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Mineral Fiber Exposure and the Development of Ovarian Cancer

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A hospital-based case–control study of the association between fiber exposure and the development of epithelial ovarian cancer was performed at the Johns Hopkins Hospital in Baltimore, Maryland. Genital and respiratory fiber exposures were ascertained from incident cases (N = 77) and age–race matched controls (N = 46) using a structured questionnaire. Cases were ascertained between 1981 and 1985. An increased risk was observed for exposure to talc on sanitary napkins (OR = 4.79, 95% CI, = 1.29–17.79), genital fiber exposure from different sources for a long (cumulative exposure ≥37.4 years) length of time (OR = 2.35, 95% CI = 0.95–5.80), and occupational fiber exposure in relatives (OR = 2.81, 95% CI = 0.90–8.75). A negative association was observed for antecedent tubal ligation (OR = 0.15, 95% CI = 0.027–0.88). Findings from this study should be confirmed in larger investigations.

INTRODUCTION

Occupational exposure to asbestos has been identified as a risk factor for ovarian cancer in several studies [1–3]. Similarly, fiber-containing substances, such as talc, have also been implicated as risk factors [4–9]. A matched case–control study of epithelial ovarian cancer was conducted, in which the role of both genital and respiratory sources of fiber was assessed, to confirm these findings.

STUDY POPULATION

Cases and controls were ascertained from the Johns Hopkins Hospital between 1981 and 1985. This analysis is restricted to the 77 cases who were matched to 46 hospital controls and treated for conditions other than gynecologic or malignant diseases. Originally 140 newly diagnosed cases of epithelial ovarian cancer who met the eligibility criteria were ascertained from the Johns Hopkins Hospital. One hundred eight (77.1%) of these cases were successfully interviewed. These cases were diagnosed within 6 months of admission, were pathologically confirmed by examination of the ovaries, were admitted as in-patients for treatment or diagnosis, and were residents of the United States. Controls were in-patient females without gynecologic or malignant conditions who were initially matched to cases by age (within 5 years), race, and date of diagnostic admission (within 1 year). Since it was difficult to find controls meeting all of the matching criteria, a control could not be found for all cases. Unmatched cases were therefore matched a posteriori to controls, to form matched triplets of 2 cases and 1 control. A posteriori matching was performed within the same 5-year interval, by race and by closest date of diagnostic admission. The matching procedure allowed for the inclusion of 77 cases in the study. There were 46 matched sets, of which 31 consisted of 2 cases and 1 control. No matched control could be found for 13 cases, which were excluded from the analysis.

METHODS

Data were ascertained primarily from a questionnaire that was administered to participants both by telephone and in the hospital. Information on previous abdominal and gynecologic operations was also ascertained from medical records.

The questionnaire elicited information on the presence and length of genital fiber and respiratory fiber exposure, reproductive factors, estrogen use, family history of cancer in first-degree relatives, and other contraceptive use. Descriptions of the questions used to ascertain fiber exposure are listed in Appendix 1. Fiber exposure was defined as exposure to asbestos, talc (which may contain asbestos), and fiberglass.

An attempt was made to estimate the overall effect of

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"dose" or length of genital and respiratory fiber exposure. This was accomplished by adding the number of years of each type of genital or respiratory exposure from all sources. Since many of these exposures occurred at the same time, these variables should be considered as crude measures of dose rather than the true length of exposure.

Conditional logistic regression [10] was used to determine the strength of the association. Odds ratios were calculated to describe the relationship of genital and respiratory fiber exposure to ovarian cancer. The odds ratio is an estimate of the relative risk for relatively rare diseases such as ovarian cancer and, in this paper, is referred to as the relative risk estimate (RR).

The following variables were assessed as potential confounders:

Tobacco use
Number of cigarettes per day
Ovulatory time period
Number of pregnancies
Cancer in mother or father
Obesity 1 year prior to diagnosis
Obesity 20 years prior to diagnosis
Obesity at highest weight during the 20 years prior to diagnosis
Obesity according to average weight during the 20 years prior to diagnosis
Husband's and subject's education
Previous cancer
Marital status
Religion
Use of oral contraceptives
Use of contraceptive foams, creams, and jellies by themselves
Use of an IUD

On the basis of the strength of their relative risk estimates and the difference in frequency with which they were observed in cases and controls, the following variables were identified as potential confounders: measures of obesity, socioeconomic status (subject's education; RR = 0.5, 95% CI = 0.2–1.1), and religion (Jewish, RR = 2.9, 95% CI = 0.6–13.8; Catholic, RR = 0.5, 95% CI = 0.2–1.5), reproductive status (total live births, 1–2, RR = 0.7, 95% CI = 0.2–1.9; live births >2, RR = 0.4, 95% CI = 0.2–1.3), and oral contraceptive use (OR = 0.9, 95% CI = 0.3–23.0).

