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Assessing Ovarian Cancer Risk When Considering Elective Oophorectomy at the Time of Hysterectomy

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Abstract

Objective—To develop a risk-factor score that may provide additional guidance to women and their physicians regarding elective bilateral salpingo-oophorectomy at the time of hysterectomy.

Methods—From a case-control study conducted from 1992 to 2008 in women residing in eastern Massachusetts or New Hampshire, we selected 1,098 women with invasive ovarian cancer (case group) and 1,363 for the control group who were older than 40 years and had neither hysterectomy nor a personal or family history of breast or ovarian cancer. Using logistic regression, we identified key risk factors and built a risk score. The score was separately assessed in 126 women in the case group and 156 in the control group with excluded prior hysterectomy to determine whether women who developed ovarian cancer could have been distinguished.

Results—Summing eight conditions found to be associated with ovarian cancer (Jewish ethnicity, less than 1 year of oral contraceptive use, nulliparity, no breastfeeding, no tubal ligation, painful periods or endometriosis, polycystic ovary syndrome or obesity, talc use), we created a five-level score. Assigning average risk to those with a score of 2, the odds ratios varied from 0.56 (95% confidence interval [CI] 0.42–0.74) for a score of 0–1 to 3.30 (95% CI 2.50–4.35) for a score of 5 or greater ($P_{\text{trend}} < .001$). The risk score was higher for women who developed ovarian cancer after hysterectomy than those who did not ($P = .01$). Lifetime risks for ovarian cancer for a woman at age 40 years are changed from 1.2% with a 0–1 score to 6.6% with a score of 5 or higher.

Conclusion—We developed a risk-assessment tool that can quantify women's risk for ovarian cancer and should be validated in other data sets.

In the 1990s, there were approximately 600,000 hysterectomies performed in the United States annually and 55% of these also involved bilateral salpin-go-oophorectomy,¹ many done solely to reduce the risk for ovarian cancer. It has been suggested that elective bilateral salpingo-oophorectomy be considered for women older than 40 years,^{2–4} whereas surveys in the United Kingdom revealed that 85–90% of physicians recommended bilateral salpingo-oophorectomy for postmenopausal women coming to hysterectomy.^{5,6} However, Parker et al,⁷ citing evidence that postmenopausal ovaries secrete androgens important to health, performed a risk-benefit analysis and concluded that ovarian conservation benefits long-term survival for women at “average risk” for ovarian cancer undergoing hysterectomy for benign disease. A subsequent study using observational data from the Nurses' Health Study

on all and various causes of mortality for hysterectomized women with and without oophorectomy supported their conclusion.⁸

In addressing the value of bilateral salpingo-oophorectomy, Parker et al distinguished average-risk women from those with known *BRCA1* or *BRCA2* mutations or a strong family history of breast and ovarian cancer. In the latter group, bilateral salpingo-oophorectomy may truly be beneficial in reducing risk for both breast and ovarian cancer.⁹ Genetic or familial risk factors or both, however, account for a small proportion of ovarian cancer. Consequently, it is important to assess ovarian cancer risk among women who lack the genetic or familial profile. In this article, we describe a risk-factor score that may be of value in further categorizing risk for ovarian cancer in women without a personal or family history of cancer to provide additional guidance to women and their physicians regarding elective bilateral salpingo-oophorectomy at the time of hysterectomy.

Materials and Methods

Data used in this study come from three enrollment phases of a case-control study of ovarian cancer in New England. The earlier two phases have been described previously.¹⁰ Briefly, we used statewide cancer registries and hospital tumor boards to identify ovarian cancer cases diagnosed in eastern Massachusetts and the entire state of New Hampshire from May 1992 to March 1997 and August 1998 to April 2003. We enrolled 1,306 women in the case group of whom 1,231 had been diagnosed with epithelial ovarian cancers. Women for the control group for the first phase of the study were identified by random-digit dialing supplemented with residents' lists for older control-group participants. Approximately 10% of households randomly dialed contained an eligible control and of these, 421 (72%) agreed to participate. All women for the control group for the second phase were identified through town resident lists (town books) in Massachusetts and drivers' license registries in New Hampshire. Of the 2,102 potential control-group participants identified through town books in both phases, 635 were ineligible, 644 declined participation, and 823 were enrolled. In total, 1,244 women were enrolled in the control group.

In the third enrollment phase, between October 2003 and November 2008, we identified 1,610 women residing in eastern Massachusetts or New Hampshire who had a diagnosis of incident ovarian cancer. Of these, 372 could not be contacted because they had died, moved, or had no telephone; did not speak English; had a nonovarian primary tumor after review; or lived outside the study area. Physicians declined permission to contact 128, and 213 declined or were too ill to participate. The remaining 897 women were enrolled; of these, 845 had epithelial ovarian tumors, including tumors of borderline malignancy.

