Ovarian Conservation at the Time of Hysterectomy for Benign Disease

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Objective: Prophylactic oophorectomy is often recommended concurrent with hysterectomy for benign disease. The optimal age for this recommendation in women at average risk for ovarian cancer has not been determined.

Methods: Using published age-specific data for absolute and relative risk, both with and without oophorectomy, for ovarian cancer, coronary heart disease, hip fracture, breast cancer, and stroke, a Markov decision analysis model was used to estimate the optimal strategy for maximizing survival for women at average risk of ovarian cancer. For each 5-year age group from 40 to 80 years, 4 strategies were compared: ovarian conservation or oophorectomy, and use of estrogen therapy or nonuse. Outcomes, as proportion of women alive at age 80 years, were measured. Sensitivity analyses were performed, varying both relative and absolute risk estimates across the range of reported values.

Results: Ovarian conservation until age 65 benefits long-term survival for women undergoing hysterectomy for benign disease. Women with oophorectomy before age 55 have 8.58% excess mortality by age 80, and those with oophorectomy before age 59 have 3.92% excess mortality. There is sustained, but decreasing, benefit until the age of 75, when excess mortality for oophorectomy is less than 1%. These results were unchanged following multiple sensitivity analyses and were most sensitive to the risk of coronary heart disease.

Conclusion: Ovarian conservation until at least age 65 benefits long-term survival for women at average risk of ovarian cancer when undergoing hysterectomy for benign disease.
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See related editorial on page 214.

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The most frequent reason that prophylactic oophorectomy is recommended concurrently with hysterectomy for benign disease is to decrease the risk of ovarian cancer. Ninety percent of the 600,000 hysterectomies performed yearly in the United States are performed for benign disease. The percentage of hysterectomies accompanied by bilateral salpingo-oophorectomy more than doubled from 1965 (25%) to 1999 (55%).[1] Clinical management guidelines published by The American College of Obstetricians and Gynecologists (ACOG) in 1999 recommended that "the decision to perform prophylactic oophorectomy should be based not only on the patient's age but also on other factors that weigh individual risk for developing ovarian cancer against loss of ovarian function."[2] However, recent data from the Centers for Disease Control and Prevention show that 38% of women have concurrent oophorectomy between ages 18 and 44 and 78% between ages 45 and 64.[1] Conservative estimates suggest that approximately 300,000 women have prophylactic bilateral oophorectomy every year.

Although the appropriate age at which prophylactic oophorectomy should be performed remains controversial, some recommend oophorectomy for all women over the age of 40 years when they have hysterectomy performed. However, the risk of developing ovarian cancer after hysterectomy performed for benign disease is 40% lower than expected based on its prevalence in the general population.[3–7] The ovaries continue to produce significant amounts of testosterone and androstenedione for many years after menopause, and these androgens are converted to estrogen peripherally.[8] The benefits of preserving ovarian function include lower risks of osteoporotic

fracture and coronary heart disease. Despite these important health concerns, no prospective trial or other evidence exists to aid women and their physicians with this choice, and many women feel that they have not been provided sufficient information regarding long-term risks and benefits on which they can base their decision.[9]

A recent decision analysis intended for women under the age of 40 years with inherited *BRCA1/2* mutations who have appreciable risk of breast and ovarian cancer suggested that prophylactic oophorectomy after completion of childbearing significantly decreased the risks of these cancers.[10] However, data for those without germ-line mutations are unclear. Our study was designed to model significant risks and benefits of prophylactic oophorectomy in conjunction with hysterectomy for benign disease and to provide guidance for women at average risk of ovarian cancer who need to make this important decision.

MATERIALS AND METHODS

A Markov decision analytic model was used to determine the optimal strategy for maximizing survival in hypothetical groups of generally healthy women, aged 40–80 years, who have a hysterectomy for benign disease and have the option of choosing or not choosing oophorectomy. A Markov model simulates large hypothetical cohorts of patients that are followed through the model over time.[11] With each 5-year cycle of the model, patients may move between several defined health states according to chance clinical events based on their probability as estimated from the medical literature. This model was chosen because women may enter (or exit) various health states after surgery. By simulating possible outcomes in large numbers of similar patients, the benefits or risks for each treatment strategy may be estimated.

