Familial ovarian cancer

Laurie Elit, MD, MSC, FRCSC

abstract

OBJECTIVE To assist family physicians in evaluating patients’ risk for hereditary ovarian cancer and to review strategies for preventing ovarian cancer.

QUALITY OF EVIDENCE The MEDLINE, EMBASE, CANCERLIT, and CINAHL databases were searched from 1970 to 1999 using key words related to hereditary ovarian cancer, screening, oral contraceptives, prophylactic oophorectomy, cancer worriers, satisfaction, and perceived risk. Recommendations in this paper are based on evidence from case-control and cohort studies and, where appropriate, consensus conferences.

MAIN MESSAGE Of all women who present with ovarian cancer, 20% have a family history of ovarian cancer and 8% carry a BRCA1 or BRCA2 mutation. Women who carry a BRCA1 mutation have a 63% lifetime risk of developing ovarian cancer, and women who carry a BRCA2 mutation have a 27% lifetime risk of developing ovarian cancer. Preventive strategies include screening (level 3 evidence for postmenopausal women and level 5 evidence for women with a family history of ovarian cancer), use of oral contraceptives (level 3 evidence for the general population and for mutation carriers), and prophylactic oophorectomy (level 3 evidence in first-degree relatives of patients with breast or ovarian cancer).

CONCLUSION Women who have a family history of ovarian cancer should be offered genetic counseling and discussion of various preventive strategies for minimizing their risk.

This article has been peer reviewed.

Cet article a fait l’objet d’une évaluation externe.

Ovarian cancer affects one in 70 Canadian women. In 1999, 2600 women were diagnosed with ovarian cancer; in that same year, 1500 women died of ovarian cancer. Most women who develop ovarian cancer have sporadic or nonfamilial disease. Twenty percent of women with ovarian cancer have at least one family member with breast or ovarian cancer.

In a large prospective study of all Ontario ovarian cancer patients from 1994 to 1995, only 8% of women who developed ovarian cancer from 1994 to 1995 had a germ-line mutation in a cancer susceptibility gene, such as BRCA 1 or BRCA 2 (level 3 evidence). In this article, we will discuss hereditary ovarian cancer and strategies for decreasing risk in genetically susceptible women.

Family doctors have an important role in identifying patients at risk of ovarian cancer. Family physicians are one avenue through which patients can access counseling and risk assessment, receive genetic testing, and be offered opportunities for surveillance or prevention. Throughout the process of counseling and genetic testing, family doctors also help to clarify information on risk and provide psychosocial support for patients and for their families as they interpret and respond to test results.

**Quality of evidence**

A literature search was conducted from 1970 to 1999 using the following databases: MEDLINE, CANCERLIT, EMBASE, and CINAHL. Search terms used were related to hereditary ovarian cancer (family history of ovarian cancer, BRCA 1, BRCA 2, screening (ultrasound, cancer antigen 125 [CA125] tests), prevention (oral contraceptives and prophylactic oophorectomy [PO]), and psychosocial effect of the disease on patients and families (ie, cancer worriers, satisfaction, and perceived risk). The search was limited to English-language abstracts and articles. Articles were selected based on their clinical relevance and availability. In addition, I used bibliographies of the articles to identify additional relevant articles.

Reviewed articles were assessed according to strength of evidence using criteria outlined by Browman et al (Table 1). I also considered the opinions of respected authorities based on clinical experience, descriptive studies, and reports of expert committees as level 5 evidence.

