

(From M. Choudhury)

Perineal Talc Exposure and Risk of Ovarian Carcinoma

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BACKGROUND. Clinical and epidemiologic studies have indicated the possible existence of an association between ovarian carcinoma and talcum powder use. Talc particles have been detected in histologic sections of ovarian carcinomas. It has also been demonstrated that inert particles travel from the perineum to the ovaries. Results from epidemiologic investigations have varied, from risks increased by twofold to no significant risk detected.

METHODS. A total of 450 patients with borderline and invasive ovarian carcinoma and 564 population controls in metropolitan Toronto and nearby areas of southern Ontario, Canada, were identified. These subjects were interviewed about their reproductive and menstrual histories as well as their exposure to dusting powders. Continuous unconditional logistic regression methods were used for analysis.

RESULTS. Exposure to talc, via sanitary napkins, direct application to the perineum, or both, was significantly associated with risk of ovarian carcinoma (odds ratio [OR] 1.42, 95% confidence interval [CI] 1.08–1.86). A borderline-significant association was detected between duration of talc exposure and risk (OR 1.09, 95% CI 0.98–1.21, per 10 years of exposure). No significant association was found between frequency of exposure and risk. In comparing invasive and borderline carcinomas, risk remained elevated for both carcinoma types. Only risk for invasive carcinoma was statistically significant.

CONCLUSIONS. This investigation supports previous contentions that exposure to talc may increase risk of ovarian carcinoma. Questionable trends in duration and frequency of exposure suggest that further studies may be needed to clarify the role of talc in the etiology of this disease. *Cancer* 1997;79:2396–401.

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Ovarian carcinoma is the most commonly fatal gynecologic malignancy.¹ In the United States, approximately 26,000 women develop the disease annually. Overall, the lifetime risk for the development of ovarian carcinoma is 1.4 in 100.² Because industrialized nations generally have higher prevalence rates of this disease, environmental exposure has been suggested as an etiologic factor.¹

Asbestos, a known sclerosing agent, has been shown to cause bronchogenic lung carcinoma and mesothelioma.³ The incidence of ovarian carcinoma generally increases with greater incidence of asbestosis.⁴ Furthermore, female asbestos workers have unusually high numbers of peritoneal neoplasms, and an association between ovarian carcinoma and asbestos exposure has also been observed in animal models.^{2,5} Due to its chemical similarity to asbestos, talc has long been suspected as a lung and ovarian carcinogen.^{2,6} Like asbestos, talc is a magnesium silicate. Pulverized talc, or talcum powder, is a popular bath and cosmetic product because of its absorbent and

water-repellent properties. Talcum powder is often applied to sanitary napkins and condoms, as well as directly to the perineum, typically after bathing. Early pathology studies have identified talc particles in ovarian tumors.^{7,8} An extraction-replication technique developed by Henderson et al.⁷ detected talc particles in approximately 75% of ovarian tumors examined. Furthermore, studies of the transport of particles in the human female reproductive tract have shown that nonmotile, inert carbon particles deposited in the vagina can be recovered 30–35 minutes later in the fallopian tubes.⁹ Although findings of talc particles in ovarian tumors initially met with skepticism, subsequent evaluations appeared to support the contention of an association between talc exposure and ovarian carcinoma.¹⁰

In addition to pathologic and clinical studies, several epidemiologic studies have addressed the plausibility of an association between talc and ovarian carcinoma. Although many of these case-control studies revealed elevated risks,^{11–18} risk estimates from other studies were not statistically significant^{19–20} or were about unity.²¹ Thus, the possibility of a risk of ovarian carcinoma that is related to talc exposure remains to be investigated further. The population-based case-control analysis described in this article was conducted to examine the role of talc in ovarian carcinoma, with consideration of the duration, frequency, and method of exposure.

MATERIALS AND METHODS

Study methods have been reported in detail elsewhere²² and will be summarized here. Our study population consisted of women between the ages of 35 and 79 years residing in the highly populated area surrounding the western end of Lake Ontario, Canada. Cases were women who had histologically confirmed primary, invasive or borderline epithelial ovarian tumors first diagnosed between November 1, 1989, and October 31, 1992. Of the 631 women identified as cases, 450 (71.3%) were interviewed. Fifty-five (8.7%) had died, but proxy interviews were not conducted; 29 (4.6%) had physicians who refused consent; 30 (4.8%) were too ill to participate; 17 (2.7%) were lost to follow-up; and 50 (7.9%) refused to participate.

