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A Review of Perineal Talc Exposure and Risk of Ovarian Cancer[1]

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The authors provide a detailed review of the events that led to the interest in talc as a possible ovarian carcinogen, the epidemiological studies published to date, and their perspective on the interpretation of the findings including potential limitations, biases, and issues surrounding the plausibility of a causal association. The authors conclude that the range of relative risk estimates from epidemiology, 1.0 to 1.8, is plausible, but that additional epidemiologic studies, especially prospective investigations are needed. In addition, clinicopathological studies are needed to confirm or deny the reports of talc embedded in human ovarian tissue and reports of talc migration through the human female reproductive tract.

INTRODUCTION

Talc is a natural mineral, hydrous magnesium silicate, that is formed by the hydrothermal alteration of chrysotile and tremolite, two types of the asbestos group minerals (Cralley *et al.*, 1968; Blejer and Arlon, 1973). Because of its chemical similarity to asbestos, it has been implicated as both a lung carcinogen (Thomas and Stewart, 1987; Kleinfeld *et al.*, 1974) and ovarian carcinogen (Longo and Young, 1979; Cramer *et al.*, 1982; Harlow *et al.*, 1992). However, there is a surprisingly small body of literature to support its ovarian carcinogenicity, especially with respect to the pathological identification of embedded particulates within ovarian tissue (Henderson *et al.*, 1971, 1979). Although several controlled epidemiological studies have investigated the talc and ovarian cancer association, few have collected enough details on methods and frequency of exposures to make a meaningful assessment. Nevertheless, its notoriety has grown to the extent that a special workshop on the health consequences of talc exposure was recently sponsored by the Food and Drug Administration and the International Society of Regulatory Toxicology and Pharmacology. As part of our contribution to the understanding of perineal talc exposure and risk of ovarian cancer, we have summarized the earlier research that forewarned of a possible association, the results from more recent epidemiological studies, and offer our assessment regarding the plausibility of such an association in light of the potential limitations and biases inherent in case–control studies.

PATHOLOGICAL AND CLINICAL STUDIES

Many pathological and clinical observations preceded epidemiological investigations of talc and ovarian cancer. Interest in talc as an ovarian carcinogen dates back more than 50 years when postoperative talc granulomas were first reported in the literature (Eiseman *et al.*, 1947). Eiseman *et al.* (1947) published a summary of more than 20 independent reports of talc-induced granulomas following surgery that were reported in the literature between 1933 and 1947. These reports included results from a clinical series of patients, laboratory-confirmed presence of talc crystals within granulomatous tissues, and inflammatory reactions as a consequence of subcutaneous and intraperitoneal injections of talc suspensions in laboratory animals.

Using an extraction–replication technique developed to examine asbestos within the tissue of various mesotheliomas, Henderson *et al.* (1971) examined multiple sections of ovarian tumors. No asbestos particles were found, but talc particulates were observed in 75% of 13 tumors examined (Henderson *et al.*, 1971). This finding was greeted with skepticism (Hildick-Smith, 1976), partly because of the possible contamination by talc on surgical gloves at the time of specimen collection and processing. A reevaluation of nine new specimens collected from deep within tissue samples extracted with the use of forceps and noncontaminated surgical gloves reported the presence of talc particulates in all nine specimens, including three from ovaries free of disease (Henderson *et al.*, 1979). Surprisingly, no further patho-

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logical analyses of talc particulates within ovarian tumor tissue have been reported in the literature.