**Table 1. Criteria for strength of evidence outlined by Browman et al**

<table>
<thead>
<tr>
<th>LEVEL OF EVIDENCE</th>
<th>TYPE OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Randomized controlled trials big enough to be positive, with small risk of false-positive conclusions, or negative, with small risk of false-negative conclusions, or meta-analyses</td>
</tr>
<tr>
<td>Level 2</td>
<td>Randomized controlled trials so small they show either positive trends that are not statistically significant, with much risk of false-positive conclusions, or no impressive trends but much risk of false-negative conclusions</td>
</tr>
<tr>
<td>Level 3</td>
<td>Formal comparisons with non-randomized contemporaneous controls, cohort or case-control studies, or well executed surveys</td>
</tr>
<tr>
<td>Level 4</td>
<td>Formal comparisons with historic controls</td>
</tr>
<tr>
<td>Level 5</td>
<td>Case series</td>
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</table>

Reprinted with permission from Browman et al.³

**Hereditary ovarian cancer**

Hereditary ovarian cancer refers to families with an autosomal dominant pattern of inheritance resulting in a high lifetime probability of cancer in predisposed women. When only one first-degree relative (ie, mother or daughter) is affected with ovarian cancer, risk of developing disease is 5% or 3.6 times normal. When two or more first-degree relatives are affected, the estimated risk increases to 30% (estimated odds ratio 3.1) (level 3 evidence); most women with two or more affected first-degree relatives have hereditary ovarian cancer.

On the basis of pedigree analysis, families with hereditary ovarian cancer can be divided into one of three syndromes: site-specific ovarian cancer, hereditary breast and ovarian cancer (HBOC), and hereditary nonpolyposis colorectal cancer (HNPCC).
Site-specific disease refers to families with three or more cases of invasive epithelial ovarian cancer at any age and no case of breast cancer occurring before the age of 50. Site-specific disease was thought to be due to single genes other than BRCA 1 or BRCA 2; but site-specific ovarian cancer is rare. In families in which clusters of ovarian cancers are reported, thorough analysis of the extended pedigrees with large numbers of potentially informative cases often show one of the other two syndromes.

Hereditary breast and ovarian cancer accounts for 90% of cases of hereditary ovarian cancer. Here, BRCA 1 mutations account for 50% to 70% of cases and BRCA 2 mutations for 15% to 25% of cases (level 3 evidence). Less than 1% of hereditary ovarian cancers are associated with HNPCC. Ovarian cancer in this scenario is associated with a family history of colon, endometrial, and other cancers that characterize Lynch syndrome type II.

BRCA 1 and BRCA 2 mutations

In 1990, BRCA 1 was the first important breast cancer susceptibility gene to be mapped. It is localized on chromosome 17. Mutations in BRCA 1 lead to the formation of truncated proteins, which are unable to maintain genomic integrity. The risk of ovarian cancer developing in a BRCA 1 mutation carrier is 63% by age 70.

In 1994, BRCA 2 was identified on chromosome 13. Members of high-risk families have a 27% risk of ovarian cancer by age 75. This risk is higher than the 1.4% risk of ovarian cancer in the general population. Most BRCA 2 ovarian cancer tumours occur after age 70.

Identical BRCA 1 or BRCA 2 mutations can appear in many families from the same geographic region or of the same ethnic group. This phenomenon is known as a “founder effect.” In these ethnic groups, higher proportions of high-risk families with breast or ovarian cancer can often be attributed to BRCA 1 mutations. Frequent BRCA 1 mutations have been reported in Russia (occurring in 79% of HBOC families, 5382insC and 4153delA mutation) and in Ashkenazi Jews (47% of HBOC families, 185delAG and 5382insC mutation). High proportions of high-risk families with HBOC are attributable to a single BRCA 2 mutation in Iceland (64% of HBOC families, 999del5 mutation). In populations where there is a founder effect, screening for the known founder effect gene mutation is an option.

Strategies for improving survival

Three management options might help prevent ovarian cancer: surveillance, ovulation suppression, and prophylactic oophorectomy. Surveillance can be conducted with transvaginal ultrasound or CA125 testing. It is hoped that screening will lead to identification of ovarian cancer at an early, curable stage. Oral contraceptives suppress ovulation and might reduce the risk of ovarian cancer. Prophylactic oophorectomy might prevent malignancy. At present, no clinical trial has been conducted to show that any of these strategies improves survival in the general population, in women with a family history of ovarian cancer or mutation, or in BRCA 1 or BRCA 2 carriers; current evidence is limited to observational data.

