Management of women at high risk of ovarian cancer

A systematic review

August 2010

Management of women at high risk of ovarian cancer: a systematic review
was developed by:

National Breast and Ovarian Cancer Centre (NBOCC)*
Locked Bag 3 Strawberry Hills NSW 2012 Australia
Tel: +61 2 9357 9400 Fax: +61 2 9357 9477
Website: www.canceraustralia.gov.au

ISBN Online: 9781741271584

Recommended citation

Cancer Australia. Management of women at high risk of ovarian cancer: a systematic review. Cancer Australia, Surry Hills, NSW, 2011

Copies of Management of women at high risk of ovarian cancer: a systematic review can be downloaded from the Cancer Australia website: www.canceraustralia.gov.au

* 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.

Contents

Acknowledgments ..... **v**

Executive summary ..... **vii**

1 Background **1**

1.1 Ovarian cancer in Australia 1

1.2 Designation of level of risk of ovarian cancer 1

1.3 Management of women at high risk of ovarian cancer 1

1.4 National Breast and Ovarian Cancer Centre clinical practice guidelines and resources 2

2 Methods **4**

2.1 Inclusion criteria 4

2.2 Literature search 5

2.3 Data extraction 7

3 Results **9**

3.1 International guidelines & recommendations 9

3.2 Systematic reviews 14

3.3 Included studies 14

3.4 Ongoing trials 45

4 Discussion **47**

5 Conclusion **49**

Appendix A Contributors **50**

Appendix B Definition of potentially high risk of ovarian cancer[4] **51**

Appendix C Literature databases searched **52**

Appendix D Search strategy **53**

Appendix E Guideline and clinical trial sites searched **54**

Appendix F Flowchart of inclusion/exclusion **55**

Appendix G Additional data tables **56**

Abbreviations **57**

References **59**

Tables

Table 1 Risk-reducing surgery guidelines and recommendations 9
Table 2 Risk assessment/surveillance recommendations and guidelines 11
Table 3 Chemoprevention and tubal ligation recommendations and guidelines 12
Table 4 Study characteristics of risk-reducing studies 16
Table 5 Ovarian cancer cases in RRSO comparative studies 22
Table 6 Occult ovarian cancer diagnosed at time of RRSO 23
Table 7 Mortality in RRSO comparative studies 25
Table 8 Probability of overall survival by age 70[45] 27
Table 9 Menopausal symptoms following RRSO compared to natural menopause[25] 29
Table 10 Symptoms following RRSO compared to age-matched controls[33] 30
Table 11 Risk of metabolic syndrome[35] 31
Table 12 Protocols used/recommended in serial sectioning papers[38,39] 35
Table 13 Occult cancers detected at RRSO in serial sectioning papers[38,39] 36
Table 14 Risk of ovarian cancer associated with oral contraceptive pill use 37
Table 15 Risk of ovarian cancer associated with tubal ligation 38
Table 16 Occult cancers detected in RRSO case series 42
Table 17 Ongoing trials investigating risk management strategies for women at high risk of ovarian cancer 46

Figures

Figure 1 Management options for women at high risk of ovarian cancer 2

Acknowledgments

This report was developed by National Breast and Ovarian Cancer Centre (NBOCC)[†].

Funding

Funding for the development of this report was provided by the Australian Government Department of Health and Ageing.

Contributors

NBOCC gratefully acknowledges the support of the many individuals who contributed to the development of this document.

See Appendix A for more information.

[†]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.

Executive summary

In 2006, ovarian cancer was the ninth most commonly diagnosed cancer among Australian women (excluding non-reportable skin cancers) and the second most commonly diagnosed gynaecological cancer, with a total of 1,226 ovarian cancer cases diagnosed.[1] Up to 15% of all cases of invasive ovarian cancers involve the inheritance of a mutated gene.[2] Women who have inherited mutations in the *BRCA1* or *BRCA2* genes have substantially elevated risks of breast and ovarian cancer, with estimates risks for ovarian cancer, ranging from 36% to 46% for *BRCA1* mutation carriers and from 10% to 27% for *BRCA2* mutation carriers.[3] NBOCC has developed *Advice about familial aspects of breast cancer and epithelial ovarian cancer – a guide for health professionals* which provides information to assess a woman's risk of developing breast or ovarian cancer, based on her family history.[4]

Clinical practice guidelines for the management of women with epithelial ovarian cancer, developed by National Breast Cancer Centre (NBCC)[‡] and the Australian Cancer Network (ACN), published in 2004, included one recommendation for women at high risk of ovarian cancer about prophylactic salpingo-oophorectomy.[5] The information within the guidelines has contributed to the development of resources for health professionals and consumers, including the consumer guide to *Epithelial Ovarian Cancer: understanding your diagnosis and treatment, Advice about familial aspects of breast cancer and epithelial ovarian cancer* and the on-line tool, *Familial Risk Assessment - Breast and Ovarian Cancer.*

National Breast and Ovarian Cancer Centre (NBOCC) undertook this systematic review of literature published between January 2003 and April 2010 to update the information on women at high risk of ovarian cancer in the 2004 clinical practice guidelines.

Risk management strategies for women at high risk of ovarian cancer include surveillance, risk-reducing salpingo-oophorectomy (RRSO), tubal ligation and chemoprevention with the oral contraceptive pill (OCP). In the papers identified, most reported on specific populations with identified *BRCA1* or *BRCA2* mutations. Most information was provided on RRSO which was consistently associated with decreased risk of ovarian cancer compared to screening or observation. A recently published prospective cohort study found that in women with *BRCA1/2* gene mutations, RRSO decreased the risk of ovarian and breast cancer and was also associated with decreased mortality. A small number of occult cancers have been identified at the time of RRSO.

In addition, some studies indicated that use of the oral contraceptive pill appears to be associated with a decreased risk of ovarian cancer, with longer duration of use associated with further reductions in risk. The association between tubal ligation and risk of ovarian cancer is less clear, with only one of three papers reporting a significant reduction in risk of ovarian cancer after tubal ligation in women with *BRCA* gene mutations.

While information on quality of life was reported in some studies specifically related to RRSO, there was limited information identified on psychosocial issues and interventions for women at high risk of ovarian cancer outside the context of genetic testing.

---

[*] In February 2008 National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

1 Background

1.1 Ovarian cancer in Australia

In 2006, ovarian cancer was the ninth most commonly diagnosed cancer among Australian women (excluding non-reportable skin cancers) and the second most commonly diagnosed gynaecological cancer, with a total of 1,226 ovarian cancer cases diagnosed.[1] It is the sixth most common cause of cancer-related death for Australian women, and the most common cause of gynaecological cancer death, representing over half (55%) of such deaths. Up to 15% of all cases of invasive ovarian cancers involve the inheritance of a mutated gene.[2] Women who have inherited mutations in the *BRCA1* or *BRCA2* genes have substantially elevated risks of breast and ovarian cancer, with estimates risks for ovarian cancer, ranging from 36% to 46% for *BRCA1* mutation carriers and from 10% to 27% for *BRCA2* mutation carriers.[3]

1.2 Designation of level of risk of ovarian cancer

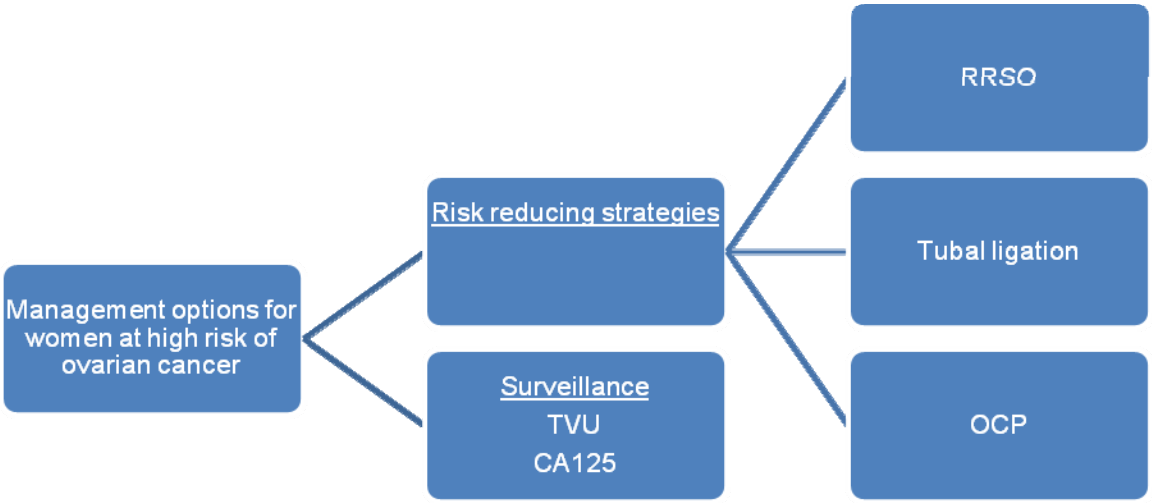
A woman who has a gene fault in *BRCA1* or *BRCA2* (*BRCA1/2*) confirmed by genetic testing is at high risk of developing ovarian or breast cancer.[3,4,6] A woman who has not had genetic testing but who has a strong family history[4] (see Appendix B) of either ovarian or breast cancer may have a gene 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.[7]

A woman who has Lynch Syndrome (or hereditary non-polyposis colorectal cancer (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. 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.[4]

1.3 Management of women at high risk of ovarian cancer

Management options for women at high risk of ovarian cancer include surveillance, risk-reducing surgery and chemoprevention, see Figure 1. Management options aim to either detect cancer as early as possible (surveillance) or to reduce the risk of ovarian cancer developing (risk-reducing strategies) in high-risk women. There are several issues around management options including, psychological, psychosocial, psychosexual and decision making issues.

Figure 1 Management options for women at high risk of ovarian cancer



OCP=oral contraceptive pill; RRSO=risk-reducing salpingo-oophorectomy; TVU=transvaginal ultrasound

1.4 National Breast and Ovarian Cancer Centre clinical practice guidelines and resources

Maintaining currency of guidelines is essential to ensuring timely, evidence-based information is available.

The purpose of this review was to identify evidence published from January 2003 to April 2010 on management options for women at high risk of developing ovarian cancer, to update current National Breast and Ovarian Cancer Centre (NBOCC) guideline recommendations.

The need to review the evidence and update guidelines about the management of women at high risk of ovarian cancer was identified following consultation with a range of stakeholders and advisors.

In 2004, NBCC and Australian Cancer Network (ACN) developed the *Clinical practice guidelines for the management of women with epithelial ovarian cancer*.[5]

The guideline included one recommendation for women at high risk of ovarian cancer:

- *Bilateral risk-reducing salpingo-oophorectomy in carriers of BRCA1 and BRCA2 mutations reduces the risk of epithelial ovarian cancer by at least 90%. It is the only proven method of reducing the risk of ovarian cancer and cancer of the fallopian tube. It may also halve the risk of breast cancer in mutation carriers. Ideally, risk-reducing surgery should always be discussed with women at potentially high risk of ovarian cancer.*

The guideline also highlighted a number of key points, which will be updated in line with the findings of this systematic review.

No supplementary guidelines have been created to date. The information within the guidelines has contributed to the development of resources for general practitioners and consumers, including the consumer guide *Epithelial Ovarian Cancer: understanding your diagnosis and treatment*, *Advice about familial aspects of breast cancer and epithelial ovarian cancer* and *Familial Risk Assessment - Breast and Ovarian Cancer tool.*

In December 2009, NBOCC published a position statement on *Surveillance of women at high or potentially high risk of ovarian cancer*.[8] The position statement was developed and agreed following the NBOCC Ovarian Cancer Forum held in February 2009 which was attended by over 40 key stakeholders including gynaecological oncologists, clinical geneticists, representatives of professional colleges, consumers and representatives of the Department of Health and Ageing, and states:

1. Ovarian cancer surveillance is not recommended for women at high or potentially high risk.

2. Evidence shows that ultrasound or CA125, singly or in combination, is not effective at detecting early ovarian cancer.

3. The most effective risk-reducing strategy for ovarian cancer is bilateral salpingo-oophorectomy.

2 Methods

The objective of the review is to investigate the management of women at high risk of ovarian cancer.

Research questions addressed in this systematic review were:

- 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?

2.1 Inclusion criteria

2.1.1 Participants

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.

2.1.2 Intervention

Risk-reducing strategies considered were:

- risk-reducing salpingo-oophorectomy (RRSO)
- chemoprevention (oral contraceptive pill (OCP))
- tubal ligation.

Surveillance strategies considered were:

- transvaginal ultrasound (TVU)
- CA125.

2.1.3 Comparison

Comparison groups of interest included:

- no risk-reducing strategies or surveillance
- different methods of risk reduction or surveillance.

2.1.4 Outcome measures

Outcome measures of interest were:

Risk-reducing strategies:

- survival, ovarian cancer, breast cancer, adverse events, quality of life (QoL), psychological impact.

Surveillance:

- survival, stage of disease at diagnosis, QoL, psychological impact.

Psychological/psychosocial:

- QoL, sexuality, fertility.

2.1.5 Additional issues of interest

The following topics were considered as additional issues of interest, and although they were not specifically searched for in the literature review, any information on these topics identified was recorded:

- Pathology of ovarian cancer in high risk women and relevance to risk-reducing surgical management
- Communication about risk including information needs of women
- Decision aid tools.

In addition to the above issues, the following topics were identified during the course of the literature review:

- Factors affecting decision making on risk-reducing strategies
- Uptake of risk-reducing strategies
- Cost-effectiveness of risk-reducing strategies.

For these topics not all information identified was included in the review. Only the highest level of evidence (systematic reviews or randomised controlled trials) available on these topics was included in this review.

2.2 Literature search

A systematic literature search was conducted in April 2010 to identify relevant studies which addressed the inclusion criteria. The search was conducted using several databases (see Appendix C), including:

- Medline (OVID)
- Embase (OVID)

- Pubmed
- Cochrane library.

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

The search strategy, developed with input from a multidisciplinary working group, used combined key terms which described epithelial ovarian cancer and high risk (see Appendix D). The search was limited to studies conducted in humans which were published from January 2003 to April 2010 in the English language. For papers on surveillance, the search was limited to articles published after January 2009 since NBOCC developed a position statement in 2009 which included evidence up to February 2009.

After the removal of duplicates and the addition of further citations sourced, a total of 1280 unique citations remained. The titles and abstracts of these citations were assessed by two reviewers independently to determine eligibility for the current review based on the criteria described previously. Ineligible studies were classified using the exclusion criteria below. For citations which provided insufficient information to assess eligibility, the full text was retrieved for assessment, by the same two reviewers.

In addition to the above databases, guideline and clinical trial websites were searched for relevant information. Specific international guideline organisations were searched as well as the National Guidelines Clearinghouse and the Guidelines International Network (GIN) guideline database. Clinical trials sites searched included clinical trials.gov (USA) and controlled trials.com (UK). Further information on sites searched can be found in Appendix E.

