRCA1 =93 BRCA2 =71 Sporadic =1550	Mean 7.9 years	No significant difference in the risks of distant recurrence and death in women with a BRCA1 mutation and women with sporadic breast cancer (with and without chemotherapy) No significant difference in the risks of distant recurrence and death in women with a BRCA2 mutation and women with sporadic breast cancer (with chemotherapy) In women who did not receive adjuvant chemotherapy, risk of death was significantly increased in women with a BRCA2 mutation compared with those with sporadic breast cancer .	Distant recurrence / BRCA1 / chemotherapy Risk of death/ BRCA1 / chemotherapy Risk of death/ BRCA2 / chemotherapy Risk of death/ BRCA2 / no chemotherapy	Distant recurrence/ sporadic/ chemotherapy Risk of death/ sporadic/ chemotherapy Risk of death/ sporadic/ chemotherapy Risk of death/ sporadic/ no chemotherapy	HR 0.80 [0.48-1.33] p=0.39 HR 0.96 [0.57-1.6] p=0.86 HR, 0.94 95% CI [0.54-1.65] HR, 3.62 95% CI [1.46-8.99]
Breklemans 2006 ¹⁴	BRCA1-unselected=170 BRCA1-late-tested index=53 Sporadic=446	5.1 years	No significant difference in BCSS in BRCA1 mutation carriers with and without chemotherapy. No significant difference in BCSS in BRCA1 mutation carriers compared to sporadic controls, with and without chemotherapy.	BCSS/ BRCA1-unselected/ chemotherapy BCSS/ BRCA1-unselected/ chemotherapy BCSS/ BRCA1-unselected / no chemotherapy	BCSS/ BRCA1-unselected/ no chemotherapy BCSS/ sporadic/ chemotherapy/ BCSS/ sporadic/ no chemotherapy	HR 0.36 [0.12-1.03] p=0.06 HR=1.39 p=0.28 HR=1.04 p=0.89

Author Year	Patients	Median follow-up (years)	Survival outcomes: Breast cancer-specific survival (BCSS) Risk of death	Cases	Controls	P value/ HR Multivariate
Rennert 2007 ¹⁵	Jewish women BRCA1=67 BRCA2=46 Non- carriers=992	10 years	For BCSS, no significant interaction between BRCA status and chemotherapy No significant difference in BCSS in BRCA1 mutation carriers, or in BRCA2 mutation carriers compared with non- carriers, with and without chemotherapy	BCSS/ BRCA1/ chemothera py BCSS/ BRCA2/ chemothera py BCSS/ BRCA1/ chemothera py 71% BCSS/ BRCA1/ no chemothera py 76%	BCSS/ BRCA1/ no chemothera py BCSS/ BRCA2/ no chemothera py BCSS/ non- carriers/ chemothera py/ 46% BCSS/ non- carriers / no chemothera py 74%	p=0.21 p=0.70 HR 0.48 [0.19- 1.21] p=0.12 HR 0.93 [0.43- 2.02] p=0.86
Robson 2004 ⁹	BRCA1=42 BRCA2=13 Non- carriers=440	9.6 years	BRCA1 mutation carriers who had chemotherapy did not have worse breast cancer-specific survival compared to non-carriers who had chemotherapy BRCA1 mutation carriers who did not have chemotherapy had worse breast cancer-specific survival compared to non-carriers who did not have chemotherapy	BCSS/ BRCA1/ chemothera py BCSS/ BRCA1 / no chemothera py	BCSS/ non- carriers / chemothera py BCSS/ non- carriers / no chemothera py	HR 1.5 [0.66- 3.49] p=0.33 HR 4.8 [2.0- 11.7] p=0.001

BCSS breast cancer-specific survival

Response rate

Four small retrospective cohort studies investigated the type of neoadjuvant chemotherapy on the rates of pathological complete response (pCR) in women diagnosed with breast cancer with a BRCA1/2 mutation.¹⁷⁻²⁰

One study investigated the effectiveness of platinum-based chemotherapy in women diagnosed with breast cancer with a BRCA1 mutation. Byrski et al (2010) found that women diagnosed with breast cancer with a BRCA1 mutation had a better response in terms of the rates of pCR to platinum-based chemotherapy compared to other types of neoadjuvant chemotherapy (such as cyclophosphamide, methotrexate and fluorouracil (CMF) or anthracycline-taxanes combination).¹⁸

Three studies investigated the effectiveness of taxane based chemotherapy in women diagnosed with breast cancer with a BRCA1/2 mutation.

Arun et al (2011) found that anthracycline-taxane based chemotherapy is as effective for women diagnosed with breast cancer with a BRCA1/2 mutation as non-BRCA1/2 carriers in terms of the rates of pCR.¹⁷

Byrski et al (2008) found that women with a BRCA1 mutation are less sensitive to taxanes compared to anthracyclines (without taxanes) or other non-taxane regimens in terms of partial or complete response.¹⁹ Overall, women with a BRCA1 mutation who received neoadjuvant chemotherapy were less likely to experience a partial or complete response than non-BRCA1 carriers (80% vs 95% $p=0.05$). The study also found that among women with a BRCA1 mutation, the response rate (complete or partial) to anthracycline-taxane (docetaxel with doxorubicin) was lower than for women given non-taxane chemotherapies ($p=0.001$).

Fourquet et al (2009) found that women diagnosed with breast cancer with a BRCA1/2 mutation have a better response rate of complete clinical response to anthracyclines (without taxanes) compared to non-BRCA carriers (46% vs 17%; $p=0.008$).²⁰

Ipsilateral breast cancer

Two large retrospective cohort studies investigated the impact of adjuvant chemotherapy on the risk of ipsilateral breast cancer (recurrence of the primary or a second primary) in women diagnosed with breast cancer with a BRCA1/2 mutation (see Table 10).^{7, 13}

Metcalfe, Lynch et al (2011) investigated the treatment predictors of nonsynchronous ipsilateral breast cancer in women diagnosed with breast cancer and a BRCA1/2 mutation ($n=396$) after breast conserving surgery.¹³ The study found that chemotherapy after breast conserving surgery significantly decreased the risk of ipsilateral breast cancer compared to women who did not receive chemotherapy, at 10 ten years (multivariate RR 0.45, 95% CI [0.24–0.84], $p=0.01$).

Pierce et al (2010) compared the long-term outcome following breast conserving treatment (breast conserving surgery and radiotherapy) and mastectomy (29% had radiotherapy) in women with a BRCA1/2 mutation ($n=655$).⁷ Chemotherapy was the only independent predictor of ipsilateral breast cancer in women treated with breast conserving treatment. For women treated with breast conserving treatment there was a large significant increase in the risk of ipsilateral breast cancer in women at 15 years who did not receive chemotherapy compared to women who received chemotherapy (multivariate HR 5.4 [2.3–13.3], $p<0.0001$).

Pierce et al (2010) found that while more ipsilateral breast cancers were observed in women treated with breast conserving treatment (breast conserving surgery and radiotherapy) *and* chemotherapy compared to a mastectomy (with and without radiotherapy), the results did not significantly differ (i.e., 8.1 vs 3.5% at 10 years; 10.7 vs 5.5% at 15 years, respectively; p=0.08).

Table 10 Impact of adjuvant chemotherapy on ipsilateral breast cancer (recurrence of the primary or a second primary) in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Patients	Median follow-up (years)	Ipsilateral breast cancer significantly different between cases/control	Ipsilateral breast cancer cases	Ipsilateral breast cancer controls	P value/ HR Multivariate
Metcalfe, Lynch 2011 ¹³	BRCA1/2=396	Mean 10.5 years Data projected to 10 years	BRCA1/2 mutation carriers who had chemotherapy had a significantly lower risk of ipsilateral breast cancer compared to BRCA1/2 mutation carriers who did not have chemotherapy	BRCA1/2/ BCT/ chemotherapy	BRCA1/2 /BCT/ no chemotherapy	RR 0.45 [0.24–0.84] p= 0.01
Pierce 2010 ⁷	BRCA1/2=655	8.2-8.9 years Data projected to 15 years	Significant increase in the risk of ipsilateral breast cancer in BRCA1/2 mutation carriers who did not receive chemotherapy compared BRCA1/2 mutation carriers who received chemotherapy	BRCA1/2/ BCT/ chemotherapy	BRCA1/2/ BCT/ no chemotherapy	HR 5.4 [2.3-13.3] p<0.0001

BCT Breast conserving treatment (breast conserving surgery and radiotherapy)
M Mastectomy

Contralateral breast cancer

Two large studies, one retrospective cohort study and one case-control study, investigated the impact of adjuvant chemotherapy on the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation (See Table 11).^{21, 23}

Metcalfe, Gershman et al (2011) in a retrospective cohort study investigated the predictors of contralateral breast cancer in 810 women diagnosed with breast cancer with a BRCA1/2 mutation [BRCA1 mutation n=498; BRCA2 mutation n=300; BRCA1 & 2 mutation n=12].²³ Overall, 149 women (18.4%) developed a contralateral breast cancer (mean follow-up of 11.5 years). The 15-year risk of developing a contralateral breast cancer was 36.1% for women with a BRCA1 mutation and was 28.5% for women with a BRCA2 mutation. The study reported that chemotherapy was not associated with a significant reduction in the risk of contralateral breast cancer (Multivariate RR 0.99 [0.67–1.45], p=0.94). The study also found that women younger than 50 years of age at the time of breast cancer diagnosis were significantly more likely to develop a contralateral breast cancer at 15 years, compared with women older than 50 years (37.6 vs 16.8%; p=0.003).

However, Reding et al (2010) in a case-control study [BRCA1/2 mutation n=181] found that chemotherapy was associated with a significant and large decrease in the risk of contralateral breast cancer for women diagnosed with breast cancer with a BRCA1 mutation (multivariate RR 0.5 [0.1-1.61]) and women with a BRCA2 mutation (RR 0.3 [0.1-1.0]).²¹ Overall, the risk reduction for women diagnosed with breast cancer with a BRCA1/2 mutation with chemotherapy was reported as multivariate RR 0.5 [0.2-1.0], p=0.04. The study did not find a significant difference between the relative risk of contralateral breast cancer with chemotherapy in women diagnosed with breast cancer with a BRCA1 mutation, or a BRCA2 mutation, and non-BRCA1/2 carriers (p=0.34). Unlike Metcalfe et al (2011) the study by Reding et al (2010) did not include deceased cases to eliminate the potential for survival bias. The study had a mean follow-up of 4.2 to 5.1 years.

Table 11 Impact of adjuvant chemotherapy on contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Patients	Median follow-up (years)	Contralateral breast cancer	Contralateral breast cancer cases	Contralateral breast cancer controls	P value/ HR Multivariate
Metcalfe, Gershman 2011 ²³	BRCA1=498 BRCA2=300 BRCA1&2=12	Mean 11.5 years Data projected to 15 years	No significant difference between rates of contralateral breast cancer in women with a BRCA1/2 mutation with and without chemotherapy	BRCA1/2 / chemotherapy	BRCA1/2 / no chemotherapy	RR 0.99 [0.67-1.45] p=0.94
Reding 2010 ²¹	BRCA1/2 =181 Non-carriers=1992	Mean 4.2-5.1 years	Chemotherapy was associated with a significant and large decrease in the risk of contralateral breast cancer for women with a BRCA1 or BRCA2 mutation No significant difference between the relative risk of contralateral breast cancer with chemotherapy in women with a BRCA1 mutation or BRCA2 mutation and non-carriers Significant difference in reduction in the risk of contralateral breast cancer with CAF/CEF regimens in women with a BRCA1/2 mutation (no significant difference found in non-carriers)	BRCA1/2 / chemotherapy BRCA1 / chemotherapy BRCA2 / chemotherapy BRCA1/2 / chemotherapy BRCA1/2 / CAF/CEF regimens Non-carriers / CAF/CEF regimens	BRCA1/2 / no chemotherapy BRCA1 / no chemotherapy BRCA2 / no chemotherapy Non-carriers / chemotherapy BRCA1/2 / No CAF/CEF regimens Non-carriers / No CAF/CEF regimens	RR 0.5 [0.2-1.0] p=0.04 RR 0.5 [0.1-1.61] RR 0.3 [0.1-1.0] p=0.34 RR 0.3 [0.1-0.81] RR 0.3 [0.1-0.8] RR 0.8 [0.5-1.2]

CAF/CEF

Cyclophosphamide epirubicin/adriamycin, 5-fluorouracil

Part B Endocrine therapy: women with a BRCA1/2 mutation

Nine observational studies investigated the impact of endocrine therapy on survival outcomes, ipsilateral breast cancer or contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation. The studies included retrospective and prospective cohort studies and a case-control study.

All the studies identified assessed the effectiveness of tamoxifen and no studies were identified that assessed the effectiveness of aromatase inhibitors or raloxifene in women diagnosed with non-metastatic breast cancer with a BRCA1/2 mutation.

Survival outcomes

Three studies, including one large prospective cohort study and two small retrospective cohort studies, investigated the impact of endocrine therapy on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation (see Table 12).^{9, 16, 24}

Goodwin et al (2012) in a large prospective cohort study (with a mean follow-up of 7.9 years) found no significant difference in the risk of distant recurrence or death in women with a BRCA1 mutation compared to women with sporadic breast cancer, with and without tamoxifen.¹⁶ There was also no significance difference found in the risk of distant recurrence in women with a BRCA2 mutation compared to women with sporadic breast cancer, with and without tamoxifen. However, in women who had a BRCA2 mutation who received tamoxifen, the risk of death was found to be significantly increased compared with women with sporadic breast cancer who received tamoxifen (HR 2.05 [1.07-3.91], p=0.03). This result was not seen in women with a BRCA2 mutation who did not receive tamoxifen (HR 0.69 [0.32-1.49]).

Robson et al (2004) in a small retrospective cohort study of Ashkenazi Jewish women diagnosed with breast cancer [BRCA1/2 mutation n=56] found there was no significant difference in breast cancer-specific survival among women who received tamoxifen with a BRCA1 mutation compared to women with sporadic breast cancer, at 10 years (multivariate HR 0.5, 95% CI [0.05-5.0], p=0.55).⁹ However, the study found a significantly lower breast cancer-specific survival among women *who did not receive* tamoxifen with a BRCA1 mutation compared to women with sporadic breast cancer, at 10 years (multivariate HR 3.5, 95% CI [1.7-7.2], p=0.001). The study was limited by the small sample size of women who received tamoxifen (n=10 received tamoxifen; n=30 did not receive tamoxifen).

Foulkes et al (2002) in a small retrospective cohort study of Ashkenazi Jewish women diagnosed with breast cancer [BRCA1 mutation n=31] did not find any significant difference in the relative risk of death from breast cancer among women who received tamoxifen with a BRCA1 mutation compared to women without a BRCA1 mutation (multivariate RR 0.30 [0.04-2.49], p=0.27).²⁴ However, the study found that there was a significantly higher relative risk of death from breast cancer among women who *did not receive* tamoxifen with a BRCA1 mutation compared to women without a BRCA1 mutation (multivariate RR 2.16 [1.0-4.68], p=0.05). The median follow-up time of the study was 8.9 years.

