Perineal Exposure to Talc and Ovarian Cancer Risk

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Objective: We sought to determine whether the use of talc in genital hygiene increases the risk for epithelial ovarian cancer.

Methods: We interviewed 235 white women diagnosed with epithelial ovarian cancer between 1984–1987 at ten Boston metropolitan area hospitals and 239 population-based controls of similar race, age, and residence.

Results: Overall, 49% of cases and 39% of controls reported exposure to talc, via direct application to the perineum or to undergarments, sanitary napkins, or diaphragms, which yielded a 1.5 odds ratio (OR) for ovarian cancer (95% confidence interval [CI] 1.0–2.1). Among women with perineal exposure to talc, the risk was significantly elevated in the subgroups of women who applied it: 1) directly as a body powder (OR 1.7, 95% CI 1.1–2.7), 2) on a daily basis (OR 1.8, 95% CI 1.1–3.0), and 3) for more than 10 years (OR 1.6, 95% CI 1.0–2.7). The greatest ovarian cancer risk associated with perineal talc use was observed in the subgroup of women estimated to have made more than 10,000 applications during years when they were ovulating and had an intact genital tract (OR 2.8, 95% CI 1.4–5.4); however, this exposure was found in only 14% of the women with ovarian cancer.

Conclusions: These data support the concept that a lifetime pattern of perineal talc use may increase the risk for epithelial ovarian cancer but is unlikely to be the etiology for the majority of epithelial ovarian cancers. *(Obstet Gynecol 1992;80:19–26)*

The theory that human ovarian cancer may be mesotheliomas that originate from asbestos exposure was first proposed by Graham and Graham.[1] Later, Parmley and Woodruff[2] suggested that effluences that may arise from the vagina, uterus, or tubes might enter the pelvic cavity and interact with ovarian surface epithelium to induce such mesotheliomas. Longo and Young[3] further speculated that cosmetic talc might act in this manner because of its chemical similarity to asbestos. Although there is little doubt that asbestos may induce mesotheliomas, the link between genital exposure to talc and ovarian cancer is less clear.

The few epidemiologic studies that have examined the association between talc and ovarian cancer reported only modest elevations of risk, but data on all potential sources of genital talc exposure were limited.[4–7] The purpose of this report was to present findings from a new case-control study of ovarian cancer conducted in the Boston metropolitan area, in which we considered a variety of modes for perineal talc exposure, the frequency and duration of use, and various reproductive characteristics that might influence the ability of talc to enter the pelvic cavity and affect the ovaries.

Materials and Methods

Between July 1984 and September 1987, we identified 394 women between 18–76 years of age diagnosed with borderline or malignant epithelial ovarian cancer at one of ten participating hospitals in the Boston metropolitan area. Permission to contact each patient was obtained in advance from the physician of record. An in-person interview was conducted with 272 (69%) of the 394 cases identified. Thirty-one percent were not interviewed because of physician and/or patient refusal, patient death, or relocation. The final sample for analysis was further restricted to the 235 white women confirmed as having an epithelial ovarian tumor based on an independent pathology review conducted by two of the authors (DAB and WRW).

Controls were selected from the Massachusetts Town Books, annual publications that list residents by name, age, and address according to voter precincts. For each new ovarian cancer case interviewed, a ran-

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Table 1. Influence of Any Perineal Talc Exposure* on Ovarian Cancer Risk by Characteristics of Study Participants, Boston Metropolitan Area, 1984–1987