ASBESTOS AND OVARIAN CANCER

Asbestos is the common name given to a number of naturally occurring hydrated mineral (inorganic) silicates. The four most common types are chrysotile, amosite, crocidolite, and anthophyllite. Two other types, tremolite and actinolite, are found less commonly. Each of these inorganic silicates are chemically different from each other (Michaels and Chissick, 1979). By the mid-1970s, a body of evidence was mounting implicating asbestos exposure as a potential risk factor for ovarian cancer. The link between asbestos and ovarian cancer was first reported by Keal (1960) when it was noted that women suffering from asbestosis appeared to have concurrent ovarian neoplasms more frequently than the general population of other women at the London Hospital. During a 5-year retrospective search of hospital records, 9 of 23 women admitted with a diagnosis of asbestosis had been diagnosed with an intraabdominal neoplasm as well. Shortly thereafter, Newhouse *et al.* (1985) identified 9 deaths associated with ovarian neoplasms (3.6 expected) from a cohort of 922 women first employed at an asbestos factory between 1933 and 1942 and followed for more than 38 years. Of these 9 cases, 5 were in women who received severe exposure for more than 2 years in which only 0.9 cases should have been expected.

Three retrospective cohorts that totaled 1827 women employed in the manufacturing of gas masks during World War II and followed for at least 30 years identified 23 deaths due to ovarian cancer compared to 10.6 deaths expected (Wignal and Fox, 1982; Acheson *et al.*, 1982). The gas masks contained filter pads consisting of activated charcoal, merino wool, and West Australian crocidolite or chrysotile. Although the intensity of the exposure is at best crudely estimated, the observed to expected ratio for developing a subsequent ovarian tumor appeared to be greater among women more severely exposed.

There are several factors that contribute to the biological plausibility of an asbestos–ovarian cancer association. First, Graham and Graham (1967) reported epithelial changes in the ovaries of guinea pigs and rabbits receiving intraperitoneal injections of asbestos products. Second, peritoneal mesotheliomas closely resemble ovarian carcinoma histologically and if the tissue of origin is unknown, they may often be indistinguishable. Some believe they are in fact the same tumor since epithelial ovarian tumors are unlike epithelial tumors elsewhere in the body and because they arise from the "germinal epithelium" which is of mesodermal origin (Parmley and Woodruff, 1974). In fact, studies have reported that some women receiving prophylactic oophorectomy because of a strong family history of ovarian cancer have subsequently developed intraabdominal lesions resembling ovarian tumors (Tobacman *et al.*, 1982). Third, environmental substances can penetrate the female peritoneal cavity through the vagina and fallopian tubes, whereas no such entry is available in males (Egli and Newton, 1961; Henderson *et al.*, 1986; Venter and Iturralde, 1979). This is consistent with the rarity with which peritoneal mesotheliomas occur in men.

EPIDEMIOLOGIC STUDIES

Since talc and asbestos are chemically similar and occur in nature together, there was some concern regarding the degree to which talc-containing products were free of asbestiform fibers. A study of 21 consumer talcum powders labeled as baby powders, facial powders, or body powders obtained from retail stores in New York City between 1971 and 1975 reported that 10 contained concentrations of tremolite and anthophyllite ranging from 0.2 to 14% (Rohl *et al.*, 1976) but these were not necessarily asbestiform. Although voluntary guidelines to limit the content of asbestiform fibers in consumer talcums were proposed by the cosmetic industry in 1976 (C.T.F.A., 1976), the magnitude of the risk of ovarian cancer as a result of prior perineal exposure to talc had never been quantitated. Because of this, a number of epidemiological studies during the late 1970s through the most recent decade began to investigate talc as a potential risk factor for ovarian cancer.

A summary of the nine interview studies that have retrospectively ascertained perineal exposure to talc among women with and without ovarian neoplasms is presented in Table 1 (Cramer *et al.*, 1982; Hartge *et al.*, 1983; Whittemore *et al.*, 1988; Harlow and Weiss, 1989; Booth *et al.*, 1989; Harlow *et al.*, 1992; Chen *et al.*, 1992; Rosenblatt *et al.*, 1992; Tzonou *et al.*, 1993). All of the studies reported an overall estimate of ovarian cancer risk in women who reported any perineal exposure to talc compared to women with no such exposure. Risk estimates were greater than 1.0 in all but two of the studies. However, only two studies reported statistically significant odds ratios. Of the five studies that reported risk of ovarian cancer as a consequence of applying talc-containing powders to sanitary napkins, only one reported a significant association. Among the seven studies that assessed talc exposure to diaphragms, four reported odds ratios greater than 1.0 and three reported odds ratios less than 1.0. None of them reached statistical significance. There were five studies that assessed exposure through direct perineal application after bathing. All five studies reported odds ratios greater than 1.0, but statistical significance was reported in only one study.