Similar to the second phase of the study, control-group participants were identified through town books in Massachusetts and drivers' license lists in New Hampshire. Age matching was accomplished by sampling control-group participants based on the age distribution of women in the case group in the previous phases of the study with adjustment as current case-group participants were enrolled. Of the 2,523 potential control-group participants identified, 850 were ineligible because they had died, moved, had no telephone, did not speak English, had no ovaries, or were seriously ill and 816 potential control-group participants declined participation either by phone or by "opt out" postcard. A total of 857 control-group participants were enrolled.

In all phases, after written informed consent, demographic information, reproductive and medical history, and habits were assessed by in-person interview. All of the questions were framed with respect to a reference date defined as 1 year before the diagnosis date for

women in the case group and the date of interview for those in the control group. Histologic type, grade, and stage of disease were abstracted from case pathology reports. This study was approved by Brigham and Women's Hospital and Dartmouth Medical Center's institutional review boards.

We used two approaches to identify women who may be at greater risk for ovarian cancer after hysterectomy and more likely to benefit from elective bilateral salpingo-oophorectomy. In the first approach, we constructed a risk-factor score that would be relevant to decision-making for “average-risk” women coming to hysterectomy. For this analysis, we excluded all women who had prior hysterectomy (n=368). We also excluded women who would be deemed to be at above-average risk because of a personal history of breast cancer or a family history of ovarian cancer at any age or breast cancer diagnosed before age 50 years (n=532). We excluded women younger than 40 years because they would unlikely be offered bilateral salpingo-oophorectomy without an indication (n=615). We also restricted the analysis to women who had an invasive ovarian cancer, whose survival is substantially worse compared with those with borderline tumors. The final sample included 1,098 women in the case group (including 17 primary peritoneal cases) and 1,363 in the control group. In the second approach, also after excluding borderline cases and women with a personal or family history of breast or ovarian cancer, we examined women in the case (n=126, including one primary peritoneal case) and control groups (n=156) who had previous hysterectomy to determine whether risk profiles or reasons for the surgery could have distinguished women who subsequently developed ovarian cancer.

In both approaches, unconditional logistic regression models were used to identify significant risk factors distinguishing women in the case group from those in the control group. Continuous variables were categorized based on quartiles of the control distributions. Associations are presented as odds ratios, 95% confidence intervals, and Wald test *P* values. We used Wald tests from logistic regression to test for trends in ordinal categorical exposures by creating ordinal variables in which the median value or midpoint of each category was assigned to all participants within that category. To evaluate whether associations between risk factors and ovarian cancer varied by study phase, we conducted stratified analyses and likelihood ratio tests comparing models with both main effects and interaction terms with models with main effects only. Because of the small amount of missing data in this study, participants with missing exposures were dropped from analyses. Combinations of factors were examined to identify the best cumulative index of experiences associated with ovarian cancer risk. In all models, we adjusted for study phase and the matching variables age (continuous) and study site (Massachusetts, New Hampshire).

We translated the relative risks obtained from the model into absolute risks by multiplying them by cumulative risks for ovarian cancer occurrence with age 85 years as an end point. Cumulative risks were calculated from 2003–2007 age-specific incidence rates for ovarian cancer provided through Surveillance, Epidemiology, and End Results (SEER) of the National Cancer Institute.¹¹ These rates are based on all women as the denominator including women with an oophorectomy, whereas we wish cumulative risk to apply only to women with intact ovaries. From a study that examined the effect of hysterectomy and oophorectomy on genital cancer rates,¹² we adjusted age-specific incidence rates upward based on estimates of the prevalence of oophorectomy by dividing each age-specific incidence rate by one minus the prevalence of oophorectomy in that age group. Cumulative incidence was calculated by summing the adjusted age-specific incidence rates times the duration of the age-specific incidence intervals as described in Rothman and Greenland.¹³

Results

Table 1 shows the distribution of women in the case and control groups by study details and well-established or potential risk factors for ovarian cancer. The majority of women enrolled in the case group were white, which limited our ability to include race as a risk factor. We observed highly significant increases in risk associated with lack of oral contraceptive use, nulliparity, never having breastfed, no tubal ligation, painful periods or endometriosis, polycystic ovarian syndrome or obesity (body mass index [calculated as weight (kg)/height (m)]² greater than 30), and long-term genital talc use. An increasing number of estimated ovulatory cycles not interrupted by pregnancies, breastfeeding, or oral contraceptive use was also strongly associated with increased risk. Having a Jewish ethnic background was associated with increased risk but of borderline significance ($P=.08$). There was no significant association with age at menarche or menopause, fertility hormones, or menopausal hormone use (except for progesterone-only regimens, which were used by few participants in this study). We observed no significant interactions between risk factors and study phase.

