OBG MANAGEMENT

By Michael G. Muto, MD
Codirector, Familial Ovarian Cancer Center, Gillette Center for Women's Cancers, Dana-Farber Cancer Institute, Boston.

Ovarian cancer: Identifying and managing high-risk patients

Two cases illustrate when to refer for genetic counseling and what to advise women concerned about prevention.

CASE 1

A 42-year-old woman of Ashkenazi Jewish ancestry, whose mother had a diagnosis of ovarian cancer a year earlier, is worried that she may also be at risk.

Her family has experienced no other cases of breast, colorectal, or ovarian cancer. She has 2 children and has used oral contraceptives for 9 years.

KEY POINTS

- **Ask every patient:** "Has anyone in your family had breast cancer under the age of 35, or colorectal, uterine, or ovarian cancer?
- **Genetic testing is appropriate only** when pre- and post-test counseling is available, the test can be interpreted, and the results will help in medical and surgical management.
- **Oral contraceptives may reduce risk by 10%** per year for up to 5 to 7 years of use.
- **Bilateral salpingo-oophorectomy in BRCA carriers** reduces the risk of ovarian cancer by more than 90% and the risk of breast cancer by more than 50%.

Primary prevention is an alternative to diagnosis of ovarian cancer at an early stage—a goal that is all too often unattainable.

If we identify women with increased risk based on their family history, environmental exposure, hormone use, or reproductive experiences, we can counsel them about lifestyle changes, chemoprophylaxis, or preventive surgery, depending on their reproductive desires and overall ovarian cancer risk.

Using 2 hypothetical cases, this article describes a quick history to screen for potential high risk, and summarizes what we can advise concerned patients, based on findings to date.

Topics include:

- genetic risk assessment
- when to refer to a genetic counselor
- risk factors
- oral contraceptives for primary prevention
- prophylactic surgery

Despite advances in medical and surgical therapies, ovarian cancer remains the deadliest gynecologic malignancy and the fifth leading cause of cancer deaths among women in the United States. This year the disease will strike an estimated 25,400 women in this country and kill more than 14,000.[1]

CONTINUED

Early detection versus primary prevention

One of the biggest problems is well known: In its early stages, ovarian cancer often is asymptomatic. Even when advanced, symptoms tend to be vague and are often dismissed by patients and their doctors. By the time the diagnosis is suspected, most women have disease beyond the ovary.

Because curability greatly depends on stage at presentation, much research is directed toward early detection. Advances in high-resolution imaging and novel blood or urine tumor markers may one day offer effective screening, but at present these methods are unproven.

3 genetic syndromes

Three genetic syndromes account for the vast majority of familial ovarian cancer and approximately 10% of all ovarian cancers. They are:

- breast-ovarian cancer syndrome,
- site-specific ovarian cancer syndrome, and
- hereditary nonpolyposis colorectal cancer syndrome (HNPCC) (Lynch II).[2]

The first 2 are caused by inherited mutations in the BRCA1 and BRCA2 genes. In fact, though often described as separate entities, these syndromes are likely phenotypic variants of the same genetic mutations. BRCA1 and BRCA2 function as classic tumor-suppressor genes and are inherited in an autosomal dominant fashion.

HNPCC is caused by mutations in a series of genes responsible for repairing errors in DNA replication. Inactivation of these so-called mismatch repair genes results in a high incidence of right-sided colon cancer, endometrial cancer, and ovarian cancer.[3]

Gene mutations in different populations

The lifetime risk of developing ovarian cancer in the United States is about 1.4%. However, among women with BRCA1 or BRCA2 mutations, the risk rises to 20% to 60%.[4]

These genes also impart a significant lifetime risk of breast cancer in women and, in the case of BRCA2, in men as well.

Less than 0.15% of the general population carries BRCA1 or BRCA2 mutations. However, the carrier rate is dependent on ethnic background.[5] Founder mutations have been identified among multiple unrelated families in Iceland, the Netherlands, and Sweden, and among Jews of Central or Eastern European descent (Ashkenazi).

The best described founder mutations are the 185delAG and 5382insC mutations in BRCA1 and the 6174delT mutation in BRCA2, occurring in Ashkenazi Jews at a carrier rate of 2%.[6]

Ovarian cancer in Ashkenazi women more likely genetic than sporadic

Although an Ashkenazi woman is no more likely to develop ovarian cancer than a noncarrier, if she does develop the disease, it is far more likely to be genetic rather than sporadic.