Table 12 Impact of endocrine therapy on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Patients	Median follow-up (years)	Survival outcomes: Breast cancer-specific survival (BCSS) Risk of death	Cases	Controls	P value/ HR Multivariate
Goodwin 2012 ¹⁶	BRCA1 =93 BRCA2 =71 Sporadic =1550	Mean 7.9 years	No significant difference in the risks of distant recurrence or death between women with a BRCA1 mutation and women with sporadic breast cancer, with and without tamoxifen A significantly increased risk of death between women with a BRCA2 mutation and women with sporadic breast cancer with tamoxifen No significant difference in the risk of distant recurrence between women with a BRCA2 mutation and women with sporadic breast cancer , with and without tamoxifen	Distant recurrence BRCA1 / tamoxifen Risk of death/ BRCA1 / tamoxifen Risk of death/ BRCA2 / tamoxifen Distant recurrence / BRCA1 / tamoxifen	Distant recurrence/ sporadic/ tamoxifen Risk of death/ sporadic/ tamoxifen/ Risk of death/ sporadic/ tamoxifen Distant recurrence/ sporadic/ tamoxifen	HR 1.02 [0.43-2.42] p=0.97 HR 1.49 [0.65-3.41] p=0.34 HR 2.05 [1.07-3.91] p=0.03 p =0.58
Robson 2004 ⁹	BRCA1 =42 BRCA2 =13 BRCA1&2=1 Non-carriers =440	9.6 years	Significantly lower BCSS among women who did not receive tamoxifen who had a BRCA1 mutation compared to women without a BRCA1 mutation No significant difference in BCSS among women who received tamoxifen who had a BRCA1 mutation compared to women without a BRCA1 mutation	BCSS/ No tamoxifen / BRCA1 BCSS/ tamoxifen/ BRCA1	BCSS/ No tamoxifen/ non-carriers BCSS/ tamoxifen/ non-carriers	HR 3.5 [1.7-7.2] p=0.001 HR 0.5 [0.05-5.0] p=0.55

Author Year	Patients	Median follow-up (years)	Survival outcomes: Breast cancer-specific survival (BCSS) Risk of death	Cases	Controls	P value/ HR Multivariate
Foulkes 2002 ²⁴	BRCA1 =31	8.9 years	A significantly higher relative risk of death from breast cancer among women who did not receive tamoxifen who had a BRCA1 mutation compared to women without a BRCA1 mutation No significant difference in the relative risk of death from breast cancer among women who received tamoxifen who had a BRCA1 mutation compared to women without a BRCA1 mutation	Risk of death from breast cancer / BRCA1 / no tamoxifen Risk of death from breast cancer / BRCA1 / tamoxifen	Risk of death from breast cancer / non-carriers / no tamoxifen Risk of death from breast cancer / non-carriers / tamoxifen	RR 2.16 [1.0-4.68] p=0.05 RR 0.30 [0.04-2.49] p=0.27

BCSS breast cancer-specific survival

Ipsilateral breast cancer

Three retrospective cohort studies investigated the impact of endocrine therapy on the risk of ipsilateral breast cancer (recurrence of the primary or a second primary) in women with breast cancer with a BRCA1/2 mutation (see Table 13).^{7, 12, 13}

Metcalfe, Lynch et al (2011) in a retrospective cohort study investigated the treatment predictors of nonsynchronous ipsilateral breast cancer in women with breast cancer and a BRCA1/2 mutation (n=396) after breast conserving surgery.¹³ The study found that tamoxifen had no effect on the risk of ipsilateral breast cancer at 10 years in women diagnosed with breast cancer with a BRCA1/2 mutation (multivariate RR 0.86 [0.36-2.02], p=0.73) or when women with a BRCA1 mutation or BRCA2 mutation were considered separately (compared to no tamoxifen).

Pierce et al (2010) in a large retrospective study also did not find any significant reduction in the risk of ipsilateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation who received tamoxifen (compared to no tamoxifen) after breast conserving treatment (breast conserving surgery and radiotherapy), at 15 years.⁷ However, there was a trend towards reduction particularly in women with a BRCA2 mutation (BRCA1 mutation: p=0.13; BRCA2 mutation: p=0.08).

Pierce et al (2006) in a retrospective cohort study [BRCA1/2 mutation n=160] also did not find any significant reduction in the risk of ipsilateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation who received tamoxifen after breast conserving treatment at 5, 10 and 15 years (multivariate HR 0.29, p=0.22).¹² In addition, the study did not find any significant difference in the risk of ipsilateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation who received tamoxifen (compared to no

tamoxifen) and who had not undergone risk-reducing salpingo-oophorectomy (multivariate $p=0.1$).

Table 13 Impact of endocrine therapy on ipsilateral breast cancer (recurrence of the primary or a second primary) in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Patients	Median follow-up (years)	Ipsilateral breast cancer	Ipsilateral breast cancer cases	Ipsilateral breast cancer controls	P value/ HR Multivariate
Metcalfe, Lynch 2011 ¹³	BRCA1/2 =396	Mean 10.5 years Data projected to 10 years	No significant effect on the risk of ipsilateral breast cancer for women with a BRCA1/2 mutation with tamoxifen or when BRCA1 or BRCA2 were considered separately	BRCA1/2 / BCT / tamoxifen BRCA1 / BCT / tamoxifen BRCA2 / BCT / tamoxifen	BRCA1/2 / BCT / no tamoxifen BRCA1 / BCT / no tamoxifen BRCA2 / BCT / no tamoxifen	RR 0.86 [0.36-2.02] $p=0.73$ RR 0.87 [0.24-3.15] $p=0.83$ RR 1.22 [0.31-4.76] $p=0.77$
Pierce 2010 ⁷	BRCA1/2 mutation= 655 BRCA1/2 + BCT=302 BRCA1/2 + M=353	8.2-8.9 years Data projected to 15 years	No significant reduction in ipsilateral breast cancer in women with a BRCA1 mutation or a BRCA2 mutation after BCT with tamoxifen	BRCA1 / BCT / tamoxifen BRCA2 / BCT / tamoxifen	BRCA1 / BCT / no tamoxifen BRCA2 / BCT / no tamoxifen	BRCA1 $p=0.13$ BRCA2 $p=0.08$
Pierce 2006 ¹²	BRCA1/2 =160 Sporadic =445	6.7-7.9 years Data projected to 15 years	No significant difference in the risk of ipsilateral breast cancer in women with a BRCA1/2 mutation with or without tamoxifen No significant difference in the risk of ipsilateral breast cancer in women with a BRCA1/2 mutation who had not undergone risk-reducing salpingo-oophorectomy with or without tamoxifen	BRCA1/2 / BCT / tamoxifen 0% 0% 22% BRCA1/2 / BCT tamoxifen/ no oophorectomy 0% 0% 0%	BRCA1/2 / BCT / no tamoxifen 5% 14% 25% BRCA1/2 / BCT no tamoxifen/ no oophorectomy 8% 17% 31%	HR 0.29 $p=0.22$ 5 years 10 years 15 years $p=0.1$ 5 years 10 years 15 years

BCT Breast conserving treatment (breast conserving surgery and radiotherapy)
M Mastectomy

Contralateral breast cancer

Four published studies, including two retrospective cohort studies and two case-control studies,^{12, 21-23} and one conference abstract⁵⁷ investigated the impact of endocrine therapy on the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation (see Table 14).

Phillips et al (2011), in a conference abstract, investigated the impact of tamoxifen on the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1 mutation (n=1642) or a BRCA2 mutation (n=919).⁵⁷ Twenty-three percent of women with a BRCA1 mutation received tamoxifen (n=374) and 48% of women with a BRCA2 mutation received tamoxifen. The study found that tamoxifen significantly decreased the risk of contralateral breast cancer in women with a BRCA1 mutation (HR 0.31 [0.22-0.45]) and a BRCA2 mutation (HR 0.24 [0.16-0.35]). The study adjusted for year of birth, age at diagnosis, country, risk-reducing salpingo-oophorectomy and risk-reducing contralateral mastectomy.

Metcalfe, Gershman et al (2011) in a retrospective cohort study investigated the predictors of contralateral breast cancer in 810 women diagnosed with breast cancer with a BRCA1/2 mutation [BRCA1 n=498, BRCA2 n=300, BRCA1&2 n=12].²³ Overall, 149 women (18.4%) developed a contralateral breast cancer (mean follow-up of 11.3 years). The 15-year risk of developing a contralateral breast cancer was 36.1% for women with a BRCA1 mutation and 28.5% for women with a BRCA2 mutation. Tamoxifen was taken by 268 (33.1%) women in the study. The study found that tamoxifen was not associated with a significant reduction in the risk of contralateral breast cancer (Multivariate RR 0.72 [0.47–1.12], p=0.14) in women with a BRCA1/2 mutation or when women with a BRCA1 mutation or BRCA2 mutation were considered separately (BRCA1 mutation: Multivariate RR 0.61 [0.33-1.13], p=0.12; BRCA2 mutation: Multivariate RR 0.86 [0.43-1.73], p=0.68). The study also found that women younger than 50 years of age at the time of breast cancer diagnosis were significantly more likely to develop a contralateral breast cancer at 15 years, compared with women older than 50 years (37.6 vs 16.8%; p=0.003).

Reding et al (2010) in a case-control study [BRCA1/2 mutation n=181] also found that tamoxifen was not associated with a significant decrease in the risk of contralateral breast cancer in women with a BRCA1/2 mutation or when women with a BRCA1 mutation or BRCA2 mutation were considered separately.²¹ The study found a significant reduction in the risk of contralateral breast cancer with tamoxifen in non-BRCA1/2 carriers (p=0.03). However, overall the study did not find any significant difference between the relative risk of contralateral breast cancer with tamoxifen in women with a BRCA1 mutation or BRCA2 mutation and non-carriers (p=0.72). The relative risk of contralateral breast cancer for women with a BRCA1/2 mutation was not found to be modified by risk-reducing salpingo-oophorectomy status, regardless of the timing of the risk-reducing salpingo-oophorectomy. The study did not include deceased cases to eliminate the potential for survival bias. The study had a mean follow-up of 4.2 to 5.1 years.

However, Pierce et al (2006) in a retrospective cohort study reported that tamoxifen significantly decreased the risk of contralateral breast cancer (compared to no tamoxifen) in women diagnosed with breast cancer with a BRCA1/2 mutation (n=160) at 15 years (Multivariate HR 0.31, p=0.05).¹² The study also compared the effect of tamoxifen on the risk of contralateral breast cancer in women with a BRCA1/2 mutation who *did not* have risk-reducing salpingo-oophorectomy and found that the risk reduction with tamoxifen was even greater with 5, 10, and 15 year estimated, with vs without tamoxifen, of 6% vs 19%, 6% vs 41%, and 6% vs 54% respectively (Multivariate HR 0.13, p=0.02). Overall, the study also found that

the risk of contralateral breast cancer (independent of treatment) was significantly greater in women with a BRCA1/2 mutation compared to women with sporadic breast cancer, with 10- and 15-year estimates of 26% and 39% for women with a BRCA1/2 mutation and 3% and 7% for sporadic controls, respectively (Multivariate HR 10.43, $p < 0.0001$).

Gronwald et al (2006) in a large case-control study [BRCA1/2 $n=285$] also reported that tamoxifen significantly decreased the risk of contralateral breast cancer (compared to no tamoxifen) in women diagnosed with breast cancer and a BRCA1/2 mutation or when women with a BRCA1 mutation or BRCA2 mutation were considered separately.²² The study found that the protective effect of tamoxifen was not evident in women who had undergone an oophorectomy but this subgroup was small, unlike the protective effect of tamoxifen seen in women who had not undergone a risk-reducing salpingo-oophorectomy. The study found that there was no protection offered by tamoxifen beyond 10 years of the first breast cancer diagnosis (1-5 years Multivariate OR 0.46 [0.2-0.79], $p=0.005$ vs >10 years Multivariate OR 0.99 [0.13-7.61], $p=0.99$). The study also found that tamoxifen had a protective effect for both pre-menopausal and post-menopausal women. The study did not include deceased cases to eliminate the potential for survival bias.

Table 14 Impact of endocrine therapy on contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Patients	Median follow-up (years)	Contralateral breast cancer	Contralateral breast cancer cases	Contralateral breast cancer controls	P value/ HR Multivariate
Metcalfe, Gershman 2011 ²³	BRCA1=498 BRCA2=300 BRCA1&2 =12	Mean 11.5 years Data projected to 15 years	No significant reduction in the risk of contralateral breast cancer with tamoxifen. in women with a BRCA1/2 mutation or when considered separately	BRCA1/2 / tamoxifen BRCA1 / tamoxifen BRCA2 / tamoxifen	BRCA1/2 / no tamoxifen/ BRCA1 / no tamoxifen BRCA2 / no tamoxifen/	RR 0.72 [0.47-1.12] p=0.14 BRCA1: RR 0.61 [0.33-1.13] p=0.12 BRCA2: RR0.86 [0.43-1.73] p=0.68
Reding 2010 ²¹	BRCA1/2 =181 Non-carriers =1922	Mean 4.2-5.1 years	No significant decrease in the risk of contralateral breast cancer with tamoxifen in women with a BRCA1/2 mutation or when considered separately A significant reduction in the risk of contralateral breast cancer with tamoxifen in non-carriers No significant difference between the relative risk of contralateral breast cancer with tamoxifen in women with a BRCA1 mutation or BRCA2 mutation compared with non-carriers	BRCA1/2 / tamoxifen BRCA1 / tamoxifen BRCA2 / tamoxifen Non-carriers / tamoxifen BRCA1/2 / tamoxifen	BRCA1/2 / No tamoxifen BRCA1 / no tamoxifen BRCA2 / no tamoxifen Non-carriers / no tamoxifen Non-carriers / tamoxifen	RR 0.7 [0.3-1.8] RR 0.2 [0.0-1.3] RR 0.9 [0.5-6.9] RR 0.7 [0.6-1.0] p=0.03 p=0.72

Author Year	Patients	Median follow-up (years)	Contralateral breast cancer	Contralateral breast cancer cases	Contralateral breast cancer controls	P value/ HR Multivariate
Pierce 2006 ¹²	BRCA1/2 =160 Sporadic =445	6.7-7.9 years Data projected to 15 years	A significant decrease in the risk of contralateral breast cancer in women with a BRCA1/2 mutation with tamoxifen The risk reduction with tamoxifen was even greater in women with a BRCA1/2 mutation who did not have bilateral oophorectomy	BRCA1/2 / tamoxifen BRCA1/2 / tamoxifen/ no oophorectomy 6% 6% 6%	BRCA1/2 / no tamoxifen BRCA1/2 / no tamoxifen/ no oophorectomy 19% 41% 54%	HR 0.31 p=0.05 5 yrs 10 yrs 15 yrs HR 0.13 p=0.02 5 yrs 10 yrs 15 yrs
Gronwald 2006 ²²	BRCA1/2 =285	7.4 years [controls (matched to case)]	A significant decrease in the risk of contralateral breast cancer in women with a BRCA1/2 mutation with tamoxifen; and when considered separately, in women with a BRCA1 mutation and women with a BRCA2 mutation. The protective effect of tamoxifen was found only in women who had not undergone an oophorectomy	BRCA1/2 / tamoxifen BRCA1 / tamoxifen BRCA2 / tamoxifen BRCA1/2 /tamoxifen/ oophorectomy BRCA1/2 / tamoxifen/ no oophorectomy	BRCA1/2 / no tamoxifen No tamoxifen / BRCA1 BRCA2 / no tamoxifen BRCA1/2 / No tamoxifen/ oophorectomy BRCA1/2 / No tamoxifen/ no oophorectomy	OR 0.47 [0.3-0.75] p=0.001 OR 0.50 [0.30-0.85] p=0.01 OR 0.42 [0.17-1.02] p=0.05 OR 0.83 [0.24-2.89] p=0.77 OR 0.44 [0.27-0.65] p=0.0009

The effectiveness of poly-adenosine 5-diphosphate-ribosyl polymerase inhibitors in women diagnosed with breast cancer with a BRCA1/2 mutation

No studies were identified that examined the effectiveness of poly-adenosine 5-diphosphate-ribosyl polymerase (PARP) inhibitors in women diagnosed with non-metastatic breast cancer with a BRCA1/2 mutation. Several Phase II trials are currently underway testing the specific DNA-repair deficiency of BRCA-associated tumours with the use of PARP inhibitors in the metastatic setting.

