Recommendations for management of

Women at high risk of ovarian cancer

SEPTEMBER 2011 | Incorporates published evidence to April 2010

A CLINICAL PRACTICE GUIDELINE DEVELOPED BY NATIONAL BREAST AND OVARIAN CANCER CENTRE (NBOCC)*

This document supplements guideline recommendation about risk-reducing surgery (page 37) contained in the National Breast Cancer Centre (NBCC) and Australian Cancer Network (ACN), Clinical practice guidelines for the management of women with *epithelial ovarian cancer*, 2004.[1]

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Purpose

This guideline includes statements and recommendations based on available evidence about the management of women at high or potentially high risk of *ovarian cancer*.[a] The guideline aims to provide health professionals with information designed to assist in making management recommendations for improved patient outcomes.

Endorsed by:

ASGO
Australian Society of Gynaecological Oncologists

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

RCPA
The Royal College of Pathologists of Australasia

* In July 2011, National Breast and Ovarian Cancer Centre (NBOCC) amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.

[a] Where recommendations apply specifically to either high-risk or potentially high-risk women this has been noted.

Background

Up to 15% of all cases of invasive *ovarian cancer* involve the inheritance of a mutated gene.[2] Women who have inherited mutations in the *BRCA1* or *BRCA2* genes have substantially elevated risk of ovarian and breast cancer, with estimated lifetime risk for ovarian cancer, ranging from 36% to 46% for *BRCA1* mutation carriers and from 10% to 27% for *BRCA2* mutation carriers.[3-4] Women with Lynch Syndrome have an elevated risk of developing certain cancers, including an increased lifetime risk of ovarian cancer of up to 10%.[5]

As a group, women at potentially high risk of developing ovarian cancer have a risk more than three times the population average. Their risk of developing ovarian cancer up to age 75 is between 1 in 30 and 1 in 2, depending on whether genetic test results are known.[5] This group covers less than 1% of the female population.

Management options aim to reduce the risk of ovarian cancer in high-risk women. Options include surgery or preventive therapy (previously known as chemoprevention). Surgical options include risk-reducing salpingo-oophorectomy (RRSO), which may or may not be performed with a *hysterectomy*, and tubal ligation. There is increasing evidence that some of these cancers originate in the fimbrial end of the fallopian tube.[6] The most effective risk-reducing strategy for ovarian cancer is bilateral salpingo- *oophorectomy*.[7] Preventive therapy (use of the oral contraceptive pill (OCP)) may be an option for pre-menopausal women who choose not to have RRSO.[5]

There are several issues to be considered in the management options of women at high risk of ovarian cancer including factors influencing decision making, psychosocial wellbeing, surgical outcomes and quality of life.

There is no evidence that surveillance of women at high risk of ovarian cancer, using *ultrasound* or *CA125*, singly or in combination, is effective in detecting early ovarian cancer.[7]

Designation of level of risk of ovarian cancer

A woman who has a gene fault in *BRCA1* or *BRCA2* (*BRCA1/2*) confirmed by genetic testing is at high risk of developing ovarian or breast cancer.[3, 5, 8] A woman who has not had genetic testing but who has a strong family history[5] of either ovarian or breast cancer *may* have a gene fault in *BRCA1/2* and is considered *potentially* at high risk of developing ovarian or breast cancer. If a woman has a strong family history where an affected family member has had genetic testing for *BRCA1/2* which was inconclusive she is still considered at potentially high risk, as there may be gene faults which affect her ovarian or breast cancer risk which are not currently tested for or not yet discovered. Women who do not have a strong family history or a confirmed gene fault are considered at average risk.[9]

A woman who has Lynch Syndrome (or HNPCC) confirmed by genetic testing is also at high risk of developing ovarian cancer, as well as endometrial cancer, colorectal cancer, gastric cancer and cancers involving the renal tract.[5] A woman who has not had genetic testing but who has a strong family history of these cancers, suggestive of Lynch Syndrome, is considered *potentially* at high risk of developing ovarian cancer. A strong family history suggestive of Lynch Syndrome is considered to be three or more 1° or 2° degree relatives on the same side of the family diagnosed with colorectal cancer (particularly if diagnosed before the age of 50), endometrial cancer, ovarian cancer, gastric cancer, and cancers involving the renal tract.[5]

Definition of potentially high risk of ovarian cancer[#]

Women have been defined as being at potentially high risk of developing ovarian cancer if they:

- Are a woman who is at high risk of breast cancer due to a gene fault e.g. in *BRCA1* or *BRCA2*
- Have one 1° or 2° relative diagnosed with *epithelial ovarian cancer* in a family of Ashkenazi Jewish ancestry*

- Have one 1° or 2° relative with ovarian cancer at any age, and another with breast cancer before the age of 50, where the women are 1° or 2° relatives of each other
- Have two 1° or 2° relatives on the same side of the family diagnosed with epithelial ovarian cancer, especially if one or more of the following features occurs on the same side of the family:
  1. additional relative(s) with breast or ovarian cancer
  2. breast cancer diagnosed before the age of 40
  3. bilateral breast cancer
  4. breast **and** ovarian cancer in the same woman
  5. breast cancer in a male relative
- Have three or more 1° or 2° relatives on the same side of the family diagnosed with a family history suggestive of Lynch Syndrome (or HNPCC) e.g. colorectal cancer (particularly if diagnosed before the age of 50), endometrial cancer, ovarian cancer, gastric cancer, and cancers involving the renal tract
- Are a member of a family in which the presence of a high-risk ovarian cancer *gene mutation* has been established

If genetic test results are known, individual risk may be higher or lower. The category of potentially high risk of ovarian cancer covers less than 1% of the female population. As a group, lifetime risk of ovarian cancer ranges between 1 in 30 and 1 in 2. This risk is more than 3 times the population average.

