Prospective Study of Talc Use and Ovarian Cancer

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Background: **Perineal talc use has been associated with an increased risk of ovarian cancer in a number of case–control studies; however, this association remains controversial because of limited supporting biologic evidence and the potential for recall bias or selection bias in case–control studies. In this study, we conducted a prospective analysis of perineal talc use and the risk of ovarian cancer.** ***Methods:*** **The Nurses' Health Study is a prospective study of 121 700 female registered nurses in the United States who were aged 30–55 years at enrollment in 1976. Talc use was ascertained in 1982 by use of a self-administered questionnaire: after exclusions, 78 630 women formed the cohort for analysis. Three hundred seven epithelial ovarian cancers subsequently diagnosed in this cohort through June 1, 1996, were confirmed by medical record review and met inclusion criteria. Proportional hazards models by use of pooled logistic regression were used to derive relative risks (RRs) and 95% confidence intervals (CIs).** ***Results:*** **In 1982, 40.4% (n = 31 789) of the cohort reported ever using talc, and 14.5% (n = 11 411) reported ever using talc daily. We observed no overall association with ever talc use and epithelial ovarian cancer (multivariate RR = 1.09; 95% CI = 0.86–1.37) and no increase in risk of ovarian cancer with increasing frequency of use. There was a modest elevation in risk for ever talc use and invasive serous ovarian cancer (multivariate RR = 1.40; 95% CI = 1.02–1.91). The risk of epithelial ovarian cancer for talc users was not greater among women who had never had a tubal ligation (multivariate RR = 0.97; 95% CI = 0.71–1.32).** ***Conclusion:*** **Our results provide little support for any substantial association between perineal talc use and ovarian cancer risk overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancer. [J Natl Cancer Inst 2000;92:249–52]**

Talc was originally implicated as a possible ovarian carcinogen because of its chemical similarity to asbestos, which has been linked to ovarian cancer in occupational settings and is associated with mesotheliomas histologically resembling epithelial ovarian cancers *(1–3)*. Perineal use of talcum powder has been positively associated with ovarian cancer risk in a number of case–control studies *(4–13)*, although the magnitude of the associations has been modest, with odds ratios ranging from 1.2 to 1.9, and not all results reached statistical significance *(5,6,8)*. Despite this relative consistency among studies, the limited supporting biologic evidence, together with the possibility of recall and selection bias in case–control studies *(1)*, has raised questions about the plausibility of the association. We, therefore, prospectively examined the relationship between perineal talc use and ovarian cancer risk in a large cohort of U.S. women.

METHODS

The Nurses' Health Study, established in 1976, is a prospective cohort of 121 700 registered nurses living in 11 of the larger states in the United States. Questionnaires were mailed to married, female nurses aged 30–55 years, requesting information on health-related issues, including medical history and potential risk factors for cancer. Follow-up questionnaires have been mailed every 2 years to update information on exposures and to ascertain newly diagnosed diseases. The study was approved by the Human Research Committee at the Brigham and Women's Hospital, Boston, MA.

Ascertainment of cases. We sought medical records from all women who reported a diagnosis of ovarian cancer or who were deceased in each follow-up cycle. Records were reviewed by physicians unaware of exposure status. Histologic subtypes were determined from pathology reports, and epithelial ovarian cancers were classified as serous cancers (including cystadenocarcinoma and papillary adenocarcinoma), mucinous cancers (including adenocarcinoma and mucinous papillary adenocarcinoma), and endometrioid cancers (clear cell and other types, including mixed epithelial tumors). Borderline histologic tumors are included in the analysis. Deaths are reported by relatives and postal authorities, as well as a search of the National Death Index. Mortality follow-up is estimated to be 98% complete in this cohort *(14)*. Cases of epithelial ovarian cancer (International Classification of Diseases Code, ICD183.0), confirmed by medical record review or death certificate, occurring between the return of the 1982 questionnaire and June 1, 1996, were included in the analysis.

Exclusions. Women who did not respond to the question on talc use in 1982 were excluded from this analysis. We also excluded women who had reported a diagnosis of cancer (other than nonmelanoma skin cancer) before 1982, as well as women who reported bilateral oophorectomy, surgery with an unknown number of ovaries removed, and a history of radiation therapy. Validity of self-reported surgical menopause has been assessed previously, and agreement with medical records was more than 97% *(15)*. These exclusions were updated every 2 years. At baseline, 78 630 women were eligible for the analysis. The resulting population after exclusions contributed 984 212 person-years of follow-up and 307 cases of epithelial ovarian cancer.

Ascertainment of talc exposure. Use of talcum powder was ascertained on the 1982 questionnaire in the following ways: "Have you ever commonly used talcum, baby powder, or deodorizing powder *a*) to apply to perineal (private) area? No, daily, one to six times per week, or less than once per week or *b*) to apply on sanitary napkins? No, Yes." We classified "ever talc use" as ever talc use on either the perineal area or sanitary napkins.

Other covariates. Potential risk factors and confounders of the association between ovarian cancer and exposures of interest in this analysis also were obtained from the biennial questionnaires and were updated every 2 years where relevant. Oral contraceptive use was asked every 2 years from 1976 through 1982, by which time use was rare. Tubal ligation history was asked as part of a question on methods of contraception from 1976 through 1984, and, in 1994, women were asked if they had ever

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See "Notes" following "References."

had a tubal ligation and, if so, at what age. Family history of ovarian cancer was not asked until 1992. Parity was defined as the number of pregnancies lasting 6 months or more and was asked through 1984.

Statistical analysis. Incidence rates (number of cases for each category of exposure divided by person months of follow-up in that cycle) were calculated for each category, adjusting for age in 5-year intervals. Proportional hazards models by use of pooled logistic regression were used to derive relative risks (RRs) and 95% confidence intervals (CIs) of disease for each exposure category *(16)*. For age-adjusted analyses, we categorized variables as follows: parity (0, 1–2, or ⩾3), oral contraceptive use (never, past, or current), tubal ligation (yes or no), postmenopausal hormone use (never, past, or current), cigarette smoking (never, past, or current), and body mass index, i.e., weight in kilograms/height in meters squared (<21, 21.0–22.9, 23.0–24.9, 25.0–28.9, or ⩾29 kg/m^2). In multivariate analyses, we adjusted for age (years) and for potential risk factors by use of indicator variables for each category as described above, except for parity (0, 1–2, 3–4, or ⩾5) and duration of oral contraceptive use (never or <3, 3–5, or >5 years), for which we used a larger number of categories to more appropriately control for confounding. In addition we controlled for age at menarche, duration of breast-feeding, and age at menopause. However, since this did not alter the estimates for talc use, further models did not control for these variables. Body mass index and duration of oral contraceptive use were also entered as continuous variables, and similar estimates were obtained. All RRs reported are multivariate unless otherwise stated. *P* values reported are two-sided.

RESULTS

Three hundred seven women developed ovarian cancer in the cohort from 1982 through 1996 who responded to the 1982 questionnaire on talc use. In 1982, 40.4% (n = 31 789) of the baseline cohort reported ever using talc, of which 14.5% (n = 11 411) were ever daily talc users. Talc use was associated with higher body mass index and inversely associated with current cigarette smoking (Table 1).

We did not observe an overall association with ever use of talc and epithelial ovarian cancer (RR = 1.09; 95% CI = 0.86–1.37). There was also no elevation in risk among daily users of perineal talc, and no trend was seen with increasing frequency of use (Table 2). Talc use on sanitary napkins was inversely related to ovarian cancer, but the association was statistically nonsignificant. Exclusion of use of talc on sanitary napkins from the ever use of talc variable did not substantially alter the results. We also evaluated the risk for women who used both perineal talc and talc on sanitary napkins but did not see an effect compared with never users of talc (RR = 0.90; 95% CI = 0.59–1.37).

When we stratified by histologic subtype, we observed a modest increase in risk for ever talc use for serous invasive cancers (RR = 1.40; 95% CI = 1.02–1.91) but not for all serous cancers (including borderline cancers), endometrioid cancers, or mucinous cancers (Table 3). For women who reported ever daily use of talc, the RR of invasive serous cancer was 1.49 (95% CI = 0.98–2.26). The RRs for ever talc users of less than once per week and one to six times per week were 1.29 (95% CI = 0.81–2.04) and 1.49 (95% CI = 0.77–2.11), respectively (*P* for trend = .05).

Table 1. Age-standardized prevalence of ovarian cancer risk factors according to perineal talc use in 1982*

	Ever perineal talc use, %† (n = 31 789)	No perineal talc use, % (n = 46 841)
Parity		
0	6.3	6.4
1–2	35.0	35.2
⩾3	58.7	58.4
Oral contraceptive use		
Current	0.5	0.6
Past	49.2	49.8
Never	50.4	49.6
Hormone use, postmenopausal women only		
Current	12.1	12.9
Past	20.5	20.4
Never	67.4	66.7
Tubal ligation, yes	17.6	17.6
Cigarette smoking		
Never	44.9	43.2
Past	30.3	28.3
Current	24.9	28.5
Body mass index quintiles, kg/m^2		
<21.0	16.0	22.1
21.0–22.9	20.9	25.4
23.0–24.9	20.1	20.6
25.0–28.9	22.8	19.6
⩾29	19.8	12.0

*Numbers do not always add up to 100% because of missing data or rounding.
†Ever talc use coded as either talc use on perineal area or talc use on sanitary napkins.

Table 2. Talc use and ovarian cancer: 1982 through 1996 (all subtypes included)*

	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR† (95% CI)
Talc use on perineum				
Never	186	608 020	1.0 (referent)	1.0 (referent)
<1/wk	43	128 923	1.10 (0.79–1.53)	1.14 (0.81–1.59)
1–6/wk	30	105 186	0.95 (0.65–1.40)	0.99 (0.67–1.46)
Daily	48	142 083	1.09 (0.79–1.49)	1.12 (0.82–1.55)
Talc use on sanitary napkins				
No	242	781 421	1.0 (referent)	1.0 (referent)
Yes	32	111 399	0.89 (0.62–1.29)	0.89 (0.61–1.28)
Ever perineal talc use				
No	179	586 758	1.0 (referent)	1.0 (referent)
Yes	128	397 454	1.05 (0.84–1.32)	1.09 (0.86–1.37)
Talc use, perineal and sanitary napkins				
None	179	586 758	1.0 (referent)	1.0 (referent)
Either talc use on perineum or use on sanitary napkins	103	307 317	1.11 (0.87–1.41)	1.15 (0.90–1.46)
Use on both sanitary napkins and perineum	25	90 137	0.89 (0.58–1.35)	0.90 (0.59–1.37)

*RR = relative risk; CI = confidence interval.
†Multivariate analyses control for age (years), parity (0, 1–2, 3–4, or ⩾5), duration of oral contraceptive use (never or <3 y, 3–5 y, or >5 y), body mass index (body weight in kilograms/height in meters squared: <21, 21.0–22.9, 23.0–24.9, 25.0–28.9, or ⩾29 kg/m^2), tubal ligation history (yes or no), smoking status (never, past, or current), and postmenopausal hormone use (never, past, or current).

Table 3. Talc use and ovarian cancer: 1982–1996 (by histologic subtype)*

Histologic subtype	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR† (95% CI)
All serous cancers, ever perineal talc use				
No	101	586 771	1.0 (referent)	1.0 (referent)
Yes	84	397 459	1.23 (0.92–1.64)	1.26 (0.94–1.69)‡
Serous invasive cancers, ever perineal talc use				
No	84	586 771	1.0 (referent)	1.0 (referent)
Yes	76	397 459	1.33 (0.98–1.82)	1.40 (1.02–1.91)‡
Endometrioid cancers, ever perineal talc use				
No	26	586 771	1.0 (referent)	1.0 (referent)
Yes	16	397 459	0.91 (0.49–1.69)	0.91 (0.49–1.87)
Mucinous cancers, ever perineal talc use				
No	30	586 771	1.0 (referent)	1.0 (referent)
Yes	20	397 459	0.98 (0.56–1.73)	0.93 (0.53–1.66)

*RR = relative risk; CI = confidence interval.

†Multivariate analyses controlling for age (years), parity (0, 1–2, or ⩾3), oral contraceptive use (never or ever), and tubal ligation history (yes or no).

‡Multivariate analyses control for age (years), parity (0, 1–2, 3–4, or ⩾5), duration of oral contraceptive use (never or <3 y, 3–5 y, or >5 y), body mass index (body weight in kilograms/height in meters squared: <21, 21.0–22.9, 23.0–24.9, 25.0–28.9, or ⩾29 kg/m^2), tubal ligation history (yes or no), smoking status (never, past, or current), and postmenopausal hormone use (never, past, or current).