	Cases		Controls			
	Total	Talc exposure	Total	Talc exposure	Crude OR	95% CI
All subjects	235	114 (48.5%)	239	94 (39.3%)	1.5	1.0–2.1
Age (y)						
<50	96	41 (42.7%)	101	28 (28.0%)	1.9	1.2–3.4
≥50	139	73 (52.5%)	138	66 (47.8%)	1.2	0.8–2.1
Education (y)						
≤12	93	51 (54.8%)	115	48 (41.7%)	1.7	1.1–3.0
>12	142	63 (44.4%)	124	46 (37.1%)	1.4	0.9–2.4
Marital status						
Never married	40	14 (35.0%)	24	6 (25.0%)	1.6	0.5–5.7
Ever married	195	100 (51.3%)	215	88 (40.9%)	1.5	1.0–2.7
Religion						
Jewish	35	21 (60.0%)	21	12 (57.1%)	1.1	0.4–3.9
Non-Jewish	200	93 (46.5%)	218	82 (37.6%)	1.4	0.9–2.5
Weight (lb)						
<140	123	53 (43.1%)	125	49 (39.2%)	1.2	0.7–1.9
≥140	112	61 (54.5%)	114	45 (39.2%)	1.8	1.1–3.1
Use of OCs (mo)						
≥3	66	31 (47.0%)	82	27 (32.9%)	1.8	0.8–4.5
<3 or never	169	83 (49.1%)	157	67 (42.7%)	1.3	0.8–2.3
No. of live-born children						
0	79	30 (38.0%)	43	12 (27.9%)	1.6	0.7–4.0
1	31	21 (67.7%)	27	5 (18.5%)	9.2	2.9–46.2
2	40	24 (60.0%)	63	26 (41.3%)	2.1	0.9–5.3
≥3	85	39 (45.9%)	106	51 (48.1%)	0.9	0.6–1.6

OR = odds ratio; CI = confidence interval; OCs = oral contraceptives.
* Sources of perineal talc exposure include: dusting of underwear, diaphragms, or sanitary napkins; use by partner on his perineal area; use as a body powder.

dom number generator selected one page from the town book corresponding to the case's precinct of residence. By working forward in the town book, we selected the first five female subjects within 2 years of age of the case as potential controls. Of these five, the first subject of the same race as the case without a history of a bilateral oophorectomy was asked to participate in the study. Of the 526 controls contacted, 239 interviews were conducted (25% could not be reached, 10% reported a history of bilateral oophorectomy, and 19% declined to participate). Further details of the study methods can be found elsewhere.[8]

The in-person interview focused on the following: demographic and occupational history; medical and reproductive histories, including pregnancies, hormones used, and gynecologic operations; dietary history; cigarette smoking; and hygienic practices. The hygienic practices included information regarding the use of douches, type of sanitary protection used, and perineal exposure to talc. Queried sources of perineal talc exposure included dusting of underwear, sanitary napkins, and diaphragms; exposure via husband's use of talc; and more direct exposure to the perineum as a body powder. No reliable information on talc exposure during infancy with diapering could be obtained, and women using talc as a body powder on areas other than the perineum were considered nonexposed. For each exposure, we inquired about brands used, age at first use, total years of use, and frequency of use per month, to enable us to estimate the total lifetime number of applications from all sources of exposure.

Differences between cases and controls in the distribution of these various exposures to talc were examined both qualitatively and quantitatively. The influence of confounders and effect modifiers was assessed first through stratification and then using unconditional logistic regression.[9] The primary matching variable, age, was retained in each logistic model. The χ^2 test for linear trend was calculated based on the change in deviance in models with and without continuous exposure variables.[9]

Results

Table 1 shows the proportion of cases and controls with any reported perineal talc exposure, and the associated crude exposure odds ratio (OR), by certain demographic and reproductive subgroups. Overall, a

Table 2. History of Talc Exposure by Types of Application, Brand of Powders, Years and Frequency of Use, and Era of Use

	Cases	Controls	Adjusted OR*	95% CI
No genital talc application	121 (51.5%)	145 (60.7%)	1.0	
Any genital talc application	114 (48.5%)	94 (39.3%)	1.5	1.0–2.1
Type of application				
Only via sanitary napkins and/or underwear	9 (3.8%)	12 (5.0%)	1.1	0.4–2.8
Via partner or applications to diaphragm†	20 (8.5%)	21 (8.8%)	1.2	0.6–2.4
Via dusting powder to perineum†	85 (36.2%)	61 (25.5%)	1.7	1.1–2.7
Applications of talc per month				
<5	32 (13.6%)	28 (11.7%)	1.5	0.8–2.7
5–29	24 (10.2%)	25 (10.5%)	1.2	0.6–2.2
≥30	58 (24.7%)	41 (16.7%)	1.8	1.1–3.0
Years of talc use				
<10	14 (6.0%)	15 (6.3%)	1.2	0.5–2.6
10–29	49 (20.9%)	39 (16.3%)	1.6	1.0–2.7
≥30	51 (21.7%)	40 (16.3%)	1.6	1.0–2.7
Age (y) at first talc use				
<20	66 (28.1%)	50 (20.9%)	1.7	1.1–2.7
20–25	27 (11.5%)	26 (10.9%)	1.2	0.6–2.2
>25	21 (8.9%)	18 (7.5%)	1.6	0.8–3.2
Years since last talc use				
Within last 6 mo	48 (20.4%)	27 (11.3%)	2.3	1.3–4.0
Between 6 mo–10 y	36 (15.3%)	39 (16.3%)	1.1	0.7–1.9
10 y or more	30 (12.8%)	28 (11.7%)	1.4	0.8–2.6
Era of use‡				
Exclusive use after 1960	29 (12.3%)	30 (12.6%)	1.1	0.6–2.1
Any use before 1960	75 (31.9%)	57 (23.9%)	1.7	1.1–2.7
Brand of application§				
Brand or generic baby powder	91 (38.7%)	72 (30.1%)	1.6	1.1–2.5
Deodorizing or other scented powders	16 (6.8%)	17 (7.2%)	1.2	0.6–2.5

