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Prophylactic bilateral oophorectomy jeopardizes long-term health

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Approximately 4.5 million women in the United States have undergone bilateral oophorectomy before reaching natural menopause, yet accumulating evidence indicates that surgical removal of the ovaries increases the risk of long-term deleterious outcomes.¹⁻⁴ Bilateral oophorectomy refers to the simultaneous or sequential removal of both ovaries. The surgery may be performed for a malignancy, benign disease of the ovaries (eg, endometriosis or a cyst), or prophylaxis against cancer. Oophorectomy is most commonly performed along with hysterectomy. Although age-adjusted rates of prophylactic oophorectomy have decreased over time, the proportion of hysterectomies accompanied by prophylactic oophorectomy in the United States has actually increased, from 29% in 1979 to 45% in 2004.⁵

Women who experience the premature loss of ovarian function as a result of bilateral oophorectomy performed before the onset of natural menopause are at increased risk for death, cardiovascular disease, stroke, lung cancer, cognitive impairment or dementia, parkinsonism, osteoporosis, depressive or anxiety symptoms,

and sexual dysfunction.²⁻⁴ The risks appear to be greater for women who are younger at the time of oophorectomy.^{2,6,7} Some studies, however, show that even women who underwent oophorectomy after the onset of natural menopause had an increased risk of deleterious outcomes.³

Health care practitioners who advise women about bilateral oophorectomy need to be aware of the risk-benefit balance and counsel patients accordingly. For premenopausal women who are not at markedly increased risk for ovarian or breast cancer, prophylactic oophorectomy should be discouraged (FIGURE).^{3,4}

Long-term consequences of prophylactic bilateral oophorectomy

Numerous studies demonstrate that surgical ovarian loss has a long-term harmful impact on women's health, especially for women who undergo oophorectomy before natural menopause. The following discussion provides an overview of specific health effects.

All-cause mortality

Bilateral oophorectomy is associ-

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Just in case versus just in time

Almost 14,000 women die each year from ovarian cancer. The high case-fatality rate of this devastating disease has been only minimally impacted by striking advances in chemotherapy and surgical techniques. Screening tests, which have served us well for cervical and breast cancer, are relatively ineffective for early detection of ovarian cancer. Unlike other cancers that predominantly strike women, ovarian cancer appears to grow too quickly to be detectable by periodic screening and is often widespread at the time of diagnosis, accounting for its overall poor prognosis.

This is one reason why “prophylactic” oophorectomy used to be viewed as a sound preventive option. Women undergoing hysterectomy who were past a certain age (35 to 45 years) were offered bilateral oophorectomy with the reassurance that the surgery would effectively protect them against the subsequent development of ovarian cancer. Because the ovaries were viewed as vestigial after menopause, the strategy appeared sound.

However, the ovaries apparently do provide benefits to women who are perimenopausal or early postmenopausal. When the ovaries are removed prior to menopause, adverse health consequences ensue. In this issue of *Menopausal Medicine*, Dr Lynne Schuster and colleagues provide epidemiologic evidence to show that many women are not well served by having their ovaries removed “just in case.” Their review compels a close look at the question “How best to balance the lifesaving benefit of ovary removal in the 1.4% of women who will develop the disease in their lifetime against the nonfatal but not insubstantial detriment that will be suffered by the rest?”

In their counterpoint article, Dr Komal Bajaj and Dr Susan Klugman provide some new and useful information. Risk-reducing salpingo-oophorectomy for women in selected high-risk groups provides unquestionable benefit to those who need it the most—women with a vastly increased risk of developing ovarian cancer. By selecting patients for surgery who are most likely to develop the disease, the benefits of risk reduction outweigh the attendant risks of premenopausal salpingo-oophorectomy.

Importantly, the conditions that occur more commonly in women who have had their ovaries removed premenopausally are not always ameliorated by the administration of estrogen and progestin therapy. The data thus further challenge our assumptions about the functional role of the ovary and its secretory products in the perimenopause and postmenopause. Sometimes, just in case, it is better to leave things be than to intervene.