Because the talc hypothesis depends on the ability of fibers to migrate up a patent genital tract to the ovaries, we evaluated the risk among women who had reported a tubal ligation and those who had not. Women who were ever talc users and had never had a tubal ligation were not at increased risk of epithelial ovarian cancer compared with women who had not used talc (RR = 0.97; 95% CI = 0.71–1.32). There was no evidence of heterogeneity of RRs between women who had a tubal ligation and women who did not. In addition, when women who had had a tubal ligation or simple hysterectomy were excluded from the analysis, the RR for ever talc use was 1.15 (95% CI = 0.89–1.49). For serous invasive cancers, the RR for women who had never had a tubal ligation was similar to that for women without a tubal ligation; however, the number of case patients who had had a tubal ligation was small (data not shown).

Cosmetic talc may have been more likely to contain asbestos fibers prior to 1976, before voluntary guidelines were proposed *(9)*. As a proxy for early talc use, we assessed risk among women 45 years old or older in 1982. There was no evidence that older women in 1982 were at greater risk of ovarian cancer overall; the RR for ever talc use compared with never talc use for women under 45 years was 0.95 (95% CI = 0.59–1.53) and among women 45 years old or older was 1.13 (95% CI = 0.86–1.47). However, women 45 years old or older in 1982 who ever used talc had a higher risk of serous invasive cancer (RR = 1.51; 95% CI = 1.07–2.15). There was no evidence of effect modification by oral contraceptive use, body mass index, or cigarette smoking for epithelial cancers overall.

Discussion

To our knowledge, this is the first prospective analysis of talc use and ovarian cancer, and it addresses some of the potential limitations of previous case–control studies. Because we ascertained talc exposure prior to case diagnosis, the possibility for recall bias, which has been raised as a potential explanation for previous positive findings in case–control studies *(1)*, is eliminated, and selection bias is reduced. We controlled for known or suspected ovarian cancer risk factors in the analysis, such as parity, oral contraceptive use, tubal ligation history, and body mass index, reducing the potential for uncontrolled confounding.

However, there are several important limitations to our study. The questions on talcum powder use referred to ever use, and we cannot determine the age at which women began using talc or the duration of use. Thus, we were unable to assess the potential effect of talc use before first pregnancy, which has been shown to be a stronger risk factor for ovarian cancer than use after pregnancy in one study *(13)*. The number of lifetime applications of talc has also been associated with increased risk of ovarian cancer in some previous studies *(9,13)*. Our relatively short follow-up period may be inadequate to detect an association if the latency for development of ovarian cancer is more than 15 years. Although we controlled for tubal ligation history, the tubal ligation question was asked as part of a question on contraceptive use; therefore, postmenopausal women and some premenopausal women who were not sexually active may not have responded to the question. Substantial residual confounding is unlikely, since there was no overall association between talc use and tubal ligation in this study. In addition, we excluded women who were postmenopausal in 1976 from analyses stratified by tubal ligation history. Finally, the prevalence of talc use in our study is somewhat higher than that in other studies and may reflect the fact that we asked about frequency of ever use rather than current regular use; this may have contributed to an attenuation of risk due to misclassification of exposure.

The potential effect of talc on the ovaries depends on migration of talc fibers through a patent genital tract, and we would, therefore, expect a stronger association among women without a tubal ligation who had used talc. However, no effect modification was seen by history of tubal ligation. Because we did not have the date of tubal ligation, some women may have begun talc use only after tubal ligation, potentially resulting in misclassification of talc use and attenuation of the RRs.

Since the first study showing an almost twofold increase in risk of ovarian cancer with any perineal talc use *(4)*, most case–control studies have demonstrated positive associations with talc use *(4–13)*, although not all have been statistically significant *(5,6,8)*. Several studies *(9,17–20)* found no overall association between any genital talc use and ovarian cancer. We did not observe a dose–response relationship with talc use, and previous studies also have been inconsistent in this regard. Some studies *(9,13,17)* have demonstrated statistically insignificant trends in risk with increased frequency of talc use, duration of use, and measures of "total lifetime applications," while other studies *(6,8)* have not observed a statistically significant dose response.

With regard to histologic subtypes, a recent study by Cramer et al. *(13)* observed the greatest risk for talc use and invasive serous cancer; however, other

studies found increased risks for endometrioid cancers *(9,12)*, serous cancers *(7)*, and invasive cancers of all subtypes *(12)*. Since serous cancers, which account for more than half of all invasive ovarian cancers, most resemble mesotheliomas, it could be hypothesized that this subtype may be most likely associated with talc use. In our stratification by subtype, we did observe a modest positive association with serous invasive cancers and ever talc use as well as a borderline significant trend for increasing frequency of ever use.

The biologic evidence for the association of talc and ovarian cancer is incomplete. Asbestos has been linked to ovarian cancer in occupational settings and is associated with peritoneal tumors similar to ovarian cancer *(2,3,21)*. Because of the chemical similarity of talc and asbestos, talc also has been implicated as a possible ovarian carcinogen. Talc is able to migrate through the genital tract and gain access to the ovaries because talc fibers have been detected in benign and malignant ovarian tissue *(22)*, although no relation between reported levels of talc exposure and ovarian talc counts has been observed *(23)*. There have been few studies *(24,25)* of talc exposure in animals, and these studies have not demonstrated an increase in ovarian cancer among animals subjected to chronic talc exposure. These data should be interpreted cautiously because there are important anatomic and physiologic differences between rodents and humans, and talc in animals is often administered at high dose via aerosol exposure *(24)*.

In summary, we did not observe an overall association between epithelial ovarian cancer and ever use of talc, and there was no apparent dose response, although we lacked information on duration of talc use. In analyses stratified by histologic subtype, we observed a modest positive association between invasive serous cancer and ever talc use. Our results provide little support for any substantial association between perineal talc use and ovarian cancer risk overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancers.

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NOTES

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Original Contribution

Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype

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Previous epidemiologic studies suggest that the major histologic subtypes of epithelial ovarian cancer may have different risk factor profiles; however, no known prospective study has systematically examined differences in risk by subtype. The authors used Cox proportional hazards regression, stratified by histologic subtype and time period, to examine the association between ovarian cancer risk factors and incidence of serous invasive, endometrioid, and mucinous ovarian cancers in the US Nurses' Health Study (1976–2006) and Nurses' Health Study II (1989–2005). For each exposure, they calculated *P*-heterogeneity using a likelihood ratio test comparing models with separate estimates for the 3 subtypes versus a single estimate across subtypes. Analysis included 221,866 women and 721 cases with the histologies of interest (496 serous invasive, 139 endometrioid, 86 mucinous). In analyses of reproductive/hormonal exposures, the associations with age, duration of breastfeeding, age at natural menopause, and duration of estrogen use differed significantly by subtype (all *P*-heterogeneity $\leq$0.05). The associations with several nonreproductive exposures also appeared to vary by subtype, but only the association with smoking differed significantly (*P*-heterogeneity = 0.03). Results suggest that associations with several ovarian cancer risk factors vary by subtype, and these differences are consistent with known similarities between each major histologic subtype and its normal tissue counterpart.

adenocarcinoma, mucinous; carcinoma, endometrioid; cystadenocarcinoma, serous; histology; ovarian neoplasms

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.

Epithelial ovarian cancers often are analyzed as a single outcome in epidemiologic studies, despite evidence of differences in their natural history, morphology, and gene/protein expression (1–4). The most common histologic subtypes of epithelial ovarian cancer each resemble a different normal tissue in morphology and gene expression (4, 5), and previous studies suggest their etiology may differ as well. In a pooled analysis of 10 case-control studies, oral contraceptive use and parity were inversely associated with all subtypes, whereas associations with nonreproductive exposures, particularly body mass index and smoking, differed by subtype (6). Other studies have reported differences in associations with both reproductive and nonreproductive exposures for mucinous versus nonmucinous cancers (7–12).

Although these studies suggest that some associations differ by subtype, the data are inconsistent (6–10, 13, 14), and no known comprehensive, prospective analysis of differences in risk factors by histologic subtype has been published. In addition, most prior studies analyzed each subtype separately and did not report a statistical test comparing results across subtypes. We therefore used polytomous regression models to examine the association between known and suspected risk factors for ovarian cancer and incidence of the serous invasive, endometrioid, and mucinous subtypes in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

MATERIALS AND METHODS

Study population

The NHS was established in 1976 and the NHSII in 1989 among 121,700 US female registered nurses aged 30–55 years and 116,430 US female registered nurses aged 25–42 years, respectively. Participants completed an initial questionnaire and biennial follow-up questionnaires,

providing information on lifestyle factors and disease diagnoses. Follow-up is high in both cohorts; we obtained 95.2% of the total possible person-years through June 2006 in the NHS and 93.6% through June 2005 in the NHSII. The Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital, Boston, Massachusetts, approved both studies.

Exposure data

We obtained information on exposures of interest from the biennial questionnaires. At baseline, participants reported their birth date, age at menarche, and height. We requested information on parity, oral contraceptive use, tubal ligation, hysterectomy/oophorectomy, menopausal status, age at menopause, postmenopausal hormone use, weight, physical activity, smoking status, and family history of breast/ovarian cancer on multiple questionnaires during follow-up. In our analysis, we updated values for these covariates when new data were available and otherwise carried forward values from the previous cycle. We requested data on total duration of breastfeeding across all pregnancies in 1986 (NHS) and 1993 (NHSII) and on duration of breastfeeding for each child in 1997 (NHSII only). Information on frequency of genital talc use was collected in 1982 (NHS only).

Identification of ovarian cancer cases

We collected information on new ovarian cancer diagnoses on each questionnaire. For all reported cases, as well as deaths due to ovarian cancer identified through family members, the National Death Index (15, 16), or the US Postal Service, we obtained medical records related to the diagnosis. A gynecologic pathologist (J. H.) blinded to exposure status reviewed the medical records to confirm the diagnosis, stage, histologic type/subtype, and invasiveness (17). Our analysis included cases of epithelial ovarian cancer ($n = 885$) and primary peritoneal cancer ($n = 39$) confirmed by pathology report review and diagnosed between baseline and June 2006 (NHS) or 2005 (NHSII).

Statistical analysis

Participants accrued person-time from the return date of the baseline questionnaire until the date of ovarian cancer diagnosis, diagnosis of any other cancer (excluding nonmelanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death, or the end of follow-up. At baseline, we excluded women with bilateral oophorectomy (NHS: $n = 7{,}669$; NHSII: $n = 2{,}229$), menopause due to pelvic irradiation (NHS: $n = 99$; NHSII: $n = 30$), or cancer other than nonmelanoma skin cancer (NHS: $n = 3{,}314$; NHSII: $n = 1{,}050$). In addition, we excluded women with missing data on any exposure of interest except breastfeeding duration, talc use, and family history of ovarian cancer, which were not collected at baseline, and age at natural menopause, which was missing for women with a hysterectomy before menopause. We included missing indicators for these 4 exposures in our models to avoid excluding too many women from the analysis. Participants contributed person-time only for follow-up periods for which data were complete. Furthermore, we excluded person-time ($\leq$0.3% of the total) when any continuous variable had an outlying value, using the generalized extreme studentized deviate many-outlier detection approach (18).

In analyses of reproductive/hormonal exposures, we modeled age, parity among parous women, duration of breastfeeding, duration of oral contraceptive use, age at natural menopause, and duration of postmenopausal use of unopposed estrogens as continuous variables to minimize the number of parameters in the model. We used binary variables to model menopausal status (postmenopause vs. premenopause/perimenopause), cohort (NHS vs. NHSII), and parity, tubal ligation, and hysterectomy without bilateral oophorectomy (yes/no). Because of evidence of a nonlinear association with age, we used a spline with a single knot at age 50 years to estimate linear associations with age separately for women younger than age 50 years versus 50 years of age or older.

In an alternative analysis, we modeled ovulatory years and duration of menopause instead of age, parity, duration of oral contraceptive use, and age at natural menopause. We calculated ovulatory years as current age (if premenopausal) or age at natural menopause minus age at menarche, years of oral contraceptive use, and parity (1 year per pregnancy), and we included a separate variable for total duration of breastfeeding. We calculated duration of menopause as current age minus age at natural menopause for postmenopausal women, and we coded premenopausal/perimenopausal women as 0. For women with an unknown age at natural menopause because of hysterectomy before menopause, we excluded person-time after hysterectomy.

