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The Association Between Talc Use and Ovarian Cancer

A Retrospective Case–Control Study in Two US States

Daniel W. Cramer,[a,b] *Allison F. Vitonis,*[a] *Kathryn L. Terry,*[a,b] *William R. Welch,*[c] *and Linda J. Titus*[d]

Background: Multiple studies of ovarian cancer and genital talc use have led only to consensus about possible carcinogenicity. Seeking greater clarity, we examined this association in 2,041 cases with epithelial ovarian cancer and 2,100 age- and-residence-matched controls.
Methods: We defined genital talc use as regular application to the genital/rectal area directly, on sanitary napkins, tampons, or underwear. To estimate "talc-years," we multiplied applications per year by years used. Unconditional logistic regression, Wald statistics, likelihood-ratio tests, and polytomous logistic regression were used to calculate adjusted odds ratios (OR) and 95% confidence intervals (CI), trends, effect-modification, and heterogeneity by ovarian cancer histologic subtype.
Results: Overall, genital talc use was associated with an OR (95% CI) of 1.33 (1.16, 1.52), with a trend for increasing risk by talc-years. Women who used talc were more likely to be older, heavier, asthma sufferers, and regular analgesic users—none of which was a confounder. Dose–responses were more apparent for premenopausal women, especially nonsmokers and those heavier or postmenopausal users of menopausal hormones (hormone therapy [HT]). Subtypes of ovarian cancer more likely to be associated with talc included invasive serous and endometrioid tumors and borderline serous and mucinous tumors. Premenopausal women and postmenopausal HT users with these subtypes who had accumulated >24 talc-years had ORs (95% CI) of 2.33 (1.32, 4.12) and 2.57 (1.51, 4.36), respectively.
Conclusion: Risks for epithelial ovarian cancer from genital talc use vary by histologic subtype, menopausal status at diagnosis, HT use, weight, and smoking. These observations suggest that estrogen and/or prolactin may play a role via macrophage activity and inflammatory response to talc.

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In the 1960s, a link between talc and ovarian cancer was suggested by observations that some talc powders contained asbestos[1] and that asbestos placed intraperitoneally in animals transformed the single layer of the ovarian surface to a multilayered one with abnormal cells.[2] A 1971 study found particles compatible with talc in human ovarian and uterine cancers.[3] A 1982 case–control study was the first to link genital talc use with ovarian cancer.[4] Dozens more followed confirming the association including some larger ones cited here.[5–13] The most recent meta-analysis reported a summary odds ratio (OR) and 95% confidence interval (CI) of 1.35 (1.26, 1.46).[14] In 2006, the International Agency for Research on Cancer declared that talc used genitally is possibly carcinogenic.[15] However, a study with null results from the Women's Health Initiative (WHI)[16] and accompanying editorial[17] cast new skepticism on the association. Here, we present data from combined phases of a case–control study of ovarian cancer involving more than 4,000 women to provide fresh perspectives on this association.

METHODS

Study Population

Data come from three enrollment phases: 1 (1992–1997), 2 (1998–2002), and 3 (2003–2008). Articles we previously published related to talc include a detailed report from phase 1,[7] data from phases 1 and 2 combined with Nurses' Health Study data,[18] and phases 1–3 data combined with data from several participants in the Ovarian Cancer Association Consortium (OCAC).[19] This is the first detailed examination of talc data from the combined phases of our study.

Details regarding enrollment are described elsewhere.[20] In brief, 3,957 women residing in Eastern Massachusetts and New Hampshire diagnosed with ovarian cancer between ages 18 and 80 were identified through tumor boards and registries.

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Eight hundred and seventy-four cases were ineligible if they had died, moved outside study area, did not have a working telephone number, or had a nonovarian primary tumor. Of the remaining 3,083 cases, 2,203 (71%) were enrolled. Excluding 127 nonepithelial and 35 mixed mesodermal tumors, 2,041 cases with epithelial tumors of ovarian, primary peritoneal, and Fallopian tube origin, including borderline malignancies (henceforth, epithelial ovarian cancer) were included. Pathology reports were reviewed and histologic subtype, grade, and stage recorded. Mixed epithelial ovarian cancer was classified as the predominant type. Undifferentiated, transitional cell, fallopian tube, or primary peritoneal tumors were counted as serous.[21] Other mixed epithelial (n = 102), malignant Brenner (n = 5), and unspecified epithelial tumors (n = 27) were classified as other.

Controls were identified through random digit dialing, driver-license lists, and town-resident lists. Between 1992 and 1997, 420 (72%) identified through random digit dialing and 102 (51%) through lists agreed to participate. From 1998 to 2008, 4,366 potential controls were identified using the lists, of whom 1,426 (33%) were ineligible if they had died, moved, or were seriously ill or if they did not have a working telephone, speak English, or have ovaries. Of eligible controls, 1,362 (46%) declined to participate by phone or via "opt-out" postcard and 1,578 (54%) were enrolled (2,100 total). Controls were frequency matched to cases by 5-year age groups and region of residence.

Exposure Assessment

Subjects were personally interviewed about potential ovarian cancer risk factors that occurred more than 1 year before diagnosis, for cases, and interview, for controls. Subjects were asked whether they "regularly" or "at least monthly" applied powder to the genital or rectal area, sanitary napkins or tampons, underwear, or areas other than the genital-rectal area. Additional details included type of powder, age begun, years used, and applications per month. Lifetime exposure was estimated by multiplying frequency of applications per month by months used. This was divided by 360 (i.e., daily use coded as 30/month) to yield talc-years. To create categorical variables for talc-years, we chose cut points based on quartiles for exposed controls and rounded to the nearest integer. In addition, we asked participants if their partners dusted or sprayed powder to their genital or rectal areas. Condom and diaphragm use as potential sources of talc exposure were also recorded.

We calculated ovulatory cycles by subtracting age at menarche from age at last period, reduced this by time spent pregnant, breastfeeding, or using oral contraceptives, and dividing the remainder by each woman's average cycle length. Family history was defined as a mother or sister with ovarian or premenopausal breast cancer. Women who reported postmenopausal hormone use were classified as hormone therapy (HT) users and type(s) of HT was recorded. Participants completed a food-frequency questionnaire[22] from which grams of alcohol consumed per day were estimated.

Statistical Methods

Unconditional logistic regression was used to model the OR and 95% CI adjusted first for matching factors (age, study center, and phase) and then fully by potential confounders. Likelihood ratio tests comparing models with and without interaction terms were used to test for effect modification. Tests for trend were based on the Wald statistic using continuous variables weighted by category midpoints with zero assigned as the exposure for nonusers. Polytomous logistic regression was used to simultaneously estimate separate ORs and 95% CIs for genital talc use by histologic subtypes. Likelihood-ratio tests were used to calculate *P* values for heterogeneity by comparing polytomous logistic regression models in which the talc association was held constant over case subgroups to models that allowed the association to differ between case subgroups.[23] Analyses were performed using SAS v9.3 (SAS Institute, Cary, NC) and polytomous logistic regression analyses were performed in Stata (StataCorp LP, College Station, TX). Sensitivity analyses to assess the influence of exposure misclassification were performed with Excel using quantitative analysis methods described previously.[24]

Ethical Approval

Institutional review boards approved the study. All participants provided written informed consent.