On a different note: It has been a pleasure and a privilege to serve as Editor of *Menopausal Medicine* for the past 3 years. I hope you have found the articles informative and relevant to your practice. My successor, Dr Cynthia Sites, will without doubt provide new perspectives and guidance as we all continue on our journey to learn as much as we can about caring for our menopausal patients.

Nanette F. Santoro, MD

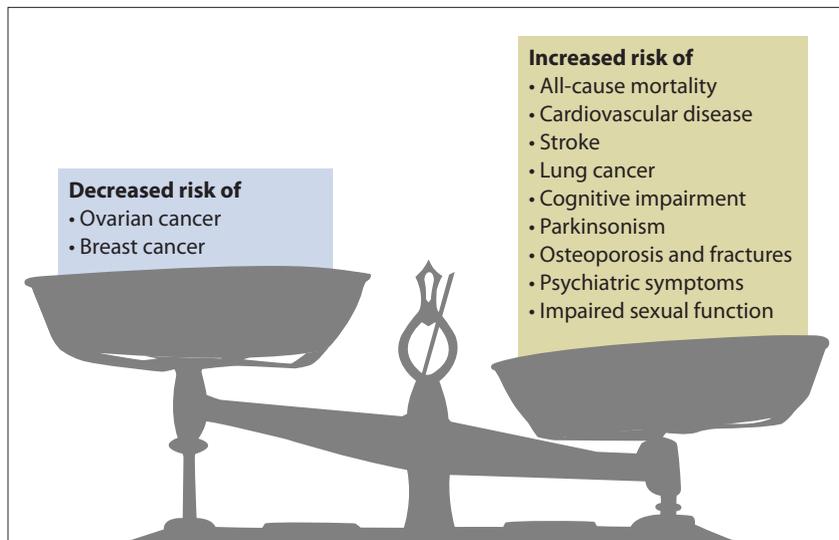


FIGURE. The risk-benefit balance for prophylactic bilateral oophorectomy in younger women at average risk of ovarian or breast cancer

Modified from Shuster LT et al. *Menopause Int.* 2008;14:111-116.

ated with excess all-cause mortality. The Mayo Clinic Cohort Study of Oophorectomy and Aging showed increased overall mortality in women who underwent prophylactic bilateral oophorectomy before age 45 years compared with referent women (hazard ratio [HR], 1.67; 95% confidence interval [CI], 1.16-2.40).⁸ The increased mortality was mainly observed in those women who did not take estrogen up to the age of 45 years (HR, 1.93; 95% CI, 1.25-2.96).

In a study using a Markov decision analysis model, Parker and colleagues projected that women undergoing oophorectomy before age 55 years would have an 8.6% excess mortality by age 80 years, and women up to age 59 years undergoing oophorectomy would have an excess mortality of 3.9%.⁹ The authors concluded that, in the absence of a specific medical indication for bilateral oophorectomy, ovarian conservation until at least age 65 years benefits survival.

Parker and colleagues subsequently reported on mortality and long-term health outcomes after

oophorectomy or ovarian conservation in the Nurses' Health Study. A total of 29,380 women underwent hysterectomy, of whom 45% had bilateral oophorectomy and 44% had ovarian conservation at the time of hysterectomy.³ Oophorectomy increased the risk of death from all causes (HR, 1.12; 95% CI, 1.03-1.21), and there was not a significant difference in risk by age at the time of oophorectomy. The authors calculated that for every 24 women who undergo bilateral oophorectomy, at least 1 woman will die prematurely as a result of the oophorectomy.³

Cardiovascular disease

In a 2006 meta-analysis evaluating 11 studies of menopausal status and age at menopause, the pooled relative risk of cardiovascular disease in women who underwent bilateral oophorectomy was 2.62 (95% CI, 2.05-3.35) compared with women who were premenopausal.¹⁰ This compared with a relative risk of 1.14 (95% CI, 0.86-1.51) for natural menopause versus premenopausal status. The pooled effect of bilateral oophorectomy before age

50 years compared with after age 50 years was 4.55 (95% CI, 2.56-8.01).¹⁰

The Danish Nurse Cohort Study showed an adjusted HR of 8.7 (95% CI, 2.0-38.1) for ischemic heart disease among women who underwent bilateral oophorectomy before age 40 years compared with after age 45 years.⁷ The risk was much smaller among women who experienced natural menopause before age 40 years (HR, 2.2; 95% CI, 1.0-4.9). Estrogen use by women who underwent bilateral oophorectomy was associated with a significant reduction in risk of ischemic heart disease (HR, 5.5 among ever-users versus 16.2 among never-users), and the relative benefit was most pronounced for women who were current users or started treatment within 1 year after oophorectomy.

