

Recommendations for the management of early breast cancer

in women with an identified BRCA1 or BRCA2 gene mutation or at high risk of a gene mutation

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A CLINICAL PRACTICE GUIDELINE DEVELOPED BY CANCER AUSTRALIA

This document supplements information contained in the *Clinical practice guidelines for the management of advanced breast cancer*, 2001.¹

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Purpose

This guideline includes statements and recommendations based on available evidence about the management of *early breast cancer* in women with an identified BRCA1 or BRCA2 *gene mutation* or at high risk of such a gene mutation predisposing to breast cancer. The guideline provides health professionals with information designed to assist in making management recommendations for improved patient outcomes.

Endorsed by:



Background

Approximately 5-10% of breast cancers are due to *germline mutations* in genes including BRCA1 and BRCA2.^{2,3} Other high risk breast cancer genes in which mutations have been identified, but at lower frequency, include TP53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome) and STK11 (Peutz-Jeghers syndrome).² More recently, moderate and low risk germline mutations have been identified in genes such as CHEK2, ATM, BRIP1, PALB2, and RAD51C.^{2,4}

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.^{5,6} 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.^{5,6} Over half of women (58%) with BRCA1 mutations and a quarter of women (28%) with BRCA2 mutations are diagnosed with cancer before the age of 50 years.²

A systematic review⁷ on the management of *early breast cancer* in women with an identified BRCA1 or BRCA2 *gene mutation* or at high risk of a gene mutation was undertaken. High risk includes women whose personal and/or family history indicates a possible genetic susceptibility but where genetic testing is yet to be conducted or is inconclusive.⁸ The scope of the systematic review was limited to studies of breast cancer in women diagnosed with non-metastatic breast cancer (early breast cancer, or potentially curable locally advanced breast cancer).

Grading Of Clinical Practice Recommendations

The recommendations are based on the statements of evidence for the management of *early breast cancer* in women with an identified BRCA1/2 mutation. Practice points and supporting information are also provided to help guide the management of early breast cancer in women with an identified BRCA 1/2 or TP53 *gene mutation* or at high risk of having a germline gene mutation. Practice points are based on expert opinion when the evidence to make a recommendation is insufficient or when the evidence is outside the scope of the systematic review.

All recommendations have been graded using the National Health and Medical Research Council (NHMRC) FORM methodology.⁹ The NHMRC grades (A-D) assigned to the recommendation given are intended to indicate the strength of the body of evidence underpinning the recommendation (refer to Table 1). Appendix 1 provides further detail of the NHMRC FORM grading methodology and the process undertaken in the grading of all recommendations contained in this guideline. See also Appendix 2 for Evidence statements underpinning all recommendations.

Table 1: Definition of NHMRC grades of recommendations^{9,10}

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Clinical Practice Recommendations And Practice Points

Recommendations and practice points should be considered in the context of clinical judgement for each woman. Considerations should include the absolute benefits and harms of treatments, other treatments used, women's preferences and *quality of life* issues. These factors should be discussed with the woman and her family, tailored to their preferences for information and decision-making involvement.

Multidisciplinary care is the best practice approach to providing evidence-based cancer care. *Multidisciplinary care* is an integrated team-based approach to cancer care where medical and allied health care professionals consider all relevant treatment options and collaboratively develop an individual treatment and care plan for each patient.¹¹



The recommendations for the management of *early breast cancer* in women with an identified BRCA1 or BRCA2 *gene mutation* or at high risk of a gene mutation should be considered within a multidisciplinary team setting.

RECOMMENDATIONS – SURGERY		Grade	Evidence State-ments	References
Surgical management, with or without <i>radiotherapy</i>, on the ipsilateral side for women diagnosed with breast cancer with a BRCA1/2 mutation				
1	<p>Offer a choice of either breast conserving treatment (breast conserving surgery and radiotherapy) or <i>mastectomy</i> to women diagnosed with breast cancer with a BRCA1/2 mutation as both are effective in terms of survival.</p> <ul style="list-style-type: none"> • If women diagnosed with breast cancer with a BRCA1/2 mutation are considering a contralateral risk-reducing mastectomy (at the time of the cancer diagnosis or in the future) inform them that therapeutic ipsilateral mastectomy may be preferable to breast conserving treatment. • Inform women diagnosed with breast cancer with a BRCA1/2 mutation that there is an increased risk of ipsilateral breast cancer after breast conserving treatment compared to mastectomy, but this is reduced by <i>adjuvant chemotherapy</i>.#(see practice points B and F). 	C*	A1, A2, A3 and A4 Also see C2	Pierce 2010 ¹² Kirova 2010 ¹³ Garcia-Etienne 2009 ¹⁴ Brekelmans 2007 ¹⁵ Pierce 2006 ¹⁶ Seynaeve 2004 ¹⁷ Robson 2004 ¹⁸ Haffty 2002 ¹⁹
2	Recommend radiotherapy after <i>breast conserving surgery</i> in women diagnosed with breast cancer with a BRCA1/2 mutation to decrease the risk of ipsilateral breast cancer (as similarly recommended to other women with breast cancer that is not attributable to a BRCA1/2 mutation).	C*	A5 and A6	Metcalfe, Lynch 2011 ²⁰ Shanley 2006 ²¹ Pierce 2000 ²²

* The grading of these recommendations reflects the low level of evidence available for this specific population.

PRACTICE POINT – GENETIC COUNSELLING AND TESTING		
A	Offer <i>genetic counselling</i> to women diagnosed with breast cancer who are considered at high risk of a mutation in a breast cancer predisposition gene at the time of diagnosis. If possible, also offer women genetic testing shortly after their breast cancer diagnosis to inform decision-making.	Schlich-Bakker 2008 ²³ Tuttle 2008 ²⁴ Evans 2005 ²⁵ Stolier 2005 ²⁶ Schwartz 2004 ²⁷ Meijers-Heijboer 2003 ²⁸



PRACTICE POINT – GENETIC COUNSELLING AND TESTING

PRACTICE POINTS – SURGERY

B	#After breast conserving treatment, <i>adjuvant endocrine therapy</i> (which may include premenopausal oophorectomy/ovarian suppression) should be used when appropriate based on hormone receptor status to reduce the risk of ipsilateral and contralateral events.	
C	Offer similar advice and care, as described in Recommendations 1 & 2 above, to women diagnosed with breast cancer with a strong family history of breast and/or <i>ovarian cancer</i> and no identified BRCA1/2 mutation.	Reiner 2013 ²⁹ Kirova 2010 ¹³ Brekelmans 2007 ¹⁵ Tilanus-Linthorst 2006 ³⁰ Seynaeve 2004 ¹⁷ Vlastos 2002 ³¹
D	When mastectomy is offered, give women the opportunity to consider breast reconstruction either at the time of the initial surgery or as a delayed procedure.	NBCC ¹
E	Avoid <i>radiotherapy</i> when possible in women with breast cancer and a germline TP53 mutation, due to possible increased second malignancy risk and other adverse effects. <i>Mastectomy</i> is preferable to <i>breast conserving surgery</i> in these women. However, offer radiotherapy if a woman chooses breast conserving surgery or if it is indicated post-mastectomy.	Heymann 2010 ³² Salmon 2007 ³³

RECOMMENDATIONS – SYSTEMIC THERAPIES	Grade	Evidence Statements	References
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Neoadjuvant/adjuvant systemic therapies in women diagnosed with breast cancer with a BRCA1/2 mutation

3	Base the <i>use of</i> neoadjuvant/adjuvant <i>chemotherapy</i> for women diagnosed with breast cancer with a BRCA1/2 mutation on similar considerations for women with breast cancer not attributable to a BRCA1/2 mutation.	C*	B1, B2, B3, B7, B8 and B9	Goodwin 2012 ³⁴ Metcalf, Lynch 2011 ²⁰ Metcalf, Gershman 2011 ³⁵ Arun 2011 ³⁶ Pierce 2010 ¹² Reding 2010 ³⁷ Rennert 2007 ³⁸ Brekelmans 2006 ³⁹ Robson 2004 ¹⁸
4	Base the <i>type of</i> neoadjuvant/adjuvant chemotherapy for women diagnosed with breast cancer with a BRCA1/2 mutation on similar considerations for women with breast cancer not attributable to a BRCA1/2 mutation.	C*	B4, B5 and B6	Arun 2011 ³⁶ Byrski 2010 ⁴⁰ Fourquet 2009 ⁴¹ Byrski 2008 ⁴²
5	Base the <i>use and type of</i> Selective Estrogen Receptor Modulators (SERMs) in women diagnosed	C*	B12, B13, B14 and, B15	Phillips 2013 ⁴³ Goodwin 2012 ³⁴



RECOMMENDATIONS – SYSTEMIC THERAPIES		Grade	Evidence Statements	References
	with ER (Oestrogen Receptor) positive breast cancer with a BRCA1/2 mutation on similar considerations for women with breast cancer not attributable to a BRCA1/2 mutation.			Metcalfe, Lynch 2011 ²⁰ Metcalfe, Gershman 2011 ³⁵ Reding 2010 ³⁷ Pierce 2010 ¹² Pierce 2006 ¹⁶ Gronwald 2006 ⁴⁴ Robson 2004 ¹⁸ Foulkes 2002 ⁴⁵

* The grading of these recommendations reflects the low level of evidence available for this specific population.

PRACTICE POINT – GENETIC COUNSELLING AND TESTING		
A	Offer <i>genetic counselling</i> to women diagnosed with breast cancer who are considered at high risk of a mutation in a breast cancer predisposition gene at the time of diagnosis. If possible, also offer women genetic testing shortly after their breast cancer diagnosis to inform decision-making.	Schlich-Bakker 2008 ²³ Tuttle 2008 ²⁴ Evans 2005 ²⁵ Stolier 2005 ²⁶ Schwartz 2004 ²⁷ Meijers-Heijboer 2003 ²⁸

PRACTICE POINT – SYSTEMIC THERAPIES		
F	#Adjuvant <i>endocrine therapy</i> (which may include premenopausal oophorectomy/ovarian suppression) should be used when appropriate based on hormone receptor status to reduce the risk of ipsilateral and contralateral events.	