Population-based controls were identified through the Ontario Ministry of Finance. Information on name, address, age, and gender was obtained from the Enumeration Composite Record listings, which include all homeowners, tenants, and family members, i.e., all persons in the province. From this listing, women living in the study area during the same 3-year period as the cases were randomly selected. Controls were matched to the cases within 3 15-year age groups.

Initial contact by letter was followed up with phone calls to determine eligibility. Women with bilateral oophorectomy performed at least 1 year previously were excluded. Overall, 873 eligible controls were identified. Of these women, 564 (64.5%) were interviewed. The remainder either refused to participate (30.2%), were too ill to participate (1.9%), or were lost to follow-up (3.2%).

A questionnaire was developed to detail the medical and reproductive histories of the subjects. This questionnaire was administered during an in-person, in-home interview after informed consent was obtained. The questionnaire focused on menstrual characteristics, pregnancies, and hormone and contraceptive use. Questions about regular talc use and type of talc use, as well as questions from which information about duration and frequency of exposure could be derived, were included. Dusting or powdering behaviors considered included regular application of talc to the perineum after showering or bathing and dusting of talc on sanitary napkins. Parallel information about cornstarch use was also obtained.

Analysis was performed by modeling the data through multiple unconditional logistic regression with the SAS statistical package. In addition to the variables of interest examined here, the models included indicator terms for the age categories of the frequency matching (35–49, 50–64, and 65–79 years), and age as a continuous variable was also included to adjust for residual age effects. Models also contained terms for total years of oral contraceptive use; number of full-term pregnancies; average duration of breastfeeding per pregnancy; and ever having had a tubal ligation, a hysterectomy, or a mother or sister with ovarian or breast carcinoma.

RESULTS

Table 1 shows the descriptive characteristics of the 450 ovarian carcinoma cases and the 564 population controls. Age at interview was used as a matching variable. As observed in many reports,^{20,22,23} controls had, on average, a greater number of full-term pregnancies. A higher percentage of controls had had a tubal ligation or a hysterectomy, whereas a higher percentage of cases had a mother or sister with ovarian or breast carcinoma. Years of oral contraceptive use and months of lactation per pregnancy showed trends of decreasing risk with increasing exposure. There were no appreciable differences in the characteristics shown in Table 1 between controls who reported ever having used talc and those not reporting talc use.

Table 2 gives the associations between dusting behaviors and risk of ovarian carcinoma. Overall, 44.0% of cases and 35.6% of controls reported exposure to

TABLE 1
Descriptive Characteristics of Study Population

| Characteristics | Cases | Controls | Adjusted ^a | |
|--|-------|----------|-----------------------|-------------|
| | | | OR | (95% CI) |
| Age at interview (yrs) | 57.2 | 57.5 | | Matched |
| Born in Canada or the U.S. (%) | 59.1 | 64.7 | 0.843 | (0.64-1.11) |
| Race (% black) | 1.56 | 1.95 | 0.804 | (0.30-2.17) |
| Length of schooling (yrs) | 12.3 | 12.5 | 0.983 | (0.95-1.02) |
| Number of full-term pregnancies | 1.90 | 2.45 | 0.820 ^b | (0.71-0.92) |
| Yrs of oral contraceptive use | 4.17 | 5.53 | 0.915 ^b | (0.88-0.95) |
| Mos of lactation per pregnancy | 3.95 | 4.21 | 0.946 ^b | (0.91-0.99) |
| Ever had tubal ligation (%) | 18.0 | 24.3 | 0.659 | (0.47-0.93) |
| Ever had hysterectomy (%) | 13.8 | 24.8 | 0.485 | (0.34-0.69) |
| Mother/sister with breast or ovarian carcinoma (%) | 12.9 | 7.98 | 1.917 | (1.24-2.97) |

OR: odds ratio; CI: confidence interval.

^a Adjusted for age at interview; yrs of oral contraceptive use; number of full-term pregnancies; average duration of breastfeeding per pregnancy; and ever having had a tubal ligation, hysterectomy, or a mother or sister with ovarian or breast carcinoma.