Women were followed in the model from the age of surgery (40 or older) until age 80. Four circumstances that could be employed were studied: ovarian conservation with and without estrogen therapy and oophorectomy with or without estrogen therapy. Five conditions (ovarian cancer, coronary heart disease [CHD], hip fracture, breast cancer, and stroke) were identified for which risk has been reported to be related to presence of postmenopausal ovaries or use of estrogen therapy.

Age-specific mortality rates, incidence rates, and case-fatality rates for these conditions in women aged 40–80 years and the relative risk associated with oophorectomy and estrogen therapy were obtained from a comprehensive review of the English literature. The model considered only mortality because no data were available on the relative risk of morbidity and effect on quality of life after ovarian conservation compared with oophorectomy. PubMed and the Cochrane database were used to identify relevant articles published from 1990 to present using the following subject headings (MeSH) and keywords: "ovarian conservation," "oophorectomy," "residual ovary," "hysterectomy," "ovarian cancer," "coronary heart disease," "CHD," "hip fracture," "breast cancer," "stroke," and "estrogen." A hand search of the bibliographies of papers published in the past 5 years was also conducted to identify additional publications. Articles pertaining to women at high risk for ovarian cancer due to inherited germ-line mutations were excluded. Consensus of the authors was used to select studies considered the highest quality of evidence based on the U.S. Preventive Service Task Force evidence grading system.[12] If disparate evidence existed within one grade, the authors discussed the articles to arrive at consensus about the best quality studies.

By using DATA 4.0 software (TreeAge Software Inc, Williamstown, MA), the proportion of women, calculated in 5-year cycles, who died of a condition of interest under each strategy was modeled. The model assumes that the conditions are mutually exclusive: death was attributed to 1 of the 5 identified conditions or to all other causes. The best available evidence was used in the base case analysis. Sensitivity analyses were performed, varying relative and absolute risk estimates across the range of reported values. Age at the time of oophorectomy was also varied. Using Monte Carlo simulations, 95% confidence intervals were constructed to gauge statistical significance.

Ovarian Cancer

Age-specific mortality estimates for ovarian cancer were based on the Surveillance, Epidemiology and End Results (SEER) statistics (Table 1).[13–19] Because hysterectomy alone has been shown to reduce ovarian cancer risk, age-specific SEER mortality estimates were multiplied by 0.645, the average risk reduction seen after hysterectomy.[3–7] This factor was varied across the range of reported values (0.50–0.78) in sensitivity analyses. The risk of ovarian cancer after oophorectomy was assumed to be zero because primary peritoneal cancer results from malignant transformation of the peritoneum, and although this disease may imitate ovarian carcinoma, it is a separate disease. Most reports suggest no increased risk of ovarian cancer resulting from estrogen therapy.[20]

Coronary Heart Disease

Absolute risk of coronary heart disease was estimated with data from the National Center for Health Statistics (Table 1).[14] Annual death rates were converted

Table 1. Model Data Input and Data Source

Condition	5-Year Probability of Death by Age Groups (%)								Source/ Reference
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–80	
Ovarian cancer	0.015	0.032	0.055	0.082	0.120	0.156	0.193	0.236	SEER[13]
Coronary heart disease*	0.100	0.100	0.210	0.410	0.790	1.340	2.340	4.000	CDC/NCHS[14]
Hip fracture*	0.012	0.012	0.019	0.028	0.267	0.508	1.224	2.108	Huang[15] Karagas,[16] Keene[17]
Stroke*	0.050	0.050	0.090	0.140	0.230	0.400	0.760	1.510	CDC/NCHS[18]
Breast cancer	0.075	0.128	0.190	0.250	0.309	0.367	0.428	0.528	SEER[13]
Other causes*	1.020	0.950	1.340	2.030	2.940	4.390	5.980	8.580	Arias[19]