Screening. The goal of screening is to identify patients with preinvasive, or early stage, cancer for which treatment is effective. For ovarian cancer, a precancerous state has not been identified, but if disease can be identified when it is confined to the ovary (stage I), the 5-year survival rate is higher than 80%.

Screening tests must have high sensitivity (ie, test results are probably positive for patients with the disease) and very high specificity (ie, test results are probably negative for patients without the disease). The consequences of a positive screening test would be surgery. To minimize the number of women undergoing surgery for benign disease, the specificity of any test would need to be in the order of 99.6% to yield a positive predictive value of 10% (ie, 10 operations for each case of ovarian cancer identified).

Table 2 shows that current surveillance techniques, including transvaginal ultrasound, CA125 testing, and Doppler ultrasound, have moderate sensitivity, moderate to high specificity, and low positive predictive value (level 3 evidence). Combination testing with CA125 and ultrasound in postmenopausal women appears to provide the highest specificity (level 3 evidence).

Three randomized controlled trials are under way in the United States and Europe evaluating the effectiveness of combination testing to identify ovarian cancer at an early stage (Table 3). Results should be available in 2004.

The American College of Obstetrics and Gynecology has stated that screening for ovarian cancer using transvaginal ultrasound and CA125 is ineffective for the general population (level 3 evidence). However, recommends use of transvaginal ultrasound and CA125 for women with a documented family history of ovarian cancer who wish to maintain their reproductive capacity (level 5 evidence). The Cancer Genetics Studies Consortium also recommended...
transvaginal ultrasound and serum CA125 be used for carriers every 6 to 12 months beginning at age 25 to 35 (level 5 evidence). Transvaginal ultrasound should not be performed around the time of ovulation in order to reduce the frequency of false-positive results. One case series describes this screening strategy in mutation carriers.28

Preventive strategies

Oral contraceptives: Case-control studies, in which cases were women with ovarian cancer and control subjects were either from hospital populations or the general population, consistently show a 40% to 60% decrease in ovarian cancer risk among women who take birth control pills (level 3 evidence).29-31 The size of the protective effect increases with the duration of oral contraceptive use, and the benefit lasts for 10 to 15 years after oral contraceptives are discontinued.

Prophylactic oophorectomy: The decision to undergo PO depends on a woman’s level of concern about developing ovarian cancer, perceived consequences of prophylactic surgery, and the role of subsequent hormonal replacement. Women who carry BRCA 1 or BRCA 2 mutations are at risk of ovarian cancer. After prophylactic surgery, however, risk of developing primary peritoneal carcinomatosis (an epithelial malignancy of the peritoneal surface of the abdominal cavity) remains. From 2% to 11% of patients who have had prophylactic bilateral salpingo-oophorectomies develop primary peritoneal carcinomatosis (level 3 evidence). Questions raised by this study include timing of pill use, role of the pill in women older than 40 years, and effectiveness of old versus new preparations of oral contraceptives.

To address the role of oral contraceptives in BRCA 1 and BRCA 2 mutation carriers, a case-control study of 207 mutation carriers and 161 sister controls was performed.32 Each participant received a questionnaire, which addressed her history of oral contraceptive use. After adjusting for year of birth and parity, risk of ovarian cancer decreased with any use of the pill (odds ratio of 0.46 in BRCA 1 and 0.36 in BRCA 2)32 (level 3 evidence). Questions raised by this study include timing of pill use, role of the pill in women older than 40 years, and effectiveness of old versus new preparations of oral contraceptives.