RESULTS

Genital use of talc, either alone or in combination with body use, was associated with elevated epithelial ovarian cancer risk (Table 1). Among women with no personal use, there was no increased risk with potential exposure from diaphragms, condoms, or partner use. Therefore, only those with personal genital talc exposure were classified as ever-users. Genital talc use was associated with an OR (95% CI) of 1.33 (1.16, 1.52) adjusted only for age, study center, and phase. Most women reported using Johnson & Johnson's Baby Powder or Shower to Shower. Fourteen women who reported exclusive use of a cornstarch-based powder were considered unexposed. The average age women began using talc was 20.0 for cases and 19.8 for controls. Almost half of users were currently using or had only recently discontinued powder use at the reference date. Risk decreased with increased time since last use. The trend for frequency of use was significant, but the trend for years used was flat. Some subjects reported they used talc only seasonally, but our original questionnaire did not capture this detail. A question to capture months-per-year-used was added in 1998 and was available for 54% of cases and 56% of controls. Year-round use was the most common pattern, and more cases than controls used powder year-round. ORs for talc-years among those who reported months-per-year-used are shown as the next-to-final entry in Table 1. An OR of 1.49 (95% CI = 1.06, 2.10) was associated with more

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TABLE 1. Type, Timing, and Duration of Genital Talc Use

	Control Subjects N (%)	Case Subjects N (%)	Adjusted[a] OR (95% CI)
Personal use			
None	1,099 (52)	1,001 (49)	1.00 (referent)
Body use only	452 (22)	398 (20)	0.99 (0.84, 1.16)
Genital use only	74 (4)	94 (5)	1.42 (1.04, 1.96)
Body and genital use	475 (23)	548 (27)	1.30 (1.12, 1.52)
Potential exposure in women with no personal use			
None	447 (41)	461 (46)	1.00 (referent)
Diaphragm only	207 (19)	155 (15)	0.73 (0.57, 0.93)
Condoms, with or without diaphragm	367 (33)	308 (31)	0.82 (0.66, 1.01)
Partner use, with or without diaphragm or condoms	78 (7)	77 (8)	0.96 (0.68, 1.35)
Any genital powder use			
No	1,551 (74)	1,399 (69)	1.00 (referent)
Yes	549 (26)	642 (31)	1.33 (1.16, 1.52)
Type of genital powder used			
No genital use	1,542 (73)	1,394 (68)	1.00 (referent)
Cornstarch use only	9 (<1)	5 (<1)	0.58 (0.19, 1.74)
Johnson and Johnson Baby Powder or Shower to Shower	316 (15)	363 (18)	1.30 (1.10, 1.54)
Other brand(s)	233 (11)	279 (14)	1.35 (1.12, 1.64)
Age first used genital powder[b]			
Never used	1,551 (74)	1,399 (69)	1.00 (referent)
<20	343 (16)	363 (18)	1.19 (1.01, 1.41)
20–29	122 (6)	183 (9)	1.71 (1.34, 2.17)
≥30	76 (4)	87 (4)	1.31 (0.95, 1.80)
Time since exposure ended			
No genital use	1,551 (74)	1,399 (69)	1.00 (referent)
≥35 years	51 (2)	52 (3)	1.18 (0.79, 1.75)
25–34 years	81 (4)	88 (4)	1.24 (0.91, 1.70)
15–24 years	72 (3)	82 (4)	1.30 (0.94, 1.80)
5–14 years	79 (4)	95 (5)	1.36 (1.00, 1.85)
Currently using or recently stopped	255 (12)	314 (15)	1.38 (1.15, 1.65)
P trend			<0.0001
Frequency of use			
No genital use	1,551 (74)	1,399 (69)	1.00 (referent)
1–7 days per month	220 (11)	227 (11)	1.17 (0.96, 1.44)
8–29 days per month	110 (5)	133 (7)	1.37 (1.05, 1.78)
≥30 days per month	205 (10)	267 (13)	1.46 (1.20, 1.78)
P trend			<0.0001
Years used			
Never used	1,551 (74)	1,399 (69)	1.00 (referent)
<8	133 (6)	152 (8)	1.31 (1.03, 1.68)
8–19	126 (6)	145 (7)	1.31 (1.02, 1.68)
20–35	147 (7)	178 (9)	1.35 (1.07, 1.70)
>35	129 (6)	152 (7)	1.33 (1.03, 1.71)
P trend			0.002
Months per year of use[c]			
No genital use	1,551 (83)	1,399 (80)	1.00 (referent)
1–3 months per year	61 (3)	60 (3)	1.11 (0.77, 1.61)
4–11 months per year	55 (3)	56 (3)	1.13 (0.77, 1.66)
12 months per year	193 (10)	229 (13)	1.35 (1.09, 1.67)
P trend			0.006

(*Continued*)

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TABLE 1. (*Continued*)

	Control Subjects N (%)	Case Subjects N (%)	Adjusted[a] OR (95% CI)
Total genital talc applications (apps) among only those who reported months per year of use[c]			
No genital use	1,551 (83)	1,399 (80)	1.00 (referent)
≤360 apps (equivalent to 1 year of daily use)	106 (6)	103 (6)	1.10 (0.83, 1.47)
361–1,800 apps (equivalent to >1–5 years of daily use)	79 (4)	96 (5)	1.38 (1.01, 1.88)
1,801–7,200 apps (equivalent to >5–20 years of daily use)	61 (3)	63 (4)	1.16 (0.80, 1.66)
>7,200 apps (equivalent to >20 years of daily use)	63 (3)	83 (5)	1.49 (1.06, 2.10)
P trend			0.02
Total genital talc applications among all (assuming 12 months/year when missing months per year of use)			
No genital use	1,551 (74)	1,399 (69)	1.00 (referent)
≤360 apps (equivalent to 1 year of daily use)	138 (7)	138 (7)	1.15 (0.89, 1.47)
361–1,800 apps (equivalent to >1–5 years of daily use)	124 (6)	148 (7)	1.36 (1.06, 1.75)
1,801–7,200 apps (equivalent to >5–20 years of daily use)	124 (6)	156 (8)	1.41 (1.10, 1.80)
>7,200 apps (equivalent to >20 years of daily use)	149 (7)	185 (9)	1.39 (1.11, 1.75)
P trend			0.003

[a]Adjusted only for the study matching factors: reference age, study center, and study phase.
[b]Nine cases and nine controls reported they knew that talc had been used on them in infancy so their age at exposure was recorded as 1.
[c]Excludes talc users from phase 1 and part of phase 2 because months/year of use was not collected.