The final entry in Table 1 shows the results of a simple score created to summarize risk by number of ovarian cancer risk factors. Conditions included in this score are Jewish ethnicity, more than 1 year of oral contraceptive use, nulliparity, no breastfeeding, no tubal ligation, painful periods or endometriosis, polycystic ovarian syndrome or obesity, and long-term genital talc use. There was a significant trend of increasing risk with increasing number of conditions ($P_{\text{trend}} < .001$). Compared with women with two conditions, women with zero to one condition had a 40% reduction in risk, whereas women with three, four, and five or more conditions had 60%, twofold, and threefold increases in risk, respectively. We examined this score by histologic subtype and stage of invasive epithelial ovarian cancer and observed significant trends of increasing risk for all subtypes and early- and late-stage disease (Table 2).

Table 3 shows the results of the analysis of ovarian cancer in women in the case and control groups who had prior hysterectomy. There were significant trends for risk of ovarian cancer to be lower with an older age at hysterectomy and greater with a longer interval since performance of the hysterectomy. The most common reasons for hysterectomy (by the woman's self-report) were heavy bleeding, leiomyomas, or both, which were diagnosed in 61.9% of women in the case groups and 57.0% of those in the control group. Compared with this group, there was a lower likelihood for developing ovarian cancer if the reported diagnosis was prolapse ($P=.06$). Risk of ovarian cancer among hysterectomized women increased monotonically with a higher risk-factor score ($P_{\text{trend}}=.01$). The average risk-factor score was 3.4 for all women in the case group compared with 3.0 for all women in the control group ($P=.009$) and 3.4 for women in the case group compared with 2.6 for those in the control group ($P=.01$) for women who underwent hysterectomy after age 45 years. Women with ovarian cancer who had prior hysterectomy had a higher frequency of serous histologic types (67%) and lower frequency of endometrioid and clear cell types (22%) compared with nonhysterectomized women in the case group, in which the respective frequencies were 52% and 36% ($P<.001$) (data not shown).

Table 4 translates the risk-factor score from Table 1 into absolute risks for the occurrence of ovarian cancer during the remaining years of life from a particular starting age beginning at age 40 years until age 85 years as an end point. Assuming that the category of two risk factors best represents risk in the general population (and therefore the referent category), we multiplied the cumulative risks by 0.6, 1.6, 2.1, and 3.3 for the score categories 0–1, 3, 4, and 5 or more, respectively. As illustrated in Table 4, a woman who is 40 years old and has zero to one risk factors would have an absolute risk of developing ovarian cancer by age 85

years of 1.2% (95% CI 0.8–1.4%), whereas a woman with five or more risk factors would have a risk of 6.6% (95% CI 5.0–8.6%).

Discussion

Current American College of Obstetricians and Gynecologist guidelines¹⁴ recommend that family history, menopausal status, and pelvic disease that might predispose to reoperation be considered in whether bilateral salpingo-oophorectomy should be offered to women coming to hysterectomy. The guidelines state that “Strong consideration should be made for retaining normal ovaries in premenopausal woman who are not at increased genetic risk of ovarian cancer.” Bilateral salpingo-oophorectomy should be offered to women with known or suspected *BRCA1* or *BRCA2* mutations after completion of childbearing. For postmenopausal women (with normal ovaries), the guidelines state: “Given the risk of ovarian cancer in postmenopausal women, ovarian removal at the time of hysterectomy should be considered for these women.” Nulligravidity and family history of ovarian cancer are mentioned as increasing risk for ovarian cancer; and pregnancy, tubal ligation, and use of oral contraceptive are mentioned as decreasing risk. However, no concrete rules are offered on how these characteristics might be used to weigh risk in an individual woman.

In this article, we derive a simple score to help physicians and women weigh individual risk for ovarian cancer. We first excluded those women who would already be viewed at high risk such as those with a personal history of breast cancer or family history (of a mother or sister) with breast cancer (before age 50 years) or ovarian cancer at any age. To make the model most relevant to women considering oophorectomy at the time of hysterectomy, we then excluded women younger than 40 years, who may be inappropriate candidates for elective oophorectomy without known ovarian pathology, as well as women in the case and control groups who had prior hysterectomy. We identified those risk factors to be considered: parity, oral contraceptive use, breastfeeding, tubal ligation, painful periods or endometriosis, obesity or polycystic ovarian syndrome, and talc use. These risk factors are concordant with published epidemiologic data related to reproductive factors,^{15–23} use of talc,^{17–19} tubal ligation,^{20,24–27} endometriosis,²⁸ and polycystic ovarian syndrome or obesity.^{29,30} It is also known that approximately 2% of Jewish women carry one of three founder mutations of *BRCA1* or *BRCA2*. Approximately 40% of Jewish women who present with ovarian cancer will carry a founder mutation.³¹ Even after removing those with a family history of breast or ovarian cancer, women with Jewish ethnic backgrounds remain at approximately a 30% increased in risk for ovarian cancer.