RECOMMENDATIONS – SURGICAL RISK-REDUCING STRATEGIES	Grade	Evidence Statements	References
Surgical risk-reducing strategies in women diagnosed with breast cancer with a BRCA1/2 mutation			
6	Discuss contralateral risk-reducing <i>mastectomy</i> with women diagnosed with breast cancer with a BRCA1/2 mutation, particularly in younger women (less than 50 years), to substantially decrease the risk of <i>contralateral breast cancer</i> .	C1 and C2	Domchek 2010 ⁴⁶ Brekelmans 2006 ³⁹ Van Sprundel 2005 ⁴⁷ Metcalfe 2004 ⁴⁸



RECOMMENDATIONS – SURGICAL RISK-REDUCING STRATEGIES	Grade	Evidence Statements	References
7 Discuss risk-reducing <i>salpingo-oophorectomy</i> with women diagnosed with breast cancer with a BRCA1/2 mutation around the age of 40 years or when child-bearing is complete to improve overall survival and substantially decrease the risk of ovarian/fallopian tube cancer.	B	C3, C4, C5 and C6	Metcalfe, Lynch 2011 ²⁰ Metcalfe, Gershman 2011 ³⁵ Pierce 2010 ¹² Domchek 2010 ⁴⁶ Pierce 2006 ¹⁶ Brekelmans 2006 ³² Van Sprundel 2005 ⁴⁷
PRACTICE POINT – GENETIC COUNSELLING AND TESTING			
A Offer <i>genetic counselling</i> to women diagnosed with breast cancer who are considered at high risk of a mutation in a breast cancer predisposition gene at the time of diagnosis. If possible, also offer women genetic testing shortly after their breast cancer diagnosis to inform decision-making.			Schlich-Bakker 2008 ²³ Tuttle 2008 ²⁴ Evans 2005 ²⁵ Stolier 2005 ²⁶ Schwartz 2004 ²⁷ Meijers-Heijboer 2003 ²⁸
PRACTICE POINTS – SURGICAL RISK-REDUCING STRATEGIES			
G Offer similar advice and care, as described in Recommendation 6 above, to women diagnosed with breast cancer with a strong family history of breast cancer and no identified BRCA1/2 mutation. Offer similar advice and care, as described in Recommendations 6 & 7 above, to women diagnosed with breast cancer with a strong family history of breast and ovarian cancer and no identified BRCA1/2 mutation.			Reiner 2013 ²⁹
H Women diagnosed with breast cancer with a BRCA1/2 mutation considering <i>endocrine therapy</i> after a risk-reducing salpingo-oophorectomy may benefit from either an <i>aromatase inhibitor</i> or <i>tamoxifen</i> .			

Statements Of Evidence

The statements of evidence are based on evidence identified in the Cancer Australia systematic review.⁷ Further details are available in the Cancer Australia systematic review and the Evidence from trial or study results section. The systematic review focused on evidence for the management of breast cancer in women with an identified BRCA1/2 mutation.

The level of evidence assigned to the recommendation is based on the NHMRC Evidence Hierarchy: Aetiology⁴⁹

STATEMENTS OF EVIDENCE – SURGERY	Level of evidence	Reference
Survival outcomes		



STATEMENTS OF EVIDENCE – SURGERY		Level of evidence	Reference
A1	Mastectomy results 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).	III-2	Pierce 2010 ¹²
A2	Breast conserving treatment [#] has 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[†] .	III-2	Kirova 2010 ¹³ Seynaeve 2004 ¹⁷ Robson 2004 ¹⁸
Ipsilateral breast cancer (recurrence of the primary or a second primary)			
A3	Breast conserving treatment [#] has similar ipsilateral breast cancer risks in women with breast cancer with a BRCA1/2 mutation in comparison to other women with breast cancer[†] (when matched for age).	III-2/3	Kirova 2010 ¹³ Garcia-Etienne 2009 ¹⁴ Brekelmans 2007 ¹⁵ Pierce 2006 ¹⁶ Seynaeve 2004 ¹⁷ Robson 2004 ¹⁸ Haffty 2002 ¹⁹
A4	Breast conserving treatment [#] in women with breast cancer with a BRCA1/2 mutation is associated with a significant increase in the risk of ipsilateral breast cancer in comparison to a mastectomy (with and without radiotherapy). However, no significant difference was seen in the risk of ipsilateral breast cancer in women who had breast conserving treatment [#] and chemotherapy compared to mastectomy alone.	III-2	Pierce 2010 ¹²
A5	Radiotherapy (in comparison to no radiotherapy) after breast conserving surgery in women with breast cancer with a BRCA1 mutation significantly decreases the risk of ipsilateral breast cancer.	III-2	Metcalfe, Lynch 2011 ²⁰
Adverse effects			
A6	There is evidence from two Level III-2 retrospective cohort studies that there is no significant increase in clinically significant acute or late toxicity from radiotherapy in women with a BRCA1/2 mutation in comparison to other women with breast cancer[†] .	III-2	Shanley 2006 ²¹ Pierce 2000 ²²
A7	Radiotherapy (in comparison to no radiotherapy) after breast surgery in women with a germline TP53 mutation may be associated with an increased risk of radiation induced malignancies.	IV	Heymann 2010 ³² Salmon 2007 ³³

[#] Breast conserving treatment refers to breast conserving surgery and radiotherapy.

[†] 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 and women who have not been proven to have a BRCA1/2 mutation with genetic testing.



STATEMENTS OF EVIDENCE – SYSTEMIC THERAPIES		Level of evidence	Reference
CHEMOTHERAPY			
Survival outcomes			
B1	Women with breast cancer with a BRCA1/2 mutation who do not receive <i>adjuvant chemotherapy</i> may have poorer overall and breast cancer-specific survival in comparison to other women with breast cancer [†] who <i>do not receive</i> chemotherapy.	II	Goodwin 2012 ³⁴ Robson 2004 ¹⁸
B2	Neoadjuvant and adjuvant chemotherapy show 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 [†] .	II/III-2	Goodwin 2012 ³⁴ Arun 2011 ³⁶ Rennert 2007 ³⁸ Brekelmans 2006 ³⁹ Robson 2004 ¹⁸
B3	Breast cancer specific survival has not been shown to differ significantly in women with a BRCA1/2 mutation treated with adjuvant chemotherapy (in comparison to no adjuvant chemotherapy), although one study showed a trend (p= 0.06) towards improvement with adjuvant chemotherapy.	III-2	Rennert 2007 ³⁸ Brekelmans 2006 ³⁹
Pathological complete response (pCR)			
B4	Women with breast cancer with a BRCA1 mutation have better rates of pathological complete response to platinum-based chemotherapy in comparison to other types of neoadjuvant chemotherapy (such as <i>CMF</i> or <i>anthracycline-taxanes</i> AT).	III-2	Byrski 2010 ⁴⁰
B5	It is unclear which <i>taxane</i> based chemotherapy, <i>anthracyclines</i> (without taxanes) or other non-taxane regimens are most effective in women with breast cancer with a BRCA1/2 mutation.	III-2	Arun 2011 ³⁶ Byrski 2008 ⁴²
B6	Women with breast cancer with a BRCA1/2 mutation may have a better response in terms of the rate of complete clinical response to anthracyclines (without taxanes) in comparison to other women with breast cancer [†] .	III-2	Fourquet 2009 ⁴¹
Ipsilateral breast cancer (recurrence of the primary or a second primary)			
B7	Adjuvant chemotherapy significantly decreases the risk of ipsilateral breast cancer (in comparison to no adjuvant chemotherapy) in women with a BRCA1/2 mutation after breast conserving surgery.	III-2	Metcalfe, Lynch 2011 ²⁰ Pierce 2010 ¹²
Contralateral breast cancer			
B8	It is unclear whether the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation is decreased with adjuvant chemotherapy (in comparison to no adjuvant chemotherapy).	III-2	Metcalfe, Gershman 2011 ³⁵ Reding 2010 ³⁷
B9	Adjuvant chemotherapy shows similar decreases in the risk of contralateral breast cancer in women with breast cancer with	III-3	Reding 2010 ³⁷



STATEMENTS OF EVIDENCE – SYSTEMIC THERAPIES		Level of evidence	Reference
	a BRCA1/2 mutation in comparison to other women with breast cancer [†] .		
ENDOCRINE THERAPY			
Survival outcomes			
B10	There was no evidence identified that investigated the effectiveness of <i>endocrine therapies</i> other than tamoxifen.		
B11	There was no evidence identified that compared survival outcomes in women with breast cancer with a BRCA1/2 mutation with and without tamoxifen.		
B12	Tamoxifen shows similar risks of death, of death from breast cancer and of breast cancer specific survival for women, for women with breast cancer with a BRCA1/2 mutation compared to other women with breast cancer [†] (although women with breast cancer with a BRCA1 mutation who do not receive tamoxifen may have a significantly higher <i>relative risk</i> of death from breast cancer and a significantly poorer breast cancer-specific survival compared to other women with breast cancer [†] who do not receive tamoxifen).	II/III-2	Goodwin 2012 ³⁴ Robson 2004 ¹⁸ Foulkes 2002 ⁴⁵
Ipsilateral breast cancer (recurrence of the primary or a second primary)			
B13	It is unclear whether tamoxifen (compared to no tamoxifen) significantly reduces ipsilateral breast cancer in women with breast cancer and a BRCA1/2 mutation (although one study showed a non-significant trend towards reduced risk of ipsilateral breast cancer (p=0.08) in women with a BRCA2 mutation treated with tamoxifen).	III-2	Metcalfe, Lynch 2011 ²⁰ Pierce 2010 ¹² Pierce 2006 ¹⁶
Contralateral breast cancer			
B14	Tamoxifen (compared to no tamoxifen) may reduce the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation.	III-2/3	Phillips 2013 ⁴³ Metcalfe, Gershman 2011 ³⁵ Reding 2010 ³⁷ Pierce 2006 ¹⁶ Gronwald 2006 ⁴⁴
B15	Tamoxifen shows similar decreases in risk of contralateral breast cancer in women with breast cancer with a BRCA1/2 mutation in comparison to other women with breast cancer [†] .	III-3	Reding 2010 ³⁷

[†] 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 and women who have not been proven to have a BRCA1/2 mutation with genetic testing.

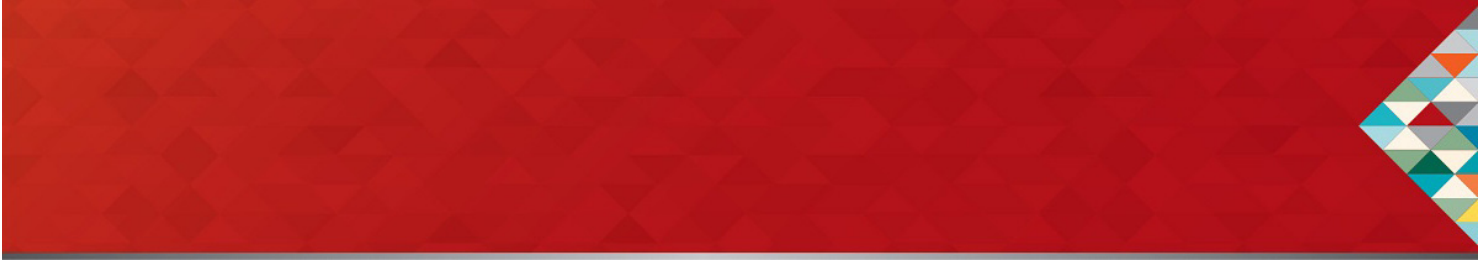


STATEMENTS OF EVIDENCE – SURGICAL RISK-REDUCING STRATEGIES		Level of evidence	Reference
CONTRALATERAL RISK-REDUCING MASTECTOMY			
Survival outcomes			
C1	It is unclear whether contralateral risk-reducing mastectomy (compared to no contralateral risk-reducing mastectomy) improves overall survival or breast cancer-specific survival in women with breast cancer and a BRCA1/2 mutation.	III-2	Brekelmans 2006 ³⁹ Van Sprundel 2005 ⁴⁷
Contralateral breast cancer			
C2	Contralateral risk-reducing mastectomy (compared to no contralateral risk-reducing mastectomy) substantially decreases (by more than 90%) the risk of contralateral breast cancer, particularly in younger women (less than 50 years) with breast cancer with a BRCA1/2 mutation.	II	Domchek 2010 ⁴⁶ Van Sprundel 2005 ⁴⁷ Metcalf 2004 ⁴⁸
RISK-REDUCING SALPINGO-OOPHORECTOMY			
Survival outcomes			
C3	Risk-reducing <i>salpingo-oophorectomy</i> (compared to no risk-reducing salpingo-oophorectomy) improves overall survival and breast cancer-specific survival in women with breast cancer and a BRCA 1/2 mutation. Risk-reducing salpingo-oophorectomy was associated with overall survival benefit in women of all ages.	II/III-2	Domchek 2010 ⁴⁶ Brekelmans 2006 ³² Van Sprundel 2005 ⁴⁷
Ipsilateral breast cancer (recurrence of the primary or a second primary)			
C4	It is unclear whether risk-reducing salpingo-oophorectomy (compared to no risk-reducing salpingo-oophorectomy) decreases the risk of ipsilateral breast cancer in women with breast cancer with a BRCA1/2 mutation.	III-2	Metcalf, Lynch 2011 ²⁰ Domchek 2010 ⁴⁶ Pierce 2010 ¹² Pierce 2006 ¹⁶
Contralateral breast cancer			
C5	Risk-reducing salpingo-oophorectomy (compared to no risk-reducing salpingo-oophorectomy) may decrease the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation under 50 years of age.	III-2	Metcalf, Gershman 2011 ³⁵
Ovarian/fallopian tube cancer			
C6	Risk-reducing salpingo-oophorectomy (compared to no risk-reducing salpingo-oophorectomy) decreases the risk of <i>ovarian cancer</i> in women diagnosed with breast cancer with a BRCA1/2 mutation.	II	Domchek 2010 ⁴⁶

† 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 and women who have not been proven to have a BRCA1/2 mutation with genetic testing.

