Evidence Summary Report 4-4 [TO BE UPDATED]

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Management Options for Women with a Hereditary Predisposition to Ovarian Cancer

Gynecology Cancer Disease Site Group

This Evidence-based Series (EBS) was reviewed in November 2013 and the Gynecology Cancer Disease Site Group (DSG) made a decision to UPDATE IT on October 2, 2014. PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol). See Section 3: Document Summary and Review Tool for details.

The reviewed EBS report, which is available on the CCO web site (http://www.cancercare.on.ca), consists of the following three sections:

Section 1: Evidence Summary Report (TO BE UPDATED)
Section 2: Full Report (TO BE UPDATED)
Section 3: Document Summary and Review Tool

Release Date: October 2, 2014

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Evidence Summary Citation (Vancouver Style): Rosen B, Kwon J, Fung Kee Fung M, Gagliardi A; Cancer Care Ontario Surgical Oncology Network, Members of the Gynecology Cancer Disease Site Group. Management options for women with a hereditary predisposition to ovarian cancer. Rosen B, Poon R,
Guideline Report History

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Management Options for Women with a Hereditary Predisposition to Ovarian Cancer
Evidence Summary Report #4-4

B Rosen, J Kwon, M Fung Kee Fung, A Gagliardi of the Cancer Care Ontario Surgical Oncology Network, and members of the Gynecology Cancer Disease Site Group

Report Date: June 2004

The 2004 guideline recommendations

REQUIRE AN UPDATE

This means that the recommendations require additional evidence but are relevant for decision making.

ORIGINAL EVIDENCE SUMMARY: September 2, 2003
MOST RECENT LITERATURE SEARCH: June 2004
NEW EVIDENCE ADDED TO EVIDENCE SUMMARY: June 2004

New evidence found by update searches since completion of the original evidence summary is consistent with the original recommendations.

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline.

SUMMARY

Question
What are the management options for women with a hereditary predisposition to ovarian cancer? Outcomes of interest were incidence of ovarian cancer, life expectancy, complication rates, additional benefits of prophylactic oophorectomy and alternatives to prophylactic oophorectomy.

Target Population
This evidence summary applies to women with known BRCA1 or BRCA2 gene mutations.
Opinions of the Gynecology Cancer Disease Site Group

The lack of sufficient high quality evidence precludes definitive recommendations from being made. Instead, the Gynecology Cancer Disease Site Group offers the following opinions based on the evidence reviewed:

- Women with a personal or family history of ovarian cancer should be assessed for genetic counselling and testing (Appendix 1) 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.
- 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.
- Hormone replacement therapy (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.
- For BRCA1 mutation carriers who may be reluctant to have definitive prophylactic surgery, oral contraceptives and/or tubal ligation may reduce their risk of developing ovarian cancer.

Methods

Entries to MEDLINE (1966 through June 2004), EMBASE (1980 through week 25, 2004), CANCERLIT (1985 through October 2002), and Cochrane Library (2004, Issue 2) databases were systematically searched for evidence relevant to this evidence summary report.

Evidence was selected and reviewed by three members of the Practice Guidelines Initiative’s Gynecology Cancer Disease Site Group and methodologists. This evidence summary report has been reviewed and approved by two cancer geneticists and the Gynecology Cancer Disease Site Group, which comprises gynecologic oncologists, medical oncologists, radiation oncologists, an oncology nurse, a pathologist, and patient representatives.

External review by Ontario practitioners is obtained for all evidence summary reports through a mailed survey. Final approval of the evidence summary report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each evidence summary report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.

Key Evidence

- No randomized controlled trials have assessed the influence of oophorectomy on the incidence of ovarian cancer in women with a hereditary predisposition for ovarian cancer. There have been four cohort studies (two retrospective) that address the role of prophylactic oophorectomy in relation to prevention of ovarian cancer.
- The three cohort studies that included control groups concluded that women with BRCA1 or 2 mutations who had prophylactic oophorectomies had a decreased incidence of ovarian/peritoneal cancers compared to women with BRCA1 or 2 mutations who did not undergo surgery.
- For women with BRCA1 or 2 mutations undergoing prophylactic oophorectomy, the subsequent lifetime risk of developing peritoneal serous carcinoma ranged from 1.8% to 4%. For women with BRCA1 or 2 mutations who do not undergo prophylactic oophorectomy, the lifetime risk of developing ovarian cancer is 25% to 50%.
There have been no systematic attempts to quantify surgical complication rates from prophylactic oophorectomy (both laparotomy and laparoscopic procedures).

Adverse effects of prophylactic oophorectomy include the early onset of menopausal effects: increased risk of coronary heart disease and osteoporosis and decreased libido.

The most appropriate surgical procedure has not yet been defined (i.e. there is some controversy regarding the necessity of hysterectomy), although the minimal surgical procedure is bilateral salpingo-oophorectomy. Since fallopian tube cancer is associated with germ line BRCA1 and 2 mutations, the only way to remove the entire tube is to include hysterectomy as part of the surgical procedure.

**Treatment Alternatives**  
For women with confirmed BRCA1 or 2 mutations who choose not to undergo surgery, oral contraceptives or tubal ligation may have some beneficial effects in reducing the risk of ovarian cancer. Currently, there is a paucity of literature concluding that either of these treatments significantly reduces the risk of ovarian cancer; therefore, more research is required. Screening using CA125 and transvaginal ultrasound has been recommended by the National Institutes of Health, but this strategy has not yet been demonstrated to be effective at reliably identifying early ovarian cancers.

_For further information about this evidence summary report, please contact Dr. Michael Fung Kee Fung, Chair, Gynecology Cancer Disease Site Group, Ottawa Regional Cancer Centre, 501 Smyth Road, Ottawa ON, K1H 8L6; TEL 613-737-7700; FAX 613-247-3511._

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_Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care._

_Visit http://www.cancercare.on.ca/ for all additional Practice Guidelines Initiative reports._
PREAMBLE: About Our Evidence Summary Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. For example, the evidence comes from uncontrolled studies, from studies with control groups that are not relevant to current practice in Ontario, or from subgroup analyses, or the evidence consists solely of preliminary results from ongoing trials. The PEBC will monitor the scientific literature and will develop a practice guideline on this topic when more evidence becomes available.