The following conference websites were searched from January 2006 to June 2010 to identify recently presented abstracts on management of women at high risk of ovarian cancer:

- American Society of Clinical Oncology (ASCO) annual meeting
- International Gynecologic Cancer Society (IGCS) biennial meeting
- Society of Gynecologic Oncologists (SGO) annual meeting.

2.2.1 Exclusion criteria

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

- not an original clinical study—publications not reporting the findings of original clinical studies including non-systematic reviews, editorials, opinion pieces and letters
- inappropriate population—studies in a population other than women at high risk for ovarian cancer. Comparison arms were allowed to contain women at general population risk.
- inappropriate intervention—studies not investigating risk management options as defined in the inclusion criteria.
- inappropriate outcomes—studies not reporting on the effect of risk management strategies.
- not published in the English language
- published prior to 2004 (prior to 2009 for surveillance studies).

Based on these criteria, 1150 articles were excluded. The full texts of the remaining 130 citations were retrieved and assessed to identify which met the inclusion criteria for the review. Non-systematic overview papers published after 2008 were sourced and reference lists were checked for further articles of interest. After full text assessment, 48 citations were identified as eligible for the current review (see Appendix F). Of the 48 citations included, 12 were included as additional issues and did not address the primary research questions. After completion of the review, an additional paper was published which described the effect of RRSO in a large prospective cohort of BRCA mutation carriers.[9] After consultation with the working group this was considered to be a key paper in this area and was included in the review retrospectively. The additional paper increased the number of citations included in the review to 49.

Full text citations for the primary research questions included:

- 3 systematic reviews
- 8 prospective cohorts
- 7 retrospective cohorts/analyses
- 3 case-control studies
- 5 cross-sectional studies
- 4 qualitative/descriptive studies
- 3 modelling studies
- 4 guideline/recommendation papers

Full text citations for the additional issues of interest included:

- 3 systematic reviews
- 3 randomised controlled trials
- 4 case series
- 2 cost-effectiveness studies

In addition to the peer-reviewed publications, eight national guidelines were identified (four from full text citations) and three abstracts of interest (one from full text citations).

2.3 Data extraction

Data extraction was performed by one reviewer and verified by a second reviewer to ensure accuracy. Descriptive data extracted from the studies included characteristics such as population, interventions and primary outcomes.

Outcome data extracted from the studies included rates of ovarian cancer, rates of breast cancer, overall survival (OS), QoL and adverse events.

In addition to the specific outcome data extracted, further issues were considered for some of the questions and information was recorded on these where available.

For papers on risk-reducing strategies, issues to be considered were:

- timing – when should surgery be performed?
- who should perform surgical procedures?
- technique of surgical procedures
- treatment of adverse effects caused by risk-reducing strategies, for example surgically induced menopause, including treatment with hormone replacement therapy (HRT)
- use of chemoprevention - when to prescribe, duration of use.

For psychological/psychosocial papers, issues to be considered were:

- interventions to address psychological/psychosocial issues and evidence of impact to reduce psychological issues.

3 Results

3.1 International guidelines & recommendations

International guidelines on risk management strategies for women at high risk of ovarian cancer were identified by the literature and internet searches. Guidelines included recommendations for risk-reducing strategies including RRSO, chemoprevention and tubal ligation, and surveillance recommendations such as use of CA125 and TVU.

Table 1 Risk-reducing surgery guidelines and recommendations

Guideline	Population	Recommendation
National Comprehensive Cancer Network (NCCN), 2009[10]	Hereditary breast and/or ovarian cancer	Recommend RRSO, ideally between 35 and 40 years, and upon completion of child bearing, or individualised based on earliest age of onset of ovarian cancer in the family. Counselling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short term hormone replacement therapy (HRT), and related medical issues.
American College of Obstetrics and Gynecology (ACOG), 2009[11]	*BRCA1* and *BRCA2* mutation carriers	Women with *BRCA1* or *BRCA2* mutations should be offered RRSO by age 40 years or when child-bearing is complete. For a risk-reducing bilateral salpingo-oophorectomy (BSO), all tissue from the ovaries and fallopian tubes should be removed. Thorough visualisation of the peritoneal surfaces with pelvic washings should be performed. Complete, serial sectioning of the ovaries and fallopian tubes is necessary, with microscopic examination for occult cancer.
National Hereditary Cancer Task Force, 2007, Canada[12]	*BRCA1* and *BRCA2* mutation carriers	The potential benefits of prophylactic BSO as a risk-reduction strategy should be raised with all women at high risk. Surgery should be directed towards complete removal of both ovaries and fallopian tubes. Laparoscopy is the procedure of choice whenever possible. Peritoneal surfaces should be inspected and fluid collected for cytological analysis. The ovarian and fallopian tube tissue specimens should be examined in their entirety for presence of cancer by a pathologist experienced in ovarian cancer pathology who is aware of the high-risk status of the patient. Women considering BSO should be counselled about age specific risks of ovarian and breast cancer and also about dealing with menopausal symptoms. They should be managed by a multidisciplinary team that includes at least a geneticist/genetic counsellor and gynaecologist. Written and oral information should be provided. In women facing premature menopause, issues relating to

Guideline	Population	Recommendation
		HRT and alternatives should be discussed explicitly before surgical intervention. Ongoing medical care addressing health issues related to premature menopause should be available (e.g., regular bone density measurements and assessment of cardiovascular risk factors). Patients should have access to the full range of ancillary supportive care services**.** Hysterectomy is not routinely recommended unless there are separate clinical indications. It should be considered if women plan to take HRT after the BSO or if they are on tamoxifen therapy**.** The possibility that histologically evident epithelial cancer may be detected as a result of the surgical procedure should be discussed in advance.
Cancer Care Ontario, 2004[13]	Hereditary predisposition	For women choosing prophylactic oophorectomy, the role of routine cytology in this procedure is not fully elucidated. When deciding on whether or not to include hysterectomy as part of the surgical procedure, the surgeon needs to inform the patient about the risk of fallopian tube cancers. HRT remains the best treatment for distressing menopausal symptoms, and therefore a short term trial of HRT may be indicated to relieve these symptoms. It is crucial that the entire ovary is removed during prophylactic surgery. Any remnant of ovarian tissue is at risk for developing carcinoma.
National Society of Genetic Counselors, 2007[14]	High-risk women	Prophylactic bilateral salpingo-oophorectomy (PBSO) is estimated to reduce the risk of ovarian cancer by 80−96% and reduces the risk of breast cancer by up to 50% in pre-menopausal women with *BRCA* mutations.
Scottish Intercollegiate Guidelines Network (SIGN), 2004[15]	High risk	Women with genetic mutations of *BRCA1* or *BRCA2* genes should be counselled regarding prophylactic oophorectomy and removal of fallopian tubes at a relevant time of their life.
Lindor, 2006[16]	At-risk members of families with Lynch Syndrome	Hysterectomy or oophorectomy should be discussed as an option after childbearing completed.

ACOG=American College of Obstetrics and Gynecology; BSO=bilateral salpingo-oophorectomy; HRT=hormone replacement therapy; NCCN=National Cancer Control Network; PBSO=prophylactic bilateral salpingo-oophorectomy; RRSO=risk-reducing salpingo-oophorectomy; SIGN=Scottish Intercollegiate Guidelines Network

Table 2 Risk assessment/surveillance recommendations and guidelines

Guideline	Population	Recommendation
NCCN 2009[10]	Hereditary breast and/or ovarian cancer	For those who have not elected RRSO, consider concurrent TVU + CA125, every 6 months starting at age 35 years or 5–10 years before the earliest age of first diagnosis of ovarian cancer in the family, and preferably day 1–10 of menstrual cycle for premenopausal women.
ACOG, 2009[11]	*BRCA1* and *BRCA2* mutation carriers	A genetic risk assessment is recommended for patients with a greater than an approximate 20- 25% chance of having an inherited predisposition to breast cancer and ovarian cancer.
National Hereditary Cancer Task Force, 2007, Canada[12]	*BRCA1* and *BRCA2* mutation carriers	With currently available technologies, ovarian cancer surveillance is not routinely recommended. Women should be counselled on the limitations of current surveillance methods. Recognition of ovarian cancer symptoms should be emphasized for both patient and the clinician. If, despite counselling, a woman strongly prefers surveillance, it should be performed every 6 to 12 months and should be accompanied by clear advice on the importance of acting on suspicion of symptoms. If a woman strongly prefers surveillance, it should be scheduled to take place immediately following menses in premenopausal women. Individualized psychosocial support should be made available to all women whether or not they opt for surveillance.
Cancer Care Ontario, 2004[13]	Hereditary predisposition	Women with a personal or family history of ovarian cancer should be assessed for genetic counselling and testing to identify *BRCA1* and 2 mutations. Other women who are concerned about their risk of ovarian cancer may also be assessed for appropriateness of genetic counselling.
Memorial Sloan Kettering (MSK), 2008[17]	Women with increased risk (relative risk of three to six times greater than that of the general public)	There is no clear evidence to suggest that ovarian cancer screening with currently available methods will result in a decrease in the number of deaths from ovarian cancer. If, after careful consideration of risks and benefits, ovarian cancer screening with serum markers such as CA125 and/or TVU is to be pursued, it is recommended that such screening be done within the framework of research studies to evaluate the efficacy of this approach. Genetic counselling may also be helpful for women in this group to better clarify the risk of ovarian and related cancers.
	Women with inherited risk (relative risk more than six times greater than that of the general public)	While it is not clear that ovarian cancer screening will result in a decrease in the number of deaths in women at inherited risk, those who have mutations in ovarian cancer susceptibility genes should undergo ovarian cancer screening using a combination of TVU and CA125 testing. For women with mutations in *BRCA1* or the mismatch repair genes, *MLH1*, *MSH2,* and *MSH6*, this screening should generally begin between ages 30 and 35. For women with mutations in *BRCA2*, ovarian cancer screening should be initiated between ages 35 and 40. Given the limitations of ovarian cancer screening, including the substantial risks of both false positive and false negative results, RRSO should be considered upon conclusion of childbearing by women with documented inherited predispositions.

Guideline	Population	Recommendation
National Society of Genetic Counselors, 2007[14]	High-risk women	Annual or semi-annual TVU, pelvic exam and testing for CA125 to screen for ovarian cancer beginning at 25 years of age or ten years younger than the earliest age of diagnosis in the family.
SIGN, 2004[15]	High risk	Screening for ovarian cancer in high-risk groups should only be offered in the context of a research study designed to gather data on: • Sensitivity and specificity of the screening tool • FIGO stages of cancers detected through screening • Residual risk of primary peritoneal cancer following prophylactic oophorectomy. Screening programmes for women at increased risk of ovarian cancer should include mechanisms for providing emotional and psychological support.
Lindor, 2006[16]	At-risk members of families with Lynch Syndrome	Transvaginal ultrasound for endometrial and ovarian cancer every year beginning at age 30-35 years.

ACOG=American College of Obstetrics and Gynecology; MSK=Memorial Sloan Kettering; NCCN=National Cancer Control Network; RRSO=risk-reducing salpingo-oophorectomy; SIGN=Scottish Intercollegiate Guidelines Network; TVU=transvaginal ultrasound

Table 3 Chemoprevention and tubal ligation recommendations and guidelines

Guideline	Population	Recommendation
NCCN 2009[10]	Hereditary breast and/or ovarian cancer	Consider chemoprevention options for breast and ovarian cancer, including discussing risks and benefits.
National Hereditary Cancer Task Force, 2007, Canada[12]	*BRCA1* and *BRCA2* mutation carriers	Oral contraceptive (OCP) use: women of childbearing age in the general population should be advised about the protective effects of pregnancy and breastfeeding on the risk of ovarian cancer. Women under 35 years of age seeking advice on OCPs should be counselled regarding the current state of evidence regarding the benefits and risks for women with a known *BRCA1* or *BRCA2* mutation. In general, the advice regarding oral contraceptives for women of this age should be the same as for the general population of that age. Women aged 35 years or over seeking advice on OCPs should be counselled regarding the current uncertainty surrounding their use, including a full discussion of potential benefits and harms. OCP use in women with a prior history of breast cancer should be carefully discussed with their medical oncologists. Women considering tubal ligation should be counselled regarding the current state of evidence regarding its potential benefits and risks for those with a known *BRCA1* or *BRCA2* mutation.

Guideline	Population	Recommendation
Cancer Care Ontario, 2004[13]	Hereditary predisposition	For *BRCA1* mutation carriers who may be reluctant to have definitive prophylactic surgery, OCP and/or tubal ligation may reduce their risk of developing ovarian cancer.
National Society of Genetic Counselors, 2007[14]	High-risk women	Oral contraceptives have been associated with up to a 50% reduction in the risk of ovarian cancer in women with *BRCA* mutations. Studies reveal that this effect can persist for up to 15 years after discontinuing their use.

NCCN=National Cancer Control Network; OCP=oral contraceptive pill

3.2 Systematic reviews

Three systematic reviews were identified which addressed the inclusion criteria of the current review. Rebbeck *et al* (2009)[3] report a meta-analysis on risk reduction estimates associated with RRSO in *BRCA1* or *BRCA2* mutation carriers and the results are reported in Section 3.3.1.

A systematic review on prophylactic oophorectomy by Rosen *et al* (2004)[18] included four cohort studies and did not provide pooled results. Two of the studies were included in the Rebbeck meta-analysis, the other two were older studies published prior to 1995. Another systematic review was reported by Bermejo-Perez *et al* (2007)[19] which included papers on the effectiveness of preventive strategies (including surgery, chemoprevention and tubal ligation) in *BRCA* mutation carriers. The reviews by Rosen *et al* (2004) and Bermejo-Perez *et al* (2007) provided narrative results with most of the included studies published prior to 2003. Any studies included in these reviews published after 2003 are either included in the current review as primary papers or are covered by the Rebbeck meta-analysis (2009)[3] therefore results from these reviews are not reported in any further detail.

An additional three systematic reviews addressed some additional issues of interest outside the primary questions for the current review (decision making, risk communication and predictors/uptake of risk-reducing strategies) and these are reported in Section 3.3.4.

3.3 Included studies

The papers identified are listed and described below under the research questions to be addressed by this review.

3.3.1 What is the effectiveness of risk-reducing strategies for women at high risk or potentially high risk of ovarian cancer?

The risk-reducing strategies considered in this section were risk-reducing salpingo-oophorectomy (RRSO), the oral contraceptive pill (OCP), and tubal ligation.

For characteristics of included studies please refer to Table 4. Twenty-five studies were identified which evaluated the effects of risk-reducing salpingo-oophorectomy, including one meta-analysis and three modelling studies (NB: modelling studies are not reported in Table 4). 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.

Five of the RRSO papers have overlapping study populations as each analysed women from the PROSE consortium (18 North American and European centres).[9,20-23] Each study reports different analyses (such as varying time periods) however, some women may be included in multiple analyses. The meta-analysis by Rebbeck *et al* (2009)[3] pooled results from non-overlapping studies only.