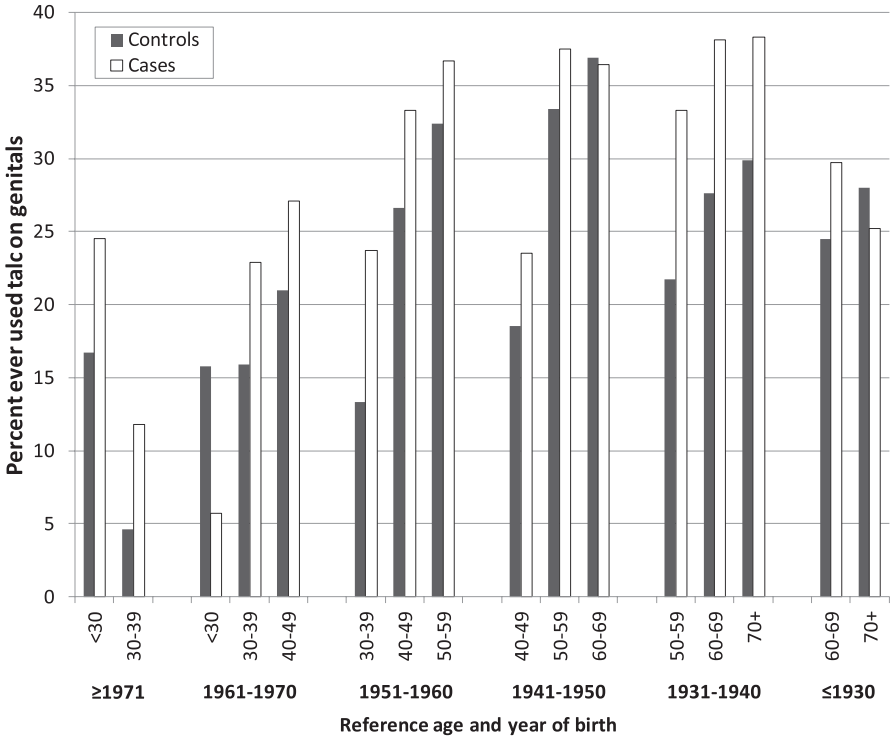


FIGURE 1. Proportions of cases and controls who ever used talc on genitals in categories by decade of birth and reference age.

than 20 talc-years (>7,200 applications) and a dose–response. For subjects missing the seasonal-use variable, we assumed 12 months per year in calculating talc-years in the final entry in Table 1, as well as in subsequent tables and figures examining talc-years. Even with this imprecision, the trend remained, although the increase was less monotonic.

Figure 1 shows the proportions of cases and controls who used talc in the genital area by decade of birth and age at diagnosis or interview. In 13 of the 16 age-and-birth categories, a greater proportion of cases used talc compared with controls. This suggests that the association between genital use of talc and epithelial ovarian cancer is not confined to any particular age or birth cohort.

Powder users, both cases and controls, were more likely to be older, heavier, asthma sufferers, and regular analgesic users (Table 2). By tests for interaction (column 3), the

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TABLE 2. Illustrating Potential Effect Modification and Confounding

	Controls		Cases				
	No Genital Talc Use N (%)	Any Genital Talc Use N (%)	No Genital Talc Use N (%)	Any Genital Talc Use N (%)	Stratum-specific OR (95% CI)[a] for Genital Talc Use	*P* Int[b]	OR (95% CI) for Genital Talc Use Adjusted[c]
Age							
<50	670 (80)	165 (20)	600 (74)	211 (26)	1.42 (1.13, 1.80)	0.63	1.30 (1.13, 1.49)[d]
50–64	599 (68)	278 (32)	541 (64)	308 (36)	1.25 (1.03, 1.53)		
≥65	282 (73)	106 (27)	258 (68)	123 (32)	1.35 (0.98, 1.85)		
Study center							
New Hampshire	319 (82)	72 (18)	316 (74)	109 (26)	1.52 (1.08, 2.14)	0.30	1.31 (1.15, 1.50)[e]
Massachusetts	1,232 (72)	477 (28)	1,083 (67)	533 (33)	1.29 (1.11, 1.50)		
Study phase							
1	430 (82)	92 (18)	409 (73)	149 (27)	1.71 (1.27, 2.30)	0.12	1.33 (1.16, 1.52)[f]
2	519 (72)	202 (28)	448 (68)	210 (32)	1.23 (0.97, 1.55)		
3	602 (70)	255 (30)	542 (66)	283 (34)	1.25 (1.02, 1.54)		
Race							
White	1,500 (74)	531 (26)	1,321 (68)	612 (32)	1.35 (1.17, 1.55)	0.002	1.33 (1.16, 1.53)
African American	17 (74)	6 (26)	16 (46)	19 (54)	5.08 (1.32, 19.6)		
Hispanic	27 (82)	6 (18)	25 (81)	6 (19)	1.10 (0.30, 4.12)		
Asian	5 (50)	5 (50)	34 (94)	2 (6)	0.04 (0.01, 0.34)		
Other	2 (67%)	1 (33)	3 (50)	3 (50)	-		
Body mass index							
<24.9	798 (76)	251 (24)	727 (72)	284 (28)	1.25 (1.03, 1.53)	0.59	1.32 (1.15, 1.51)
≥24.9	753 (72)	298 (28)	672 (65)	358 (35)	1.38 (1.14, 1.67)		
Height (m)							
<1.63	755 (73)	283 (27)	689 (68)	325 (32)	1.28 (1.06, 1.56)	0.71	1.32 (1.16, 1.52)
≥1.63	795 (75)	266 (25.)	710 (69)	317 (31)	1.37 (1.13, 1.66)		
Weight (lbs)							
<148	799 (77)	241 (23)	727 (73)	272 (27)	1.24 (1.01, 1.52)	0.58	1.32 (1.15, 1.51)
≥148	745 (71)	307 (29)	670 (64)	370 (36)	1.38 (1.15, 1.66)		
Parity							
Nulliparous	284 (75)	94 (25)	455 (70)	195 (30)	1.28 (0.96, 1.71)	0.71	1.33 (1.15, 1.52)
Parous	1,267 (74)	455 (26)	944 (68)	447 (32)	1.34 (1.15, 1.57)		
Ever breastfed							
No	781 (72)	296 (28)	953 (69)	430 (31)	1.21 (1.01, 1.45)	0.16	1.30 (1.13, 1.50)
Yes	770 (75)	253 (25)	446 (68)	212 (32)	1.48 (1.19, 1.85)		
Oral contraceptive use							
Never or <3 months	559 (73)	207 (27)	672 (69)	302 (31)	1.25 (1.01, 1.55)	0.38	1.32 (1.15, 1.51)
≥3 months	992 (74)	342 (26)	727 (68)	340 (32)	1.39 (1.16, 1.67)		
Intrauterine device use							
No	1,300 (74)	447 (26)	1,203 (69)	547 (31)	1.35 (1.16, 1.56)	0.59	1.33 (1.16, 1.52)
Yes	251 (71)	102 (29)	196 (67)	95 (33)	1.20 (0.85, 1.70)		
Ovulatory cycles							
<366	748 (78)	214 (22)	542 (74)	191 (26)	1.28 (1.02, 1.61)	0.76	1.31 (1.14, 1.52)
≥366	680 (71)	281 (29)	733 (65)	402 (35)	1.37 (1.13, 1.65)		
Endometriosis or painful periods							
No	1,006 (74)	345 (26)	814 (70)	351 (30)	1.29 (1.08, 1.55)	0.77	1.31 (1.14, 1.50)
Yes	545 (73)	204 (27)	585 (67)	291 (33)	1.35 (1.09, 1.67)		
Jewish ethnicity							
No	1,455 (74)	518 (26)	1,277 (69)	585 (31)	1.33 (1.15, 1.53)	0.72	1.33 (1.16, 1.52)
Yes	96 (76)	31 (24)	122 (68)	57 (32)	1.39 (0.83, 2.33)		