Evidence From Trial Or Study Results





A Cancer Australia systematic review⁷ on the management of *early breast cancer* in women with an identified BRCA1 or BRCA2 *gene mutation* or at high risk of a gene mutation was undertaken, with available evidence published between January 2001 and April 2012. Additional relevant articles, published after the completion of the review up until August 2013 have also been considered.

A systematic literature search was conducted in Medline, Embase, Pubmed and the Cochrane Database of Systematic Reviews to identify relevant studies which addressed the inclusion criteria. A search of key oncology organisations, guidelines organisations, clinical trial websites and conference websites was also conducted.

The systematic review focused on evidence for the management of women with an identified germline BRCA1/2 mutation and a diagnosis of non-metastatic breast cancer. Outcome measures of interest were survival, risk of ipsilateral breast cancer (recurrence of the primary or a second primary) and *contralateral breast cancer*, ovarian (and/or fallopian tube) cancer, adverse events, *quality of life* and patient preferences.

After the removal of duplicates, a total of 1307 unique citations remained. Following application of the exclusion criteria, a total of 76 citations (72 original research studies and 4 systematic reviews) were identified as eligible for the current review.

These citations addressed the three primary research questions and 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:

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 diagnosed 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?

No *randomised controlled trials* or pseudo-randomised trials or non-randomised trials were identified for inclusion in the review. Most of the relevant trial data were limited to observational studies, including prospective and retrospective cohort studies and case-control studies.

A narrative description of the literature is also provided in relation to the management of 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); and the management of women diagnosed with breast cancer with non-BRCA *germline mutations* (such as TP53, PTEN, STK11, RAD51C, CHEK2, ATM, BRIP1, and PALB2). There was no attempt to specifically search for all key terms related to these areas or to provide a systematic review of the literature in these areas.

Refer to the Cancer Australia systematic review⁷ for detailed evidence from studies on the management of early breast cancer in women with an identified BRCA1 or BRCA2 gene mutation or at high risk of a gene mutation.

Evidence From Trial Or Study Results: Surgery

Eight observational studies were identified that investigated the impact of the type of breast surgery (ipsilateral) on survival outcomes or the risk of ipsilateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation. All the studies were retrospective cohort studies.



Survival outcomes

Four studies were identified that investigated the impact of the type of breast surgery (ipsilateral) on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation.^{12,13,17,18}

Of the four studies, only one study compared survival outcomes following breast conserving treatment (breast conserving surgery and radiotherapy) and *mastectomy* in women with a BRCA1/2 mutation.¹² Pierce et al (2010) in a large retrospective study found that treatment with mastectomy does not significantly increase overall and breast cancer-specific survival in women with breast cancer with a BRCA1/2 mutation compared to breast conserving treatment (breast conserving surgery and radiotherapy).¹² The study had a median follow-up of around 8 years with data projected to 15 years.

Three small retrospective cohort studies compared survival outcomes after breast conserving treatment in women with a BRCA1/2 mutation to women with sporadic breast cancer.^{13,17,18} The studies found that breast conserving treatment is as effective for women with breast cancer with a BRCA1/2 mutation compared to women with sporadic breast cancer in terms of overall survival and breast cancer-specific survival.^{13,17,18} Kirova et al (2010)¹³ found no significant difference in overall survival after breast conserving treatment in women with a BRCA1/2 mutation at 13.4 years compared to women with sporadic breast cancer and Seynaeve et al (2004)¹⁷ found no significant difference in overall survival after breast conserving treatment in women with a BRCA1 mutation at 6 years compared to women with sporadic breast cancer. Robson et al (2004) in a study of *Ashkenazi Jewish* women 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).¹⁸

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.¹²⁻¹⁹ Of the eight studies, only one study compared the risk of ipsilateral breast cancer following breast conserving treatment (breast conserving surgery and radiotherapy) and *mastectomy* in women with a BRCA1/2 mutation.¹² Pierce et al (2010) in a large retrospective cohort study found that breast conserving treatment in women diagnosed with breast cancer with a BRCA 1/2 mutation is associated with a significant increase in the risk of ipsilateral breast cancer compared to a mastectomy (with and without radiotherapy).¹² 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.

Seven retrospective cohort studies compared the risk of ipsilateral breast cancer after breast conserving treatment in women with a BRCA1/2 mutation to women with sporadic breast cancer.¹²⁻¹⁹ Five of the seven 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.¹²⁻¹⁹ Kirova et al (2010)¹³ Brekelmans et al (2007)¹⁵ Pierce et al (2006)¹⁶ and Seynaeve et al (2004)¹⁷ found no significant difference in the risk of ipsilateral breast cancer in women with a BRCA1/2 mutation following breast conserving treatment compared to women with sporadic breast cancer, with a median follow-up of 13 years, 4 years, 7 years and 6 years respectively. Robson et al (2004) in a study of *Ashkenazi Jewish* women also found no significant difference in the risk of ipsilateral breast cancer in women with a BRCA1/2 mutation after breast conserving treatment compared to women with sporadic breast cancer at 10 years.¹⁸

Only two small studies found a significantly increased risk of ipsilateral breast cancer in women with a BRCA1/2 mutation following breast conserving treatment compared to sporadic controls.^{14,19} The study by Garcia-Etienne



et al (2009)¹⁴ had a median follow-up of four years and the study by Haffty et al (2002)¹⁹ had a median follow-up of 12.7 years. However, the studies were limited by the lack of control for potential confounding factors such as the use of *endocrine therapy*.

A large retrospective cohort study by Metcalfe, Lynch et al (2011) investigated the effectiveness of radiotherapy after *breast conserving surgery* in women diagnosed with breast cancer with a BRCA1/2 mutation.²⁰ 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. *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 effects

Two retrospective cohort studies investigated potential adverse effects from *radiotherapy* in women with a BRCA1/2 mutation.^{21,22} The studies found that there was no significant increase in clinically significant acute or late toxicity from radiotherapy in women with a BRCA1/2 mutation compared to other women with breast cancer. 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 compared to sporadic controls, with a median follow-up of 6.75 to 7.75 years.²¹ Pierce et al (2000) also found no increase in acute or chronic morbidity in the skin, subcutaneous tissue, bone or lung in women with a BRCA1/2 mutation undergoing radiotherapy after *breast conserving surgery*, with a median follow-up of 4.6-5.3 years.²²

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.¹² 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.¹²

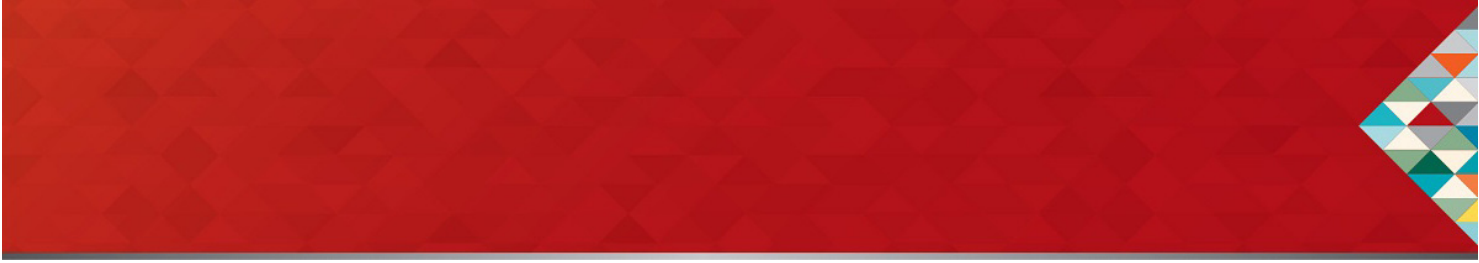
Two studies, including one case series and one small case study, investigated potential adverse effects from radiotherapy in women diagnosed with breast cancer with a germline TP53 mutation.^{32,33} Heymann et al (2010) in a small case series (n=8) assessed the incidence of radiation-induced malignancies in women with a germline TP53 mutation who had been treated for breast cancer.³² 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 the rapid development of post-radiotherapy sarcoma and a second breast cancer in a young woman (age 27 years) originally presenting with contralateral breast cancer with a germline TP53 mutation.³³

Patient preferences

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.^{3,25-27}

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

Evidence From Trial Or Study Results: Systemic Therapies

CHEMOTHERAPIES

Thirteen observational studies investigated the impact of *adjuvant* or *neoadjuvant chemotherapy* 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.

Adjuvant chemotherapy and survival outcomes

Four studies investigated the effectiveness of *adjuvant chemotherapy* on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation.^{18,34,38,39} Goodwin et al (2012) in a large prospective cohort study (with a mean follow-up of 7.9 years) 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.³⁴ 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 hazard ratio (HR) 3.62; 95% CI, 1.46-8.99).³⁴ Robson et al (2004) in a small retrospective cohort study 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.¹⁸ 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 .

Brekelmans et al (2006) in a retrospective cohort study found no significant difference in breast cancer-specific survival in women diagnosed with breast cancer with a BRCA1 mutation with and without adjuvant chemotherapy.³⁹ However, there was a trend towards improvement in breast cancer-specific survival with adjuvant chemotherapy (multivariate HR 0.36; 95% CI, 0.12-1.03, p=0.06). The study also found that there was no significant difference in breast cancer-specific survival between women with a BRCA1 mutation *and women with sporadic breast cancer* in women who received adjuvant chemotherapy and women who did not receive adjuvant chemotherapy. The study had a median follow-up of 5.1 years. Rennert et al (2007) in a retrospective cohort study also found no significant difference in breast cancer-specific survival at 10 years in Ashkenazi Jewish women diagnosed with breast cancer with a BRCA1 mutation or women with a BRCA2 mutation with and without adjuvant chemotherapy.³⁸ 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 and without adjuvant chemotherapy.