^b OR per each yr of mo, respectively.

talc. Women with any regular talc exposure were at an increased risk (odds ratio [OR] 1.42, 95% confidence interval [CI] 1.08-1.86). The use of cornstarch, or cornstarch sometimes and talc sometimes, did not yield a significant association with risk (cornstarch OR 0.31, 95% CI 0.06-1.66; cornstarch/talc OR 0.68, 95% CI 0.18-2.55). However, application of cornstarch to sanitary napkins or directly to the perineum was not common in this population; less than 2% of the study population reported this behavior. With respect to the type of exposure, substantially more women reported applying talc to their bodies after bathing or showering than using talc on their sanitary napkins. Some 11.3% of cases and 8.7% of controls reported using talc on sanitary napkins. A nonsignificant increase in odds was observed for talc exposure via sanitary napkins (OR 1.26, 95% CI 0.81-1.96). In total, 38.2% of cases and 32.4% of controls reported that they had, at some time, regularly used talc after bathing or showering. The odds ratio seen for use of talc after bathing or showering alone was of borderline statistical significance (OR 1.31, 95% CI 1.00-1.73).

The association between duration and frequency of talc use and ovarian carcinoma was also examined. The mean years of after-bath talc use were 32.9 for cases who had ever used talc after bathing and 35.4 for controls. A borderline-significant trend for years of talc exposure and risk of ovarian carcinoma was found (OR per 10 years of use 1.06, 95% CI 0.99-1.14). When duration was considered categorized by tertiles of control use, only durations of less than 30 years of talc

use showed increased risk, relative to no talc exposure. The mean frequency of talc use among those who had ever used it was 14.6 applications per month for cases; for controls, it was 17.2 applications per month. As a continuous variable, monthly frequency did not significantly increase risk of ovarian carcinoma. Categorical analysis of frequency showed that frequencies of less than 10 applications per month may be associated with increased risk; greater frequencies, however, did not show significant increases in risk.

To examine the effects of calendar time of exposure and of hysterectomy or tubal ligation, we assumed that regular after-bath talc use commenced at age 20 years. Table 2 shows that duration of after-bath talc use both before and after 1970 appeared to be associated with risk of ovarian carcinoma. As might be expected, the increased risk seemed to be related mostly to talc use prior to tubal ligation or hysterectomy (Table 2). There were no differences in these results when various starting ages between 15 and 25 years were considered.

The association between talc exposure and invasive ovarian carcinoma, as compared with borderline ovarian carcinoma, was also examined (Table 3). Although the risk remained elevated for both carcinoma types, only the risk for invasive carcinoma was statistically significant. No differences in risk with respect to serous, mucinous, or endometrioid tumors were observed in our data.

Substantial alteration in risk of ovarian carcinoma was not observed for general sanitary napkin use com-

TABLE 2
Risk of Ovarian Carcinoma with Use of Talcum Powder or Cornstarch

| | No. (%) | | Case mean ^a | Control mean ^a | Adjusted ^b | |
|------------------------------------|------------|------------|------------------------|---------------------------|-----------------------|-------------|
| | Cases | Controls | | | OR | (95% CI) |
| Any talc exposure | 198 (44.0) | 201 (35.6) | | | 1.420 | (1.08-1.86) |
| Any cornstarch | 2 (0.44) | 5 (0.85) | | | 0.305 | (0.06-1.66) |
| Cornstarch/talc | 4 (0.89) | 7 (1.24) | | | 0.681 | (0.18-2.55) |
| Type of talc exposure | | | | | | |
| Sanitary napkin | 51 (11.3) | 49 (8.69) | | | 1.262 | (0.81-1.96) |
| After bathing | 172 (38.2) | 183 (32.4) | | | 1.312 | (1.00-1.73) |
| After-bath talc use/mo | | | 14.6 | 17.2 | 0.890 ^c | (0.74-1.07) |
| <10 | 76 (16.9) | 59 (10.5) | | | 1.836 | (1.24-2.73) |
| 10-25 | 54 (12.0) | 84 (11.3) | | | 1.128 | (0.74-1.72) |
| >25 | 41 (9.11) | 60 (10.6) | | | 0.951 | (0.61-1.49) |
| Yrs of after-bath talc use | | | 32.9 | 35.4 | 1.091 ^c | (0.98-1.21) |
| <30 | 60 (13.3) | 52 (9.22) | | | 1.697 | (1.09-2.64) |
| 30-40 | 71 (15.8) | 67 (11.9) | | | 1.435 | (0.96-2.15) |
| >40 | 41 (9.11) | 64 (11.3) | | | 0.865 | (0.54-1.38) |
| Yrs of after-bath talc use | | | | | | |
| Before 1970 | | | 26.4 | 24.9 | 1.090 ^c | (0.98-1.22) |
| After 1970 | | | 6.5 | 10.4 | 1.095 ^c | (0.89-1.35) |
| Yrs of after-bath talc use | | | | | | |
| Before tubal ligation/hysterectomy | | | 28.4 | 26.9 | 1.105 ^c | (0.99-1.24) |
| After tubal ligation/hysterectomy | | | 4.5 | 8.5 | 1.031 ^c | (0.82-1.29) |