Consequently, if a woman of Ashkenazi Jewish descent develops ovarian cancer, there is a 40% chance she carries a mutation in one of these 2 genes.[7] Her first-degree relatives (mother, sisters, daughters) have a 20% risk of being gene carriers (50% in autosomal dominant transmission).

Therefore, an Ashkenazi Jewish woman needs only 1 first-degree relative with ovarian cancer to be considered for further genetic counseling.

The 3-2-1 rule for genetic counseling

Genetic counseling is indicated when the patient meets the "3-2-1" rule, known as the modified Amsterdam criteria:

- 3 affected individuals with either colorectal or ovarian cancer, in
- 2 successive generations, with at least
- 1 who developed cancer under the age of 50 years.

An Ashkenazi woman with only 1 first-degree relative with ovarian cancer is eligible for genetic counseling.

CONTINUED

When HNPCC is present

Women with documented HNPCC have a 70% lifetime risk of developing endometrial cancer and a lifetime risk of ovarian cancer of 11% or more. Testing for mutation in mismatch repair genes can be performed on peripheral leukocytes. Alternatively, the primary tumor from affected individuals can be assessed for the presence of microsatellite instability, a consequence of defective mismatch repair.[3]

How to obtain a family history

Women with a significant family history of breast, colorectal, endometrial, or ovarian cancer may face an elevated risk of ovarian cancer. Basic questions about the occurrence of these malignancies in first-degree (mother, sister, daughter) or second-degree (aunt, grandmother) relatives must be a component of every gynecologic history.

1-question assessment

The following question is a simple but effective way to assess familial cancer risk: "Has anyone in your family had breast cancer under the age of 35, or colorectal, uterine, or ovarian cancer?" If so, ask further questions about the relative's age at onset and how the affected person is related to the patient.

Although an informal pedigree can be constructed in a few moments, a formal pedigree is a more daunting task. More than half of family histories of ovarian cancer are inaccurate—and the error rate increases if the affected family member is a distant relative.[8]

Moreover, not all ovarian cancers are associated with genetic syndromes. Serous epithelial ovarian, fallopian tube, and peritoneal cancers dominate in BRCA-associated syndromes, whereas mucinous epithelial cancers are very rare. Germ-cell and stromal neoplasms as well as epithelial tumors of low malignant potential are excluded when assessing genetic risk.

We want to hear from you!

Have a comment on an article, editorial, illustration, or department? Drop us a line and let us know what you think. **You can send letters 1 of 3 ways:**

E-mail: obg@dowdenhealth.com

Fax: 201-391-2778

Mail: OBG MANAGEMENT, 110 Summit Ave, Montvale, NJ 07645

Letters should be addressed to the Editor, OBG MANAGEMENT, and be 200 words or less. They may be edited prior to publication.

Please take a moment to share your opinion!

OBG MANAGEMENT

Additional documentation is often necessary to verify the history. Such medical detective work may be beyond what a generalist is willing to perform. In that case, referral to a genetic counselor is the next step.

When to refer

Recommendation. If she is of Ashkenazi Jewish descent, like the patient described at the beginning of this article, only 1 first-degree relative indicates referral for genetic counseling.

If the patient claims at least 2 first-degree or second-degree relatives with breast cancer under the age of 35, or with ovarian cancer, suspect a genetic syndrome.

Family histories of particular concern include breast and ovarian cancer in a single individual, or any case of male breast cancer. Refer these patients to genetic counseling for formal pedigree analysis and possible testing for genetic predisposition. In the case of HNPCC, refer the patient if the modified Amsterdam criteria are met.

What does a genetic counselor do?

One of the most important roles of a genetic counselor is constructing as accurate a pedigree as possible. In some cases, this requires much effort on the part of both patient and counselor. It is not uncommon for the counselor to request outside pathology reports, operative notes, and death certificates to verify cancer cases. Pathology slides also may be necessary, while tissue blocks occasionally are requested to assist in genetic testing.

When testing is warranted

Genetic predisposition testing should be undertaken only after formal consultation with a genetic counselor who has expertise in cancer predisposition syndromes. As a policy statement from the American Society of Clinical Oncology concludes, genetic testing for cancer susceptibility should be performed only when:

- pre- and post-test counseling is available,
- the test can be interpreted, and
- the results will help in medical and surgical management.

Ideally, testing should take place in the setting of a multidisciplinary team with expertise in the interpretation of verified family cancer pedigrees and in the medical, emotional, financial, and legal ramifications of genetic testing.[9]

CASE 2

A 65-year-old obese nullipara is currently on year 10 of combined hormone replacement therapy (HRT). Although she has no family history of breast or ovarian cancer, she asks about her risk of developing ovarian cancer.