Neoadjuvant chemotherapy and survival outcomes

One small retrospective cohort study investigated the effectiveness of *neoadjuvant chemotherapy* on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation.³⁶ 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.³⁶

Pathological complete response (pCR)

Four small retrospective cohort studies investigated the type of *neoadjuvant chemotherapy* on the rates of pCR in women diagnosed with breast cancer with a BRCA1/2 mutation.^{36,40-42} Of the four studies, one study investigated the effectiveness of platinum-based chemotherapy in women diagnosed with breast cancer with a BRCA1 mutation.⁴⁰ 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 pathological *complete response* to platinum-based chemotherapy compared to other types of neoadjuvant chemotherapy (such as *CMF* or *anthracycline-taxanes* combination).⁴⁰

Three studies investigated the effectiveness of *taxane* based chemotherapy in women diagnosed with breast cancer with a BRCA1/2 mutation.^{36,41,42} 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.³⁶ 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.⁴² 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).⁴² 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). In a small retrospective cohort study Fourquet et al (2009) found that women diagnosed with breast cancer with a BRCA1/2 mutation have a better response in terms of the rate of complete clinical response to anthracyclines (without taxanes) compared to non-BRCA carriers (46% vs 17%; p=0.008).⁴¹

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.^{12,20} Pierce et al (2010)¹² and Metcalfe, Lynch et al (2011)²⁰ found that *chemotherapy* after *breast conserving surgery* significantly decreased the risk of ipsilateral breast cancer compared to women who do not receive chemotherapy. Pierce et al (2010) also 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 (8.1 vs 3.5% at 10 years; 10.7 vs 5.5% at 15 years, respectively; p= 0.08).¹²

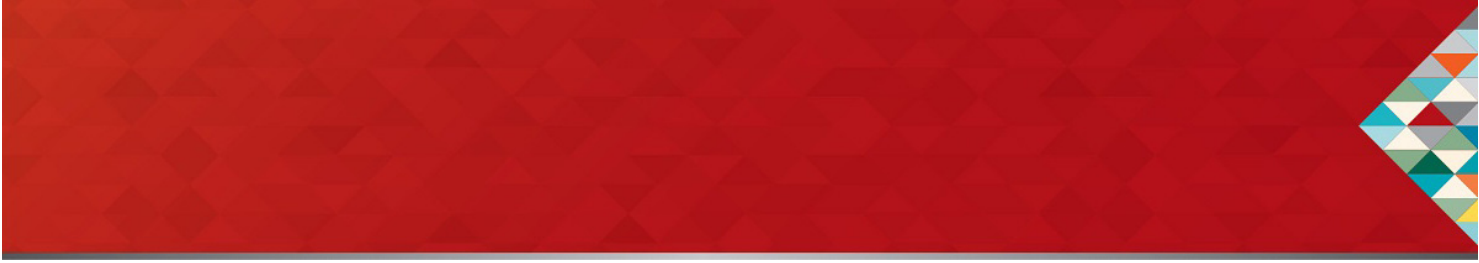
Contralateral breast cancer

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.^{35,37}

Metcalfe, Gershman et al (2011) in a retrospective cohort study found that *chemotherapy* was not associated with a significant reduction in the risk of contralateral breast cancer.³⁵ 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 found that chemotherapy was associated with a reduced risk of contralateral breast cancer for women diagnosed with breast cancer with a BRCA1 mutation (multivariate





RR=0.5; 95% CI, 0.1-1.6) and women with a BRCA2 mutation (RR=0.3; 95% CI, 0.1-1.0).³⁷ Overall, the risk reduction for women diagnosed with breast cancer with a BRCA1/2 mutation with chemotherapy was reported as multivariate RR=0.5; 95% CI, 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).

ENDOCRINE THERAPY

Ten 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. There was no evidence identified that investigated the effectiveness of *endocrine therapies* other than *tamoxifen*.

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.^{18,34,45}

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* and death in women with a BRCA1 mutation and women with sporadic breast cancer (with and without endocrine therapy).³⁴ There was also no significant difference found in the risk of distant recurrence in women with a BRCA2 mutation and women with sporadic breast cancer (with and without endocrine therapy).

Robson et al (2004) in a small retrospective cohort study of *Ashkenazi Jewish* women diagnosed with breast cancer found there was no significant difference in breast cancer-specific survival among women who had a BRCA1 mutation who received *tamoxifen* compared to women with sporadic breast cancer who received tamoxifen, at 10 years (multivariate HR 0.5; 95% CI, 0.05-5.0, p=0.55).¹⁸ However, the study found a significantly lower breast cancer-specific survival among women who had a BRCA1 mutation *who did not receive* tamoxifen compared to women with sporadic breast cancer *who did not receive* tamoxifen, at 10 years (multivariate HR 3.5; 95% CI, 1.7–7.2, p=0.001). Foulkes et al (2002) in a small retrospective cohort study of Ashkenazi Jewish women diagnosed with breast cancer did not find any 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 (multivariate RR 0.30; 95% CI, 0.04-2.49, p=0.27).⁴⁵ However, the study found that there was 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 (multivariate RR 2.16, 95% CI, 1.0-4.68, p=0.05). The median follow-up time of the study was 8.9 years.

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.^{12,16,20} Metcalfe, Lynch et al (2011) 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 or when women with a BRCA1 or BRCA2 mutation were considered separately.²⁰ Pierce et al (2010) 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 (breast conserving surgery and radiotherapy), at 15 years.¹² However, there was a trend towards reduction in the risk of ipsilateral breast cancer particularly in women with a



BRCA2 mutation (BRCA1: $p=0.13$; BRCA2: $p=0.08$). Pierce et al (2006) 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.¹⁶ 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 and who had not undergone risk-reducing *salpingo-oophorectomy*.

Contralateral breast cancer

Five studies, including three cohort studies and two case-control studies^{16,35,37,43,44} investigated the impact of *endocrine therapy* on the risk of *contralateral breast cancer* in women diagnosed with breast cancer with a BRCA1/2 mutation. Metcalfe, Gershman et al (2011) in a retrospective cohort study found that *tamoxifen* was not associated with a significant reduction in the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation or when women with a BRCA1 or BRCA2 mutation were considered separately, at 15 years.²⁸ Reding et al (2010) in a case-control study 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 or BRCA2 mutation were considered separately.³⁷ The study had a mean follow-up of 4.2-5.1 years.

However, Pierce et al (2006) in a retrospective cohort study found 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.¹⁶ 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 contralateral breast cancer with and without tamoxifen of 6% vs 19%, 6% vs 41%, and 6% vs 54% respectively (multivariate HR 0.13, $p=0.02$).

Gronwald et al (2006) in a large case-control study also found 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 or BRCA2 mutation were considered separately.⁴⁴ The study found that the protective effect of tamoxifen was not evident in women who had undergone a risk-reducing *salpingo-oophorectomy* (but this subgroup was small), unlike the protective effect of tamoxifen seen in women who had not undergone an *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 odds ratio (OR) 0.46; 95% CI 0.2–0.79, $p=0.005$ vs >10 years multivariate OR 0.99; 95% CI 0.13–7.61, $p=0.99$). The study also found that tamoxifen had a protective effect for both premenopausal and postmenopausal women.

Phillips et al (2013) in a large cohort study found that women with breast cancer and a BRCA1/2 mutation, who took tamoxifen, exhibited a trend towards a reduction in the risk of contralateral breast cancer (multivariate HR 0.58; 95% CI, 0.29-1.13, $p=0.1$ and multivariate HR 0.48; 95% CI, 0.22-1.05, $p=0.07$ for BRCA1 and BRCA2 mutation carriers respectively) and that contralateral risk reduction was seen in women who had either ER positive or ER negative first breast cancer.⁴³

Evidence From Trial Or Study Results: Surgical Risk-reducing Strategies

CONTRALATERAL RISK-REDUCING MASTECTOMY

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.



Survival outcomes

Two retrospective cohort studies investigated the impact of contralateral risk-reducing *mastectomy* on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation.^{39,47} Brekelmans et al (2006) 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; 95% CI 0.47-4.13, $p=0.56$).³⁹ Van Sprundel et al (2005) did not find any overall survival benefit in women diagnosed with breast cancer with a BRCA1 or a BRCA2 mutation at 5 years after a contralateral risk-reducing mastectomy after adjustment for risk-reducing *salpingo-oophorectomy*.⁴⁷

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.^{35,51,52} Women with a BRCA1/2 mutation younger than 50 years at the time of their breast cancer diagnosis are significantly more likely to develop a contralateral breast cancer at 15 years compared to women over 50 years.^{35,51}

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.⁴⁶⁻⁴⁸ Domchek et al (2010) undertook a prospective multi-centre cohort study of women with a BRCA1/2 mutation, which included a subset of women with a prior diagnosis of breast cancer.⁴⁶ 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) and Metcalfe et al (2004) in two retrospective cohort studies also found that contralateral risk-reducing mastectomy substantially reduced the risk of contralateral breast cancer in women diagnosed with breast cancer with a BRCA1/2 mutation.^{47,48} Van Sprundel et al (2005) found that contralateral risk-reducing mastectomy reduced the risk of contralateral breast cancer by 91%, independent of the effect of risk-reducing *salpingo-oophorectomy*, at 5 years.⁴⁷ Metcalfe et al (2004) found that only one contralateral breast cancer 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; $p=0.005$), at a mean follow-up of 9.2 years.⁴⁸

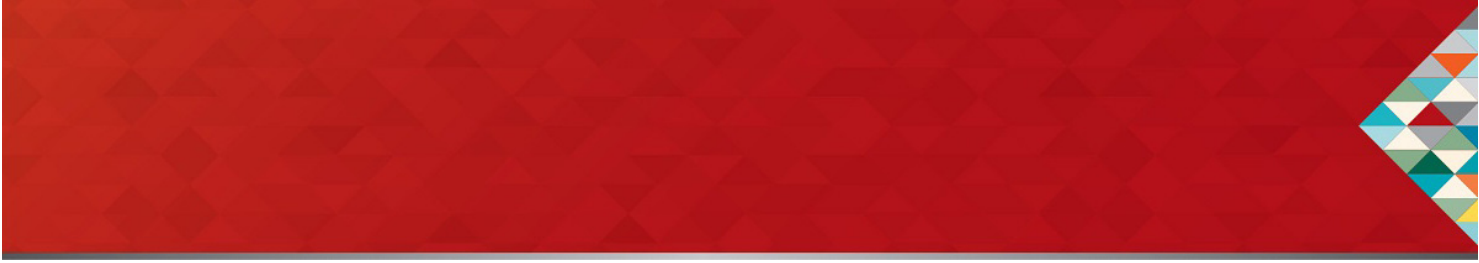
Quality of life

One study found that women diagnosed with breast cancer who had an identified BRCA1/2 mutation or who had inconclusive results from BRCA1/2 mutation testing and 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

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.^{12,53} 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.⁵³ 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 mastec-





tomy (12% vs 40%, $p < 0.001$).⁵³ 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%, $p < 0.001$).⁵³ 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% vs 14.6%, $p < 0.0001$).¹²

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.^{24-28,54}

RISK-REDUCING SALPINGO-OOPHORECTOMY

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.