Obesity 1 year prior to diagnosis (RR = 2.3, 95% CI = 0.9–6.1), obesity 20 years prior to diagnosis (RR = 2.1, 95% CI = 0.7–6.9), and obesity according to highest weight during the 20 years prior to diagnosis (RR = 1.5, 95% CI = 0.7–3.2) were also found to be potential confounders. Obesity was defined as a height/weight index greater than that exhibited by women in the 85th percentile [11] of the population.

TABLE 1
Distribution of Matched Cases and Controls

	Cases		Controls	
	N	%	*N*	%
Age (years)				
Less than 30	3	3.9	2	4.4
30–39	1	1.3	1	2.2
40–49	11	14.3	8	17.4
50–59	21	27.3	10	21.7
60–69	35	45.4	21	45.6
70–79	5	6.5	3	6.5
80 or higher	1	1.3	1	2.2
Total	77		46	
Race				
White	70	90.9	41	89.1
Black	7	9.1	5	10.9
Total	77		46	

If a potential confounder changed the relative risk estimate associated with a fiber exposure by more than 15% it was retained in the multivariate model. Confounders were sequentially added to multivariate models, depending on the level with which they changed the odds ratio of a fiber related exposure.

Interaction between fiber exposures and potential confounders was evaluated by comparing the deviance of models with and without the interaction term [12].

RESULTS

Age and Racial Distribution

Table 1 lists the age and racial distribution of cases and controls. Most cases and controls were in the age group 40 to 69. It was difficult to obtain controls that did not have a chronic disease, resulting in a lower than expected number of controls.

Diagnoses of Controls

Controls were selected so that they did not have their primary diagnostic condition for more than 1 year. Table 2 lists the primary diagnosis of the controls included in the study.

Genital Fiber Exposure

Different sources of genital fiber exposure were examined (Table 3). Exposure from any of the potential sources of genital fiber was highly prevalent (91.1% in controls) and not found to be related to ovarian cancer (RR = 1.0, 95% CI = 0.2–4.0). Since it was felt that this index did not accurately characterize cumulative exposure, the median length of exposure from all genital sources (with the time since tubal ligation subtracted) was

TABLE 2
Distribution of Matched Controls by Primary Diagnosis

Diagnosis of restricted controls	*N*	%
Infectious and parasitic diseases	1	2.2
Diseases of the digestive system	6	13.0
Opthamologic disorders	15	32.6
Diseases of the circulatory system	11	23.9
Symptoms, signs, and ill-defined conditions	8	17.4
Diseases of musculoskeletal and connective tissue	1	2.2
Diseases of the endocrine system or metabolic or immunologic disorders	1	2.2
Diseases of the respiratory system	1	2.2
Benign neoplasms	1	2.2
Injury and poisoning	1	2.2
Total	46	100.00

used to categorize the dose of genital fiber exposure. A relative risk estimate of borderline significance was seen for exposure above the median length of time (37.4 years, RR = 2.4, 95% CI = 1.0–5.8). A significant negative association was observed for previous tubal ligation (RR = 0.2, 95% CI = 0.03–0.9).

A history of several gynecologic and abdominal operations, given by responses to the questionnaire, was examined to determine if exposure to talc from surgeon's gloves increased risk [13]. No statistically significant relationships were detected but, with the exception of ovarian biopsies, relative risk estimates were generally below 1. An attempt was made to combine information from the questionnaire and medical records, with no important changes in the relative risk estimates.

Moderately elevated relative risk estimates, which were not statistically significant, were observed with use of condoms, diaphragms (when powder was used), and genital bath talc. The level of association observed with exposure to talc on sanitary napkins (RR = 4.8, 95% CI = 1.3–18.0) was significantly greater than unity.

Respiratory Fiber Exposure

Numerous sources of respiratory fiber exposure were evaluated (Table 4): the only such source showing an important effect was occupational fiber exposure in relatives (RR = 2.8, 95% CI = 0.9–8.8). This relative risk estimate was calculated after three cases who were both exposed to asbestos themselves and received asbestos exposure from their relatives were excluded.

DISCUSSION

Genital talc exposure has been proposed as an etiologic agent of ovarian cancer [14] because talc was observed more frequently in cancerous ovaries [15] than in noncancerous ovaries, occupational studies of talc-containing asbestos showed an increased risk of lung cancer [16], asbestos has been observed in cosmetic face powders [17–19], and papillary growth has been observed after implantation of asbestos [20] and talc [21] into the peritoneal cavity.