Other risk factors

Findings on the following potential risk factors for ovarian cancer may help address this patient's concerns:

Dietary factors

In a recent study, obesity was associated with an increased risk of ovarian cancer mortality.[10] Women who eat a diet high in saturated fat and low in vegetable fiber also may face an increased risk.

In 1989, the observation that Swedish women had both a high risk of ovarian cancer and the highest per capita dairy consumption in the world led some investigators to postulate a relationship between lactose consumption and ovarian cancer. The reason: When compared with matched controls, women with ovarian cancer were more likely to have high levels of galactose, a component sugar of the disaccharide lactose and a known oocyte toxin.[11]

This observation, however, has been inconsistent. Therefore, no specific dietary strategy can be recommended to reduce the risk of ovarian cancer.

Recommendation. I would advise this patient to maintain a normal body mass index. Data are insufficient to support more specific diet recommendations.

Obesity is associated with increased risk of ovarian cancer mortality.

CONTINUED

Talc exposure

When talc is placed on the perineum, it may enter the vagina and ascend to the upper genital tract. Because talc is structurally similar to asbestos, it may theoretically increase the ovarian cancer risk. The observation that women who undergo tubal sterilization procedures or hysterectomy have a lower risk of ovarian cancer supports the ascending-carcinogen hypothesis.

Multiple case-control studies have shown a small but consistent increased risk with perineal application of talc (odds ratio 1.3, 95% confidence interval [CI], 1.1–1.6).[12] The risk appears to be time- and dose-dependent, with greater risk associated with more frequent application of perineal talc over a long duration.

Recommendation. The practice of applying genuine talc to the perineum should be discouraged. Cornstarch-based dusting powders are widely available.

Infertility drugs

One of the most difficult issues to study is the relationship between infertility drugs and ovarian cancer, although we know that unexplained infertility is an independent risk factor for ovarian cancer.

Long-term estrogen users should consider increased risk of ovarian cancer.

A retrospective study that claimed an association between prolonged clomiphene exposure and ovarian cancer[13] was not restricted to invasive epithelial ovarian cancers, but included granulosa cell tumors. These estrogen-secreting neoplasms of stromal origin may directly contribute to infertility by disrupting normal follicular maturation and the menstrual cycle.

A number of studies—including a large collaborative analysis of 12 case-control studies—have reported an association between fertility drugs and invasive epithelial ovarian cancer.[14] In addition, many of the theoretical models of epithelial ovarian cancer pathogenesis implicate both incessant ovulation and high gonadotropin levels as important steps in malignant transformation of ovarian epithelium.

Oral contraceptives (OCs), which reduce ovulatory events, and moderate gonadotropin levels are associated with a consistent and significant protective effect.

Recommendation. It seems prudent, in the absence of convincing data, to use fertility medication only when absolutely indicated, at the lowest effective dose, and for the shortest duration possible without compromising treatment success.

However, prior exposure to these agents should not be considered an indication for increased surveillance or prophylactic surgery.

Estrogen replacement therapy

Women on estrogen replacement therapy appear to have an increased risk of ovarian cancer. When compared to nonusers, "ever-users" had a relative risk of ovarian cancer of 2.[2] (95% CI, 1.53–3.17), and the risk increased with the duration of use.[15] Long-term users, defined as women who used estrogen replacement therapy for at least 20 years, had a relative risk of 3.2 (95% CI, 1.7–5.7).[16]

Although some studies suggest a protective effect of combination hormone replacement regimens that include both estrogen and progesterone, this observation has not been confirmed. Thus, long-term estrogen users should consider an increased risk of developing ovarian cancer when deciding whether to initiate or continue estrogen replacement therapy.

Recommendation. I would advise the Case 2 patient to stop HRT.

Primary prevention

Oral contraceptives

OCs reduce the risk of ovarian cancer significantly. A number of studies have demonstrated a 10% risk reduction per year for up to 5 to 7 years of use.[17] This effect appears to persist for at least 10 years after OCs are discontinued. It also has been observed in patients known to be BRCA1 and BRCA2 carriers and is the basis for recommending OCs as a chemoprophylactic method in known carriers who wish to retain fertility.[18]

However, use of OCs by BRCA carri-

ers is not without some controversy. An Israeli population-based study[19] of ovarian cancer and OC use demonstrated a protective effect of pregnancy but not use of OCs. It is unclear why the Israeli data is inconsistent with prior published reports.

Recommendation. In Case 1, the patient has taken OCs for 9 years. Her risk has been substantially reduced, and I would advise her to continue OC pills when not attempting to get pregnant, until she is near menopause.