Quality of life and patient preferences in women diagnosed with breast cancer with a BRCA1/2 mutation

No studies were identified that examined quality of life or patient preferences in women diagnosed with breast cancer with a BRCA1/2 mutation.

Part C Systemic therapy: women with a family history and no identified BRCA1/2 mutation; and women with a non-BRCA germline mutation

The impact of systemic therapies on outcomes in women diagnosed with breast cancer with a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation

No studies were identified that examined the impact of systemic therapies on outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation and the risk of contralateral breast cancer in women diagnosed with breast cancer with a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation (including women who have not been proven to have a BRCA1/2 mutation with genetic testing and women who have not had genetic testing).

The impact of systemic therapies on outcomes in women diagnosed with breast cancer with non-BRCA germline mutations

No studies were identified that examined the impact of systemic therapies on outcomes in women diagnosed with breast cancer with non-BRCA germline mutations (such as TP53, PTEN, STK11, RAD51C, CHEK2, ATM, BRIP1, and PALP2).

Endocrine replacement therapy after risk-reducing salpingo-oophorectomy in women diagnosed with breast cancer with a BRCA1/2 mutation

No studies were identified that examined the impact in terms of the risk of a second breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation who take endocrine replacement therapy after risk-reducing salpingo-oophorectomy.

Summary

Are there particular neoadjuvant and adjuvant systemic therapies which are specifically effective for women diagnosed with breast cancer with a BRCA1/2 mutation?

Part A Chemotherapy

Survival outcomes

- In two Level III-2 retrospective cohort studies^{14, 15} in women diagnosed with breast cancer with a BRCA1/2 mutation, adjuvant chemotherapy did not significantly improve breast cancer-specific survival compared to no adjuvant chemotherapy.
- There is evidence from one Level II prospective cohort study¹⁶ and three Level III-2 retrospective cohort studies^{9, 14, 15} that, adjuvant chemotherapy shows similar overall survival and breast cancer specific survival for women with breast cancer with a BRCA1/2 mutation, in comparison to other women with breast cancer.*
- There is evidence from one Level II prospective cohort study¹⁶ and one Level III-2 retrospective cohort study⁹ of patients from four studies (one Level II prospective cohort study and three Level III-2 retrospective cohort studies) that women diagnosed with breast cancer with a BRCA1 mutation⁹ or a BRCA2 mutation¹⁶ who do not receive adjuvant chemotherapy have significantly poorer breast cancer-specific survival⁹ and significantly greater increased risk of death¹⁶ compared to women with breast cancer not attributable to a BRCA1/2 mutation* who do not receive chemotherapy.
- In one Level III-2 retrospective cohort study¹⁷, neoadjuvant chemotherapy shows similar breast cancer-specific survival and overall survival for women with breast cancer with a BRCA1/2 mutation, in comparison to other women with breast cancer.*

Response rate

- In one small Level III-2 retrospective cohort study,¹⁸ women diagnosed with breast cancer with a BRCA1 mutation had significantly better rates of pathological complete response (pCR) to platinum-based chemotherapy, compared to other types of neoadjuvant chemotherapy (such as cyclophosphamide, methotrexate and fluorouracil (CMF) or anthracycline-taxanes).
- There is inconsistent evidence on the effectiveness of taxane based chemotherapy compared to anthracyclines (without taxanes) or other non-taxane regimens, in women with a BRCA 1/2 mutation.^{17, 19}
- In one small Level III-2 retrospective cohort study²⁰ women diagnosed with breast cancer with a BRCA1/2 mutation had significantly better rates of complete clinical response to anthracyclines (without taxanes), compared to other women with breast cancer.*

Ipsilateral breast cancer (recurrence of the primary or a second primary)

- There is evidence from two large Level III-2 retrospective cohort studies^{7, 13} that adjuvant chemotherapy after breast conserving surgery significantly decreases the risk of

* Women with sporadic breast cancer or women who have not been proven to have a BRCA1/2 mutation with genetic testing

ipsilateral breast cancer, compared to no adjuvant chemotherapy in women with a BRCA 1/2 mutation.

Contralateral breast cancer

- In one large Level III-3 case-control study²¹, adjuvant chemotherapy showed similar decreases in risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation, as in other women with breast cancer.*
- There is inconsistent evidence on the effectiveness of adjuvant chemotherapy compared to no adjuvant chemotherapy on the risk of contralateral breast cancer in women with breast cancer with a BRCA 1/2 mutation.^{12, 21-23}

Part B Endocrine therapy

Survival outcomes

- There was no evidence identified that investigated the effectiveness of endocrine therapies other than tamoxifen.
- There was no evidence identified that compared survival outcomes in women with breast cancer with a BRCA1/2 mutation treated with or without tamoxifen.
- There is evidence from one large Level II prospective cohort study¹⁶ and two small Level III-2 retrospective cohort studies^{9, 24} that tamoxifen is as effective in terms of the risk of death¹⁶, breast cancer-specific survival⁹ and the risk of death from breast cancer²⁴ for women diagnosed with breast cancer with a BRCA1 mutation^{9, 16} or a BRCA2 mutation,²⁴ as in other women with breast cancer.*
- There is evidence from two small Level III-2 retrospective cohort studies^{9, 24} that in women who did not receive tamoxifen, those with breast cancer with a BRCA1 mutation have a significantly higher relative risk of death from breast cancer²⁴, and a significantly poorer breast cancer-specific survival⁹ compared to other women with breast cancer.* However, in women who received tamoxifen, there was no significant difference in survival outcomes in women diagnosed with breast cancer with a BRCA1 mutation, compared to other women with breast cancer.*

Ipsilateral breast cancer (recurrence of the primary or a second primary)

- In three Level III-2 retrospective cohort studies^{7, 12, 13} in women diagnosed with breast cancer and a BRCA1/2 mutation, tamoxifen did not significantly reduce the risk of ipsilateral breast cancer compared to no tamoxifen.

Contralateral breast cancer

- The evidence on effectiveness of tamoxifen, compared to no tamoxifen, on risk of contralateral breast cancer in women with breast cancer and a BRCA1/2 mutation, is inconsistent.
- There is evidence from one Level III-3 case-control study²¹ that tamoxifen shows similar decreases in the risk of contralateral breast cancer for women diagnosed with breast cancer with a BRCA1/2 mutation, compared to other women with breast cancer.*

* Women with sporadic breast cancer or women who have not been proven to have a BRCA1/2 mutation with genetic testing

3.2.3 Research Question 3: surgical risk-reducing strategies

What is the effectiveness of the use of surgical risk-reducing strategies for women with a BRCA1/2 mutation subsequent to diagnosis of breast cancer?

Surgical risk-reducing strategies to prevent second events (a second breast cancer in the ipsilateral, contralateral breast and ovarian/fallopian cancer) in women diagnosed with breast cancer with a BRCA1/2 mutation, or are at high risk of a BRCA1/2 mutation, include contralateral risk-reducing mastectomy (CRRM) and risk-reducing salpingo-oophorectomy (RRSO). Non-surgical risk-reducing strategies such as tamoxifen are discussed in Research question 2.

Part A Contralateral risk-reducing mastectomy

Systematic reviews

A Cochrane systematic review by Lostumbo et al (2010) summarised descriptively the literature about the effectiveness of contralateral risk-reducing mastectomy in women diagnosed with breast cancer who were at risk of developing breast cancer in the contralateral breast and the effectiveness of prophylactic mastectomy in women who were at risk of developing breast cancer but had no previous diagnosis of breast cancer.⁵⁸ Participants in the studies included in the Lostumbo et al review comprised women at risk of developing breast cancer, 'at risk' being defined as, '. . . women with a positive family history of breast cancer, BRCA1/2 mutation carriers, previous cancer in one breast, previous multiple breast biopsies, and previous diagnosis of lobular carcinoma in situ, atypical hyperplasia, or proliferative breast disease'.⁵⁸ For the purpose of the present review we included only studies from the Lostumbo et al review that involved women diagnosed with breast cancer with a BRCA1/2 mutation or at high risk of having a BRCA1/2 mutation. In addition, studies were only included in the present review if they were published within the inclusion period of the review (2001 to April 2012). Four studies from the Lostumbo et al review were included in the present review, including two studies with women diagnosed with breast cancer with a BRCA1/2 mutation^{25, 27} and two studies with women diagnosed with breast cancer with a family history of breast cancer.^{59, 60}

Intervention studies

No randomised controlled trials or pseudo-randomised trials or non-randomised trials were identified for inclusion in the review.

Observational studies

Four observational studies investigated the impact of contralateral risk-reducing mastectomy on survival outcomes or contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation. The studies included retrospective and prospective cohort studies.^{14, 25-27} Refer to Table 15 for study characteristics.

Table 15 Study characteristics of observational studies that investigated the impact of contralateral risk-reducing mastectomy (CRRM) on outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Design, Period	Study population	Patients	Cases + treatment	Controls + treatment	Median age (range) yrs	Ethnicity	Menopause status	Median follow-up (range) years
Brekelmans 2006 ¹⁴	Retrospective cohort study 1980-2001 Matched for age and year of treatment	Family Cancer Clinic, Rotterdam, Netherlands	BRCA1-unselected =170 BRCA1-late-tested index =53 Sporadic =446	BRCA1-unselected + CRRM=37	BRCA1-unselected + no CRRM=133	39(23-82)	Not reported	Not reported	5.1(0.1-21.9) years
Van Sprundel 2005 ²⁵	Retrospective study	Netherlands Cancer Institute, Amsterdam Leiden University Medical Centre, Leiden	BRCA1/2 =148 BRCA1 = 115 BRCA2 = 33	BRCA1/2 + CRRM =79	BRCA1/2 + no CRRM=69	CRRM 41.5(27-61) No CRRM 46.7(26-76)	Not reported	Not reported	Mean 3.5 years
Domcheck 2010 ²⁶	Prospective multi-centre cohort study 1974-2008	22 centres in the Prevention and Observation of Surgical Endpoints (PROSE) consortium	BRCA1/2 =2482	BRCA1/2 + CRRM =172 [prior to RRSO]	BRCA1/2 + no CRRM =787 [prior to RRSO]	At time of CRRM 40.7(22.4-64.6)	Not reported	Not reported	3.65(0.52-27.4)-4.29(0.5-27.9) years
Metcalfe 2004 ²⁷	Retrospective cohort study 1975-2000	10 participating cancer clinics	BRCA1 =327 BRCA2 =152 BRCA1/2 =12	BRCA1/2 + CRRM =146	BRCA1/2 + no CRRM =336	Mean 42.1 (24-65)	Not reported	Not reported	Mean 9.2 years

CRRM Contralateral risk reducing mastectomy
RR Risk Reducing
RRSO Risk-reducing salpingo-oophorectomy

Outcomes

Contralateral risk-reducing mastectomy: women with a BRCA1/2 mutation

Survival outcomes

Two original studies, one modelling study and one conference abstract investigated the impact of contralateral risk-reducing mastectomy on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation (see Table 16).^{14, 25, 61, 62}

Brekelmans et al (2006) in a retrospective cohort study investigated survival and prognostic factors in BRCA1-associated breast cancer.¹⁴ The study included 170 women diagnosed with breast cancer with a BRCA1 mutation (after exclusion of women that had genetic testing more than two years after their breast cancer diagnosis). The study did not find any breast cancer-specific survival benefit in women diagnosed with breast cancer with a BRCA1 mutation after a contralateral risk-reducing mastectomy, with a median follow-up of 5.1 years (HR 1.39 [0.47-4.13], p=0.56).

Van Sprundel et al (2005) in a retrospective study investigated overall survival after contralateral risk-reducing mastectomy in women diagnosed with breast cancer with a BRCA1 mutation (n=115) or BRCA2 mutation (n=33).²⁵ The mean follow-up was 3.5 years and started at the time of contralateral risk-reducing mastectomy or at the date of mutation testing, whichever came last, that is, on average 5 years after diagnosis of the first breast cancer. At five years follow-up, overall survival was reported to be 94% for the contralateral risk-reducing mastectomy group (Total n=79; BRCA1=60; BRCA2=19) vs 77% for the surveillance group (Total n=69; BRCA1=55; BRCA2=14) (p=0.03). However, after adjustment for risk-reducing salpingo-oophorectomy in multivariate analysis, the effect of contralateral risk-reducing mastectomy on overall survival was found to be no longer significant.

Narod (2011) applied an actuarial method to a theoretical cohort of women with breast cancer to determine the number of women diagnosed with breast cancer with a BRCA1 mutation or BRCA2 mutation that would die of contralateral breast cancer (in women who retained the contralateral breast) within 5 and 10 years.⁶² Narod estimated that 0.4% of women would die of contralateral breast cancer within 5 years and 6.8% would die within 20 years (assuming that the risk of contralateral breast cancer is 2% annually, equivalent to a cumulative risk of 18% at 10 years or 33% at 20 years).

Heemskerk-Gerritsen et al (2010) in a conference abstract compared distant disease free survival and overall survival in 144 women diagnosed with breast cancer with a BRCA1 mutation or a BRCA2 mutation who had contralateral risk-reducing mastectomy and 231 women diagnosed with breast cancer with a BRCA1 mutation or a BRCA2 mutation who did not have contralateral risk-reducing mastectomy and found only a small difference between the groups.⁶¹ However, the follow-up period of the study was short (mean 4.6 years after contralateral risk-reducing mastectomy).

Table 16 Impact of contralateral risk-reducing mastectomy on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Patients	Median follow-up (years)	Survival outcomes: Breast cancer- specific survival (BCSS) Overall survival (OS)	Cases	Controls	P value/ HR Multivariate
Brekelmans 2006 ¹⁴	BRCA1- unselected =170 BRCA1-late- tested index =53 Sporadic =446	5.1 years	The study did not find any survival benefit (breast cancer-specific survival) in women with breast cancer with a BRCA1 mutation after a contralateral risk-reducing mastectomy	BCSS BRCA1- unselected /CRRM	BCSS BRCA1- unselected /no CRRM	HR 1.39 [0.47-4.13] p=0.56
Van Sprundel 2005 ²⁵	BRCA1 =115 BRCA2 =33	Mean 3.5 years	After adjustment for risk-reducing salpingo-oophorectomy in multivariate analysis, the effect of contralateral risk-reducing mastectomy on overall survival was found to be no longer significant	OS BRCA1/2 /CRRM	OS BRCA1/2 /no CRRM	HR 0.28 [0.07-1.11] p=0.07

CRRM Contralateral risk-reducing mastectomy
BCSS Breast cancer-specific survival
OS Overall survival

Contralateral breast cancer

Three studies, including one prospective cohort study and two retrospective cohort studies, investigated the impact of contralateral risk-reducing mastectomy on the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation.²⁵⁻²⁷

Domchek et al (2010) undertook a prospective multi-centre cohort study of women with BRCA1 or BRCA2 mutations, which included a subset of women with a prior diagnosis of breast cancer.²⁶ The study found that risk-reducing mastectomy was associated with a decreased risk of breast cancer in women with a BRCA1/2 mutation. The study reported that no breast cancer events were seen in women who underwent risk-reducing mastectomy during 3 years of prospective follow-up. In contrast, 7% of women without risk-reducing mastectomy over a similar follow-up period were reported to be diagnosed with breast cancer.