Table 2. Screening for ovarian cancer

<table>
<thead>
<tr>
<th>DESCRIPTION OF STUDY</th>
<th>SPECIFICITY (%)</th>
<th>SENSITIVITY (%)</th>
<th>POSITIVE PREDICTIVE VALUE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAGINAL EXAMINATION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacobs et al15</td>
<td>97.3</td>
<td>If 100</td>
<td>Then 1.5</td>
</tr>
<tr>
<td>CANCER ANTIGEN 125 TEST (CA125)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receiver operating characteristic curve16</td>
<td>99.7</td>
<td>83</td>
<td>16</td>
</tr>
<tr>
<td>ULTRASOUND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal ultrasound in 5540 women17</td>
<td>94.6</td>
<td>Not reported</td>
<td>25.7</td>
</tr>
<tr>
<td>Morphology index in 8500 women18</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Doppler ultrasound in 1000 women19</td>
<td>95</td>
<td>96</td>
<td>10.5</td>
</tr>
<tr>
<td>MULTIMODAL SCREENING</td>
<td></td>
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<tr>
<td>Cancer antigen 125 test followed by ultrasound for abnormal CA125 in 5500 women20 (level 3 evidence)</td>
<td>97.6</td>
<td>Not reported</td>
<td>50</td>
</tr>
<tr>
<td>Cancer antigen 125 test and ultrasound if abnormal CA125 in 22000 postmenopausal women (level 3 evidence)</td>
<td>99.9</td>
<td>78.6</td>
<td>26.8</td>
</tr>
</tbody>
</table>

Table 3. Randomized controlled trials under way to address screening24

<table>
<thead>
<tr>
<th>DESCRIPTION OF STUDY</th>
<th>SPECIFICITY (%)</th>
<th>SENSITIVITY (%)</th>
<th>POSITIVE PREDICTIVE VALUE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institutes of Health prostate, lung, colorectal, and ovary study: 74 000 women older than 60 randomized to control or ultrasound and CA12523 (level 1 evidence)</td>
<td></td>
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<tr>
<td>St Bartholomew’s Hospital study: 120 000 postmenopausal women randomized to control or annual screen using CA125. The women are divided into risk groups based on CA125. Women would be followed up with CA125 or ultrasound depending on risk (level 1 evidence)</td>
<td>97.6</td>
<td>Not reported</td>
<td>50</td>
</tr>
<tr>
<td>European Multicentre Study: 120 000 postmenopausal women randomized to a control group or ultrasound every 1.5 years or ultrasound every 3 years (level 1 evidence)</td>
<td>97.6</td>
<td>83.6</td>
<td>26.8</td>
</tr>
</tbody>
</table>

Data from MacDonald and Jacobs.24

To address the role of oral contraceptives in BRCA 1 and BRCA 2 mutation carriers, a case-control study of 207 mutation carriers and 161 sister controls was performed.32 Each participant received a questionnaire, which addressed her history of oral contraceptive use. After adjusting for year of birth and parity, risk of ovarian cancer decreased with any use of the pill (odds ratio of 0.46 in BRCA 1 and 0.36 in BRCA 2)32 (level 3 evidence). Questions raised by this study include timing of pill use, role of the pill in women older than 40 years, and effectiveness of old versus new preparations of oral contraceptives.

Prophylactic oophorectomy: The decision to undergo PO depends on a woman’s level of concern about developing ovarian cancer, perceived consequences of prophylactic surgery, and the role of subsequent hormonal replacement. Women who carry BRCA 1 or BRCA 2 mutations are at risk of ovarian cancer. After prophylactic surgery, however, risk of developing primary peritoneal carcinomatosis (an epithelial malignancy of the peritoneal surface of the abdominal cavity) remains. From 2% to 11% of patients who have had prophylactic bilateral salpingo-oophorectomies develop primary peritoneal carcinomatosis (level 5 evidence). Streeuwj et al35 followed a cohort of first-degree relatives of breast or ovarian cancer patients and estimated that PO was associated with a relative risk of peritoneal carcinomatosis of 0.44 (level 3 evidence).

A consensus conference of the National Institutes of Health recommended that women with two or more first-degree relatives with ovarian cancer be offered PO after completion of childbearing or at age 3536 (level 3 evidence). The American College of Obstetrics and Gynecology advocates that women who carry BRCA 1 or BRCA 2 mutations consider PO37 (level
Familial ovarian cancer

5 evidence). The consensus of the Cancer Genetics Studies Consortium was that there was insufficient evidence to recommend for or against PO (level 3 evidence) but that the option be made available to women with BRCA 1 or BRCA 2 mutations.