Survival outcomes

Three studies investigated the impact of risk-reducing *salpingo-oophorectomy* on survival outcomes in women diagnosed with breast cancer with a BRCA1/2 mutation.^{39, 46, 47} Domchek et al (2010) in a large prospective cohort study found that in women with a BRCA1/2 mutation and prior breast cancer, risk-reducing salpingo-oophorectomy was associated with significantly lower all-cause mortality and breast cancer specific mortality.⁴⁶ The study also found 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 but did not have significantly better breast cancer-specific survival, at 5 years.⁴⁷ Brekelmans et al (2006) in a retrospective cohort study also found that risk-reducing salpingo-oophorectomy did not significantly improve breast cancer specific survival in women diagnosed with breast cancer with a BRCA1 mutation, with a median follow-up of 5.1 years.³⁹

Ipsilateral breast cancer

Four observational studies, including one prospective cohort study and three retrospective cohort studies, investigated the risk of ipsilateral breast cancer after risk-reducing *salpingo-oophorectomy* in women diagnosed with breast cancer with a BRCA1/2 mutation.^{12,16,20,46} Of the four studies, only one large 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 mutation.²⁰

Contralateral breast cancer

One large retrospective cohort study investigated the risk of *contralateral breast* cancer after risk-reducing *salpingo-oophorectomy* in women diagnosed with breast cancer with a BRCA1/2 mutation.³⁵ Metcalfe, Gershman et al (2011) found 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, $p = 0.0006$).³⁵ 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 investigated the risk of ovarian/fallopian tube cancer after risk-reducing *salpingo-oophorectomy* in women diagnosed with breast cancer with a BRCA1/2 mutation.⁴⁶ Domchek et al (2010) found that, in women with a BRCA1 mutation and a prior diagnosis of breast cancer, risk-reducing salpingo-oophorectomy was associated with a significantly reduced risk of *ovarian cancer* (HR 0.15; 95% CI, 0.04-0.63).⁴⁶ No cases of ovarian cancer were diagnosed in women with a BRCA2 mutation after risk-reducing salpingo-oophorectomy.

Patient factors and preferences

Metcalf et al (2008) in a large retrospective cohort study found that women diagnosed with breast cancer with a BRCA1/2 mutation who had risk-reducing *salpingo-oophorectomy* were significantly more likely to have contralateral risk-reducing *mastectomy* (33% vs 18%, p=0.001).⁵³

Supporting Information For Practice Points: Surgery

This section provides additional information relating to the practice points. This information was not sourced through a systematic review of the literature; relevant articles were identified by the working group and by Cancer Australia.

The supporting explanatory information below relates to women diagnosed with breast cancer with an identified BRCA1/2 mutation.

- Women having breast conserving treatment at diagnosis and who later test positive for a BRCA1/2 mutation may then elect for a bilateral *mastectomy*. However this may mean restricted reconstructive options and women may be at risk of a poorer cosmetic outcome on the side treated with irradiation.^{55,56}

See *Surgical risk-reducing strategies* for further consideration of *contralateral breast cancer* risk and contralateral risk-reducing mastectomy.

The supporting explanatory information below relates to 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 had a BRCA1/2 mutation identified with genetic testing and women who have not had genetic testing).

- There is evidence that breast conserving treatment or mastectomy are both effective treatment options in terms of survival and ipsilateral breast cancer in women with breast cancer who have a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation.^{13,15,17,30,31}
- There is evidence that women diagnosed with breast cancer with a strong family history of breast cancer and no identified BRCA1/2 mutation have an increased risk of contralateral breast cancer compared to women without a strong family history of breast cancer.²⁹
- No evidence was identified that investigated the risk of future ipsilateral breast cancer after breast conserving treatment compared to a mastectomy in women with breast cancer with a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation.
- No evidence was identified that investigated the risk of ipsilateral breast cancer with or without *chemotherapy* in women with breast cancer with a strong family history of breast and/or ovarian cancer and no identified BRCA1/2 mutation.



Supporting Information For Practice Points: Systemic Therapies

The supporting explanatory information below relates to women diagnosed with breast cancer with an identified BRCA1/2 mutation.

- There is insufficient evidence to support a change to the type of neoadjuvant/adjuvant standard *chemotherapy* regimen in women with breast cancer with a BRCA1/2 mutation compared to other women with breast cancer (not attributable to a BRCA1/2 mutation). In particular, there is insufficient evidence that platinum-based chemotherapy is better than other types of neoadjuvant/adjuvant chemotherapy (such as *CMF* or anthracycline-taxanes),^{40,41} or that *anthracyclines* (without taxanes) are better than a *taxane* regimen without an anthracycline or other non-anthracycline regimens in women with a BRCA1/2 mutation.^{36,40,41}
- There is insufficient evidence to determine whether there should be a lower threshold for consideration of chemotherapy based on tumour size in women diagnosed with breast cancer with a BRCA1/2 mutation.
- There is insufficient evidence to support a particular chemotherapy regimen (such as carboplatin-based regimen over a non carboplatin-based regimen) in women with a HER2 positive breast cancer with a BRCA1/2 mutation.
- There is insufficient evidence to determine the effectiveness of SERMs as a medical prevention for *contralateral breast cancer* in women with ER negative breast cancer with a BRCA1/2 mutation.
- No evidence was identified that investigated the effectiveness of *endocrine therapies* other than *tamoxifen* in women diagnosed with breast cancer with a BRCA1/2 mutation. However, endocrine therapies other than tamoxifen should be considered in a similar manner to tamoxifen in terms of the benefits for women with breast cancer with a BRCA1/2 mutation.

Therefore, consideration of the use of neoadjuvant/adjuvant chemotherapy and *adjuvant endocrine therapy* in women diagnosed with breast cancer with a BRCA1/2 mutation should be similar to other women with breast cancer not known to be attributable to a BRCA1/2 mutation.

Supporting Information For Practice Points: Surgical Risk-reducing Strategies

The supporting explanatory information below relates to 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 had a BRCA1/2 mutation identified with genetic testing and women who have not had genetic testing).

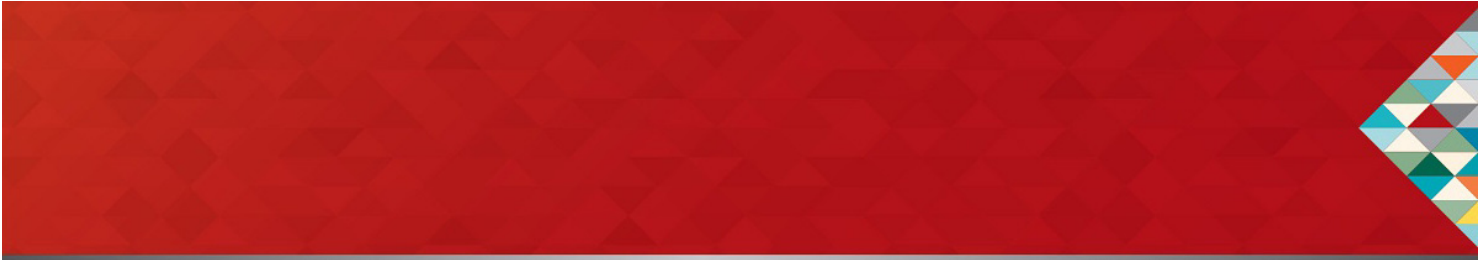
- There is evidence that contralateral risk-reducing *mastectomy* should be considered in women diagnosed with breast cancer with a strong family history of breast cancer, particularly in younger women (less than 50 years).⁵⁷⁻⁵⁹
- There is evidence that risk-reducing *salpingo-oophorectomy* should be considered in women diagnosed with breast cancer with a strong family history of breast and ovarian cancer, around the age of 40 years or when child-bearing decisions are complete.¹⁵

Supporting Information For Practice Points: Genetic Counselling And Testing

The supporting explanatory information below relates to genetic counselling and testing after a breast cancer diagnosis.

Familial cancer services have developed in Australia and internationally in response to a rapidly evolving demand for genetic counselling and testing, for cancer risk.⁶⁰ Treatment-focused genetic counselling and testing refers to genetic counselling and testing undertaken around the time of a cancer diagnosis that aims to assist in treatment





decision-making. *Genetic counselling* and testing may occur shortly after the cancer diagnosis or during the initial phases of active cancer treatment. Genetic testing may take as little as two weeks or may take several months to receive a result depending on the timeframe of clinical need.

Not all women considered at high risk of a mutation in a breast cancer predisposition gene may want to undergo genetic testing at the time of their breast cancer diagnosis. However it is important to offer women genetic counselling at this time as part of the management of a newly diagnosed breast cancer.

Characteristics that may guide selection for genetic counselling and testing in women with breast cancer include a strong family history, young age at onset, histopathological features such as triple negative tumours, bilateral breast cancer, and being from a population with a high frequency of known founder mutations, such as having *Ashkenazi Jewish* ancestry.⁶⁰⁻⁶²

Genetic counselling is also important after the results are disclosed in order to interpret the implications of the test result, whether or not a mutation is identified. The aim of genetic counselling is to increase cancer related knowledge, to decrease *distress* and to assist in treatment decision making. Implications of test results for the person and their family are discussed in detail. Furthermore, women already known to carry a BRCA1/2 mutation prior to their current breast cancer diagnosis may also benefit from additional genetic counselling at the time of their new diagnosis to assist them in making decisions about their treatment.⁶³

Treatment-focused genetic counselling and/or testing around the time of a breast cancer diagnosis, but before delivery of *adjuvant radiotherapy*, can influence surgical treatment choices. Women who become aware through testing before definitive surgery that they carry a BRCA1/2 mutation are more likely to choose a therapeutic (ipsilateral) *mastectomy*, with or without a contralateral risk-reducing mastectomy, rather than breast conserving treatment (breast conserving surgery and radiotherapy).^{42,43,44,46,53}

However, treatment-focused genetic counselling and/or testing at the time of a breast cancer diagnosis is not widely available in Australia and the *psychosocial* impact of genetic counselling and testing at the time of a breast cancer diagnosis is an emerging area of research. A small qualitative Australian study indicated that clinical genetics practitioners raised concerns that women were emotionally vulnerable following their diagnosis and may not be able to deal with information about, and implications of, genetic testing at this point in time.⁶⁴ However, practitioners also expressed the view that not providing this information could have a negative impact on a patient's ability to make informed management decisions.⁶⁴

This view was supported by a subsequent larger study by Burcher et al (2013) of oncology health professionals, the majority of whom reported that treatment-focused genetic testing was useful for patient care and valuable for the treatment and management of breast cancer, as it facilitated decision-making about management options.⁶⁵

Prospective studies in the Netherlands and the US involving women offered genetic counselling and testing have found no short- or long-term increases in distress in women approached for genetic testing at the time of a breast cancer diagnosis.^{23,27}

Similarly results from an Australian trial showed no evidence of an adverse psychological impact of genetic counselling and testing at the time of a breast cancer diagnosis⁶⁶ and that brief educational materials provided by the woman's surgeon at the time the test is offered are an effective means of supporting informed decision-making about such testing.^{67,68}

Limited evidence on the uptake of counselling and testing around a new breast cancer diagnosis is currently available. A Dutch study found that 60% of women at high risk take up a referral for genetic counselling and testing when it is offered at the start of adjuvant radiotherapy.²³

These data suggest that genetic counselling and/or testing undertaken around the time of a breast cancer diagnosis and before the completion of active breast cancer treatment may assist in decision-making about risk reducing



strategies such as contralateral risk-reducing mastectomy and *salpingo-oophorectomy* to reduce the risk of a second breast cancer and *ovarian cancer* respectively.^{60,69}

Strengths And Weaknesses Of The Evidence

Limited high quality evidence was available for the three primary research questions.