For the nonreproductive exposures, we modeled body mass index (weight (kg)/height $(m)^2$) and physical activity (cumulative average metabolic equivalent task-hours/week) continuously, regular genital talc use ($\geq$once/week vs. $<$once/week) and family history of breast/ovarian cancer (yes/no) as binary variables, and smoking status as 2 indicator variables for past or current (vs. never) smoking. Metabolic equivalent task-hours captures both duration and intensity of activity (3 metabolic equivalent task-hours is equivalent to walking 2–2.9 mph for 1 hour (1 mile = 1.6 km)), and cumulative average levels better reflect long-term activity and minimize within-person variation. In the NHS, data on metabolic equivalent task-hours were not available until 1986; we therefore assigned all participants 0 activity from 1976 to 1986 and secondarily evaluated the association with physical activity with follow-up beginning in 1986.

We used Cox proportional hazards regression, stratified by time period, to model the incidence rate ratio and 95% confidence interval of epithelial ovarian cancer for each exposure in the NHS and NHSII combined. We then restricted the analysis to cases with serous invasive/poorly differentiated, endometrioid, or mucinous histology and used Cox proportional hazards regression, stratified by type of outcome and time period, to allow for different associations by histologic subtype (19). We used data augmentation, such that each participant had a separate observation for each subtype. We coded the event variable as 1 (failed) if

the participant was diagnosed with the histologic subtype corresponding to that data row and as 0 otherwise; cases were censored for other subtypes at the time of diagnosis.

We compared a model that assumed different associations for all exposures by histologic subtype (full model) with a model with a single estimate across subtypes for one exposure at a time (reduced model). We calculated the *P*-heterogeneity using a likelihood ratio test, with the degrees of freedom equal to the difference between the numbers of parameters in the 2 models. Using a stepwise-down approach, we set exposures with a nonsignificant *P*-heterogeneity to have a single estimate across subtypes, so that the final model estimated 3 separate associations for exposures that differed significantly by subtype and a single estimate for all other exposures. All *P* values were 2-sided and were considered statistically significant if ≤ 0.05.

We evaluated goodness of fit by calculating the area under the receiver operating characteristic curve (AUC) for all cancers and stratified by subtype. For each observation, we determined a risk score using parameter estimates from the model, and we used the risk scores to calculate the Wilcoxon rank sum test statistic W by 5-year age group t. We calculated the Mann-Whitney $U_t = W_t - \frac{m_t(m_t+1)}{2}$ and $\hat{\theta}_t = \frac{U_t}{m_t n_t}$, where $\hat{\theta}_t$ is the probability that a random case has a higher risk score than a random control within age group t. We calculated the variance of $\hat{\theta}_t$ under the alternative hypothesis (20), and we calculated the overall AUC as the weighted average of $\hat{\theta}_t$ across t with weights $= 1/\mathrm{var}(\hat{\theta}_t)$.

We did not have adequate power to examine associations with clear-cell cancers separately because of the small number of cases ($n = 48$). However, we evaluated differences between serous versus nonserous (endometrioid/mucinous/clear-cell) and mucinous versus nonmucinous (serous/endometrioid/clear-cell) cancers. In secondary analyses, we examined differences between all 4 subtypes for the reproductive exposures only.

RESULTS

Our analysis included 221,866 women with 924 incident cases of confirmed epithelial ovarian cancer (NHS: 108,870 women and 797 cases; NHSII: 112,996 women and 127 cases). Of the cases of cancer, 496 were serous invasive (54%), 139 were endometrioid (15%), and 86 were mucinous (9%). The remaining 203 cases of cancer included 48 clear cell (5% of total), 71 noninvasive serous (8%), 21 carcinosarcoma (2%), 17 mixed (2%), and 46 other/unknown (5%).

In general, baseline characteristics of cases versus noncases were similar to those expected based on previous studies of known risk factors (Table 1). NHSII participants were younger than NHS participants and were more likely to have used oral contraceptives or have had a tubal ligation, were less likely to be parous or to smoke, were more physically active, and had lower mean parity but a longer mean duration of breastfeeding among parous women.

When we compared baseline characteristics of women subsequently diagnosed with a serous invasive, endometrioid, or mucinous tumor (Table 1), we found that serous invasive cases were slightly older, had higher parity, and were more physically active than endometrioid/mucinous cases. Endometrioid cases had a longer mean duration of estrogen use (NHS only) and a higher mean body mass index (NHSII only), were less likely to be parous (NHS only) or to have smoked, and were more likely to have a family history of breast cancer. Mucinous cases had a shorter mean duration of estrogen use (NHS only) and breastfeeding and were less physically active, less likely to have had a hysterectomy, and were more likely to have regularly used talc or to currently smoke (NHS only).

The associations with age (*P*-heterogeneity <0.001), duration of breastfeeding (*P*-heterogeneity $= 0.03$), age at natural menopause (*P*-heterogeneity $= 0.05$), and duration of estrogen use (*P*-heterogeneity $= 0.009$) differed significantly by subtype, whereas other exposures (e.g., oral contraceptive use) exhibited similar associations across the 3 subtypes (Table 2). Age among women less than 50 years was more strongly associated with serous invasive (incidence rate ratio (RR) $= 1.15$ per year, 95% confidence interval (CI): 1.10, 1.19) and endometrioid (RR $= 1.12$ per year, 95% CI: 1.06, 1.17) tumors than mucinous tumors. Among women aged 50 years or older, age was associated with a modest increase in risk of serous invasive cancers, was associated with a modest decrease in risk of endometrioid tumors, and was unassociated with mucinous cancers. Duration of breastfeeding was inversely associated with all 3 subtypes, but the association was strongest for mucinous tumors (RR $= 0.43$ per year). Age at natural menopause was positively associated with the endometrioid subtype only (RR $= 1.13$ per year, 95% CI: 1.04, 1.22). Duration of estrogen use was associated with a strong increase in risk of endometrioid cancers (RR $= 1.87$ per 5-year increase, 95% CI: 1.52, 2.31) and a weaker increase in risk of the other subtypes.

Although not statistically significant, there was some evidence of heterogeneity by subtype for parity, tubal ligation, and hysterectomy; the inverse association for oral contraceptive use was similar across subtypes. A first birth was associated with a borderline significant decrease in risk of serous invasive and endometrioid cancers but was unassociated with mucinous tumors. Each additional birth significantly decreased risk of the endometrioid subtype only (RR $= 0.85$, 95% CI: 0.74, 0.99). In general, tubal ligation and hysterectomy were more strongly inversely associated with endometrioid and mucinous cancers.

In an alternative reproductive model with ovulatory years and duration of menopause, associations with number of ovulatory years (*P*-heterogeneity $= 0.04$), duration of menopause (*P*-heterogeneity <0.001), and duration of breastfeeding (*P*-heterogeneity $= 0.03$) differed significantly by subtype (Table 3). Each 1-year increase in the number of ovulatory years was associated with a significant 8% increase in risk of serous invasive and endometrioid tumors but only a 3% increase in risk of mucinous tumors.

Building on the final reproductive model, the associations with several nonreproductive exposures appeared to differ by subtype, but only smoking differed significantly (*P*-heterogeneity $= 0.03$) (Table 4). Past smoking was associated with decreased risk of endometrioid tumors (RR $=$ 0.59, 95% CI: 0.39, 0.90), whereas past/current smoking

Table 1. Baseline Characteristics of Epithelial Ovarian Cancer Cases and Noncases Among 108,870 Women in the NHS in 1976 and 112,996 Women in the NHSII in 1989

	NHS					NHSII				
	Noncases (n = 108,073)	All Epithelial (n = 797)	Serous Invasive (n = 451)	Endometrioid (n = 115)	Mucinous[a] (n = 69)	Noncases (n = 112,869)	All Epithelial (n = 127)	Serous Invasive (n = 45)	Endometrioid (n = 24)	Mucinous[a] (n = 17)
Reproductive/hormonal characteristics										
Mean										
Age, years	42	45	45	44	44	35	37	38	36	35
Duration of oral contraceptive use, months[b]	47	44	44	36	38	53	49	39	62	57
Duration of estrogen use, months[b]	34	44	43	75	20	15	0	0	0	0
Parity among parous women, no.	3.1	3.0	3.2	2.9	2.9	2.1	2.0	2.2	1.8	1.8
Duration of breastfeeding, months[c]	6	4	4	4	2	13	8	11	10	7
Ovulatory years, no.[d]	24	27	28	27	27	17	20	21	18	17
Percentage of the population										
Ever used oral contraceptives	48	38	35	38	43	83	85	87	83	82
Parous	94	90	91	82	95	70	63	67	67	53
Tubal ligation	13	8	9	7	10	16	13	18	4	6
Hysterectomy	13	14	18	10	6	4	6	7	8	0
Other characteristics										
Mean										
Body mass index, kg/m^2	24	24	24	24	23	24	26	24	29	24
Physical activity, MET-hours/week[e]	13	14	15	13	9	21	22	25	18	17
Percentage of the population										
Genital talc use >once/week[f]	28	29	29	30	40					
Past smoker	23	27	29	17	26	21	22	23	8	20
Current smoker	33	31	29	33	44	13	12	16	8	13
Family history of breast cancer	6	8	7	12	8	6	13	20	21	7
Family history of ovarian cancer[g]	3	5	6	0	19	2	1	4	0	0

Abbreviations: MET, metabolic equivalent task; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.

[a] Includes borderline and invasive tumors.

[b] Among ever users of oral contraceptives or postmenopausal unopposed estrogens; in the NHSII, only 32 women had used unopposed estrogens at baseline.

[c] Total duration among parous women in 1986 for the NHS and 1993 for the NHSII.

[d] Current age (if premenopausal) or age at natural menopause minus (age at menarche + duration of oral contraceptive use in years + parity).

[e] Physical activity from 1986 for the NHS and 1989 for the NHSII; 3 MET-hours is equivalent to walking at an average pace of 2.0–2.9 miles/hour for 1 hour (1 mile = 1.6 km).

[f] Use among NHS participants only; collected in 1982.

[g] First collected in 1992 in the NHS and 1993 in the NHSII.

Table 2. Association Between Reproductive/Hormonal Exposures and Risk of Epithelial Ovarian Cancer, by Histologic Subtype, Among 108,870 Women in the NHS From 1976 to 2006 and 112,996 Women in the NHSII From 1989 to 2005[a]

	All Epithelial (n = 924)		Serous Invasive (n = 496)		Endometrioid (n = 139)		Mucinous (n = 86)[b]		P-Heterogeneity[c]
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Age among women <50 years, (per 1-year increase)[d]	1.11	1.09, 1.14	1.15	1.10, 1.19	1.12	1.06, 1.17	1.06	1.00, 1.12	<0.001
Age among women ≥50 years, (per 1-year increase)[e]	1.02	1.01, 1.04	1.04	1.02, 1.06	0.97	0.94, 1.00	1.00	0.96, 1.04	
Parous[f]	0.71	0.57, 0.89	0.73	0.53, 1.02	0.61	0.37, 1.03	1.17	0.56, 2.47	0.09
Parity among parous women[f]	0.94	0.89, 0.99	1.00	0.94, 1.06	0.85	0.74, 0.99	0.95	0.81, 1.13	
Breastfeeding (per 1-year increase)[g]	0.82	0.74, 0.91	0.84	0.73, 0.96	0.74	0.55, 1.00	0.43	0.25, 0.74	0.03
Oral contraceptive use (per 5-year increase)	0.84	0.75, 0.93	0.78	0.66, 0.91	0.77	0.58, 1.02	0.84	0.60, 1.17	0.91
Tubal ligation	0.68	0.56, 0.84	0.83	0.63, 1.09	0.59	0.34, 1.02	0.50	0.25, 1.01	0.26
Hysterectomy	0.69	0.52, 0.91	0.86	0.61, 1.20	0.68	0.39, 1.17	0.45	0.20, 0.98	0.20
Age at natural menopause (per 1-year increase)	1.03	1.00, 1.05	1.02	0.99, 1.06	1.13	1.04, 1.22	1.01	0.93, 1.10	0.05
Estrogen use (per 5-year increase)[h]	1.37	1.25, 1.50	1.28	1.14, 1.44	1.87	1.52, 2.31	1.31	0.89, 1.93	0.009

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.

[a] Estimates were adjusted for all variables in the table, plus cohort (NHS or NHSII), menopausal status (postmenopause vs. premenopause/perimenopause), missing data on breastfeeding duration (yes/no) because of noncompletion of questionnaire, and missing age at natural menopause (yes/no) because of hysterectomy prior to menopause.