OR = odds ratio; CI = confidence interval.

* Adjusted for parity (0, 1–2, >2), education (<12 years, >12 years), marital status (never married, ever married), religion (Jewish, non-Jewish), use of sanitary napkins (no, yes), douching (no, yes), age (continuous), and weight (<140 lb, ≥140 lb).

† Includes combinations with sanitary napkins or underwear.

‡ Restricted to women older than 10 years in 1960; 100 cases and 118 controls were unexposed and used as the referent group.

§ Excludes seven cases and five controls with unknown powders. Seven cases and four controls reported combinations of more than one brand and were classified according to the brand used most frequently and for the longest period. Specific brands mentioned by cases were: Johnson and Johnson, 71; generic baby powder, 20; Shower to Shower, four; other scented, 12. Specific brands mentioned by controls were: Johnson and Johnson, 54; generic baby powder, 18; Shower to Shower, three; other scented powder, 14.

greater percentage of cases (48.5%) than controls (39.3%) reported any perineal exposure to talc-containing powders. Subgroups of controls in which exposure to talc appeared to be more common were women older than 50 years ($P = .002$), ever married ($P = .12$), Jewish ($P = .08$), and parous ($P = .05$). Controls who reported no oral contraceptive (OC) use also reported greater talc use. However, this interaction may be explained by the older age distribution among controls who reported perineal application of talc. We observed stronger associations between talc and ovarian cancer risk in the subgroups of cases and controls younger than age 50, less well educated, heavier than 140 lb 5 years before diagnosis, and reporting a history of one or two live births. The number of live births was the only factor that produced statistically significant heterogeneity in the ORs for the talc and ovarian cancer association. Age, education, marital status, religion, weight, and parity were considered confounders and were included as covariates in subsequent multivariate models. Use of OCs did not confound the talc-ovarian cancer association.

Table 2 examines the association between talc use and ovarian cancer by variables related to the specific types and kinds of applications, and measures of duration including length, frequency, and period of use. Compared with women with no genital talc exposure, women exposed to talc only through use as a dusting powder on sanitary napkins or underwear had no appreciable increased risk for ovarian cancer. There was also no substantial increase in risk among women exposed to talc only through a husband's use or use in the storage of diaphragms, or in combination with applications to sanitary napkins or underwear. The most frequent method of perineal talc exposure was use as a dusting powder directly to the perineum,

Table 3. Estimated Total Lifetime Perineal Applications of Talc-Containing Powders in Cases and Controls

Applications	Cases	Controls	Adjusted OR*	95% CI
Total applications				
None	121	145	1.0	
<1000	18	19	1.3	0.7–2.7
1000–10,000	54	44	1.5	0.9–2.4
>10,000	42	31	1.8	1.0–3.0
χ^2 1*df* test for linear trend = 2.85, P = .094†				
Applications excluding use after hysterectomy or tubal ligation				
None	121	148	1.0	
<1000	19	19	1.4	0.7–2.9
1000–10,000	57	46	1.5	0.9–2.4
>10,000	38	29	1.7	1.0–3.0
χ^2 1*df* test for linear trend = 3.19, P = .077†				
Applications excluding use after hysterectomy or tubal ligation, and use during nonovulatory months‡				
None	124	149	1.0	
<1000	24	23	1.5	0.8–2.9
1000–10,000	55	51	1.3	0.8–2.0
>10,000	32	16	2.8	1.4–5.4
χ^2 1*df* test for linear trend = 6.15, P = .015†				

Abbreviations as in Table 2.