* Formula used to convert the annual rates to 5-year probabilities: $P = 1 - e^{-R \times 5}$ (P = 5-year probability; R = annual rate).

to the 5-year death probabilities using the formula $P = 1 - e^{-R \times 5}$ (P = 5-year death probability, R = annual death rate). In the base case, the relative risk of coronary heart disease was derived from a prospective study of 121,700 nurses demonstrating double the risk of myocardial infarction for women after oophorectomy up to age 55 years when estrogen was not used (relative risk 2.2, 95% confidence interval 1.2–4.2).[21] Other studies report that the risk of myocardial infarction increases 50–60% in women after oophorectomy, and a range of 1–2.2 was used for the sensitivity analysis.[22–24] The risk of CHD decreases 6% for each year oophorectomy is delayed after menopause, and the relative risk was adjusted accordingly from age 55 to age 65.[25] No data were found for relative risk for women older than 65, and relative risk was therefore assumed to be 1. In our base case, estrogen therapy was assumed to reduce the risk of dying from CHD.[21] The Women's Health Initiative found that estrogen therapy alone did not affect the rate of CHD, although this study was not stratified for presence or absence of ovaries in the subjects studied.[26]

Osteoporotic Hip Fracture

No direct mortality rate for osteoporotic hip fracture was found, so annual incidence rates were multiplied by the case-fatality rates and converted to the 5-year death probabilities. Annual incidence rates were derived from 2 studies.[15,16] Case-fatality rates were based on estimated age-specific excess mortality (Table 1).[17]

A 50% increased risk of hip fracture after oophorectomy was reported in women over 49 years of age.[27] In our base case, we conservatively assumed that the relative risk at ages 40–49 was the same as at ages greater than 50. The relative risk was varied from 1 to 2 in sensitivity analyses. The Women's Health Initiative found that estrogen therapy reduced hip fractures by 6 per 10,000 women-years.[26]

Stroke

Mortality rates from stroke were derived from data reported by the National Center for Health Statistics (Table 1).[18] Annual rates were converted to 5-year death probabilities using the aforementioned formula. No evidence was found regarding the risk of stroke in women after oophorectomy, and thus the relative risk of stroke was assumed to be 1 in the model. The Women's Health Initiative found 12 more strokes per 10,000 women-years among estrogen users, which was incorporated into our model.[26]

Breast Cancer

Breast cancer mortality statistics were derived from SEER (Table 1).[13] Relative risk was derived from a study that found women who had oophorectomy before age 50 had a 50% reduction in breast cancer for 10 years following surgery.[28] This effect was not present in women who had surgery after the age of 50. The Women's Health Initiative found no increased risk of breast cancer in women using estrogen-only.[26]

Estrogen Therapy

Data on the effect of estrogen therapy on the above conditions were derived from the estrogen-only arm of the Women's Health Initiative.[26] The Women's Health Initiative studies have not reported risk estimates stratified by ovarian conservation versus oophorectomy, so the base case had data applied equally to both cohorts. In the base case, estrogen therapy after oophorectomy was calculated as 0% (not taking estrogen therapy) or 100% (taking estrogen therapy).

Death From Other Causes

Data for all-cause mortality for women were derived from the National Vital Statistics Reports for 2001 and were stratified for 5-year cohorts.[19] These data were used to derive death probabilities due to all

causes, excluding the 5 specific conditions of interest (Table 1).

Surgical Mortality

The mortality rates for hysterectomy, with and without oophorectomy, were obtained from the National Inpatient Sample of the Healthcare Cost and Utilization Project (HCUP) database of the Agency for HealthCare Research and Quality.[29] For example, for women ages 50–59, mortality for hysterectomy was 9 per 10,000 surgeries performed and 10 per 10,000 for hysterectomy with oophorectomy. Therefore, surgical mortality was estimated to be unaffected by the decision to perform oophorectomy. The incidence of reoperation for adnexal pathology of retained ovaries is low, and, therefore, mortality from this surgery was also estimated to have negligible effect on the overall mortality rate.[30]