Population characteristics

High-risk populations included in the studies were most often women with proven *BRCA1* or *BRCA2* mutations; one study included women with Lynch Syndrome. Other studies included women considered at potentially high risk for ovarian cancer due to their family history.

Table 4 Study characteristics of risk-reducing studies

Study	Population	Intervention	Comparison	Outcomes
Antoniou 2009[24] Retrospective cohort	N=3319 *BRCA1/2* mutation carriers	OCP use Tubal ligation	No OCP, duration of OCP use (>0-1, >1-3, >3-5, >5 years) No tubal ligation, age at tubal ligation (≤35, >35)	Incidence of ovarian cancer
Benshushan 2009[25] Retrospective analysis	N= 108 Post-menopausal women (surgical or natural), not using HRT. Including *BRCA* mutation carriers	Women who had RRSO (n=48; n=33 premenopausal at time of surgery)	Postmenopausal women who visited gynaecologic menopause clinic (n=60)	Type, severity & duration of climacteric symptoms - vasomotor, psychological, somatic
Domchek 2010a[20] Prospective cohort*	N=647 RRSOs plus 16 OC patients diagnosed outside of RRSO *BRCA1/2* mutation carriers	Women who had RRSO (n=647)	Women who did not have RRSO but were diagnosed with OC after disclosure of positive genetic test result (n=16)	Occult ovarian cancer
Domchek 2010b[9] Prospective multicentre cohort*	N=2842 *BRCA1/2* mutation carriers, with or without prior history of breast cancer	Women who had RRSO (numbers range from 544 to 993 depending on outcome analysis, see individual outcome tables)	Women who did not have RRSO (numbers range from 1377 to 1678 depending on outcome analysis, see individual outcome tables)	Mortality (all cause, ovarian cancer-specific, breast-cancer specific), ovarian cancer, breast cancer
Domchek, 2006[21] Prospective multicentre cohort*	N= 426 matched analysis; 666 unmatched analysis Including *BRCA1/2* mutation carriers	BPSO (n=155); unmatched analysis (n=188)	Matched controls, no BPSO (n=271); unmatched analysis (n=478)	Mortality, breast cancer, ovarian cancer

Study	Population	Intervention	Comparison	Outcomes
Evans 2009[26] Prospective cohort	N=803 Women at risk for ovarian cancer, including 40% *BRCA1/2* mutation carriers	BSO (n=300)	Annual screening with ovarian ultrasound and serum CA125 (n=503); [some additional patients originally chose screening but eventually had BSO before symptoms/abnormalities on screening (n=135)]	Incidence of ovarian cancer, breast cancer
Fang 2009[27] Prospective cohort	N=75 Women at increased risk of ovarian cancer due to family history or presence of a known disease-related gene mutation in the family	RRSO (n=38)	Screening (n=37)	QoL
Finch, 2006a[28] Prospective cohort	N=1828 *BRCA1/2* mutation carriers	Bilateral prophylactic oophorectomy (n=555 at baseline; plus n=490 during follow-up)	No bilateral prophylactic oophorectomy (n=783; n=1273 prior to study entry)	Incidence of ovarian, fallopian tube and peritoneal cancer
Hallowell 2004[29] Qualitative/descriptive	N=23 High-risk premenopausal women due to family history	Undergone prophylactic oophorectomy	N/A	Psychosocial implications
Kauff, 2008[22] Multicentre prospective cohort*	N= 1079 *BRCA1/2* mutation carriers	RRSO cohort-if they had BSO for reasons other than known or suspected cancer after the receipt of genetic test results (n=509 OC analysis; n=303 BC analysis)	Observation/surveillance cohort-all women with mutations who did not elect to undergo RRSO. (n=283 OC analysis; n=294 BC analysis)	Breast cancer or BRCA associated gynaecological cancer

Study	Population	Intervention	Comparison	Outcomes
Madalinska 2005[30] Multicentre, cross-sectional, observational study	N= 846 Women at increased risk of hereditary ovarian cancer	PBSO (n=369)	Screening (pelvic examination, transvaginal sonography, CA125 serology) (n=477)	Quality of life (generic and condition-specific)
Madalinska 2006[31] Cross-sectional study	N=450 Women from a hereditary breast/ovarian cancer family who were premenopausal	PBSO (n=164) PBSO (n=164). After surgery women were prescribed standard doses of HRT (oestrogen/progesterone or tibolone) administered either orally or transdermally. PBSO HRT users (n=77), PBSO HRT non-users (n=87)	Screening (n=286)	Impact of HRT use of endocrine symptoms & sexual functioning among premenopausal women who had PBSO
McLaughlin 2007[32] Case-control	N=3223 *BRCA1/2* mutation carriers	Ovarian cancer cases (n=799)	Matched controls (n=2424)	Association of OCP & tubal ligation with OC
Michelsen 2009a[33] Cross-sectional study	N=2028 Cases - either carriers of *BRCA1* or *BRCA2* mutation or at risk for hereditary breast/ovarian cancer due to pedigree evidence	RRSO after genetic counselling at single centre (n=503; 338 responders)	Age matched controls - sample of general population who had not had hysterectomy or oophorectomy - NB not high-risk women (n=1690)	Anxiety, depression, somatic complaints
Michelsen 2009b[34] Cross-sectional study	Including high-risk women due to presence of BRCA mutations or family history	RRSO (n=450; 301 responses)	Age matched controls - normative population sample (NORM). NORM-05 (n=301); NORM-04 (n=602)	Fatigue, QoL, anxiety, depression

Study	Population	Intervention	Comparison	Outcomes
Michelsen 2009c[35] Cross-sectional study	N=1005 Women with increased hereditary risk compared with general population	RRSO in women with hereditary risk (n=326)	General population (n=679)	Association of RRSO with metabolic syndrome
Olivier 2004[36]	N=128 *BRCA1/2* mutation carriers or women with breast cancer from a hereditary breast-ovarian cancer (HBOC) family	RRSO (n=90)	Bilateral oophorectomy (n=38)	Ovarian cancer
Olivier 2005[37]	N=42 *BRCA1/2* mutation carriers or women with breast cancer from a hereditary breast cancer (HBC) family or women from a HBOC family	Additional bilateral prophylactic salpingectomy after bilateral prophylactic oophorectomy (n=15)	Bilateral prophylactic oophorectomy (n=27)	Ovarian cancer
Powell 2005[38] Multicentre retrospective analysis	N=67 BRCA mutation carriers	RRSO with complete pathology records	N/A	Adherence to surgical-pathologic protocol; detection of occult cancer
Rabban 2009a[39] Retrospective analysis	N=102 Women with *BRCA* germline mutations	RRSO specimens - analysis with multistep level section on blocks containing tubal fimbriae.	Original examination - sliced at 2 to 3mm intervals, original pathologic examination based on single H&E slide from each block of tissue from the RRSO specimen.	Diagnostic utility of multistep level sections

Study	Population	Intervention	Comparison	Outcomes
Rebbeck 2009[3] Meta-analysis of cohorts & case-control studies	10 studies included *BRCA1/2* mutation carriers	RRSO	No RRSO	Risk reduction estimate - breast cancer, gynaecologic cancer
Rebbeck 2005[23] Prospective cohort*	N=462 *BRCA1/2* mutation carriers	BPO	No BPO	Incidence of breast cancer & association with use of HRT
Rutter, 2003[40] Case control	N= 1124 cases, 2396 controls 70% Ashkenazi Jewish Case patients included 251 *BRCA1/2* mutation carriers	Gynecologic surgeries - bilateral oophorectomy (8 cases,), unilateral oophorectomy, oophorectomy and/or hysterectomy, tubal ligation (20 cases,), ovarian cystectomy	Gynecologic surgeries - bilateral oophorectomy (128 controls), unilateral oophorectomy, oophorectomy and/or hysterectomy, tubal ligation (60 controls), ovarian cystectomy	Risk of ovarian cancer
Schmeler 2006[41] Retrospective cohort	N=315 Women with documented mutations associated with Lynch Syndrome (*MLH1, MSH2, MSH6*)	Prophylactic surgery n=61 (n=47 women prophylactic BSO and hysterectomy)	No prophylactic surgery n=254 (n=223 matched controls for ovarian analysis)	Endometrial, ovarian or primary peritoneal cancer. Risk reduction of surgery
Whittemore 2004[42] Case-control	N=451 *BRCA1/2* mutation carriers	Ovarian cancer cases (n=147)	Matched controls (n=304)	Association of OCP use with OC

* These papers have overlapping study populations as each analysed women from the PROSE consortium (18 North American and European centres)
BC=breast cancer; BPO=bilateral prophylactic oophorectomy; BPSO=bilateral prophylactic salpingo-oophorectomy; BSO= bilateral salpingo-oophorectomy; HBOC= hereditary breast-ovarian cancer; HRT=hormone replacement therapy; N/A=not applicable; OCP=oral contraceptive pill; RRSO=risk-reducing salpingo-oophorectomy

RRSO

Description of studies

Twenty-five studies were identified which evaluated the effects of risk-reducing salpingo-oophorectomy, including one meta-analysis.[3] Some of the papers that were identified were included in the Rebbeck meta-analysis, which only included studies on women with *BRCA* mutations. Three papers reporting on reduction of ovarian cancer after RRSO were identified that were not included in the meta-analysis. Two papers were published after the meta-analysis; one compared 300 women who had a RRSO with 503 women who attended annual screening with ultrasound and CA125 testing,[26] the other described an international prospective cohort of 2482 *BRCA1/2* mutation carriers comparing those who had RRSO with those who did not have RRSO (these women were offered increased surveillance).[9] The third paper reported a study in women with germ-line mutations associated with Lynch Syndrome.[41]

Outcomes reported in the papers include ovarian cancer, breast cancer, occult cancer detected at oophorectomy, mortality, quality of life and adverse events/symptoms. Most of the RRSO papers described prospective cohorts, some retrospective cohorts and additional information was provided by cross-sectional and qualitative studies (particularly regarding QoL).

In addition to the full text papers, two abstracts were identified regarding RRSO and QoL.[43,44]

Within the studies, women who had RRSO were often older than those in the surveillance/screening or control groups[22,28,30,31] and more likely to have taken HRT.[22,23,33]

Results

Ovarian cancer

The number of ovarian cancer cases reported after RRSO in the studies is presented in Table 5. Primary peritoneal cancers can occur after RRSO, although this is rare with reported rates around 1%.[9,21,22,28] While the meta-analysis by Rebbeck *et al* (2009)[3] identified six papers on the risk of OC after RRSO, some of the papers had overlapping study populations (PROSE consortium). Therefore, 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. Pooled results were not available for *BRCA1* and *BRCA2* mutations carriers separately.[3]

In two papers identified which were not included in the meta-analysis, no cases of ovarian cancer were reported in the groups which had RRSO performed. This is compared to 15 cases (3%) in the screening group in the study by Evans *et al* (2009),[26] and 12 cases (5%) in the group without prophylactic surgery in the study reported by Schmeler *et al* (2006).[41] In the study by Domchek *et al* (2010b),[9] 10 primary peritoneal cancers (1.1%) occurred in the RRSO group after median follow-up 3.65 years, all in *BRCA1* mutation carriers; 98 ovarian cancers (5.8%) occurred in the no-RRSO group after median follow-up 4.29 years. 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).[9]

Table 5 Ovarian cancer cases in RRSO comparative studies

Study	Intervention/ control	Number of cases	Type of cases	HR (95% CI)	p-value
Meta-analysis – Rebbeck 2009[3] *BRCA1/2* mutation carriers	RRSO n=1555	NR	NR	0.21 (0.12 to 0.39)	NR
	No RRSO n=1285	NR	NR		
Finch, 2006a[28]* *BRCA1/2* mutation carriers n=1828	RRSO n=1045	7	All primary peritoneal (6 *BRCA1* and 1 *BRCA2*)	0.20 (0.07 to 0.58)	0.003
	No RRSO n=783	32	29 ovarian, 2 fallopian tube, 1 primary peritoneal (29 *BRCA1* and 3 *BRCA2*)		
Kauff, 2008[22]* *BRCA1/2* mutation carriers n=792	RRSO n=509	3	all peritoneal cancer; *BRCA* 1:3; *BRCA2*: 0	0.12 (0.03 to 0.41)	0.001
	Observation/ surveillance n=283	12	invasive epithelial ovarian, fallopian tube or peritoneal cancers (10 *BRCA1* and 2 *BRCA2*		
Rutter, 2003[40]* *BRCA1/2* mutation carriers; 70% were of Ashkenazi Jewish origin	RRSO	5	5 epithelial, 3 serous	0.29 (0.12 to 0.73)	
	No RRSO	223			
Domchek, 2006[21]^ *BRCA1/2* mutation carriers n=666	RRSO (n=155)	2 (1%)	Ovarian or primary peritoneal	0.11 (0.03 to 0.47)	0.02
	No RRSO (n=271)	16 (6%)	Ovarian or primary peritoneal		
Evans, 2009[26†] Women at risk for ovarian cancer, including 40% *BRCA1/2* carriers	RRSO (n=300)	0	N/A		
	No RRSO (n=503)	15 (3%)	2 stage I, 3 stage II, 9 stage III, 1 stage IV		
Schmeler, 2006[41†] Lynch mutations	Prophylactic RRSO surgery (n=47)	0	N/A		0.09
	No RRSO(n=223)	12 (5%)	5 stage I, 3 stage II, 2 stage III, 0 stage IV, 2 unknown		
Domchek 2010b[9†] *BRCA1/2* mutation carriers	RRSO (n=939)	10 (1.1%)	primary peritoneal cancers all in *BRCA1* (1.5%) (6 in women without prior BC, 4 in women with prior BC)	Without prior BC: 0.28 (0.12 to 0.69) With prior BC: 0.14 (0.04 to 0.59)	
	No RRSO (n=1678)	98 (5.8%)	ovarian cancers (76 in *BRCA1* (7.6%), 22 in *BRCA2* (3.3%); 63 without prior BC, 35 with prior BC)		

*studies included in meta-analysis pooled estimate; ^not included in pooled results of meta-analysis as sample set overlaps with that of other reports; †not included in meta-analysis
BC=breast cancer; CI=confidence interval; HR=hazard ratio; N/A=not applicable; NR=not reported; RRSO=risk-reducing salpingo-oophorectomy

Occult ovarian cancer

Occult ovarian cancers refer to those which were not clinically evident prior to prophylactic surgery and were detected by histological examination of RRSO specimens. The rate of occult ovarian cancer detected at time of RRSO reported in the studies ranged from 0 to 3%. Occult cancers were only detected in *BRCA1/2* mutation carriers, and more often in *BRCA1* mutation carriers than *BRCA2* mutation carriers.[20,22,28] The characteristics of the occult cancers detected are presented in Table 6. Occult cancers were often detected at an early stage.[20,22,28] In women considered at high risk but without identified BRCA mutations[26] and those with Lynch Syndrome,[41] no occult cancers were detected.

Domchek *et al* (2010a)[20] 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).