This evidence summary report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of an evidence summary by the Coordinating Committee does not necessarily mean that the evidence summary has been adopted as a practice policy of CCO. The decision to adopt an evidence summary as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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FULL REPORT

I. QUESTION
What are the management options for women with a hereditary predisposition to ovarian cancer? Outcomes of interest were incidence of ovarian cancer, life expectancy, complication rates, additional benefits of prophylactic oophorectomy, and alternatives to prophylactic oophorectomy.

II. CHOICE OF TOPIC AND RATIONALE
Kerlikowske and Ponder detected a high lifetime risk of ovarian cancer in women with two first-degree relatives with ovarian or breast cancer (1,2). This subgroup was later identified as women with BRCA1 and 2 germ line mutations. These mutations have been identified as the genetic links to the increased lifetime risk of ovarian cancer (Table 1) (3). BRCA1 mutation carriers have an estimated 40 to 50% lifetime risk of ovarian cancer. BRCA2 mutation carriers have an estimated 25% lifetime risk of ovarian cancer (4,5). Approximately 10% of ovarian cancer cases can be attributed to the inheritance of a BRCA1 or 2 mutation (6,7). Due to the high mortality rate and the absence of effective screening, prophylactic oophorectomy has been advocated as a preventive approach for ovarian cancer (8-13). In 1995, the National Institutes of Health (NIH) published a consensus statement recommending prophylactic oophorectomy after age 35 in women with a significant family history of ovarian cancer (9). This statement did not specify either the surgical approach (laparoscopy versus laparotomy) or whether the procedure should include a hysterectomy along with the oophorectomy.

Table 1. Rates of ovarian cancer according to gene mutations BRCA1 or BRCA2 (3).

<table>
<thead>
<tr>
<th>Gene Mutation</th>
<th>All cases of invasive ovarian cancer</th>
<th>All cases of serous ovarian cancer</th>
<th>Inherited cases</th>
<th>Risk to age 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mutation</td>
<td>88%</td>
<td>84%</td>
<td>NA</td>
<td>1.4%</td>
</tr>
<tr>
<td>BRCA1</td>
<td>7%</td>
<td>9.5%</td>
<td>60%</td>
<td>20-40%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>5%</td>
<td>6.5%</td>
<td>40%</td>
<td>10-25%</td>
</tr>
</tbody>
</table>

Note: NA, not applicable

Women with a diagnosis of ovarian cancer who have serous histology have been found to have a 16% risk of carrying a BRCA mutation (3) or 14% chance of fallopian tube cancer (14). Those at risk are eligible for genetic testing, which is available at regional cancer centres across Ontario. The Ontario Genetics Network, a collaborative group comprising geneticists, oncologists, genetic counsellors, psychologists, and Ministry of Health personnel, have developed guidelines for genetic testing (Appendix 1).

This evidence summary will present the current literature surrounding the management options for women with a hereditary predisposition to ovarian cancer.

III. METHODS
Evidence Summary Development
This evidence summary report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC) using methods of the Practice Guidelines Development Cycle (15). Evidence was selected and reviewed by three members of the PGI’s Gynecology Cancer Disease Site Group (Gynecology Cancer DSG) and
methodologists. Members of the Gynecology Cancer DSG disclosed potential conflict of interest information.

The evidence summary report is a convenient and up-to-date source of the best available evidence on prophylactic oophorectomy developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. In contrast to the practice guidelines, the body of evidence in an evidence summary is less mature and is comprised of data primarily from non-randomized controlled trial data or data available only in abstract form. This precludes the development of definitive recommendations and instead, opinions of the DSG are offered. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all evidence summary reports through a mailed survey consisting of items that address the quality of the evidence summary report, the interpretation of the available evidence, and whether there is a need to develop an evidence-based practice guideline when sufficient evidence is available. Final approval of the original evidence summary is obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each evidence summary report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.

**Literature Search Strategy**

MEDLINE (1966 through December 2002), CANCERLIT (1985 through October 2002) and Cochrane Library (2002, Issue 4) databases were searched. “Ovariectomy” (Medical subject heading (MeSH)) and “oophorectomy” (MeSH) were combined with “ovarian neoplasms” (MeSH), “prophylactic” (MeSH) and “elective” (MeSH). These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, controlled clinical trials, case series, and cohort studies.

**Update**

The original literature search has been updated using MEDLINE (through June 2004), EMBASE (through week 25, 2004), and the Cochrane Library (2004 Issue 2) and the 2004 proceedings of the annual meeting of the American Society of Clinical Oncology.

**Inclusion Criteria**

Articles were selected for inclusion in this systematic review of the evidence if they met one of the following criteria:

- Randomized controlled trials or meta-analyses comparing elective or prophylactic oophorectomy to another strategy for the prevention of ovarian cancer in women with confirmed BRCA1 or 2 mutations.
- Phase II trials, cohort studies, or case series examining the outcome of prophylactic oophorectomy in women with confirmed BRCA1 or 2 mutations.

**Exclusion Criteria**

- Abstracts, letters, and editorials.
- Papers published in a language other than English.

**Synthesizing the Evidence**

The results of the cohort studies cannot be pooled due to the heterogeneity of the studies. The studies varied according to the demographics of participants (i.e. age restrictions), the
outcomes measured, and study designs. Thus, the Gynecology Cancer DSG decided to present the results of each cohort study individually.

IV. RESULTS

Literature Search Results
There are no randomized controlled trials comparing prophylactic oophorectomy to no surgery in women with confirmed BRCA1 or 2 mutations. However, there were four cohort studies (two retrospective) that examined the outcome of prophylactic oophorectomy in women with a significant family history (16) or confirmed BRCA1 or 2 mutations (17-19). Three of the cohort studies (one retrospective) compared prophylactic oophorectomy to observation in women with germ line BRCA mutations and subsequently compared rates of developing ovarian and peritoneal cancers (17,18,20). The other cohort study reviewed cases of familial ovarian cancer entered on a familial ovarian cancer registry over a period of ten years (19).

Update
One retrospective study was identified that met the inclusion criteria since the original evidence summary was completed. The study reviewed the clinical outcomes of women with a hereditary predisposition to ovarian cancer who had undergone bilateral prophylactic oophorectomies (1u).