RESULTS

For women at average risk of ovarian cancer, coronary heart disease, osteoporosis, breast cancer, and stroke, the probability of surviving to age 80 years after hysterectomy at ages 50–54 varies from 62.46% for ovarian conservation without estrogen therapy to 53.88% for oophorectomy without estrogen therapy. Ovarian conservation without estrogen therapy reduces the proportion of women succumbing to CHD in the base case from 15.95% to 7.57% and of those succumbing to hip fracture from 4.96% to 3.38%. These reductions far outweigh the increase in the proportion of women who die from ovarian cancer, which varies from 0% to 0.47% (Table 2). As age at oophorectomy increases, the point estimate of the risk of dying approaches, but is always greater than the risk of dying with ovarian conservation. Above age 64, the 95% confidence interval bands for oophorectomy overlap ovarian conservation, suggesting that there is no statistically significant difference in survival between these strategies after age 64 (Fig. 1). Estrogen therapy after oophorectomy was assumed to reduce the proportion of women dying from CHD.[21] The probability of surviving to age 80 after hysterectomy at ages 50–54 with ovarian conservation and no estrogen therapy (62.5%) is slightly greater than with oophorectomy and estrogen therapy (62.2%) (Table 2).

For a hypothetical cohort of 10,000 women undergoing hysterectomy who chose oophorectomy between the ages of 50 and 54 without estrogen therapy, our analyses predict that, by the time they reach age 80, 838 more women will have died from CHD than in a similar cohort of women who chose ovarian preservation; 158 more will have died from hip fracture; 47 fewer women will have died from ovarian cancer. In the base case analyses, oophorectomy in women ages 50–54 leads to an overall excess mortality of 858 per 10,000 women subjected to surgery.

Sensitivity Analyses

The increased risk of CHD after oophorectomy was varied, based on estimates from the literature, from 2.2 to no increased risk, showing that the model was very sensitive to changes in the relative risk of CHD, with the probability of death by 80 changing from 46% in the base case (relative risk = 2.2) to about 39% in the extreme case (relative risk = 1) (Table 3). Using the extreme assumption of no deleterious effect of oophorectomy on CHD, for women who had oophorectomy at ages 50–54, the risk of dying by age 80 approached the estimate for ovarian conservation (38.74% and 37.54%). Varying the relative risk of hip fracture mortality between 1 and 2 showed that the model was only slightly sensitive to this measure (Table 3). Based on reported literature, the relative risk of ovarian cancer after ovarian conservation compared with the general population varied between 0.5 and 0.78, and the model was insensitive to this change (results not shown). No sensitivity analyses showed that oophorectomy improved survival.

DISCUSSION

We designed the model to study the major risks and benefits related to the decision to have prophylactic bilateral oophorectomy when hysterectomy is performed for benign disease in women who have average risk of ovarian cancer. The model shows that

Table 2. Variation in Mortality by Oophorectomy (at Ages 50–54) and Estrogen Therapy Status

		Proportion Dead From Specific Condition by Age 80 (%)					
Strategy	Proportion Alive at Age 80 (%)	Hip Fracture	Ovarian Cancer	Breast Cancer	Stroke	Coronary Heart Disease	Other
Ovarian conservation, no ET	62.46	3.38	0.47	1.82	2.59	7.57	21.72
Oophorectomy, no ET	53.88	4.96	0.00	1.77	2.47	15.95	20.97
Ovarian conservation, ET	62.75	2.06	0.47	1.82	3.60	7.57	21.72
Oophorectomy, ET	62.15	3.17	0.00	1.82	3.59	7.56	21.71

ET, estrogen therapy.