Table 6 Occult ovarian cancer diagnosed at time of RRSO

Study	**Number of RRSOs performed**	**Number of occult ovarian cancers detected (%)**	**Characteristics of occult ovarian cancers detected**			**Additional cancers detected**
			Mutation status	*Type of cancer*	*Stage of cancer*	
Domchek, 2010a[20] *BRCA1/2* mutation carriers	647	16 (2.5%)	75% *BRCA1*	18.8% primary fallopian tube cancers	37.5% stage I, 19% stage II, 19% stage III, 6% stage IV, 19% unknown	NR
Domchek, 2010b[9] *BRCA1/2* mutation carriers	993	22 (2.3%) (NB these were excluded from study analysis)	77% *BRCA1*			
Evans, 2009[26] Women at risk for ovarian cancer, including 53% *BRCA1/2* mutation carriers	300	3 (1%)	2 *BRCA1* 1 *BRCA2*	NR	1 stage IB, 1 stage IC, 1 stage III	1 disseminated abdominal malignancy from original primary breast cancer (*BRCA1*)
Finch, 2006a[28] *BRCA1/2* mutation carriers	490	11 (2.2%)	9 *BRCA1* 2 *BRCA2*	7 ovarian, 3 primary fallopian tube, 1 malignant cytology	3 stage IA, 4 stage IIIC, 4 stage unknown	NR

Study	Number of RRSOs performed	Number of occult ovarian cancers detected (%)	Characteristics of occult ovarian cancers detected			Additional cancers detected
			Mutation status	*Type of cancer*	*Stage of cancer*	
Kauff, 2008[22] *BRCA1/2* mutation carriers	509	15 cases (NB these were excluded from study analysis)	13 *BRCA1* 2 *BRCA2*	NR	NR	NR
Schmeler, 2006[41] Lynch syndrome	47	0	N/A	N/A	N/A	NR

N/A=not applicable; NR=not reported; RRSO=risk-reducing salpingo-oophorectomy

Breast cancer

The meta-analysis by Rebbeck *et al* (2009)[3] identified eight papers on the risk of breast cancer after RRSO, however due to some of the papers having overlapping study populations, 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. For *BRCA1* mutation carriers alone, the HR was 0.47 (95% CI 0.35 to 0.64). For *BRCA2* mutation carriers alone, the HR was 0.47 (95% CI 0.26 to 0.84).[3]

The recently published study by Domchek *et al* (2010b)[9] reported that for *BRCA1/2* mutation carriers with no prior breast cancer, RRSO decreased the risk of breast cancer by 46% (HR 0.54, 95% CI 0.37 to 0.79). RRSO did not have an effect on subsequent breast cancer for *BRCA1/2* mutations carriers with prior breast cancer (HR 1.00, 95% CI 0.56 to 1.77).

In one of the studies included in the meta-analysis, Kauff *et al* (2008),[22] RRSO appeared to be more protective against non-invasive breast cancer than invasive breast cancer. RRSO also appeared to be protective against ER-positive invasive breast cancer but not ER-negative invasive breast cancer. It was noted that neither of these associations were statistically significant, that the analysis was limited by small number of events in each group, and therefore should only be viewed as hypothesis generating.[22]

One study, Evans *et al* (2009),[26] (not included in the meta-analysis) reported that one women who had RRSO had disseminated abdominal malignancy from her original primary breast cancer detected. This study also reported that 14 women in the RRSO group (4.7%) developed breast cancer in the follow-up period compared with 13 women in the screened group (2.6%). The authors note that they were not able to comment on any benefit from the prevention of breast cancer or breast cancer death due to the absence of direct matching of cases in this study.

HRT after RRSO

Rebbeck *et al* (2005)[23] reported on the effect of short term HRT after RRSO on breast cancer risk in *BRCA1/2* mutation carriers. Women who had RRSO (n=155) were compared to those who did not have RRSO (n=307) and specific information was collected regarding HRT use. Women who had RRSO were more likely to have ever taken HRT (60% vs. 7%, p<0.001). After a mean

follow-up of 3–4 years, eight breast cancer cases were diagnosed in the RRSO group (8%) compared to 65 cases in the non-RRSO group (21%) (p<0.001). The reduction in breast cancer risk associated with RRSO was not different in women who had taken HRT compared to those in the overall cohort.

Survival

Most of the papers identified did not provide information on survival after RRSO. The strongest mortality data are provided in the prospective cohort by Domchek *et al* (2010b)[9] which reported all cause mortality, ovarian cancer- and breast cancer-specific mortality. The papers which reported mortality data are presented in Table 7.

Domchek *et al* (2010b)[9] reported RRSO reduced all cause mortality for all eligible women in their study of *BRCA1/2* mutation carriers. The effect was evident for both women who had RRSO before age 50 years (HR 0.41, 95% CI 0.25 to 0.67) and for those who were 50 years or over at time of RRSO (HR 0.37, 95% CI 0.15 to 0.94).

Finch *et al* (2006a)[28] reported the average survival was 3 years for four patients, who were diagnosed with primary peritoneal cancer following oophorectomy and who died of disease. In addition, a study investigating women who had an occult cancer detected at time of RRSO (n=16, median follow-up 2 years) had similar survival compared to a control ovarian cancer group (n=16, median follow-up 3 years) who did not undergo RRSO: one death vs. two deaths respectively, p=1.[20]

Table 7 Mortality in RRSO comparative studies

Study	**Mortality**		**HR (95% CI)**
	Intervention (RRSO)	*Control (no-RRSO)*	
Domchek 2010b[9]	31 deaths (3.1%) • 21 from breast cancer (2,1%) • 4 from ovarian cancer (0.4%) NB n=993 for all-cause mortality analysis; n=983 for breast cancer-specific mortality analysis; n=966 for ovarian cancer-specific mortality analysis	146 deaths (9.8%) • 81 from breast cancer (5.7%) • 34 from ovarian cancer (2.5%) NB n=1489 for all-cause mortality analysis; n=1424 for breast cancer-specific mortality analysis; n=1377 for ovarian cancer-specific mortality analysis	all-cause mortality: 0.40 (0.26 to 0.61) BC-specific mortality: 0.44 (0.26 to 0.76) OC-specific mortality: 0.21 (0.06 to 0.80)
Domchek 2006[21]; age-*matched analysis*	4 deaths (3%) Breast cancer-specific mortality:1; Ovarian/peritoneal cancer-specific mortality: 1	12 deaths (4%) Breast cancer-specific mortality: 6; Ovarian/peritoneal cancer-specific mortality: 3	0.24 (0.08 to 0.71)
Domchek 2006[21]; *unmatched analysis*	5 deaths (3.2%) • Breast cancer-specific mortality: 1; • ovarian/peritoneal cancer-specific mortality: 2	18 deaths (6.6%) • Breast cancer-specific mortality: 8; • ovarian/peritoneal cancer-specific mortality: 7	0.28 (0.10 to 0.74)

Study	Mortality		HR (95% CI)
	Intervention (RRSO)	*Control (no-RRSO)*	
Evans 2009[26]	8 deaths (2.7%) • 1 ovarian cancer death (occult); • 7 breast cancer deaths*; • 0 other deaths	16 deaths (3.2%) • 6 ovarian cancer deaths; • 6 breast cancer deaths*; • 4 other deaths	
Finch 2006a[28]	5 deaths† • 1 death after ovarian cancer diagnosis at oophorectomy (occult cancer), mean follow-up of 2.2 years for other 10 patients with occult cancer • 4 deaths after primary peritoneal cancer diagnosis following oophorectomy	Deaths not reported for women who did not undergo RRSO	

*Only one breast cancer death per group was attributable to a breast cancer occurring after commencement of follow-up in either RRSO or screening group †deaths only reported for women who were diagnosed with cancer at or following oophorectomy. BC=breast cancer; CI=confidence interval; HR=hazard ratio; OC=ovarian cancer; RRSO=risk-reducing salpingo-oophorectomy

Modelling studies – survival analyses

Three modelling studies were identified which reported on survival analyses, and while these papers are based on hypothetical populations and assumptions, they were considered of interest. One model reports a survival analysis of cancer risk-reducing strategies for *BRCA1*/2 mutation carriers,[45] one model provides information on expected outcomes of prophylactic oophorectomy with or without HRT for *BRCA1*/2 mutation carriers,[46] and the third model compares management strategies for women who carry a Lynch/HNPCC mutation.[47]

The model reported by Kurian *et al* (2010)[45] calculated probabilities of survival by age 70 following various screening, or surgical intervention - prophylactic oophorectomy, prophylactic mastectomy. The probability of surviving to age 70 was estimated at 84% for the general US female population, 53% for *BRCA1* mutation carriers and 71% for *BRCA2* mutation carriers (with no intervention for *BRCA* mutation carriers).[45] This model found that the most effective single intervention for *BRCA1* mutation carriers was RRSO at age 40 which increased the probability of surviving to age 70 to 68% (15% increase compared to no intervention), see Table 8. For *BRCA2* mutation carriers, the most effective single intervention is prophylactic mastectomy (survival by age 70: 79%, an 8% increase compared to no intervention). The combination of prophylactic mastectomy and RRSO at age 40 yields a 24% survival gain for *BRCA1* mutation carriers (survival by age 70: 77%) and 11% survival gain for *BRCA2* mutation carriers (survival by age 70: 82%). In *BRCA1* mutation carriers, delaying RRSO until age 50 provides half the survival gain of RRSO at age 40 (8% vs. 15% respectively), the difference is less pronounced in *BRCA2* mutation carriers (4% vs. 6% respectively).[45]

Table 8 Probability of overall survival by age 70[45]

Variable	*BRCA1* mutation carriers (survival gain*)	*BRCA2* mutation carriers (survival gain*)
No screening, no PO, no PM	53%	71%
No screening, PO at age 40, no PM	68% (15%)	77% (6%)
No screening, PO at age 50, no PM	61% (8%)	75% (4%)
Screening, PO at age 40, no PM	74% (21%)	80% (9%)
Screening, PO at age 40, PM at age 40	77% (24%)	82% (11%)

*compared to having no intervention. PM=prophylactic mastectomy; PO=prophylactic oophorectomy

The model investigating the effect of using HRT after RRSO[46] found that RRSO lengthened life expectancy, irrespective of HRT use. The gain in life expectancy from RRSO decreases as age at the time of oophorectomy increases (RRSO at age 30: +4.65 years (life expectancy 75.26 years vs. 70.61 years with no surgery), RRSO at age 40: +3.34 years (life expectancy 78.30 years vs. 74.96 years with no surgery)). The addition of prophylactic mastectomy to RRSO, without HRT, is associated with an additional increase in life expectancy (+2.15 to +2.98 years). Use of HRT after RRSO was associated with relatively small changes in life expectancy (+0.17 to -0.34 years) when HRT was stopped at age 50, but larger decrements in life expectancy if HRT was continued for life (-0.79 to -1.09 years). The authors recommend that women with *BRCA1*/2 mutations undergo RRSO after completion of childbearing, decide about short-term HRT after oophorectomy based largely on QoL issues rather than life expectancy, and if using HRT, consider discontinuing treatment at the time of expected natural menopause (~50 years).[46]

In the model on management strategies for women who carry a Lynch/HNPCC mutation,[47] surgical management (hysterectomy and RRSO) led to the longest expected survival age of 79.98 years, followed by 79.31 years for screening (ultrasound, CA125, endometrial biopsy, examination), then 77.41 years for those with annual examination (with no further testing).[47]

Adverse events/symptoms

Some studies reported on adverse events or symptoms experienced following RRSO. In two studies, rates of these events/symptoms were compared to high-risk women undertaking screening/observation,[27,31] in other studies, the comparison group consisted of women in the general population (not at high risk of developing ovarian cancer).[25,33,35]

Surgical complications

Only one paper[41] specifically reported on surgical complications related to RRSO. In this paper one surgical complication occurred (rate 1.6%). At the time of prophylactic abdominal hysterectomy with RRSO, a ureteral injury occurred and was repaired. The patient subsequently had an ureterovaginal fistula as well as an ureteroenteral fistula to the Hartmanns pouch and underwent an ureteronectomy. The patient later had a rectovaginal fistula.

Symptoms

The main symptoms experienced after RRSO are those associated with surgically induced menopause.

Fang *et al* (2009)[27] reported that after controlling for age, women in the surgery group were more likely to report hot flashes and vaginal dryness than the screening group. However, these differences were already evident at baseline (prior to surgery), suggesting a potential self-selection for women closer to menopause choosing to undergo RRSO.[27]

Benshushan *et al* (2009)[25] reported that compared to women who underwent natural menopause, women who became menopausal due to RRSO reported either significantly higher or equivalent percentages of menopausal symptoms. Women who became menopausal due to RRSO most commonly reported sweating at night, difficulty in sleeping, hot flushes and loss of interest in sex. These percentages were statistically significantly higher than for women who underwent natural menopause, except for hot flushes, see Table 9. The somatic symptoms were significantly different at 6 months (after cessation of menses or RRSO) ($p=0.025$) and 1 year ($p=0.038$). The vasomotor symptoms scores were significantly more severe in the RRSO group as compared to controls ($p\leq0.001$). At all time points, the sexual dysfunction score was significantly higher in the RRSO group compared to the control group ($p\leq0.01$).

In the study by Michelsen *et al* (2009a)[33] compared to the general population, women who had undergone RRSO had significantly more palpitations, constipation, musculoskeletal disease and osteoporosis than the control group, see Table 10.[33] Similar rates of heartburn, diarrhoea, nausea and dyspnoea were observed in both groups. Overall, pain & stiffness were the most commonly reported somatic complaints in both groups. Within the RRSO group, those who had RRSO before aged 50 years had more palpitations than those with RRSO ≥50 years. Also within RRSO group, those with a history of cancer had more nausea than those without cancer.[33]

Another study by Michelsen *et al* (2009b)[34] reported rates of fatigue (chronic, physical, mental), after RRSO, these results are reported in detail in the later Section on Quality of Life.

