

Ovarian Cancer and Talc

A Case-Control Study

DANIEL W. CRAMER, MD,*†‡ WILLIAM R. WELCH, MD,§ ROBERT E. SCULLY, MD,[¶]
AND CAROL A. WOJCIECHOWSKI, RN‡

Opportunities for genital exposure to talc were assessed in 215 white females with epithelial ovarian cancers and in 215 control women from the general population matched by age, race, and residence. Ninety-two (42.8%) cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls. Adjusted for parity and menopausal status, this difference yielded a relative risk of 1.92 ($P < 0.003$) for ovarian cancer associated with these practices. Women who had regularly engaged in both practices had an adjusted relative risk of 3.28 ($P < 0.001$) compared to women with neither exposure. This provides some support for an association between talc and ovarian cancer hypothesized because of the similarity of ovarian cancer to mesotheliomas and the chemical relation of talc to asbestos, a known cause of mesotheliomas. The authors also investigated opportunities for potential talc exposure from rubber products such as condoms or diaphragms or from pelvic surgery. No significant differences were noted between cases and controls in these exposures, although the intensity of talc exposure from these sources was likely affected by variables not assessed in this study.

Cancer 50:372-376, 1982.

THE POSSIBILITY that ovarian cancer may be caused by exposure to certain hydrous magnesium silicates such as talc and asbestos has been raised by several researchers.¹⁻³ The lack of epidemiologic studies regarding this hypothesis prompted us to investigate talc exposure in a case-control study of ovarian cancer.

From the Departments of *Obstetrics, †Gynecology, and §Pathology, Boston Hospital for Women, Division of the Brigham and Women's Hospital, the ‡Department of Epidemiology, Harvard School of Public Health and the ¶Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Supported by Grant Number 5-RO1 CA24209, awarded by the National Institutes of Health, DHEW.

Address for reprints: Dr. Cramer, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, MA 02115.

This study could not have occurred without the generous participation of many clinicians and institutions in the greater Boston area including: Dr. Emanuel Friedman of the Beth Israel Hospital, Drs. Robert Knapp and Thomas Griffiths of the Brigham and Women's Hospital and Sidney Farber Cancer Institute, Dr. Arthur Hassett of the Brockton Hospital, Dr. Joel Rankin of the Framingham Union Hospital, Dr. Edward Copenhaver of the Lahey Clinic Foundation, Dr. James Nelson of the Massachusetts General Hospital, Dr. Clement Yahia of the New England Deaconess Hospital, Dr. Lalita Gandbhir of the Pondville Hospital, Dr. James Whelton of Saint Elizabeth's Hospital, Dr. Stephen Alpert of the Salem Hospital, Dr. Richard Hunter of the University of Massachusetts Medical School. The superb clerical and technical assistance of Ms. Eileen McManus, Ms. Sally Cassells, and Ms. Christine Peters is also gratefully acknowledged.

Accepted for publication December 29, 1981.

Methods

The cases studied were women with ovarian cancer, diagnosed between November 1978 and September 1981 and identified through the pathology logs or tumor boards of twelve participating hospitals in the Greater Boston area. The study was restricted to English-speaking residents of Massachusetts ranging in age from 18 to 80 years. During the study period, 297 eligible cases were identified. Physicians denied permission to contact their patients in 13 instances. Fourteen patients declined to participate, and 14 other patients had died or moved before they could be contacted.

For each of the 256 interviewed cases, slides of the surgical specimens were reviewed by two authors (W.R.W. or R.E.S.). Eighteen cases were excluded as nonovarian primaries. Each ovarian tumor was classified according to the Histological Classification of Ovarian Tumors of the World Health Organization.⁴ The present analysis was restricted to 215 white women with epithelial cancers, including 39 with tumors of borderline malignancy and their matched controls.

Control cases were identified through the Massachusetts Town Books, annual publications that list residents by name, age, and address. Controls were selected randomly from those women who matched cases by precinct of residence, race, and age within two years. Additionally, it was required that a subject be excluded

0008-543X/82/0715/0372 \$0.75 © American Cancer Society

372

Plaintiff's Exhibit
No.

P-3

exhibitsicker.com

as a control if she had had a bilateral salpingo-oophorectomy, but subjects were not excluded because of prior hysterectomy or other types of pelvic operations. Women who had had pelvic operations were generally confident in their knowledge of whether their ovaries had been removed, but the nature of the operations could not be verified by hospital records in each instance. Women whose statements could not be verified were included or excluded on the basis of their recollection of the surgery. The 215 controls in this study were eventually obtained from a total of 475 potential controls identified through the Town Books. Fifty-six (12%) of the total could not be reached because they had moved, died, or had disconnected or unlisted phones. Twenty-nine (6%) of the total were ineligible because of a history of bilateral salpingo-oophorectomy, while 20 (4%) were of the wrong age or race or did not speak English. Of the total potential controls, 155 (33%) refused to participate. If the 215 cases are characterized as to ease of matching, 121 (56%) cases were matched with no refusals, 58 (27%) were matched after one refusal, and 36 (17%) were matched only after two or more refusals.