Evidence That Prophylactic Oophorectomy Protects Against Ovarian Cancer
All four cohort studies examining the outcome of prophylactic oophorectomy on the incidence of ovarian cancer determined that prophylactic oophorectomy has a protective effect (17-20). Table 2 outlines the studies that are included in the evidence summary that compared patients who underwent prophylactic oophorectomy with a control group.
Table 2. Outline of the studies included in the evidence summary that compared patients who underwent prophylactic oophorectomy with a control group.

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Type of Study</td>
<td>Prospective follow-up</td>
<td>Retrospective</td>
<td>Prospective follow-up</td>
</tr>
<tr>
<td>Age of patients</td>
<td>&gt; 35 years old</td>
<td>No age restrictions</td>
<td>NR</td>
</tr>
<tr>
<td># patients with BRCA1 or 2 mutations</td>
<td>170</td>
<td>551</td>
<td>390</td>
</tr>
<tr>
<td># patients undergoing PO</td>
<td>98</td>
<td>259</td>
<td>44</td>
</tr>
<tr>
<td># patients in control group</td>
<td>72 with mutations but chose not to undergo PO</td>
<td>292 matched according to age (within 5 years), BRCA1 or 2 status, location</td>
<td>346 first degree relatives of oophorectomized women</td>
</tr>
</tbody>
</table>

**Outcomes**

<table>
<thead>
<tr>
<th>Incidence of cancer among PO group</th>
<th>1 peritoneal 3 breast</th>
<th>6 ovarian (diagnosed at time of surgery) 2 peritoneal</th>
<th>2 peritoneal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of cancer among control group</td>
<td>4 ovarian 1 peritoneal 8 breast</td>
<td>58 ovarian/peritoneal</td>
<td>8 ovarian</td>
</tr>
<tr>
<td>Mean follow-up</td>
<td>24.2 months</td>
<td>8.2 years for PO 8.8 years for control</td>
<td>NR</td>
</tr>
<tr>
<td>Outcomes measured</td>
<td>Disease-free survival: 98% PO group 83% control group p=0.04</td>
<td>Incidence of BRCA1 or 2 related cancers in follow-up: 0.8% for PO 19.9% for control group p &lt; 0.001</td>
<td>Women who underwent PO had a lifetime risk developing ovarian 13 times greater than the general population, women who in control group had 24 times the lifetime risk</td>
</tr>
</tbody>
</table>

Note: NR, not reported; PO, prophylactic oophorectomy

The results of the cohort studies could not be pooled because the patient populations varied, and they did not measure the same outcomes. Kauff et al (17) put a restriction on the age of participants (older than 35 years), while the other studies did not restrict age (18,20).

The data from Struwing et al's (18) study suggest a 50% reduction in the incidence of ovarian cancer. It is important to note, however, that these results are not statistically significant due to the small sample size. In their study, there were 44 women in the prophylactic oophorectomy group versus 346 women in the control group. Both Kauff et al (17) and Rebbeck et al (20) had more evenly matched intervention groups. However, in the study by Kauff et al, participants were given the choice between prophylactic oophorectomy and surveillance. More women in the prophylactic oophorectomy group had had bilateral mastectomies prior to the study (p=0.02).

The fourth study included in the evidence summary reviewed the incidence of ovarian cancer reported on a familial ovarian cancer registry over a ten year period (19). Piver et al reviewed 324 cases of women with a history of familial ovarian cancer (two or more 1st or 2nd degree relatives with ovarian cancer) who underwent prophylactic oophorectomy (19). Six women developed primary peritoneal carcinoma (1.9%); however, there was no comparison to women with similar family histories who did not have prophylactic oophorectomy. The assumption...
is that the risk reduction of ovarian cancer conferred by prophylactic oophorectomy exceeds the risk of primary peritoneal carcinoma. That is, it is supposed that there is less risk of developing peritoneal carcinoma after oophorectomy than there is of developing ovarian cancer without oophorectomy.

Based on the evidence from the four cohort studies, prophylactic oophorectomy seems to be protective against development of ovarian cancer. The decreased incidence of ovarian cancer after prophylactic oophorectomy reported by Rebbeck et al (20) and Kauff et al (17) is clinically important because this procedure appears to prevent a cancer that in general has a high mortality rate.

**Update**

The retrospective study by Olivier et al (1u) compared the clinical outcomes of 38 women who underwent prophylactic bilateral oophorectomy (PBO group) to 90 women who underwent prophylactic bilateral salpingo-oophorectomy (PBSO group). Women were included in the study if they were confirmed BRCA1 or 2 carriers, or if they had previous breast cancer from a hereditary breast-ovarian cancer family. The majority of the women included in the trial had previous breast cancer (74% in PBO group, and 61% in PBSO group). During surgery there were no occult cancers found in the PBO group, and five cases of ovarian cancer were found in the PBSO group. All the women who had cancer detected were BRCA1 mutation carriers. Three of the cancers were stage I, one was stage III, and one cancer was detected at stage IV.

The mean follow-up of the women undergoing bilateral oophorectomy was 45 months (24.1-93.1) and the mean follow-up of the women undergoing bilateral salpingo-oophorectomy was 12 months (0.5-65.5). Among the women in the PSO group, three cases of stage III peritoneal papillary serous carcinoma (PPSC) were detected. All three women with cancer detected were BRCA1 mutation carriers. There were no additional cases of cancer detected during follow-up in the women in the PBSO group, however, the mean follow-up for this group was substantially less than the follow-up for women in the PSO group.

**Life Expectancy Following Prophylactic Oophorectomy**

Three decision analyses have examined life expectancy through the use of Markov modelling based on the probability of ovarian cancer in women with a genetic predisposition and in women without such predisposition (8,16,21). All three analyses detected similar results. One decision analyses determined that a 30-year-old BRCA1 or 2 carrier would gain an additional 0.3 to 1.7 years in life expectancy following prophylactic oophorectomy and that prophylactic oophorectomy could be delayed for 10 years with little loss in life expectancy (8). The second decision analysis detected that prophylactic oophorectomy would contribute an additional 0.4 to 2.6 years of life expectancy to high-risk women and that prophylactic oophorectomy plus prophylactic mastectomy would improve survival by 3.3 to 6.0 years compared with surveillance-alone (16). This decision analysis also reported quality-adjusted life years (QALY), a value which takes into account the negative features of prophylactic oophorectomy as perceived by the women undergoing the procedure. The QALYs saved were 0.5 for prophylactic oophorectomy and 1.9 for the combined procedure in high-risk women. The third decision analysis found that there was prolongation in quality-adjusted life expectancy for those undergoing prophylactic oophorectomy with or without prophylactic mastectomy, and this advantage was greatest before the age of 40 (21).