In the Nurses' Health Study, there was a slightly increased risk of coronary heart disease in the women who had bilateral oophorectomy versus ovarian conservation (HR, 1.17; 95% CI, 1.02-1.35) and a further increase in risk for women undergoing oophorectomy before age 45 years (HR, 1.26; 95% CI, 1.04-1.54). Women who underwent bilateral oophorectomy before age 50 years and did not receive estrogen treatment also had an increased risk of stroke (HR, 2.19; 95% CI, 1.16-4.14).³

The preponderance of evidence suggests that bilateral oophorectomy is associated with increased cardiovascular risk and premature cardiac death, and oophorectomy at a young age further increases this risk. Estrogen therapy started early after a bilateral oophorectomy or after a premature or early natural menopause appears to reduce this risk.^{7,11}

Lung cancer

In the Nurses' Health Study, both lung cancer incidence and mortality were increased in women who underwent

hysterectomy with oophorectomy compared with those who had ovarian conservation (HR for incidence, 1.26; 95% CI, 1.02-1.56; HR for mortality, 1.31; 95% CI, 1.02-1.68).³ Unfortunately, there are no other studies of this association.

Cognitive impairment or dementia

In the Mayo Clinic Cohort Study of Oophorectomy and Aging, women who underwent bilateral oophorectomy before the onset of menopause had an increased risk of cognitive impairment or dementia compared with referent women (HR, 1.33; 95% CI, 0.98-1.81; $P=.07$). The risk increased with younger age at oophorectomy, and women who underwent oophorectomy before age 43 years had the greatest risk (HR, 1.74; 95% CI, 0.97-3.14; $P=.06$). However, the increased risk with younger age at oophorectomy was restricted to women who underwent oophorectomy before age 49 years and did not take estrogen until they were at least 50 years of age (HR, 1.89; 95% CI, 1.27-2.83; $P=.002$).^{12,13}

Several observational studies identified a 20% to 40% reduction in the risk of dementia for women who started estrogen therapy around the time of menopause.^{14,15} By contrast, the Women's Health Initiative Memory Study controlled clinical trials did not confirm a cognitive benefit of estrogen, but rather showed an increased risk of cognitive impairment or dementia in women who initiated estrogen at age 65 years or older.¹⁶ Unfortunately, current information about the effect of estrogen treatment on risk of cognitive decline or dementia remains inadequate for women who have undergone bilateral oophorectomy or have experienced premature or early natural menopause.¹⁷

Small prospective trials evaluating neurocognitive function after bilateral oophorectomy have identified a sig-

nificant decrease in specific cognitive functions, including verbal fluency, verbal memory, procedural learning, and some other executive functions.^{2,15} Neurocognitive performance was worse when oophorectomy occurred at a younger age and worse with greater declines in estradiol levels, but it was better when hormone therapy was initiated after oophorectomy.¹⁵ It is important to note that some of these studies did not evaluate the effects of estrogen on vasomotor symptoms and sleep disruption, which can also affect neurocognitive performance.

Small prospective trials evaluating neurocognitive function after bilateral oophorectomy have identified a significant decrease in specific cognitive functions.

Women who undergo bilateral oophorectomy at younger ages appear to be at an increased risk for cognitive impairment or dementia; estrogen therapy may be particularly important for neuroprotection in these women.^{15,18} Further studies are needed to confirm this association.