* High-risk ovarian and breast cancer gene mutations are more common in people of Ashkenazi Jewish ancestry

Clinical practice recommendations

The recommendations are based on the statements of evidence for management of women at high risk of ovarian cancer. The level of evidence assigned to the recommendation is based on the NHMRC Evidence Intervention Hierarchy.[10]

Recommendations to individuals should be based on their circumstances, the absolute benefits and harms of treatment, and their personal preferences. These factors should be discussed with the woman.[11]

RECOMMENDATIONS	LEVEL OF EVIDENCE[10]	REFERENCE
For women at high/potentially high risk of ovarian cancer		
For women at high risk of ovarian cancer due to a confirmed *BRCA1/2* gene mutation, risk-reducing gynaecological surgery should be recommended. This should include complete removal of the extra-uterine component of both *fallopian tubes* as well as *ovaries*, and should be considered around the age of 40.	III-2	Rebbeck 2009[3] Domchek 2010a[12]
For women at high risk of ovarian cancer due to confirmed Lynch Syndrome, risk-reducing surgery should be considered. This should include *hysterectomy* and *bilateral salpingo-oophorectomy* and should be considered from around the age of 35.	III-2	Schmeler 2006[13]
For other women at potentially high risk of ovarian cancer, referral to a familial cancer clinic is recommended for risk assessment, possible genetic testing and management planning (which may include risk-reducing surgery).		NBOCC 2010[5]
Information about procedures should be discussed with the patient. The patient should be adequately prepared for the procedure. For women at high risk or potentially high risk of ovarian cancer this includes: • a clear description of the risk-reducing surgery technique • clear information about the objective of the procedure • discussion of management of *menopausal symptoms* and other long-term side-effects post risk-reducing surgery, including use of *hormone replacement therapy* (HRT) • discussion of factors influencing psychosocial wellbeing post risk-reducing surgery.	I	NBCC & NCCI[11]
Ongoing assessment of the effects of *surgical menopause* is required after surgery		
Risk-reducing surgery should be performed by a surgeon appropriately experienced in gynaecological surgery		
All removed tissue should be embedded and examined for full pathological assessment, and cut through at no more than 3mm intervals, including the fimbrial end of the fallopian tube sectioned longitudinally		

RECOMMENDATIONS	LEVEL OF EVIDENCE[10]	REFERENCE
Ovarian cancer surveillance is not recommended for women at high or potentially high risk. Evidence shows that *ultrasound* or *CA125*, singly or in combination, is not effective at detecting early ovarian cancer.		NBOCC[7]

Statements of evidence

Below are the statements of evidence on which the recommendations are based.

STATEMENTS	LEVEL OF EVIDENCE[10]	REFERENCE
For women at high/potentially high risk of *ovarian cancer*, including BRCA1 and BRCA2 mutation carriers and those with Lynch Syndrome.		
Gynaecological cancer risk for women with BRCA1/2 mutations or Lynch Syndrome		
In women with a *BRCA1/2* mutation, there is an increased risk of cancer in the *fallopian tubes* and ovary	IV	NBOCC[5]
In women with Lynch Syndrome, there is an increased risk of cancer of the *uterus* and ovaries	IV	NBOCC[5]
Gynaecological and breast cancer risk following RRSO		
Risk-reducing salpingo-oophorectomy provides a substantial risk reduction in developing ovarian and fallopian tube cancers in *BRCA1/2* mutation carriers.	III-2	Rebbeck 2009[3] Domchek 2010a[12]
Risk-reducing salpingo-oophorectomy before the age of 50 provides a risk reduction for developing breast cancer in *BRCA1/2* mutation carriers.	III-2	Rebbeck 2009[3] Domchek 2010a[12]
There is no apparent increase in risk of breast cancer in *BRCA1/2* mutation carriers, unaffected by breast cancer, who take short-term HRT after RRSO performed before the age of 50 compared to those who do not take HRT.	III-2	Rebbeck 2005[14]
Occult cancers have been detected in the fallopian tubes and *ovaries* at RRSO.		Rabban 2009b[15] Hirst 2009[16] Callahan 2007[17] Domchek 2010a[12] Finch 2006a[18] & 2006b[19] Olivier 2004[20]
Primary peritoneal *carcinoma* may occur despite risk-reducing surgery but is uncommon.	III-2	Domchek 2010a[12] Domchek 2006[21] Kauff 2008[22] Finch 2006a[18]
Limited data are available for the efficacy of risk-reducing surgery in women with Lynch Syndrome.	III-2	Schmeler 2006[13]
Survival/life expectancy		