**Complications of the Prophylactic Oophorectomy Procedure**

An Ontario hospital-based study (22) evaluated 41 institutions where prophylactic oophorectomies were performed. Surgical complications were reported in 15.7% of patients, including bleeding, injury to pelvic organs, and infection. However, on review of these complications, only 50% of these were arguably significant (injury to bowel or bladder, reoperation required, blood loss necessitating transfusion). Most of these procedures had been
done by laparotomy. There is an increasing trend toward using laparoscopy for various gynecologic procedures including prophylactic oophorectomy. The risk of complications with laparoscopy are well recognized with overall complication rates in the range of 0.22-4.0% (17,23,24). From the Canadian Institute of Health Information database (CIHI), a retrospective review of laparoscopic complication rates in Ontario from 1992 to 1999 revealed a total of 213,150 operative laparoscopies (25). The rate of major hemorrhage was 7/100,000, visceral or vessel injury, 7/1000, and postoperative fistula, 8/100,000. Therefore, serious and potentially fatal complications from operative laparoscopy appear to be rare (25).

**Long-term Adverse Effects of Prophylactic Oophorectomy**

Prophylactic oophorectomy can lead to some long-term adverse effects, mainly the early onset of menopause (6). There are some known risks associated with menopause, including adverse changes in lipid profile (26), a two-fold increase in coronary heart disease (27), and an increased incidence of osteoporosis (28). A cohort of 101 premenopausal women undergoing hysterectomy and bilateral salpingo-oophorectomy experienced a higher rate of decreased libido and sexual satisfaction compared with women undergoing hysterectomy alone, as assessed by a questionnaire (29).

The Society of Obstetricians and Gynaecologists of Canada (SOGC) recently published revisions to the Canadian Consensus on menopause and osteoporosis (30) in light of the recent findings in the Women's Health Initiative (WHI) study (31) that evaluated the long-term benefits and risks of hormone replacement therapy (HRT) among healthy postmenopausal women. The SOGC concluded that HRT should not be recommended for the sole purpose of preventing future cardiovascular events; however, it remains the best treatment for distressing menopausal symptoms and therefore, a short term trial of HRT may be indicated to relieve these symptoms. According to the WHI study, the use of estrogen-progestin treatment increases the lifetime risk of breast cancer after five years of use, but this increase is not statistically significant (an additional eight cases per 10,000 women per year). The lifetime risk returns to baseline at five years after discontinuing HRT (31). Since women who have undergone hysterectomies require estrogen (without progestin) treatment, it is important to note that the WHI’s study on the use of estrogen-only treatment is still ongoing, and the results of that study are not yet known (31).

**Surgical Options**

The optimal type of prophylactic surgery has not been determined. There is controversy in the medical community regarding which medical procedures should be performed. There is one prospective cohort study (32) and one case series (33) that suggest that the minimal procedure is bilateral salpingo-oophorectomy. Their argument for salpingectomy in addition to oophorectomy is the identification of occult ovarian or fallopian tube carcinoma in a significant percentage of patients undergoing prophylactic oophorectomy. Colgan et al’s prospective study (32) detected two cases of occult fallopian tube cancer and three cases of ovarian cancer in 27 women with BRCA1 mutations undergoing prophylactic bilateral salpingo-oophorectomy. This represents an occult malignancy rate of 18.5%. In the case series by Paley et al (33), two BRCA1 positive patients underwent prophylactic oophorectomy, and both were diagnosed as having occult fallopian tube carcinoma (33).

Another prospective cohort study by Colgan et al (34) examined the utility of peritoneal lavage for cytology during prophylactic oophorectomy. Of the 35 women who underwent peritoneal lavage at the time of prophylactic surgery, three had malignant cells on cytology, one had malignant cytology with no histopathologic evidence of carcinoma in the ovaries or fallopian tubes, and another had only adenocarcinoma-in-situ of the fallopian tube (34). In Paley et al’s case series (33), they also reported malignant cells in peritoneal lavage specimens from a patient with adenocarcinoma-in-situ of the fallopian tube. The presence of malignant cells in peritoneal
lavage, while not necessarily indicative of an undetected invasive malignancy, may assist in detection of occult malignancy.

Several cohort studies have attempted to determine the role of bilateral salpingo-oophorectomy at the time of hysterectomy (35-37); however, only one retrospective study by Piver et al (19) commented on whether hysterectomy should be performed at the time of bilateral salpingo-oophorectomy. Piver et al concluded that only an oophorectomy is necessary. They recommended cytologic washings and complete evaluation of the abdomen and pelvis laparoscopically (19). At this time, there does not appear to be an increased risk of endometrial cancer in women with BRCA1 or 2 mutations (38,39). The rationale for concurrent hysterectomy would be the assurance of complete resection of the fallopian tube and simplification of HRT. However, the risks of hysterectomy are also well recognized--there is a higher rate of infections, vault hematomas, and blood loss (40,41).

**Additional Benefits**

Women with BRCA1 and 2 germ line mutations are at an increased lifetime risk of developing breast cancer in addition to ovarian cancer. Both Rebbeck et al (42) and Kauff et al (17) determined that prophylactic surgery was protective against future development of breast cancer in women with BRCA1 and 2 mutations, which is consistent with earlier reports from Struewing et al (18). Rebbeck et al (42) reported the relative risk of breast cancer to be 0.47 (95%CI 0.29-0.77) for those undergoing prophylactic oophorectomy. While not statistically significant, Kauff et al (17) determined that the projected proportion of women who will be free of breast cancer or BRCA-related gynecologic cancer five years from the time of surgery or the beginning of surveillance is 94% in the prophylactic oophorectomy group and 69% in the surveillance group (p=0.07). Rebbeck et al concluded that the use of HRT did not negate the reduction in breast cancer risk after surgery.