Table 9 Menopausal symptoms following RRSO compared to natural menopause[25]

Symptom	Following RRSO	Natural menopause	P-value
Sweating at night	**97%**	72%	**0.002**
Difficulty in sleeping	**88%**	60%	**0.005**
Hot flushes	88%	78%	0.277
Loss of interest in sex	**84%**	54%	**0.005**
Feeling tired/lack of energy	**75%**	55%	**0.048**
Vaginal dryness	70%	58%	0.273
Feeling tense or nervous	69%	49%	0.072
Feeling unhappy or depressed	**59%**	29%	**0.007**
Loss of interest in most things	**56%**	29%	**0.048**
Irritability	50%	31%	0.075
Crying spells	**44%**	17%	**0.006**
Headaches	**44%**	22%	**0.030**
Difficulty in concentrating	38%	36%	1.000
Pressure/tightness in head/body	31%	29%	0.814
Feeling dizzy or faint	28%	29%	1.000
Excitable	25%	19%	0.590
Muscle and joint pains	25%	25%	1.000
Attacks of panic	19%	9%	0.185
Heart beating quickly/strongly	19%	30%	0.321
Urinary incontinence	19%	29%	0.325
Breathing difficulties	16%	7%	0.269
Loss of feeling in hands or feet	16%	14%	0.764
Parts of body feel numb/tingle	16%	19%	0.781

RRSO=risk-reducing salpingo-oophorectomy

Table 10 Symptoms following RRSO compared to age-matched controls[33]

Symptom	Following RRSO (n=338)	Age-matched controls (n=1690)	P-value
Pain and stiffness	52%	56%	**0.02**
Constipation	**34%**	25%	**0.01**
Palpitations	**29%**	21%	**0.02**
Heartburn	28%	29%	0.44
Diarrhoea	20%	14%	0.12
Nausea	18%	11%	0.15
Musculoskeletal disease	**13%**	6%	**0.01**
Dyspnoea	10%	7%	0.20
Osteoporosis	**8%**	3%	**0.02**

RRSO=risk-reducing salpingo-oophorectomy

Treatment of menopausal symptoms/HRT use

Madalinska *et al* (2006)[31] reported on the impact of HRT use on premenopausal women who had undergone RRSO. Results were reported for women who had HRT after RRSO (HRT users), those who had RRSO but did not use HRT (HRT non-users) and women who did not have RRSO but underwent screening. The study found that RRSO HRT users reported significantly fewer endocrine symptoms than RRSO HRT non-users; significant between-group differences were found for hot flushes, and cold and night sweats. RRSO HRT users reported significantly more endocrine symptoms overall than the screening group; significant group differences were found with RRSO HRT users experiencing more vasomotor symptoms, vaginal dryness, pain/discomfort during intercourse, and loss of interest in sex. No significant differences between RRSO HRT users and non-users were observed in sexual functioning. No significant differences were found in levels of endocrine symptoms and sexual functioning between those who used oestrogen/progesterone versus tibolone (though numbers were small).[31]

Metabolic syndrome

A paper was identified which investigated the association of RRSO with metabolic syndrome.[35] This controlled observational study compared 326 women at risk of hereditary breast ovarian cancer who had undergone RRSO with 679 women from the general population. After a mean follow-up of 6.5 years after surgery, in a multiple logistic model, RRSO was associated with metabolic syndrome as defined by both the International Diabetes Federation (IDF) and the 2005 National Cholesterol Education Program Adult Treatment Panel III criteria (ATP). Increasing age and body mass index (BMI) were also associated with metabolic syndrome.[35]

Table 11 Risk of metabolic syndrome[35]

Study	Characteristic	OR (95% CI)
Michelsen 2009c[35]	If RRSO	IDF criteria: OR 2.13 (1.31 – 3.46) p=0.002 ATP criteria: OR 2.12 (1.26 – 3.57) p=0.005
	Age	IDF criteria: OR 1.04 (1.02 – 1.06) p<0.001 ATP criteria: OR 1.04 (1.02 – 1.06) p<0.001
	BMI	IDF criteria: OR 1.26 (1.21 – 1.31) p<0.001 ATP criteria: OR 1.30 (1.24 – 1.36) p<0.001

ATP=National Cholesterol Education Program Adult Treatment Panel; BMI=Body Mass Index; CI=confidence interval; IDF=International Diabetic Foundation; OR=odds ratio; RRSO=risk-reducing salpingo-oophorectomy

Quality of life

Some studies reported on quality of life following RRSO. In three studies the QoL for women who had undergone RRSO was compared to high-risk women undertaking screening/observation.[27,30,31] In other studies, the comparison group consisted of women in the general population (not at high risk of developing ovarian cancer).[33,34]

Quality of life was measured by a range of scales. Fang *et al* (2009) measured quality of life using the Medical Outcomes Survey (MOS) Short-Form Health Survey (SF-36).[27] In addition two component scale values were computed: the Physical Components Score (PCS) and Mental Components Score (MCS). Women were assessed at baseline, 1 month, 6 months and 12 months post-baseline. The surgery group reported significantly lower physical well-being score (PCS) at 1 month follow-up compared to baseline, there was no such difference for the screening group. It was noted that older women (>45 years) had lower mean PCS scores than younger women (≤45 years). No difference between the surgery or screening groups was seen for the mental component summary (MCS) score. For the following subscales: physical functioning, role-physical, bodily pain, vitality and social functioning, no differences were seen over time in the screening group, however women in the surgery group did worse on these scales at 1 month assessment compared to baseline. In the surgery group, these decrements were no longer apparent by 6 and 12 month assessment, except for bodily pain where lower scores (indicating greater pain) were seen at the 12 month assessment compared to baseline.

To measure generic QoL, Madalinska and colleagues (2005) used four of the eight subscales of the Short Form-36 (SF-36) Health Survey (general health perceptions, vitality, role limitations caused by emotional problems, and general mental health) and the global QoL item of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30.[30] Overall, high generic QoL was reported, with no statistically significant difference between the RRSO and screening groups and on average each were no different from the general population. The study also reported condition-specific QoL included measures of cancer-specific distress (intrusive thoughts, cancer worries, and anxiety), cancer risk perception, endocrine symptoms, and sexual functioning. No difference was observed between groups for mean levels of intrusive thoughts about cancer or level of sexual activity. Compared to the screening group, patients in the RRSO group had less cancer worries (less worried about their OC risk, less worried about cancer risk among family members, fewer indicated cancer worries had affected their mood and functioning); more discomfort (vaginal

dryness and dyspareunia); less pleasure and satisfaction during sexual activity; more endocrine symptoms. Those with RRSO and prophylactic mastectomy expressed the fewest worries.

The study by Benshushan *et al* (2009) used a modified Greene Climacteric Scale to evaluate climacteric symptoms.[25] The perceived QoL of the women undergoing RRSO decreased after the surgical procedure (8.08 compared to 8.52 preoperatively) but this difference did not reach statistical significance (p=0.34).

Michelsen *et al* (2009b) used a range of scales including the EORTC QLQ C30, Hospital Anxiety and Depression Scale (HADS) and Fatigue Questionnaire (FQ) to assess QoL.[34] These scales were compared to age-matched controls from two samples of the general Norwegian population (NORM-04, NORM-05) obtained by previous surveys conducted in 2004 and 2005. On EORTC QLQ C30 those in the RRSO group had significantly higher scores on physical functioning, role functioning and overall QoL than those in the NORM-04 group; no differences were observed for emotional functioning or cognitive functioning. The authors noted that for the statistically significant differences, the effect sizes (ESs) were less than 0.12 and therefore not clinically significant (ES>0.40 were considered by the authors as clinically significant). Within the RRSO group, those with a history of cancer had statistically significantly lower scores on physical, cognitive and social functioning compared to those without cancer (physical functioning clinically significant). Chronic fatigue was reported in 16.9% of women in RRSO group, and 11.3% in the NORM-05 group, p=0.29. Rates of physical, mental and total fatigue were not significantly different between RRSO and NORM-05 groups. Within the RRSO group, no significant differences in levels of total, physical, mental or chronic fatigue were observed between *BRCA1*/2 carriers and those from hereditary breast ovarian cancer families without the mutation. Those in the RRSO group with a history of cancer had higher levels of total, physical, mental or chronic fatigue compared to those in the RRSO group without a history of cancer (p=0.001, p=0.001, p=0.007, p=0.02 respectively). Within RRSO group, no differences were seen for any QoL or fatigue measures between those aged <50 years at RRSO compared to those aged ≥50 years at surgery.

In an abstract presented by McArthur *et al* at ASCO 2007,[43] 101 women who had RRSO between April 2000 and April 2004 at Memorial Sloan-Kettering Cancer Centre completed questionnaires on QoL up to one year after surgery. Overall QoL as measured by SF-36 did not change over time.

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 loss of interest in sex.[25,31] Fang *et al* (2009) reported that while women in the surgery group reported reduced frequency of sexual activity at 1 month assessment post-surgery compared to baseline, over the 6 and 12 month assessments, a gradual return to usual levels was indicated.[27] Madalinska *et al* (2005) found no difference between RRSO and screening groups for level of sexual activity.[30] One abstract by Michelsen *et al* (2010)[44] actually reported higher levels of sexual activity in the RRSO group.

McArthur *et al* at ASCO 2007 reported that at 6 and 12 months after surgery 36.4% and 42.3%, respectively, of respondents reported a worsened sex life.[43]

Madalinska *et al* (2005) reported that women in the RRSO group had less pleasure and satisfaction during sexual activity than those in the screening group.[30] However the abstract by

Michelsen *et al* (2010)[44] reported higher levels of sexual pleasure in the RRSO group compared to the general population.

Women with RRSO consistently reported more pain/discomfort during sexual activity than control groups.[27,31,44]

Psychological impact

Psychological impact of RRSO was reported in four studies. A range of scales to measure psychological impact were used, with levels of anxiety and depression most often reported.

The study by Madalinska *et al* (2005) reported condition-specific QoL including measures of cancer-specific distress (intrusive thoughts, cancer worries, and anxiety). The study found that 82% of women who had RRSO reported that their anxiety about developing ovarian cancer had decreased substantially since their surgery, and 45% reported decreased anxiety about breast cancer.[30] Further information regarding cancer specific distress in this study was reported in the previous Section on Quality of Life.

Fang *et al* (2009) reported that no differences were observed between surgery and screening groups regarding satisfaction with their overall body image or depressive symptoms.[27] However, older women were less satisfied with their body image but reported fewer depressive symptoms than younger women.

Michelsen *et al* (2009a) reported that RRSO and control groups had similar levels of anxiety ($p=0.52$) however the RRSO group had significantly lower levels of depression ($p<0.001$) and total mental distress (HADS-T) ($p=0.002$) than controls.[33] Within the RRSO group, there was no difference in any of the above measures between those with RRSO <50 years versus RRSO ≥50 years and between those with or without a history of cancer. Multivariate analysis showed higher levels of HADS-depression were significantly associated with belonging to control group, not having paid work, history of cancer, palpitations, musculoskeletal disease and pain and stiffness. Multivariate analysis showed higher levels of HADS-total were significantly associated with belonging to control group, not having paid work, history of cancer, daily smoking, palpitations, constipation, musculoskeletal disease and pain and stiffness.[33]

In the study by Benshushan *et al* (2009), psychological symptom scores were significantly higher at all time points in the study group (baseline, 3 months, 6 months, 1 year after surgery/last menstrual period) compared to the control group, $p=0.001$.[25] For those who had RRSO, the concern about ovarian cancer decreased significantly after surgery ($p\leq0.001$).

Psychosocial experience of having RRSO

Hallowell *et al* (2004) reported a thematic analysis of interviews of 23 high-risk women who had RRSO.[29] Approximately half of the women (11 out of 23) received specialist genetic counselling about their family history of cancer, five of these took place post-surgery. The costs/harms of RRSO that were identified included: postoperative complications, menopausal symptoms (and lack of information regarding these prior to surgery), side effects of HRT, emotional changes, and body image. Only three women expressed any regrets about having prophylactic surgery. The perceived benefits identified included: reducing OC risk, peace of mind, fulfilment of family obligations, and incidental benefits (such as no more periods, no need for contraception, no more screening, positive emotional changes).

Satisfaction with decision

Madalinska *et al* (2005) reported that significantly more patients who had RRSO were satisfied with their decision (97%) compared to those who chose to undergo screening (82%) ($p<0.01$).[30] However, there was no difference in the percentage of women who regretted their decision between those who had RRSO and those who had screening (5% vs. 6%, $p>0.05$). For those who had RRSO, 86% would choose this procedure again and 63% would recommend it to a friend with familial risk of OC. For those in the screening group, 14% expressed their intention to undergo RRSO within 5 years, 4% within 10 years and 15% at some unspecified time in the future.[30]

In an abstract presented by McArthur *et al* at ASCO 2007, of 101 women who had RRSO, approximately 85% were satisfied with their decision to undergo RRSO.[43]

RRSO technique and pathological examination

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.[26,27,29,41]

Prophylactic oophorectomy compared to prophylactic salpingo-oophorectomy

Olivier *et al* (2004/2005) reported two retrospective analyses of women at high risk of developing ovarian cancer who had undergone bilateral prophylactic oophorectomy (BPO). One compared these women with those who had bilateral salpingo-oophorectomy (BSO),[36] the other compared those who had BPO to those who had additional bilateral salpingectomy (BPS) after BPO.[37]

In the analysis comparing BPO to BSO, five occult cancers were found in the group who had BSO compared with none in the BPO group.[36] All of the occult cancers were diagnosed in women with *BRCA1* mutations, three were in the fallopian tube (one stage Ia, one stage IIIb, one stage IV) and two were in the ovary (one stage Ic, one stage Ia). After a mean follow-up of 45 months, three cases of papillary serous peritoneal cancer were diagnosed in the BPO group. After a mean follow-up of 12 months, no cases of peritoneal cancer were diagnosed in the BSO group.[36]

In the analysis comparing BPO to additional BPS after BPO, no signs of malignancy were detected in the women who had additional BPS.[37] After a mean follow-up of 66 months, three cases of peritoneal papillary serous cancer were detected in the BPO alone group compared to none in the group who had an additional BPS (with a mean follow-up of 80 months).[37]

Serial sectioning

Two papers described the use of serial sectioning of RRSO specimens to detect occult cancers.[38,39] The protocols used/recommended in these papers are in Table 12.