* Adjusted for parity (0, 1–2, >2), education (<12 years, >12 years), marital status (never married, ever married), religion (Jewish, non-Jewish), use of sanitary napkins (no, yes), douching (no, yes), age (continuous), and weight (<140 lb, ≥140 lb).

† Trend test based on actual applications as a continuous variable.

‡ Excludes exposures while taking oral contraceptives, while pregnant or breast-feeding, or occurring after menopause. There were three cases and four controls who moved from "exposed" to "nonexposed" in this category, as all of the exposure occurred during oral contraceptive use, pregnancies, or after menopause.

alone or in combination with either a partner's use or use in the storage of diaphragms. This exposure occurred in 85 cases (36.2%) and 61 controls (25.5%) (P = .01). Of the application modes studied, direct perineal application produced the greatest risk (OR 1.7, 95% confidence interval [CI] 1.1–2.7).

We also examined the talc-ovarian cancer association by frequency and years of use (Table 2). When monthly frequency was considered as a continuous variable in the logistic model, the χ^2 linear test of trend was 4.06 (P = .046), indicating that the risk for ovarian cancer increased significantly with increasing frequency of applications per month. The categorical analysis showed that relative to non-users, the risk was greatest in women who applied talc at least once per day. When years of use was included as a continuous variable, the test for linear trend was 3.32 (P = .07). The categorical analysis showed that relative to non-users, women who applied talc for more than 10 years were at 60% greater risk for ovarian cancer. Likewise, perineal applications of talc early in life (before age 20) or applications within 6 months of diagnosis (reference age for controls) produced the stronger ORs.

To assess whether the risk of ovarian cancer with perineal exposure to talc was affected by the time when talc-containing products were manufactured, we examined the association separately in women who only used talcum powder after 1960 and in women who reported any use of talcum powder before 1960 (Table 2). After restricting the population to women older than age 10 in 1960 and adjusting for age, parity, and a number of other demographic characteristics, we found that the association of talc and ovarian cancer was greater in women using talc products before 1960 (P = .025).

The last entry in Table 2 shows the risks by brand of powder used. No subjects could recall exclusive use of starch-based powders. Brand or generic "baby powder" was used most frequently and was the category associated with a statistically significant risk for ovarian cancer. With respect to other powders, four cases and three controls reported primary use of deodorizing powders, and 12 cases and 14 controls reported primary use of other scented powders. It should be appreciated that, because the period of exposure often occurred over decades, verification of brands was not possible.

Table 3 examines the ovarian cancer risk associated with the total number of applications to the perineum, estimated by cumulating frequency and years of use for the various kinds of exposures. An 80% excess risk was associated with an estimated exposure of more than 10,000 applications (equivalent to daily use for 30

Table 4. Adjusted Odds Ratios and 95% Confidence Intervals for Ovarian Cancer by Any Perineal Exposure to Talc* and Indicators of Ovulation and Tubal Occlusion

	Cases		Controls			
	Total	Talc exposure	Total	Talc exposure	Adjusted OR†	95% CI
All subjects	235	114 (48.5%)	239	94 (39.3%)	1.5	1.0–2.1
Mid-cycle pain						
No	181	88 (48.6%)	184	77 (41.9%)	1.4	0.9–2.2
Yes	54	26 (48.2%)	55	17 (30.9%)	2.0	0.8–5.2
Regular period						
No	26	12 (46.2%)	34	16 (47.1%)	1.1	0.4–3.4
Yes	209	102 (48.8%)	205	78 (38.1%)	1.7	1.1–2.5
PID or ectopic pregnancy						
No	226	113 (50.0%)	230	92 (40.0%)	1.6	1.1–2.4
Yes	9	1 (11.1%)	9	2 (22.2%)	0.1	0.01–7.0

PID = pelvic inflammatory disease; other abbreviations as in Table 2.

* Sources of perineal talc exposure include: dusting of underwear, diaphragms, or sanitary napkins; use by partner on his perineal area; use as a body powder.