Another benefit of prophylactic oophorectomy is the detection of early disease. In Rebbeck et al’s (20) review, six of 259 women with BRCA1 or 2 mutations had stage I ovarian cancer detected at time of surgery. Identifying malignancies at an early stage results in the greater potential for cure. There is evidence that BRCA1 mutation carriers with ovarian cancer have a longer survival and potentially respond better to chemotherapy than non-carriers (43,44). Therefore prophylactic surgery has the potential to prevent death from ovarian cancer through prevention or early detection of cancer in women who are BRCA mutation carriers.

**Alternatives to Prophylactic Oophorectomy**

*Oral contraceptives*

The lifetime risk reduction in ovarian cancer in women with BRCA1 or 2 mutations who have used oral contraceptives is addressed in two case-control studies. Narod et al (45) reported a significant risk reduction of 60% in women with BRCA1 or 2 mutations for over six years of oral contraceptive use. In contrast, Modan et al’s (46) population-based case-control study did not find a risk reduction among pill users in their study in Israel. However, a small number of women in their cohort were long-term pill users, and the confidence limits they reported were wide.

*Tubal ligation*

Tubal ligation has been associated with a decrease in the risk of ovarian cancer among women in the general population. There is no clear reason for this association (47,48). One case-control study addressed the risk of ovarian cancer after tubal ligation in women with BRCA1 mutations. Narod et al (49) reported that among 232 BRCA1 mutation carriers, tubal ligation was associated with an odds ratio of 0.39 (95% confidence interval 0.22-0.70) for ovarian cancer. The combination of tubal ligation and past use of an oral contraceptive was associated with an odds ratio of 0.28 (95% confidence interval 0.15-0.52). No protective effect of tubal ligation was detected in carriers of BRCA2 mutations.
**Perceptions of Women with Confirmed BRCA1 or 2 Mutations**

Tiller et al (50) performed psychological testing on a group of women with confirmed BRCA1 or 2 mutations choosing prophylactic surgery and compared those results to a group choosing observation. They reported that cancer anxiety was significantly reduced in those undergoing surgery. Eighty-six percent also reported a high degree of satisfaction with the surgical procedure, suggesting that prophylactic oophorectomy is well accepted by those women with a hereditary lifetime risk.

**V. ONGOING TRIALS**

The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/clinicaltrials) was searched for reports of new or ongoing trials. No clinical trials involving prophylactic oophorectomy alone were identified.

**VI. INTERPRETIVE SUMMARY**

There are no randomized controlled studies comparing prophylactic oophorectomy to no surgery in women with germ line BRCA1 and 2 mutations. However, three cohort studies (one retrospective) have identified a risk reduction with prophylactic oophorectomy by comparing the incidence of ovarian cancer in the control group to the incidence of primary peritoneal carcinoma in the prophylactic oophorectomy group. There is a significant lifetime risk reduction of developing ovarian cancer and a low probability of peritoneal cancer in those undergoing surgery.

Complications associated with prophylactic surgery are estimated in the range of 15% based on a provincial hospital chart survey, although the risk of major complications comprises less than half of all complications reported. While it may not be possible to extrapolate information from CIHI to the setting of prophylactic surgery, it appears that the rate of injury resulting from operative laparoscopy in Ontario is exceedingly low. Other complications resulting from prophylactic surgery are related to menopause: change in lipid profile, decreased bone density, increase in coronary artery disease, as well as urogenital symptoms such as decrease in libido and sexual satisfaction.

The optimal surgical procedure for prophylaxis is not well defined. The minimal procedure should be a bilateral salpingo-oophorectomy. There appears to be a risk of occult ovarian or fallopian tube malignancy in a small percentage of patients undergoing prophylactic surgery. The rate of occult malignancy has been reported to be as high as 18.5% in BRCA-mutation carriers undergoing this procedure. For this reason, a detailed pathologic examination of prophylactic specimens is necessary. It is strongly encouraged that the surgeon and pathologist directly communicate about these cases to ensure appropriate pathologic examination. The benefit of identifying these occult malignancies as a result of prophylactic surgery may be the greater potential for cure because of diagnosis at an early stage. In addition to this, BRCA-mutation carriers with ovarian cancer appear to have a more favourable prognosis than non-carriers.

There may be alternatives to surgery in reducing the risk of ovarian cancer in women with BRCA1 or 2 mutations, such as oral contraceptives and tubal ligation.

**VII. EXTERNAL REVIEW OF THE EVIDENCE SUMMARY REPORT**

This section describes the external review activities undertaken for the original evidence summary report.

**Practitioner Feedback**

Based on the evidence contained in the original report, feedback was sought from Ontario clinicians.
Methods
Practitioner feedback was obtained through a mailed survey of 70 practitioners in Ontario (40 medical oncologists, 18 surgeons, and 12 gynecologists). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on February 14, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gynecology Cancer DSG reviewed the results of the survey.

Results
Thirty-one responses were received out of the 70 surveys sent (44% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 19 indicated that the report was relevant to their clinical practice and completed the survey. Results of the survey are summarized in Table 3.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing an evidence summary, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>19 (100%) 0 0</td>
</tr>
<tr>
<td>There is a need for an evidence summary on this topic.</td>
<td>18 (95%) 1 (5%) 0</td>
</tr>
<tr>
<td>The literature search is relevant and complete in this evidence summary.</td>
<td>16 (84%) 3 (16%) 0</td>
</tr>
<tr>
<td>I agree with the methodology used to summarize the evidence.</td>
<td>19 (100%) 0 0</td>
</tr>
<tr>
<td>I agree with the overall interpretation of the evidence in the evidence summary.</td>
<td>18 (100%) 0 0</td>
</tr>
<tr>
<td>The Opinions of the Disease Site Group section of this evidence summary is useful.</td>
<td>19 (100%) 0 0</td>
</tr>
<tr>
<td>An evidence summary of this type will be useful for clinical decision making.</td>
<td>19 (100%) 0 0</td>
</tr>
<tr>
<td>At present, there is insufficient evidence to develop a practice guideline on this topic.</td>
<td>8 (42%) 6 (32%) 5 (26%)</td>
</tr>
<tr>
<td>There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.</td>
<td>12 (75%) 3 (19%) 1 (6%)</td>
</tr>
</tbody>
</table>

Summary of Written Comments
Five respondents (26%) provided written comments. There were no suggestions to modify the current evidence summary. The overall feedback was positive. Two respondents commented that due to the lack of high quality evidence regarding the management of women with a hereditary risk for ovarian cancer that coherent opinions are necessary and appreciated. Other respondents indicated that the evidence summary was well done.