[b] Includes borderline and invasive tumors.

[c] P value from likelihood ratio test comparing, for each covariate, the model with separate estimates for the serous invasive, endometrioid, and mucinous histologic subtypes with the model with a single estimate across the 3 subtypes.

[d] RR for each 1-year increase in age prior to age 50 years.

[e] RR for each 1-year increase in age at age 50 years or older.

[f] Parous: RR for 1 versus 0 children; parity among parous women: RR for each additional child after the first.

[g] Breastfeeding duration first collected in 1986 in the NHS and 1993 in the NHSII.

[h] Duration of postmenopausal use of unopposed estrogens.

was associated with a nonsignificant increased risk of mucinous cancers. Body mass index was positively associated with the endometrioid subtype (RR = 1.18 per 5 kg/m^2, 95% CI: 1.02, 1.38) but was unassociated with the other subtypes (P-heterogeneity = 0.06). There also were nonsignificant positive associations between physical activity and serous invasive cancers and between talc use and mucinous tumors. The results for physical activity were unchanged when 1986 was used as the baseline (results not shown).

For the association with all epithelial cancers, the AUC for the reproductive model (AUC = 0.624) was slightly higher than that for the ovulatory years model (AUC = 0.617), indicating that these models have similar discriminatory ability (Table 5). The goodness of fit for the reproductive model was highest for the endometrioid subtype (AUC = 0.714), intermediate for the mucinous subtype (AUC = 0.678), and lowest for the serous invasive subtype (AUC = 0.614). Adding the nonreproductive exposures improved the goodness of fit overall and for each subtype. Although the AUC for each model was based on a slightly different study population, the results were similar when we used the same population for all models (results not shown).

All results were essentially unchanged when we restricted analyses to the NHS only or excluded primary peritoneal cases (results not shown). In analyses of serous versus nonserous cancers, there were significant differences for the associations with age, parity, tubal ligation, and duration of breastfeeding but no differences for nonreproductive exposures (results not shown). When mucinous cancers were compared with nonmucinous cancers, the associations with only age, duration of breastfeeding, and number of ovulatory years differed significantly (results not shown). When we included clear-cell cancers in the reproductive model, the associations with age, parity, duration of estrogen use, and duration of breastfeeding differed significantly across the 4 subtypes (results not shown).

DISCUSSION

These results suggest that associations with several ovarian cancer risk factors differ by histologic subtype. We observed significant heterogeneity across the serous invasive, endometrioid, and mucinous subtypes for associations with both reproductive and nonreproductive exposures, including age, duration of breastfeeding, duration of estrogen use, and smoking status. There was some evidence of heterogeneity by subtype for several other exposures, including parity and

Table 3. Association Between Ovulatory Years and Other Reproductive/Hormonal Exposures and Risk of Epithelial Ovarian Cancer, by Histologic Subtype, Among 107,352 Women in the NHS From 1976 to 2006 and 112,632 Women in the NHSII From 1989 to 2005[a,b]

	All Epithelial (n = 767)		Serous Invasive (n = 397)		Endometrioid (n = 118)		Mucinous[c] (n = 80)		*P*-Heterogeneity[d]
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Ovulatory years (per 1-year increase)[e]	1.07	1.05, 1.08	1.08	1.06, 1.10	1.08	1.05, 1.11	1.03	1.00, 1.07	0.04
Duration of menopause (per 1-year increase)	1.02	1.01, 1.04	1.04	1.02, 1.06	0.96	0.93, 0.99	1.00	0.97, 1.04	<0.001
Breastfeeding (per 1-year increase)[f]	0.80	0.71, 0.89	0.85	0.73, 0.98	0.68	0.49, 0.94	0.45	0.27, 0.77	0.03
Tubal ligation	0.69	0.55, 0.85	0.86	0.65, 1.16	0.57	0.32, 1.00	0.51	0.25, 1.04	0.21
Hysterectomy	0.69	0.52, 0.92	0.77	0.53, 1.13	0.78	0.42, 1.44	0.57	0.23, 1.42	0.81
Estrogen use (per 5-year increase)[g]	1.36	1.13, 1.64	1.45	1.16, 1.81	2.33	1.53, 3.53	0.93	0.38, 2.26	0.08

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.

[a] Estimates were adjusted for all variables in the table, plus cohort (NHS or NHSII), parous (yes/no), menopausal status (postmenopause vs. premenopause/perimenopause), and missing data on breastfeeding duration (yes/no) because of noncompletion of questionnaire.

[b] Model excludes women with missing age at natural menopause because of hysterectomy prior to menopause.

[c] Includes borderline and invasive tumors.

[d] *P* value from likelihood ratio test comparing, for each covariate, the model with separate estimates for the serous invasive, endometrioid, and mucinous histologic subtypes with the model with a single estimate across the 3 subtypes.

[e] Current age (if premenopausal) or age at natural menopause minus (age at menarche + duration of oral contraceptive use in years + parity).

[f] Breastfeeding duration first collected in 1986 in the NHS and 1993 in the NHSII.

[g] Duration of postmenopausal use of unopposed estrogens.

body mass index, but these differences were not statistically significant.

Previous epidemiologic studies have reported differences in the risk factors for each histologic subtype of ovarian cancer, although most studies were retrospective and few reported a statistical test of differences in risk across subtypes. In a pooled analysis, parity and oral contraceptive use were inversely associated with all 4 major subtypes, although parity was most protective for endometrioid and clear-cell tumors, and breastfeeding was inversely

Table 4. Association Between Nonreproductive Exposures and Risk of Epithelial Ovarian Cancer, by Histologic Subtype, Among 108,446 Women in the NHS From 1976 to 2006 and 112,054 Women in the NHSII From 1989 to 2005[a]

	All Epithelial (n = 876)		Serous Invasive (n = 468)		Endometrioid (n = 134)		Mucinous[b] (n = 84)		*P*-Heterogeneity[c]
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Body mass index (per 5-kg/m^2 increase)	1.05	0.98, 1.12	0.97	0.88, 1.07	1.18	1.02, 1.38	0.90	0.72, 1.13	0.06
Activity (per 15-MET-hour/week increase)[d]	1.05	0.98, 1.13	1.08	0.98, 1.19	0.94	0.76, 1.16	0.82	0.61, 1.10	0.11
Talc use (≥once/week vs. <once/week)[e]	1.06	0.89, 1.28	1.06	0.84, 1.35	1.06	0.66, 1.69	1.50	0.84, 2.66	0.55
Past smoker	1.05	0.91, 1.22	1.09	0.89, 1.34	0.59	0.39, 0.90	1.54	0.94, 2.53	0.03
Current smoker	1.11	0.92, 1.35	1.14	0.88, 1.49	0.93	0.59, 1.47	1.52	0.85, 2.74	
Family history of breast cancer	1.29	1.07, 1.56	1.34	1.04, 1.73	1.94	1.24, 3.03	1.42	0.76, 2.63	0.38
Family history of ovarian cancer[f]	1.75	1.19, 2.57	1.85	1.13, 3.03	0.47	0.07, 3.39	4.50	1.76, 11.51	0.06

Abbreviations: CI, confidence interval; MET, metabolic equivalent task; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.

[a] Estimates were adjusted for all variables in the table, plus all covariates in the final reproductive model (Table 2) and variables for missing data on talc use or family history of ovarian cancer (yes/no).

[b] Includes borderline and invasive tumors.

[c] *P* value from likelihood ratio test comparing, for each covariate, the model with separate estimates for the serous invasive, endometrioid, and mucinous histologic subtypes with the model with a single estimate across the 3 subtypes.

[d] Cumulative average physical activity beginning in 1986 for the NHS and 1989 for the NHSII.

[e] Information on regular genital talc use available for NHS participants only; collected in 1982.

[f] Information on family history of ovarian cancer first collected in 1992 in the NHS and 1993 in the NHSII.

Table 5. AUC for Total Epithelial Ovarian Cancer and Each Histologic Subtype Among Women in the NHS From 1976 to 2006 and the NHSII From 1989 to 2005

Model	All Epithelial		Serous Invasive		Endometrioid		Mucinous[a]	
	No. of Cases	AUC	No. of Cases	AUC	No. of Cases	AUC	No. of Cases	AUC
Reproductive (Table 2)	924	0.624	496	0.614	139	0.714	86	0.678
Ovulatory years (Table 3)[b]	767	0.617	397	0.616	118	0.703	80	0.650
Reproductive + nonreproductive exposures (Table 4)	876	0.645	468	0.644	134	0.748	84	0.744
Ovulatory years + nonreproductive exposures[b,c]	731	0.643	378	0.652	114	0.746	78	0.719

Abbreviations: AUC, area under the receiver operating characteristic curve; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.
[a] Includes borderline and invasive tumors.
[b] Excludes women with missing age at natural menopause because of hysterectomy prior to menopause.
[c] Results from this model are not shown.

associated with the serous, endometrioid, and mucinous subtypes but was most protective for mucinous cancers (6). These results, as well as the pooled associations for family history, body mass index, and smoking, were consistent with our study (6). Tubal ligation was inversely associated with serous and clear-cell cancers in the pooled analysis (6), but other studies have reported inverse associations for tubal ligation or hysterectomy and risk of endometrioid and/or mucinous tumors (8, 13, 14, 21). Age at menopause was associated with an increased risk of endometrioid tumors in a small study ($n = 41$ endometrioid cases) (22) but not in 2 other studies (7, 23), and estrogen use was more strongly positively associated with endometrioid cancers in some (24–26) but not all (13, 27) previous studies. Three studies of ovulatory years reported a positive association with nonmucinous cancers but no association with the mucinous subtype (9, 10, 14), similar to our study.

Among the nonreproductive exposures, recent physical activity was inversely associated with risk of all 4 histologic subtypes in one study, although the association was statistically significant for serous cancers only (28). Similarly, another study noted inverse associations with risk of serous, endometrioid, and mucinous tumors (29). However, prospective studies, including ours (30), generally have observed null or positive associations (31–33). Several previous studies of genital talc use, including an analysis in the NHS (34), observed a stronger positive association with serous or serous invasive cancers (35–38), although 2 studies reported no difference by subtype (39, 40) and 1 reported a positive association with mucinous tumors (38). Although our results generally are consistent with the existing literature, apparent differences, such as those for talc use, may be due to the limited number of cases of endometrioid or mucinous histology.

At one time, it was believed that the majority of epithelial ovarian cancers, regardless of histology, arose through transformation of the ovarian surface epithelium. However, growing evidence suggests a varied origin of these cancers; for example, high-grade serous carcinomas may arise in the distal fallopian tube (41–43). Morphologically, serous tumors resemble normal fallopian tube epithelium, endometrioid tumors resemble normal endometrium, and mucinous tumors resemble benign intestinal mucosa or cervical epithelium (4). In addition, there are similarities in gene expression between each subtype and its corresponding normal tissue (5).

The risk factor profiles we observed are consistent with evidence that each subtype resembles a different normal tissue. For example, parity, duration of breastfeeding, and smoking were inversely associated with risk of endometrioid tumors, whereas duration of estrogen use and body mass index were positively associated with risk. This pattern of risk factors is similar to that for endometrial cancer, which is influenced by estrogens and is positively associated with hormone-related exposures, most notably obesity and estrogen use (44). For the mucinous subtype, our results suggest that exposure to carcinogens and other chemicals (e.g., tobacco smoke or talc) may increase risk, whereas surgical procedures that decrease ovarian exposure to exogenous agents (e.g., tubal ligation or hysterectomy) may be protective. Although these results generally are not consistent with known risk factors for colon or cervical cancer (45, 46), evidence exists that smoking (47, 48) and exposure to certain chemicals (49–51) may increase risk of these cancers. The serous invasive subtype was associated with reproductive and hormonal exposures, including parity, duration of oral contraceptive use, and duration of estrogen use. Limited data are available on risk factors for fallopian tube carcinoma, although parity and tubal ligation appear to be protective (52). Information on the epidemiology of serous ovarian tumors may be informative for future research of fallopian tube primary carcinomas.

Strengths of our study include the prospective data with repeated measures for most exposures and the large combined study population. In addition, methods used in this analysis allowed for estimation of separate associations with each subtype simultaneously, as well as formal tests for differences across subtypes.