† Adjusted for parity (0, 1–2, >2), education (<12 years, >12 years), marital status (never married, ever married), religion (Jewish, non-Jewish), use of sanitary napkins (no, yes), douching (no, yes), age (continuous), and weight (<140 lb, ≥140 lb).

years) as compared with non-users. When considered as a continuous variable in the logistic model, the χ^2 linear test of trend was 2.85 ($P = .094$). The remaining entries in Table 3 show how conditions that either close the upper genital tract or are associated with anovulation affect the dose response of number of applications on ovarian cancer risk. The second entry shows the effect of censoring applications that occurred after tubal ligation or hysterectomy. No appreciable change in the ORs or the dose response was noted. The third entry shows the effect of censoring applications after hysterectomy and tubal ligation and use during presumed nonovulatory periods. Excluded were exposures occurring while taking OCs, while pregnant or breast-feeding, and after menopause. The risk associated with fewer than 10,000 applications was not substantially altered. However, the risk associated with more than 10,000 applications was nearly threefold and statistically significant. The χ^2 test for a linear trend of risk, by number of applications as a continuous variable, increased to 6.15 ($P = .015$).

Table 4 shows the association of talc exposure and ovarian cancer based on other clinical factors that may predict either ovulation or tubal occlusion. The ORs were greater in women with a history of mid-cycle pain or regular periods—potential clinical predictors of ovulatory cycles. An association between talc and ovarian cancer was absent in women with a history of either pelvic inflammatory disease or ectopic pregnancy—potential markers of a closed genital tract. However, only nine cases and nine controls reported a history of pelvic inflammatory disease or ectopic pregnancy, and the CI on the exposure OR was correspondingly wide.

Table 5 shows the relative risk for any perineal use of talc when restricted to specific histologic type and grade of ovarian tumors. The greatest association was found in women diagnosed with an endometrioid tumor or borderline ovarian tumor.

Discussion

Animal and epidemiologic studies have addressed the plausibility of an association between talc and ovarian cancer. Intraperitoneal injection of talc in rodents produced papillary changes in the surface epithelium not inconsistent with the first stage in the development of surface papillary epithelial neoplasms.[10] However, because the ovaries of small rodents are surrounded by a

Table 5. History of Talc Use by Histologic Type and Grade

Histologic type	Any use of talc	No use of talc	Adjusted OR*	95% CI
Controls	94	145	1.0	
Histologic type				
Serous	60	64	1.4	0.9–2.2
Mucinous	17	25	1.2	0.6–2.5
Endometrioid	18	11	2.8	1.2–6.4
Other	19	21	1.6	0.8–3.3
Histologic grade				
Borderline	32	30	2.4	1.2–4.5
Grade 1	6	11	1.0	0.3–2.8
Grade 2	21	22	1.5	0.7–3.0
Grade 3	27	24	1.5	0.8–2.8
Undifferentiated	28	34	1.2	0.7–2.2

Abbreviations as in Table 2.

* Adjusted for parity (0, 1–2, >2), education (<12 years, >12 years), marital status (never married, ever married), religion (Jewish, non-Jewish), age (continuous), and weight (<140 lb, ≥140 lb).

Table 6. Odds Ratios With 95% Confidence Intervals of Ovarian Cancer in Relation to Any Perineal Exposure to Talc as Reported in Previous Epidemiologic Studies

Author(s) (year)	Cases		Controls		Crude OR	95% CI
	Total	Talc exposure	Total	Talc exposure		
Cramer et al[4] (1982)	215	92 (42.8%)	215	61 (28.4%)	1.9	1.3–2.9
Hartge et al (1983)*	135	67 (49.6%)	171	100 (58.5%)	0.7	0.4–1.1
Whittemore et al[5] (1988)	188	98 (52.1%)	539	248 (46.0%)	1.4	0.9–2.0
Harlow and Weiss[6] (1989)†	116	49 (42.2%)	158	64 (40.5%)	1.1	0.7–2.1
Booth et al[7] (1989)	217	141 (65.0%)	434	256 (59.0%)	1.3	0.9–1.9
Harlow et al (1992) (current study)	235	114 (48.5%)	239	94 (39.3%)	1.5	0.9–1.8
All studies‡	1106	561 (50.7%)	1756	823 (46.9%)	1.3	1.1–1.6

Abbreviations as in Table 2.