Creating simple dichotomies from these factors and summing them allowed a five-level risk score to be constructed, which correlated directly with increasing relative risks for ovarian cancer. Combining various risk factors to create a risk score for ovarian cancer has been performed in studies that have looked at the estimated number of ovulatory cycles, which also directly correlates with ovarian cancer risk.^{10,32} However, we did not include ovulatory cycles in our model because estimating them would require a calculator or paper and pencil. Thus, a simple linear combination of diverse risk factors, even those that do not logically fit into an ovulatory cycles score, adds cumulatively to increase ovarian cancer risk. We previously have discussed the potential basis for this phenomenon as indicating a common pathway for many ovarian cancer risk factors operating through their ability to affect immunity related to important cell surface glycoproteins, known as mucins, especially MUC1.³³

We also performed an analysis on women who had previous hysterectomy. Most case–control studies of ovarian cancer allow women with hysterectomy to be included in the control group as long as they said their operation did not include oophorectomy. Nearly all

hysterectomized women who later developed ovarian cancer would be correct in their recollection that they did not have a bilateral salpingo-oophorectomy. However, there is a greater likelihood that those who did not develop ovarian cancer may have incorrectly stated their ovaries were left, leading to misclassification. We are uncertain whether this may partially explain the greater percentage of control-group participants who reported hysterectomy without bilateral salpingo-oophorectomy after age 46 years compared with women in the case group observed in this study. Because historical medical records could not be retrieved for participants, it was also necessary to rely on the woman's recollection of why the surgery was performed. Women who went on to develop ovarian cancer after hysterectomy were less likely to have had hysterectomy for prolapse ($P=.06$). Regarding our risk score, we again found a significant trend for a higher cumulative score to predict greater risk for ovarian cancer occurring after hysterectomy. Notably, the average score for women who had hysterectomy after age 45 years and subsequently developed ovarian cancer was 3.4 for women in the case group compared with 2.6 for those in the control group ($P=.01$). It may be particularly important to initiate a dialogue about ovarian cancer risk factors before hysterectomy after this age.

Potential weaknesses of this study derive from the fact that case-control data were used to create our scoring system. Biases may occur in case-control studies that can affect risk estimates, including recall bias leading to misclassification of exposure. In addition, selection biases may occur in that exposures for women with rapidly fatal disease who could not be interviewed may be underrepresented. Nevertheless, the risk factors we observed agree with published data, some of which come from cohort studies in which these biases are less likely to occur and our scoring system was applied to both early- and late-stage disease (Table 2). Another limitation of case-control data is that it allows only relative, not absolute, risks to be calculated directly. To overcome this limitation, we multiplied the odds ratio for each score by estimated lifetime risks of ovarian cancer. The age-specific incidence rates used to calculate lifetime risks were first adjusted upward based on the prevalence of oophorectomy in the general population.

Our risk score does not provide a precise formula for when elective oophorectomy should be recommended because we did not perform a cost-benefit analysis taking into consideration the competing risks from long-term complications of bilateral salpingo-oophorectomy, including bone fracture and cardiovascular diseases. Based on the rarity of ovarian cancer relative to other conditions considered by Parker et al in their analysis of the Nurses' Health Data, it is possible that, even if all cases of ovarian cancer could be predicted and eliminated, overall benefits might not be shifted toward selective bilateral salpingo-oophorectomy. Nevertheless, we think it is important for physicians and their patients to weigh individual risk for ovarian cancer when considering elective oophorectomy and have a discussion about individual risk for ovarian cancer. Even if the woman at elevated risk elects to conserve ovaries, bilateral salpingectomy without oophorectomy might be considered. Emerging evidence suggests that many high-grade invasive ovarian cancers may have their origin in the fallopian tubes rather than ovaries,³⁴ prompting Canadian health officials in British Columbia to urge gynecologists to perform salpingectomy (without oophorectomy) on women coming for hysterectomy. Our risk score might enable selection of women who would be candidates for this surgical alternative to oophorectomy if women at higher risk do not elect to have oophorectomy. Although we believe our scoring system is an improvement over existing methods for assessing risk for ovarian cancer in women without a family history, it should be viewed as a prototype until it can be validated in other data sets, especially with prospectively collected data from women including more nonwhites who were underrepresented in our study.