STATEMENTS	LEVEL OF EVIDENCE[10]	REFERENCE
In women with a *BRCA1/2* mutation, RRSO is associated with a significant reduction in all-cause mortality (including breast and ovarian cancer-specific mortality).	III-2	Domchek 2010a[12]
Symptoms associated with RRSO		
Symptoms from RRSO are mainly associated with surgically-induced *menopause*.	III-2	Fang 2009[23] Benshushan 2009[24]
Women with surgically-induced menopause more commonly report night sweats, sleep disturbance, hot flushes, and decreased *libido* and have significantly more severe vasomotor symptoms than women who go through natural menopause.	III-2	Benshushan 2009[24]
Use of HRT for menopausal symptoms		
HRT is effective in the management of most *menopausal symptoms* following RRSO.	III-2	Madalinska 2006 [14]
Quality of life following RRSO		
There is evidence of reduced cancer worry following RRSO, but there is no consistent evidence on the effect on quality of life following RRSO		De Leeuw 2008[25] Madalinska 2005[26]
RRSO technique and pathology assessment		
Attending a specialist gynaecologic oncologist for risk-reducing gynaecological surgery is more likely to result in adequate surgery and pathological examination	III-2	Kiely 2011[27]
The ovarian and fallopian tube tissue should be examined appropriately with specimens cut through at no more than 3mm intervals, and all tissue processed and embedded with at least one section cut from each block	IV	Rabban 2009[15]
The fallopian tube-peritoneal junction is a potential site of carcinogenesis		Seidman 2011[28]
Cost-effectiveness of risk-reducing strategies		
Bilateral salpingo-oophorectomy and combined bilateral salpingo-oophorectomy and *mastectomy* are the most cost-effective risk-reducing strategies for women with a *BRCA1/2* gene mutation. Surveillance and mastectomy alone are the least cost-effective strategies.	Modelling study	Anderson 2006[29]
Use of the oral contraceptive pill		
Use of the oral contraceptive pill reduces rates of ovarian cancer in *BRCA1/2* mutation carriers, with greater reductions with increasing duration of use.	III-2	Antoniou 2009[30]McLaughlin 2007[31] Whittemore 2004[32]
In women with *BRCA1/2* mutations the risk of breast cancer with OCP use is uncertain	III-2	Narod 2002[33]

STATEMENTS	LEVEL OF EVIDENCE[10]	REFERENCE
Tubal ligation		
While there is evidence of reduced risk of ovarian cancer after tubal ligation in the general population, the association between tubal ligation and risk of ovarian cancer is not clear in high-risk women.	III-2	Antoniou 2009[30] McLaughlin 2007[31] Rutter 2003[34]
Surveillance strategies for women at high risk		
Evidence shows that *ultrasound* or *CA125*, singly or in combination, is not effective in detecting early ovarian cancer in women at high or potentially high risk of ovarian cancer.		NBOCC[7]
There is no evidence for the use of gynaecological surveillance after risk-reducing surgery for women at high risk		
Communication about risk		
Risk perception and knowledge are improved following genetic counselling		Braithwaite 2006[35]
Decision making		
Use of a decision aid or shared decision-making, compared to a general educational pamphlet about risk-reducing strategies, reduces decisional conflict improves knowledge and increases satisfaction with the decision.	II	Tiller 2005[36] Armstrong 2005[37] van Roosmalen 2004[38]

Summary of evidence

The NBOCC statements and recommendations about the management of women at high risk of ovarian cancer are based on a NBOCC systematic literature review[39] of available evidence published between January 2003 and April 2010. Additional relevant articles, published after the completion of the review up until April 2010, have also been considered.

The NBOCC systematic review includes 49 published citations. Papers that included women at high risk or potentially high risk of ovarian cancer, including women with known *BRCA1/2* mutations, women with Lynch Syndrome, and women with a strong family history of breast or ovarian cancer were identified. Most papers reported on populations with *BRCA1* or *BRCA2* mutations and most information was provided on risk-reducing salpingo-oophorectomy (RRSO).

Thirty-seven citations addressed the primary research questions:

- What is the effectiveness of risk-reducing strategies for women at high risk or potentially high risk of ovarian cancer?
- What is the effectiveness of surveillance strategies for women at high risk or potentially high risk of ovarian cancer?
- What are the psychological/psychosocial issues encountered by women at high risk or potentially high risk of ovarian cancer?

The remaining 12 citations addressed additional issues of interest including pathology of ovarian cancer in high risk women and relevance to risk-reducing surgical management, communication about risk including information needs of women and decision aid tools. Other topics identified were factors affecting decision making on risk-reducing strategies, uptake of risk-reducing strategies and cost-effectiveness of risk-reducing strategies.

Twenty-five studies were identified which evaluated the effects of risk-reducing salpingo-oophorectomy, including one meta-analysis.[3] Three studies evaluated the association of oral contraceptive use and ovarian cancer risk and three studies evaluated the association of tubal ligation and ovarian cancer risk.

Risk-reducing salpingo-oophorectomy

Risk-reducing salpingo-oophorectomy is a surgical procedure which includes the complete removal of both *fallopian tubes* and *ovaries*. RRSO provides a substantial reduction in the risk of developing ovarian and fallopian tube cancers in women with a *BRCA1/2* gene mutation.[3, 12]

Benefits of risk-reducing surgery

Impact on survival

A large prospective cohort study by Domchek[12] reported that in *BRCA1/2* mutation carriers, RRSO reduced all-cause mortality by 60% (HR 0.40, 95% CI 0.26 to 0.61), ovarian cancer-specific mortality by 79% (HR 0.21, 95% CI 0.06 to 0.80) and breast cancer-specific mortality by 56% (HR 0.44, 95% CI 0.26 to 0.76). Modelling studies also suggest a survival benefit of RRSO,[40-41] particularly when performed by age 40 and when combined with prophylactic *mastectomy*. Most of the other papers identified did not provide information about survival after RRSO.