Although our analysis included a large number of epithelial cases, we had a limited number of cases with certain subtypes (e.g., clear-cell and noninvasive serous cancers). Furthermore, we classified histologic subtype based on a review of pathology reports rather than a central pathology review or immunostaining. Although this categorization likely resulted in some misclassification of histologic subtype, a validation study within the NHS found that histologic subtype based on central pathology review corresponded to

the pathology report for a high percentage of cases (17). The incomplete data for a few exposures, in particular talc use and family history of ovarian cancer, also are weaknesses because the limited data may have influenced the observed associations for these exposures. The association with talc use in our analysis differed from the association in a previous analysis of the NHS cohort (34), possibly because of a greater degree of exposure misclassification over 24 years of follow-up. However, the suggestive positive association with the mucinous subtype may reflect a longer latency period between talc exposure and development of mucinous tumors. Finally, the use of a single summary measure for certain exposures, such as physical activity, also may have limited our ability to detect an association. Additional analyses of different types/intensities of physical activity and risk of each subtype would help clarify this association.

In summary, our study provides additional evidence that associations with several ovarian cancer risk factors differ by histologic subtype and that these differences are consistent with known similarities between each subtype and a corresponding normal tissue. Differences in risk by subtype may help explain variability in the association with certain exposures across study populations, because the observed associations may differ depending on the distribution of the exposure and histologies. Future epidemiologic studies of ovarian cancer therefore should examine the histologic subtypes separately to determine whether heterogeneity in the association exists across subtypes. Analyses not taking into account differences in ovarian cancer risk by histologic subtype could be misleading.

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ARTICLE

Perineal Powder Use and Risk of Ovarian Cancer

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Background Case-control studies have reported an increased risk of ovarian cancer among talc users; however, the only cohort study to date found no association except for an increase in serous invasive ovarian cancers. The purpose of this analysis was to assess perineal powder use and risk of ovarian cancer prospectively in the Women's Health Initiative Observational Study cohort.

Methods Perineal powder use was assessed at baseline by self-report regarding application to genitals, sanitary napkins, or diaphragms and duration of use. The primary outcome was self-reported ovarian cancer centrally adjudicated by physicians. Cox proportional hazard regression was used to estimate risk, adjusting for covariates, including person-time until diagnosis of ovarian cancer (n = 429), death, loss to follow-up, or September 17, 2012. All statistical tests were two-sided.

Results Among 61 576 postmenopausal women, followed for a mean of 12.4 years without a history of cancer or bilateral oophorectomy, 52.6% reported ever using perineal powder. Ever use of perineal powder (hazard ratio $[HR]_{adj}$ = 1.06, 95% confidence interval [CI] = 0.87 to 1.28) was not associated with risk of ovarian cancer compared with never use. Individually, ever use of powder on the genitals (HR_{adj} = 1.12, 95% CI = 0.92 to 1.36), sanitary napkins (HR_{adj} = 0.95, 95% CI = 0.76 to 1.20), or diaphragms (HR_{adj} = 0.92, 95% CI = 0.68 to 1.23) was not associated with risk of ovarian cancer compared with never use, nor were there associations with increasing durations of use. Estimates did not differ when stratified by age or tubal ligation status.

Conclusion Based on our results, perineal powder use does not appear to influence ovarian cancer risk.

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In 2013, it is estimated that there will be 22 240 new cases of ovarian cancer and 14 030 ovarian cancer deaths in the United States (US) alone (1). Since the 1960s, there has been speculation that the use of perineal powder is associated with ovarian cancer. In 2006, the International Agency for Research on Cancer (IARC) reviewed studies examining perineal powder use and ovarian cancer and classified talc as a possible carcinogen (2,3). The proportion of US women ever using talc powder on the perineum was estimated in 2001 to be approximately 40% (4), whereas 52% reported ever use of perineal powder in 1993–1998 within the Women's Health Initiative (WHI) (5).

The primary proposed mechanism linking perineal powder use to ovarian cancer is an inflammatory response (6). Talc particulates from perineal application have been shown to migrate to the ovaries (6), disrupting the surface ovarian epithelial tissue leading to entrapment of the talc particles within inclusion cysts (7). Furthermore, tubal ligation and/or hysterectomy, which would eliminate the pathway of talc particulates to the ovaries, are associated with reduced ovarian cancer risk (6).

A meta-analysis examining the risk of ovarian cancer among ever perineal powder users vs non-users showed odds ratios (ORs) of 1.40 (95% confidence interval [CI] = 1.29 to 1.52) for population-based case-control, 1.12 (95% CI = 0.92 to 1.36) for hospital based case-control, and 1.35 (95% CI = 1.26 to 1.46) for all case-control studies (2). More recently, a large pooled analysis found that ever use of perineal powder increased epithelial ovarian cancer risk by 24% compared with non-use (OR = 1.24, 95% CI = 1.15 to 1.33) (8). Increased risk was associated with invasive serous, endometrioid, clear cell, and borderline serous subtypes of epithelial ovarian cancer (8). However, when looking at the lifetime number of applications of perineal powder, there was no statistically significant trend for increasing applications, attributed to difficulty in recalling details of frequency and duration of perineal powder use (8).

To date there has only been one prospective study conducted examining perineal powder use and risk of ovarian cancer (9). In the Nurses' Health Study (NHS) cohort, no overall association was found between ever use of perineal powder and epithelial ovarian cancer (relative risk [RR] = 1.09, 95% CI = 0.86 to 1.37) or serous ovarian cancers (RR = 1.26, 95% CI = 0.94 to 1.69) (9). However, there was a 40% (95% CI = 1.02 to 1.91) increase in risk for serous

invasive ovarian cancer with ever perineal powder use, which comprises 86% of serous ovarian cancers in this cohort (9).

Limitations of recall bias and misclassification make it difficult to determine the true relationship between perineal powder (10), a commonly used cosmetic product, and ovarian cancer, a disease with poor survival and few known modifiable risk factors. The prior prospective cohort study, which should not be affected by recall bias, had no information on duration of use limiting interpretation. Here we expand on the available evidence by assessing perineal powder use and risk of ovarian cancer in the Women's Health Initiative Observational Study (WHI-OS). The WHI-OS is a large cohort that collected information on several application areas of perineal powder use and their respective durations of use.

Methods

Study Population

The WHI-OS enrolled 93 676 women from 40 clinical centers across the United States from 1993 to 1998 (11). Women were eligible if they were aged 50 to 79 at enrollment, postmenopausal, and planned to reside in the area for at least three years (11). Women were excluded from the WHI-OS if they were participating in another clinical trial, unlikely to survive three years due to medical conditions, or had conditions that would interfere with study participation (11). Participants completed annual mailed questionnaires to update information on risk factors and outcomes, including ovarian cancer (11). Written informed consent was obtained from participants, and all clinical centers were approved by their respective institutional review boards (11). The current analysis was approved by the University of Massachusetts, Amherst Human Subjects Review Committee.

For this analysis, participants were additionally excluded if they reported a bilateral oophorectomy or an unknown number of ovaries at baseline (n = 20 960), a history of any cancer at baseline except nonmelanoma skin cancer (n = 10 622), or were missing exposure or follow up information (n = 516). After applying the exclusion criteria, 61 576 participants with 429 adjudicated incident ovarian cancer cases remained.

Exposure Ascertainment

Perineal powder use was assessed via self-report at baseline. Participants were asked, "Have you ever used powder on your private parts (genital areas)?" Those who responded yes further indicated the duration of use with the following possible responses: less than 1 year, 1–4 years, 5–9 years, 10–19 years, or 20 or more years. For persons that reported ever use of a diaphragm, participants were asked, "Did you ever use powder on your diaphragm?" and those who responded yes further indicated duration. The third category evaluated was "Did you ever use powder on a sanitary napkin or pad?" with those responding yes also reporting duration. Each area of application variable was assessed dichotomously and the duration of use, collapsed into fewer categories because of small numbers, was assessed categorically as never, 9 years or less, or 10 or more years. A combined ever perineal powder variable and duration variable for any powder use was created; where ever use was defined as report of ever use of any of the three application categories, never was report of never use for all three categories, and duration was the maximum duration reported of any single area of application, because we could not exclude the possibility that applications were concurrent. Lastly, all possible combinations of the three application areas were assessed.

Outcome Ascertainment

Ovarian cancer cases were initially self-reported by participants in the WHI-OS on annual questionnaires. Medical records, including hospital discharge summaries and pathology reports, were requested for each self-reported case and adjudicated by a physician at the local Clinical Center and then centrally by the WHI's Clinical Coordinating Center (11).

Covariate Ascertainment

Potential covariates considered included age, race, education, alcohol servings per week, smoking status, metabolic equivalent (MET) hours per week of recreational physical activity, Body Mass Index (BMI), and self-reported family history of ovarian or breast cancer. Reproductive factors considered were age at menarche, age at menopause, age at first birth, age at last birth, parity, breastfeeding duration, history of tubal ligation, history of hysterectomy, history of irregular cycles, history of endometriosis, duration of oral contraceptive use, and duration of postmenopausal hormone use. All covariates were from baseline and were not updated.

Statistical Analysis

To estimate the association between perineal powder use and ovarian cancer, proportional hazard regression models were used. Participants contributed person-time until diagnosis of ovarian cancer, death, loss to follow-up, or September 17, 2012, whichever came first. Participants with other cancers were still considered at risk for ovarian cancer and were not censored at the time of other cancer diagnoses. Information on incident oophorectomy during follow-up was not available and thus participants were not censored in this analysis. The proportional hazards assumption was tested using weighted Schoenfeld residuals.

Covariates were included in the adjusted model according to purposeful selection, where covariates with Wald *P* values of .25 or less in age-adjusted models were entered into an initial multivariable model and then each covariate was subsequently tested individually via likelihood ratio tests in order of decreasing Wald *P* values. Variables that had *P* values of .10 or less during the backwards elimination were kept in the model until a parsimonious model was obtained. Additional variables shown in previous literature (8,9) but not statistically significant in our population were also included in the final multivariable model. Lastly, family history of breast cancer and personal history of endometriosis did not change estimates and were not included in the final multivariable model.

Models fitted included the following independent variables: 1) combined ever perineal powder use, 2) ever powder use by application area (ie, applied to genitals, applied to diaphragm, or applied to sanitary napkins), 3) duration of use by application area, and 4) application area combinations (ie, genital only, diaphragm only, sanitary napkin only, genital and sanitary napkin, genital and diaphragm, diaphragm and sanitary napkin, and all three areas of application). For duration models, test for trend was used to evaluate linear trends across duration categories by modeling the

categories as a continuous variable in the multivariable regression models.

Because powder particles may not reach the ovaries due to tubal ligation and because previous studies have shown a stronger association between powder use and ovarian cancer in women without tubal ligation (4), we separately examined women without tubal ligation. We also stratified by age at baseline, because older women may have had more potential for exposure to talc contaminated with asbestos. Additionally, associations by ovarian cancer histological subtype were evaluated. All analyses were performed using Stata v.12.1 (StataCorp, College Station, TX) and two-sided *P* values of .05 or less were considered statistically significant.

Results

The average age of the participants at baseline was 63.3 years. Participants were followed for a mean of 12.4 years; never powder users were followed for a mean of 12.2 years (range = 0.12 to 17.9 years) and ever powder users were followed for a mean of 12.6 years (range = 0.03 to 18.0). The majority of the participants were white (83.7%), had less than a college degree (56.1%), and were overweight/obese (57.2%). Approximately half (52.6%) of the population reported ever use of perineal powder. Ever powder users were heavier (27.5 kg/m^2 vs 26.5 kg/m^2, $P < .0001$) and were more likely to have used oral contraceptives (44% vs 36%, $P < .0001$) and/or diaphragms (50.8% vs 37.3 %, $P < .0001$) than never users (Table 1).

Use of powder on the genitals was associated with a 12% increase in the multivariable-adjusted hazard ratio of ovarian cancer (HR_{adj} = 1.12, 95% CI = 0.92 to 1.36), though this was not statistically significant (Table 2). Use of powder on sanitary napkins (HR_{adj} = 0.95, 95% CI = 0.76 to 1.20) or diaphragms (HR_{adj} = 0.92, 95% CI = 0.68 to 1.23) also was not associated with risk. Duration of powder use on the genitals, sanitary napkins, or on the diaphragm was not associated with ovarian cancer; P_{trend} for years of use: .67, .69, and .67 respectively. Combined ever powder use from any of the three application areas did not show an association with ovarian cancer risk (HR_{adj} = 1.06, 95% CI = 0.87 to 1.28). For combined duration of use, which was the longest duration of use among the three areas of application, there was no evidence of an association with risk of ovarian cancer [P_{trend} for years of use: .77]. Use of powder on genitals, the most common application area, for 20 or more years was not associated with increased risk of ovarian cancer compared with never users (HR_{adj} = 1.10, 95% CI = 0.82 to 1.48). In a sensitivity analysis, invasive serous ovarian cancer risk was not increased (HR_{adj} = 0.96, 95% CI = 0.65 to 1.41), even in women reporting durations of use greater than 10 years.