(*Continued*)

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TABLE 2. (*Continued*)

	Controls		Cases				
	No Genital Talc Use N (%)	Any Genital Talc Use N (%)	No Genital Talc Use N (%)	Any Genital Talc Use N (%)	Stratum-specific OR (95% CI)[a] for Genital Talc Use	*P* Int[b]	OR (95% CI) for Genital Talc Use Adjusted[c]
Family history[g]							
No	1,446 (74)	510 (26)	1,267 (68)	585 (32)	1.34 (1.16, 1.55)	0.61	1.33 (1.16, 1.52)
Yes	105 (73)	39 (27)	132 (70)	57 (30)	1.19 (0.73, 1.93)		
Personal history of breast cancer							
No	1,498 (74)	519 (26)	1,299 (68)	606 (32)	1.38 (1.20, 1.59)	0.01	1.33 (1.16, 1.53)
Yes	53 (64)	30 (36)	100 (74)	36 (26)	0.67 (0.37, 1.22)		
Hysterectomy or tubal ligation							
No	1,135 (74)	401 (26)	1,134 (70)	480 (30)	1.22 (1.04, 1.43)	0.02	1.34 (1.16, 1.53)
Yes	416 (74)	148 (26)	265 (62)	162 (38)	1.73 (1.31, 2.27)		
Menopausal status and HT							
Premenopausal	735 (79)	197 (21)	653 (73)	247 (27)	1.41 (1.13, 1.75)	<0.001	1.33 (1.16, 1.53)
Postmenopausal, no HT	507 (69)	230 (31)	549 (70)	238 (30)	0.97 (0.78, 1.20)		
Postmenopausal, HT	309 (72)	122 (28)	197 (56)	157 (44)	2.21 (1.63, 3.00)		
Current smoking							
No	1,332 (74)	473 (26)	1,149 (68)	538 (32)	1.35 (1.16, 1.56)	0.60	1.32 (1.16, 1.52)
Yes	219 (74)	76 (26)	250 (71)	104 (29)	1.19 (0.84, 1.69)		
Ever smoked							
No	759 (75)	248 (25)	669 (70)	291 (30)	1.34 (1.10, 1.64)	0.72	1.32 (1.16, 1.52)
Yes	792 (72)	301 (28)	730 (68)	351 (32)	1.31 (1.09, 1.58)		
Asthma							
No	1,442 (75)	492 (25)	1,310 (69)	586 (31)	1.34 (1.16, 1.55)	0.70	1.33 (1.16, 1.52)
Yes	109 (66)	57 (34)	89 (61)	56 (39)	1.25 (0.78, 2.01)		
Alcohol (grams per day)							
≤2.32	753 (74)	269 (26)	738 (70)	311 (30)	1.19 (0.98, 1.45)	0.29	1.30 (1.13, 1.50)
>2.32	763 (75)	259 (25)	623 (68)	291 (32)	1.43 (1.17, 1.75)		
Any acetaminophen use							
No	1,190 (76)	373 (24)	1,076 (71)	431 (29)	1.30 (1.10, 1.53)	0.83	1.32 (1.15, 1.52)
Yes	361 (67)	176 (33)	323 (60)	211 (40)	1.41 (1.09, 1.82)		
Any aspirin or ibuprofen use							
No	936 (77)	285 (23)	901 (71)	361 (29)	1.32 (1.10, 1.59)	0.94	1.34 (1.17, 1.53)
Yes	615 (70)	264 (30)	498 (64)	281 (36)	1.36 (1.11, 1.68)		
Adjusted for all variables	1,551	549	1,399	642	-	-	1.32 (1.15, 1.53)

[a]Adjusted for reference age (continuous), study center, and study phase.
[b]*P* for interaction from likelihood ratio tests comparing models with main effects and interaction terms to models with main effects only.
[c]Adjusted for reference age (continuous), study center, study phase, and each variable listed (individually). BMI, height, weight, and ovulatory cycles were adjusted for with indicators for quartiles and parity (nulliparous, 1, 2, ≥2), breastfeeding (never, <4, 4–9, 10–19, >19 months), and OC use (never, <23, 23–49, 50–96, >96 months) were adjusted for with indicators for categories.
[d]Adjusted for reference age only.
[e]Adjusted for reference age and study center.
[f]Adjusted for reference age, study center, and study phase.
[g]Family history of ovarian or early onset breast cancer in a mother or sister.

association was significantly greater for women who were African American, had no personal history of breast cancer, had a tubal ligation or hysterectomy, were premenopausal, or were postmenopausal and used HT. The latter finding, together with the dose–response data, is illustrated in Figure 2. Among the HT users, 92% used estrogen (alone or in combination), 2% used progesterone alone, and 5% used creams or suppositories. Increased epithelial ovarian cancer risk with genital talc use was found in both women who had used estrogen alone or estrogen plus progesterone. Too few women used progesterone only HT or estrogen creams or suppositories to examine risk with talc use in these groups (data not shown). The median duration of HT use was 5 years. Subjects with <5 years of HT use had an overall OR (95% CI) for EOC risk with ever-use of talc on genitals of 2.93 (1.86, 4.62). Subjects with ≥5 years of HT use had an OR (95% CI) that was slightly lower, 1.73

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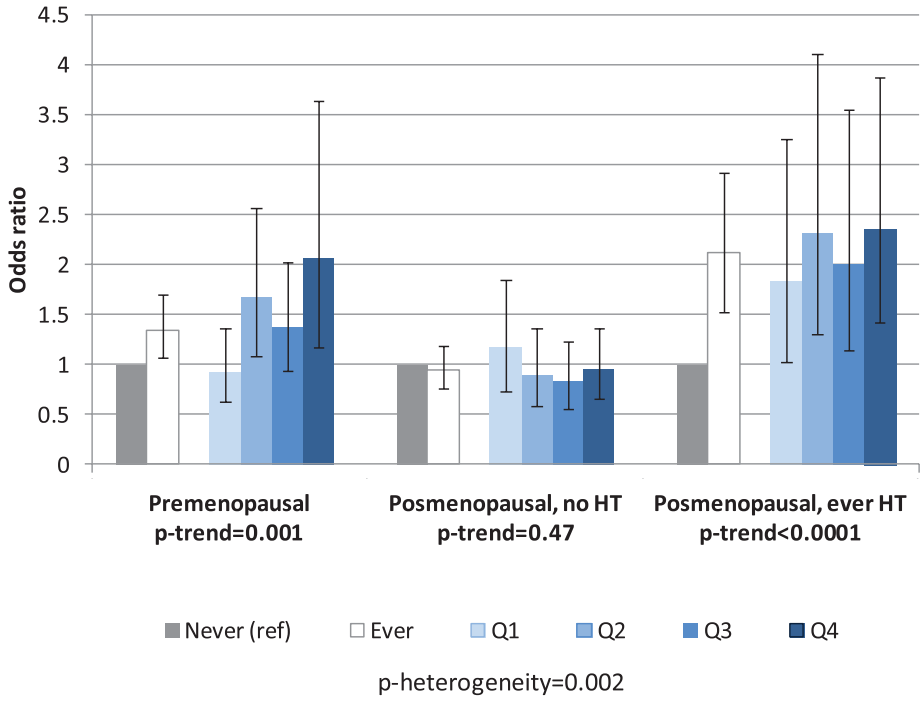


FIGURE 2. Associations between use of talc on genitals (never/ever and quartiles of talc-years) and ovarian cancer by menopausal status and postmenopausal hormone therapy.