Parkinsonism and Parkinson's disease

In the Mayo Clinic Cohort Study of Oophorectomy and Aging, women who underwent bilateral oophorectomy before the onset of menopause had an increased risk of parkinsonism (a neurological syndrome that includes Parkinson's disease) compared with referent women (HR, 1.78; 95% CI, 1.06-3.01; $P=.03$), and the risk increased with younger age at oophorectomy (test for linear trend; $P=.02$). The findings were also consistent specifically for Parkinson's disease, but did not reach statistical significance.^{13,19}

Osteoporosis

Oophorectomy before age 45 years is a well-established risk factor for osteoporosis.²⁰ Even in women who undergo bilateral oophorectomy after natural menopause, the risk for osteoporotic fractures may be increased compared with the risk in women who have intact ovaries.²¹ Although estrogen may reduce this risk, nonhormonal alternative treatments are now generally used to prevent osteoporosis.

Mental health and sexual function

Although some studies report that hysterectomy performed for benign disease is associated with improved psychological well-being and quality of life, early bilateral oophorectomy along with hysterectomy is more commonly associated with worsened psychological well-being and negative affect.¹

In a prospective study of 101 women, those who underwent oophorectomy along with hysterectomy had significantly greater anxiety and depression and less positive well-being than women who underwent hysterectomy alone.²² However, women who took estrogen after the oophorectomy reported less anxiety and depression, and their psychological well-being was similar to that of the women whose ovaries were conserved. Similarly, oophorectomized women reported more impaired sexual function compared with women who had intact ovaries, but their sexual symptoms were not ameliorated by taking estrogen.²²

The Mayo Clinic Cohort Study of Oophorectomy and Aging followed 666 women with bilateral oophorectomy and 673 referent women, using structured questionnaires and telephone interviews to assess depressive and anxiety symptoms. Women who underwent bilateral oophorectomy before the onset of natural menopause had an increased risk of developing depressive



(HR, 1.54; 95% CI, 1.04-2.26) and anxiety symptoms (HR, 2.29; 95% CI, 1.33-3.95).²³ The increase in depressive and anxiety symptoms occurred in women who had not suffered from depression or anxiety before the surgery, and persisted many years after surgery.

Several studies have reported negative psychosocial and sexual outcomes among women undergoing prophylactic oophorectomy because of an increased risk for ovarian cancer. Madalinska and colleagues identified more frequent problems of dyspareunia and decreased sexual satisfaction in women who underwent prophylactic oophorectomy compared with women who underwent only medical surveillance.²⁴ Other smaller cohort studies similarly showed an increased risk of dyspareunia and a decrease in sexual satisfaction following prophylactic bilateral oophorectomy in women at increased risk for cancer.²

Adverse effects of bilateral oophorectomy on sexual function may involve several different domains, including libido, arousal, and orgasm.¹ In a survey of European women not known to be at increased risk of cancer, those who underwent bilateral oophorectomy were twice as likely to have symptoms of hypoactive sexual desire disorder compared with women who were premenopausal or experienced natural menopause.²⁵

Summary

Prophylactic bilateral oophorectomy reduces the risk of ovarian and breast cancer at the expense of increasing risk for all-cause mortality, cardiovascular disease, stroke, lung cancer, cognitive impairment or dementia, parkinsonism, osteoporosis, depressive or anxiety symptoms, and sexual dysfunction.^{4,18} The younger a woman is at the time of bilateral oophorectomy,

the greater her risk. Now that estrogen use is declining, the long-term risks might prove to be even greater.

One of the most important findings from recently reported studies on the health effects of oophorectomy is the temporal relationship between oophorectomy and the emergence of severe deleterious outcomes. Many of the adverse health outcomes manifest only after 15 or more years of follow-up. Because of this long lag time, the associations had not been recognized in routine postsurgical follow-up studies. In light of the current scientific evidence favoring ovarian conservation, clinicians have an obligation to offer thorough counseling and advice to patients who are considering prophylactic oophorectomy. For women up to 65 years of age who are not known to be at increased risk for ovarian or breast cancer, prophylactic oophorectomy should be discouraged. ■

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Risk-reducing salpingo-oophorectomy: A good option for high-risk patients

► KOMAL BAJAJ, MD, FACOG, AND SUSAN KLUGMAN, MD, FACOG, FACMG

Ovarian cancer is a devastating disease that has the highest mortality rate of all gynecologic cancers. In the United States, it is the fifth leading cause of cancer death among women. According to the American Cancer Society, 21,880 new cases of ovarian cancer will be diagnosed in the United States in 2010, and 13,850 women will die of the disease.¹ To date, screening strategies have not been effective in detecting early ovarian cancer or in decreasing mortality from the disease. The most effective way to prevent ovarian cancer is to surgically remove the ovaries and fallopian tubes.² We believe that, based on current data and guidelines, salpingo-oophorectomy is beneficial, especially for women who are at high-risk for developing ovarian malignancy.