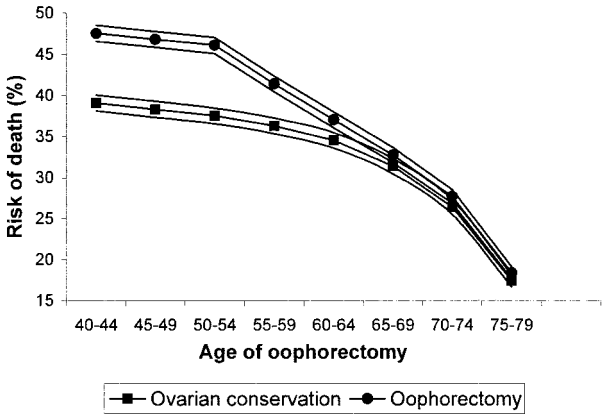

Fig. 1. Risk of death by age 80 years for nonusers of estrogen therapy as a function of age at oophorectomy with 95% confidence interval.

Parker. Ovarian Conservation. Obstet Gynecol 2005.

women younger than 65 years of age clearly benefit from ovarian conservation, and at no age is there clear benefit from oophorectomy. For women younger than 65 at the time of surgery, oophorectomy increases the risk of dying from coronary heart disease. After age 65, increased mortality is primarily from hip fracture. Because ovarian cancer is a relatively uncommon cause of death when one excludes patients with documented germ-line mutations and pedigrees with high risk for ovarian cancer, our data show no substantial reduction in mortality if oophorectomy is performed before age 65.

For women choosing ovarian conservation at ages 50–54, there is an 8.58% survival advantage measured at age 80, and with surgery at ages 55–59, the survival advantage is 3.92% (results not shown). After age 65, definite conclusions are more difficult to reach. However, at no age does the model suggest a higher mortality for women who chose ovarian preservation because the relative risk of dying from ovarian cancer is overshadowed by the risks from cardiovascular disease and hip fracture.

Hysterectomy alone reduces the risk of ovarian cancer, and the protective effect persists for 10–20 years, long after that expected from screening bias. Interruption of the reproductive tract may be responsible for the decreased risk, because tubal ligation also has a protective effect.[3] Heavy menstrual bleeding is associated with a higher risk of ovarian cancer, suggesting that endometrial tissue reflux via the tubes may be the inciting agent. Potential carcinogens, including talc and human papillomavirus, have been found within ovarian cancer tissue.[31,32] Epidemiologic studies show decreased ovarian function lowers the risk of developing breast cancer. Women with oophorectomy before age 50 had a 50% decreased risk of breast cancer, which persisted for 10 years after surgery.[28]

Premenopausal oophorectomy causes an immediate and significant loss of ovarian hormones. Postmenopausal ovaries continue to make small amounts of estrogen for years, and significant levels of ovarian testosterone and androstenedione have been documented in the eighth decade.[33] Androstenedione is converted to estrone in fat and muscle, and estrone and testosterone are converted to estradiol. After oophorectomy, menopausal women have significantly lower plasma levels of testosterone than naturally menopausal women.[34]

Oophorectomy increases the risk of cardiovascular disease, the major cause of death for women. The Nurses' Health Study, a well-conducted prospective study of 121,700 women, determined that oophorectomy between ages 40 and 44 years doubled the risk of myocardial infarction compared with women with intact ovaries.[23] Later analysis of the same cohort confirmed these findings.[21] These 2 nurses studies report the largest cohort, with the longest-term follow-up, available for CHD data. Earlier age of surgical or natural menopause has been shown to correlate with the risk of cardiovascular mortality.[25] Oophorectomy after age 50 increased risk of developing a first myocardial infarction by 40% (relative risk 1.4, 95% confidence interval 1.0–2.0) compared with con-

Table 3. Probability of Death by Age 80: Results From Sensitivity Analysis by Varying Relative Risk of Death From CHD and Hip Fracture

	Relative Risk							
Treatment Group	**1**	**1.25**	**1.4**	**1.5**	**1.75**	**1.8**	**2**	**2.2**
Ovarian conservation (%)	38	38	38	38	38	38	38	38
Oophorectomy (%)								
Varying relative risk of CHD	39	. . .	41	. . .	. . .	44	. . .	**46**
Varying relative risk of hip fracture	45	45	. . .	**46**	47	. . .	47	. . .

CHD, coronary heart disease.