Ovarian cancer

Pooled results from three non-overlapping studies, which included 2840 participants, were used to provide a summary estimate for ovarian/fallopian tube cancer in *BRCA1/2* mutation carriers. For *BRCA1/2* mutation carriers

treated with RRSO relative to those who did not receive this treatment the summary hazard ratio (HR) was 0.21 (95% CI 0.12 to 0.39) indicating a 79% reduction in gynaecologic cancer.[3] The study by Domchek[12] supported these findings for BRCA mutation carriers. Results were reported separately for women without or with prior breast cancer, each had reduced rates of ovarian cancer after RRSO (without prior breast cancer: HR 0.28 (95% CI 0.12 to 0.69); with prior breast cancer: HR 0.14 (95% CI 0.04 to 0.59).[12]

Breast cancer

Risk-reducing salpingo-oophorectomy also reduces the risk of developing breast cancer in *BRCA1/2* mutation carriers. Pooled results from three non-overlapping studies, which included 5703 participants, provided a summary estimate for breast cancer in *BRCA1/2* mutation carriers. For *BRCA1/2* mutation carriers treated with RRSO relative to those who did not receive this treatment, the summary hazard ratio (HR) was 0.49 (95% CI 0.37 to 0.65) indicating a 51% reduction in breast cancer.[3] A prospective cohort published after this meta-analysis supported these results for BRCA mutation carriers with no prior breast cancer.[12] The risk reduction may be more for *BRCA2* mutation carriers than for *BRCA1* mutation carriers.[12] There was evidence for an age effect, with greater reduction in breast cancer risk for *BRCA1* carriers who had RRSO before the age of 50, compared to after age 50.[12] Since there is evidence that risk of ovarian cancer increases later in *BRCA2* mutation carriers than for *BRCA1*,[4] RRSO in *BRCA2* mutation carriers could be delayed until age 45, but this may not provide the same degree of breast cancer risk reduction as RRSO at age 40.

Peritoneal cancer

Primary peritoneal *carcinoma* may occur despite risk-reducing salpingo-oophorectomy but is uncommon (≤1%).[12, 18, 21-22]

Lynch Syndrome

In women with Lynch Syndrome, there is an increased risk of cancer of the *uterus* and ovaries, among other cancers.[5] Limited evidence is available about the efficacy of risk-reducing surgery to reduce the risk of ovarian cancer in women with Lynch Syndrome. A retrospective cohort of women with documented germ-line mutations associated with the Lynch Syndrome reported no cases of ovarian cancer after RRSO compared to 5% in the *control group*.[42] Prophylactic surgery should be considered in these women from around the age of 35 in those who do not wish to preserve their fertility.[42]

Tubal ligation

Whilst there is evidence of reduced risk of ovarian cancer after tubal ligation in the general population, the association between tubal ligation and risk of ovarian cancer is not clear in high-risk women. One study has reported statistically significant reduction (over 50%) in ovarian cancer for *BRCA1* mutation carriers who had undergone tubal ligation.[30] Two other studies reported non-significant reductions in ovarian cancer risk after tubal ligation.[31, 34]

Occult cancers

Occult cancers have been detected in the fallopian tubes and ovaries at RRSO. Rates of occult ovarian cancer detected at RRSO ranged from 0 to 17%.[39] They were more often detected in *BRCA1* mutation carriers and were often of fallopian tube origin. Occult cancers are likely more often detected in *BRCA1* mutation carriers as cancers tend to develop at an earlier age in this population.[19] The rate of occult cancer detected is also related to how the pathological examination is performed.[19, 43] Domchek *et al*[44] reported that women who had occult ovarian cancer at RRSO were older (mean age 51.7 vs. 46.6) and less likely to have used oral contraceptives (60% vs. 80%) than women who did not have occult ovarian cancer detected at RRSO. This study also reported that more occult ovarian

cancers were diagnosed at an earlier *stage* compared to ovarian cancers detected outside the context of RRSO (37.5% stage I vs. 0% stage I, respectively, p=0.023).

Cost-effectiveness

Two cost-effectiveness studies evaluating preventive strategies for women with BRCA *gene mutations* both found that either RRSO alone or RRSO combined with prophylactic mastectomy were the most cost-effective for the study population.[29, 45] The Norwegian study confirmed that the significant reduction in risk of breast and ovarian cancer, prolonged survival and productivity gain from having both RRSO and prophylactic mastectomy produced savings that more than compensated for the up-front costs of the investigation and prophylactic therapy.[45]

Consequences of risk-reducing surgery

The procedures used for risk-reducing surgery in women at high risk are the same as those used for other indications. There is no reason to believe that the surgical complication rate for risk-reducing surgery for women with a gene mutation is different to that of the general population having similar surgery.[13] A study by Schmeler[13] in women with Lynch Syndrome did not identify any data to indicate a change in the surgical complication rate for this sub-group.

Menopausal symptoms

The main symptoms experienced after RRSO are those associated with surgically-induced *menopause*. Women with surgically-induced menopause more commonly report night sweats, sleep disturbance, hot flushes, and decreased *libido* and have significantly more severe vasomotor symptoms than women who go through natural menopause.[24] Another study reported that within the RRSO group, those who had RRSO before age 50yrs had more palpitations than those with RRSO at $\geq$ 50yrs.[46]

Hormone replacement therapy (HRT) is effective in the management of menopausal symptoms following RRSO.[47] Based on evidence from the systematic review there appears to be no increased risk of breast cancer in unaffected *BRCA1/2* mutation carriers taking short-term HRT following RRSO performed before the age of 50.[14] Further prospective studies may clarify this issue. Discussion about management of menopausal symptoms, including use of HRT, and psychosocial wellbeing should occur prior to risk-reducing surgery. Ongoing assessment of the effects of *surgical menopause* is required after surgery.

Long-term health effects

No studies were found reporting on the potential long-term health effects of RRSO on women at high risk of ovarian cancer. One review,[9] outside the scope of the systematic review, identified several articles on the potential impacts on long-term health effects of RRSO on women at average risk of ovarian cancer. Studies showed women who had RRSO before age 45 and who had not received exogenous *oestrogen* up to age 45 had significantly higher cardiovascular mortality, compared to women who did have oestrogen following RRSO up until age 45 who showed no increase in mortality.[48] In addition to adverse effects on cardiovascular and bone health, increased risk of Parkinson disease[49] and dementia[50] were also reported. While these studies are on the general population, they may provide possible insight into the effects of risk-reducing surgery on high risk women, however further research is required.