There were few large prospective trials identified that investigated the use of surgery, *adjuvant* and *neoadjuvant* systemic therapies and risk-reducing surgery for the management of women diagnosed with breast cancer with a BRCA1/2 mutation. No *randomised controlled trials* or pseudo-randomised trials or non-randomised trials were identified for inclusion. Most of the relevant trial data were limited to observational studies, including prospective and retrospective cohort studies and case-control studies.

Two well-conducted prospective cohort studies are included. However, many of the studies included 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.

Unanswered Questions

Important unanswered questions about the management of women with breast cancer with a *gene mutation* or at high risk of a gene mutation are outlined below. Some of these questions may be addressed in ongoing trials.

- Whether platinum-based *chemotherapy* is better than other types of *neoadjuvant* chemotherapy (such as *CMF* or *anthracycline-taxanes* combinations) or whether *anthracyclines* (without taxanes) are better than *taxanes* or other non-taxane regimens in women diagnosed with breast cancer with a BRCA1/2 mutation.
- Whether the threshold for consideration of chemotherapy based on tumour size should be lower in women diagnosed with breast cancer with a BRCA1/2 mutation.
- Whether a platinum-containing chemotherapy regimen such as TCH (docetaxel, *carboplatin*, and trastuzumab) should be preferred in women with a HER2 positive breast cancer with a BRCA1/2 mutation.
- Whether SERMs as a medical prevention strategy for *contralateral breast* cancer should be given to women with ER negative breast cancer with a BRCA1/2 mutation.
- Whether *endocrine therapies* other than *tamoxifen* are as effective as tamoxifen in women diagnosed with breast cancer with a BRCA1/2 mutation.
- Whether *hormone replacement therapy* (HRT) can be given to young women diagnosed with ER negative breast cancer with a BRCA1/2 mutation after risk-reducing *salpingo-oophorectomy*.
- Whether women diagnosed with breast cancer with a BRCA1/2 mutation or 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 had a BRCA1/2 mutation identified with genetic testing and women who have not had genetic testing) who have breast conserving treatment on the ipsilateral side should have the residual tissue removed if they are considering a contralateral risk-reducing *mastectomy*.
- Whether women diagnosed with breast cancer with a BRCA1/2 mutation or 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 had a BRCA1/2 mutation identified with genetic testing and women who have not had genetic testing) who have breast conserving treatment on the ipsilateral side should have a mastectomy on the contralateral side if they have a new diagnosis of contralateral breast cancer.
- What are the implications of treatment-focused *genetic counselling* and/or testing for service delivery, including the health economic implications, and the impact of genetic testing at the time of a breast cancer diagnosis on treatment decision-making?



- What is the optimal follow-up, including *magnetic resonance imaging* (MRI), post-treatment for women with a BRCA1/2 gene mutation?

International Guidelines

Only one international guideline was identified that addressed the management of women with breast cancer and a family history of breast cancer in its recommendations.

National Institute for Health and Clinical Excellence (NICE)⁷⁰

Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer (June 2013). These recommendations were based on an evidence review.

Ongoing And Additional Trials

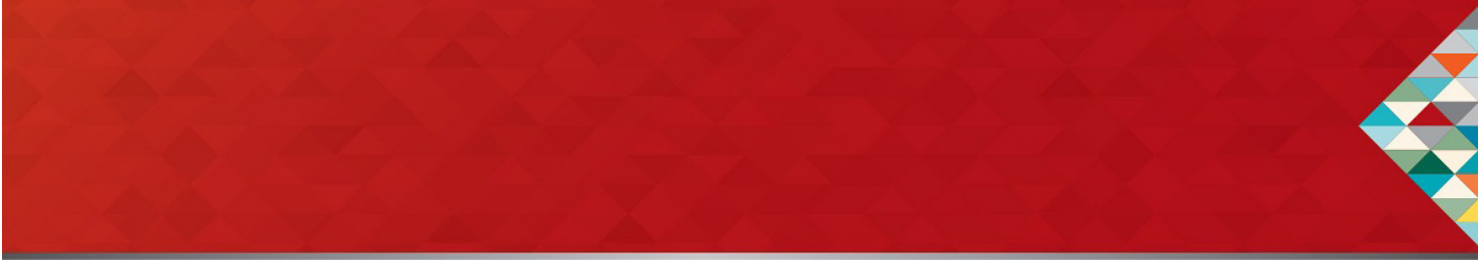
Clinical trials registries were searched to identify any additional studies among women diagnosed with breast cancer with a BRCA1/2 mutation or at high risk of a *gene mutation*, and are noted in the Cancer Australia systematic review⁷. The following trials were identified:

- Single centre, non-randomised, open label phase II trial in Poland (NCT01630226)⁷¹ is evaluating the clinical and pathologic response of *neoadjuvant* cisplatin-monotherapy in BRCA1 positive patients (recruiting participants as of July 2012).
- A US phase II *randomised controlled trial* (NCT01074970)⁷² of participants with a triple negative breast cancer with a BRCA1/2 mutation treated with *cisplatin* in combination with Rucaparib following preoperative *chemotherapy* (not recruiting participants as of May 2013).
- A US (NCT00579007)⁷³ observational prospective cohort study on female participant decision making to undergo prophylactic *mastectomy* and *oophorectomy* when seeking *genetic counselling* and testing for BRCA1/2 mutations (not recruiting participants as of November 2012).
- A Netherlands (NCT00783822)⁷⁴ open-label randomised controlled trial of the effects of rapid genetic counselling and testing of breast cancer patients identified as having at least a 10% risk of carrying a mutation in the BRCA1 or BRCA2 genes (study completed as of November 2012).
- A UK prospective cohort study examining outcomes in sporadic versus hereditary breast cancer of 3000 women (aged between 41 and 50 years) diagnosed with *invasive breast cancer*, with a known BRCA1 or BRCA2 gene mutation (study completed as of April 2007).⁷⁵
- The Korean Hereditary Breast Cancer ongoing trial (prospective multicentre cohort) is examining the prevalence of BRCA1/2 mutations and *ovarian cancer* among a high-risk group of 2000 patients with hereditary breast cancer and their families (recruiting participants as of May 2011).⁷⁶

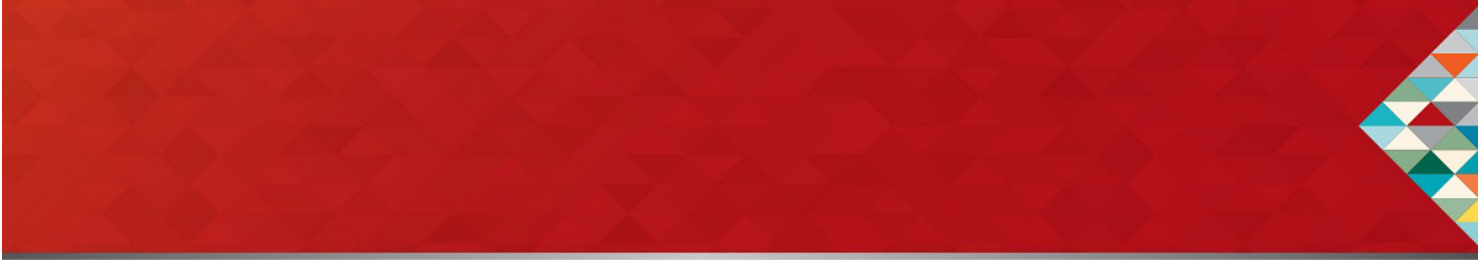
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Guideline Development Process

Priority topic areas for guideline development are determined in consultation with key stakeholders including experts in relevant disciplines and consumer representatives. A specific multidisciplinary working group, including consumers, is established for each topic identified and is involved in all aspects of guideline development. A systematic evidence review is undertaken for each guideline. All members are asked to declare any conflicts of interest and these declarations are recorded. The content of the guideline is not influenced by any external funding



body. The guideline is reviewed externally by key stakeholders and the wider community and endorsement is sought from relevant professional colleges and groups in Australia.

Additional Information

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Glossary

Adjuvant therapy - Additional cancer treatment given after the primary treatment to lower the risk of cancer *recurrence*. *Adjuvant* therapy for breast cancer may include *chemotherapy*, radiation therapy, endocrine therapy, oophorectomy, targeted therapy, or biological therapy.

Anthracyclines - A class of chemotherapy drugs used in the treatment of cancer that is derived from certain types of *Streptomyces* bacteria.



Anthracycline-taxanes - Describes the combined use of both anthracyclines and taxane chemotherapy agents.

Aromatase inhibitor - A drug used only in postmenopausal women that prevents the formation of estradiol, a female hormone, by interfering with an aromatase enzyme.

Ashkenazi Jewish - The Eastern European Jewish population primarily from Germany, Poland, and Russia, as opposed to the Sephardic Jewish population primarily from Spain, parts of France, Italy, and North Africa.

BRCA1/2 - BRCA1 and BRCA2 are genes in which germline mutations result in a greatly increased risk of developing breast cancer and *ovarian cancer*.

CMF - An abbreviation for a chemotherapy combination (cyclophosphamide, methotrexate and fluorouracil) used alone or with other therapies to treat breast cancer.

Complete response - The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured.

Endocrine therapy - Treatment that blocks or reduces the production of hormones.

Familial cancer - Cancer that occurs in families more often than would be expected by chance. These cancers often occur at an early age, and may indicate the presence of a *gene mutation* that increases the risk of cancer. They may also be a sign of shared environmental or lifestyle factors.

Genetic counselling - *Genetic counselling* provides an individual or family with information and support regarding health concerns which run in their family. Genetic counselling may involve the diagnosis of a genetic condition, the provision of information and supportive counselling (advice and guidance) by a team of health professionals, so that families and individuals may be better able to adjust to diagnosis.

Germline mutation - A heritable gene fault present in all cells.

Human epidermal growth factor receptor 2 (HER2) negative - Describes cancer cells that lack cell surface expression of a protein called HER2. In normal cells, HER2 helps to control cell growth. When it is made in larger than normal amounts by cancer cells, the cells may grow more quickly and be more likely to spread to other parts of the body.

Human epidermal growth factor receptor 2 (HER2) positive - Describes cancer cells that have excess cell surface expression of the HER2 protein.

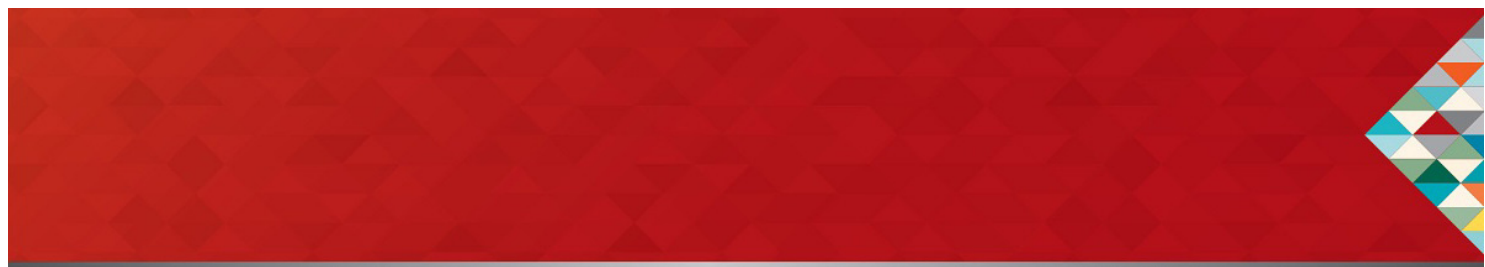
Local therapies - Treatments that target specific areas, such as surgery or *radiotherapy*. Different to systemic therapies such as chemotherapy and endocrine therapy which treat cancer through the bloodstream.