Practice Guidelines Coordinating Committee Approval Process
The evidence summary report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eleven of 15 members of the PGCC
returned ballots. Nine members approved the report as written. One member approved the report with modifications that are required to the report and one member approved the report and offered a suggestion for consideration by the Gynecology Cancer DSG.

**Modifications/Actions**

One PGCC member thought that the Gynecology Cancer DSG should provide reasons why tubal ligation would be considered as a potential risk reduction strategy for women with BRCA1 mutations. One member suggested that the bullet regarding genetic counselling in Opinions of the DSG section be clarified.

The Gynecology Cancer DSG reviewed the comments from the PGCC and revised the evidence summary accordingly. Firstly, there are no clear answers why tubal ligation seems to decrease the risk of ovarian cancer. This statement was added to the paragraph on tubal ligation. Also, the bullet in the Opinions section was clarified as per the suggestion of a PGCC member.

**VIII. OPINIONS OF THE GYNECOLOGIC CANCER DISEASE SITE GROUP**

The lack of sufficient high quality evidence precludes definitive recommendations from being made. Instead, the Gynecology Cancer DSG offers the following opinions based on the evidence reviewed:

- Women with a personal or family history of ovarian cancer should be assessed for genetic counselling and testing (Appendix 1) 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.
- For women choosing prophylactic oophorectomy, 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.
- Hormone replacement therapy (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.
- For BRCA1 mutation carriers who may be reluctant to have definitive prophylactic surgery, oral contraceptives and/or tubal ligation may reduce their risk of developing ovarian cancer.

**IX. JOURNAL REFERENCE**


**X. ACKNOWLEDGMENTS**

The Gynecology Cancer DSG would like to thank Dr Barry Rosen, Dr Janice Kwon, Dr Michael Fung Kee Fung, Ms Alexandra Chambers, and Ms. Anna Gagliardi of the Cancer Care Ontario Surgical Oncology Network for taking the lead in drafting and revising this evidence summary report.

For a complete list of the Gynecology Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO Web site at: http://www.cancer care.on.ca/access_PEBC.htm
REFERENCES


Update

APPENDIX 1

The guidelines for genetic testing are as follows (Ontario Genetics Network Criteria for Genetic Testing): Please note that breast cancer means invasive breast cancer and ovarian cancer means invasive epithelial ovarian cancer.

One cancer:
(1) Ashkenazi Jewish and breast cancer < 50 years, or ovarian cancer at any age (testing is limited to ethnic specific mutations)
(2) Breast cancer < 35 years of age
(3) Male breast cancer (testing limited to BRCA2)
(4) Invasive papillary serous carcinoma (fallopian tube or ovary)

Two cases of cancer on the same side of the family:
(1) Breast cancer < 60 years, and a 1st or 2nd degree relative with ovarian cancer or male breast cancer
(2) Breast and ovarian cancer in the same individual, or bilateral breast cancer with the 1st case < 50 years
(3) Two cases of breast cancer, both < 50 years, in 1st or 2nd degree relatives
(4) Two cases of ovarian cancer, any age, in 1st or 2nd degree relatives
(5) Ashkenazi Jewish and breast cancer at any age, and any family history of breast / ovarian cancer (testing is limited to ethnic specific mutations unless the individual meets other criteria).

Three or more cases of breast or ovarian cancer on the same side of the family, at any age, is a pattern suggestive of an inherited form of breast/ovarian cancers.
Evidence Summary Report 4-4: Section 2

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Management Options for Women with a Hereditary Predisposition to Ovarian Cancer

Guideline Review Summary

B. Rosen, R. Poon, and the Gynecology Cancer Disease Site Group

Review Date: October 2, 2014

<table>
<thead>
<tr>
<th>The 2004 guideline recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>REQUIRE AN UPDATE</td>
</tr>
<tr>
<td>This means that the recommendations require additional evidence but are relevant for decision making.</td>
</tr>
</tbody>
</table>

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario’s Program in Evidence-based Care in 2004. In November 2013, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert reviewed and interpreted the new eligible evidence and proposed the existing recommendations are to be updated. The recommendations and the systematic review in this version are the same as the version released in June 2004.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

What are the management options for women with a hereditary predisposition to ovarian cancer? Outcomes of interest were incidence of ovarian cancer, life expectancy, complication rates, additional benefits of prophylactic oophorectomy, and alternatives to prophylactic oophorectomy.
Literature Search and New Evidence

The new search (June 2004 to November 25, 2013) yielded 3 prospective cohort studies, 1 historic cohort study and 1 cross-sectional study. A supplementary search for ongoing studies on clinicaltrials.gov yielded 1 potentially relevant ongoing trial. In addition, 1 prospective cohort study (Finch et al., 2014) was identified by the clinical expert and included in the new evidence. Brief results of these publications are shown in the Document Summary and Review Tool.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations. However, there needs to be an added discussion on the fallopian tube being the site of origin for high grade serous carcinoma and the new evidence supporting the appropriate procedure. The optimal age for prophylactic surgery should also be discussed along with new issue surrounding the risks and benefits of salpingectomy as an alternative to salpingo-oophorectomy among BRCA mutation carriers. Lastly, breast cancer risk related to bilateral salpingo-oophorectomy needs to be discussed in greater detail. Hence, the Gynecology Cancer DSG decided to update the 2004 recommendations on the management options for women with a hereditary predisposition to ovarian cancer.