OR: odds ratio; CI: confidence interval.

^a Mean among those who had ever used talc.

^b Adjusted as in Table 1.

^c OR for the continuous variable, shown per 10 applications per mo or 10 yrs of use, as appropriate.

TABLE 3
Risk of Ovarian Carcinoma for Women Who Ever Used Talcum Powder Regularly, by Case Histology

| Histologic type | Total no. of cases | No. (%) who used talcum powder | Adjusted ^a | |
|-----------------|--------------------|--------------------------------|-----------------------|-------------|
| | | | OR | (95% CI) |
| Invasive | 357 | 166 (45.2) | 1.513 | (1.13-2.02) |
| Borderline | 83 | 32 (38.6) | 1.237 | (0.76-2.02) |
| Serous | 254 | 109 (42.9) | 1.336 | (0.96-1.85) |
| Mucinous | 80 | 35 (43.8) | 1.585 | (0.97-2.58) |
| Endometrioid | 74 | 36 (48.6) | 1.671 | (1.00-2.79) |

OR: odds ratio; CI: confidence interval.

^a Adjusted as in Table 1.

pared with tampon use. Because few women used sanitary napkins or tampons exclusively, the risk was examined as a percentage of the length of time that sanitary napkins were used and a percentage of the length of time that tampons were used. Significant trends in risk were not detected for a 10% difference in napkin use (OR 1.06, 95% CI 0.99-1.13) or for a 10% increase in tampon use (OR 0.99, 95% CI 0.93-1.05).

DISCUSSION

Results from experimental and epidemiologic studies conducted thus far indicate a possible association between talc exposure and ovarian carcinoma. Histologic evidence first indicated that contaminants such as talc may become embedded in ovarian tumors.^{11,21} Experimental studies have shown that external talc exposure may eventually reach the ovaries. Henderson et al.¹⁰ demonstrated that talc was present in ovaries after deposition of a talc suspension in the vagina and cervical os in rats. Similarly, Egli and Newton⁹ revealed in human studies that inert carbon particles deposited in the vagina can later be recovered in the fallopian tubes. Although these studies demonstrated a possible route of exposure to talc, they were nevertheless unable to address the effects of long term talc use.

Surprisingly, few subsequent pathologic and clinical studies have been conducted. Epidemiologic studies addressing the possible association between talc and ovarian carcinoma have generally reported increased risk estimates. Cramer et al.¹¹ found a relative risk of 1.92 (95% CI 1.3-2.9). Rosenblatt et al.¹² reported a relative risk of 2.4 (95% CI 1.1-5.3) for any genital talc exposure. Likewise, Purdie et al. found a

significant positive association between talc and ovarian carcinoma,¹⁴ and other recent studies also support the hypothesis of elevated risk of ovarian carcinoma with talc exposure, reporting risk increases of approximately two-fold.¹⁶⁻¹⁸ A few studies have found only marginally significant or nonsignificant elevations in risk.¹⁹⁻²¹ However, in investigations such as that reported by Tzonou et al., the number of women who reported talc usage was low.²¹ More detailed discussion of many of those studies may be found in reviews elsewhere.^{25,26}