(1.15, 2.62), but a clearer trend for increasing risk with talc-years was more apparent in the longer term HT users (data not shown). To explore the potential interaction between talc use and hysterectomy or tubal ligation, we restricted this analysis to subjects who had either or both procedures (Table 3). For premenopausal women, risk for EOC was increased in women who used talc before the procedure, while risk was elevated for use both before and after the procedure in postmenopausal women who used HT. No associations were seen in postmenopausal women who had not used HT. There were too few subjects who had used talc only after a hysterectomy or tubal ligation to permit reliable estimates of risk.

Returning to Table 2, we applied the convention that a variable may be a confounder if adjustment yields a 10% difference compared with the crude OR (or, in our study, compared with the OR of 1.33 adjusted for age, study center, and study phase). A 10% lower or greater change corresponds to an OR ≤1.20 or ≥1.46. As seen in the far right column, the OR of 1.33 for ovarian cancer risk was not materially changed after adjustment for any individual or all variables.

Because Figure 2 suggests that EOC risk with talc varies by menopausal status, we revisited the issue of interaction in eTable 1 (http://links.lww.com/EDE/B2) in which subjects are stratified by menopausal status. Although few significant interactions were seen, categories for several variables revealed contrasting overall associations and/or clearer dose–responses (Fig. 3). For premenopausal women, these included women with a BMI > 25, those who had breastfed, those who were not current smokers, and those who consumed more than 2.32 g of alcohol per day. In addition, the association was stronger for both pre- and post-menopausal women who were least likely to have a genetic basis for their ovarian cancer, defined as women with no personal history of breast cancer, without a primary relative with either ovarian cancer or premenopausal breast cancer, and non-Jewish women (eTable 1; http://links.lww.com/EDE/B2). No important interactions were observed for postmenopausal women, except for weight and BMI, HT use, and the combined "genetic" variable.

Table 4 shows ORs stratified by menopausal status and histologic subtype of epithelial ovarian cancer. Overall, talc use increased risk for serous and endometrioid invasive and serous borderline tumors with the dose–response most apparent for serous invasive cancer. For premenopausal women, both the overall associations and dose–responses were stronger with serous invasive and serous borderline tumors. Premenopausal women also had an increased risk for mucinous borderline tumors at the highest quartile of talc use OR = 2.28 (1.23, 4.26) and a dose–response. For postmenopausal women, dose–responses were strongest for women with invasive serous and endometrioid tumors. Talc use was not associated with clear cell or mucinous invasive epithelial ovarian cancer regardless of menopausal status. The ORs and dose–responses for the combined histologic subtypes relevant to pre- and post-menopausal women are shown in Table 5. Except for a few categories, these were not materially different than those illustrated in Figure 2. However, notably, premenopausal women and postmenopausal HT-users with the relevant subtypes who had accumulated >24 talc-years had ORs (95% CI) of 2.33 (1.32, 4.12) and 2.57 (1.51, 4.36), respectively.

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TABLE 3. Effect of Tubal Ligation and Hysterectomy by Menopausal Status and Hormone Therapy on Association Between Genital Talc Use and Ovarian Cancer

Genital Talc Use Among Women Who Had a Hysterectomy or Tubal Ligation[a]	Premenopausal			Postmenopausal, Never Used HT			Postmenopausal, Ever Used HT		
	Controls	Cases	Adjusted[b]	Controls	Cases	Adjusted[b]	Controls	Cases	Adjusted[b]
	N (%)	N (%)	OR (95% CI)	N (%)	N (%)	OR (95% CI)	N (%)	N (%)	OR (95% CI)
Never used	147 (79)	94 (71)	1.00 (referent)	139 (67)	113 (67)	1.00 (referent)	130 (77)	58 (48)	1.00 (referent)
Used both before and after	26 (14)	17 (13)	0.99 (0.48, 2.06)	45 (22)	36 (21)	1.00 (0.58, 1.72)	21 (13)	40 (33)	5.85 (2.88, 11.9)
Used before only	10 (5)	20 (15)	4.40 (1.73, 11.2)	20 (10)	16 (10)	0.99 (0.46, 2.10)	12 (7)	18 (15)	3.49 (1.39, 8.75)
Used after only	3 (2)	1 (1)	0.33 (0.03, 3.60)	3 (1)	4 (2)	1.66 (0.34, 8.21)	5 (3)	5 (4)	2.11 (0.49, 9.17)

[a]The median ages for tubal ligation and hysterectomy, respectively, were 34 and 39 for cases and 34 and 40 for controls.
[b]Adjusted for reference age (continuous), study center, study phase (3, 4, 5), parity (nulliparous, 1, 2, ≥2), breastfeeding (never, <4, 4–9, 10–19, >19 months), OC use (never, <23, 23–49, 50–96, >96 months), IUD (never, ever), endometriosis or painful periods, personal history of breast cancer, Jewish ethnicity, tubal ligation, and BMI (<22.2, 22.2–24.8, 24.9–28.6, >28.6).