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References

1. Keshavarz H, Hillis S, Kieke B, Marchbanks PA. Hysterectomy surveillance—United States, 1994–1999. *MMWR CDC Surveill Summ.* 2002; 51:1–8.
2. Coukos G, Rubin SC. Prophylactic oophorectomy. *Best Pract Res Clin Obstet Gynaecol.* 2002; 16:597–609. [PubMed: 12413937]
3. Kontoravdis A, Kalogirou D, Antoniou G, Kontoravdis N, Karakitsos P, Zourlas PA. Prophylactic oophorectomy in ovarian cancer prevention. *Int J Gynaecol Obstet.* 1996; 54:257–62. [PubMed: 8889634]
4. Studd J. Does retention of the ovaries improve long-term survival after hysterectomy? Prophylactic oophorectomy. *Climacteric.* 2006; 9:164–6. [PubMed: 16766429]
5. Geary M, Geoghegan A, Foley M. Prevention of ovarian cancer: a survey of the practice of prophylactic oophorectomy by consultant gynaecologists in Ireland. *Ir Med J.* 1997; 90:186–7. [PubMed: 9345830]
6. Jacobs I, Oram D. Prevention of ovarian cancer: a survey of the practice of prophylactic oophorectomy by fellows and members of the Royal College of Obstetricians and Gynaecologists. *Br J Obstet Gynaecol.* 1989; 96:510–5. [PubMed: 2757978]
7. Parker WH, Broder MS, Liu Z, Shoupe D, Farquhar C, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. *Clin Obstet Gynecol.* 2007; 50:354–61. [PubMed: 17513923]
8. Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol.* 2009; 113:1027–37. [PubMed: 19384117]
9. Kauff ND, Barakat RR. Risk-reducing salpingo-oophorectomy in patients with germline mutations in BRCA1 or BRCA2. *J Clin Oncol.* 2007; 25:2921–7. [PubMed: 17617523]
10. Terry KL, De Vivo I, Titus-Ernstoff L, Shih MC, Cramer DW. Androgen receptor cytosine, adenine, guanine repeats, and haplotypes in relation to ovarian cancer risk. *Cancer Res.* 2005; 65:5974–81. [PubMed: 15994977]
11. Altekruse, SF.; Kosary, CL.; Krapcho, M.; Neyman, N.; Aminou, R.; Waldron, W., et al. SEER cancer statistics review, 1975–2007. Bethesda (MD): National Cancer Institute; 2010. Available at: http://seer.cancer.gov/csr/1975_2007/ based on November 2009 SEER data submission. Retrieved January 18, 2011
12. Merrill RM. Impact of hysterectomy and bilateral oophorectomy on race-specific rates of corpus, cervical, and ovarian cancers in the United States. *Ann Epidemiol.* 2006; 16:880–7. [PubMed: 17027290]
13. Rothman, KJ.; Greenland, S. *Modern epidemiology.* 2nd. Philadelphia (PA): Lippincott Williams & Wilkins; 1998.
14. *Obstet Gynecol.* Vol. 111. ACOG Practice Bulletin No. 89. American College of Obstetricians and Gynecologists; 2008. Elective and risk-reducing salpingo-oophorectomy; p. 231–41.
15. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol.* 1992; 136:1184–203. [PubMed: 1476141]
16. Kumle M, Weiderpass E, Braaten T, Adami HO, Lund E. Risk for invasive and borderline epithelial ovarian neoplasias following use of hormonal contraceptives: the Norwegian-Swedish Women's Lifestyle and Health Cohort Study. *Br J Cancer.* 2004; 90:1386–91. [PubMed: 15054460]
17. Cramer DW, Liberman RF, Titus-Ernstoff L, Welch WR, Greenberg ER, Baron JA, et al. Genital talc exposure and risk of ovarian cancer. *Int J Cancer.* 1999; 81:351–6. [PubMed: 10209948]
18. Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. *Cancer.* 1982; 50:372–6. [PubMed: 7083145]