Metastasis - Also known as a secondary cancer is a cancer that has spread from one part of the body to another.

Neoadjuvant therapy - Treatment given as a first step to shrink a tumour before the main treatment, which is usually surgery. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and endocrine therapy.

Oestrogen Receptor (ER) negative - Cells that do not have a protein to which the hormone oestrogen will bind. Cancer cells that are ER negative do not need oestrogen to grow, and usually do not stop growing when treated with hormones that block the binding and actions of oestrogen.





Oestrogen Receptor (ER) positive - Cells that have a receptor protein that binds the hormone oestrogen. Cancer cells that are ER positive may need oestrogen to grow, and may stop growing or die when treated with substances that block the binding or production of oestrogen.

Oophorectomy - Surgical removal of the *ovaries*.

Ovarian suppression - Temporary suppression of ovarian function using drugs that interfere with the hypothalamic-gonadal axis. An example of this is gonadotropin-releasing hormone (GnRH) or luteinizing hormone releasing hormone (LHRH) analogues.

Salpingo-oophorectomy - Surgical removal of the *fallopian tubes* and ovaries.

Selective Estrogen Receptor Modulator (SERM) - The family of drugs that interacts with the oestrogen receptor, for example, tamoxifen or raloxifene.

Tamoxifen - A drug used to treat certain types of breast cancer. It is a type of antioestrogen that blocks the oestrogen receptor in breast tissue. It is also used to prevent breast cancer in women who are at high risk of developing breast cancer. *Tamoxifen* is a type of SERM.

Targeted therapy - A type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells. Some *targeted therapies* block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells. Other types of targeted therapies help the immune system kill cancer cells or deliver toxic substances directly into cancer cells and kill them. An example of this is trastuzumab (Herceptin®).

Taxane - A type of chemotherapy drug that blocks cell growth by stopping mitosis (cell division). *Taxanes* interfere with microtubules (cellular structures that help move *chromosomes* during mitosis). They are used to treat cancer.

Triple-negative breast cancer - Describes breast cancer that is negative for oestrogen receptors, *progesterone* receptors and HER2/neu protein.

Appendix 1: Grading The Recommendations

Grading methodology

To accurately assess the strength of evidence available, the NHMRC methodology (FORM) was used in this clinical practice guideline to formulate and grade recommendations. The aim of this approach by NHMRC is to assist clinical practice guideline developers with a structured process for evaluating the evidence base corresponding to a particular key clinical question, in the context of the setting in which it is to be applied.⁹

The grading methodology allows for both the quality of the evidence and the strength of recommendations to be determined. Where insufficient evidence exists to formulate a grade, a practice point may be assigned instead. The NHMRC grading framework allows for these practice points to be included when developers consider it is important to provide non-evidence-based guidance.⁹

The NHMRC Evidence Statement Form sets out the basis for rating five key components of the 'body of evidence' for each recommendation. These components are:

1. The evidence base, in terms of the number of studies, level of evidence and quality of studies (risk of bias).

2. The consistency of the study results
3. The potential clinical impact of the proposed recommendation
4. The generalisability of the body of evidence to the target population for the guideline
5. The applicability of the body of evidence to the Australian healthcare context⁹

The first two components describe the internal validity of the study data in support of efficacy (for an intervention), accuracy (for a diagnostic test), or strength of association (for a prognosis or aetiological question). As suggested, the third component gives the likely clinical impact of the proposed recommendation. The final two components assess external factors that may influence the effectiveness of the proposed recommendation in practice, in terms of generalisability of study results to the intended target population for the Guideline and setting of the proposed recommendation, and applicability to the Australian (or other local) health care system.¹⁰

These described components should be rated according to the body of evidence matrix (refer to table 3). The matrix system is used to summarise the rating of the five key components which allows each recommendation to be assigned an overall NHMRC Grade of Recommendation (A-D).⁹

Table 3: NHMRC Body of evidence matrix¹⁰

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base[#]	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency[*]	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Populations/s studied in body of evidence differ to the target population for the guideline but it is clinically sensible to apply this evidence to target population [^]	Populations/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

[#]Level of evidence determined from the NHMRC evidence hierarchy

^{*}If only one study is present, component is ranked as 'not applicable'



^For example, results in adults that are clinically sensible to apply to children OR *psychosocial* outcomes for one cancer that may be applicable to patients with another cancer.

There is also capacity to note any other relevant factors that were considered by the guideline developers and the respective working group when judging the body of evidence and developing the wording of the recommendation.

The NHMRC grades given (A-D) are intended to indicate the strength of the body of evidence underpinning the recommendation (refer to table 1). Grade A or B recommendations are generally based on a body of evidence that can be trusted to guide clinical practice, whereas Grades C or D recommendations must be applied cautiously to individual clinical and organisational circumstances and should be interpreted with care. A recommendation cannot be graded A or B unless evidence base and consistency of the evidence are both rated A and B respectively.⁹

Table 4: Definition of NHMRC grades of recommendations^{9,10}

Note: This table is replicated on page 3

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

By referring to the statements of evidence in combination with the NHMRC body of evidence matrix, a grade for each recommendation was derived from the respective grades allocated to the five key components. Grading the components of evidence base, consistency, clinical impact, generalisability and applicability, was undertaken by the working group members, who discussed each section, and based on consensus achieved across the working group, arrived at these ratings.

The use of the NHMRC evidence table hierarchy table, categorises the respective study level according to the study design (refer to table 4). This is used to determine the respective grades for evidence base and consistency of the recommendation.

Implementing the NHMRC Evidence Hierarchy, each included study in a systematic review should be assessed according to the following three dimensions of evidence:

1. Strength of evidence (level of evidence, quality of evidence (risk of bias) and statistical precision)
2. Size of effect (assessing the clinical importance of the findings of each study and hence addressing the clinical impact component of the body of evidence matrix).
3. Relevance of evidence (translation of research evidence into clinical practice and is potentially the most subjective of the evidence assessments).^{9,10}

Table 5: NHMRC Evidence Hierarchy: designations of ‘levels of evidence’ according to type of research question¹⁰



Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> • Non-randomised, experimental trial • Cohort study • Case-control study • Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> • Non-randomised, experimental trial • Cohort study • Case-control study



Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group 	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Appendix 2: Evidence Statements For Grading The Recommendations

Key question 1: What is the optimal surgical management, with or without <i>radiotherapy</i> , on the ipsilateral side for women diagnosed with breast cancer with a BRCA 1/2 mutation?	
Recommendation 1:	
Offer a choice of either breast conserving treatment (breast conserving surgery and radiotherapy) or <i>mastectomy</i> to women diagnosed with breast cancer with a BRCA1/2 mutation as both are effective in terms of survival.	
<ul style="list-style-type: none"> • If women diagnosed with breast cancer with a BRCA1/2 mutation are considering a contralateral risk-reducing mastectomy (at the time of the cancer diagnosis or in the future) inform them that therapeutic ipsilateral mastectomy may be preferable to breast conserving treatment. • Inform women diagnosed with breast cancer with a BRCA 1/2 mutation that there is an increased risk of ipsilateral breast cancer after breast conserving treatment compared to mastectomy, but this is reduced by <i>adjuvant chemotherapy</i> (see practice points B and F). 	
Pierce 2010 ¹² ; Kirova 2010 ¹³ ; Garcia-Etienne 2009 ¹⁴ ; Brekelmans 2007 ¹⁵ ; Pierce 2006 ¹⁶ ; Seynaeve 2004 ¹⁷ ; Robson 2004 ¹⁸ ; Haffty 2002 ¹⁹	
Component	Grading
1. Evidence base Seven level III-2 retrospective cohort studies and one level III-3 case-control study with a low risk of bias (A1, A2, A3 and A4 evidence statements) included in a systematic review.	C (One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias)
2. Consistency	B



Key question 1: What is the optimal surgical management, with or without <i>radiotherapy</i>, on the ipsilateral side for women diagnosed with breast cancer with a BRCA 1/2 mutation?	
Taking account of other studies there were slight inconsistencies reported, however most inconsistency can probably be explained.	(Most studies consistent and inconsistency may be explained)
3. Clinical impact Moderate clinical impact (lower risk of subsequent breast cancer) when considering relevance, duration of therapy, risks and benefits of mastectomy compared to breast conserving treatment.	C (Moderate)
4. Generalisability Population studied in body of evidence and target population in guideline are directly generalisable.	A (Population/s studied in body of evidence are the same as the target population in the guideline)
5. Applicability Directly applicable to Australian healthcare context.	A (Directly applicable to Australian healthcare context)
Overall grade of recommendation:	C Body of evidence provides some support for recommendation(s) but care should be taken in its application

UNRESOLVED ISSUES	
None identified.	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care? Yes as women with a mutation may opt for bilateral mastectomy rather conservation, resulting in increased demand for bilateral mastectomy.	YES
Are there any resource implications associated with implementing this recommendation? There are no significant resource implications associated with implementing this recommendation.	NO
Will the implementation of this recommendation require changes in the way care is currently organised? This recommendation will not result in changes in the way care is currently organised.	NO
Is the guideline development group aware of any barriers to the implementation of this recommendation? Yes as may potentially be limited by availability of breast reconstructive surgery across Australia. Additionally uncertainty surrounding requesting genetic testing in those without a known genetic mutation.	YES

Key question 1: What is the optimal surgical management, with or without radiotherapy, on the ipsilateral side for women diagnosed with breast cancer with a BRCA 1/2 mutation?	
Recommendation 2: Recommend radiotherapy after <i>breast conserving surgery</i> in women diagnosed with breast cancer with a BRCA1/2 mutation to decrease the risk of ipsilateral breast cancer (as similarly recommended to other women with breast cancer that is not attributable to a BRCA1/2 mutation). Metcalfe, Lynch 2011 ²⁰ ; Shanley 2006 ²¹ ; Pierce 2000 ²²	
Component	Grading



Key question 1: What is the optimal surgical management, with or without radiotherapy, on the ipsilateral side for women diagnosed with breast cancer with a BRCA 1/2 mutation?	
1. Evidence base Three Level III-2 retrospective cohort studies (A5 and A6 evidence statements) included in systematic review with generally a low risk of bias.	C (One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias)
2. Consistency Most studies consistent and any inconsistency may be explained.	B (Most studies consistent and inconsistency may be explained)
3. Clinical impact This course of treatment is already used in practice and therefore does not alter the recommended treatment of women post breast conserving surgery.	D (Slight/Restricted)
4. Generalisability Population/s studied in body of evidence are the same as the target population in the guideline.	A (Population/s studied in body of evidence are the same as the target population in the guideline)
5. Applicability Directly applicable to Australian healthcare context.	A (Directly applicable to Australian healthcare context)
Overall grade of recommendation:	C Body of evidence provides some support for recommendation(s) but care should be taken in its application