Sexual dysfunction

A number of papers described sexual activity and function for women after RRSO. Some papers reported that more women in RRSO groups had a decreased libido,[24, 47] and it was consistently reported that women who underwent RRSO experienced more pain/discomfort during sexual activity than those in control groups.[23, 47, 51]

Psychological impact

Four studies reported on psychological impact of RRSO. A range of scales to measure psychological impact were used, with levels of anxiety and depression most often reported. Inconsistent results were reported in the studies so the psychological impact of RRSO is uncertain.

For those who had RRSO, anxiety about developing ovarian cancer and breast cancer decreased substantially after surgery.[24, 26]

RRSO technique and pathology assessment

RRSO technique

The specific technique of how RRSO was performed was often not provided in detail in the studies reporting effectiveness of RRSO. Where specific details were reported, the majority of patients underwent RRSO at the same time as total abdominal *hysterectomy*.[13, 23, 52-53] In a retrospective study of risk-reducing surgery in Australian patients by Keily *et al*, 91% were assessed as having adequate surgery, whereas 23% were assessed as having adequate pathology (paraffin embedding of all removed ovarian and tubal tissue).[27]

Olivier *et al* (2004) reported a retrospective analysis on the outcomes of high-risk women who had undergone bilateral *prophylactic oophorectomy* (BPO) compared to women who had *bilateral salpingo-oophorectomy* (BSO).[20] Occult cancers (3 fallopian tube; 2 ovarian) were only found in the women who had undergone BSO (8.6%, 5 out of 58), who were all *BRCA1* mutation carriers. Three women from the BPO group went on to develop papillary peritoneal serous cancer within 45 months of follow-up after surgery.

Olivier *et al* (2005) also reported another retrospective analysis of women who had BPO compared to women who had additional bilateral salpingectomy (BPS) after BPO.[54] The study reported three cases of peritoneal papillary serous cancer detected in the BPO alone group (mean follow-up of 66 months) compared to none in the group who had an additional BPS (mean follow-up 80 months) suggesting an additional risk reduction from BPS in *BRCA1/2* carriers after having had BPO.[54]

Powell et al[43] compared the detection of occult ovarian cancers depending on the level of adherence to an intensive RRSO protocol which included:

- bilateral salpingo-oophorectomy and removal of entire fallopian tube
- cytologic examination of peritoneal washings
- random peritoneal and omental biopsies
- serial sectioning of entire fallopian tubes and ovaries at 2mm intervals and microscopic examination of all sections.

The authors note that the rate of occult cancers detected in women who had full or partial adherence to the intensive protocol (17%, 7 out of 41) was considerably higher than in recent studies of BRCA mutation carriers whose RRSO procedures are routine (laparoscopic removal of the ovaries and fallopian tubes but without serial sectioning) with rates around 2.5%.[43]

Kiely *et al* reported that women attending a specialist gynaecologic oncologist for risk-reducing gynaecological surgery were more likely to have appropriate surgery and the surgical specimen more likely to have an adequate pathological examination.[27]

Pathology assessment

In addition to Powell[43], Rabban[55] described the use of serial sectioning of RRSO specimens to detect occult cancers. Rabban *et al* reported that there does not appear to be any diagnostic value in automatically performing multistep deeper level sections of RRSO specimens if the tissue is sectioned appropriately and if the specimen is sliced at intervals that are no more than 3mm thick.[55] It was noted that pathological assessment should be performed by an experienced *pathologist*, and include all tissue from both tubes and ovaries, cut through at no more than 3mm intervals, processed and embedded with at least one section cut from each block.[55] Informing the pathologist as to the reasons for the surgery is important in ensuring adequate assessment of the specimens. [27]

Quality of life following RRSO

There is no consistent evidence of an overall impact on quality of life, either positive or negative, following RRSO.

In a study where women who had RRSO were compared to women who chose screening, more women who had RRSO were satisfied with their decision, 97% versus 82% respectively.[26] For those who had RRSO, 86% would choose this procedure again and 63% would recommend it to a friend with familial risk of ovarian cancer.[26] A systematic review on predictors of uptake of risk reduction and surveillance reported evidence of reduced anxiety in women following RRSO and also a high level of satisfaction with their decision. [25]

There is evidence of reduced cancer worry in women, about both ovarian and breast cancer, following RRSO. Cancer worry is lowest in women who had both RRSO and prophylactic mastectomy.[24, 26]

There is evidence that women who have RRSO report more bodily pain at 12 months post-assessment than before the surgery.[23] Women who have RRSO also report more discomfort (vaginal dryness and dyspareunia), less pleasure and satisfaction during sexual activity and more endocrine symptoms than women who have not undergone RRSO, and who participate in periodic gynaecologic screening only.[23, 26]

Factors affecting decision making on risk-reducing strategies

A systematic review on decision-making related to cancer risk-reducing strategies for women at high risk of hereditary breast and ovarian cancer, including 43 papers, reported factors that impact on decision making about RRSO. They included medical and physical factors, psychological factors, social context factors, *BRCA1/2* mutation status and parity.[56]

Psychological factors of perceived cancer risk, and cancer related distress, anxiety and worry also appear to be influential in risk-reducing surgery decisions as well as the presence and number of relatives affected with cancer.[56]

Attitudes

Another systematic review, including 37 articles, 20 of which were prospective study design, reported that women's attitude about risk-reducing surgery is a significant and useful predictor of undergoing risk-reducing surgery, as is age.[25] They did not find a significant association between cancer worry and uptake of RRSO, although anxiety was significantly reduced after RRSO and women expressed a high level of satisfaction with their decision. [25]