We found an increased relative risk (4.8) for talc use on sanitary napkins with a smaller effect for genital bath talc exposure (RR = 1.7). This is in accordance with the original finding of a significant increased risk for perineal talc exposure (RR = 1.9, 95% CI = 1.3–2.9) by Cramer *et al.* [4]. Preliminary findings from a Chinese study also suggest that perineal application of talc-containing dusting powder increased the risk of epithelial ovarian cancer (RR = 3.9, 95% CI = 1.1–13.8) [5]. A nonsignificant effect for genital talc exposure (on genitals, sanitary napkins, or underwear) was detected in the study of Hartge *et al.* [6] (RR = 2.5, 95% CI = 0.7–10.0). Whittemore *et al.* [7] detected an increased risk (RR = 1.4, $P = 0.06$) for perineal exposure. In a study of borderline ovarian tumors, an increased risk was also observed with talc exposure from use on sanitary napkins (RR = 1.9, 95% CI = 0.9–6.9, 8).

We also investigated the relationship with cumulative duration of all forms of genital fiber exposure (with the time since tubal ligation subtracted). The positive association (RR = 2.35) in our study for exposure longer than the median length of time contrasts with the lack of association with duration observed by Whittemore *et al.* [7]. Whittemore *et al.* [7], however, did observe a positive dose–response relationship with frequency of exposure (1–20 times per month, RR = 1.3, 95% CI = 0.8–2.0; >20 times per month, RR = 1.4, 95% CI = 0.9–2.2). Although Booth *et al.*, [9] did not observe a significant ($P = 0.05$) trend of increasing risk with more frequent use, weekly genital talc use (RR = 2.0, 95% CI = 1.3–3.4) was associated with an increased risk of ovarian cancer.

The results of our study and others suggest that genital fiber exposure may be associated with an adverse effect [4–8] but further study is needed to determine if this relationship is causal in nature.

The present study also showed a significant negative association with tubal ligation (RR = 0.15). Harlow [22] (RR = 0.3, 95% CI = 0.3–1.1), Booth *et al.* [9] (RR = 0.2, 95% CI = 0.1–0.6), Mori *et al.* [23] (RR = 0.4, 95% CI = 0.2–1.0), Whittemore *et al.* [7] (RR = 0.6, $P = 0.07$), and Irwin *et al.* [24] (RR = 0.7, 95% CI = 0.5–1.0) also observed negative associations. Although the findings of our study differ from the positive association observed by Koch *et al.* [25] the comparison rates [26] used in Koch's cohort study may have been underestimated.

Tubal ligation may protect against ovarian cancer by inhibiting the carcinogenic action of talc through blockage

TABLE 3
Number and Frequency Distribution of Cases and Controls with Odds Ratios for Genital Fiber Exposure and Other Related Variables

Exposure interval	Attribute	Cases		Controls		Odds ratio	95% confidence interval
		N	%	*N*	%		
Genital fiber use	Yes	67	87.0	40	88.0	1.0	0.2–4.0[b]
	No	10	13.0	5	11.1		
	Missing	0		1			
Length of use of genital fiber[a] (years)	≥37.4	39	55.7	16	39.0	2.4	1.0–5.8[f]
	<37.4	31	44.3	25	61.0		
	Missing	7		5			
(Median of cases and controls)	Median		41.9		24.0		
Ovarian biopsies	Yes	6	7.8	3	6.5	1.1	0.3–4.4
	No	71	92.2	43	93.5		
Unilateral oophorectomy	Yes	8	10.4	5	10.9	0.8	0.2–2.5[d]
	No	69	89.6	41	89.1		
Tubal ligation	Yes	4	5.2	6	13.0	0.2	0.3–0.9[d,e]
	No	73	94.8	40	87.0		
Hysterectomy	Yes	19	24.7	12	26.1	0.7	0.3–1.7[d]
	No	58	75.3	34	73.9		
Condom use	Yes	35	49.3	22	51.2	1.6	0.6–3.9[b,d]
	No	37	50.7	21	48.8		
	Missing	5		3			
Diaphragm use with powder	Yes	14	18.9	5	11.4	3.0	0.8–10.8[c,d]
	No	60	81.1	39	88.6		
	Missing	3		2			
Genital bath talc	Yes	22	28.9	8	18.6	1.7	0.7–3.9
	No	54	71.0	35	81.4		
	Missing	1		3			
Sanitary napkin with talc exposure	Yes	21	30.0	6	13.6	4.8	1.3–17.8[f]
	No	49	70.0	38	86.4		
	Missing	7		2			

[a] After subtraction of the time since tubal ligation, for those who had ligation.
[b] Adjusted for number of live births.
[c] Adjusted for religion.
[d] Adjusted for years of education on subject.
[e] Adjusted for highest weight 20 years prior to diagnosis.
[f] Adjusted for highest weight 1 year prior to diagnosis.

of the fallopian tube or through a "screening" effect [27]. The effects of antecedent tubal ligation should be evaluated in future studies of ovarian cancer to determine if a negative association is consistently observed and to determine the reason for this.