Among women not using estrogen therapy who have oophorectomy between ages 50 and 54, compared with women who have ovarian conservation. In the base case, relative of CHD = 2.2; relative risk of hip fracture = 1.5.

Base cases are shown in boldface type.

trols.[22] Indirect evidence supports this increased risk. Analysis of data derived from the Women's Health Initiative found that hysterectomy with oophorectomy is an independent predictor of Framingham risk of myocardial infarction or coronary death.[35] After oophorectomy, women have higher levels of atherogenic lipids and stress-induced lipids and higher stress-induced systolic and diastolic blood pressures.[36] Increased coronary atherosclerosis is found at autopsy in women with prior bilateral oophorectomy.[37] Earlier menopause, either natural or surgical, is associated with more subclinical atherosclerosis, as measured by carotid artery intima-media thickness, and this finding is related to the risk of clinical cardiac events.[38,39] The Women's Health Initiative found that estrogen therapy did not affect the rate of CHD, suggesting that retention of ovaries and endogenous estrogen may be the best strategy for decreasing the risk of CHD.[26]

Estrogens and androgens inhibit bone resorption and androgens increase bone formation. Levels of testosterone and estradiol correlate with hip fractures in postmenopausal women.[40,41] After a median follow-up of 15 years, women who were postmenopausal at the time of oophorectomy had 54% more osteoporotic fractures than women with intact ovaries.[27] Hip fracture is a well-documented cause of increased mortality in older women. A prospective cohort study found that women older than 60 had a 2-fold increase in mortality (odds ratio 2.18, 95% confidence interval 2.03–2.32) after low-trauma hip fractures.[17] Women who suffered a hip fracture between ages 60 and 64 were found to have lost 11 years of life, and women with fractures between ages 70 and 74 lost 4.4 years.[42]

Although quality of life issues are of great importance, insufficient data were available to include these in the decision analysis model. Premenopausal oophorectomy leads to the sudden onset of hot flushes and mood disturbances if estrogen is not taken. Other problems may include a decline in a sense of well-being, a decline in cognitive functioning, poor sleep quality, depression, and a decline in sexual desire and frequency.[43] Additionally, a study of functional status found that, before hip fracture, 28% of patients were housebound, but one year later 46% were housebound.[17]

Although estrogen therapy may reduce some of this risk, one study of 169,000 women enrolled in health maintenance organizations found that, after publication of the Women's Health Initiative results, use of estrogen therapy declined from 12.6% to 9%.[44] A previous decision analysis found that, when actual hormone-taking behavior was considered, women who had ovarian conservation had a survival advantage.[45]

Our study has several weaknesses. The probability estimates were derived mostly from case-control studies, with the inherent weaknesses of selection bias, reporting bias, and chance. One study of coronary heart disease used in our model did not provide information regarding subjects' use of estrogen therapy and may be biased.[25] However, our model does not rely on the use of estrogen after oophorectomy. In fact, if estrogen therapy does not reduce CHD mortality, this makes a stronger case for ovarian conservation. No published data were found for coronary risk when oophorectomy is performed after menopause. Further research is needed in this area. Women chosen for most selected studies were predominantly white, and further study is needed to confirm these estimates for nonwhite women. Notwithstanding these limitations, because of the long interval between natural menopause or oophorectomy and the subsequent development of osteoporosis, CHD, breast cancer, or ovarian cancer, it is unlikely that these outcomes will ever be studied in a large, prospective, randomized fashion.

This study was designed to aid women and their doctors in the choice between ovarian conservation and oophorectomy when hysterectomy is performed for benign disease. The risk of developing ovarian cancer becomes substantially lower after hysterectomy, and this risk is overshadowed by increased mortality from CHD and hip fracture for women under the age of 65 when oophorectomy is performed. We did not demonstrate a survival benefit after oophorectomy at any age because the risks and benefits approximate each other after age 65. Our model suggests that the decision to perform prophylactic oophorectomy should be approached with great caution for the majority of women who are under the age of 65 and who are at average risk of developing ovarian cancer.

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