Rabban *et al* (2009a) compared findings on multistep level sectioning (defined as three additional sections cut at three successively deeper intervals from the tissue block and stained with haematoxylin and eosin (H&E)), with original H&E slides.[39] Multistep sections had blinded examination; examined without knowledge of the original diagnosis and without concurrently examining the original H&E slides. Diagnosis of carcinoma was independently confirmed by two pathologists. The types of occult cancers detected are described in Table 13. Diagnosis in the original fimbriae slides and their level sections were concordant in all cases. All tubal cancers

were detected in both the original sections and in the multistep level sections. None of the tubal carcinomas that were non-invasive on the original slides showed invasive growth on additional level sections. No tubal carcinoma was identified in the level sections of any case originally classified as benign. The authors propose 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.[39]

Powell *et al* (2005) compared outcomes depending of the level of adherence to the intensive RRSO protocol described in Table 12.[38] For 20 patients (30%), there was full protocol adherence, for 21 (31%) there was partial adherence, for 26 (39%) there was no adherence. Reasons for incomplete protocol adherence varied considerably. Sometimes only ovaries, but not fallopian tubes, were serially sectioned. Sometimes peritoneal washings or biopsies were omitted. All malignant tumours detected were in women who underwent full (4 tumours detected) or partial (3 cancers detected) protocol procedures (p=0.026). The types of occult cancers detected are described in Table 13. No cancers were found in random peritoneal or omental biopsies, and the authors note the yield of these procedures must await further study. The authors also note that the rate of occult cancers detected in women who had full or partial of the intensive protocol adherence (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%.[38]

Table 12 Protocols used/recommended in serial sectioning papers[38,39]

Proposed protocol for processing RRSO specimens by Rabban *et al* 2009a[39]	**Full protocol used in Powell 2005[38] for RRSO in women carriers of *BRCA* mutations**
1) Fix specimen in formalin for several hours prior to any dissection 2) Ink surgical margin of tubal isthmus 3) Amputate tubal fimbriae from rest of tube and dissect ovary away from tube 4) All tissue slices should be no more than 3mm thick 5) Slice tubal fimbriae parallel to long axis 6) Slice remainder of tube in cross-section 7) Slice ovary perpendicular to its long axis 8) Submit all slices from entire specimen for microscopic examination 9) Prepare 1 H&E stained section from each block of entire specimen 10) Prepare several unstained sections from blocks containing tubal fimbriae and reserve for potential confirmatory immunostains	1) Bilateral salpingo-oophorectomy and removal of entire fallopian tube (open or laparoscopic) 2) Cytologic examination of peritoneal washings 3) Random peritoneal and omental biopsies 4) Serial sectioning of entire fallopian tubes and ovaries at 2mm intervals and microscopic examination of all sections

H&E=haematoxylin and eosin; RRSO=risk-reducing salpingo-oophorectomy

Table 13 Occult cancers detected at RRSO in serial sectioning papers[38,39]

Study	Number of RRSOs performed	Number of occult cancers detected	Characteristics of occult cancers detected		
			Mutation status	*Type of cancer*	*Stage of cancer*
Rabban, 2009a[39]	102	11 (11%)	NR	5 in tubal fimbriae only, 1 in tubal isthmus only, 2 in fimbriae and ovary, 3 in ovary only	NR
Powell, 2005[38]	67 in total 41 with full/partial protocol adherence	7 (10%) 7 (17%)	5 *BRCA1*, 2 *BRCA2*	4 fallopian tube, 3 ovarian. All serous and moderately to poorly differentiated.	NR

NR=not reported; RRSO=risk-reducing salpingo-oophorectomy

In addition, a number of case series were reported regarding detection of occult cancers from RRSO specimens. These case series provided more detailed information, especially on pathological examination. These papers are discussed in Section 3.3.4 *Additional issues of interest*.

Oral Contraceptive Pill

Description of studies

Three primary studies were identified which assessed the impact of OCP use and ovarian cancer.[24,32,42] Studies were either case-controls or retrospective cohorts; no prospective trials on use of OCP and prevention of ovarian cancer were identified. The studies on OCP use only report on risk of OC, no information was provided on survival, adverse events or quality of life. All studies investigated women with identified BRCA mutations. Some papers provided risk estimates based on duration of OCP use.[24,32,42]

Results

Ovarian cancer

All three studies reported reduced rates of ovarian cancer for *BRCA1/2* mutation carriers who had used OCP. Increasing duration of OCP use led to greater reductions in risk of ovarian cancer.

Table 14 Risk of ovarian cancer associated with oral contraceptive pill use

Study	Population	OCP use	HR/OR (95% CI)
Antoniou 2009[24]	N=3319 *BRCA1/2* mutation carriers	Ever vs. never	*BRCA*1/2: HR 0.55 (0.40-0.76), p=0.0003 *BRCA*1: HR 0.52 (0.37-0.73) p=0.0002 *BRCA*2: HR 1.04 (0.42-2.54) p=0.94
		Duration of use (vs. never) >0-1 yr	Decreased ovarian cancer rate with increasing OCP use *BRCA*1/2: HR 1.04 (0.66-1.62), p=0.88 *BRCA*1: HR 1.03 (0.64-1.65) p= 0.91 *BRCA*2: NR
		>1-3 yrs	*BRCA*1/2: HR 0.60 (0.35-1.03), p=0.06 *BRCA*1: HR 0.51 (0.28-0.93) p=0.03 *BRCA*2: HR 1.33 (0.52-3.39) p=0.56
		>3-5 yrs	*BRCA*1/2: HR 0.41 (0.19-0.87), p=0.02 *BRCA*1: HR 0.40 (0.17-0.91) p=0.03 *BRCA*2: NR
		>5 yrs	*BRCA*1/2: HR 0.35 (0.22-0.55), p=0.00005 *BRCA*1: HR 0.34 (0.21-0.54) p=0.00006 *BRCA*2: HR 0.59 (0.16-2.24) p=0.44
McLaughlin 2007[32]	N=3223 *BRCA1/2* mutation carriers	Ever vs. never	*BRCA*1/2: OR 0.51 (0.42-0.64) p=<0.0001 *BRCA*1/2: OR 0.53 (0.43-0.66) p=<0.0001 (multivariate analysis) *BRCA*1: OR 0.55 (0.43-0.69) p=<0.0001 (univariate analysis) *BRCA*1: OR 0.56 (0.45-0.71) p=<0.0001 (multivariate analysis) *BRCA*2: OR 0.39(0.24-0.64) p=0.0002 (univariate analysis) *BRCA*2: OR 0.39 (0.23-0.66) p=0.0004 (multivariate analysis)

Study	Population	OCP use	HR/OR (95% CI)
		Duration of use	A significant trend in risk reduction with duration of usage was seen (p<0.0001) with the maximum observed protection seen with 3-5 years of use.
Whittemore 2004[42]	N=451 *BRCA1/2* mutation carriers	OCP use ≥1yr vs. <1yr/non-use	OR 0.85 (0.53-1.4)
		OCP use ≥6yrs vs. <1yr/non-use	OR 0.62 (0.35- 1.1)
		Duration of use	Trend of decreasing risk with increasing duration of use Overall 5% reduction in risk per year of use (p=0.01)

CI=confidence interval; HR=hazard ratio; NR=not reported; OCP=oral contraceptive pill; OR=odds ratio

Tubal ligation

Description of studies

Three primary studies were identified which assessed the impact of tubal ligation on ovarian cancer.[24,32,40] The studies on tubal ligation only report on risk of OC; no information was provided on survival, adverse events or quality of life.[24,32,40] Two studies investigated women with identified *BRCA* mutations.[24,32] The other study was a population based case-control study of Israeli women,[40] of which approximately 70% were of Ashkenazi Jewish origin. While not all cases had genetic testing, 22% of the cases were identified as *BRCA1/2* mutation carriers.

Results

Ovarian cancer

One study reported a significant reduction in risk of OC in *BRCA1* mutation carriers who had tubal ligation compared to those who did not have this surgery.[24] This study reported no significant difference between having tubal ligation before or after the age of 35. The hazard ratios for tubal ligation in this study were adjusted for oral contraceptive use and number of full term pregnancies. One study reported a reduction in OC risk on a univariate analysis but this association was not apparent on a multivariate analysis.[32] The multivariate analysis included parity, breastfeeding, oral contraceptive use, tubal ligation and ethnicity. Another study reported a non-significant reduction in risk after tubal ligation.[40]

Table 15 Risk of ovarian cancer associated with tubal ligation

Study	Population	Tubal ligation	HR/OR (95% CI)
Antoniou 2009[24]	N=3319 *BRCA1/2* mutation carriers	Yes vs. never	*BRCA*1/2: HR 0.43 (0.24-0.75) p=0.003 *BRCA*1: HR 0.42 (0.22-0.80) p=0.008 *BRCA*2: HR 0.47 (0.18-1.21) p=0.12
		Never vs. age at tubal ligation ≤35	*BRCA*1/2: HR 3.40 (1.45-7.99) p=0.005 *BRCA*1: HR 4.60 (1.51-13.96) p=0.007
		Age at tubal ligation > 35 vs. ≤35	*BRCA*1/2: HR 2.00 (0.68-5.86) p=0.21 *BRCA*1: HR 3.14 (0.87-11.28) p=0.08

Study	Population	Tubal ligation	HR/OR (95% CI)
McLaughlin 2007[32]	N=3223 *BRCA1/2* mutation carriers	Yes vs. never	*BRCA*1/2: OR 0.74(0.57-0.95) p=0.02 (univariate analysis) *BRCA*1/2: OR 0.78(0.60-1.0) p=0.06 (multivariate analysis) *BRCA*1: OR 0.73(0.55-0.97) p=0.03 (univariate analysis) *BRCA*1: OR 0.80(0.59-1.08) p=0.15 (multivariate analysis) *BRCA*2: OR 0.76(0.44-1.29) p=0.30 (univariate analysis) *BRCA*2: OR 0.63(0.34-1.15) p=0.13 (multivariate analysis)
Rutter 2003[40]	1124 cases, 2396 controls 70% Ashkenazi Jewish Case patients include 251 *BRCA1/2* mutation carriers	Yes vs. no	OR 0.70 (0.42-1.18)

CI=confidence interval; HR=hazard ratio; OR=odds ratio

3.3.2 What is the effectiveness of surveillance strategies for women at high risk or potentially high risk of ovarian cancer?

Description of studies

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.[8]

The current systematic review did not identify any further publications comparing performance of surveillance to having no surveillance for high-risk women published after the NBOCC position statement.

3.3.3 What are the psychological/psychosocial issues encountered by women at high risk or potentially high risk of ovarian cancer?

Description of studies

Much of the information identified regarding psychological or psychosocial issues for high-risk women related to genetic testing (such as the decision to undertake genetic testing and the impact of genetic testing) which was outside the scope of this review and therefore excluded.

The psychological impact of having RRSO is described in the results of Section 3.3.1.

Two Australian papers were identified which specifically described psychosocial issues for partners of women at high risk.[48,49]

An abstract was identified which describes the impact of a hospital-based counsellor-led support group for *BRCA* carriers.[50]

Results

Mireskandari *et al* reported two papers regarding distress, information and support needs for high-risk women and their partners.[48,49] Overall, partners' levels of distress were comparable with the Australian normative sample (males).[48] However, some partners had scores indicative of severe to extremely severe levels of depression (8%), anxiety (4%), stress (6%) and cancer-related distress (4%).[48] While some partners reported they were well informed about breast/ovarian cancer and issues related to being at high risk, many reported they would like more information about breast/ovarian cancer.[48,49] The majority of partners reported coping well with their wife's increased cancer risk, however approximately one third would like more support.[48] Most partners reported that there was no impact on the couple's relationship however others described positive and negative impacts.[48,49] Partners often worried about their children having inherited the wife's increased cancer risk.[48] Other attitudes relating to children included not wanting to contemplate the possibility of their children being at risk, being hopeful that rapid advances in technology might result in their children not having to face cancer and fears about possibly losing their wife and having to raise children on their own.[49]

An abstract was identified which described the impact of a hospital-based counsellor-led support group for *BRCA* carriers.[50] The study implemented a hospital-based support group for *BRCA* mutation carriers led by genetic counsellors. Forty-two individuals (of 115 invited) completed an online questionnaire regarding their experience of the support group. Of the respondents:

- 85% felt that attending the support group significantly improved their medical knowledge
- 70% felt that the group provided significant emotional support
- 96% felt that they were better able to broach the subject of their *BRCA* status with family members
- 56% experienced significantly lower anxiety levels regarding their *BRCA* status
- 78% reported diminished feelings of isolation since attending the support group.

3.3.4 Additional issues of interest

Papers in the following section were not specifically searched for and did not explicitly meet the inclusion criteria for the primary research questions.

Pathology of ovarian cancer in high-risk women and relevance to risk-reducing surgical management

Four case series[51-54] were identified which reported detailed pathological information from oophorectomy specimens. Detailed pathological and histological examination methods are provided in Appendix G.

The rate of occult ovarian cancer reported was between 4% and 9%. These rates are higher than those reported in the comparative studies reported in Section 3.3.1 (0–3%). The types of occult ovarian cancers detected at RRSO are presented in Table 16, many of which were fallopian tube cancers.

The majority of occult cancers identified in these series involved the fallopian tube. Two studies noted that ultrasound and/or CA125 performed within 12 months prior to surgery failed to raise suspicion of disease.[52,53]

Table 16 Occult cancers detected in RRSO case series

Study	Population	Number of RRSOs performed	Number of occult ovarian cancers detected (%)	Characteristics of occult ovarian cancers detected			Additional cancers detected at time of RRSO
				Mutation status	*Type of cancer*	*Stage of cancer*	
Callahan 2007[51]	*BRCA1/2* mutation carriers	122	7 (5.7)	4 *BRCA*1 mutation 3 *BRCA*2 mutation	7 fallopian tube – all originated in the fimbrial or ampullary region of the tube; 5 serous, 2 endometriod	1 stage IC 1 stage IIA 1 stage IIIA	NR
Finch 2006b[52]	*BRCA1/2* mutation carriers	159	7 (4.4)	6 *BRCA*1 mutation 1 *BRCA*2 mutation	4 fallopian tube 2 ovarian 1 peritoneal	1 fallopian tube stage 0 1 fallopian tube stage IB 1 fallopian tube stage IIA 1 fallopian tube stage IIB 1 ovarian stage IA 1 ovarian stage IIC 1 peritoneal no staging	1 metastatic cancer of the myometrium from a previous breast cancer
Hirst 2009[53]	*BRCA1/2* mutation carriers	45	4 (9)	2 *BRCA*1 mutation 2 *BRCA*2 mutation	3 microinvasive tubal cancer 1 in situ tubal cancer		1 micrometastatic breast cancer in the ovary
Rabban 2009b[54]	*BRCA* mutation carriers	108	7 (6.5)		1 ovary alone 1 ovary and fallopian tube 5 fallopian tube alone		1 metastatic breast cancer
	Patients who underwent RRSO based on strong family history or patients with PTEN mutations or lynch syndrome	32	0	N/A	N/A	N/A	

N/A=not applicable; NR=not reported; RRSO=risk-reducing salpingo-oophorectomy

Communication about risk including information needs of women

A systematic review on risk communication was identified.[55] The review included 28 articles. Most of the research identified in the review addressed risk communication about cancer (mainly breast and/or ovarian cancer). The review reported that risk communication interventions achieved some benefits for users, mainly on cognitive outcomes (knowledge, risk perception), and less clearly so on measures of affect (anxiety, satisfaction with decision making, intentions), behavioural (use of tests, treatments) or health status. There was some evidence that risk communication was less important to users than addressing issues of loss, unresolved grief and relationship problems. The counselling and psychosocial interventions evaluated alongside, or with risk communication, appeared more effective in achieving benefits for users in the above outcomes.

Decision aid tools

Three randomised controlled trials investigated various decision aid tools for risk management for women at high risk of ovarian cancer.

An Australian study randomised 131 high-risk women to receive either a tailored decision aid or a general educational pamphlet on risk-reducing strategies.[56] The decision aid consisted of a booklet and a separate values clarification exercise. The booklet contained information on the risk factors for ovarian cancer, the impact of family history on risk, issues of genetic testing, four options for managing increased risk (watchful waiting, screening, OCP, prophylactic oophorectomy), and the benefits and risks associated with each option. The values clarification exercise took the information presented in the booklet one step further by asking women to rate the importance of each risk and benefit as "leaning" toward each of the four management options, and it is included to facilitate a decision in line with personal values. The aid was developed in accordance with the NHMRC guidelines *How to present evidence for consumers*. No significant differences between groups were observed for any of the psychological outcomes or with regard to the actual risk management decision made. The authors concluded that in the shorter term (2 weeks) the decision aid was superior to the pamphlet in decreasing decisional conflict and increasing knowledge about options. Longer term (6 months), the aid was perceived as being significantly more helpful and acceptable as a form of educational material than the pamphlet.