19. Gates MA, Tworoger SS, Terry KL, Titus-Ernstoff L, Rosner B, De Vivo I, et al. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:2436–44. [PubMed: 18768514]
20. Tworoger SS, Fairfield KM, Colditz GA, Rosner BA, Hankinson SE. Association of oral contraceptive use, other contraceptive methods, and infertility with ovarian cancer risk. *Am J Epidemiol.* 2007; 166:894–901. [PubMed: 17656616]
21. Titus-Ernstoff L, Rees JR, Terry KL, Cramer DW. Breastfeeding the last born child and risk of ovarian cancer. *Cancer Causes Control.* 2010; 21:201–7. [PubMed: 19902367]
22. Purdie DM, Siskind V, Bain CJ, Webb PM, Green AC. Reproduction-related risk factors for mucinous and nonmucinous epithelial ovarian cancer. *Am J Epidemiol.* 2001; 153:860–4. [PubMed: 11323316]
23. Danforth KN, Tworoger SS, Hecht JL, Rosner BA, Colditz GA, Hankinson SE. Breastfeeding and risk of ovarian cancer in two prospective cohorts. *Cancer Causes Control.* 2007; 18:517–23. [PubMed: 17450440]
24. Green A, Purdie D, Bain C, Siskind V, Russell P, Quinn M, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. *Int J Cancer.* 1997; 71:948–51. [PubMed: 9185694]
25. Hankinson SE, Hunter DJ, Colditz GA, Willett WC, Stampfer MJ, Rosner B, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer. A prospective study. *JAMA.* 1993; 270:2813–8. [PubMed: 8133619]
26. Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology.* 2000; 11:111–7. [PubMed: 11021606]
27. Purdie D, Green A, Bain C, Siskind V, Ward B, Hacker N, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. *Int J Cancer.* 1995; 62:678–84. [PubMed: 7558414]
28. Vlahos NF, Kalampokas T, Fotiou S. Endometriosis and ovarian cancer: a review. *Gynecol Endocrinol.* 2010; 26:213–9. [PubMed: 19718562]
29. Chittenden BG, Fullerton G, Maheshwari A, Bhattacharya S. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. *Reprod Biomed Online.* 2009; 19:398–405. [PubMed: 19778486]
30. Olsen CM, Green AC, Whiteman DC, Sadeghi S, Kolahdooz F, Webb PM. Obesity and the risk of epithelial ovarian cancer: a systematic review and meta-analysis. *Eur J Cancer.* 2007; 43:690–709. [PubMed: 17223544]
31. Robles-Diaz L, Goldfrank DJ, Kauff ND, Robson M, Offit K. Hereditary ovarian cancer in Ashkenazi Jews. *Fam Cancer.* 2004; 3:259–64. [PubMed: 15516850]
32. Tung KH, Wilkens LR, Wu AH, McDuffie K, Nomura AM, Kolonel LN, et al. Effect of anovulation factors on pre- and postmenopausal ovarian cancer risk: revisiting the incessant ovulation hypothesis. *Am J Epidemiol.* 2005; 161:321–9. [PubMed: 15692075]
33. Cramer DW, Titus-Ernstoff L, McKolanis JR, Welch WR, Vitonis AF, Berkowitz RS, et al. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:1125–31. [PubMed: 15894662]
34. Salvador S, Gilks B, Kobel M, Huntsman D, Rosen B, Miller D. The fallopian tube: primary site of most pelvic high-grade serous carcinomas. *Int J Gynecol Cancer.* 2009; 19:58–64. [PubMed: 19258943]

Table 1
Conditions and Exposures Associated With Invasive Ovarian Cancer

	No. of Women in the Case Group (n = 1,098)	No. of Women in the Control Group (n = 1,363)	OR (95% CI)*	P
Study				
Phase 1: 1992–1997	284 (25.9)	316 (23.2)		
Phase 2: 1998–2003	327 (29.8)	456 (33.5)		
Phase 3: 2003–2008	487 (44.4)	591 (43.4)		
Site				
Massachusetts	860 (78.3)	1,117 (82.0)		
New Hampshire	238 (21.7)	246 (18.0)		
Race				
White	1,056 (96.2)	1,335 (98.0)	1.00	
African American	15 (1.4)	11 (0.8)	1.79 (0.82–3.93)	.15
Hispanic	9 (0.8)	12 (0.9)	1.02 (0.42–2.43)	.97
Asian	14 (1.3)	3 (0.2)	6.28 (1.80–21.9)	.004 [†]
Other	4 (0.4)	2 (0.2)	2.52 (0.46–13.8)	.29
Jewish ethnicity				
No	1,017 (92.6)	1,283 (94.1)	1.00	
Yes	81 (7.4)	80 (5.9)	1.34 (0.97–1.85)	.08
Oral contraceptive use				
1 y or more	436 (39.7)	726 (53.3)	1.00	
Less than 1 y or no use	662 (60.3)	637 (46.7)	1.81 (1.52–2.15)	<.001
Parity				
Parous	794 (72.3)	1,162 (85.2)	1.00	
Nulliparous	304 (27.7)	201 (14.8)	2.34 (1.91–2.87)	<.001
Breastfeeding				
Any	353 (32.2)	690 (50.6)	1.00	
None	745 (67.8)	673 (49.4)	2.18 (1.84–2.57)	<.001
Tubal ligation				
Yes	142 (12.9)	294 (21.6)	1.00	
No	956 (87.1)	1,069 (78.4)	1.87 (1.50–2.33)	<.001
Pain with periods or endometriosis				
No	642 (58.5)	925 (67.9)	1.00	
Yes	456 (41.5)	438 (32.1)	1.53 (1.30–1.81)	<.001
PCOS or obesity (BMI more than 30 kg/m ²)				
No	785 (71.5)	1,039 (76.2)	1.00	
Yes	313 (28.5)	324 (23.8)	1.27 (1.06–1.52)	.01
Long-term genital talc use (10 y or more)				
No	932 (84.9)	1,211 (88.8)	1.00	
Yes	166 (15.1)	152 (11.2)	1.42 (1.12–1.81)	.004
Ovulatory cycles				
Quartile 1	149 (14.5)	317 (25.0)	1.00	