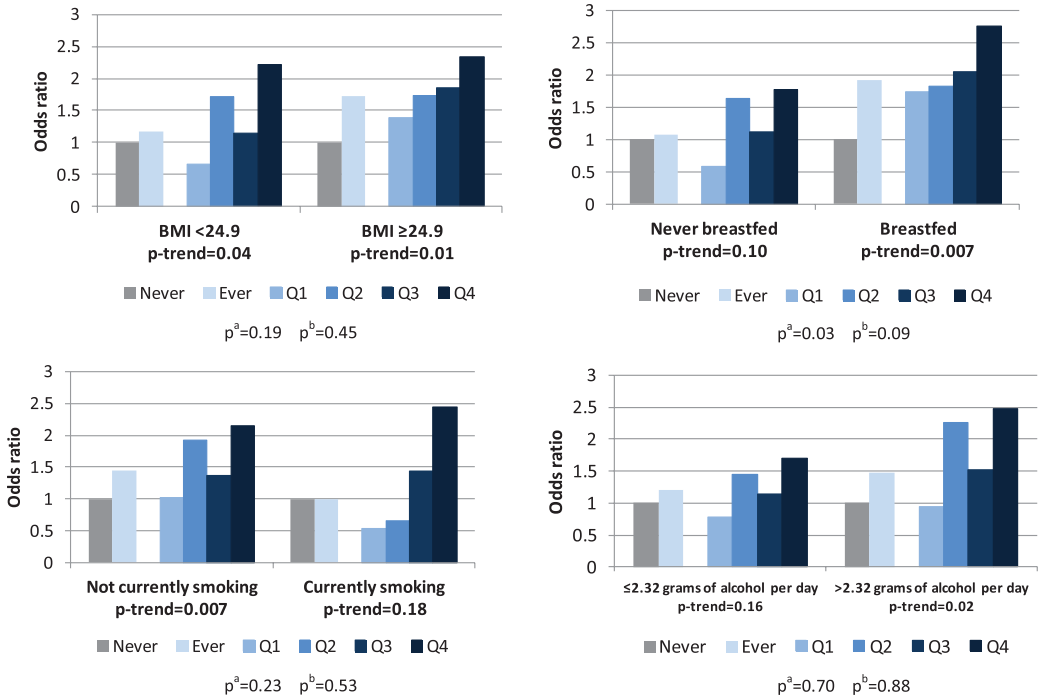


FIGURE 3. Variables modifying the talc association in premenopausal women. [a]*P* heterogeneity from likelihood ratio tests comparing a model with ever/never talc use and the effect modifier to a model with these plus the interaction term between them. [b]*P* heterogeneity from likelihood ratio tests comparing a model with indicators for each quartile of talc-years and the effect modifier to a model with these plus their interacton terms.

DISCUSSION

We analyzed case–control data collected over 16 years on talc use and epithelial ovarian cancer risk to address issues related to definition of the exposure, bias and confounding, effect modification, histologic heterogeneity, and dose–response. Talc used regularly in the genital area was associated with a 33% increase in ovarian cancer risk overall while no apparent risk was associated with talc used only in nongenital areas. Our results are consistent with a recent pooled analysis from the OCAC which reported that use of powder on genitals is associated with a 24% increased risk and no effect of nongenital use of talc.[19] There was general agreement on risk by histologic type of epithelial ovarian cancer except that OCAC found an association with clear cell cancer and we did not. The findings from OCAC and our study contrast with null results from the WHI cohort analysis[17] raising the issue of recall bias in case–control studies.

Addressing recall bias, we conducted a sensitivity analysis that assumed truly nonexposed cases and controls were accurately classified as unexposed (i.e., specificity 99%) and

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TABLE 4. Genital Talc Applications by Histologic Type and Menopausal Status

Characteristic	Controls %	Serous Invasive Cases %	Serous Invasive Adjusted[a] OR (95% CI)	Mucinous Invasive Cases %	Mucinous Invasive Adjusted[a] OR (95% CI)	Endometrioid Invasive Cases %	Endometrioid Invasive Adjusted[a] OR (95% CI)	Clear Cell Invasive Cases %	Clear Cell Invasive Adjusted[a] OR (95% CI)	*P* Het	Serous Borderline Cases %	Serous Borderline Adjusted[a] OR (95% CI)	Mucinous Borderline Cases %	Mucinous Borderline Adjusted[a] OR (95% CI)	*P* Het
All women	N = 2,100	N = 968		N = 95		N = 327		N = 114			N = 250		N = 147		
No use	74	65	1.00	78	1.00	67	1.00	74	1.00	0.13	70	1.00	78	1.00	0.20
Any use	26	35	1.42 (1.19, 1.69)	22	0.87 (0.53, 1.44)	33	1.38 (1.06, 1.80)	26	1.01 (0.65, 1.57)		30	1.40 (1.03, 1.90)	22	1.02 (0.67, 1.54)	
No genital use	74	66	1.00	78	1.00	67	1.00	74	1.00		70	1.00	78	1.00	
≤1 talc-year	7	7	1.30 (0.94, 1.79)	8	1.30 (0.60, 2.82)	8	1.30 (0.81, 2.07)	6	0.94 (0.42, 2.14)		8	1.38 (0.80, 2.36)	2	0.33 (0.10, 1.06)	
>1–5 talc-years	6	7	1.45 (1.05, 2.01)	3	0.57 (0.18, 1.85)	8	1.54 (0.96, 2.48)	7	1.44 (0.66, 3.13)		8	1.72 (1.02, 2.89)	6	1.31 (0.63, 2.71)	
>5–24 talc-years	7	9	1.33 (0.99, 1.79)	8	1.15 (0.54, 2.46)	8	1.14 (0.72, 1.80)	5	0.63 (0.27, 1.51)		8	1.18 (0.69, 2.00)	11	1.64 (0.92, 2.92)	
>24 talc-years	6	11	1.54 (1.15, 2.07)	2	0.38 (0.09, 1.60)	9	1.67 (1.06, 2.63)	8	1.35 (0.64, 2.84)		6	1.55 (0.87, 2.77)	3	0.84 (0.32, 2.16)	
P trend			0.003		0.24		0.04		0.64	0.16		0.16		0.76	0.55
Premenopausal	N = 932	N = 282		N = 51		N = 177		N = 56			N = 175		N = 108		
No use	79	70	1.00	78	1.00	70	1.00	79	1.00	0.49	72	1.00	78	1.00	0.44
Any use	21	30	1.43 (1.04, 1.98)	22	1.04 (0.52, 2.10)	30	1.34 (0.91, 1.98)	21	0.87 (0.44, 1.75)		28	1.56 (1.06, 2.31)	22	1.25 (0.75, 2.06)	
No genital use	79	70	1.00	78	1.00	71	1.00	79	1.00		72	1.00	78	1.00	
≤1 talc-year	7	5	0.71 (0.38, 1.34)	14	1.81 (0.75, 4.37)	9	1.13 (0.60, 2.11)	4	0.33 (0.08, 1.47)		9	1.51 (0.82, 2.80)	1	0.13 (0.02, 0.99)	
>1–5 talc-years	5	7	1.71 (0.94, 3.12)	4	1.01 (0.23, 4.42)	7	1.58 (0.77, 3.27)	9	2.41 (0.83, 7.01)		7	1.58 (0.78, 3.21)	6	1.57 (0.66, 3.74)	
>5 talc-years	9	18	1.85 (1.21, 2.80)	4	0.44 (0.10, 1.90)	13	1.33 (0.77, 2.31)	9	0.87 (0.32, 2.38)		12	1.66 (0.96, 2.88)	15	2.28 (1.23, 4.26)	
P trend			0.003		0.24		0.34		0.88	0.06		0.09		0.005	0.28
Postmenopausal	N = 1,168	N = 686		N = 44		N = 150		N = 58			N = 75		N = 39		
No use	70	63	1.00	77	1.00	63	1.00	69	1.00	0.29	65	1.00	77	1.00	0.43
Any use	30	37	1.36 (1.10, 1.67)	23	0.70 (0.34, 1.46)	37	1.36 (0.94, 1.97)	31	1.10 (0.61, 1.99)		35	1.15 (0.69, 1.91)	23	0.80 (0.37, 1.75)	
No genital use	70	64	1.00	77	1.00	63	1.00	69	1.00		65	1.00	77	1.00	
≤5 talc-years	13	15	1.44 (1.07, 1.93)	5	0.34 (0.08, 1.46)	15	1.39 (0.82, 2.33)	14	1.32 (0.58, 2.99)		16	1.40 (0.70, 2.79)	10	1.24 (0.41, 3.77)	
>5–24 talc-years	8	9	1.19 (0.83, 1.71)	14	1.67 (0.66, 4.20)	9	1.15 (0.61, 2.19)	3	0.39 (0.09, 1.69)		8	1.11 (0.45, 2.73)	8	1.03 (0.30, 3.55)	
>24 talc-years	9	12	1.33 (0.96, 1.85)	5	0.45 (0.10, 1.91)	13	1.60 (0.93, 2.77)	14	1.59 (0.70, 3.60)		11	0.99 (0.44, 2.21)	5	0.39 (0.09, 1.76)	
P trend			0.13		0.49		0.12		0.44	0.58		0.91		0.23	0.29