Van Sprundel et al (2005) in a retrospective cohort study investigated the risk of contralateral breast cancer after contralateral risk-reducing mastectomy in women diagnosed with breast cancer with a BRCA1 mutation (n=115) or BRCA2 mutation (n=33).²⁵ The mean follow-up was 3.5 years and started at the time of contralateral risk-reducing mastectomy or at the date of mutation testing, whichever came last, that is, on average 5 years after diagnosis of the first breast cancer. The study found that

contralateral risk-reducing mastectomy reduced the risk of contralateral breast cancer by 91%, independent of the effect of risk-reducing salpingo-oophorectomy. Only one woman was found to develop a contralateral breast cancer after contralateral risk-reducing mastectomy (1.3%) compared to six women who did not have contralateral risk-reducing mastectomy (14%)($p < 0.001$).

Metcalfe et al (2004) in a retrospective cohort study investigated the factors associated with contralateral breast cancer in women with breast cancer with a BRCA1 mutation ($n=327$) or a BRCA2 mutation ($n=152$) or both ($n=12$).²⁷ The study had a mean follow-up period of 9.2 years. The study found that only one contralateral breast cancer (in the chest wall) occurred among the 146 women treated with bilateral mastectomy, prior or delayed contralateral risk-reducing mastectomy compared to 97 contralateral breast cancers among the 336 women who did not have contralateral risk-reducing mastectomy (HR 0.03, $p=0.005$).

Quality of life

Tercyak et al (2007) in a study of newly diagnosed women with breast cancer who had BRCA1/2 mutation testing at the time of their diagnosis found that women who chose mastectomy of the affected breast and contralateral risk-reducing mastectomy of the unaffected breast did not report diminished quality of life or elevated distress compared with women who chose breast conservation or unilateral mastectomy.⁵⁰ The study involved 149 women diagnosed with breast cancer with at least 10% risk of carrying a BRCA1/2 mutation. All women had undergone genetic testing and 22 women were found to have a BRCA1/2 mutation.

Patient preferences

Two studies investigated patient factors and preferences in decision-making about contralateral risk-reducing mastectomy in women diagnosed with breast cancer with a BRCA1/2 mutation.^{7, 63}

Metcalfe et al (2008) found large differences in uptake of contralateral risk-reducing mastectomy by country, ranging from 0% in Norway to 49.3% in the United States.⁶³ Women who initially underwent breast-conserving surgery were found to be significantly less likely to undergo contralateral risk-reducing mastectomy than were women who underwent a mastectomy (12% vs 40%, $p < 0.001$). Women who had elected for a risk-reducing oophorectomy were found to be more likely to have had their contralateral breast removed than women with intact ovaries (33% vs 18%, $p < 0.001$).

Pierce et al (2010) found that women who had a mastectomy of the initially affected breast were more likely to have a risk-reducing contralateral mastectomy of the other breast compared to women who had breast-conserving treatment (38.0% vs 14.6%, $p < 0.0001$).⁷

Preliminary research also indicates that genetic testing before surgery may increase the uptake of a therapeutic (or ipsilateral) mastectomy, with or without a contralateral risk-reducing mastectomy, rather than breast conserving treatment (breast conserving surgery and radiotherapy) in women found to carry a BRCA1/2 mutation.^{3, 44-49}

Contralateral risk-reducing mastectomy: women with a strong family history but no identified BRCA1/2 mutation; and women with a non-BRCA germline mutation

Survival outcomes

Two studies investigated the impact of contralateral risk-reducing mastectomy on survival in women diagnosed with breast cancer with a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation.

Boughey et al (2010) in a retrospective cohort study investigated survival in women with breast cancer and a family history of breast cancer (n=385) after contralateral risk-reducing mastectomy.⁶⁴ The study had a median follow-up of 17.3 years. The study found that contralateral risk-reducing mastectomy improved overall survival (HR 0.77, p=0.03) and disease free survival (HR 0.67, p=0.0005).

Kiely et al (2010) in a prospective cohort study investigated the outcomes in 1018 women with breast cancer and a strong family history of breast cancer, including a proportion of women with detected BRCA1/2 mutations (29%).⁶⁵ The median follow-up of the study was 11.1 years. The study reported no significant difference in overall survival in women who did and did not have a contralateral risk-reducing mastectomy with 144 (93.5%) of the women who elected to have contralateral risk-reducing mastectomy and 800 (92.6%) of the women who did not elect to have a contralateral risk-reducing mastectomy still alive at last follow-up. However, the study found a significant difference in the metastatic breast cancer rate in women who did and did not have a contralateral risk-reducing mastectomy. The study reported a metastatic breast cancer rate of 6.2 per 1,000 women-years for women who opted for a contralateral risk-reducing mastectomy and 10.4 per 1,000 women-years for women who did not have a contralateral risk-reducing mastectomy, p=0.04.

Contralateral breast cancer

Two studies investigated the impact of contralateral risk-reducing mastectomy on the risk of contralateral breast cancer in women diagnosed with breast cancer with a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation.

Kiely et al (2010) in a prospective cohort study (described above) found that a contralateral breast cancer event (invasive or in situ) occurred in 177 (20.5%) of the 864 women who did not have contralateral risk-reducing mastectomy, compared with one chest wall event of the 154 women (0.6%) who had contralateral risk-reducing mastectomy which occurred in a BRCA2 mutation carrier (p<0.0001).⁶⁵ Of the 177 women who developed contralateral breast cancer, 82 (46%) were BRCA1/2 mutation carriers, 71 had uninformative results, and 24 were untested.

McDonnell et al (2001) investigated the effectiveness of contralateral risk-reducing mastectomy in women with breast cancer and a family history of breast or ovarian cancer (n=745). The median follow-up period of the study was 10 years.⁶⁰ Of the eight women who developed a contralateral breast cancer, six of these women were pre-menopausal. The study estimated that the reduction in contralateral breast cancer was 94.4% in pre-menopausal women and 96% in post-menopausal women (adjusted for tamoxifen and other adjuvant therapy).⁶⁰

Quality of life

Two studies were identified that investigated quality of life after contralateral risk-reducing mastectomy in women diagnosed with breast cancer with a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation.^{50, 59}

As described above, Tercyak et al (2007) in a study of newly diagnosed women with breast cancer who had BRCA1/2 mutation testing at the time of their diagnosis found that women who chose mastectomy of the affected breast and contralateral risk-reducing mastectomy of the unaffected breast did not report diminished quality of life or elevated distress compared with women who chose breast conservation or unilateral mastectomy.⁵⁰ The study involved 149 women diagnosed with breast cancer with at least 10% risk of carrying a BRCA1/2 mutation. All women were genetic tested and 22 women were found to have a BRCA1/2 mutation.

Frost et al (2005) investigated quality of life after contralateral risk-reducing mastectomy in 583 women who had a personal and family history of breast cancer.⁵⁹ The study found that 83% of women were satisfied with the contralateral risk-reducing mastectomy. However, the study also found that contralateral risk-reducing mastectomy affected some women's quality of life negatively: 33% negative effect on body image, 26% less feminine, 23% adverse sexual relations, 12% adverse emotional stability, and 27% had unanticipated reoperations following contralateral risk-reducing mastectomy with or without reconstruction, with 72% of these related to implants.

Patient preferences

One study investigated patient factors and preferences in decision-making about contralateral risk-reducing mastectomy in women diagnosed with breast cancer with a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation.⁶⁵

Kiely et al (2010) in a prospective cohort study (discussed above) found that women were found to be more likely to undergo contralateral risk-reducing mastectomy if they were younger at breast cancer diagnosis (OR=0.94 per year of age, $p<0.001$), were recently diagnosed (OR=1.16 per calendar year, $p<0.001$), and underwent a therapeutic (ipsilateral) mastectomy (OR=5.2, $p<0.001$).⁶⁵

There was no evidence identified about the effectiveness of contralateral risk-reducing mastectomy in women with breast cancer with non-BRCA germline mutations such as TP53.

Part B Risk-reducing salpingo-oophorectomy

Systematic reviews

There were no systematic reviews identified for inclusion in the review.

Intervention studies

No randomised controlled trials or pseudo-randomised trials or non-randomised trials were identified for inclusion in the review.

Observational studies

Seven observational studies investigated the impact of risk-reducing salpingo-oophorectomy on survival outcomes, ipsilateral breast cancer or contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation. The studies included retrospective and prospective cohort studies.^{7, 12-14, 23, 25, 26} Refer to Table 17 for study characteristics.

Table 17 Study characteristics of studies that investigated the impact of risk-reducing salpingo-oophorectomy (RRSO) on outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation

Author Year	Design, Period	Study population	Patients	Cases + treatment	Controls + treatment	Median age (range) yrs	Ethnicity	Menopause status	Median follow-up (years)
Domchek 2010 ²⁶	Prospective multi-centre cohort study 1974-2008	22 centres in the Prevention and Observation of Surgical Endpoints (PROSE) consortium	BRCA1/2 =2482	BRCA1/2 + RRSO =993 [Prior breast cancer]	BRCA1/2 + no RRSO =1489 [Prior breast cancer]	Mean 47.6(29.7-75.2) [Age at RRSO]	Not reported	Not reported	3.65(0.52-27.4)-4.29(0.5-27.9) years
Van Sprundel 2005 ²⁵	Retrospective	Netherlands Cancer Institute, Amsterdam Leiden University Medical Centre, Leiden	BRCA1/2=148	BRCA1/2 +RSSO=61	BRCA1/2 + no RRSO=18	43.3(30-60) 47.1(35-64) [Age at RRSO]	Not reported	Not reported	Mean 3.5 years
Brekelman 2006 ¹⁴	Retrospective cohort study 1980-2001 Matched for age and year of treatment	Family Cancer Clinic, Rotterdam, Netherlands	BRCA1-unselected =170 BRCA1-late-tested index =53 Sporadic =446	BRCA1-associated+RRSO =80	BRCA1-associated+ no RRSO=143	39(23-81)	Not reported	Not reported	5.1(0.1-21.9) years
Metcalfe, Lynch 2011 ¹³	Retrospective cohort study 1975-2008	10 cancer genetics clinics, North America	BRCA1/2=396	BRCA1/2 + RRSO =132	BRCA1/2 + no RRSO =255	Age at diagnosis Mean 42.4(21-65)	Not reported	Not reported	10.5 (0.9-27.1) years

Author Year	Design, Period	Study population	Patients	Cases + treatment	Controls + treatment	Median age (range) yrs	Ethnicity	Menopause status	Median follow-up (years)
Pierce 2010 ⁷	Retrospective cohort study 2001	Multi-institutional: USA, Spain, Israel, Australia and New Zealand (kConFab)	BRCA1/2 =655	BRCA1/2 + RRSO =161 [+BCT]	BRCA1/2 + no RRSO =141 [+BCT]	40.5 (20.1-85.0) [+BCT]	Not reported	Pre-Menopausal: BCT =79.5%	8.2-8.9 years Data projected to 15 years
Pierce 2006 ¹²	Retrospective cohort study	Multi-institutional: USA, Canada, Israel	BRCA1/2 =160 Sporadic=445	BRCA1/2 + RRSO =no data	BRCA1/2 + no RRSO =no data	No data for RRSO BRCA1/2 =40.1(21.9-74.3) Sporadic =41.0(22.6-75.1)	White: No data for RRSO BRCA1/2 =91% Sporadic =83%	Pre-Menopausal: No data for RRSO BRCA1/2 =74% Sporadic= 75%	6.7-7.9 years
Metcalfe, Gershman 2011 ²³	Retrospective cohort study 1975-2008	10 participating cancer genetics clinics, North America	BRCA1/2 = 810	BRCA1/2 + RRSO =489	BRCA1/2 + no RRSO =303	Age at diagnosis Mean 42.2 (21-65)	Not reported	Not reported	Mean 11.5 (0.3-33.1) years

RRSO Risk-reducing salpingo-oophorectomy
BCT Breast conserving therapy

Outcomes

Risk reducing salpingo-oophorectomy: women with a BRCA1/2 mutation

Survival outcomes

Three studies, including one prospective and two retrospective studies, investigated the impact of risk-reducing salpingo-oophorectomy on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation.^{14, 25, 26}

Domchek et al (2010) undertook a prospective multi-centre cohort study of women with a BRCA1 mutation or a BRCA2 mutation, which included a subset of women with a prior diagnosis of breast cancer.²⁶ In 1027 women with a BRCA1/2 mutation and prior breast cancer, risk-reducing salpingo-oophorectomy was found to be associated with significantly lower all-cause mortality (HR 0.30, 95% CI [0.17-0.52]). Domchek et al (2010) also reported that in 636 women with a BRCA1 mutation with prior breast cancer, risk-reducing salpingo-oophorectomy was associated with significantly lower breast cancer specific mortality (HR 0.27, 95% CI [0.12-0.58]). The study also reported that in women with a BRCA1/2 mutation with prior breast cancer, overall survival was associated with risk-reducing salpingo-oophorectomy in women younger than 50 years (HR 0.28, 95% CI [0.14-0.55]) and in women 50 years and older (HR 0.37, 95% CI [0.13-1.03]).

Van Sprundel (2005) in a retrospective cohort study found that women diagnosed with breast cancer with a BRCA1/2 mutation who underwent risk-reducing salpingo-oophorectomy had significantly better overall survival than women who did not have risk-reducing salpingo-oophorectomy ((HR 0.23, 95% CI [0.07-0.78], p=0.018 at 5 years) after controlling for important factors such as contralateral risk-reducing mastectomy, time between first breast cancer, start of follow-up, and chemotherapy.²⁵ However, the study did not find significantly better breast cancer-specific survival at 5 years in women who underwent risk-reducing salpingo-oophorectomy after controlling for important factors (HR 0.28, 95% CI [0.07-1.11], p=0.07).