Three studies provided inconsistent results on whether frequency of perineal talc exposure or years of exposure influenced ovarian cancer risk. Neither study by Whittemore *et al.* (1988) or Booth *et al.* (1989) showed a significant increase in risk with increasing applications

TABLE 1
Relative Risk Estimates (with 95% Confidence Intervals) of Ovarian Cancer in Relation to Perineal Exposure to Talc

Authors	(Year)	Any genital exposure	Application to sanitary napkins	Diaphragm exposure	Direct application after bathing
Cramer *et al.*	(1982)	1.9 (1.3–2.9)	1.5 (0.7–3.2)	1.6 (0.6–3.9)	1.6 (1.0–2.7)
Hartge *et al.*	(1983)	2.5 (0.7–10.0)	[b]	0.8 (0.4–1.4)	[b]
Whittemore *et al.*	(1988)	1.4 (0.9–1.8)	0.6 (0.2–1.8)	1.5 (0.6–3.6)	1.5 (0.8–2.6)
Harlow and Weiss	(1989)[a]	1.1 (0.7–2.1)	1.9 (0.9–6.9)	0.5 (0.2–1.3)	1.2 (0.6–2.6)
Booth *et al.*	(1989)	1.3 (0.9–1.9)	[b]	0.7 (0.4–1.1)	[b]
Harlow *et al.*	(1992)	1.5 (0.9–1.8)	1.1 (0.4–2.8)	1.2 (0.6–2.4)	1.7 (1.1–2.7)
Chen *et al.*	(1992)	3.9 (0.9–10.6)	[b]	[b]	[b]
Rosenblatt *et al.*	(1992)	2.4 (1.1–5.3)	4.8 (1.3–17.8)	3.0 (0.8–10.8)	1.7 (0.7–3.9)
Tzonou *et al.*	(1993)	0.9 (0.3–2.7)	[b]	[b]	[b]

[a] Restricted to borderline ovarian tumors.
[b] Data not available.

per month, or years of talc exposure, whereas the study by Harlow *et al.* (1992) showed a marginally significant trend of increasing ovarian cancer risk with increasing applications per month ($P = 0.05$) and increasing years of exposure ($P = 0.07$).

Because the risk of any one outcome is dependent upon both the frequency and length of the exposure, Harlow *et al.* (1992) created a continuous measure of total lifetime applications for each case and control. In Table 3, odds ratios are shown in columns of categories of lifetime applications including none, no more than 1000, 1000 to 10,000, and 10,000 or more applications. Although the odds ratios increased with increasing lifetime applications, the trend was marginally significant ($P = 0.09$). After excluding talc exposure after tubal ligation or hysterectomy, little change in the odds ratios or test of trend was observed. However, when nonovulatory periods of exposure were excluded (i.e., exposure during pregnancy or breast feeding, while on oral contraceptives, or after menopause), there was a sizable increase in risk among those with more than 10,000 applications of talc which persisted after multivariate adjustment for parity, education, marital status, douching, weight, and use of sanitary napkins.

Two studies sought to determine whether the brand of talc-containing products influenced ovarian cancer risk. A study of borderline tumors by Harlow and Weiss (1989) reported that women who applied deodorizing powders with or without baby powder had nearly three times the risk of developing a borderline ovarian tumor compared with women who reported no perineal use of powder (RR = 2.8, 95% CI = 1.1–11.7), whereas women who applied only baby powder had no increase in risk of borderline tumors compared to nonusers. Attempts to replicate this finding in a different population of women with and without malignant ovarian tumors showed no such differences, mainly due to the lack of women reporting the use of deodorizing powders and the likelihood of potential recall bias in obtaining an accurate exposure assessment (see following section).