Increasingly, PO is being done laparoscopically. This approach is associated with less morbidity, especially of postoperative pain and bowel dysfunction, than laparotomy. Laparotomy is usually conducted if laparoscopic surgical expertise is minimal or if the patient’s medical history makes the conservative approach unsafe. Laparotomy is associated with a higher risk of postoperative complications, such as need for blood products, infection (ie, bladder or wound infection or pneumonia), and thromboembolic disease. Currently there is no consensus on what the surgery entails (ie, oophorectomy with or without hysterectomy). Some gynecologists recommend that the surgery include staging (including omentectomy and multiple peritoneal biopsies) in the event that a microscopic focus of ovarian cancer is defined.

Prophylactic oophorectomy in premenopausal women results in surgical menopause. Immediate symptoms include hot flashes, mood swings, and sleep deprivation. Vaginal dryness is often noted. Urinary tract frequency and bladder infections can result from thinning of the trigone epithelium. Long-term concerns include cardiovascular disease and osteoporosis.

If there is a family history of cardiac disease or osteoporosis, the benefits of estrogen replacement therapy in decreasing mortality and improving quality of life are well known. Estrogen replacement therapy is associated with a slightly elevated risk of breast cancer in the general population after 8 years of use (level 3 evidence). Recently published studies suggest that estrogen-progestin regimens increase breast cancer risk beyond that associated with estrogen alone (level 3 evidence).

Now, oophorectomized premenopausal patients with higher risk of breast cancer known from genetic history are faced with decisions concerning use of hormone replacement therapy. Only one case series of hormone replacement therapy studied women with a family history of ovarian cancer who have undergone PO. Of 76 women developed breast cancer (level 5 evidence). The American College of Obstetrics and Gynecology advocates hormone replacement therapy for women who have undergone PO and who do not have a personal history of breast cancer (level 5 evidence). Estrogen replacement therapy appears safer than estrogen-progestin therapy in minimizing the risk of breast cancer; however, estrogen replacement therapy mandates hysterectomy as a component of the prophylactic surgery.

Psychosocial issues in genetic testing have been outlined by Carroll and colleagues; psychosocial issues related to prophylactic surgery include balancing the potential beneficial effect in terms of disease prevention with psychological considerations and satisfaction with decision. The literature suggests that high levels of perceived risk, an information-style of coping, and “cancer worriers” are predictive factors related to the pursuit of genetic testing among women at risk for cancer (level 3 evidence). A primary motivation for having surgery is to reduce cancer worries and to minimize risk. Future research will be required to determine whether, in fact, women experience a decrease in their perception of personal risk and receive psychological benefit from their decision to have POs.

Conclusion

Genetic testing is offered to women at high risk of breast or ovarian cancer based on their family history or ethnic background. A high probability (10%) of mutations in BRCA 1 or BRCA 2 exists if there is a family history (Table 4). Genetic counseling and testing of unaffected family members depends on detecting a mutation in an affected family member or the potential for a founder gene because a woman belongs to a high-risk ethnic group.

Initially, family physicians have an important role in identifying families with a history of cancer. Family physicians can inform families that counseling and testing are available. Family physicians can assist patients by referring them to regional genetic centres for risk assessment and counseling concerning genetic testing and follow-up screening.

Genetic counselors have a vital role in collecting and verifying information about family history of cancer, educating families about cancers that have a sporadic versus genetic basis, evaluating risk for a gene mutation, and explaining the risks and benefits of genetic testing to clients. Regardless of interest in testing, genetic counselors can inform clients about potential strategies for improving survival in the event that ovarian cancer is diagnosed. These include transvaginal ultrasound and CA125 screening (level 5 evidence for women with an ovarian cancer syndrome or known mutation carriers), oral contraceptives (level 3 evidence in the general population and known mutation carriers), and PO (level 3 evidence for women with a family history of ovarian cancer).