* Hartge P, Hoover R, Lesher LP, et al. Talc and ovarian cancer (letter). JAMA 1983;250:1844. Odds ratio may include nonperineal talc exposure as well.

† Restricted to borderline ovarian tumors.

‡ Meta-analysis.[19]

peritoneal bursa which often becomes occluded and distended with follicular fluid after intraperitoneal injection of foreign bodies,[1] it is difficult to distinguish whether the papillary changes are the effects of foreign-body exposure or bursal distention. It would be worthwhile to repeat the talc experiments in guinea pigs or rabbits, the animals used in the original research of Graham and Graham.[1]

Is there evidence to suggest that talc can translocate from the vagina to the peritoneal cavity? It is known that red cells and endometrial tissue are capable of retrograde flow from the fallopian tubes.[11] Experiments in rats confirmed the presence of talc in the ovaries after the introduction of a talc suspension into the vagina and cervical os.[12] In humans, two studies observed the migration of inert carbon particles[13] and radioactively labeled human albumin microspheres[14] from the vagina to the fallopian tubes. In addition, several investigators have observed birefringent crystals embedded in ovarian tissue.[15–17] However, critics have argued that these findings resulted from poorly designed studies or lack of precision in measuring particulates, due to leaching of radionucleotide markers from the test materials or the introduction of contaminants during tissue processing.[18] In six multiparous cynomolgus monkeys separately caged, no translocation of talc was observed after 30 consecutive days of douching with a suspension of neutron-activated talc coupled with weekly injections of oxytocin.[18] However, this study was not able to address the effects of long-term use or coitus, which might facilitate talc translocation.

Several epidemiologic studies[4–7] have addressed the genital talc-ovarian cancer association (Table 6). Each study has consistently reported little or no association with the use of talc-dusted diaphragms, and stronger associations with direct perineal application. Dose response of perineal talc exposure from all sources by frequency or years of use was not available in the studies by Hartge et al (Hartge P, Hoover R, Lesher LP, et al. Talc and ovarian cancer [letter]. JAMA 1983;250:1844), Harlow and Weiss,[6] or Cramer et al.[4] Whittemore et al[5] reported no significant dose response by years or frequency of use, whereas Booth et al[7] reported a marginally significant trend with frequency of use. Using the techniques of meta-analysis, in which ORs from multiple studies are weighted by their variances,[19] we calculated a statistically significant OR of 1.3 for any perineal talc exposure and ovarian cancer risk (95% CI 1.1–1.6) from the various studies. We therefore conclude that there is an association, albeit modest, between ovarian cancer and perineal talc use. However, insufficient detail has been available to rule out a stronger association in certain subgroups of users.

Our study included greater detail on genital talc use, including methods, frequency, and years of use (Table 2). Talc applied as a dusting powder directly to the perineum carried a greater risk than less direct exposure via a partner's use or the dusting of undergarments, sanitary napkins, or diaphragms. Current use of talc was associated with a greater ovarian cancer risk than past use. Daily versus less than daily talc use, and talc use for more than 10 years versus less than 10 years, were associated with greater risk for ovarian cancer.

Most subjects reported use of "baby powder." We were unable to confirm a previous finding that powders with "deodorizing" agents were associated with particular risk.[6] Thus, this study failed to answer a key issue in the talc-ovarian cancer association: whether the risk pertains to all cosmetic talcs or only to certain

preparations likely to be contaminated by asbestos. Crailey et al[20] and Rohl et al[21] found considerable variation in the purity of cosmetic talcs, with fiberform contents varying from less than 1 to 30%. Most of these products were manufactured before 1970 and it is likely that the asbestiform content has decreased since 1976, when manufacturers instituted voluntary guidelines on asbestos contamination. Our finding of a lower ovarian cancer risk in women with exclusive use of talc after 1960 may support this theory. Because of the difficulty in obtaining a complete and detailed history of powders used, the issue of whether risk pertains only to asbestos-contaminated powders may need to be settled by animal experiments.