Finally, in the study by Harlow *et al.*, the authors stratified talc exposure by those whose use occurred only after 1960 and those who reported any talc use before 1960 with the idea that if the carcinogenic potential of talc is due to asbestos contamination, it is likely to manifest a greater risk in women who applied older talc-containing products. There was a 70% increase in risk among women who used talc before 1960 (95% CI = 1.1–2.7) and only a 10% increase in risk (95% CI = 0.6–2.1) among women whose use was exclusively after 1960, compared to nonexposed women.

LIMITATIONS AND BIASES IN RESULTS FROM EPIDEMIOLOGICAL STUDIES

The current data all derive from case–control studies, and their limitations stem from three primary sources: selection of controls that may not accurately reflect the underlying study base or population from which the cases derive, incomplete inclusion of the selected subjects because of refusals and other forms of nonresponse, and errors in the data collected, principally because of errors in recollection or reporting of talc exposures. To estimate the possible impact of these limitations, one can compare the nine studies to each other and use data from ancillary sources.

Selection of Subjects

Seven of the nine studies enrolled subjects from selected hospitals. No enumerated underlying population census exists from which to draw a sample of the study base population, so various approximations are employed. In Cramer *et al.* (1982) and Harlow *et al.* (1992), controls were drawn from the towns in which the cases reside. This is a reasonable approach that assumes

TABLE 2
Relative Risk Estimates (with 95% Confidence Intervals) of Ovarian Cancer in Relation to Frequency and Years of Exposure to Talc

		Frequency of exposure		Years of exposure	
	None[a]	<Daily	Daily	<10	>10
Whittemore *et al.* (1988)	1.0	1.3 (0.8–2.0)	1.5 (0.9–2.2)	1.6 (1.0–2.6)	1.1 (0.7–1.7)
Booth *et al.* (1989)	1.0	1.4 (0.9–2.1)	1.3 (0.8–1.9)	[b]	[b]
Harlow *et al.* (1992)	1.0	1.4 (0.7–2.4)	1.8 (1.1–3.0)	1.2 (0.5–2.6)	1.6 (1.0–2.7)

[a] Referent group.
[b] Data not available.

women from the same towns reflect the medical referral population from which the cases were admitted to the hospitals. The overall relative risks for use of powders after bathing in these two studies were 1.9 and 1.5. The relative risks associated with the known risk factors in these two studies were generally similar with estimates from all other case–control studies and from cohort studies.

In Hartge *et al.* (1983), Whittemore *et al.* (1988), Booth *et al.* (1989), and Rosenblatt *et al.* (1992), controls were drawn from women admitted to the same hospitals as cases for conditions unrelated to talc or any of the known or suspected risk factors under investigation. This also is a sound approach often applied in studies with cases from selected hospitals without an enumerated underlying population. The relative risks from these studies ranged from 0.7 to 2.4, but the two studies with substantial numbers and some details on exposure (Booth *et al.*, 1989; Whittemore *et al.*, 1988) were closer to each other with relative risks of 1.3 and 1.4, respectively.

The study by Tzonou *et al.* (1993) selected controls from people who were visiting the cases. This is a less common approach that may yield a control group more like the case group in social class and other variables than is the underlying study base. On the other hand, the protective effect of parity and oral contraceptive use was seen in this study. Nevertheless, the relative risk due to talc exposure was 0.9.

Cases from an enumerated population were used in the studies by Harlow and Weiss (1989) in Seattle (relative risk = 1.1) and by Chen *et al.* (1992) in Beijing, China (RR = 3.9). The former study was limited to borderline ovarian cancers, but the etiologic similarity of these and invasive cancers has been amply demonstrated (Harlow *et al.*, 1988).