Decision-aid tools

Use of a decision aid or shared decision-making, compared to a general educational pamphlet about risk-reducing strategies, reduces decisional conflict, improves knowledge and increases satisfaction with the decision. [36]

Communication

A systematic review on risk communication including 28 articles reported that risk communication interventions achieved some benefits for users, mainly on cognitive outcomes such as risk perception and knowledge. [57]

Preventive therapy

Oral contraceptive pill

Three primary studies were identified which assessed the impact of OCP use and ovarian cancer in women with *BRCA 1/2* mutations.[30-32] The studies on OCP use only report on risk of ovarian cancer and no information was provided on survival, adverse events or quality of life. Some papers provided risk estimates based on duration of OCP use.[30-32] Studies indicated that use of OCP's is associated with a risk reduction in ovarian cancer of almost 50%, with longer duration of use (>3 years) associated with further reductions in risk,[30-31] and in the general population, the risk reduction persists after cessation of the OCP.[58]

The cardiovascular risks for women in the general population taking the OCP are well known,[59] however both the breast cancer[33] and cardiovascular risk for women at high risk of ovarian cancer taking the OCP is uncertain.

The possible risks need to be balanced against the likely benefits of prescribing the OCP to women to reduce their risk of ovarian cancer.

Issues around surveillance

In December 2009, NBOCC published a position statement on surveillance of women at high or potentially high risk of ovarian cancer, which included evidence published up to January 2009.[7] The current systematic review did not identify any new evidence that would alter the position statement.

NBOCC's position statement on Surveillance of women at high or potentially high risk of ovarian cancer states:

- Ovarian cancer surveillance is not recommended for women at high or potentially high risk.
- Evidence shows that *ultrasound* or *CA125*, singly or in combination, is not effective at detecting early ovarian cancer.

The most effective risk-reducing strategy for ovarian cancer is bilateral salpingo-oophorectomy.[7]

Strengths and weaknesses of evidence

Limited high quality evidence was available:

- no randomised controlled trials were identified
- several international guidelines were identified, however these did not include high quality evidence
- three systematic reviews were identified, which were based on low-level evidence

The majority of evidence on management of women at high risk of *ovarian cancer* was from prospective and retrospective cohort studies (level III).

Unanswered questions

Important unanswered questions about the management of women at high risk of *ovarian cancer* are outlined below:

- Effectiveness of tubal ligation in reducing risk of developing ovarian cancer in women with a BRCA gene mutation
- Psychosocial wellbeing of women following risk-reducing surgery
- Benefits versus risks of the use of *hormone replacement therapy* in women at high risk of ovarian cancer

Ongoing studies

Three ongoing studies are investigating the management of women at high risk of ovarian cancer:

- one ongoing study is investigating surveillance in women at high risk of ovarian/fallopian tube cancer (UK FOCSS)[60]
- one ongoing study(now in follow-up) is comparing surveillance and risk-reducing strategies in women at high risk of *ovarian cancer* (GOG-199)[61]
- one ongoing randomised control trial is investigating the use of preventive therapy prior to surgery in women at high risk of ovarian cancer (NCT-00098800)[62]

References

1. Australian Cancer Network & National Breast Cancer Centre. Clinical practice guidelines for the management of women with *epithelial ovarian cancer*. Camperdown: National Breast Cancer Centre 2004.

2. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Fan I. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst. 2006;98(23):1694-706.

3. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst. 2009 Jan 21;101(2):80-7.

4. Antoniou AC, Pharoah PDP, Narod SA, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72:1117-30.

5. National Breast and Ovarian Cancer Centre. Advice about familial aspects of breast cancer and epithelial ovarian cancer. A guide for health professionals. Surry Hills: National Breast and Ovarian Cancer Centre 2010.

6. Crum CP, Drapkin R, Kindelberger DW, Medeiros F, Miron A, Lee Y. Lessons from BRCA: The tubal fimbria emerges as an origin for pelvic serous cancer. Clin Med Res. 2007;5(1):35-44.

7. National Breast and Ovarian Cancer Centre. Surveillance of women at high or potentially high risk of ovarian cancer - NBOCC Position Statement 2009. http://www.nbocc.org.au/our-organisation/position-statements/surveillance-of-women-at-high-or-potentially-high-risk-of-ovarian-cancer.

8. Schorge JO, Modesitt SC, Coleman DE, Cohn DE, Kauff ND, Duska LR, et al. SGO White Paper on ovarian cancer: etiology, screening and surveillance. Gynecol Oncol. 2010;119(1):7-17.

9. Berek JS, Chalas E, Edelson M, Moore D, Burke W, Cliby W, et al. Prophylactic and risk-reducing bilateral salpingo-oophorectomy: Recommendations based on risk of ovarian cancer. Obstet Gynecol. 2010;116(3):733-43.

10. National Health and Medical Research Council. NHMRC additional levels of evidence and *grades* for recommendations for developers of guidelines. Canberra: Commonwealth of Australia; 2009.

11. National Breast Cancer Centre and National Cancer Control Initiative. Clinical practice guidelines for the psychosocial care of adults with cancer. Camperdown: National Breast Cancer Centre 2003.

12. Domchek S, Friebel T, Singer CF, Evans DG, Lynch H, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304(9):967-75.

13. Schmeler KM, Lynch HT, Chen LM, Munsell MF, Soliman PT, Clark MB, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006 Jan 19;354(3):261-9.

14. Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral *prophylactic oophorectomy* in BRCA1 and BRCA2 mutation carriers: The PROSE Study Group. J Clin Oncol. 2005;23(31):7804-10.