[a]Adjusted for reference age (continuous), study center, study phase (3, 4, 5), parity (nulliparous, 1, 2, ≥2), breastfeeding (never, <4, 4–9, 10–19, >19 months), OC use (never, <23, 23–49, 50–96, >96 months), HT use (premenopausal, postmenopausal never used, postmenopausal used HT), IUD (never, ever), endometriosis or painful periods, personal history of breast cancer, Jewish ethnicity, tubal ligation, and BMI (<22.2, 22.2–24.8, 24.9–28.6, >28.6).

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TABLE 5. Associations Between Genital Talc Use (Never/Ever and Quartiles of Talc-years) and Ovarian Cancer by Menopausal Status and Postmenopausal Hormone Therapy Among Restricted Histologic Types

	Premenopausal			Postmenopausal, Never Used HT			Postmenopausal, Ever Used HT		
Genital Talc Use	Controls N (%)	Cases[a] N (%)	Adjusted[b] OR (95% CI)	Controls N (%)	Cases[a] N (%)	Adjusted[b] OR (95% CI)	Controls N (%)	Cases[a] N (%)	Adjusted[b] OR (95% CI)
Never	735 (79)	531 (72)	1.00 (referent)	507 (69)	378 (69)	1.00 (referent)	309 (72)	152 (53)	1.00 (referent)
Ever	197 (21)	211 (28)	1.42 (1.12, 1.81)	230 (31)	173 (31)	1.00 (0.78, 1.28)	122 (28)	133 (47)	2.32 (1.64, 3.27)
No genital use	735 (79)	531 (72)	1.00 (referent)	507 (69)	378 (69)	1.00 (referent)	309 (72)	152 (54)	1.00 (referent)
≤1	70 (8)	47 (6)	0.90 (0.60, 1.37)	40 (6)	36 (7)	1.32 (0.80, 2.17)	28 (7)	28 (10)	2.02 (1.10, 3.70)
>1–5	44 (5)	52 (7)	1.66 (1.06, 2.60)	52 (7)	32 (6)	0.81 (0.50, 1.32)	28 (7)	29 (10)	2.56 (1.40, 4.67)
>5–24	59 (6)	68 (9)	1.54 (1.04, 2.28)	61 (8)	41 (8)	0.86 (0.55, 1.33)	26 (6)	30 (11)	2.18 (1.19, 4.00)
>24	21 (2)	41 (6)	2.33 (1.32, 4.12)	70 (10)	56 (10)	1.00 (0.68, 1.49)	36 (8)	43 (15)	2.57 (1.51, 4.36)
P trend			0.0006			0.88			0.001

[a]Postmenopausal cases are restricted to serous and endometrioid invasive, premenopausal cases additionally include serous and mucinous borderline cases.

[b]Adjusted for reference age (continuous), study center, study phase (3, 4, 5), parity (nulliparous, 1, 2, ≥2), breastfeeding (never, <4, 4–9, 10–19, >19 months), OC use (never, <23, 23–49, 50–96, >96 months), IUD (never, ever), endometriosis or painful periods, personal history of breast cancer, Jewish ethnicity, tubal ligation, and BMI (<22.2, 22.2–24.8, 24.9–28.6, >28.6).

truly exposed cases were also correctly classified (sensitivity 99%). The OR of 1.33 in our study would be nullified if the sensitivity of correctly classified controls fell to 82% or 18% misclassification. Unfortunately, there are no external records to validate talc use reported by study participants to assess whether this degree of misclassification is reasonable. Somewhat analogous to talc and ovarian cancer is alcohol use and breast cancer. Nurses' Health Study investigators examined the latter association both with prospective data collected at baseline and retrospective data obtained by resurveying subjects after diagnosis.[25] They found an (age adjusted) OR for breast cancer of 1.42 associated with 30 or more grams of alcohol/day relative to nondrinkers from the prospective data compared with 1.33 from the retrospective data. This change between two analyses would occur if the sensitivity of controls correctly recalling alcohol use dropped to 91% (or 9% misclassification). This suggests some degree of misclassification in retrospective data but not as great as the 18% required to nullify the association between use of talc on genitals and ovarian cancer risk in our study. No comparable study on talc comparing results from prospective versus retrospective data has been performed. However, several observations are incompatible with the possibility that recall bias explains the association: (1) ORs are generally lower in studies which asked about "ever use" of talc[5,8,11] compared with those that specified regular use,[6,7,9,12,13] whereas higher ORs would be expected if cases are more likely to recall limited ever-use; (2) no association with nongenital talc use; (3) risk varies by histologic type; (4) the association is stronger in premenopausal women who are closer in time to talc use and less likely to have forgotten it; and (5) ORs from recent studies[11,13] are lower than those from earlier ones,[6,7] whereas increasing publicity about the association over time might lead to greater recall bias and higher ORs in more recent studies. Related arguments that cases initiate talc use because of treatment of ovarian cancer or early symptoms of disease also lack merit because we censored exposures 1 year before the date of diagnosis and most talc-users began the habit around age 20—a decade or more before the ovarian cancer diagnosis.

Whether the association is a result of confounding must also be addressed. A 1998 article identified BMI, smoking, and alcohol use as potential correlates of talc use in the general population.[26] In our study, powder users were more likely to be older, from more urban/suburban areas, heavier, asthma sufferers, and regular analgesics users. However, none of these or other Table 2 variables altered the overall association by more than 10%, providing no indication of confounding. Talc use was also greater in African Americans and notably associated with a high, albeit imprecise, OR (and 95% CI) of 5.08 (1.32, 19.6). This finding clearly requires further study.

The observation that talc users, both case and control subjects, were more likely to say they had asthma has not been previously reported. The link between powder use and asthma may not be fully appreciated from Table 2 since women who used talc as a body powder but not to the genital area were classified as nonexposed. Making no body or genital exposure the nonexposed referent group and asthma the outcome, the ORs (and 95% CI) for asthma for body exposure to talc is 1.27 (0.80, 2.03) for cases and 1.02 (0.66, 1.57) for controls. The comparable OR for genital use of talc with or without body use is 1.48 (1.00, 2.18) for cases and 1.45 (1.00, 2.10) for controls. Sixty of 85 cases (70%) with asthma and 57 of 89 (64%) controls reported that talc use predated asthma onset. Although chance must be considered a possible explanation for this novel finding, talc is a cause of occupational asthma[27] and respiratory distress has been reported in infants after talc was accidentally inhaled.[28] That asthma may be associated with use of talc is important not only because of health

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consequences on its own but also because it may shed light on biologic mechanisms potentially relevant to the talc and ovarian cancer association.