In our analysis, we first calculated all genital applications of talc based upon frequency and years of use. As a continuous variable in a multivariate model, no significant dose response was observed between total genital applications of talc and ovarian cancer risk. Because the "translocation" theory assumes an open genital tract, we then excluded application after tubal ligation or hysterectomy, but observed no appreciable change in the dose response. Further restricting talc exposure to months when the women were likely to be ovulatory, we observed a significant dose response, such that women with an intact genital tract and more than 10,000 applications during ovulatory cycles had nearly a threefold increase in risk for ovarian cancer. Some additional evidence that might support an interaction with ovulation includes stronger associations in women with regular periods and mid-cycle pain. Cramer et al[4] suggested that talc contamination around the time of ovulation might lead to the incorporation of talc particulates into inclusion cysts that may form with ovulation. Experiments on foreign-body tumorigenesis have shown that implantation of foreign bodies into the lumens of epithelial-lined organs provides a favorable environment for carcinogenesis.[22] Alternatively, Mostafa et al[18] speculated that foreign-body exposure might produce cortical "granulomas" whose link to stromal hyperactivity (and hormonally related cancers) is argued in older literature.[23]

We observed that the talc association was strongest in women with endometrioid or borderline ovarian tumors. However, an earlier study by Cramer et al[4] reported no such variation in risk by histologic subtype. It was noted that a greater proportion of women with endometrioid tumors than with other histologic types of ovarian cancer reported more than 10,000 lifetime applications of talc during ovulatory cycles while having an intact genital tract (34 versus 16%). Although this may explain in part the strong talc-ovarian cancer association noted in women with endometrioid tumors, it does not explain the strong association noted in women with borderline ovarian tumors, of whom only 13% reported long-term talc exposure. This variation in risk among histologic subtypes may reflect a chance finding or a need to examine endometrioid and borderline tumors more carefully for evidence of a foreign-body effect.

An unusual observation was the strong association between talc use and ovarian cancer in the subgroup of women with one or two pregnancies but a lower risk in women with either no children or three or more children. Although chance may be the most likely explanation for this finding, we wonder whether this peculiar interaction might reflect, in part, an effect of pregnancy on the degree of openness of the cervical os and its ability to allow translocation of vaginal particulates. The parous cervix has a larger os than the nulliparous cervix, and this could explain the greater risk in women with one child compared with women with no live births. At the other extreme, multiple pregnancies may offer other protective mechanisms (such as reduced ovulation as discussed above) that could outweigh this effect. Clearly, this is a very speculative hypothesis but one that might be tested in experimental studies (ie, repeating the vaginal talc experiments in nulliparous and parous mice or primates).

Noncausal explanations are possible in any epidemiologic research. We cannot rule out the possibility of differential over- or under-reporting of talc exposure in our cases and controls, especially in those with reproductive events that enhance ORs. In addition, though we were successful in interviewing 69% of eligible ovarian cancer cases and 81% of eligible controls contacted, we cannot assess whether the cases and controls not interviewed could have selectively differed in their reproductive characteristics or in their use of talc-containing powders. Because our associations are based upon responses from participating cases and controls, the validity of our results depends upon the assumption that respondents and non-respondents were similar with respect to talc and other relevant exposures, or that the magnitude of any respondent-non-respondent difference was similar for cases and controls. Because the interview provided the only source of "exposure" information, we were unable to assess the likelihood of this assumption. The extent of this bias, however, is likely to be small because the reproductive characteristics and history of talc exposure in participating cases and controls are, for the most part, reasonably consistent with earlier epidemiologic studies of ovarian cancer. Finally, in our attempt to present the most accurate ORs, we made a variety of adjustments to account for the confounding influence of factors associated with both ovarian cancer risk and

talc exposure. Nevertheless, we cannot rule out the presence of other unknown factors that might have influenced, in part, our observed associations.

Because the overall association between genital use of talc and ovarian cancer remains weak, it is unlikely that this exposure-disease pathway is the principal one involved in ovarian cancer etiology. We have previously discussed the role of dietary and metabolic factors in a model for ovarian cancer involving gonadotropin stimulation of failing ovaries.[8] Even if an etiologic association were to pertain in the subgroups of daily users or users with more than 10,000 applications during ovulatory months, we calculate that by applying these ORs to the exposure rate among cases.[24] the proportion of ovarian cancer incidence attributable to this level of talc exposure is about 10%. Nevertheless, given the poor prognosis for ovarian cancer, any potentially harmful exposures should be avoided, particularly those with limited benefits. For this reason, we discourage the use of talc in genital hygiene, particularly as a daily habit.

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