The general population lifetime risk for ovarian cancer is 1.4% (1 in

70).¹ Multiparity, use of hormonal contraceptives, and breastfeeding are associated with a decreased risk of ovarian cancer. A woman may be considered at “high risk” if she has any factors—heritable or acquired—that increase her risk for ovarian cancer above that of the baseline population.

Family history is key in risk assessment

A thorough family history is critical in assessing a woman’s risk for ovarian cancer, because several inherited cancer syndromes are associated with an increased risk of ovarian cancer. In fact, women with a genetically increased risk account for more than 10% of all cases of ovarian malignancies that might be prevented if these risks were identified.³ A family history of cancer occurring at a young age, cancer in multiple generations, and multiple cancers in a single individual suggest a hereditary cancer syndrome.

A family history of both ovarian cancer and early-onset breast cancer (under the age of 50) suggests the presence of inherited *BRCA1* or *BRCA2* gene mutations. Women with a *BRCA1* mutation have a 39% to 46% lifetime risk of ovarian cancer, while lifetime risk for *BRCA2* mutation carriers is 12% to 20%. A mutation in either *BRCA1* or *BRCA2* (*BRCA1/2*) confers a 65% to 74% lifetime risk of breast cancer. The American College of Obstetricians and Gynecologists and other groups have developed guidelines for determining which patients would benefit from a genetic risk assessment.⁴

An increased risk of ovarian cancer (10% to 12% lifetime risk) is associated with hereditary nonpolyposis colorectal cancer, also known as Lynch syndrome.³ Individuals with Lynch syndrome also have an elevated risk of uterine cancer as well as other nongynecologic cancers. There are other breast-only and ovarian-only familial cancer syndromes, but their overall incidence is much smaller than those of *BRCA1/2* mutations and Lynch syndrome. For some of these familial cancer syndromes, the associated gene or genes have not yet been identified. Thus, for a woman who has a first-degree relative with ovarian cancer not associated with a *BRCA1/2* mutation, the lifetime risk of ovarian cancer is still double that of the baseline population.⁵

Women identified with a genetic predisposition should be counseled by appropriate specialists regarding strategies to reduce their risk of breast and ovarian cancer. Current strategies are listed in the **TABLE**.

Screening tests are inadequate

Unfortunately, less than one-fourth of women with ovarian cancer present with localized disease at the time of diagnosis. Bimanual pelvic examination, a part of routine gynecologic evaluation, usually detects advanced disease. Other modalities have been evaluated as potential screening tests, including transvaginal ultrasonography alone or in combination with assessment of serum cancer antigen 125 (CA-125). Multiple large trials

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TABLE Management strategies for women at high risk for a hereditary cancer syndrome

TYPE OF CANCER	MANAGEMENT STRATEGY	BENEFIT	LIMITATIONS
Breast cancer	Chemoprevention (ie, selective estrogen receptor modulators or aromatase inhibitors)	Potential decrease in estrogen receptor-positive cancers	Limited data on efficacy in high-risk women
	Screening (ie, mammography, ultrasound, MRI, clinical breast exams and/or self-exams)	Avoids surgery	Focus is on detection of disease, not prevention
	Risk-reducing surgery: mastectomy	Significant decrease in cancer risk (approximately 90% lifetime risk reduction)	Surgical risks and body image concerns
	Risk-reducing surgery: bilateral salpingo-oophorectomy	Significant decrease in cancer risk (reduction depends on age at time of surgery)	iatrogenic menopause and infertility
Ovarian/fallopian tube cancer	Chemoprevention (ie, oral contraceptive pills)	30%-60% reduction in ovarian cancer risk	Potential increase in risk of breast cancer
	Screening	Avoids surgery	Has not been shown to decrease mortality
	Risk-reducing surgery: bilateral salpingo-oophorectomy	Significant decrease in cancer risk (80%-90% lifetime risk reduction)	iatrogenic menopause and infertility

MRI, magnetic resonance imaging.

have not demonstrated adequate utility of these tools, however, and they are therefore not recommended for screening in the general population.⁴ Proteomic studies have identified serum marker patterns that may prove to be clinically useful in the future.