Brekelmans et al (2006) in a retrospective cohort study also reported that risk-reducing salpingo-oophorectomy did not significantly improve breast cancer specific survival in women diagnosed with breast cancer with a BRCA1 mutation (n=223), with a median follow-up of 5.1 years (HR 0.38, 95% CI [0.10–2.07], p=0.21).¹⁴

Ipsilateral breast cancer

Four observational studies, including one prospective cohort study and four retrospective cohort studies, investigated the risk of ipsilateral breast cancer after risk-reducing salpingo-oophorectomy in women with breast cancer with a BRCA1/2 mutation.^{7, 12, 13, 26}

Of the four studies, only one retrospective cohort study, by Metcalfe, Lynch et al (2011), found a significant reduction in the risk of ipsilateral breast cancer after risk-reducing salpingo-oophorectomy in women diagnosed with breast cancer with a BRCA1/2 (n=396) mutation (RR 0.33, 95% CI [0.13–0.81], p=0.02).¹³

Domchek et al (2010) in a prospective cohort study reported that in 647 women with a BRCA1/2 mutation and prior breast cancer, there was no evidence for reduction in risk of

a second diagnosis of primary breast cancer with risk-reducing salpingo-oophorectomy (HR 1.00, 95% CI [0.56-1.77]).²⁶

Pierce et al (2010) in a retrospective cohort study reported that in 302 women diagnosed with breast cancer with a BRCA1/2 mutation treated with breast conserving therapy, risk-reducing salpingo-oophorectomy did not significantly decrease the risk of ipsilateral breast cancer at 15 years (HR 0.88, p=0.75).⁷

Pierce et al (2006) in a retrospective cohort study reported that risk-reducing salpingo-oophorectomy did not significantly decrease the risk of ipsilateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation (n=160) after breast conserving surgery compared to women who did not have a risk-reducing salpingo-oophorectomy at 15 years (HR 0.55, p=0.44).¹²

Contralateral breast cancer

One large retrospective cohort study reported that the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation was significantly reduced with risk-reducing salpingo-oophorectomy for women aged less than 50 years old at initial breast cancer diagnosis (RR 0.39, 95% CI [0.23-0.67], p=0.0006).²³ The risk reduction associated with risk-reducing salpingo-oophorectomy was not found to be significant for women over 50 years (RR 0.90, 95% CI [0.30-2.64], p=0.84).

Ovarian/fallopian tube cancer

One large prospective cohort study reported that, in women with a BRCA1 mutation (n=563) and a prior diagnosis of breast cancer, risk-reducing salpingo-oophorectomy was associated with significantly reduced risk of ovarian cancer (HR 0.15, 95% CI [0.04-0.63]).²⁶ No cases of ovarian cancer were diagnosed in women with a BRCA2 mutation after risk-reducing salpingo-oophorectomy.

Patient factors and preferences

Metcalfe et al (2008) in a large retrospective cohort study found that women diagnosed with breast cancer with a BRCA1/2 mutation (n=927) who had risk-reducing salpingo-oophorectomy were significantly more likely to have contralateral risk-reducing mastectomy (33% vs 18%, p=0.001).⁶³ Van Sprundel et al (2005) also found that women more often underwent risk-reducing salpingo-oophorectomy if they had also opted for contralateral risk-reducing mastectomy (61/79) than surveillance (39/69), p=0.009.²⁵

Pierce et al (2010) in a large retrospective cohort study with women diagnosed with breast cancer with a BRCA1/2 mutation [BRCA1/2 mutation n=655] found that women who had a mastectomy underwent risk-reducing salpingo-oophorectomy at a similar rate to women who had breast-conserving therapy (57.5% vs 53.3%, p=0.28).⁷

Carroll et al (2011) in a retrospective cohort study of 58 women diagnosed with breast cancer with a BRCA1/2 mutation found that risk-reducing salpingo-oophorectomy was chosen by 39 (67.2%) of women with 30 (76.9%) of women being over the age of 40 years.⁶⁶

Meijers-Heijboer et al (2003) conducted a prospective study of 172 women diagnosed with breast cancer with a BRCA1/2 mutation.⁴⁵ The decision to undergo risk-reducing oophorectomy correlated with the stage of the breast cancer with women with stage I breast cancer more often having risk-reducing salpingo-oophorectomy ($p=0.04$). The study also found that the mean time between genetic diagnosis and risk-reducing salpingo-oophorectomy was eight months, and that at a follow-up of one and two years, 40% and 47% respectively, of eligible women had risk-reducing salpingo-oophorectomy (after this period only two women had risk-reducing salpingo-oophorectomy).⁴⁵

Risk reducing salpingo-oophorectomy: women with a strong family history, but no identified BRCA1/2 mutation; and women with a non-BRCA germline mutation

Survival outcomes

Brekelmans et al (2007) in a retrospective cohort study of women with hereditary breast cancer found that risk-reducing salpingo-oophorectomy was a significant independent prognostic factor for breast cancer-specific survival in women with hereditary breast cancer, with approximately 50% of women with hereditary breast cancer having an identified BRCA1/2 mutation (HR 0.40, 95% CI [0.16–0.99], $p=0.05$).¹¹

There was no evidence identified about the effectiveness of risk-reducing salpingo-oophorectomy in women with breast cancer with non-BRCA germline mutations such as TP53.

Summary

What is the effectiveness of the use of surgical risk-reducing strategies for women with a BRCA1/2 mutation subsequent to diagnosis of breast cancer?

Part A Contralateral risk-reducing mastectomy

Survival outcomes

- In two Level III-2 retrospective cohort studies^{25,14} in women diagnosed with breast cancer with a BRCA1/2 mutation, contralateral risk-reducing mastectomy did not significantly improve overall survival²⁵ or breast cancer-specific survival,¹⁴ compared to no contralateral risk-reducing mastectomy.

Contralateral breast cancer

- There is evidence from one Level II prospective cohort study²⁶ and two Level III-2 retrospective cohort studies^{25, 27} that, in women diagnosed with breast cancer with a BRCA1/2 mutation, contralateral risk-reducing mastectomy substantially decreases (by more than 90%) the risk of contralateral breast cancer, compared to no contralateral risk-reducing mastectomy.

Part B Risk-reducing salpingo-oophorectomy

Survival outcomes

- There is evidence from one Level II prospective cohort study²⁶ and one Level III-2 retrospective cohort study²⁵ that, in women diagnosed with breast cancer and a BRCA1/2 mutation, risk-reducing salpingo-oophorectomy significantly improves overall survival (two studies)^{25, 26} and breast cancer-specific survival (one study)²⁶ compared to no risk-reducing salpingo-oophorectomy.

Ipsilateral breast cancer (recurrence of the primary or a second primary)

- There is evidence from only one Level III-2 retrospective cohort study¹³ of patients from four studies^{7, 12, 13, 26} (one Level II prospective cohort study and three Level III-2 retrospective cohort studies) that, in women with breast cancer with a BRCA1/2 mutation, risk-reducing salpingo-oophorectomy significantly decreases the risk of ipsilateral breast cancer compared to no risk-reducing salpingo-oophorectomy.

Contralateral breast cancer

- In one Level III-2 retrospective cohort study²³ in women diagnosed with breast cancer with a BRCA1/2 mutation under 50 years of age, risk-reducing salpingo-oophorectomy significantly decreases the risk of contralateral breast cancer, compared to no risk-reducing salpingo-oophorectomy.

Ovarian cancer

- There is evidence from one Level II prospective cohort study²⁶ that, in women diagnosed with breast cancer with a BRCA1/2 mutation, risk-reducing salpingo-oophorectomy significantly decreased the risk of ovarian cancer, compared to no risk-reducing salpingo-oophorectomy.

3.3 Other Issues

3.3.1 Outcomes for women with breast cancer and a BRCA1/2 mutation

Survival outcomes, risk of ipsilateral breast cancer and contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation

The evidence in this section is derived from three systematic reviews, including Lee et al (2010),⁶⁷ Bordeleau et al (2010),⁶⁸ and Liebens et al (2007),³⁷ original research studies published since these systematic reviews and key original research studies highlighted in the main research questions sections.

Survival outcomes

The impact of a germline BRCA1/2 mutation as an independent factor in breast cancer survival is still unclear.^{1, 43, 68}

Lee et al (2010) conducted a meta-analysis of eleven studies that compared survival outcomes in women with a BRCA1/2 mutation and non-BRCA carriers.⁶⁷ Included studies were published between 1993 and 2010. The authors concluded that women with a BRCA1 mutation had significantly lower short-term and long term-term overall survival relative to non-carriers (HR 1.92, 95% CI [1.45-2.53]; HR 1.33 [1.12-1.58] respectively) while short-term and long-term overall survival of women with a BRCA2 mutation did not differ from non-carriers. Women with a BRCA1 mutation were also found to have significantly lower short-term progression-free survival (HR 1.54, 95% CI [1.12-2.12]) but not long-term progression-free survival. The short-term and long-term progression-free survival in women with a BRCA2 mutation did not differ from non-carriers. However, the results of this meta-analysis are limited due to the authors combining survival data from studies (particularly studies published more than five years ago) that had major methodological flaws such as selection and sampling biases, and a lack of adjustment for known prognostic factors, clinical and treatment factors.

Bordeleau et al (2010) conducted a systematic review of the evidence related to survival outcomes in women with a BRCA1/2 mutation with consideration for the methodological limitations of the included studies.⁶⁸ The authors separated the results into early studies (prior to 1997; and 1998-2002) and more recent studies conducted during the period 2003-2008. The early studies were considered to be methodologically problematic and the more recent studies (2003-2008) although retrospective in design were considered to be greatly improved by larger sample sizes and greater adjustment for confounding factors. The authors concluded that the more recent studies failed to demonstrate, for the most part, a significant overall survival difference between BRCA-associated breast cancer and sporadic breast cancers. In one study BRCA1 mutation predicted increased breast cancer mortality only among women who did not receive chemotherapy.⁹ However, as discussed in Research Question 1, this study included only Ashkenazi Jewish women and was limited by the small sample size and lack of adjustment for whether women were treated by oophorectomy.

Liebens et al (2007) also conducted a systematic review of the evidence (period 1994 to 2006) related to survival outcomes in women with a BRCA1/2 mutation and found that four of fourteen studies showed worse survival in women with a BRCA1/2 mutation.³⁷ Three of the four studies which showed worse survival in women with a BRCA1/2 mutation

were published prior to 2003, and the remaining study by Robson et al (2004)⁹ was limited by the factors stated above.

Subsequent to the publication of the systematic review by Bordeleau et al (2010), a large prospective study¹⁶ conducted in Canada, the United States and Australia has been published that compares breast cancer prognosis in women with a BRCA1 mutation (n=94) and a BRCA2 mutation (n=72) and sporadic controls (n=1550). Goodwin et al (2012) reported that women with a BRCA1 mutation did not have an increased risk of distant breast cancer and death than sporadic controls (HR 0.83, 95% CI [0.51-1.35], p=0.46; HR 0.99, 95% CI [0.62-1.59], p=0.98; respectively) and women with a BRCA2 mutation did not have an increased risk of distant breast cancer and death than sporadic controls (HR 1.00, 95% CI [0.62-1.61], p=1.00; HR 1.12, 95% CI [0.70-1.79], p=0.64, respectively).¹⁶ The study adjusted for demographic and clinical factors such as age, year of diagnosis, tumour stage and grade, nodal status, hormone receptor status, and treatment factors such as chemotherapy, endocrine therapy and oophorectomy. The study had a median follow-up of 7.9 years.

Although Goodwin et al (2012) did not find that BRCA1 or BRCA2 mutations were independent predictors of breast cancer prognosis in multivariate analyses, the study found that breast cancers in women with a BRCA1 and BRCA2 mutation differed in their presentation from those in women with sporadic breast cancer and that the association of adverse prognostic factors with a BRCA1/2 mutation affected breast cancer prognosis.¹⁶ The study found that the risk of distant breast cancer and death was significantly higher in women with a BRCA2 mutation compared with those with sporadic breast cancer in univariate analysis (with no adjustment for age, tumour and nodal status, grade, hormone receptor status, year of diagnosis). However, women with a BRCA2 mutation were significantly more likely to be younger at diagnosis, have axillary node involvement and have high grade tumours than sporadic controls. Although women with a BRCA1 mutation were significantly more likely to be younger at diagnosis and have high grade tumours, and less likely to have Stage 1 tumours and be ER or PG positive than sporadic controls, the study did not find any significantly increased risk of distant breast cancer and death in women with a BRCA1 mutation compared to sporadic controls in univariate analysis.

Ipsilateral breast cancer

The risk of ipsilateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation following breast conserving treatment (BCT: breast conserving surgery and radiotherapy) compared to women with sporadic breast cancer is discussed in Research Question 1. Seven studies were identified that compared ipsilateral breast cancer in women with a BRCA1/2 mutation after BCT with sporadic controls.^{8-12, 38, 39} Only two small studies found a significantly increased risk of ipsilateral breast cancer in women with a BRCA1/2 mutation following BCT compared to sporadic controls.^{38, 39} However, the studies were limited by the small sample sizes,^{38, 39} sampling biases³⁹ and lack of control for potential confounders.^{38, 39} Liebens et al (2007) also conducted a systematic review of the evidence (period 1994 to 2006) related to ipsilateral breast cancer in women with a BRCA1/2 mutation and found an increased risk of ipsilateral breast cancer in five of the seventeen studies.³⁷

As highlighted in Research Question 1, a large retrospective study found that the risk of ipsilateral breast cancer in women with a BRCA1/2 mutation treated with BCT was

significantly higher compared with mastectomy.⁷ This result contrasts to the findings of multiple trials with women with sporadic breast cancer which have shown that BCT has comparable rates of tumour control as mastectomy.^{69, 70} Pierce et al (2010) investigated the risk of ipsilateral breast cancer in 655 women diagnosed with breast cancer with a BRCA1/2 mutation and estimated the cumulative risk of ipsilateral breast cancer as 23.5% following BCT compared to 5.5% following a mastectomy at 15 years ($p < 0.0001$). Chemotherapy was the only treatment factor found to be an independent predictor of ipsilateral breast cancer in women treated with BCT.

Pierce et al (2010) also reported that most ipsilateral breast cancers appeared to be second primary cancers rather than failure to control the primary tumour due to the breast cancers largely being detected in different quadrants of the breast, the different histology of the breast cancers to the primary cancers, and the long median time after the primary cancers to ipsilateral breast cancer.⁷ The study reported that the median time to ipsilateral breast cancer was 7.8 years for women who had BCT and 9.4 years for women who had a mastectomy.

Similarly, a large retrospective non-comparative study assessed the risk of ipsilateral breast cancer in 396 women diagnosed with early breast cancer with a BRCA1/2 mutation and found that the average time between the first primary breast cancer and the ipsilateral breast cancer was 7.5 years.¹³ The authors report a cumulative risk of ipsilateral breast cancer in women with a BRCA1 mutation of 6% at 5 years, 11% at 10 years, and 14% at 15 years; and a cumulative risk of ipsilateral breast cancer in women with a BRCA2 mutation of 6% at 5 years, 18% at 10 years, and 21% at 15 years. Chemotherapy (RR 0.28, 95% CI [0.24-0.84], $p = 0.01$), radiotherapy (RR 0.28, 95% CI [0.12-0.63], $p = 0.002$) and oophorectomy (RR 0.33, 95% CI [0.13-0.81], $p = 0.02$) were found to be associated with a significant reduction in ipsilateral breast cancer.