Document Summary and Review Tool

<table>
<thead>
<tr>
<th>Number and title of document under review</th>
<th>#4-4 Management Options for Women with a Hereditary Predisposition to Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Report Date</td>
<td>June 2004</td>
</tr>
<tr>
<td>Clinical Expert</td>
<td>Dr. Barry Rosen</td>
</tr>
<tr>
<td>Research Coordinator</td>
<td>Raymond Poon</td>
</tr>
<tr>
<td>Assessment Date</td>
<td>November 2013</td>
</tr>
<tr>
<td>Approval Date and Review Outcome (once completed)</td>
<td>October 2, 2014</td>
</tr>
</tbody>
</table>

Original Question(s):
What are the management options for women with a hereditary predisposition to ovarian cancer? Outcomes of interest were incidence of ovarian cancer, life expectancy, complication rates, additional benefits of prophylactic oophorectomy, and alternatives to prophylactic oophorectomy.

Target Population:
This evidence summary applies to women with known BRCA1 or BRCA2 gene mutations.

Study Section Criteria:

Inclusion Criteria
Articles were selected for inclusion in this systematic review of the evidence if they met one of the following criteria:
- Randomized controlled trials or meta-analyses comparing elective or prophylactic oophorectomy to another strategy for the prevention of ovarian cancer in women with confirmed BRCA1 or 2 mutations.
- Phase II trials, cohort studies, or case series examining the outcome of prophylactic oophorectomy in women with confirmed BRCA1 or 2 mutations.

Exclusion Criteria
- Abstracts, letters, and editorials.
- Papers published in a language other than English.
Search Details:
June 2004 to November 25, 2013 (Medline, Embase, the Cochrane Library, ASCO, and clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:
Of 73 total hits from Medline and Embase + 94 hits from ASCO + 1 hit from clinicaltrials.gov + 3 hits from the Cochrane Library, 5 references representing 3 prospective cohort studies, 1 historic cohort study and 1 cross-sectional study were found that met the inclusion criteria. There was 1 ongoing trial identified. In addition, 1 prospective cohort study (Finch et al., 2014) was identified by the clinical expert and included in the new evidence.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>N</th>
<th>Mean follow up</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>bilateral prophylactic salpingo-oophorectomy (BPSO) vs. control (non-BPSO)</td>
<td>Women with germline, disease-associated BRCA1 or BRCA2 mutations who were cancer-free at enrolment and did not have a cancer diagnosis within 6 months after enrolment and had no previous prophylactic surgery. Mean age=44.8 vs. 42.6 years</td>
<td>426</td>
<td>2.5 years</td>
<td>• Incidence of cancer</td>
<td>• Among women who had BPSO, 11 (7%) were diagnosed with breast cancer compared with 34 (13%) in the non-BPSO group. The difference was not significant. HR=0.36 (95% CI: 0.20-0.67; p=0.11). The incidence of ovarian or primary peritoneal cancer was significantly lower in women who underwent BPSO (2 women; 1%) than in those who did not (16 women; 6%). HR=0.11 (95% CI: 0.03-0.47; p=0.02).</td>
<td>Domchek et al., 2006</td>
</tr>
<tr>
<td>risk-reducing salpingo-oophorectomy (RRSO) vs. surveillance</td>
<td>Women (&gt;30 years) with a documented deleterious mutation in BRCA1 or BRCA2, at least one ovary in situ and no personal history of BRCA-associated gynecologic cancer before genetic testing. Median age=45.3 vs. 38.8 years</td>
<td>792</td>
<td>40.3 months</td>
<td>• Incidence of cancer</td>
<td>• Among women who underwent RRSO, 3 (0.6%) peritoneal cancers were diagnosed compared with 12 (4.2%) BRCA-associated gynecologic cancer diagnoses in the surveillance group. RRSO was significantly associated with an 88% reduction in BRCA-associated gynecologic cancer risk. HR=0.12 (95% CI: 0.03-0.41; p=0.001).</td>
<td>Kauff et al., 2008</td>
</tr>
<tr>
<td>prophylactic oophorectomy vs.</td>
<td>Women who had a BRCA1 or BRCA2 mutation and free of</td>
<td>1828 (1018 had a previous</td>
<td>3.5 years</td>
<td>• Incidence of cancer</td>
<td>• There were 32 cancers diagnosed among women with intact ovaries (29 ovarian, 2 fallopian tube, and 1 primary</td>
<td>Finch et al., 2006</td>
</tr>
</tbody>
</table>
no prophylactic oophorectomy ovarian cancer at the time of genetic testing. Women with a diagnosis of breast cancer prior to study entry were not excluded. Mean age=47.3 years diagnosis of breast cancer) peritoneal cancer). The observed incidence rate was 1015/100000 per year. Of the women who underwent prophylactic oophorectomy, 7 primary peritoneal cancers were diagnosed. The corresponding observed incidence rate was 217/100000 per year. The estimated cumulative incidence of peritoneal cancer is 4.3% at 20 years following oophorectomy. There was an 80% significant overall (adjusted) reduction in cancer risk associated with prophylactic oophorectomy. HR=0.20 (95% CI: 0.07-0.58; p=0.003).

prophylactic oophorectomy vs. no prophylactic oophorectomy

Women with a BRCA1 or BRCA2 mutation and free of ovarian, fallopian tube, or peritoneal cancer before baseline questionnaire (breast cancer was eligible). Mean age=46.0 years 5.6 years Incidence of cancer

Finch et al., 2014

Historic Cohort Studies

prophylactic bilateral salpingo-oophorectomy (PBSO) vs. surveillance (annual gynecological examination, transvaginal ultrasound, and serum CA125 measurement)

Women who are BRCA1/2 mutation carriers and no personal history of ovarian cancer. 152 2.4 vs. 2.6 years Incidence of cancer