Surgery as a preventive measure

The distinction between the terms “elective” and “risk-reducing” salpingo-oophorectomy is important. Elective salpingo-oophorectomy (ESO) refers to removal of the ovaries at the time of another indicated procedure. Risk-reducing salpingo-oophorectomy (RRSO) refers to the removal of normal ovaries and is performed as a stand-alone surgical procedure.³

Several techniques can help max-

imize the efficacy of the RRSO procedure itself and the pathology evaluation of the specimen afterward. For example, risk-reducing surgery should include thorough inspection of the peritoneal cavity. Cytologic evaluation of pelvic washings should be strongly considered. According to the Society of Gynecologic Oncologists, “surgeons should isolate the ovarian blood supply adequately proximal to its insertion into the ovarian hilum.”² If hysterectomy is not performed at the time of surgery, the fallopian tubes should be amputated as close to the uterine cornua as possible. Both the ovaries and the fallopian tubes should be serially sectioned at 2- to 3-mm intervals and examined by an experienced gynecologic pathologist.²

Multiple small studies, including

a prospective analysis of 113 women at high risk for ovarian cancer (67% of whom had *BRCA1/2* mutation), demonstrated that up to 6% of women undergoing RRSO had ovarian or tubal neoplasm at the time of surgery.⁶ Age greater than 45 years and a mutation in *BRCA1/2* are 2 factors predictive of occult neoplasia.⁶ The literature suggests that the incidence of complications associated with RRSO is low (4%) and is similar to that of other gynecologic laparoscopic procedures.⁷ Hysterectomy at the time of RRSO is not required but may be considered based on individual patient factors, such as risk for endometrial and cervical cancer.

Women with *BRCA1/2* mutation achieve an 80% to 90% reduction in their lifetime risk of ovarian cancer, as well as a 50% to 60% reduction in risk of breast cancer, if RRSO is performed

prior to menopause.⁸ These risks may vary based on the type of mutation.⁹ After salpingo-oophorectomy, women remain at risk for peritoneal cancer. *BRCA1/2* mutation carriers who undergo RRSO have a 1% to 6% residual lifetime cumulative risk of peritoneal cancer.^{7,9} The degree of cancer risk reduction in women without hereditary risk factors is less clear and requires further study.

Drawbacks of RRSO

The major disadvantage of removal of the ovaries is the loss of hormone secretion. The mean age of menopause in developed countries is 51.4 years. After menopause, estradiol production decreases by 90%, and estrone becomes the main estrogen. Androstenedione levels decrease by half due to the loss of ovarian contribution. The hormonal profile after surgical intervention mimics natural menopause.³

A study of 846 high-risk women, of whom 44% underwent RRSO and 56% had periodic surveillance, demonstrated no difference between the 2 groups in quality-of-life (QOL) scores.¹⁰ The women who underwent

The decision to undergo surgery must be an informed one, with the patient fully understanding the risks, benefits, potential complications, and long-lasting postoperative effects of surgery.

RRSO had more endocrine symptoms but fewer cancer worries and a more favorable cancer risk perception.¹⁰ Other studies have found similar results.^{11,12} A study that employed a Markov model to examine various treatment strategies for women with *BRCA1/2* mutations concluded that

with quality adjustment, the most cost-effective strategy for a 35-year-old woman was RRSO.¹³

Conclusion

RRSO is clearly beneficial for women who are at high risk for a hereditary cancer syndrome. These patients must be cared for by a multidisciplinary team that includes genetic and surgical experts. Furthermore, the decision to undergo surgery must be an informed one, with the patient fully understanding the risks, benefits, potential complications, and long-lasting postoperative effects of surgery. In addition, the timing of surgery should be individualized to maximize cancer risk reduction.

Important future directions for research include the development of reliable screening tools to detect early ovarian cancer and the identification of additional genes associated with heritable risk. ■

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