There was no evidence of an association between perineal powder use and ovarian cancer risk by category of application (Table 3). Combined ever powder use was not associated with individual subtypes of ovarian cancer (Table 4). The multivariable-adjusted hazard ratio for serous ovarian cancer was 1.16 (95% CI = 0.88 to 1.53). Additionally, duration of combined ever powder use was also not shown to be associated with any subtype of ovarian cancer (results not shown).

The associations of combined ever powder use and ovarian cancer did not statistically differ by tubal ligation status (results not shown). When stratified by age group at baseline, hazard estimates also did not statistically differ ($P_{interaction}$ = .37); HR_{adj} for younger than 50 to 59 years = 1.29, 95% CI = 0.91 to 1.82; HR_{adj} for those 60 to 69 years = 0.94, 95% CI = 0.70 to 1.26; and HR_{adj} for those 70 to 79 years = 1.01, 95% CI = 0.68 to 1.48. When restricted to only whites or to those who had never used oral contraceptives, results were again unchanged.

Table 1. Characteristics of postmenopausal women according to perineal powder use status (n = 61 285): Women's Health Initiative Observational Study, 1993–2012

	Never perineal powder use	Ever perineal powder use
Characteristic, n (%)	**n = 29 066**	**n = 32 219**
Race		
White	24 006 (82.6)	27 336 (84.8)
Nonwhite	4991 (17.2)	4811 (14.9)
Body mass index category, kg/m^2		
<25.0	13 056 (44.9)	12 461 (38.7)
25.0–29.9	9734 (33.5)	10 799 (33.5)
30.0 +	5935 (20.4)	8571 (26.6)
Smoking status		
Never	15 347 (52.8)	15 621 (48.5)
Past	11 481 (39.5)	14 339 (44.5)
Current	1912 (6.6)	1881 (5.8)
Duration of oral contraceptive use, y		
Never	17 877 (61.5)	17 954 (55.7)
<5	6241 (21.5)	7858 (24.4)
5 to <10	2528 (8.7)	3270 (10.2)
10 to <15	1650 (5.7)	2125 (6.6)
15+	760 (2.6)	1005 (3.1)
Diaphragm use	10 826 (37.3)	16 353 (50.8)
Tubal ligation	4929 (17.0)	5901 (18.3)
Hysterectomy	6878 (23.7)	8285 (25.7)
Family history of ovarian cancer	606 (2.1)	660 (2.1)
Parity		
0	3687 (12.7)	3769 (11.7)
1–2	9773 (33.6)	11 585 (36.0)
3–4	11 101 (38.2)	12 609 (39.1)
5+	4365 (15.0)	4098 (12.7)
Age at last birth, y		
Never had term pregnancy	6219 (21.4)	6260 (19.4)
< 20	210 (0.7)	324 (1.0)
20–29	9143 (31.5)	11480 (35.6)
30+	13 011 (44.8)	13 668 (42.4)
Duration of postmenopausal hormone use, y		
Never	13 381 (46.0)	13 880 (43.1)
<5	6498 (22.4)	7546 (23.4)
5 to <10	3783 (13.0)	4567 (14.2)
10 to <15	2688 (9.3)	3128 (9.7)
15+	2716 (9.3)	3097 (9.6)

Discussion

In this large prospective study, ever perineal powder use was not associated with ovarian cancer risk, nor was it associated with ovarian cancer when assessed by area of application, duration of use, or ovarian cancer subtype. While many case-control studies have shown an approximately 24–40% increase in risk of ovarian cancer (2,8) for powder users, we did not find evidence of this association in our large, prospective analysis.

The meta-analysis of 20 case-control studies by Langseth and colleagues found a 35% increase in the odds of epithelial ovarian

Table 2. Age and multivariable-adjusted hazard ratios of ovarian cancer by area of perineal powder application (n = 61 576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR (95% CI)	P_{trend} †	Multivariable HR* (95% CI)	P_{trend} †
Powder use on genitals						
Never	247	457 855	1.0 (referent)	.63	1.0 (referent)	.67
Ever‡	181	304 867	1.13 (0.93 to 1.37)		1.12 (0.92 to 1.36)	
Less than 9 years	112	173 118	1.24 (0.99 to 1.55)		1.23 (0.98 to 1.54)	
10 or more years	68	129 647	0.98 (0.75 to 1.29)		0.98 (0.75 to 1.29)	
Powder use on sanitary napkins						
Never	336	590 351	1.0 (referent)	.70	1.0 (referent)	.69
Ever‡	93	172 712	0.96 (0.76 to 1.21)		0.95 (0.76 to 1.20)	
Less than 9 years	62	114 305	0.98 (0.75 to 1.28)		0.96 (0.73 to 1.26)	
10 or more years	30	56 174	0.93 (0.64 to 1.35)		0.95 (0.65 to 1.37)	
Powder use on diaphragm						
Never	373	661 239	1.0 (referent)	.78	1.0 (referent)	.67
Ever‡	52	97 714	0.94 (0.70 to 1.25)		0.92 (0.68 to 1.23)	
Less than 9 years	35	67 468	0.93 (0.66 to 1.32)		0.91 (0.64 to 1.30)	
10 or more years	17	29 202	0.99 (0.61 to 1.60)		0.95 (0.58 to 1.56)	
Combined ever powder use§						
Never	197	361 583	1.0 (referent)	.67	1.0 (referent)	.77
Ever‡	232	404 983	1.07 (0.89 to 1.30)		1.06 (0.87 to 1.28)	
Less than 9 years	135	228 931	1.12 (0.90 to 1.39)		1.09 (0.88 to 1.36)	
10 or more years	97	173 307	1.03 (0.81 to 1.31)		1.02 (0.80 to 1.30)	

* Adjusted for: Age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m^2 (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children, missing).

† Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models; P_{trend} was estimated by modeling categories as continuous. All statistical tests were two-sided.

‡ Person-years may not add up; duration information was missing for some.

§ Combined ever powder use is the longest duration of use among the applications to genitals, sanitary napkins, and diaphragms.

Table 3. Age and multivariable-adjusted hazard ratios for ovarian cancer by combined categories of powder use (n = 61 576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR* (95% CI)	Multivariable HR* (95% CI)
Powder Type Used				
No powder	193	355 523	1.0 (referent)	1.0 (referent)
Only genital powder	96	158 130	1.14 (0.90 to 1.46)	1.13 (0.88 to 1.45)
Only diaphragm powder	19	42 367	0.82 (0.51 to 1.32)	0.80 (0.50 to 1.29)
Only sanitary napkin powder	28	50 051	1.04 (0.70 to 1.54)	1.01 (0.68 to 1.50)
Genital and sanitary napkin powder	55	96 173	1.09 (0.80 to 1.47)	1.08 (0.80 to 1.46)
Genital and diaphragm powder	24	29 858	1.49 (0.98 to 2.28)	1.45 (0.95 to 2.23)
Diaphragm and sanitary napkin powder	4	6858	1.06 (0.40 to 2.86)	1.02 (0.38 to 2.74)
Genital, diaphragm, and sanitary napkin powder	5	18 331	0.51 (0.21 to 1.24)	0.50 (0.21 to 1.22)

* Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models. All statistical tests were two-sided. Multivariable HR adjusted for: age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m^2 (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children missing).

cancer among ever perineal powder users compared to never-users (2), and the pooled analysis of eight case-control studies by Terry and colleagues found a 24% increase in the same group (8). Langseth and colleagues did not assess dose-response or risk among subtypes of ovarian cancer (2). Terry and colleagues assessed lifetime applications of perineal powder and found no statistically significant trend with increasing lifetime applications (8). This corroborates our results that there was no statistically significant risk with increasing duration of perineal powder use, though they were able to capture both frequency and duration (8), whereas we only had duration. Terry and colleagues found elevated risks for invasive serous, borderline serous, endometrioid, and clear cell subtypes of ovarian cancer (8), which we did not observe. One potential reason that case-control studies have found slight increases in risk is the potential for an overestimation of the true association due to recall bias, because the participants are aware of their ovarian cancer status when reporting powder

Table 4. Age and multivariable-adjusted hazard ratios for combined ever powder use by subtype of ovarian cancer (n = 61 576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR* (95% CI)	Multivariable HR* (95% CI)
Serous†				
Never	87	355 523	1.0 (referent)	1.0 (referent)
Ever	117	404 983	1.18 (0.89 to 1.56)	1.16 (0.88 to 1.53)
Serous Invasive				
Never	80	355 523	1.0 (referent)	1.0 (referent)
Ever	105	404 983	1.16 (0.87 to 1.55)	1.13 (0.84 to 1.51)
Mucinous				
Never	12	355 523	1.0 (referent)	1.0 (referent)
Ever	13	404 983	0.98 (0.44 to 2.14)	1.03 (0.47 to 2.27)
Endometrioid				
Never	13	355 523	1.0 (referent)	1.0 (referent)
Ever	20	404 983	1.39 (0.69 to 2.79)	1.29 (0.64 to 2.61)
Other				
Never	47	355 523	1.0 (referent)	1.0 (referent)
Ever	54	404 983	1.04 (0.71 to 1.54)	1.04 (0.70 to 1.54)

* Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models. All statistical tests were two-sided. Multivariable HR adjusted for: age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m^2 (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children missing).

† Includes borderline cancers.

exposure. The prospective nature of our study would eliminate the potential for recall bias. Additionally, the case-control studies tended to have a younger population than our study, which included both premenopausal and postmenopausal ovarian cancers (2,8), whereas the WHI cohort consisted only of postmenopausal ovarian cancers. Ovarian cancer that occurs prior to menopause may have a different etiology than ovarian cancer occurring afterwards.

We found similar results to that of the NHS, the only other prospective cohort, which had a similar sample size and number of ovarian cancer cases to our study. Ever use of perineal powder did not appear to be associated with ovarian cancer in the NHS (9), similar to our findings. The results of Gertig and colleagues were also null for use on the genitals and for use on sanitary napkins (9). Additionally, neither our study nor the NHS found associations with serous ovarian cancer, endometrioid, or mucinous ovarian cancers, although subgroup sample size may have reduced statistical power to test these associations. In contrast to our results, the study by Gertig and colleagues found a 40% increase in invasive serous ovarian cancer among ever powder users compared with never powder users (9).

Strengths of our study included large sample size with a substantial number of ovarian cancer cases, a prospective cohort design, good case ascertainment, and detailed information on most ovarian cancer risk factors. We also had information on duration of powder use, qualifiers not available in several earlier studies, including the previous cohort study (2,8,9).

One potential limitation of our analyses includes a lack of information regarding oophorectomy after baseline, which would result in the inclusion of some women not at risk for ovarian cancer in the analytical cohort. However, the impact was likely to be minor, as a previous study in the WHI-OS had reported the number of persons with incident bilateral oophorectomies to be less than 250 (out of more than 90 000 participants) during nearly eight years of follow-up (12). While the prospective nature of the study design eliminates recall bias, it does not eliminate potential for nondifferential misclassification of the exposure. Women still needed to recall past perineal powder use and duration and thus may have trouble recollecting specifics regarding the use of perineal powder, leading to a bias toward the null. Information regarding powder use was not collected after baseline, and there is potential for never users to begin using powder; however, this is unlikely because the women are postmenopausal, reducing need to use perineal powder on diaphragms or sanitary napkins. We also had no specific data regarding the frequency of powder use in our sample. Frequency of use, as well as duration may influence ovarian cancer risk. We may have been comparing long-term infrequent users with short-term frequent users. If we had frequency of use in addition to the duration, we could have looked at intensity of use, which may be more accurate, and shown a dose response relationship. However, Terry and colleagues did not find a dose response relationship either when taking into account frequency and duration (8).

When restricted to women without tubal ligation status, the estimates for the association between combined ever perineal powder use and ovarian cancer were not increased. While some studies have found stronger associations between powder use and ovarian cancer in women that have not undergone a tubal ligation (4), the results from our study did not support this previous finding. The pooled analysis (8) and the NHS cohort (9) also did not find evidence of stronger associations in women without tubal ligations.