	No. of Women in the Case Group (n = 1,098)	No. of Women in the Control Group (n = 1,363)	OR (95% CI)*	P
Quartile 2	218 (21.2)	316 (24.9)	1.51 (1.16–1.97)	.002
Quartile 3	300 (29.1)	317 (25.0)	2.14 (1.65–2.77)	<.001
Quartile 4	363 (35.2)	319 (25.1)	2.63 (2.02–3.43)	<.001
Early menarche (younger than 12 y)				
Younger than 12	237 (21.7)	283 (20.8)	1.03 (0.85–1.25)	.77
12–15	815 (74.5)	1,006 (74.0)	1.00	
Older than 15	42 (3.8)	71 (5.2)	0.73 (0.49–1.08)	.11
Age at natural menopause (y)				
Younger than 49	243 (33.2)	283 (33.0)	1.00	
49–51	228 (31.1)	272 (31.7)	0.99 (0.77–1.27)	.93
Older than 51	262 (35.7)	303 (35.3)	1.03 (0.81–1.32)	.80
Postmenopausal hormone use				
None	839 (76.8)	983 (72.6)	1.00	
Estrogen only	54 (5.0)	77 (5.7)	0.77 (0.54–1.12)	.18
Estrogen and progesterone	174 (15.9)	245 (18.1)	0.83 (0.66–1.03)	.10
Progesterone only	4 (0.4)	17 (1.2)	0.28 (0.09–0.84)	.02
Oral contraceptives	3 (0.3)	8 (0.6)	0.46 (0.12–1.73)	.25
Other	18 (1.6)	25 (1.8)	0.82 (0.44–1.52)	.52
Fertility hormones				
No	1,014 (92.4)	1,255 (92.1)	1.00	
Yes	84 (7.6)	108 (7.9)	0.97 (0.72–1.31)	.84
Total number of risk factors [‡]				
0–1	98 (8.9)	311 (22.8)	0.56 (0.42–0.74)	<.001
2	201 (18.3)	361 (26.5)	1.00	
3	312 (28.4)	340 (24.9)	1.66 (1.31–2.09)	<.001
4	255 (23.2)	222 (16.3)	2.10 (1.64–2.70)	<.001
5 or more	232 (21.1)	129 (9.5)	3.30 (2.50–4.35)	<.001

OR, odds ratio; CI, confidence interval; PCOS, polycystic ovarian syndrome; BMI, body mass index.

Data are n (%) unless otherwise specified.

* Adjusted for study center, reference age, and study phase.

[†] The excess of Asian ovarian cancer cases simply may reflect limited ability to recruit Asian women for the control group.

[‡] Risk factors include Jewish ethnicity, less than 1 year of oral contraceptive use, nulliparity, no breastfeeding, no tubal ligation, painful periods or endometriosis, PCOS or BMI greater than 30 kg/m², and long-term talc use.

Table 2
Cumulative Index of Experiences Associated With Invasive Ovarian Cancer by Histologic Type and Stage

Total No. of Risk Factors *	Serous Invasive (n=566) [†]	Mucinous (n=62) [†]	Endometrioid (n=223) [†]	Clear Cell (n=175) [†]	Other or Undifferentiated (n=72) [†]	Early Stage (I-II) (n=462) [†]	Late Stage (III-IV) (n=634) [†]
0-1	0.56 (0.39-0.80)	0.61 (0.24-1.56)	0.66 (0.36-1.20)	0.34 (0.16-0.71)	0.88 (0.32-2.40)	0.52 (0.33-0.82)	0.58 (0.42-0.81)
2	1.00	1.00	1.00	1.00	1.00	1.00	1.00
3	1.39 (1.04-1.84)	1.62 (0.79-3.33)	2.38 (1.50-3.77)	1.43 (0.88-2.33)	3.56 (1.66-7.63)	2.11 (1.51-2.96)	1.43 (1.09-1.87)
4	1.65 (1.22-2.24)	1.46 (0.65-3.27)	3.02 (1.86-4.89)	2.92 (1.82-4.68)	2.95 (1.28-6.83)	3.28 (2.32-4.63)	1.55 (1.16-2.09)
5 or more	2.75 (1.98-3.82)	2.01 (0.86-4.75)	5.78 (3.54-9.42)	3.54 (2.11-5.93)	3.16 (1.25-7.99)	5.17 (3.58-7.47)	2.39 (1.73-3.30)
P trend	<.001	.01	<.001	<.001	<.001	<.001	<.001

Data are odds ratio (95% confidence interval) unless otherwise specified.