Contralateral breast cancer

It is well established that the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation is significantly increased compared to women with sporadic breast cancer.^{3, 9, 11, 15, 38, 68, 71, 72} Bordeleau et al (2010) in a systematic review reported that the risk of contralateral breast cancer is significantly increased in BRCA carriers with an estimated 10 year risk ranging from 20 to 42% compared to 5 to 6% for sporadic controls.⁶⁸

Subsequent to the publication of the systematic review by Bordeleau et al (2010), three large retrospective studies have been published that also demonstrate that the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation is substantial,^{7, 23, 73} and that the risk of contralateral breast cancer in women with a BRCA1/2 mutation is significantly increased compared to women without a BRCA1/2 mutation.⁷³

Metcalfe et al (2011) estimated the risk of contralateral breast cancer in women with BRCA1/2 mutations diagnosed with early breast cancer ($n = 810$).²³ The authors reported that the 10-year actuarial risk of contralateral breast cancer was 24% for women with a BRCA1 mutation and 19% for women with a BRCA2 mutation. The 15-year actuarial risk of contralateral breast cancer reported was 36% (BRCA1 mutation) and 29% (BRCA2 mutation). Similarly, Pierce et al (2010) in a study of 655 women diagnosed with breast cancer with a BRCA1/2 mutation reported that the risk of contralateral breast cancer

was high, with a cumulative estimated risk of contralateral breast cancer of greater than 40% at 15 years.⁷ Liebens et al (2007) also conducted a systematic review of the evidence (period 1994 to 2006) and found an increased risk of contralateral breast cancer in women with a BRCA1/2 mutation in fourteen of the sixteen studies.³⁷

Metcalf et al (2011) also estimated the extent to which demographic and clinical factors, family history and treatment factors modified the risk of contralateral breast cancer.²³ Women younger than 50 years of age at the time of breast cancer diagnosis were reported to be significantly more likely to develop a contralateral breast cancer at 15 years compared with those older than 50 years (38 vs 17%; $p=0.003$). Women aged less than 50 years with two or more first degree relatives with early-onset breast cancer were reported to be at high risk of contralateral breast cancer compared with women with fewer, or no first-degree relatives with breast cancer (50 vs 36%; $p=0.005$). Among women with a BRCA1 mutation, each first-degree relative affected with breast cancer before 50 years of age was associated with a 40% increase risk of contralateral breast cancer. In terms of whether any treatment modified the risk of contralateral breast cancer in women with a BRCA1/2 mutation, the authors found that only oophorectomy in women with a BRCA1 mutation under the age of 50 years significantly reduced the risk of contralateral breast cancer (BRCA1 mutation: RR 0.48, 95% CI [0.27–0.84], $p=0.01$). Chemotherapy and tamoxifen were not found to significantly reduce the risk of contralateral breast cancer in women with a BRCA1/2 mutation overall, or in women with a BRCA1 or BRCA2 mutation, in the multivariate analyses.

Malone et al (2010) compared the risk of contralateral breast cancer in women diagnosed with breast cancer with and without a BRCA1/2 mutation ($n=181$) and found that women with a BRCA1 mutation had a 4.5-fold increased risk of contralateral breast cancer (95% CI, 2.8- to 7.1-fold) and women with a BRCA2 mutation had a 3.4-fold increased risk of contralateral breast cancer (95% CI, 2.0- to 5.8-fold) compared to non-carriers (adjusting for demographic, clinical and treatment factors).⁷³ As supported by Metcalf et al (2011), the risk of contralateral breast cancer for women with BRCA1 mutations was found to increase as age of first diagnosis decreased.²³ Malone et al (2010) reported that the relative risk of developing contralateral breast cancer for women with a BRCA1 mutation (compared with BRCA1/BRCA2 non-carriers) decreased with older age at first diagnosis, with an 11-fold increased contralateral breast cancer risk among women first diagnosed before age 35 years, a four-fold increased risk among women age 35 to 44 years at first diagnosis, and a 2.6-fold increased risk in women age 45 to 54 years at first diagnosis.⁷³ Age-specific contralateral breast cancer relative risks for BRCA2 mutation carriers showed no clear trend. Overall, the study estimated that women diagnosed with breast cancer before age 55 years and have a BRCA1 mutation have a 21% risk of developing contralateral breast cancer within 10 years, and women with a BRCA2 mutation have a 16% risk of developing contralateral breast cancer within 10 years. The study estimated that non-carriers have a 5% risk of developing contralateral breast cancer within 10 years.

Summary

- The impact of a germline BRCA1/2 mutation as an independent factor in breast cancer survival is still unclear. However, young age at diagnosis and tumours displaying a triple-negative phenotype have been shown to be associated with BRCA-related breast cancers and these factors have been shown to be independent predictors of poor outcome.^{74,75}
- Although most of the studies that compared the risk of ipsilateral breast cancer after breast conserving treatment in women with a BRCA1/2 mutation and sporadic controls did not find any significant difference in the risk of ipsilateral breast cancer, a large retrospective well-designed study that compared the risk of ipsilateral breast cancer after BCT and after mastectomy in women with a BRCA1/2 mutation found that the risk of ipsilateral breast cancer in women with a BRCA1/2 mutation treated with BCT was significantly higher compared with mastectomy. This result contrasts to the findings of multiple trials with women with sporadic breast cancer which have shown that BCT has comparable rates of tumour control as mastectomy. The study found that chemotherapy was the only treatment factor found to be an independent predictor of ipsilateral breast cancer in women with a BRCA1/2 mutation treated with BCT.
- It is well established that the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation is significantly increased compared to women with sporadic breast cancer.

3.3.2 Genetic testing

Issues related to genetic testing to inform the management of breast cancer

This section considers treatment-focused, or rapid genetic testing, undertaken shortly after cancer diagnosis. Recent evidence, as considered in the research questions in this systematic review, has suggested that the presence of a germline BRCA1/2 mutation defines a subgroup of patients whose immediate management may be influenced by knowledge of this information. In addition, advances in sequencing technologies mean that the cost and time frame for germline BRCA testing will substantially decrease.⁴³

The evidence in this section was sourced using non-systematic methods. Targeted searches were undertaken in PubMed. Additional papers were provided by working group members and the reference lists of these papers were also reviewed.

Criteria to guide treatment-focused or rapid genetic testing

Evidence to inform criteria to guide selection of women diagnosed with breast cancer for treatment-focused genetic testing, has been systematically searched in a review by Meiser et al (2008), and 22 papers were included for detailed review.⁷⁶ In addition to strong family history of breast and/or ovarian cancer, the review identified evidence to support adoption of additional selection criteria to identify patients most likely to carry germline mutations. These include women with early onset breast cancer and a family history of breast cancer, women with early onset bilateral breast cancer, women whose tumours have certain histological characteristics, and women with early onset breast cancer from populations with BRCA founder mutations.⁷⁶ The authors of this review summarised features that may guide selection for treatment-focused genetic counselling and testing (Table 18).

Table 18 Features that may guide selection for treatment-focused genetic counselling and testing identified in systematic review by Meiser et al⁷⁶

<p>Strong family history consistent with dominantly inherited breast and/or ovarian cancer</p>	<p>Two or more first- or second-degree relatives on one side of the family plus one or more of the following features on the same side of the family^a:</p> <ul style="list-style-type: none"> • Additional relatives with breast or ovarian cancer • Breast cancer diagnosed before the age of 40 years • Bilateral breast cancer • Breast and ovarian cancer in the same woman • Ashkenazi Jewish ancestry • Breast cancer in a male relative <p>One or more first- or second-degree relatives with breast cancer at age 45 years or younger plus another first- or second-degree relative on the same side of the family with sarcoma (bone/soft tissue) at age 45 years or younger</p>
<p>Young age of onset^b especially in combination with:</p>	<p>At least one first-degree relative with breast or ovarian cancer; or Bilateral breast cancer; or Specific ethnic group with known founder mutations, for example, Ashkenazi Jewish ancestry; or Presence of a triple negative breast tumours (ER, progesterone receptor and HER2 negative) or their subgroup of basal-cell like tumours</p>

^a National Breast Cancer Centre

^b The age cut-off to be used will depend on local availability of resources and the future cost of mutation detection

Another recent review by Trainer et al (2010) highlighted features correlating with a $\geq 10\%$ likelihood of a germline BRCA1/2 mutation, including: young age at diagnosis (< 40 years), populations with a high prevalence of BRCA founder mutations, such as those of Ashkenazi Jewish ethnicity and families from the Netherlands, Iceland, Poland and Sweden, and histopathological features (triple negative tumours, CK5/6-positive breast tumours among patients with sporadic early-onset breast cancer, < 40 years).⁴³ Refer to Appendix G.

International guidelines have also defined criteria for genetic counselling and testing (see Appendix E).

Women's decision-making about treatment-focused or rapid genetic testing

Genetic counselling

Currently, many women newly diagnosed with breast cancer and with a strong family history of breast cancer are referred to a family cancer service for genetic counselling and for consideration of genetic testing. Family cancer services were developed to assess and communicate future cancer risk and provide guidance on risk reduction and surveillance strategies for individuals and families. It seems likely that more women will be offered rapid treatment-focused genetic counselling and testing for inherited BRCA1/2 mutations soon after diagnosis. Genetic testing, with all its familial considerations, would be undertaken at a vulnerable time when the woman is coming to terms with her diagnosis and making decisions about treatment options.^{43, 76}

Genetic counselling is an essential component of the genetic risk assessment in order to interpret the implications of a genetic test result, both for informative results (genetic mutation identified) and 'uninformative' results (no mutation identified with current techniques). The clinical implications of an uninformative result depend on whether or not a woman has a relevant family history of breast and/or ovarian cancer.⁷⁶

In a recent study of women who received genetic counselling before or after surgery for breast cancer, Christie et al (2012) reported that genetic counselling increased cancer-related knowledge in both patients before ($p=0.004$) and after ($p<0.001$) surgery. It decreased distress in patients who had not yet undergone surgery ($p=0.041$) and it improved informed decision making in patients who had already undergone surgery ($p=0.056$).⁷⁷

Psychological impacts

In a retrospective focus group study from the UK of young women who had completed breast cancer treatment and health professionals, Ardern-Jones et al (2005) reported concerns from both groups about information and emotional overload of offering genetic testing at the same time as cancer diagnosis.⁷⁸ The majority felt that offering genetic testing would add too much additional stress. Some of the common themes were; 'there was no perfect time', 'possibility of decision regret', 'benefits of waiting' and 'delivery of information should be someone with the time and who is an expert in the field'. However some members of both groups thought that offering genetic testing around the time of breast cancer diagnosis would be more important if the results could alter treatment decisions.

A prospective study by Schlich-Bakker et al (2006) reported no increase in short-term psychological distress in recently diagnosed breast cancer patients after an active approach for genetic counselling at the start of adjuvant radiotherapy.⁷⁹ Analysis of the women who were classified as being in a high distress group indicated the following as predictors of distress: being younger, single with little social support, less optimistic, experiencing a lower quality of life and being highly distressed prior to approach for genetic counselling. Longer-term follow up to one year after diagnosis reported by Schlich-Bakker et al (2008) indicated that patients who were actively approached for genetic counselling showed no more long term distress than patients not eligible for such counselling.⁸⁰ Predictors for longer-term distress or an increase in distress over time were pre-existing high distress and a low quality of life, having children and having no family members with breast cancer.

Lobb et al (2010) reported the opinions of 34 clinicians working in cancer genetics services in familial cancer clinics in Australia.⁸¹ Many of the clinicians commented that women were emotionally vulnerable following their diagnosis and questioned whether they were able to deal with information about and implications of genetic testing at this point in time. However it was also raised that not providing this information to women at this vulnerable time could have a negative impact on their ability to make informed treatment decisions.

An observational study by Wevers et al (2012) found that BRCA1/2 mutations were found in 10 of 26 breast cancer patients who received rapid genetic testing (and optional testing) offered between diagnosis and surgery.⁸² Six of the 10 had an immediate bilateral mastectomy. Five patients reported that they had frequent worries of recurrence; none indicated that such worries impaired daily functioning. Six patients had clinically relevant levels of breast cancer-specific distress at the time of assessment.

From a recent Australian study based on interviews with women diagnosed with breast cancer aged 50 years or younger, Zilliacus et al (2012) reported the main advantage of treatment focused genetic testing expressed by the women, was the opportunity to receive and emotionally deal with all the bad news at one time.⁸³ Some women also identified increased anxiety, particularly in relation to waiting for the test result, at an otherwise overwhelming time, was a potential disadvantage, however only a small number of these were women who had actually had treatment focused genetic testing.

The protocol of a multicentre randomised clinical trial of rapid genetic counselling and testing in newly diagnosed breast cancer patients has been published by Wevers et al (2011).⁸⁴ The study outcomes include: uptake of direct bilateral mastectomy or delayed prophylactic contralateral mastectomy, cancer risk perception, cancer-related worry and distress, health-related quality of life, decisional satisfaction and the perceived need for and use of additional decisional counselling and psychosocial support. Results of this trial have not yet been published.⁸⁴

Information needs and preferences

The development of resources to support women considering genetic counselling and testing is critical and should provide information on the potential advantages and disadvantages.⁷⁶ Advantages and disadvantages identified by Meiser et al (2008) include: the added stress of undergoing genetic testing around the time of a breast cancer diagnosis, the implications of uninformative genetic test results; the possibility of

delaying surgery for a short time while waiting for genetic testing results, and the implications of this information for the wider family.⁷⁶

Arden-Jones et al (2010) concluded that 'professionals believed that women should be supported in whatever management decisions they considered best, provided these decisions were based on complete and accurate understanding of the genetic test...'.⁸⁵ In particular this study focused on patients with inconclusive test results and the dilemmas around decisions to undertake prophylactic breast surgery.

A recent Australian study undertook in-depth interviews to identify the information and communication needs regarding treatment-focused genetic testing of 26 women newly diagnosed with breast cancer who were aged 50 years or younger, and a psychoeducational resource was developed and pilot tested.^{83, 86} Meiser et al (2012) reported from this study that most women wanted to be informed about treatment-focused genetic testing at or around the time of their cancer diagnosis via a face-to-face consultation, with no clear preference for which type of health professional should provide the information.⁸⁶ Brief written information was viewed as important supporting material and the educational resource developed and piloted was well received.

The protocol for a randomised non-inferiority trial in Australia comparing two different ways of delivering information (brief written information in an educational pamphlet versus standard pre-test genetic counselling about treatment focused genetic testing to younger women newly diagnosed with breast cancer has been reported by Watts et al (2012).⁸⁷ Preliminary results reported for 62 women, all of whom opted for treatment focussed genetic testing, indicated decrease in decisional conflict following receipt of information about genetic testing with no difference in mean change between the two groups.⁸⁸ These early data suggests that both of delivering information about genetic testing to women at breast cancer diagnosis are equally effective.⁸⁸

Acceptability

In a prospective study by Weitzel et al (2003), 32 of 37 women who underwent genetic cancer risk assessment at the time of breast cancer diagnosis, chose to proceed with genetic analysis.⁸⁹ All seven women that were found to have a deleterious BRCA1/2 mutation opted for bilateral mastectomy. Of the 22 women with negative results, two opted for bilateral mastectomy, whereas 20 chose stage-appropriate treatment. The effect of BRCA test results on the use of concurrent risk reduction (bilateral) surgery compared to unilateral surgery was significant ($p < 0.001$).

Stolier et al (2004) reported that of 25 patients who were initially undergoing breast-conserving surgery, five were found to have deleterious mutations.⁹⁰ All five patients who were mutation carriers elected to undergo bilateral mastectomy.

Schwartz et al (2004) reported that rapid genetic testing was declined by 27 (14%) women with newly diagnosed breast cancer who were at high risk of a BRCA1/2 mutation.⁴⁶ Patients in whom a BRCA1/2 mutation was identified, were more likely to undergo bilateral mastectomy (48%), compared to those with uninformative results (24%), or those who declined genetic testing (4%), $p < 0.001$.

In a later report by Schwartz et al (2005), 76% of newly diagnosed women who were offered genetic testing before definitive surgery, chose to have BRCA1/2 testing.⁴⁷ The decision to undergo testing was associated with physician recommendation and

indecision about definitive local treatment. The results suggested that if rapid testing is available and genetic referrals are made for appropriate patients, a high proportion of women are likely to opt for testing. Those who have not yet reached a decision about definitive local treatment may benefit from a genetic referral.