UNRESOLVED ISSUES	
None identified.	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care? There is no perceived change to standard clinical practice and care.	NO
Are there any resource implications associated with implementing this recommendation? There are no significant resource implications associated with implementing this recommendation.	NO
Will the implementation of this recommendation require changes in the way care is currently organised? This recommendation will not result in changes in the way care is currently organised.	NO
Is the guideline development group aware of any barriers to the implementation of this recommendation? There are no barriers identified to the implementation of this recommendation.	NO

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

Recommendation 3:



Key question 2: Are there particular <i>neoadjuvant</i> and <i>adjuvant</i> systemic therapies which are specifically effective for women diagnosed with breast cancer and a BRCA1/2 mutation?	
Base the <i>use of</i> neoadjuvant/adjuvant <i>chemotherapy</i> for women diagnosed with breast cancer with a BRCA1/2 mutation on similar considerations for women with breast cancer not attributable to a BRCA1/2 mutation. Goodwin 2012 ³⁴ ; Metcalfe, Lynch 2011 ²⁰ ; Metcalfe, Gershman 2011 ³⁵ ; Arun 2011 ³⁶ ; Pierce 2010 ¹² ; Reding 2010 ³⁷ ; Rennert 2007 ³⁸ ; Brekelmans 2006 ³⁹ ; Robson 2004 ¹⁸	
Component	Grading
1. Evidence base One Level II prospective cohort study, seven Level III-2 retrospective cohort studies and one Level III-3 case-control study (B1, B2, B3, B4, B8, B9 and B10 evidence statements) included in systematic review generally with low risk of bias.	B (Several Level II/III studies with a low risk of bias)
2. Consistency Rated as C due to inconsistencies in some study results comparing adjuvant chemotherapy to no adjuvant chemotherapy. Also different variables were compared and measured across the separate studies.	C (Some inconsistency, reflecting genuine uncertainty around clinical question)
3. Clinical impact No significant change to current clinical practice – this evidence reaffirms the use of these clinical practices.	C (Moderate)
4. Generalisability Population/s studied in the body of evidence are similar to the target population for the guideline.	B (Population/s studied in the body of evidence are similar to the target population for the guideline)
5. Applicability Types of chemotherapy treatments readily available in Australia and currently widespread clinical practice. Therefore directly applicable to Australian healthcare context	A (Directly applicable to Australian healthcare context)
Overall grade of recommendation:	C Body of evidence provides some support for recommendation(s) but care should be taken in its application

UNRESOLVED ISSUES	
None identified.	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care? There is no perceived change to standard clinical practice and care.	NO
Are there any resource implications associated with implementing this recommendation? There are no significant resource implications associated with implementing this recommendation.	NO
Will the implementation of this recommendation require changes in the way care is currently organised? This recommendation will not result in changes in the way care is currently organised.	NO
Is the guideline development group aware of any barriers to the implementation of this recommendation?	NO



UNRESOLVED ISSUES	
None identified.	
There are no barriers identified to the implementation of this recommendation.	

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

Recommendation 4:
 Base the *type of* neoadjuvant/adjuvant chemotherapy for women diagnosed with breast cancer with a BRCA1/2 mutation on similar considerations for women with breast cancer not attributable to a BRCA1/2 mutation.
 Arun 2011³⁶; Byrski 2010⁴⁰; Fourquet 2009⁴¹; Byrski 2008⁴²

Component	Grading
1. Evidence base Four small Level III-2 retrospective cohort studies (B5, B6 and B7 evidence statements) with a low risk of bias included in the systematic review.	C (One or two level III studies with a low risk of bias)
2. Consistency Inconsistent results and findings across three small studies, suggesting an unclear conclusion from these studies.	C (Some inconsistency, reflecting genuine uncertainty around clinical question)
3. Clinical impact Results demonstrate largely unconvincing findings, therefore a slight/restricted clinical impact and insufficient evidence to prefer one type of chemotherapy over another.	D (Slight/Restricted)
4. Generalisability Population/s studied in the body of evidence are similar to the target population for the guideline.	B (Population/s studied in the body of evidence are similar to the target population for the guideline)
5. Applicability Directly applicable to Australian healthcare context.	A (Directly applicable to Australian healthcare context)
Overall grade of recommendation:	C Body of evidence provides some support for recommendation(s) but care should be taken in its application

UNRESOLVED ISSUES	
None identified.	

IMPLEMENTATION OF RECOMMENDATION

Will this recommendation result in changes in usual care? There is no perceived change to standard clinical practice and care.	NO
Are there any resource implications associated with implementing this recommendation? There are no significant resource implications associated with implementing this recommendation.	NO



UNRESOLVED ISSUES	
None identified.	
Will the implementation of this recommendation require changes in the way care is currently organised? This recommendation will not result in changes in the way care is currently organised.	NO
Is the guideline development group aware of any barriers to the implementation of this recommendation? There are no barriers identified to the implementation of this recommendation.	NO

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

Recommendation 5:
Base the *use* and *type* of Selective Estrogen Receptor Modulators (SERMs) in women diagnosed with ER positive breast cancer with a BRCA1/2 mutation on similar considerations for women with breast cancer not attributable to a BRCA1/2 mutation.
Phillips 2013⁴³; Goodwin 2012³⁴; Metcalfe, Gershman 2011³⁵; Metcalfe, Lynch 2011²⁰; Reding 2010³⁷; Pierce 2010¹²; Pierce 2006¹⁶; Gronwald 2006⁴⁴; Robson 2004¹⁸; Foulkes 2002⁴⁵

Component	Grading
1. Evidence base One Level II prospective cohort study, five Level III-2 retrospective cohort studies and one Level III-3 case-control study (B13, B14, B15, and B16 evidence statements) included in systematic review.	B (Several Level II/III studies with a low risk of bias)
2. Consistency Studies have a degree of inconsistency due to mixed populations and older cohorts.	C (Some inconsistency, reflecting genuine uncertainty around clinical question)
3. Clinical impact No change to current practice so minimal clinical impact.	D (Slight/Restricted)
4. Generalisability Population/s studied in body of evidence are the same as the target population for the guideline.	A (Population/s studied in body of evidence are the same as the target population for the guideline)
5. Applicability Directly applicable to Australian healthcare context.	A (Directly applicable to Australian healthcare context)
Overall grade of recommendation:	C Body of evidence provides some support for recommendation(s) but care should be taken in its application

UNRESOLVED ISSUES	
None identified.	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	NO



UNRESOLVED ISSUES	
None identified.	
There is no perceived change to standard clinical practice and care.	
Are there any resource implications associated with implementing this recommendation?	NO
There are no significant resource implications associated with implementing this recommendation.	
Will the implementation of this recommendation require changes in the way care is currently organised?	NO
This recommendation will not result in changes in the way care is currently organised.	
Is the guideline development group aware of any barriers to the implementation of this recommendation?	NO
There are no barriers identified to the implementation of this recommendation.	

Key question 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?

Recommendation 6:
 Discuss contralateral risk-reducing mastectomy with women diagnosed with breast cancer with a BRCA1/2 mutation, particularly in younger women (less than 50 years), to substantially decrease the risk of *contralateral breast cancer*.
 Domchek 2010⁴⁶; Brekelmans 2006³⁹; Van Sprundel 2005⁴⁷; Metcalfe 2004⁴⁸

Component	Grading
1. Evidence base One Level II prospective cohort study and three Level III-2 retrospective cohort studies (C1 and C2 evidence statements) included in systematic review, generally with a low risk of bias.	B (One level II study with low risk of bias, and several level III studies mostly with low risk of bias)
2. Consistency All studies consistent with one another.	A (All studies consistent)
3. Clinical impact Recommending surgical risk-reducing strategies so substantial clinical impact.	B (Substantial)
4. Generalisability Population/s studied in body of evidence are the same as the target population for the guideline.	A (Population/s studied in body of evidence are the same as the target population for the guideline)
5. Applicability Directly applicable to Australian healthcare context.	A (Directly applicable to Australian healthcare context)
Overall grade of recommendation:	B Body of evidence can be trusted to guide practice in most situations

UNRESOLVED ISSUES
None identified.
IMPLEMENTATION OF RECOMMENDATION



UNRESOLVED ISSUES	
None identified.	
Will this recommendation result in changes in usual care? This recommendation involves consideration of both ipsilateral and contralateral breast surgery.	YES
Are there any resource implications associated with implementing this recommendation? Yes, issue of cost of operating on both breasts (compared to one breast); accessibility to <i>genetic counselling</i> and testing; and accessibility to breast reconstructive options, particularly in rural areas.	YES
Will the implementation of this recommendation require changes in the way care is currently organised? This recommendation will not result in changes in the way care is currently organised. Level of organisation care depends on capacity of organisation providing care to patients. Need for access to plastic surgery but this need is the same for women requiring single mastectomy, regardless.	NO
Is the guideline development group aware of any barriers to the implementation of this recommendation? Yes, accessibility to genetic counselling and testing and accessibility to breast reconstructive options, which may be limited particularly in rural areas.	YES

Key question 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?

Recommendation 7:
Discuss risk-reducing *salpingo-oophorectomy* with women diagnosed with breast cancer with a BRCA1/2 mutation around the age of 40 years or when child-bearing is complete to improve overall survival and substantially decrease the risk of ovarian/fallopian tube cancer.
Metcalf, Lynch 2011²⁰; Metcalf, Gershman 2011³⁵; Pierce 2010¹²; Domchek 2010⁴⁶; Pierce 2006¹⁶; Brekelmans, 2006³⁹; Van Sprundel 2005⁴⁷

Component	Grading
1. Evidence base One Level II prospective cohort study and six Level III-2 retrospective cohort studies (C3, C4, C5 and C6 evidence statements) included in systematic review generally with a low risk of bias.	B (One level II study with low risk of bias, and several level III studies mostly with low risk of bias)
2. Consistency The evidence measures different outcomes: Two studies measure survival outcomes, one study measures ipsilateral breast cancer, one study measures contralateral breast cancer and one study measures <i>ovarian cancer</i> .	B (Some caveats)
3. Clinical impact Implementing a recommendation for risk-reducing salpingo-oophorectomy will have a very large clinical impact for these women.	A (Very large)
4. Generalisability Population/s studied in body of evidence are the same as the target population for the guideline.	A (Population/s studied in body of evidence are the same as the target population for the guideline)
5. Applicability Directly applicable to Australian healthcare context.	A (Directly applicable to Australian healthcare context)



Key question 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?

Overall grade of recommendation:	B Body of evidence can be trusted to guide practice in most situations
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UNRESOLVED ISSUES
None identified.

IMPLEMENTATION OF RECOMMENDATION

Will this recommendation result in changes in usual care? Yes as involves consideration of salpingo-oophorectomy by women with a BRCA1/2 mutation, at around 40 years or when child-bearing decisions are complete, which is not considered usual care. Also dependent on where the patient is located.	YES
Are there any resource implications associated with implementing this recommendation? Yes as requirement for surgical and pathology evaluations and additionally referral to gynaecological specialists (limited availability of speciality oncologists in rural areas).	YES
Will the implementation of this recommendation require changes in the way care is currently organised? This recommendation will not result in changes in the way care is currently organised.	NO
Is the guideline development group aware of any barriers to the implementation of this recommendation? Yes as requires referral to <i>gynaecological oncologists</i> (limited availability of specialty oncologists).	YES