This study sought to elucidate further the relationship between talc and ovarian carcinoma. Talc exposure through direct perineal application and via sanitary napkins, the frequency and duration of exposure, and the effect of talc within specific histologic subtypes were examined. Dusting with talcum powder was common behavior for more than one-third of cases and controls. The primary mode of talc exposure appeared to be direct application to the perineum. Although talc exposure via contraceptives such as condoms and diaphragms has been previously investigated,²⁷ this type of behavior was rare in the current study population and therefore omitted from analyses. Overall, greater risk was associated with any regular talc exposure (OR 1.42, 95% CI 1.08-1.86). Any talc exposure included talc accumulated from sanitary napkins, from powdering after bathing, or from both behaviors. Talc exposures via sanitary napkin alone or after bathing conveyed similar magnitudes of increased risk.

Commercial talc substitutes often replace talc with cornstarch. Furthermore, women may choose to powder or dust with cornstarch instead of talc. When cornstarch was assessed in relation to risk of ovarian carcinoma, no associations were found. This suggests that the association between talc use and risk of ovarian carcinoma may not be due simply to a difference in focus on hygiene between cases and controls. Use of cornstarch, however, was rare in our population, as less than 1% of the cases and controls reported use of cornstarch alone, and very few cases and controls reported use of cornstarch sometimes and talc sometimes.

A questionable dose-response relationship was observed between duration or frequency of exposure and risk. Duration as a continuous variable indicated that risk may increase with increasing years of talc exposure. These results are similar to findings by Cramer et al.,¹¹ Harlow et al.,¹³ Harlow and Weiss,²⁸ Cook et al.,¹⁸ and Whittemore et al.,¹⁹ in which trends of duration and frequency were not significant. Booth et al.²⁹ reported a marginally significant trend with frequency. It is noteworthy that exposures of less than

30 years, at frequencies of less than 10 applications per month, and prior to tubal ligation or hysterectomy showed the most significant elevations in risk in the current study.

When the outcome, ovarian carcinoma, was further segregated into invasive and borderline carcinomas, talc exposure was associated with both but was only significant for invasive carcinomas. This result contrasts with the observations of Harlow et al.,¹³ who found the strongest talc-ovarian carcinoma associations among women with endometrioid and borderline tumors. Cook et al.¹⁸ reported no increase in risk of mucinous tumors; this was similar to our observation that mucinous tumors may not be associated with other ovarian carcinoma risk factors.²⁹ An earlier study, however, found no variation in risk by histologic subtype,¹¹ and the current study also found no differences in talc use associated with serous, mucinous, or endometrioid tumors.

Several lines of evidence support the argument for an association between talc usage and ovarian carcinoma. Talc and asbestos are chemically related; and although asbestos contamination in talc products has been closely regulated, talc and asbestos are frequently found together in mining strata. Asbestos is a known cause of pleural and peritoneal mesotheliomas, which are histologically similar to ovarian carcinomas.¹⁹ Two possible mechanisms have been suggested for the role of talc in the etiology of ovarian carcinoma. With ovulation, entrapment of the ovarian epithelium within the stroma occurs. During this time, talc, if present, may become incorporated into these inclusion cysts, providing a favorable environment for carcinogenesis.¹¹ Alternatively, talc may serve to stimulate the entrapment of the surface epithelium and may act in a manner similar to "incessant ovulation," which has been proposed as an etiologic factor in ovarian carcinoma.^{11,30}

Differences in talc concentration among various baby powders, body powders, and deodorizing powders were not investigated in this study. Furthermore, reporting error in reported talc use and failure to interview all eligible case and control subjects may also have led to biases. As with any case-control study, the possibility of selection bias and information bias exists, although the consistency of this study with others that have addressed reproductive factors and ovarian carcinoma is reassuring.²⁹ Further discussion of the strengths and weaknesses of the current study may be found in a previous report.²⁹

The results of this study appear to support the contention that talc exposure increases risk of ovarian carcinoma. Dusting with talcum powder is not an unusual practice for women, and, given the heterogeneity

of the etiology and course of ovarian carcinoma, any possible harmful practices, particularly those with little benefit, should be deliberated. It should be emphasized, however, that further studies are needed to clarify the role of talc in the etiology of ovarian carcinoma.

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