Thus, the basic design of these nine case–control studies shows no clear pattern of effects being seen with one design but not others. There may be a very slight gradient of decreasing risk estimates going from hospital–town studies (highest) to hospital–hospital studies to the one U.S. population-based study. This pattern was also observed in the extensive analysis of population-based studies and hospital-based studies by Whittemore *et al.* (1992), which showed consistent but subtle effects of study design in 12 case–control studies of ovarian cancer. For example, the population-based studies showed a slightly stronger effect of oral contraceptive use than did the hospital-based studies, but the protection by oral contraceptives was readily apparent in both (Whittemore *et al.*, 1992). The differences reflect the combination of two distinct effects: hospitalized patients are heavier, generally less healthy, slightly poorer, and otherwise not perfectly representative of the general population-based cases and controls (a difference that favors using population-based cases and controls whenever possible), but hospitalized patients generally are more willing to participate in studies (a difference that may make hospital-based studies superior depending upon response rates).

Participation Rates

In all the U.S. studies, participation rates were similar to each other and in the low but acceptable range, 69–77% in cases and 60–80% in controls. Rates were not available from the study in Britian (Booth *et al.*, 1989) but were likely to be higher than in the United States. Response rates were very high, in excess of 90%, in China and Greece, but talc use was so uncommon in these regions that estimates of the talc effect were quite unstable (as measured in the confidence intervals). Thus, differences in participation rates among the studies are not likely to explain differences in talc findings.

In general, a high rate of nonresponse in either cases or controls can distort results, and a much higher rate in one or the other causes alarm. Neither of these problems appears to be present in the nine studies. There also is no reason to suspect that talc use is moderately or strongly related to willingness to participate. While bias from nonresponse cannot be utterly discounted, it does not appear to be an important or obvious problem in these data.

Recollection of Talc Exposures

If exposures to talc were recalled differently by cases and controls, relative risk estimates would be distorted.

TABLE 3

Relative Risk Estimates[a] (with 95% Confidence Intervals) of Ovarian Cancer in Relation to Lifetime Applications of Perineal Talc Exposure

	Lifetime applications			
	None	<1000	1000–10,000	>10,000
All exposures	1.0	1.3 (0.7–2.7)	1.5 (0.9–2.4)	1.8 (1.0–3.0)
Exposure prior to tubal ligation or hysterectomy only	1.0	1.4 (0.7–2.9)	1.5 (0.9–2.4)	1.7 (1.0–3.0)
Exposure prior to tubal ligation or hysterectomy and during ovulatory periods only	1.0	1.5 (0.8–2.9)	1.3 (0.8–2.0)	2.8 (1.4–5.4)

[a] Adjusted for parity (0, 1–2, ≥3), 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 lbs, ≥140 lbs).

Cases could overreport talc use if they were anxious to assign a cause to their cancer or underreport it if they were anxious to avoid providing this information. However, this differential response bias would have to be claimed to occur for talc and not for the numerous other exposures queried in these interviews that typically last for 1 hr and involve more than 100 questions. Differential misclassification and random error are most likely to occur if the question is too long or too vague and if the behavior itself is intermittent and trivial.

In the nine studies, the questions pertaining to talc were generally short. The behavior is trivial and not memorable, but habitual for many and thus not particularly likely to be misremembered. Forthcoming data from the Nurses Health Study (Hankinson *et al.*, 1993), a prospective cohort analysis, will relate ovarian cancer to talc habits queried before diagnosis. Until then, recollection bias should not be regarded as a likely explanation for the talc effect.

Analysis of Data

Three features of analysis should be considered: (a) uncorrected confounding effects of factors that cause ovarian cancer and are related to talc use; (b) analysis of the data to separate distinct aspects of the exposure, particularly dose, route, type, and timing; and (c) analysis of the combined effect of talc and other factors. None of the studies shows obvious failure to control for the effects of potential confounders. Data from Harlow *et al.* (1992) illustrate that talc use does vary with age, parity, and oral contraceptive use. These effects are controlled in all of the overall relative risk estimates under review. How plausible is it that unidentified confounders are at work? If weight is a confounder, as suggested by Rosenblatt *et al.* (1992), then it must have a stronger relation to ovarian cancer risk than has been reported to date. If the association with talc is actually null, then a confounder needs to be very closely linked to talc and must have an effect on ovarian cancer risk that is higher than the 1.4–1.8 estimated for talc.