Several cohort studies of women with respiratory exposure to asbestos detected an increased relative risk for ovarian cancer [1–3]. We elicited information about employment by relatives in occupations with asbestos or fiberglass exposure [28] and the relative risk was found to be elevated (RR = 2.8). In a previous case–control study of ovarian cancer, the relative risk for occupational asbestos exposure in relatives was not elevated [29], although the authors did not describe how the asbestos exposure was ascertained. Our initially suggestive findings regarding asbestos or fiberglass exposure in relatives should be evaluated further in additional studies.

In summary, our study shows that the development of ovarian cancer may be associated with genital fiber exposure (especially talc on sanitary napkins) and occupational exposure to fibers in relatives. Given its small sample size and the potential selection bias stemming from inclusion of patients from only one hospital, further research needs to be performed in order to confirm our findings.

APPENDIX 1

Questions Asked to Ascertain Fiber Exposures

Genital Fiber Exposure

1. Have you had any of the following operations prior to your hospitalization in _____?
   —Biopsy or removal of part of an ovary
   —Removal of one ovary
   —Removal of uterus (hysterectomy)

TABLE 4
Number and Frequency Distribution of Cases and Controls with Odds Ratios for Selected Characteristics Related to Respiratory Fiber Exposure

Exposure interval	Attribute	Cases		Controls		Odds ratio	95% conf interv
		N	%	N	%		
Respiratory fiber exposure	Yes	69	89.6	41	89.1	1.3	0.3–3.
	No	8	10.4	5	10.4		
Cosmetic face powder use	Yes	38	50.7	24	54.5	1.1	0.4–2.
	No	37	49.3	20	45.4		
	Missing	2		2			
Insulation installed at residence	Yes	30	39.5	17	37.8	1.2	0.3–4.
	No	46	60.5	28	62.2		
	Missing	1		1			
Living in the vicinity of a fiber-emitting industrial establishment	Yes	7	9.2	4	8.9	1.0	0.3–3.
	No	69	90.8	41	91.1		
	Missing	1		1			
Applied bath talc to body (respiratory exposure)	Yes	47	61.8	24	55.8	1.6	0.6–2.
	No	29	38.2	19	44.2		
	Missing	1		3			
Fiber exposure in relatives	Yes	18[d]	24.3	5	10.9	2.8	0.9–8.
	No	56	75.7	41	89.1		
Use of spackling and taping compounds	Yes	20	29.0	14	31.1	1.6	0.5–3.
	No	49	71.0	31	68.9		
	Missing	8		1			

[a] Adjusted for highest weight 1 year prior to diagnosis.
[b] Adjusted for years of education on subject.
[c] Adjusted for number of live births.
[d] Three cases were excluded because they had been directly exposed to fibers and had a household member who had been occupati exposed to fibers. Fiber exposure included asbestos, talc, or fiberglass exposure.
[e] Adjusted for religion.

—Tubal ligation
—Any other abdominal operation
(These items were confirmed by examination of medical records)

2. Did you use a diaphragm prior to your hospitalization in _____?

If yes: Did you use a powder to dust and dry the diaphragm?

If yes: Was it talc?

3. Did you and your sexual partner ever use a condom prior to your hospitalization in _____?

4. Have you regularly applied talcum powder to your body after bathing or for other reasons prior to your hospitalization in _____?

Did you commonly apply the talcum powder to your genital area?

5. Have you used talc on sanitary napkins or any other sanitary products used during your menstrual period prior to your hospitalization in _____?

Respiratory Fiber Exposure

1. Prior to your hospitalization in _____ had you ever regularly used cosmetic face powder?

2. Have you ever had insulation installed in a place that you lived in prior to your hospitalization in _____?

3. Have you ever lived in the vicinity of a shipyard asbestos or talc mine, or an asbestos, talc, or fiber processing plant prior to your hospitalization in _____?

4. Have you regularly applied talcum powder to body after bathing or for other reasons prior to hospitalization in _____?

Did you commonly apply the talcum powder to face, upper torso, or legs and feet?

5. Have you or anyone who has ever lived in household (including your husband) been employe any of the following industries prior to your hospi zation in _____?

(a) Installation or removal of insulation materia
(b) Brake lining manufacture
(c) Automobile repair involving brake repair
(d) Roofing using asbestos materials
(e) Asbestos milling or mining
(f) Asbestos textile or paper manufacture
(g) Building construction
(h) Other industries where asbestos is used
(i) Talc mining and milling
(j) Other industries where talc is used
(k) Fiberglass or mineral wool manufacture
(l) Other industries where fiberglass or mineral wool was used

6. Did you ever use spackling and taping compounds?

If the respondent answered yes to any of these questions, they were asked when the exposure started and stopped. If they could not answer this question, they were asked how long the exposure occurred.

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