Similarly, Armstrong *et al* (2005) reported a RCT with 27 US women comparing a decision support system with an educational booklet to the educational booklet alone.[57] The decision support system (DSS) presented complex risk information about the expected outcomes of alternative management options in the format of individualised survival and cancer incidence curves. Women did not differ in their decisions about cancer risk management strategies, however women in the DSS arm reported higher satisfaction with their decisions than women in the control arm. Women in the DSS arm did not differ significantly from women in the control arm in their estimates of cancer risk in alternative management scenarios, however there was a trend towards these women reporting higher estimates of cancer risk. Women did not differ in levels of anxiety or depression between groups.

In 2004, van Roosmalen *et al* (2004) reported a RCT of 88 women in the Netherlands, comparing usual care to a shared decision making intervention (SDMI) administered by a trained research assistant 2 months after women received their genetic test result.[58] In the short term (3 months after test result), the SDMI had no effect on any of the wellbeing outcomes. In the long term (9

months after test result) the SDMI group had less intrusive thoughts about cancer in the family, a better general health, and tended to be less depressed. The SDMI did not have an effect on anxiety. No differences were found between the SDMI and control groups on the intended treatment choice or on the treatment performed treatment on breasts and ovaries. No differences were found for the ratings of the treatment options. No effects were found, in the short or long term with respect to the decision-related outcomes for the ovaries. More women in the SDMI group felt specialists held a strong preference for breast treatments, however no difference was found between groups for specialists' preference of ovarian treatment. Women in the SDMI group appeared to want more support and advice from the specialists regarding treatment choice for breasts (p=0.09, not statistically significant), but not for ovaries (p=0.24). In the short term, no interaction effects between the SDMI and cancer history were found for any of the wellbeing or decision-related outcomes. In the long term, with respect to well-being, an interaction effect was found for anxiety (p=0.04) and general health (p=0.02), and with respect to the decision-related outcomes for the ovaries, an interaction effect was found for strength of preference (p≤0.01) and decision uncertainty (p≤0.01)

Factors affecting decision making on risk-reducing strategies

Howard *et al* (2009)[59] report a systematic review on decision making related to cancer risk-reducing strategies for women at high risk for hereditary breast and ovarian cancer. Forty-three papers are included in this review, including questionnaires, medical records reviews and qualitative research.[59] Three main factors were identified from the 43 published papers that influence decision making about risk-reducing strategies: a) medical and physical factors, b) psychological factors, and c) social context factors. Evidence from moderate sized studies (n=30 to 554) in several countries suggested that *BRCA1*/2 mutation status and parity influence women's decisions about RRSO. 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. Findings on the influence of other factors such as previous cancer diagnosis, age and menopausal status on decision making are contradictory.

Uptake of risk-reducing and surveillance strategies

A systematic review on predictors of uptake of risk reduction strategies and/or surveillance was identified.[60] The review included 37 articles, 20 of which were of prospective study design. Nine studies reported significant predictors of use of RRSO. Eight studies investigated predictors of ovarian cancer surveillance.

Predictors of use of RRSO included:

- being a mutation carrier
- age
- personal history of BC
- risk perception
- cancer anxiety
- family history
- attitude.

Factors other than anxiety were reported as more powerful predictors of RRSO. Women's attitude about RRSO is a significant and useful indicator of actual uptake, as is age. No

significant association between cancer worry and uptake of RRSO was found, although anxiety was significantly reduced after RRSO and women expressed a high level of satisfaction with their decision.

The main predictors of ovarian cancer surveillance included:

- being a carrier of *BRCA* mutation
- perceived risk
- cancer worries
- age
- the number of affected relatives
- employment status
- Jewish ancestry.

Among mutation carriers there was an increased rate of compliance to surveillance compared to non-carriers and women who received a negative or uninformative DNA test result.

Cost-effectiveness of risk-reducing strategies

A US study evaluated the cost-effectiveness of preventative strategies for women aged 35 to 50 years with a single *BRCA1* or *BRCA2* mutation.[61] Using a Markov Model, the interventions investigated were prophylactic bilateral salpingo-oophorectomy, prophylactic mastectomy, having both surgeries, tamoxifen, oral contraceptives, and surveillance. Quality of life adjustments were made using preference ratings. Bilateral salpingo-oophorectomy and combined bilateral salpingo-oophorectomy and mastectomy proved to be the most cost-effective risk-reducing strategies for women with either *BRCA1* or *BRCA2* mutation. Surveillance and mastectomy alone were the least cost-effective strategies.

A Norwegian cost-effectiveness study was reported in 2008 which focused on *BRCA*1 mutation carriers and compared RRSO at age 35 years, with or without prophylactic bilateral mastectomy at age 30 years, to no intervention.[62] The survival gain was largest for women undergoing both RRSO and prophylactic mastectomy. The model suggested that the up-front costs of investigation and prophylactic therapy is well compensated for by later savings due to the significant reduction in the risk of breast and ovarian cancer, prolonged survival and productivity gain.

3.4 Ongoing trials

Two clinical trials registries (Clinical trials.gov: www.clinicaltrials.gov and Current Controlled Trials: www.controlled-trials.com) were searched to identify any additional studies investigating the management of women at high risk of ovarian cancer which have not yet reported.

Three ongoing clinical trials were identified from the search, see Table 17; one on surveillance,[63] one comparing surveillance and risk-reducing strategies,[64] and one on the use of chemoprevention prior to surgery.[65] One trial is a randomised trial.[65]

Table 17 Ongoing trials investigating risk management strategies for women at high risk of ovarian cancer

Trial and Location	Study design	Participants	Intervention	Control	Outcome measures
UK FOCSS[63] UK Currently recruiting	Non-randomised single arm intervention Phase II	Planned accrual: 5000 Women with family history of ovarian or fallopian tube cancer	Surveillance: 4-monthly CA125 blood tests and annual TVU	N/A	Diagnosis/stage/grade of primary invasive epithelial ovarian/fallopian tube cancer, measured during and one year after the end of active screening
GOG-199[64] International Currently recruiting	Prospective non-randomised	Planned accrual: 2332 Women at increased risk of ovarian cancer, based on a strong family history, or a personal or family history of a mutation in the *BRCA*1 or *BRCA*2 genes	RRSO	CA125 screening	Incidence of ovarian cancer and breast cancer Prevalence of clinically occult ovarian cancer and fallopian tube cancer and precursor lesions in participants who undergo RRSO Positive predictive value and specificity of the Risk of Ovarian Cancer Algorithm (ROCA) based on serial CA125 measurements for ovarian cancer in participants who do not undergo RRSO
NCT-00098800[65] USA Completed	Multi-centre RCT	Planned accrual: 40 Women at high risk of developing ovarian cancer and planning to undergo PBO	Oral fenretinide once daily. Treatment continues for 6-8 weeks in the absence of unacceptable toxicity	Oral placebo once daily. Treatment continues for 6-8 weeks in the absence of unacceptable toxicity	Induction of apoptosis in the ovarian epithelial and stromal cells

GOG=Gynecologic Oncology Group; N/A=not applicable; PBO=prophylactic bilateral-oophorectomy; RCT=randomised controlled trial; RRSO=risk-reducing salpingo-oophorectomy; TVU=transvaginal ultrasound; UK FOCSS=UK Familial Ovarian Cancer Screening Study

4 Discussion

In this systematic review about management strategies for women at high risk of ovarian cancer, over 40 papers were reviewed. Most papers reported on populations with identified *BRCA1* or *BRCA2* mutations and most information was related to RRSO.

RRSO was consistently associated with decreased risk of ovarian cancer compared to screening. Primary peritoneal cancers can occur after RRSO, although this is rare with reported rates around 1%.[9,21,22,28,40] A recent meta-analysis reported that in *BRCA1/2* mutation carriers, RRSO provided a 79% risk reduction for gynaecological cancers and a 51% risk reduction for breast cancer.[3] A large prospective cohort study of *BRCA1/2* mutation carriers[9] published after the meta-analysis, supported these findings. This study also reported that RRSO was associated with a reduction in all-cause mortality, ovarian cancer-specific mortality and breast cancer-specific mortality.[9] Similarly, modelling studies suggest a survival benefit of RRSO,[45,46] particularly by age 40 and when combined with prophylactic mastectomy. RRSO is associated with menopausal symptoms which are often more prevalent and severe than symptoms experienced during natural menopause.[25,33] HRT may alleviate these symptoms[31] however a modelling study suggests that if HRT is continued for life this may impact survival.[46]

Rates of occult ovarian cancer detected at RRSO ranged from 0 to 17% and were often detected in *BRCA1* mutation carriers and primary fallopian tube cancers. No occult cancers were detected in the limited number of women who were considered at high risk of ovarian cancer but were not *BRCA* mutation carriers.[26,41,54] The rate of occult cancer detected is also related to how the pathological examination is performed.[38,52]

The technique of performing RRSO was often not described in detail in the comparative papers. The papers on serial sectioning of RRSO specimens and the case series reporting occult cancer provide details on pathological examination.

Studies indicated that use of the oral contraceptive pill appears to be associated with a decreased risk of ovarian cancer (almost 50%), with longer duration of use (>3 years) associated with further reductions in risk.[24,32]

The association between tubal ligation and risk of ovarian cancer is less clear with one of three studies reporting a statistically significant reduction (over 50%) in ovarian cancer for *BRCA1* mutation carriers.[24] The two other studies reported non-significant reductions in ovarian cancer risk.[32,40]

While information on quality of life was reported in some studies specifically related to RRSO, there was limited information identified on psychosocial issues and interventions for women at high risk of ovarian cancer outside the context of genetic testing. Two Australian studies investigated the impact on partners of women at high risk.[48,49] Issues raised included information and support needs of partners and the impact on relationships and partners' distress levels. A small study, reported only in an abstract, found that a support group for BRCA carriers had many benefits including increased medical knowledge and emotional support.[50]

Additional papers of interest were identified. Multiple factors affect the decision and uptake of risk-reducing strategies including physical and psychological factors.[59,60] Well constructed decision aids led to higher satisfaction with the risk management decision made.[56-58] It was noted

that these decision aids were developed and trialled when there was less evidence available regarding RRSO. RRSO was considered cost-effective by both a US[61] and a Norwegian study.[62]

Results from large ongoing trials investigating risk management options are awaited with interest.

5 Conclusion

Management options for women at high risk of ovarian cancer include surveillance, RRSO, tubal ligation or use of oral contraception. Evidence supports that RRSO significantly reduces the risk of ovarian cancer and breast cancer for *BRCA1/2* mutation carriers. Recent evidence suggests that RRSO reduces all-cause mortality, ovarian cancer-specific mortality and breast cancer-specific mortality for *BRCA1/2* mutation carriers. Adverse events such as menopausal symptoms are common following this surgery however, quality of life does not appear to be adversely affected in the long term. The oral contraceptive pill is associated with decreased risk of ovarian cancer, particularly with increasing duration of use and in *BRCA1* mutation carriers. Evidence is unclear on the association between tubal ligation and ovarian cancer risk. No further evidence was identified to add to NBOCC's 2009 position statement on surveillance for women at high risk of ovarian cancer. Results from large ongoing trials investigating risk management options are awaited with interest.

Appendix A Contributors

Working group members

The management of women at high risk of ovarian cancer: a systematic review was developed with input from an expert multidisciplinary Working Group with the following members:

• A/Prof Peter Grant (Chair)	Gynaecological Oncologist
• Prof Phyllis Butow	Clinical Psychologist
• Prof Jon Emery	General Practitioner
• A/Prof Judy Kirk	Clinical Geneticist
• Ms Eugenia Koussidis	Consumer representative
• Dr Deborah Neesham	Gynaecological Oncologist
• Prof Andreas Obermair	Gynaecological Oncologist
• Prof Peter Russell	Pathologist

National Breast and Ovarian Cancer Centre[§] staff

The following NBOCC staff were involved in the development of *Management of women at high risk of ovarian cancer: a systematic review*

• Ms Katrina Anderson	Project Officer – Research
• Ms Jane Francis	Program Manager – Ovarian Cancer
• Ms Emma Hanks	Senior Project Officer
• Dr Karen Luxford	General Manager
• Dr Anne Nelson	Evidence Review & Research Leader
• Ms Rosemary Wade	Senior Project Officer – Research

[§] 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.

Appendix B Definition of potentially high risk of ovarian cancer[4]

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
- 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° degree 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

Individual risk may be higher or lower if genetic test results are known. 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 gene mutations are more common in people of Ashkenazi Jewish ancestry.*

Appendix C Literature databases searched

Database	Results/Retrievals
Pubmed	609
Medline and Embase (Ovid)	1155
Psych Info	39
Cochrane Library	0