15. Rabban JT, Barnes M, Chen LM, Powell CB, Crawford B, Zaloudek CJ. Ovarian pathology in risk-reducing salpingo-oophorectomies from women with BRCA mutations, emphasizing the differential diagnosis of occult primary and metastatic *carcinoma*. Am J Surg Pathol. 2009 Aug;33(8):1125-36.

16. Hirst JE, Gard GB, McIllroy K, Nevell D, Field M. High rates of occult fallopian tube cancer diagnosed at prophylactic *bilateral salpingo-oophorectomy*. Int J Gynecol Cancer. 2009 Jul;19(5):826-9.

17. Callahan MJ, Crum CP, Medeiros F, Kindelberger DW, Elvin JA, Garber JE, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. J Clin Oncol. 2007 Sep 1;25(25):3985-90.

18. Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA. 2006 Jul 12;296(2):185-92.

19. Finch A, Shaw P, Rosen B, Murphy J, Narod SA, Colgan TJ. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecol Oncol. 2006 Jan;100(1):58-64.

20. Olivier RI, van Beurden M, Lubsen MA, Rookus MA, Mooij TM, van de Vijver MJ, et al. Clinical outcome of prophylactic *oophorectomy* in BRCA1/BRCA2 mutation carriers and events during follow-up. Br J Cancer. 2004 Apr 19;90(8):1492-7.

21. Domchek SM, Friebel TM, Neuhausen SL, Wagner T, Evans G, Isaacs C, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol. 2006 Mar;7(3):223-9.

22. Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, Garber JE, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol. 2008 Mar 10;26(8):1331-7.

23. Fang CY, Cherry C, Devarajan K, Li T, Malick J, Daly MB. A prospective study of quality of life among women undergoing risk-reducing salpingo-oophorectomy versus gynecologic screening for ovarian cancer. Gynecol Oncol. 2009 Mar;112(3):594-600.

24. Benshushan A, Rojansky N, Chaviv M, Arbel-Alon S, Benmeir A, Imbar T, et al. Climacteric symptoms in women undergoing risk-reducing bilateral salpingo-oophorectomy. Climacteric. 2009 Oct;12(5):404-9.

25. De Leeuw JR, van Vliet MJ, Ausems MG. Predictors of choosing life-long screening or prophylactic surgery in women at high and moderate risk for breast and ovarian cancer. Fam Cancer. 2008;7(4):347-59.

26. Madalinska JB, Hollenstein J, Bleiker E, van Beurden M, Valdimarsdottir HB, Massuger LF, et al. Quality-of-life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer. J Clin Oncol. 2005 Oct 1;23(28):6890-8.

27. Kiely BE, Friedlander M, Milne RL, Stanhope L, Russell P, Jenkins MA, et al. Adequacy of risk-reducing gynaecologic surgery in BRCA1 or BRCA2 mutation carriers and other women at high risk of pelvic serous cancer. Fam Cancer. 2011 22nd March 2011.

28. Seidman JD, Yemelyanova A, Zaino RJ, Kurman RJ. The fallopian tube-peritoneal junction: A potential site of carcinogenesis. Int J Gynecol Cancer. 2010;30(1):4-11.

29. Anderson K, Jacobson JS, Heitjan DF, Zivin JG, Hershman D, Neugut AI, et al. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. Ann Intern Med. 2006 Mar 21;144(6):397-406.

30. Antoniou AC, Rookus M, Andrieu N, Brohet R, Chang-Claude J, Peock S, et al. Reproductive and hormonal factors, and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: results from the International BRCA1/2 Carrier Cohort Study. Cancer Epidem Biomar. 2009 Feb;18(2):601-10.

31. McLaughlin JR, Risch HA, Lubinski J, Moller P, Ghadirian P, Lynch H, et al. Reproductive *risk factors* for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet Oncol. 2007 Jan;8(1):26-34.

32. Whittemore AS, Balise RR, Pharoah PDP, DiCioccio RA, Oakley-Girvan I, Ramus SJ, et al. Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. Brit J Cancer. 2004;91(11):1911-5.

33. Narod SA, DubeÃ#' M, Klijn J, et al. Oral Contraceptives and the Risk of Breast Cancer in BRCA1 and BRCA2 Mutation Carriers. J Natl Cancer Inst. 2002;94(23):1773-9.

34. Rutter JL, Wacholder S, Chetrit A, Lubin F, Menczer J, Ebbers S, et al. Gynecologic surgeries and risk of ovarian cancer in women with BRCA1 and BRCA2 Ashkenazi founder mutations: an Israeli population-based case-control study. J Natl Cancer Inst. 2003 Jul 16;95(14):1072-8.

35. Braithwaite D, Emery J, Walter F, Prevost AT, Sutton S. Psychological impact of genetic counseling for familial cancer: a systematic review and meta-analysis. Fam Cancer. 2006;5:61-75.

36. Tiller K, Meiser B, Gaff C, Kirk J, Dudding T, Phillips KA, et al. A randomized controlled trial of a decision aid for women at increased risk of ovarian cancer. Med Decis Making. 2006 Jul-Aug;26(4):360-72.

37. Armstrong K, Weber B, Ubel PA, Peters N, Holmes J, Schwartz JS. Individualized survival curves improve satisfaction with cancer risk management decisions in women with BRCA1/2 mutations. J Clin Oncol. 2005 Dec 20;23(36):9319-28.

38. van Roosmalen MS, Stalmeier PF, Verhoef LC, Hoekstra-Weebers JE, Oosterwijk JC, Hoogerbrugge N, et al. Randomized trial of a shared decision-making intervention consisting of trade-offs and individualized treatment information for BRCA1/2 mutation carriers. J Clin Oncol. 2004 Aug 15;22(16):3293-301.