* Risk factors include Jewish ethnicity, less than 1 year of oral contraceptive pill use, nulliparity, no breastfeeding, no tubal ligation, painful periods or endometriosis, polycystic ovarian syndrome or body mass index greater than 30 kg/m², and long-term talc use.

[†] Adjusted for study center, reference age, and study phase.

Table 3
Hysterectomy Details and Cumulative Index of Experiences Among Women With Invasive Ovarian Cancer and Women in the Control Group Who Had Hysterectomy and Who Had No Personal History of Breast Cancer, Family History of Ovarian Cancer, or Early-Onset Breast

	No. of Women in the Case Group (n = 126)	No. of Women in the Control Group (n=156)	OR (95% CI)*	P
Age at hysterectomy (y)				
Younger than 35	35 (27.8)	36 (23.1)	1.00	
35–40	44 (34.9)	43 (27.6)	0.96 (0.50–1.82)	.89
41–46	30 (23.8)	39 (25.0)	0.77 (0.39–1.52)	.45
Older than 46	17 (13.5)	38 (24.4)	0.42 (0.20–0.90)	.02
Ptrend				.02
Time between hysterectomy and reference date (y)				
10 or less	27 (21.4)	42 (28.8)	1.00	
11–20	19 (15.1)	39 (25.0)	0.87 (0.39–1.92)	.72
21–30	45 (35.7)	43 (27.6)	1.84 (0.84–4.03)	.13
More than 30	35 (27.8)	29 (18.6)	2.17 (0.84–5.60)	.11
Ptrend				.04
Reason for hysterectomy				
Leiomyomas or heavy periods	78 (61.9)	89 (57.0)	1.00	
Endometriosis	10 (7.9)	13 (8.3)	0.92 (0.38–2.24)	.86
Prolapsed uterus	9 (7.1)	22 (14.1)	0.45 (0.19–1.05)	.06
Other	29 (23.0)	32 (20.5)	0.98 (0.54–1.77)	.94
Total number of risk factors [†]				
0–1	11 (8.7)	23 (14.7)	0.97 (0.39–2.38)	.94
2	21 (16.7)	41 (26.3)	1.00	
3	33 (26.2)	34 (21.8)	1.88 (0.92–3.86)	.08
4	33 (26.2)	35 (22.4)	1.83 (0.89–3.76)	.10
5 or more	28 (22.2)	23 (14.7)	2.45 (1.14–5.28)	.02
Ptrend				.01

OR, odds ratio; CI, confidence interval.

Data are n (%) unless otherwise specified.

* Adjusted for study center, reference age, and study phase.

[†] Risk factors include Jewish ethnicity, less than 1 year of oral contraceptive use, nulliparity, no breastfeeding, no tubal ligation, painful periods or endometriosis, polycystic ovarian syndrome or body mass index greater than 30 kg/m², and long-term talc use. The score was adjusted to estimate that which would have been observed before hysterectomy.

Table 4
Cumulative Risk of Developing Ovarian Cancer by Age 85 Years Using Oophorectomy-Adjusted Cumulative Incidence and the Relative Risks Associated With Each Level of the Risk-Factor Score

Total No. of Risk Factors	Probability of Developing Ovarian Cancer by Age 85 y Starting at Age									
	40	45	50	55	60	65	70	75	80	
0-1	1.2 (0.8-1.4)	1.2 (0.8-1.4)	1.1 (0.8-1.3)	1.1 (0.7-1.3)	1.0 (0.6-1.1)	0.8 (0.6-1.0)	0.7 (0.4-0.8)	0.5 (0.3-0.6)	0.2 (0.2-0.3)	
2*	2.0	2.0	1.9	1.8	1.6	1.4	1.1	0.8	0.4	
3	3.2 (2.6-4.2)	3.2 (2.6-4.2)	3.0 (2.5-4.0)	2.9 (2.3-3.8)	2.6 (2.1-3.4)	2.2 (1.8-2.9)	1.8 (1.4-2.3)	1.3 (1.0-1.7)	0.6 (0.5-0.8)	
4	4.2 (3.2-5.4)	4.2 (3.2-5.4)	4.0 (3.0-5.1)	3.8 (2.9-4.9)	3.4 (2.6-4.3)	2.9 (2.2-3.8)	2.3 (1.8-3.0)	1.7 (1.3-2.2)	0.8 (0.6-1.1)	
5 or more	6.6 (5.0-8.6)	6.6 (5.0-8.6)	6.3 (4.8-8.2)	5.9 (4.5-7.7)	5.3 (4.0-6.9)	4.6 (3.5-6.0)	3.6 (2.8-4.7)	2.6 (2.0-3.4)	1.3 (1.0-1.7)	

* Two risk factors was chosen as the referent category.

Data are cumulative risk (95% confidence interval).