Zilliagus et al (2012) reported from a recent Australian study based on interviews with women diagnosed with breast cancer aged 50 years or younger, positive attitudes towards treatment-focused genetic testing.⁸³ It was reported that women did not feel that an offer of treatment-focused genetic testing shortly after, or at the time of diagnosis, added undue psychological burden and the majority of women in the study felt treatment-focused genetic testing should be incorporated into standard clinical care.

Wevers et al (2012) reported that of 26 female breast cancer patients who had rapid genetic counselling, 25 were happy to have received genetic counselling and testing; 24 were satisfied with the timing, and 23 were satisfied with speed in which DNA test results were made available.⁸²

Summary

Features identified to guide selection for treatment focused genetic counselling and testing include:

- strong family history (family or personal history of breast or ovarian cancer; male family member with breast cancer)
- young age at diagnosis
- triple negative breast cancer
- bilateral breast cancer
- being from an ethnic group with known founder mutations (eg Ashkenazi Jewish ancestry).

Genetic counselling is important to clearly interpret the implications of the test, increase cancer related knowledge, decrease distress pre-operatively and assist in decision making. The delivery of accurate and thorough information by an expert will support women considering genetic counselling and testing.

The psychological impacts of genetic testing reported vary. There are issues such as whether this is too much information at an already vulnerable time further increasing distress levels, as well as uncertainty with decision making. However, the importance of availability of results that could alter treatment decisions was recognised, and in one prospective study, no short- or long-term increase in distress was reported for patients approached for rapid genetic testing. Predictors for higher distress may help identify those individuals at increased risk of distress. Providing adequate information to allow patients to make informed decisions should also be considered.

Levels of acceptability were high with 77-86% of patients opting for rapid genetic testing after it was offered. Factors that influenced the uptake of genetic testing were physician recommendations and indecision about local treatment.

3.4 Ongoing trials

Clinical trials registries were searched to identify any additional studies (see Appendix F).

4 Discussion

Women diagnosed with breast cancer with a germline gene mutation or at high risk of having a germline gene mutation face complex treatment and prevention decisions. The present review systematically appraises and summarises the evidence related to the management of women diagnosed with breast cancer with a BRCA1/2 mutation. It also provides a narrative description of the evidence related to the management of women diagnosed with breast at high risk of having a germline gene mutation due to a strong family history of breast cancer and/or ovarian cancer and those with non-BRCA germline mutations (such as TP53, PTEN, STK11, RAD51C, CHEK2, ATM, BRIP1, and PALB2).

The review will be used to inform the development of recommendations about the management of women diagnosed with breast cancer who have an identified germline gene mutation or are at high risk of having a germline gene mutation.

This systematic review included 76 published articles, published between January 2001 and April 2012 in the English language. The studies identified included prospective and retrospective cohort studies and case-control studies. No randomised controlled trials or pseudo-randomised trials were identified for inclusion in the systematic review. Two well-conducted prospective cohort studies are included in the review. However, many of the studies included in the review are limited by their retrospective design, relatively short-follow-up, sampling biases or lack of control for important demographic characteristics, clinical features and treatment factors in the study design or analysis.

It has been reported that treatment with mastectomy compared to breast conserving treatment (breast conserving surgery and radiotherapy), does not significantly increase survival in women diagnosed with breast cancer with a BRCA1/2 mutation.⁷ Breast conserving treatment has been shown to be as effective in terms of survival for women diagnosed with breast cancer with a BRCA1/2 mutation, as for women with breast cancer not attributable to a BRCA1/2 mutation.⁸⁻¹⁰ There is also evidence that breast conserving treatment and mastectomy are both as effective in decreasing the risk of ipsilateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation, if women are also treated by adjuvant chemotherapy.⁷

There is evidence that adjuvant chemotherapy is as effective in terms of survival for women diagnosed with breast cancer with a BRCA1/2 mutation compared to women with breast cancer not attributable to a BRCA1/2 mutation.^{9, 14-16} There is also evidence that adjuvant chemotherapy (compared to no adjuvant chemotherapy) significantly decreases the risk of ipsilateral breast cancer in women with a BRCA1/2 mutation after breast conserving surgery.^{7, 13} One small retrospective study reported that platinum-based neoadjuvant chemotherapy is better than other types of neoadjuvant chemotherapy (such as CMF or anthracycline-taxanes) in women diagnosed with breast cancer with a BRCA1/2 mutation.¹⁸ The evidence is inconsistent, and derived from small studies,^{17, 19} about whether anthracyclines (without taxanes) are better than taxane regime without an anthracycline or other non-anthracycline regimens in women diagnosed with breast cancer with a BRCA1/2 mutation.

There is evidence that tamoxifen is as effective in terms of survival for women diagnosed with breast cancer with a BRCA1/2 mutation compared to women with breast cancer not attributable to a BRCA1/2 mutation.^{9, 16, 24} There is insufficient evidence to support that tamoxifen significantly reduces ipsilateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation.^{7, 12, 13} The evidence about the effectiveness of tamoxifen (compared to no tamoxifen) on the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation is inconsistent.^{12, 21-23} However, there is evidence that tamoxifen is as effective in terms of reducing the risk of contralateral breast cancer for women diagnosed with breast cancer with a BRCA1/2 mutation compared to women with breast cancer not attributable to a BRCA1/2 mutation.²¹

Women diagnosed with breast cancer, particularly women younger than 50 years, with a BRCA1/2 mutation have a substantially increased risk of contralateral breast cancer.^{23, 73} There is also evidence that contralateral risk-reducing mastectomy in women diagnosed with breast cancer with a BRCA1/2 mutation substantially decreases the risk of contralateral breast cancer.²⁵⁻²⁷ For women diagnosed with breast cancer with a strong family history of breast cancer and no identified BRCA1/2 mutation, there is evidence that these women also have an increased risk of contralateral breast cancer compared to women without a strong family history of breast cancer.⁹¹ Contralateral risk-reducing mastectomy in women diagnosed with breast cancer with a strong family history of breast cancer and no identified BRCA1/2 mutation has been reported to substantially decrease the risk of contralateral breast cancer.^{60, 65}

Risk-reducing salpingo-oophorectomy in women diagnosed with breast cancer with a BRCA1/2 mutation (including women younger and older than 50 years) has been shown to decrease the risk of ovarian/fallopian tube cancer and improves overall survival.²⁶ There is also evidence that, in pre-menopausal women diagnosed with breast cancer with a BRCA1/2 mutation, risk-reducing salpingo-oophorectomy also decreases the risk of contralateral breast cancer.²³ In addition, risk-reducing salpingo-oophorectomy is a significant independent prognostic factor for survival in hereditary breast cancer patients.¹¹

Treatment-focused genetic counselling with and without testing around the time of a breast cancer diagnosis, but before delivery of adjuvant radiotherapy, can influence surgical treatment choices. Preliminary research indicates that genetic testing before definitive surgery may increase the uptake of a therapeutic (ipsilateral) mastectomy, with or without a contralateral risk-reducing mastectomy, rather than breast conserving treatment in women found to carry a BRCA1/2 mutation.^{44, 45, 47-49} Women having breast conserving treatment at diagnosis and who later test positive for a BRCA1/2 mutation and elect for a bilateral mastectomy may have restricted reconstructive options and be at risk of a poorer cosmetic outcome on the irradiated side.^{92, 93} The psycho-social impact of genetic counselling and testing at the time of a breast cancer diagnosis is an emerging area of research.^{47, 80}

5 Conclusion

The present review indicates that the evidence about the management of women diagnosed with breast cancer with a germline gene mutation or at high risk of having a germline gene mutation is limited by the lack of randomised controlled trials or large prospective cohort studies.

However, there is evidence that women diagnosed with breast cancer with a BRCA1/2 mutation have an increased risk of contralateral breast cancer and ovarian cancer and benefit from risk-reducing surgical strategies such as contralateral risk-reducing mastectomy and risk-reducing salpingo-oophorectomy. There is also evidence that breast conserving treatment (breast conserving surgery and radiotherapy) and mastectomy are both as effective in decreasing the risk of ipsilateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation, if women are also treated by adjuvant chemotherapy. There is insufficient evidence to support that women with a BRCA1/2 mutation have increased sensitivity to particular systemic therapies.

Appendix A Contributors

Working group members

Membership of Cancer Australia's *Management of breast cancer in women with an identified gene fault or at high risk of a gene fault* Working Group

This guideline was developed by a multidisciplinary working group convened by Cancer Australia. The chair of this Working Group is Clinical Associate Professor Judy Kirk.

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- A/Prof John Eden Gynaecologist & Reproductive Endocrinologist
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Cancer Australia gratefully acknowledges the contribution from Ms Philippa Middleton, Executive Director, Australian Research Centre for Health of Women and Babies, Robinson Institute, The University of Adelaide.

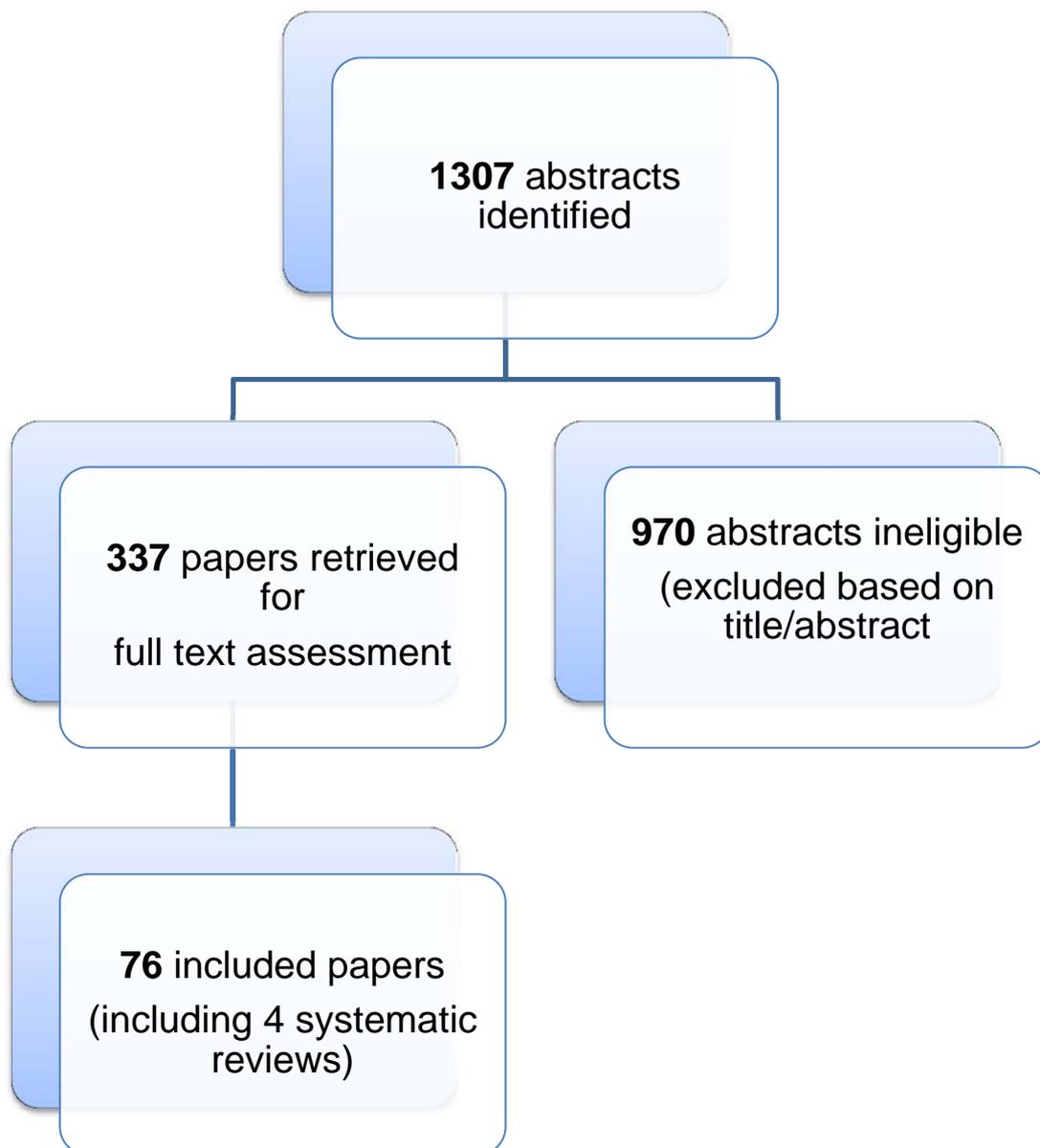
Appendix B Search strategy

Breast cancer	Breast Neoplasms/therapy Breast Neoplasms/disease management
High risk of a gene mutation	Gene mutation Gene mutation, mutation carrier BRCA and mutation, BRCA1, BRCA2 Strong family history Hereditary breast ovarian cancer syndrome Breast Neoplasms/genetics
Surgical management	Breast Neoplasms/surgery Mastectomy, breast conserving therapy, breast conserving surgery
Systemic therapies	Breast Neoplasms/drug therapy Antineoplastic agents/ Chemotherapy, endocrine therapy, systemic therapy
Risk-reducing strategies	contralateral risk-reducing mastectomy, risk reducing salpingo oophorectomy, RRSO, risk-reducing oophorectomy, risk-reducing salpingo oophorectomy, BSO, risk-reducing surgery risk-reducing medication, chemoprevention

Appendix C Health technology assessment, guidelines, and clinical trials websites searched

Acronym	Organisation	Website
<i>Canada</i>		
CCO	Cancer Care Ontario	http://www.cancercare.on.ca/
<i>International</i>		
HTAi	Health Technology Assessment International	http://www.htai.org/
<i>Scotland</i>		
SIGN	Scottish Intercollegiate Guidelines Network	http://www.sign.ac.uk/
<i>UK</i>		
CCT	Current Controlled Trials	http://www.controlled-trials.com/
NICE	National Institute for Health and Clinical Excellence	http://www.nice.org.uk/
NRR	National Research Register	http://www.nrr.nhs.uk/
<i>US</i>		
	ClinicalTrials.gov	http://www.clinicaltrials.gov/
NCI	National Cancer Institute Clinical Trials	http://www.cancer.gov/clinicaltrials
NGC	National Guideline Clearinghouse	http://www.guideline.gov/

Appendix D Flowchart-inclusion/exclusion



Appendix E International guidelines and recommendations

National Breast Cancer and Ovarian Cancer Centre (NBOCC)^a *Advice about familial aspects of breast cancer and epithelial ovarian cancer (2010)*³²

Management of women considered at potentially high risk of breast cancer (but without breast cancer)

- Clarify risk. See <http://www.canceraustralia.gov.au/>
- Advise that although there is a high or potentially high risk of developing breast cancer, and perhaps other cancers, many women in this group will not develop breast cancer
- Advise referral to a family cancer clinic for risk assessment, possible genetic testing and management plan

Discuss risk reduction strategies which may include:

- Risk-reducing surgery
- Consideration of the use of medication, such as tamoxifen or raloxifene, to reduce risk of developing breast cancer

Ongoing surveillance strategies which may include:

- Regular clinical breast examination
- Annual breast imaging with mammography, MRI or ultrasound
- Consideration of ovarian cancer risk (see page 3)
- Discuss possible participation in a relevant clinical trial for risk reduction/prevention of breast cancer. For available trials see www.australiancancertrials.gov.au, www.anzctr.org.au, www.anzbctg.org.au
- Discuss modifiable risk factors for breast cancer
- Encourage all women to be aware of the normal look and feel of their breasts and promptly report persistent or unusual changes to their GP
- Investigate women with symptoms using the Triple Test

^a On 30 June 2011, National Breast and Ovarian Cancer Centre (NBOCC) amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer

European Society of Medical Oncology (ESMO) *Clinical Practice Guidelines* (2011)³⁵

Information provided on the treatment of breast cancer in BRCA1/2 mutation carriers regarding surgery and systemic treatment, relevant excerpts are below:

- “Decisions about surgical treatment of breast cancer in BRCA1/2 mutation carriers should be based on the same parameters as sporadic cancer, while considering the higher risk of contralateral breast cancer”
- “Whether [risk-reducing risk-reducing salpingo-oophorectomy] (PBSO) is associated with a significantly decreased risk of breast cancer in those patients with previous breast cancer in both BRCA1 and BRCA2 is still under investigation. Recent studies show no effect of PBSO on second primary breast cancer risk”
- “Current evidence suggests that the overall prognosis of breast cancer in BRCA carriers is similar to sporadic breast cancers, and BRCA deficiency seems to be predictive of chemosensitivity”
- “[T]here is no definitive conclusion on the best chemotherapy regimen for BRCA breast cancer patients, and standard prognostic features should be used to decide treatment in BRCA1/2 mutation carriers with breast cancer”
- “Contralateral risk-reducing mastectomy is an option to consider in BRCA1/2 mutation carriers with early breast cancer and unilateral mastectomy”
- “Adjuvant tamoxifen reduces the risk of contralateral breast cancer in affected BRCA1/2 mutation carriers”

ESMO 2011 guidelines also include information on referral for BRCA testing.