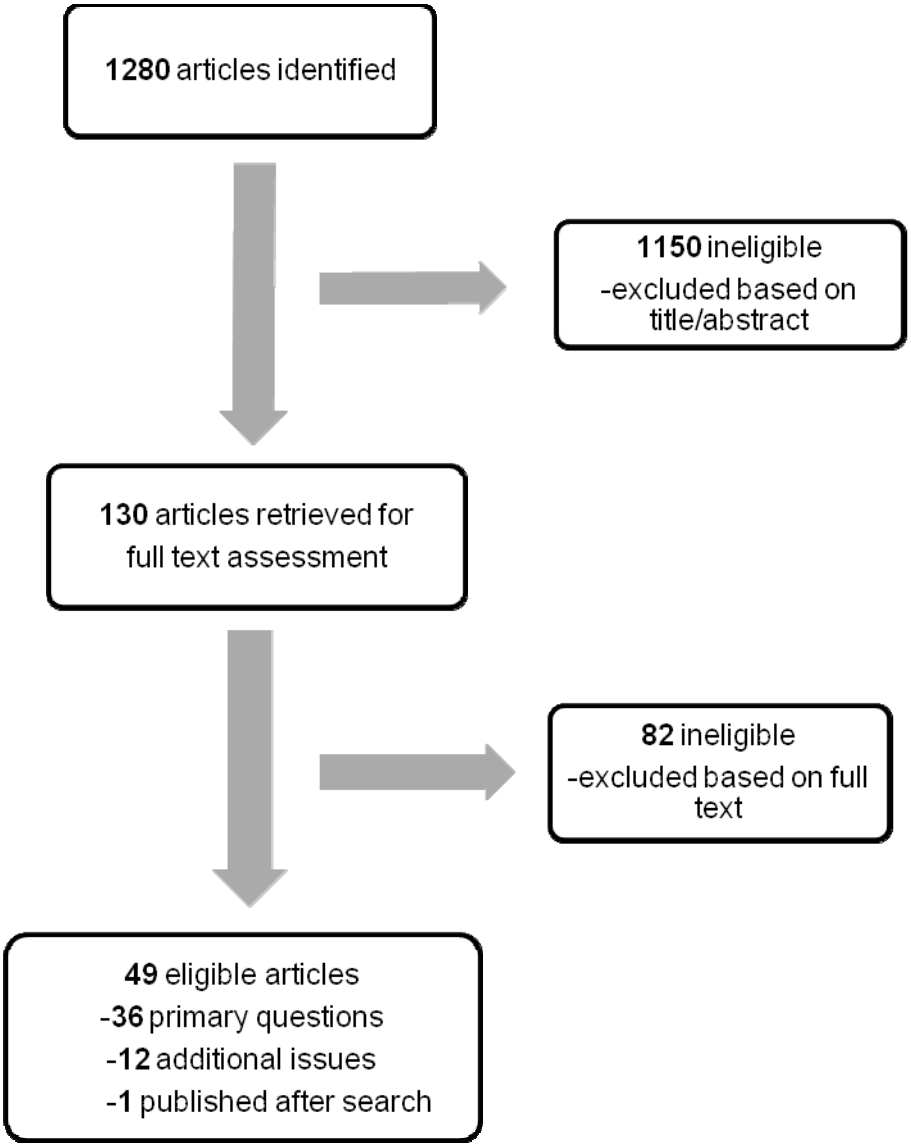
Appendix D Search strategy

Ovarian cancer	Ovarian Neoplasms/ Ovarian or ovary and (cancer or carcinoma or tumour or tumor or neoplasm*)
High risk	"High risk" or "high-risk" or "strong family history" or (*BRCA* and mutation) or *BRCA1* or *BRCA2* or *BRCA1*/2 or "lynch syndrome" or "hereditary non-polyposis colorectal cancer" or HNPCC or "hereditary breast ovarian cancer syndrome or "genes, *BRCA1*/" or "genes, *BRCA2*/" or "genetic predisposition to disease/"
Risk-reducing strategies	"risk reduction" or "risk reducing" or prevention AND ("oral contraceptive pill" or OCP or "tubal ligation" or oophorectomy) or RRSO or "risk reducing salpingo oophorectomy" or "bilateral salpingo oophorectomy" or BSO or "prophylactic surgery or chemoprevention or "risk management" or "risk reduction behaviour/" or ovariectomy/
Surveillance (2009-2010)	Screening and (TVU or TVUS or "transvaginal ultrasound" or "CA 125" or CA125 or "CA-125") or surveillance or "transvaginal ultrasound" or TVU or TVUS or "CA 125" or CA125 or "CA-125" or "tumour markers" or "tumor markers" or biomarkers
Psychological issues	Psychosocial or psychological or psychosexual

Appendix E Guideline and clinical trial sites searched

Acronym	Organisation	Website
CCO	Cancer Care Ontario (Canada)	http://www.cancercare.on.ca/
ESMO	European Society of Medical Oncology	http://www.esmo.org/
GIN	Guidelines International Network	http://www.g-i-n.net/
NCCN	National Comprehensive Cancer Network (US)	http://www.nccn.org/index.asp
NGC	National Guideline Clearinghouse (US)	http://www.guideline.gov/
NICE	National Institute for Health and Clinical Excellence (UK)	http://www.nice.org.uk/
SIGN	Scottish Intercollegiate Guidelines Network	http://www.sign.ac.uk/
	ClinicalTrials.gov	http://www.clinicaltrials.gov/
	Current Controlled Trials	http://www.controlled-trials.com/

Appendix F Flowchart of inclusion/exclusion



Appendix G Additional data tables

Detailed pathological & histological examination methods described in case series

Study	Examination methods
Callahan 2007[51]	In all patients, the entire adnexa were submitted for histopathologic examination, with both tubes and ovaries sectioned at 2- to 3-mm intervals before analysis. From February 2005, a modification was introduced in accordance with the SEE-FIM protocol. This modification entailed amputation of the fimbriated end with serial sagittal rather than cross sections of this segment. Peritoneal washings were performed for 97.5% of the patients.
Finch 2006[52]	Resected ovaries were examined grossly, serially sectioned and submitted for histological examination. Both ovaries were submitted for examination in their entirety. Prior to 2000, only representative sections of the fallopian tubes were submitted for microscopy, but the protocol was amended in 2000 where both tubes were submitted in their entirety for examination. Ninety-three per cent of women had pelvic washings done.
Hirst 2009[53]	Laparoscopic BSO was performed using a standard technique involving dissection and ligation of the infundibulopelvic ligaments bilaterally with bipolar diathermy and ligation of the ovarian ligament with a delayed absorbable ligature. The fallopian tube was excised flush with the uterine corpus using bipolar diathermy. The peritoneal cavity was inspected at the time of laparoscopy. Peritoneal washings were not routinely taken. Histopathological examination was performed by two experienced gynecological pathologists. After adequate fixation in formalin, the fallopian tubes and ovaries were submitted entirely for histological examination. The distal 2 cm of the fallopian tube was amputated from the rest of the tube. This fimbriated end was then sectioned longitudinally so that the maximum surface area of the fimbrial mucosa was available for histological examination. The remaining fallopian tube was then cross-sectioned at 2- to 3-mm intervals and embedded in toto as per the SEE-FIM protocol. The pathologists were aware that these specimens were “high-risk ovaries and fallopian tubes” and the histopathological technique involved embedding of the entire fallopian tube and ovary in paraffin blocks.
Rabban 2009b[54]	The tubes and ovaries were entirely submitted in 2 to 3mm thick sections for microscopic evaluation using our previously described dissection protocol. Tubes were entirely submitted in serial cross-sections whereas the fimbriae were entirely submitted in longitudinal sections and the ovaries were entirely submitted in sections cut perpendicular to the long axis. Immunohistochemical staining was performed on paraffin-embedded, formalin-fixed tissue sections to confirm difficult diagnoses.

Abbreviations

ACN	Australian Cancer Network
ACOG	American College of Obstetrics and Gynecology
ASCO	American Society of Clinical Oncology
ATP	National Cholesterol Education Program Adult Treatment Panel
BC	breast cancer
BMI	body mass index
BPO	bilateral prophylactic oophorectomy
BPS	bilateral prophylactic oophorectomy with additional bilateral salpingectomy
BSO	bilateral salpingo-oophorectomy
CI	confidence interval
DSS	decision support system
EORTC	European Organisation for Research and Treatment of Cancer
ES	effect size
FQ	Fatigue Questionnaire
GIN	Guidelines International Network
GOG	Gynecologic Oncology Group
HADS	Hospital Anxiety and Depression Scale
H&E	haematoxylin and eosin
HNPCC	hereditary non-polyposis colorectal cancer
HR	hazard ratio
HRT	hormone replacement therapy
IDF	International Diabetes Federation
IES	Impact of Event Scale
IGCS	International Gynecologic Cancer Society
MCS	Mental Components Score
MOS	Medical Outcomes Survey

MSK	Memorial Sloan Kettering
NBOCC	National Breast and Ovarian Cancer Centre
NCCN	National Comprehensive Cancer Network
OC	ovarian cancer
OCP	oral contraceptive pill
OR	odds ratio
OS	overall survival
PCS	Physical Components Score
PM	prophylactic mastectomy
PO	prophylactic oophorectomy
QLQ	Quality of Life Questionnaire
QoL	quality of life
RRSO	risk-reducing salpingo-oophorectomy
SDMI	shared decision making intervention
SF-36	Short-Form 36
SGO	Society of Gynecologic Oncologists
SIGN	Scottish Intercollegiate Guidelines Network
TVU	transvaginal ultrasound
UK FOCSS	UK Familial Ovarian Cancer Screening Study

References

1. Australian Institute of Health and Welfare & National Breast and Ovarian Cancer Centre. Ovarian cancer in Australia: an overview, 2010. Canberra: AIHW 2010.

2. Risch HA, McLaughlin JR, Cole DE, et al. 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;101(2):80-7.

4. 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.

5. 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.

6. Narod SA, Ghadirian P, Lynch H, Isaacs C, Garber JE. Tubal Ligation and risk of ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet. 2001;357:1467-70.

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

8. 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.

9. Domchek S, Friebel T, Singer 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.

10. Daly MB, Axilbund JE, Buys S, et al. The NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian. Journal of the National Comprehensive Cancer Network. 2010;8(5):562-94.

11. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. Obstet Gynecol. 2009;113(4):957-66.

12. Horsman D, Wilson BJ, Avard D, et al. Clinical management recommendations for surveillance and risk-reduction strategies for hereditary breast and ovarian cancer among individuals carrying a deleterious BRCA1 or BRCA2 mutation. J Obstet Gynaecol Can. 2007;29(1):45-60.

13. Cancer Care Ontario. Management options for women with a hereditary predisposition to ovarian cancer: evidence summary report #4-4. 2004.

14. Berliner JL & Fay AM. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2007;16(3):241-60.

15. Scottish Intercollegiate Guidelines Network (SIGN). Epithelial Ovarian Cancer: guideline number 75. 2004.

16. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: A systematic review. JAMA. 2006;296(12):1507-17.

17. Memorial Sloan Kettering (MSK). Ovarian cancer screening guidelines. 2008. www.mskcc.org/mskcc/html/78334.cfm.

18. Rosen B, Kwon J, Fung Kee Fung M, Gagliardi A, Chambers A. Systematic review of management options for women with a hereditary predisposition to ovarian cancer. Gynecol Oncol. 2004;93(2):280-6.

19. Bermejo-Perez MJ, Marquez-Calderon S, Llanos-Mendez A. Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review. Int J Cancer. 2007;121(2):225-31.

20. Domchek SM, Friebel TM, Garber JE, et al. Occult ovarian cancers identified at risk-reducing salpingo-oophorectomy in a prospective cohort of BRCA1/2 mutation carriers. Breast Cancer Res Treat. 2010;124:195-203. Epub 2010 Feb 24.

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

22. Kauff ND, Domchek SM, Friebel TM, 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;26(8):1331-7.

23. Rebbeck TR, Friebel T, Wagner T, 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.

24. Antoniou AC, Rookus M, Andrieu N, 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 Epidemiol Biomarkers Prev. 2009;18(2):601-10.

25. Benshushan A, Rojansky N, Chaviv M, et al. Climacteric symptoms in women undergoing risk-reducing bilateral salpingo-oophorectomy. Climacteric. 2009;12(5):404-9.

26. 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;17(11):1381-5.

27. Fang CY, Cherry C, Devarajan K, et al. A prospective study of quality of life among women undergoing risk-reducing salpingo-oophorectomy versus gynecologic screening for ovarian cancer. Gynecol Oncol. 2009;112(3):594-600.

28. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the Risk of Ovarian, Fallopian Tube, and Peritoneal Cancers in Women With a BRCA1 or BRCA2 Mutation. JAMA. 2006;296(2):185-92.

29. 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;8(2):148-56.

30. Madalinska JB, Hollenstein J, Bleiker E, 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;23(28):6890-8.

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

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

33. 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;113(1):128-33.

34. Michelsen TM, Dorum A, Trope CG, Fossa SD, Dahl AA. Fatigue and quality of life after risk-reducing salpingo-oophorectomy in women at increased risk for hereditary breast-ovarian cancer. Int J Gynecol Cancer. 2009;19(6):1029-36.

35. Michelsen TM, Pripp AH, Tonstad S, Trope CG, Dorum A. Metabolic syndrome after risk-reducing salpingo-oophorectomy in women at high risk for hereditary breast ovarian cancer: a controlled observational study. Eur J Cancer. 2009;45(1):82-9.

36. Olivier RI, van Beurden M, Lubsen MA, et al. Clinical outcome of prophylactic oophorectomy in BRCA1/BRCA2 mutation carriers and events during follow-up. Br J Cancer. 2004;90(8):1492-7.

37. 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;96(2):439-43.

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

39. Rabban JT, Krasik E, Chen LM, et al. 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;33(12):1878-85.

40. Rutter JL, Wacholder S, Chetrit A, 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;95(14):1072-8.

41. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354(3):261-9.

42. Whittemore AS, Balise RR, Pharoah PDP, et al. Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. Br J Cancer. 2004;91(11):1911-5.

43. McArthur HL, Hensley M, Brown CL, Chi DS. Impact of risk-reducing oophorectomy on quality of life in women at risk for ovarian cancer. J Clin Oncol. 2007;25(18S):1520.

44. 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.

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

46. 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;22(6):1045-54.

47. Chen LM, Yang KY, Little SE, Cheung MK, Caughey AB. Gynecologic cancer prevention in Lynch syndrome/hereditary nonpolyposis colorectal cancer families. Obstet Gynecol. 2007;110(1):18-25.

48. Mireskandari S, Sherman KA, Meiser B, et al. Psychological adjustment among partners of women at high risk of developing breast/ovarian cancer. Genet Med. 2007;9(5):311-20.

49. Mireskandari S, Meiser B, Sherman K, et al. Evaluation of the needs and concerns of partners of women at high risk of developing breast/ovarian cancer. Psychooncology. 2006;15(2):96-108.

50. Ducaine W, Dohany L, Zakalik D. Impact of a hospital-based focused, counsellor-led support group among BRCA carriers. Curr Oncol. 2009;16(5):108.

51. Callahan MJ, Crum CP, Medeiros F, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. J Clin Oncol. 2007;25(25):3985-90.

52. Finch A, Shaw P, Rosen B, et al. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecol Oncol. 2006;100(1):58-64.

53. 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;19(5):826-9.

54. Rabban JT, Barnes M, Chen LM, et al. 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;33(8):1125-36.

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

56. Tiller K, Meiser B, Gaff C, et al. A randomized controlled trial of a decision aid for women at increased risk of ovarian cancer. Med Decis Making. 2006;26(4):360-72.

57. Armstrong K, Weber B, Ubel PA, et al. Individualized survival curves improve satisfaction with cancer risk management decisions in women with BRCA1/2 mutations. J Clin Oncol. 2005;23(36):9319-28.

58. van Roosmalen MS, Stalmeier PF, Verhoef LC, 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;22(16):3293-301.

59. 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;18(6):578-97.

60. 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.

61. Anderson K, Jacobson JS, Heitjan DF, et al. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. Ann Intern Med. 2006;144(6):397-406.

62. Norum J, Hagen AI, Maehle L, et al. 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;44(7):963-71.

63. Institute for Women's Health UK. UK Familial Ovarian Cancer Screening Study (UK FOCSS). Accessed: April 2010

http://www.instituteforwomenshealth.ucl.ac.uk/academic_research/gynaecologicalcancer/gcrc/ukfocss

64. National Cancer Institute (NCI). Gynecologic Oncology Group (GOG) 199. Accessed: April 2010; http://ovariancancer.gog199.cancer.gov/about.html.

65. 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) Accessed: April 2010; http://clinicaltrials.gov/ct2/show/NCT00098800.