Prophylactic surgery

In high-risk women, preventive surgery may substantially reduce but not completely eliminate the risk of ovarian cancer. For example, bilateral salpingo-oophorectomy in BRCA carriers reduces the risk of ovarian cancer by more than 90% and the risk of breast cancer by more than 50%.[20,21]

The operation should be reserved for women with known mutations in BRCA1 or BRCA2 or who have a family history consistent with one of the genetic syndromes associated with ovarian cancer.

The addition of hysterectomy does not appear to increase the efficacy of the operation and should be performed only for concurrent gynecologic indications or if the patient has HNPCC.

Patients should be informed that prophylactic surgery does not protect against subsequent papillary serous carcinoma of the peritoneum. They also should be warned that about 7% of operations detect occult ovarian or tubal carcinoma, which may not be identified until final pathology reports are issued.[22] Pathologists should be instructed to submit the entire specimen for sectioning to reduce risk of missing microscopic occult malignancy.

In addition, the patient should be prepared for surgical menopause.

Effective primary prevention strategies such as chemoprophylaxis and prophylactic surgery, when appropriately applied, may spare many women the devastating consequences of this dreaded disease. ■

The author reports no financial relationships relevant to this article.

Internet resources

Ovarian Cancer (PDQ): Prevention of ovarian cancer
http://www.cancer.gov/cancerinfo/pdq/prevention/ovarian/healthprofessional

Myriad Genetics: BRCA1/2 mutation prevalence tables
http:///www.myriadtests.com/provider/mutprevo.htm

National Society of Genetic Counselors:
Locate a genetic counselor specializing in cancer risk assessment
http://www.nsgc.org/resourcelink.asp

REFERENCES

1. American Cancer Society. Cancer Facts and Figures 2003. Atlanta, Ga: American Cancer Society; 2003.
2. Trimble EL, Karlan BY, Lagasse LD, et al. Diagnosing the correct ovarian cancer syndrome. Obstet Gynecol. 1991;78:1023–1026.
3. Vasen HFA, Watson P, Mecklin J-P, Lynch HT, and the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer. New clinical criteria for hereditary nonpolyposis colon cancer (HNPCC, Lynch Syndrome): proposed by the International Collaborative Group on HNPCC. Gastroenterology. 1999;116:1453–1456.
4. Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Am J Hum Genet. 1995;56:265–271.
5. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72:1117–1130.
6. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med. 1997;336:1401–1408.
7. Lu K, Muto MG, Cramer DW, et al. Prevalence of BRCA mutations among women of Ashkenazi Jewish descent with epithelial ovarian cancer. Obstet Gynecol. 1998:92;596–600.
8. Parent ME, Ghadirian P, Lacroix A, et al. The reliability of recollections of family history: implications for the medical provider. J Cancer Educ. 1997;12:114–120.
9. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol. 2003;21:2397–2406.
10. Engeland A, Tretli S, Bjorge T. Height, body mass index, and ovarian cancer. A follow-up of 1.1 million Norwegian women. J Natl Cancer Inst. 2003:95;1244–1248.
11. Cramer DW, Harlow BL, Willett WC, et al. Galactose consumption and metabolism in relation to the risk of ovarian cancer. Lancet. 1989;2:66–71.
12. Gertig DM, Hunter DJ, Cramer DW, et al. Prospective study of talc use and ovarian cancer. J Natl Cancer Inst. 2000;92:249–252.
13. Rossing MA, Daling JR, Weiss NS, et al. Ovarian tumors in a cohort of infertile women. N Engl J Med. 1994; 331:771–776.
14. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk II. Invasive epithelial cancers in white women. Collaborative Ovarian Cancer Group. Am J Epidemiol. 1992;136:1184–1203.
15. Rodriguez C, Patel AV, Calle EE, et al. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. JAMA. 2001;285:1460–1465.
16. Lacey JV Jr, Mink PJ, Jubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. JAMA. 2002;288:334–341.
17. The reduction in risk of ovarian cancer associated with oral contraceptive use. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. N Engl J Med. 1987;316:650–655.
18. Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Study Group. N Engl J Med. 1998;339:424–428.
19. Modan B, Hartge P, Hirsh-Yechezkel G, et al. Parity, oral contraceptives and the risk of ovarian cancer among carriers and non-carriers of a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345:235–240.
20. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. 2002;346:1616–1622.
21. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346:1609–1615.
22. Lu KH, Garber JE, Cramer DW, et al. Occult ovarian tumors in women with BRCA1 or BRCA2 mutations undergoing prophylactic oophorectomy. J Clin Oncol. 2000;18:2728.