Although we found no evidence of confounding, we did find several examples of effect modification of the association between talc and epithelial ovarian cancer. Overall, the association was greater in women with no personal history of breast cancer, those who had a tubal ligation or hysterectomy, in premenopausal women, and postmenopausal women who had used HT. Among these factors, perhaps the most important is effect modification of the association by menopausal status and menopausal HT.

Apparent lack of an elevated risk for epithelial ovarian cancer from talc use in postmenopausal women without HT use has not been reported previously. Explanations might include that there is no association with talc use in the absence of endogenous or exogenous estrogen, fading memory of past exposures, women who will develop ovarian cancer from talc use leave the at risk pool before they reach menopause, or more complex interactions with multiple risk factors and gene–environment interactions. Of possible relevance, Moorman et al.[29] observed that reproductive events that clearly affect risk in premenopausal women may not affect risk to the same degree in postmenopausal women. Whatever the explanation, our observation challenges the relevance of the WHI study to the ovarian cancer/talc association since only postmenopausal women were enrolled in WHI and HT use was examined only as a confounder, not an effect modifier.[16] Further study will be necessary to clarify the role that talc may play in postmenopausal women who did not use HT with a focus on those factors that may increase endogenous estrogen, such as greater BMI.

That the association is more apparent in premenopausal women and in postmenopausal women who used hormonal therapy suggests that estrogen plays a role in the association. In talc inhalation studies conducted by the National Toxicology Program, only female rats developed lung tumors.[30] Literature on airway inflammation from particulates is also relevant. Citing evidence that asthma may be exacerbated during pregnancy, Zhang et al.[31] postulated this may be due to an effect of estrogen on macrophage activity and inflammatory response to particulates normally considered inert, like titanium dioxide (TiO_2). Their in-vivo studies demonstrated that macrophages from pregnant mice transplanted to nonpregnant recipients conferred an inflammatory phenotype in response to TiO_2. Such studies should be repeated with talc, another particulate considered "inert."

An exploratory analysis of other potential effect modifiers led to several other observations that may have biologic relevance. The overall associations and dose–responses were "stronger" for premenopausal women who had a greater BMI, had breastfed, were not current smokers, and consumed alcohol (Fig. 3). Due to the large number of associations tested, chance must be the first explanation considered. However, a common denominator could be prolactin since its levels are higher in women who have greater BMI,[32] breastfed,[33] do not currently smoke,[34] consume alcohol,[35] and are postmenopausal and use HT.[36] Like estrogen, prolactin may have multiple effects on immune cells, especially monocytes and macrophages[37] whose role in scavenging talc in tissue is described.[38] These observations provide a framework for talc carcinogenicity in EOC involving chronic inflammation.[9]

Biologic credibility of the talc/EOC association is enhanced by persuasive evidence that inert particles the size of talc, present in the vagina, can migrate to the upper genital tract. In a technique called hysterosalpingoscintigraphy, technetium-labeled albumen microspheres are placed in the vagina and their migration to the upper tract was confirmed using serial scintograms.[39] The microspheres are 5 to 40 μm in diameter—a range which includes the size of sperm and talc. Migration from the vagina is the obvious explanation for why talc can be found in diseased (and some normal) ovaries.[3] Unfortunately, no epidemiologic study of epithelial ovarian cancer and talc has taken the opportunity to determine whether talc can actually be found in tissues removed at surgery and correlated with exposure to talc. A clue to talc's presence is birefringent particles found when slides are examined under polarized-light microscopy. Although confirmation that the material is actually talc requires scanning electron microscopy and X-ray dispersion spectroscopy, presence of birefringence is a practical screening technique as illustrated by a case report of a woman with ovarian cancer and long-term talc use who had talc in her pelvic lymph nodes first suggested by birefringence.[40]

There are inherent limitations quantifying a dose–response due to a lack of metrics for how much talc is in an "application," how much enters the vagina, and how much reaches the upper genital tract where, presumably, any deleterious effect is mediated. This may account for the failure to identify a dose–response in many papers on talc and ovarian cancer. Our 1999 study[7] suggested that adjusting total applications by whether the genital tract was "open" (i.e., excluding use after a tubal ligation or hysterectomy and examining use during times when ovulation was occurring) yielded significant dose–responses. Mills et al.[10] found a dose–response by frequency of use. Wu et al.,[12] looking at all types of body use, found a dose–response with estimated applications. Merritt et al.[11] reported a significant trend in risk for invasive serous ovarian cancer with years of talc use. The recent OCAC analysis reported no trend with increasing lifetime applications *when restricted to talc users*.[19] However, an increase in risk with increasing applications was found for nonmucinous epithelial ovarian cancer *when nonusers were included*. Virtually all papers that have looked at dose–response for talc and epithelial ovarian cancer risk have included nonusers in the trend analysis. In our article, we calculated talc-years and showed that, overall, there is a significant trend for epithelial ovarian cancer risk and talc-years when nonusers are included, and the

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trend is even more apparent in premenopausal women with certain epithelial ovarian cancer subtypes.

In summary, this study on talc and epithelial ovarian cancer has contributed the following perspectives, some new, regarding this association:

(1) Overall, there is an association between genital talc use and EOC and a significant trend with increasing "talc-years" of use.
(2) Among many epidemiologic variables, no confounders for the association were identified.
(3) Talc users, both cases and controls, were more likely to report a medical history of asthma.
(4) The talc/epithelial ovarian cancer association was largely confined to premenopausal women and postmenopausal women who used HT. Other potential effect modifiers in premenopausal women included BMI, breastfeeding, current smoking, or alcohol use. These observations may suggest a role for estrogen and/or prolactin, both known to affect macrophage function and inflammatory response.
(5) Histologic subtypes of epithelial ovarian cancer more likely to be associated with talc include serous and mucinous borderline tumors and invasive serous and endometrioid tumors.
(6) For epithelial ovarian cancer categories based on certain effect modifiers or histologic subtypes, stronger overall associations and dose–responses were observed.
(7) The association may be stronger in African Americans.

An editorial[17] accompanying the WHI study[16] noted that "several case–control studies have reported associations between talc use and ovarian cancer risk" and "no epidemiologic studies have demonstrated a dose–response" (page 2). We believe these appraisals understate the epidemiologic evidence. There have been dozens of case–control studies and several have, in fact, found a dose–response. The editorial further notes that "it does not seem likely that additional conventional epidemiologic studies will strengthen the evidence for or against talc carcinogenicity" (page 2). We believe the observations made here present a good case for talc carcinogenicity and that reanalyses of existing data from already published studies might provide confirmatory evidence. To encourage consolidation of data, we have provided a copy of the "raw" and derived variables examined in our study to NCI dbGaP (available here: http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001034.v1.p1) as well as the SAS and Stata programs used in this analysis (eAppendix 1; http://links.lww.com/EDE/B2).

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