Finally, family physicians can then provide psychosocial support for women deciding to undergo genetic
testing or determining the appropriate gynecologic intervention for preventing ovarian cancer.46 Both regional genetic centres and local gynecologists can address options for prevention of ovarian cancer.43,47,48

Women who have a family history of ovarian cancer should be informed that genetic counseling is available. Counseling provides a more accurate assessment of personal risk of breast and ovarian cancer based on patients’ family history and ethnicity. Counseling also provides information concerning the availability and limitations of preventive strategies.

Family doctors have a pivotal role in helping patients sort through many decisions (such as the decision to be tested or the decision to be screened) that arise in this process.

Acknowledgment
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Competing interests
None declared

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References

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### Table 4. Genetic testing is offered in these high-risk situations

<table>
<thead>
<tr>
<th>Original criteria</th>
<th>Revised criteria: Original criteria have been modified with time so that some units offer testing for</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Single affected relative younger than 30 with breast or ovarian cancer</td>
<td>• A minimum of three cases of breast cancer while younger than 50; ovarian cancer at any age; or male breast cancer at any age in first-, second-, or third-degree relatives</td>
</tr>
<tr>
<td>• Sister pair both younger than 50 when breast cancer developed; breast cancer while younger than 50 and ovarian cancer while younger than 60; ovarian cancer while younger than 60 and another ovarian cancer at any age</td>
<td>• A minimum of two cases of female breast cancer while younger than 40 or male breast cancer at any age, or ovarian cancer at any age in first-, second-, or third-degree relatives</td>
</tr>
<tr>
<td>• More than three cases of breast cancer while younger than 60 or more than two cases of breast cancer and one case of ovarian cancer</td>
<td>• Patients with primary breast cancer and primary ovarian cancer with the first diagnosis while younger than 50 or primary breast cancer diagnosed while younger than 35 or primary bilateral breast cancer first diagnosed while younger than 50</td>
</tr>
<tr>
<td></td>
<td>• Ashkenazi Jewish ethnicity and breast cancer while younger than 45 or ovarian cancer at any age or one first-degree relative with ovarian cancer at any age or minimum of three cases of breast cancer while younger than 60 or ovarian cancer at any age in first- or second-degree relatives</td>
</tr>
</tbody>
</table>

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### Editor’s key points
- Twenty percent of women with ovarian cancer have a first-degree relative with breast or ovarian cancer; 8% have positive test results for BRCA 1 or BRCA 2.
- Most ovarian cancer is associated with breast cancer.
- Prevention options include surveillance with cancer antigen 125 tests and transvaginal ultrasonography, use of oral contraceptives, and prophylactic oophorectomy.
- Prophylactic oophorectomy will not completely eliminate the risk of ovarian cancer and raises issues of hormone replacement therapy; use of estrogens and progestins slightly increases risk of breast cancer.

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Points de repère du rédacteur
- Vingt pour cent des femmes qui présentent un cancer des ovaires ont des parents du premier degré ayant souffert d’un cancer du sein ou des ovaires; 8% d’entre elles ont des résultats de test positifs de mutation aux gènes BRCA1 ou BRCA2.
- La majorité des cas de cancer ovarien sont associés au cancer du sein.
- Les options de prévention comportent une surveillance au moyen du dépistage de l’antigène cancer 125, l’échographie transvaginale, le recours aux contraceptifs oraux et l’ovariectomie prophylactique.
- L’ovariectomie prophylactique n’éliminera pas complètement le risque de cancer ovarien et soulève des questions concernant l’hormonothérapie de remplacement; le recours aux œstrogènes et aux progestatifs augmente légèrement le risque de cancer du sein.


45. Olopade OJ, Lynch PM. Genetic testing, guidelines, ethics—when to test and what to do with the results. ASCO 1997;1638-62.