39. National Breast and Ovarian Cancer Centre. Management of women at high risk of ovarian cancer: a systematic review. Surry Hills, NSW: National Breast and Ovarian Cancer Centre 2010.

40. Kurian AW, Sigal BM, Plevritis SK. Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers. J Clin Oncol. 2010 Jan 10;28(2):222-31.

41. Armstrong K, Schwartz JS, Randall T, Rubin SC, Weber B. *Hormone replacement therapy* and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. J Clin Oncol. 2004 Mar 15;22(6):1045-54.

42. Schmeler KM, Lu KH. Gynecologic cancers associated with Lynch syndrome/HNPCC. Clin Transl Oncol. 2008 Jun;10(6):313-7.

43. Powell CB, Kenley E, Chen LM, Crawford B, McLennan J, Zaloudek C, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. J Clin Oncol. 2005 Jan 1;23(1):127-32.

44. Domchek SM, Friebel TM, Garber JE, Isaacs C, Matloff E, Eeles R, et al. Occult ovarian cancers identified at risk-reducing salpingo-oophorectomy in a prospective cohort of BRCA1/2 mutation carriers. Breast Cancer Res Tr. 2010 Feb 24.

45. Norum J, Hagen AI, Maehle L, Apold J, Burn J, Moller P. Prophylactic bilateral salpingo-oophorectomy (PBSO) with or without prophylactic bilateral *mastectomy* (PBM) or no intervention in BRCA1 mutation carriers: a cost-effectiveness analysis. Eur J Cancer. 2008 May;44(7):963-71.

46. Michelsen TM, Dorum A, Dahl AA. A controlled study of mental distress and somatic complaints after risk-reducing salpingo-oophorectomy in women at risk for hereditary breast ovarian cancer. Gynecol Oncol. 2009 Apr;113(1):128-33.

47. Madalinska JB, van Beurden M, Bleiker EM, Valdimarsdottir HB, Hollenstein J, Massuger LF, et al. The impact of hormone replacement therapy on *menopausal symptoms* in younger high-risk women after prophylactic salpingo-oophorectomy. J Clin Oncol. 2006 Aug 1;24(22):3576-82.

48. Rocca WA, Grossadt BR, M. de Andrade M, Malkasian GD, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 2006;7:821-8.

49. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, al E. Increased risk of parkinsonism in women who underwent oophorectomy before *menopause*. Neurology. 2008;70:200-9.

50. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology 2007;69(11):1074-83.

51. Michelsen TM, Dahl AA, Trope C, Dorum A. Sexual activity and functioning in women who underwent salpingo-oophorectomy to prevent hereditary breast ovarian cancer. J Clin Oncol. 2010;28(7S):5097.

52. Evans DG, Clayton R, Donnai P, Shenton A, Lalloo F. Risk-reducing surgery for ovarian cancer: outcomes in 300 surgeries suggest a low peritoneal primary risk. Eur J Hum Genet. 2009 Nov;17(11):1381-5.

53. Hallowell N, Mackay J, Richards M, Gore M, Jacobs I. High-risk premenopausal women's experiences of undergoing prophylactic oophorectomy: a descriptive study. Genet Test. 2004 Summer;8(2):148-56.

54. Olivier RI, Lubsen-Brandsma LA, van Boven H, van Beurden M. Additional salpingectomy after previous prophylactic oophorectomy in high-risk women: sense or nonsense? Gynecol Oncol. 2005 Feb;96(2):439-43.

55. Rabban JT, Krasik E, Chen LM, Powell CB, Crawford B, Zaloudek CJ. Multistep level sections to detect occult fallopian tube carcinoma in risk-reducing salpingo-oophorectomies from women with BRCA mutations: implications for defining an optimal specimen dissection protocol. Am J Surg Pathol. 2009 Dec;33(12):1878-85.

56. Howard AF, Balneaves LG, Bottorff JL. Women's decision making about risk-reducing strategies in the context of hereditary breast and ovarian cancer: a systematic review. J Genet Couns. 2009 Dec;18(6):578-97.

57. Edwards A, Gray J, Clarke A, Dundon J, Elwyn G, Gaff C, et al. Interventions to improve risk communication in clinical genetics: Systematic review. Patient Educ Couns. 2008;71(1):4-25.

58. Collaborative Group on Epidemiological Studies of Ovarian Cancer. *Ovarian cancer* and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. The Lancet. 2008;371(9609):303 -14.

59. Chrisandra L. Shufelt, C. Noel Bairey Merz. Contraceptive Hormone Use and Cardiovascular Disease. J Am Coll Cardiol. 2009;53(3).

60. Institute for Women's Health UK. UK Familial Ovarian Cancer Screening Study (UK FOCSS). [April 2010]; Available from: http://www.instituteforwomenshealth.ucl.ac.uk/academic_research/gynaecologicalcancer/gcrc/ukfocss.

61. National Cancer Institute (NCI). Gynecologic Oncology Group (GOG) 199. [April 2010]; Available from: http://ovariancancer.gog199.cancer.gov/about.html.

62. Clinicaltrials.gov. Fenretinide in Preventing Ovarian Cancer in Participants Who Are at High Risk for Developing Ovarian Cancer and Planning to Undergo Surgery to Remove the *Ovaries* (NCT00098800) Available from: http://clinicaltrials.gov/ct2/show/NCT00098800.

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External Review

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Additional Information

Topic-specific guideline development process

Priority topic areas for Cancer Australia 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

Conflict of Interest

Editorial independence was maintained and no conflict of interest was declared by Working Group members in the development of this guideline.

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