Meeuwissen et al., 2005

Cross-sectional studies

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>N</th>
<th>Median follow up</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>prophylactic bilateral salpingo-oophorectomy (PBSO) vs. gynecologic screening (pelvic examination, transvaginal sonography, and CA-125)</td>
<td>Women from a hereditary breast or ovarian cancer family and without terminal cancer or any other severe medical comorbidity. Mean age=49 vs. 47 years</td>
<td>846 (368 with BRCA 1 or 2 mutations)</td>
<td>Not reported</td>
<td>QOL</td>
<td>There were no significant group differences in mean scores of the generic QOL (e.g. general health perceptions, vitality, role limitations caused by emotional problems, and general mental health). Additionally, the mean levels of intrusive thoughts about cancer were similar between the two groups (p=0.37). Women who underwent PBSO were associated with significantly fewer worries about ovarian cancer (p&lt;0.001), worries affected mood (&lt;0.001), worries</td>
<td>Madalinska et al., 2005</td>
</tr>
</tbody>
</table>
affected functioning (<0.01), and worries about other family members at risk (<0.05) compared with those in the gynecologic screening group. However, significantly more endocrine symptoms (p<0.001) and lower sexual functioning (<0.05) were reported in the PBSO group.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Official title</th>
<th>Status</th>
<th>Protocol ID</th>
<th>Estimated primary completion date</th>
<th>Last updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>radical fimbriectomy</td>
<td>Radical Fimbriectomy for Young BRCA Mutation Carriers at Risk of Pelvic Serous Carcinoma</td>
<td>Recruiting</td>
<td>NCT01608074</td>
<td>June 2016</td>
<td>August 19, 2013</td>
</tr>
</tbody>
</table>

**Abbreviations:** RCT=randomized clinical trial; QOL=quality of life; HR=hazard ratio; CI:confidence interval

**Clinical Expert Interest Declaration:**
None

**Instructions.** For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?  
   No

2. On initial review,
   a. Does the newly identified evidence support the existing recommendations?  
      a) Yes  
      b) No
   b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?  
   No

3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:  
   No
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?  

Yes

Review Outcome | UPDATE
---|---
DSG/GDG Approval Date | October 2, 2014
DSG/GDG Commentary | None

New References Identified (alphabetic order):

Literature Search Strategy:
Medline
1. exp ovarian neoplasms/
2. (ovar$ adj5 (neoplasm$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$)).tw.
3. 1 or 2
4. hereditar$.tw.
5. (gene$ adj5 mutation$).tw.
6. BRCA?.tw.
7. or/4-6
8. 3 and 7
9. (prophylactic or elective).tw.
10. exp ovariectomy/
11. exp oophorectomy/
12. ovariectom$.tw.
13. oophorectom$.tw.
14. or/10-13
15. 9 and 14
16. meta-analysis as topic/
17. meta analysis.pt.
18. (meta analy$ or metaanaly$).tw.
19. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthesis$ or quantitative overview).tw.
20. (systematic adj (review$ or overview?)).tw.
21. (exp Review Literature as topic/or review.pt or exp review/) and systematic.tw.
22. or/ 16-21
23. (cochrane or embase or psychlit or psyclin or psychinfo or psycinfo or cinahl or chinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
24. (reference list$ or bibliography$ or hand-search$ or relevant journals or manual search$).ab.
25. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
27. 25 or 26
28. review.pt.
29. 27 and 28
30. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
31. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
32. random allocation/ or double blind method/ or single blind method/
33. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
34. or/ 30-33
35. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
36. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
37. (clinic$ adj trial$1).tw.
38. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
39. placebos/
40. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
41. (allocated adj2 random).tw.
42. or/ 35-41
43. exp cohort studies/
44. cohort$.tw.
45. controlled clinical trial.pt.
46. epidemiologic methods/
47. (case$ and series).tw.
48. or/ 43-47
49. 22 or 23 or 24 or 29 or 34 or 42 or 48
50. 8 and 15
51. 49 and 50
52. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or abstract).pt.
53. 51 not 52
54. limit 53 to English
55. Animal/
56. Human/
57. 55 not 56
58. 54 not 57
59. (200406$ or 200407$ or 200408$ or 200409$ or 200410$ or 200411$ or 200412$ or 2005$ or
2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).ed.
60. 58 and 59

Embase
1. exp ovarian neoplasms/
2. (ovar$ adj5 (neoplasm$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$)).tw.
3. 1 or 2
4. hereditar$.tw.
5. (gene$ adj5 mutation$).tw.
6. BRCA?.tw.
7. Or/4-6
8. 3 and 7
9. (prophylactic or elective).tw.
10. exp ovariectomy/
11. exp oophorectomy/
12. ovariectom$.tw.
13. oophorectom$.tw.
14. or/10-13
15. 9 and 14
16. exp Meta Analysis/ or exp “Systematic Review”/
17. (meta analy$ or metaanaly$).tw.
18. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or
statistical summar$ or mathematical summar$ or quantitative synthe$ or quantitative
overview).tw.
19. (systematic adj (review$ or overview$)).tw.
20. exp “Review”/ or review.pt.
21. (systematic or selection criteria or data extraction or quality assessment or jadad scale or
methodological quality).ab.
22. (study adj selection).ab.
23. 20 and (21 or 22)
24. or/ 16-19, 23
25. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or chinhal or
science citation index or scisearch or bids or sigle or cancerlit).ab.
26. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
27. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
28. randomization / or single blind procedure/ or double blind procedure/
29. (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
30. or/ 27-29
31. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical
trial/
32. (clinic$ adj trial$1).tw.
33. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
34. placebo/
35. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
36. (allocated adj2 random).tw.
37. or/ 31-36
38. exp cohort analysis/
39. exp longitudinal study/
40. exp prospective study/
41. exp follow up/
42. exp retrospective study/
43. cohort$.tw.
44. exp case study/
45. (case$ and series).tw.
46. or/ 38-45
47. 24 or 25 or 26 or 30 or 37 or 46
48. 8 and 15
49. 47 and 48
50. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/
51. 49 not 50
52. limit 51 to English
53. Animal/
54. Human/
55. 53 not 54
56. 52 not 55
57. (200406$ or 200407$ or 200408$ or 200409$ or 200410$ or 200411$ or 200412$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).dd.
58. 56 and 57

Searched http://clinicaltrials.gov/ct2/search/advanced (clinicaltrials.gov) with keywords: “ovarian” AND “BRCA” AND “oophorectomy”. Filter was used to limit results to Phase 2-4 trials.

Searched http://www.ascopubs.org/search (ASCO) and http://onlinelibrary.wiley.com/cochranelibrary/search/ (the Cochrane Library) with keywords: “ovarian” AND “BRCA” AND “oophorectomy”.

OUTCOMES DEFINITION

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word “ARCHIVED”.

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY** – A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** – An update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.