While we had information on duration of use, it is unknown during which years the perineal powder was used. Talc powder had potential for asbestos contamination (13) until 1976, when the Cosmetic, Toiletry, and Fragrance Association required all cosmetic talc products to be free of asbestos (14). Therefore, those using powder prior to 1976 may have been potentially exposed to asbestos, a known carcinogen. The pooled analysis and meta-analysis also included case-control studies not within the United States

(2,8), which potentially have different regulations regarding perineal powder and earlier studies that may have been more likely to include exposure to contaminated perineal powder (2). However, risk estimates in more recent studies are similar to earlier studies (2), reducing the likelihood that confounding by asbestos is driving the findings. Additionally, assuming older women in the cohort could have been exposed longer to perineal powder with potential contamination compared with younger women, we did not see statistically significant differences in risk when stratified by age group, further suggesting asbestos contamination is not a likely explanation.

The WHI-OS queried general perineal powder use rather than talc powder use, and we had no specific information regarding the content of talc in products used, which the previous literature reviewed by IARC suggested to be the possible carcinogen of concern (2). However, the NHS cohort and most studies included within the pooled analyses asked about general perineal powder use as well (2,8,9). In summary, perineal powder use did not appear to be associated with ovarian cancer risk in this large sample of postmenopausal women, even with use for long durations.

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Douching, Talc Use, and Risk of Ovarian Cancer

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Background: Douching was recently reported to be associated with elevated levels of urinary metabolites of endocrine disrupting phthalates, but there is no literature on douching in relation to ovarian cancer. Numerous case–control studies of genital talc use have reported an increased risk of ovarian cancer, but prospective cohort studies have not uniformly confirmed this association. Behavioral correlation between talc use and douching could produce confounding.

Methods: The Sister Study (2003–2009) enrolled and followed 50,884 women in the US and Puerto Rico who had a sister diagnosed with breast cancer. At baseline, participants were asked about douching and talc use during the previous 12 months. During follow-up (median of 6.6 years), 154 participants reported a diagnosis of ovarian cancer. We computed adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for ovarian cancer risk using the Cox proportional hazards model.

Results: There was little association between baseline perineal talc use and subsequent ovarian cancer (HR: 0.73, CI: 0.44, 1.2). Douching was more common among talc users (odds ratio: 2.1, CI: 2.0, 2.3), and douching at baseline was associated with increased subsequent risk of ovarian cancer (HR: 1.8, CI: 1.2, 2.8).

Conclusions: Douching but not talc use was associated with increased risk of ovarian cancer in the Sister Study.

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Cancer of the ovary is the most lethal gynecological cancer in women, and its etiologies remain poorly understood. In 2015, there were an estimated 21,290 new cases and 14,180 ovarian cancer deaths among women in the United States.[1] Family history of ovarian or breast cancer is a major risk factor. Nulliparity is also associated with increased risk of ovarian cancer, whereas tubal ligation and oral contraceptive use are reportedly associated with reduced risk.[2]

Genital talc use and douching could plausibly introduce particles and toxicants into the upper reproductive tract and increase the risk of cancers and infections. Talc particles have been found embedded in cervical and ovarian tumors.[3] Fragranced douching products can contain phthalates, which disrupt endocrine pathways and could influence ovarian cancer risk through hormone disruption.[4] A recent analysis of data from the National Health and Nutrition Examination Survey found an association between douching and urinary concentrations of phthalates.[5] Douching has also been associated with adverse health effects and reproductive problems, such as pelvic inflammatory disease and ectopic pregnancy,[6] as well as decreased fertility.[7]

To the best of our knowledge, no existing studies have investigated the association between douching and ovarian cancer, but talc use was associated with ovarian cancer in many case–control studies.[8–13] A meta-analysis of 14 population-based, case–control studies[14] and a large, pooled case–control analysis[15] both reported positive associations between genital talc use (ever vs. never) and ovarian cancer. The only prospective studies to examine talc and ovarian cancer[16,17] found no strong associations overall, but one observed increased risk for invasive serous ovarian cancer, specifically.[17] In this study, we investigate the association between ovarian cancer and both douching and talc use, using prospective data from the Sister Study cohort.

METHODS

The Sister Study, launched in 2003, enrolled 50,884 women across the United States and Puerto Rico. Enrollees were aged 35 to 74 years and had never had breast cancer but each had a full or half-sister who had been diagnosed with breast cancer. More than one sister per family could participate.

After excluding participants who had bilateral oophorectomies (N = 9,023) or ovarian cancer (N = 167) before enrollment or who had no follow-up information (N = 40), we included 41,654 participants in this analysis. As of July 2014 (median follow-up 6.5 years), 154 incident ovarian cancer cases had occurred. We included tumors of the ovary (N = 135), fallopian tubes (N = 7), peritoneum (N = 4), or of uncertain origin but likely from one of the three aforementioned

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primary sites (N = 8). The Institutional Review Boards of the National Institute of Environmental Health Sciences and the Copernicus Group approved this study and all participants provided written consent.

Participants completed computer-assisted telephone interviews, which included questions about reproductive history (including any oophorectomies), health conditions, and lifestyle factors. Participants also completed a self-administered questionnaire about personal care products used in the 12 months before enrollment, which included questions about frequency of douching and about genital talc use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once a month, used 1–3 times per month, 1–5 times per week, or more than 5 times per week. Because most members of the cohort reported not douching and not using talc, we used dichotomous use/nonuse variables for analysis.

Updated information on oophorectomies was collected in follow-up questionnaires administered every 2–3 years. We ascertained information on any new cancers via an annual health update and the follow-up questionnaires and were able to confirm 96 of the ovarian cancer cases using medical records (N = 87) or death certificate/National Death Index data (N = 9). For the remaining 58 cases, we relied on information provided by the participant herself (N = 52) or her next of kin (N = 6). Among women with available medical records who self-reported ovarian cancer, 90% were confirmed.

There were five eligible cases with an unknown exact age at diagnosis. For them, we imputed an age midway between their last ovarian cancer-free follow-up interview and their age at the time we were notified of the diagnosis (or death). Although we did not genotype women directly for *BRCA1* or *BRCA2* mutations, we asked each woman in her baseline interview whether she had ever been tested and, if so, what the result of those tests were. For the purposes of this analysis, a woman was treated as *BRCA1/2* mutation positive if (1) she had a positive test or (2) she had a sister with a known positive test and she had no known negative test.

Statistical Analyses

We computed adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of talc use and douching with ovarian cancer risk using Cox proportional hazards models, with age as the primary time scale. Follow-up lasted from age at baseline until age at diagnosis of ovarian cancer. Follow-up time was censored at their age of bilateral oophorectomy after baseline, death, or last contact. Because some participants had sisters who also enrolled in the cohort, we used generalized estimating equation methods to calculate robust variances to account for family clustering. We evaluated proportionality assumptions of the Cox model by assessing the improvement in goodness-of-fit provided by including an age-by-factor interaction term.

In addition to the main effect, we evaluated the joint effect of both douching and using talc. We classified participants into four categories: neither exposure, talc use exclusively, douching exclusively, or both exposures. We also carried out a number of stratified analyses. We stratified by reproductive factors, such as menopausal status, parity, hysterectomy, and tubal ligation to explore possible effect modification.[10,13] We tested for differences across strata using the *P* value for an exposure-by-modifier interaction term.

We selected potential confounders or effect modifiers of the association between ovarian cancer and the exposures of interest in this analysis a priori based on assumed causal relationships among the covariates,[18] and included patency (yes/no blockage of reproductive tract by tubal ligation or hysterectomy), menopausal status (pre- or postmenopausal), duration of oral contraceptive use (none, <2 years, 2-<10 years, 10 or more years), parity (yes/no), race (non-Hispanic white, non-Hispanic black, Hispanic or other), and body mass index (<25, 25–29.9, or >30 kg/m^2), all of which were fixed at baseline levels.

We conducted six sensitivity analyses. In the first, we restricted to the 96 cases confirmed by medical record or death certificate/National Death Index data. For our second sensitivity analysis, we looked for evidence of etiologic heterogeneity by further restricting this pool to medically confirmed cases with serous ovarian cancer (N = 49). For our third sensitivity analysis, we included all 154 eligible ovarian cancer cases as well as five additional cases that had unknown ages at diagnosis and prebaseline oophorectomies (N = 159 cases total). We did this to examine the influence of our assumptions about the relative timing of their oophorectomies versus their ovarian cancer diagnoses. We further examined the influence of imputing age at diagnosis in our fourth sensitivity analysis by excluding the five cases with imputed diagnosis ages but intact ovaries (N = 149 cases total). For our fifth sensitivity analysis, we excluded participants from families known to carry *BRCA* mutations (N = 347 exclusions, including 10 cases) since the lifetime risk of ovarian cancer for individuals with a *BRCA1/2* mutation is substantially higher[19] and the etiology may be different. Finally, we conducted analyses excluding the first year of follow-up, to minimize the possibility that symptoms of undiagnosed ovarian cancer were leading participants to use douche or talc. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and using the Sister Study data release version 4.1.

RESULTS

Table 1 summarizes characteristics of cases and noncases at baseline. Most participants were non-Hispanic white (84%), and most were postmenopausal (56%). Women who later became cases were somewhat older (mean 57.8 vs. 54.8), more often white, and more often nulliparous. Cases were also more likely to have a first-degree family history of ovarian cancer and more than one first-degree relative with

TABLE 1. Baseline Characteristics of the Sister Study Cohort (2003–2009)[a]

	Noncases (N = 41,500)	Ovarian Cancer Cases (N = 154)
Race; N (%)		
Non-Hispanic White	34,745 (84)	138 (90)
Non-Hispanic Black	3,598 (9)	9 (6)
Hispanic	2,076 (5)	5 (3)
Other	1,068 (2)	2 (1)
Education; N (%)		
High school or less	6,001 (14)	24 (15)
Some college	13,556 (33)	49 (32)
Bachelor's degree	11,579 (28)	46 (30)
Graduate degree	10,354 (25)	35 (23)
BMI; N (%)		
<25.0 kg/m^2	16,610 (40)	51 (33)
25–29.9 kg/m^2	13,012 (31)	51 (33)
≥30 kg/m^2	11,866 (29)	52 (34)
Menopausal status; N (%)		
Premenopausal	15,238 (37)	40 (26)
Hysterectomy with ovaries retained	2,996 (7)	8 (5)
Postmenopausal	23,239 (56)	106 (69)
Hysterectomy; N (%)		
No	34,481 (83)	120 (78)
Yes	6,995 (17)	34 (22)
Tubal ligation; N (%)		
No	29,511 (71)	115 (75)
Yes	11,973 (29)	39 (25)
Oral contraception		
Duration of Use; N (%)		
None	6,452 (16)	25 (16)
<2 years	6,382 (15)	37 (24)
2–10 years	17,769 (43)	67 (44)
10 years or more	10,865 (26)	25 (16)
Parity; N (%)		
No live births	7,657 (18)	37 (24)
1 or more live births	33,816 (82)	116 (76)
First-degree family history of ovarian cancer; N (%)		
No	40,149 (97)	138 (90)
≥1 first-degree relative	1,322 (3)	16 (10)
Breast cancer; N (%)		
1 affected sister	31,291 (75)	109 (71)
>1 sister or sister + mom	10,207 (25)	45 (29)
BRCA1/2 mutation status; N (%)		
No known mutation	41,163 (99)	144 (94)
Known mutation	337 (1)	10 (6)

Missing values: race (13 noncases), education (10 noncases), BMI (12 noncases), menopausal status (27 noncases), tubal ligation (16 noncases), hysterectomy (24 noncases), oral contraception use (32 noncases), parity (1 case, 27 noncases), ovarian cancer family history (29 noncases), and breast cancer family history (2 noncases).

[a]Excludes women who were diagnosed with ovarian cancer before completion of the baseline interview (N = 167), women who had a bilateral oophorectomy before the baseline interview (N = 9,023), and women lost to follow-up (N = 40).

BMI indicates body mass index.

breast cancer. They were also more likely to carry a deleterious mutation in *BRCA1* or *BRCA2*. While ever/never use of oral contraceptive was similar across cases and noncases, the distribution of duration of use differed. More noncases (26%) than cases (16%) had used oral contraceptives for more than 10 years. Compared with women who neither douched nor used talc, women who douched were more likely to be non-Hispanic black (23% vs. 6%) and to have less than a college degree (62% vs. 44%) and women who used talc were more likely to have a body mass index over 30 kg/m^2 (41% vs. 25%; eTable; http://links.lww.com/EDE/B74).