Source of exposure does show a pattern in the studies reviewed, with direct application to the perineum carrying the greatest risk. Brands do not appear to be separable. Dose–response data are available from only a few studies (Tables 2, 3). Frequency shows an effect in two of the three studies and duration in one of the two. For duration and cumulative dose, the relative risk rises to 1.8 and possibly higher in women whose use occurs during ovulatory time periods. The typical user applied talc daily for at least a decade.

Possible cofactors include tubal ligation, hysterectomy, tubal occlusions, parity, and sexual activity because they might affect the likelihood of talc migration to the ovary and indicators of ovulation which may affect ovarian cancer susceptibility. Various techniques are employed to assess these types of interactions.

We have elaborated on the existing data reported in the study by Harlow *et al.* (1992) to illustrate the joint effect of talc and number of ovulations (Table 4). The effect of talc is stronger among women with fewer than the median number of ovulations. It is possible that the talc effect is most easily seen against a background of lower risk. On the other hand, the data suggest that the effects of talc and ovulation do not exaserbate each other. However, this simple analysis does not separate talc exposure occurring during ovulatory and nonovulatory time periods. When applications of talc during nonovulatory time periods were evaluated using data from Harlow *et al.* (1992), there was no excess ovarian cancer risk associated with increasing applications of talc during nonovulatory time periods (data not shown), and virtually all of the ovarian cancer risk occurred as a consequence of talc exposure during time periods when women were ovulatory. We therefore cannot rule out the possibility that this pattern may represent an interaction with ovulation.

Table 4 also shows the joint effect of talc and midcycle pain—a symptom of ovulation. Although talc does appear to operate most strongly in women reporting midcycle pain, such pain is not related to risk, suggesting that it is not a reliable index of ovulation. Finally, the joint effect of talc and gynecologic surgery in

TABLE 4

Relative Risk Estimates of Ovarian Cancer in Relation to Perineal Talc Exposure by Control Median Months of Ovulation, History of Midcycle Pain, or Gynecologic Surgery

	Number of ovulations[a]		Midcycle pain[a]		Gynecological surgery[b]	
	<Median	≥Median	No pain	Any pain	No surg.	Surgery
No talc						
Cases:controls	49:80	72:65	93:107	28:38	70:182	21:110
Odds ratios[c]	1.0[d]	2.2	1.0[d]	0.9	1.0[d]	0.5
Any talc						
Cases:controls	40:39	74:55	88:77	26:17	71:151	26:96
Odds ratios[c]	2.1	3.3	1.4	1.7	1.3	0.8

[a] Data from Harlow *et al.* (1992).

[b] Data from Whittemore *et al.* (1988).

[c] Adjusted for parity (0, 1–2, ≥3), 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 lbs, ≥140 lbs) for odds ratios stratified by ovulations and midcycle pain and only parity for odds ratios stratified by gynecological surgery.

[d] Referent group.

data from Whittemore *et al.* (1988) is also shown in Table 4. The association with talc does not appear to depend on whether tubal ligation or hysterectomy had occurred. It is certainly possible that talc exerts an effect in the years before surgery. A more detailed analysis of timing might uncover such an effect, but a large study would be required.

SUMMARY

Since Cramer *et al.* (1982) presented epidemiologic data in support of the hypothesis that exposure to cosmetic talc is associated with increased risk of developing ovarian cancer, eight additional case–control studies have provided data to assess the potential association. Of these, four also have implicated use of body powders, three with odds ratios of 1.5 or more. If talcum powder use cannot induce ovarian cancer, what is likely to explain the positive studies? The play of chance is possible, but this is not where suspicion most logically points. The cumulative effect of several modest errors during data collection, perhaps not even the same errors in all studies, theoretically could produce these findings. However, no obvious error in collection or analysis clearly explains the studies with positive findings, and one must regard the range of relative risk estimates from epidemiology, 1.0 to 1.8, as plausible.

Additional epidemiologic studies, especially those with different designs, may help, but the greatest need is to confirm or deny the reports of talc embedded in human ovarian tissue and the report of easy transportation of particles through the human female reproductive tract.

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