National Comprehensive Cancer Network (NCCN) *Guidelines on invasive breast cancer* (2012)³⁶

No specific treatment recommendations for known BRCA1/2 mutation carriers. However, special considerations for breast-conserving therapy requiring radiation therapy note that a relative contraindication for this therapy includes women with a known or suspected genetic predisposition to breast cancer as they may have an increased risk of ipsilateral breast cancer or contralateral breast cancer with breast conserving therapy. Risk-reducing risk-reducing mastectomy for risk reduction may be considered for these women.

NCCN *guidelines on Breast and/or Ovarian Cancer Genetic Assessment* (2012)³⁶

Criteria for people who require further risk evaluation

An affected individual with one or more of the following:

- Early-age-onset breast cancer (≤ 50 y)
- Triple negative breast cancer (ER-, PR-, HER2-)
- Two breast cancer primaries in a single individual

- Breast cancer at any age, with
 - ≥1 close blood relative with breast cancer ≤50y, or
 - ≥1 close blood relative with epithelial ovarian/fallopian tube/primary peritoneal cancer at any age, or
 - ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age
- A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumours, diffuse gastric cancer, dermatologic manifestations or leukemia/lymphoma on the same side of family.
- Ovarian/fallopian tube/primary peritoneal cancer
- Male breast cancer

New Zealand Guidelines Group *Management of Early Breast Cancer* (2009)³⁴

Surgery

Good practice point:

- Breast conserving surgery should be used with caution in known BRCA gene carriers as it may result in high local breast cancer rates.

Follow-up

Good practice point:

- For a woman at high risk of contralateral breast cancer (eg, BRCA1 or BRCA2 gene carriers) mammography of the contralateral breast should be performed no later than 12 months after the post-diagnostic mammogram and other imaging modalities may also be considered.

Genetic Testing

Recommendations:

- All women from high risk families* should be offered referral to their regional genetics centre for information on genetic testing.

* Important risk factors include: early onset breast cancer, multiple affected family members, male breast cancer, risk-reducing breast cancer, ovarian cancer, Ashkenazi Jewish ancestry, or a known BRCA1 or BRCA2 mutation in the family.

- Genetic counselling should be undertaken by a health practitioner with appropriate training (a certified genetic counsellor or medical geneticist)
- Pre-test genetic counselling should include discussion of the following:
 - Aim of testing, inheritance, accuracy of the test (sensitivity and specificity)

- Timeframe for providing results
 - Uncertainty of cancer risk estimates with a mutation
 - Possible test results (positive, negative, uninformative or variant of unknown clinical significance)
 - Implications for the individual and family including clinical management options, psychosocial impact of testing, potential risks of discrimination (eg, by life and health insurers)
 - Alternative options to testing
- Genetic testing aimed at identifying a mutation in a family should be offered to an affected family member. If a mutation is identified, predictive testing can then be offered to adult at-risk family members.
 - Women or men with an estimated probability of 20% or greater of carrying a BRCA1 or BRCA2 mutation (probability estimated by use of models such as BRCAPRO or BOADICEA, and clinical judgment) should have access to genetic testing.
 - Interpretation of test results and estimation of cancer risks for the family should take into account pedigree information, the analytical and clinical validity of the test methodology, and the penetrance and nature of the detected mutation.

Risk-reducing Surgery

Note: For women with a high genetic or familial risk for breast cancer, rather than diagnosed with breast cancer.

Recommendations:

- A woman with a significant family history of breast cancer or who is known to carry a BRCA1 or BRCA2 gene mutation should be offered the option of risk-reducing mastectomy. Risk-reducing salpingo-oophorectomy should also be discussed.
- A woman with a significant family history of breast cancer or who is known to carry a BRCA1 or BRCA2 gene mutation should have genetic counselling in a specialist cancer genetics clinic.
- For pre-menopausal women with a significant family history of breast cancer or who are known to carry a BRCA1 or BRCA2 mutation, information about risk-reducing salpingo-oophorectomy as a potential risk-reducing strategy for breast cancer should be made available.
- In women considering risk-reducing salpingo-oophorectomy, the lack of efficacy of screening should be discussed.

International guidelines for genetic counselling and testing

NCCN Guidelines Version 1. 2012. *Breast and/or Ovarian Cancer Genetic Assessment (2012)*³⁶

Criteria for people who require further risk evaluation^a

An affected individual with one or more of the following:

- Early-age-onset breast cancer (≤ 50 y)^b
- Triple negative breast cancer (ER-, PR-, HER2-)
- Two breast cancer primaries^c in a single individual
- Breast cancer at any age, and
 - ≥ 1 close blood relative^d with breast cancer ≤ 50 y, or
 - ≥ 1 close blood relative^d with epithelial ovarian^e cancer at any age, or
 - ≥ 2 close blood relatives^d with breast cancer and/or pancreatic cancer at any age
 - From a population at increased risk^f
- A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumours, diffuse gastric cancer,^g dermatologic manifestations^h or leukemia/lymphoma on the same side of family.
- Ovarian^e cancer
- Male breast cancer

Genetic counselling is highly recommended when genetic testing is offered and after results are disclosed. A genetic counsellor, medical geneticist, oncologist, surgeon, oncology nurse or other health professional with expertise and experience in cancer genetics should be involved early in counselling patients who potential meet criteria.

^aThe criteria for further risk evaluation and genetic testing are not identical. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer

^bClinically use age ≤ 50 y because studies define early onset as either ≤ 40 or ≤ 50 y

^cTwo breast primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously

^dClose blood relatives include first-, second-, and third-degree relatives

^eFor the purposes of these guidelines, fallopian tube and primary peritoneal cancers are included

^fFor populations at increased risk, requirements for inclusion may be modified (eg, women of Ashkenazi Jewish descent with breast or ovarian cancer at any age)

^gFor lobular breast cancer with a family history of diffuse gastric cancer, CDH1 gene testing should be considered

^hFor dermatologic manifestations

New Zealand Guidelines Group *Management of Early Breast Cancer (2009)*³⁴

Genetic Testing Recommendations

All women from high risk* families should be offered referral to their regional genetics centre for information on genetic testing. *Important risk factors include: early onset breast cancer, multiple affected family members, male breast cancer, bilateral breast cancer, ovarian cancer, Ashkenazi Jewish ancestry, or a known BRCA1 or BRCA2 mutation in the family.

Genetic counselling should be undertaken by a health practitioner with appropriate training (a certified genetic counsellor or medical geneticist).

Pre-test genetic counselling should include discussion of the following:

- Aim of testing, inheritance, accuracy of the test (sensitivity and specificity)
- Timeframe for providing results
- Uncertainty of cancer risk estimates with a mutation
- Possible test results (positive, negative, uninformative or variant of unknown clinical significance)
- Implications for the individual and family including clinical management options, psychosocial impact of testing, potential risks of discrimination (eg, by life and health insurers)
- Alternative options to testing

Genetic testing aimed at identifying a mutation in a family should be offered to an affected family member. If a mutation is identified, predictive testing can then be offered to adult at-risk family members.

Women or men with an estimated probability of 20% or greater of carrying a BRCA1 or BRCA2 mutation (probability estimated by use of models such as BRCAPRO or BOADICEA, and clinical judgment) should have access to genetic testing.

Interpretation of test results and estimation of cancer risks for the family should take into account pedigree information, the analytical and clinical validity of the test methodology, and the penetrance and nature of the detected mutation.

Appendix F Ongoing trials

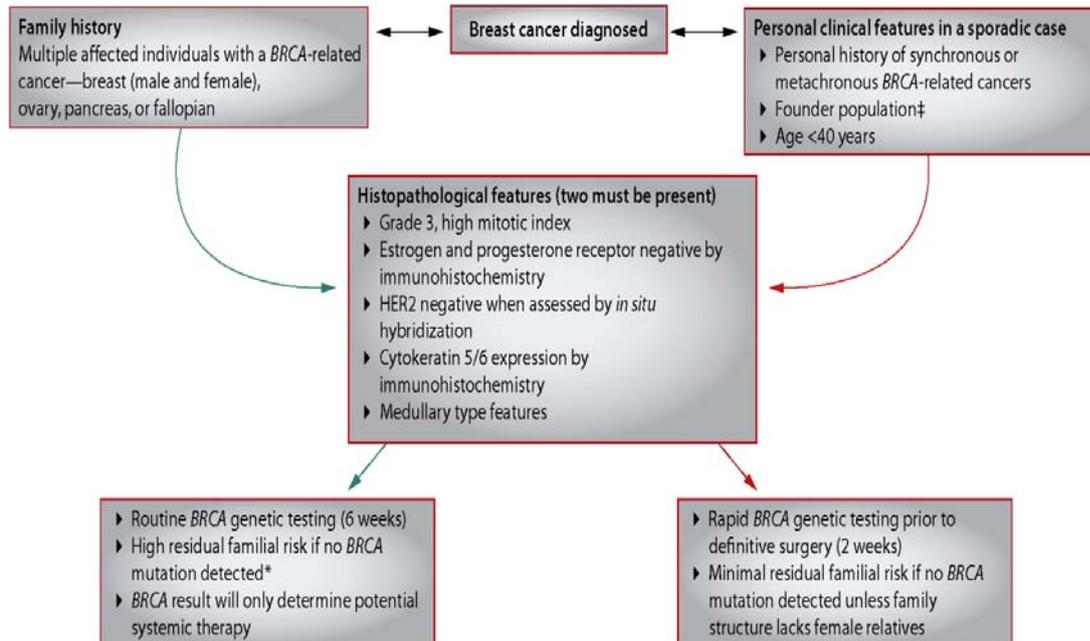
Trial name Location	Study design	Participants	Intervention	Control	Completion Status
NCT01630226 ⁹⁴ Poland	Single center, non-randomised, open label phase II trial	Patients diagnosed with breast cancer with a BRCA1 mutation n=estimated enrolment is 100	Patients will be treated with neoadjuvant cisplatin chemotherapy at a dose of 75mg/m ² every three weeks for a total of four cycles (4 cycles of neoadjuvant chemotherapy)	No control group.	Currently recruiting participants
NCT01074970 ⁹⁵ US	Multicentre, randomised, open label phase II trial	Triple Negative Breast Cancer (ER-/PR- /HER2-)With BRCA1/2 Mutations n=estimated enrolment is 135	Single agent cisplatin Cisplatin 75 mg/m ² IV infusion over 60 minutes, D1 every 21 days for 4 cycles	Patients treated with cisplatin in combination with Rucaparib following preoperative chemotherapy Rucaparib 24mg C1,30mg C2-4, D1,2,3 every 21 days for 4 cycles Cisplatin 75 mg/m ² IV infusion over 60 minutes, D1 every 21 days for 4 cycles	Ongoing, not recruiting participants

Trial name Location	Study design	Participants	Intervention	Control	Completion Status
NCT00579007 ⁹⁶ USA	Observational, prospective cohort	Personal or family history of breast and/or ovarian cancer showing clinical features associated with increased risk of carrying a BRCA1/2 mutation or having first degree relative with known BRCA1 or BRCA2 mutation n=estimated enrolment 224	Behavioural: telephone interviews Baseline, 1 week, 6 months and 12 months post-notification of the individuals genetic testing, follow up interviews will take place 1 month, 6 months and 12 months after the initial counselling visit.	No control group	Ongoing, not recruiting participants
NCT00783822 ⁹⁷ The Netherlands	Randomised controlled, open label trial	Newly diagnosed breast cancer 10% or higher chance of carrying BRCA1/2 gene mutation n=estimated enrolment 265	Rapid genetic counselling and testing	Usual care	Ongoing, not recruiting participants

Trial name Location	Study design	Participants	Intervention	Control	Completion Status
Prospective study of Outcomes: Sporadic versus Hereditary breast cancer (POSH): study protocol ⁹⁸	Prospective Cohort study	Women diagnosed with invasive breast cancer, aged between 41 and 50 years plus a known BRCA1 or BRCA2 gene mutation n=3000	<i>Aim of the study</i> Measuring prognosis of patients with breast cancer who harbour BRCA1 and BRCA2 gene mutations and if this differs from non-carrier patients	See Intervention	Ongoing, not recruiting participants
Korean Hereditary Breast Cancer ⁹⁹	Multicentre, Prospective cohort	Subjects with breast cancer n=2000	<i>Aim of the study</i> Estimate the prevalence of BRCA1/2 mutations and ovarian cancer among a high-risk group of patients with hereditary breast cancer and their families	See Intervention	Currently recruiting participants

Appendix G Indications for germline testing in a patient presenting with breast cancer

Indications for genetic testing, from review by Trainer et al.⁴³



Indications for germline testing in a patient presenting with breast cancer. *In the presence of a strong family history of breast cancer, *BRCA* testing is less informative with regard to definitive surgery, as the absence of a mutation still leaves a potential high residual familial breast cancer risk. A targeted founder screen involves looking for common founder mutations associated with a high-risk geographic or ethnic group. If a founder screen is negative, a full *BRCA* screen should be considered if warranted on the basis of family history.⁴³

Appendix H Abbreviations

BCSS	breast cancer-specific survival
BCT	breast conserving treatment (breast conserving surgery and radiotherapy)
CBC	contralateral breast cancer
CRRM	contralateral risk-reducing mastectomy
CI	confidence Interval
Cul	cumulative Incidence
HBC	non-specified hereditary breast cancer (Non-carriers and non-tested familial cases)
HR	hazard ratio
IBC	ipsilateral breast cancer
M	mastectomy
OS	overall survival
NS	no statistically significant difference
NSD	no significant difference
NST	neoadjuvant systemic chemotherapy
RRSO	risk-reducing salpingo-oophorectomy
SD	significant difference
Yr	year

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