Douching in the 12 months before study enrollment was reported by 13% of noncases and 20% of cases (Table 2). Talc use in the 12 months before study enrollment was reported by 14% of noncases and 12% of cases. Only seven cases (5%) reported both douching and talc use.

Ever douching during the 12 months before study entry was associated with increased ovarian cancer risk (adjusted HR: 1.8, 95% CI: 1.2, 2.8; Table 2). By contrast, talc use during the 12 months before study entry was associated with reduced risk after the same confounder adjustments (HR: 0.73, CI: 0.44, 1.2) and there was a negligible change in the estimated effect with additional adjustment for douching (HR: 0.70, CI: 0.42, 1.1). We observed no proportional hazards assumption violations for any of the examined models.

Douching with no talc use was also associated with increased risk of ovarian cancer compared with use of neither talc nor douching (adjusted HR: 1.9, CI: 1.2, 2.9), which is similar to the overall effect estimate of douching. There was an inverse association between exclusive talc use and ovarian cancer, and a positive association for douching and talc use combined (HR: 1.8, CI: 0.81, 3.9). There was no evidence for interaction on a multiplicative ($P = 0.39$) or additive ($P = 0.72$) scale.

To explore effect modification, we performed analyses stratified by a number of reproductive factors including tubal ligation status, hysterectomy status, menopause status, and parity (Figure). We also stratified by patency to see if blockage of access to the ovaries by either tubal ligation or hysterectomy might modify the association between ovarian cancer and douching or talc use. For all stratifications, there were no modifications of effect estimates for either douching or talc use (all heterogeneity P values >0.05).

HRs for talc use differed little in the first five sensitivity analyses, showing a HR change no greater than 0.04. By contrast, exclusion of ovarian cancers without medical record or death certificate confirmation (by censoring their follow-up at the reported diagnosis age) attenuated the association between douching and ovarian cancer (HR: 1.1, CI: 0.62, 2.1). Likewise, restriction to medically confirmed serous ovarian cancer also attenuated effect estimates (HR: 1.4, CI: 0.64, 3.2). However, ovarian cancer cases who had reported that they douched were substantially less likely to have a medical record available (40%) than ovarian cases who did not douche (69%),

suggesting that medical records were informatively missing, biasing results based on the restricted analysis. There was very little change in douching effect estimates when excluding the five cases with uncertain diagnosis dates or including the five women reporting oophorectomies before the diagnosis of ovarian cancer. Exclusion of known positive *BRCA1/2* families slightly strengthened the association between douching and ovarian cancer (HR: 1.9, CI: 1.3, 2.9). In our sixth sensitivity analysis, exclusion of the first year of follow-up time resulted in negligible changes in the HRs for douching and talc use (HR: 1.8, CI: 1.2, 2.8 and HR: 0.86, CI: 0.52, 1.4, respectively).

DISCUSSION

In this large prospective cohort, which gave rise to 154 incident cases of ovarian cancer, there was a positive association between douching and incident ovarian cancer. Talc use was associated with a slight reduction of ovarian cancer risk. Our study of ovarian cancer grouped together all cancers designated as ovarian (88%), fallopian (5%), peritoneal (3%), or those designated as uncertain but ovarian, fallopian, or peritoneal (5%). With recent literature suggesting that most cancers classified as ovarian likely originated in the fallopian tubes,[20] we felt that this grouping was appropriate.

Interest in talc as a carcinogen arose because of its chemical similarity to asbestos, which has been previously linked to ovarian cancer.[21] One challenge with studying talc is that the chemical formulation of talc has changed over time,[9] and not all powders contain the mineral talc (e.g., cornstarch-based products). Previous case–control studies have noted evidence for a positive association,[8–13] with some evidence that the effect is strongest in premenopausal women.[13] Given these results, the biological plausibility, the rarity of the exposure, and imprecision of estimates, we cannot exclude a small increase in risk associated with talc use, despite our inverse findings. Then again, with the exception of the finding that talc use was positively associated with serous ovarian cancer in the Nurses' Health Study,[17] the prospective studies have not provided evidence supporting an association between talc use and ovarian cancer overall[17] or between talc use and ovarian cancer overall among postmenopausal women.[16]

The numbers for the Sister Study as a whole given in Table 2 reveal an odds ratio of 2.1 (CI: 2.0, 2.3) for douching in relation to talc use. Thus, the two practices are correlated. If douching is a risk factor for ovarian cancer, some of the earlier reports on talc could have been subject to confounding bias. However, the one case–control study that did include douching as a covariate still observed a positive association between talc use and ovarian cancer risk.[8] Another factor that may contribute to our null findings is that we categorized the exposure based on the 12 months before enrollment as a dichotomous ever/never factor rather than a quantitative measure of total applications, as has been done in previous studies.

Because Sister Study participants all have a first-degree family history of breast cancer, they are more likely than the general population to develop ovarian cancer (estimated observed/expected number of cases = 1.6 based on SEER rates). We also note that, by design, we excluded women with a previous history of breast cancer, thereby discounting some individuals who were at increased risk for ovarian cancer. While these selective factors may limit generalizability, there is no clear mechanism by which they would bias the estimated effect of talc use or douching on ovarian cancer.

Our review of the literature suggests that our study is the first to examine the association between douching and ovarian cancer. This association could reflect uncontrolled confounding by behavioral factors we have not captured well. For example, women may be more likely to douche if they are prone to infections or other reproductive health problems that could themselves be related to ovarian cancer.

If the association is causal, it could be related to the recently reported positive association between douching

TABLE 2. Exposure Prevalence and Hazard Ratios for Their Associations with Ovarian Cancer in the Sister Study

	Noncases (N = 41,500)	Ovarian Cases (N = 154)	Fully Adjusted Hazard Ratio[a]
Douching past 12 months			
No	34,653 (87)	121 (80)	1.00
Yes	5,364 (13)	30 (20)	1.8 (1.2, 2.8)
Talc use past 12 months			
No	33,770 (86)	130 (88)	1.00
Yes	5,718 (14)	17 (12)	0.73 (0.44, 1.2)
Douched and used talcum powder past 12 months			
Neither	29,596 (76)	106 (72)	1.00
Talc use/no douching	4,399 (11)	10 (7)	0.60 (0.31, 1.1)
Douching/no talc use	3,936 (10)	23 (16)	1.9 (1.2, 2.9)
Both	1,237 (3)	7 (5)	1.8 (0.81, 3.9)

Missing values: douching (3 cases, 1,483 noncases), talc use (7 cases, 2,012 noncases).
[a]Adjusted for race, body mass index, parity, duration of oral contraceptive use, baseline menopause status, and patency.

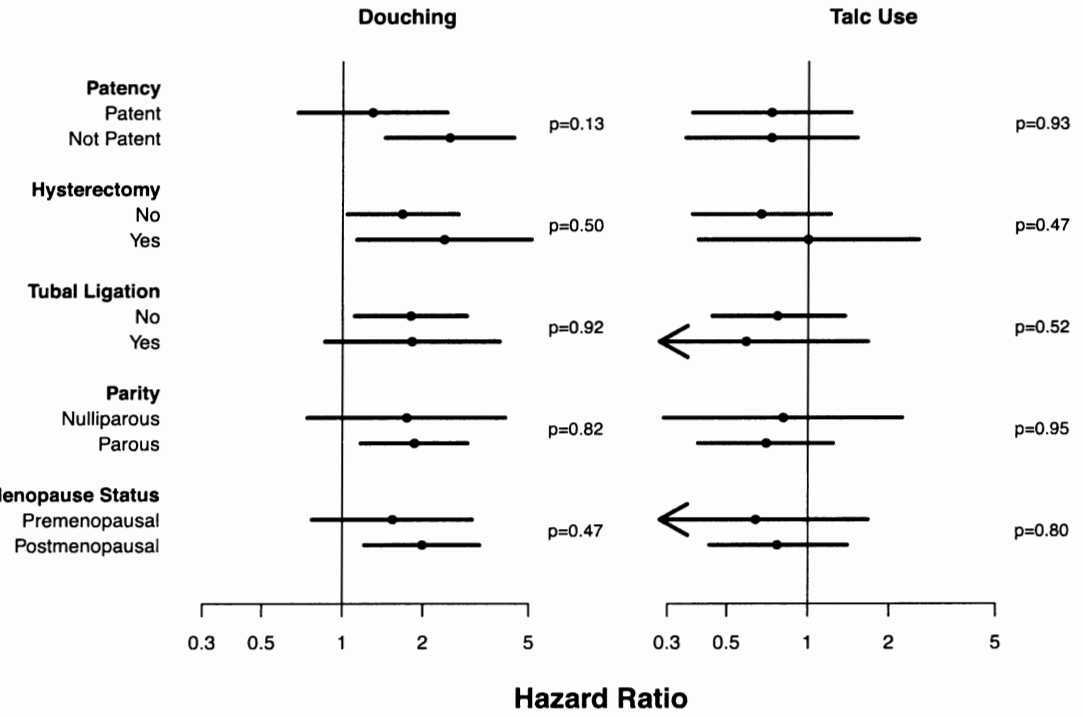

FIGURE. Effect estimates of douching and talc use in the Sister Study when stratified by multiple reproductive factor, adjusted for race, body mass index, parity, duration of oral contraceptive use, baseline menopause status, and patency. The reported heterogeneity *P* values are for tests of an exposure-by-modifier interaction term.

and higher urinary levels of phthalate metabolites observed in National Health and Nutrition Examination Survey participants.[5] Phthalates are endocrine-disrupting chemicals and may be harmful to the fallopian tubes or the ovaries.[22] In an animal study, exposure to di-(2-ethylhexyl) phthalate at 500 and 2,000 mg/kg demonstrated ovarian toxicity through decreased progesterone and increased apoptosis in granulosa cells.[23] Furthermore, ovarian cancer cell lines have been found to increase cell proliferation and to up-regulate cell-cycle regulatory genes following treatment with di-*n*-butyl phthalate.[24] We did not collect detailed information about specific products used in douching, so we are unable to estimate exposure to individual phthalates.

Douching could also force tissue, menstrual fluids, or foreign materials up the reproductive tract, resulting in inflammation (e.g., pelvic inflammatory disease[6]) or infection of the fallopian tubes or ovaries themselves. This inflammation and infection could also contribute to ovarian cancer risk, as supported by the observed positive association between pelvic inflammatory disease and ovarian cancer.[25]

If the association is causal and related to the transfer of xenobiotics into the upper reproductive tract, we would expect to see a stronger association in women with both a uterus and patent fallopian tubes. However, the evidence in our data appeared to be driven by the subcohort of women with hysterectomy and/or tubal ligation (Figure).

Because our study was prospective in nature, it is robust to potential differential reporting bias as exposures are recorded before development of cancer. Another important strength of the study was that we controlled for many potentially confounding factors.

An important limitation of our study is that we collected douching and talc information on individuals for the year before study entry and have not accounted for the latency of ovarian cancer, which is likely to be long.[26] If latency is 15 to 20 years, douching habits at baseline do not accurately reflect the period of risk, although women who douched at baseline are likely to have been douching for a substantial amount of time before that as well. Also, given that there have been health advisories against douching because of its other potential risks, participants who douched in the past may have stopped douching and would be misclassified. Thus, the relative risk for douching in relation to ovarian cancer could be underestimated. Future studies that ascertain a complete history of douching are warranted.

Although the baseline questionnaire did ask women about their use of douche and talc between the ages 10 and 13, very few women responded yes to douching (2%), and we were unable to make use of those data. By contrast, talc use during ages 10–13 had a prevalence of 18% in the cohort, but there was no detectable effect of prepubertal talc use on risk (HR: 1.1, CI: 0.74, 1.7).

Exposure information was very complete, with only 831 participants (2%) missing the personal care products questionnaire entirely, and an additional 655 and 1,188 missing data for the questions about douching or talc use, respectively. However, for approximately 37% of cases, we have not yet received medical records to confirm the diagnosis. We found that medical record retrieval was differential by exposure, with a lower proportion with medical records among women who douched than among women who did not. This informative missingness mathematically contributed to the substantial attenuation in the HR estimate for the association between vaginal douching and ovarian cancer when we restricted to cases with medical record confirmation. Medical record retrieval for ovarian cancer began only recently, and women with cancers diagnosed early in follow-up are more likely to be missing medical record information. Some of the unconfirmed diagnoses may be confirmed later via medical records or the national death index.

In this large, prospective study, we did not observe an association between recent talc use and ovarian cancer risk, but did find a strong positive association between douching and ovarian cancer risk.

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