Interviews were conducted personally to assess a number of factors from the menstrual and reproductive history, medical and family history, and environmental exposures. This report will deal only with the results of several questions related to potential or definite talc exposure by way of contraceptive practices, operations, or perineal hygiene. Subjects were stratified by potential confounders described below, and adjusted relative risks associated with these exposures were calculated by the Mantel-Haenszel procedure as adapted by Rothman and Boice.⁵ To accommodate other confounders as well as the matched design in the data collection, logistic analysis for matched data as described by Breslow *et al.*⁶ was also employed.

Results

The average age (and standard error of the mean, SEM) for cases was 53.2 (1.0) years and for controls,

TABLE 1. Characteristics of Cases and Controls

Characteristic	Cases (Total = 215)		Controls (Total = 215)	
	No.	%	No.	%
Educational level (completed college)	48	22.3	49	22.8
Religion (Roman Catholic)	126	58.6	128	59.5
Marital status (never married)	46	21.4	24	11.2
Nulliparous	78	36.3	39	18.1
Menopausal status (postmenopausal*)	137	63.7	129	60.0

* Postmenopausal at time of diagnosis for cases or for interview for controls.

53.5 (1.0) years. Table 1 shows other characteristics of subjects. Controls were comparable to cases in educational level and religion. Cases and controls differed significantly in marital status and parity with parity being the more important discriminator between them. Sixty-four percent of the cases were postmenopausal at the time of diagnosis, whereas 60% of controls were postmenopausal. Of these, 15 cases and 20 controls had had an artificial menopause. Parity and menopausal status were considered important potential confounders in this analysis and were adjusted for as described above.

Relative risks associated with potential talc exposure from contamination on rubber products are explored in Table 2. Although surgical gloves of recent vintage are dusted with starch, talc contamination may still be found.⁷ Thus, a history of pelvic operations (appendectomy, cesarean section, hysterectomy, and other operations on internal genital organs other than bilateral salpingo-oophorectomy) was determined in cases and controls. Excluding operations associated with the diagnosis or treatment of the ovarian cancer among the cases, no excess in the occurrence of pelvic operations was noted. The greatest opportunity for talc exposure from surgery occurred before 1950, when talc was the

TABLE 2. Relative Risks (RR) for Common Epithelial Ovarian Cancers Associated with Potential Talc Exposure from Contamination on Rubber Products

Exposure	Cases		Controls		Crude RR	Adjusted RR*	95% Confidence limits
	Total	No. (%) with exposure	Total	No. (%) with exposure			
Pelvic surgery	215	78 (36.3)	215	75 (34.9)	1.06	1.17	(0.76-1.79)
Pelvic surgery (prior to 1950)	215	51 (23.7)	215	48 (22.3)	1.08	1.12	(0.69-1.82)
Use of condom†	169	19 (11.2)	191	30 (15.7)	0.68	0.77	(0.41-1.44)
Use of diaphragm†	169	37 (21.9)	191	35 (18.3)	1.24	1.19	(0.69-2.05)

* Adjusted for parity (nulliparous, parous) and menopausal status (pre- and postmenopausal).

† Restricted to subjects who had ever been married.

TABLE 3. Relative Risks (RR) Associated with Using Talc for Storage Among Diaphragm Users* by Duration of Use of Diaphragm

Duration of diaphragm use	Cases		Controls		Crude RR	Adjusted RR†	95% Confidence limits
	Total	No. (%) who used talc on diaphragm	Total	No. (%) who used talc on diaphragm			
Total diaphragm use less than five years	13	6 (46.2)	21	8 (38.1)	1.39	1.82	(0.42-8.00)
Total diaphragm use five or more years	27	16 (59.3)	19	11 (57.9)	1.06	1.23	(0.36-4.17)
All users	40	22 (55.0)	40	19 (47.5)	1.35	1.56	(0.62-3.88)

* Includes all women who used diaphragm regardless of marital status.

† Adjusted for parity and menopausal status.

predominantly used dusting powder for surgical gloves. However, no significant excess of pelvic operations prior to 1950 was observed for cases.

The patients (cases) who, at sometime, had been married, chose condoms less frequently and diaphragms more frequently for contraception than the control group, but neither difference was statistically significant. Condom use is not necessarily associated with talc exposure. Not all brands of condoms are dusted with talc, and lubricants could affect the shedding of talc from the condom. Unfortunately, details on specific brands of condoms were not obtained. Similarly, talc exposure is not a necessary consequence of diaphragm use. We inquired specifically about the practice of dusting the diaphragm with talc for storage after use (Table 3). Among all subjects who had used a diaphragm, there was no significant excess of cases who regularly stored their diaphragm using talc, nor was any greater risk associated with this practice observed among women who had used the diaphragm for longer durations. Before the risk from this exposure can be adequately assessed, greater detail is needed including frequency of use and whether the powder was washed off prior to use. Furthermore, contraceptive jellies used with the diaphragm could affect the transport of talc in the genital tract.

Hygienic practices involving talc were also studied. Specifically, we inquired whether women had regularly used talc as a dusting powder on the perineum or regularly dusted sanitary napkins with talc (Table 4). Ninety-two (42.8%) of the cases had talc exposure by either or both of these routes compared with 61 (28.4%) of the controls. The adjusted relative risk was 1.92 ($P < 0.003$) with 95% confidence limits of 1.27-2.89 compared to subjects who had neither exposure. Sixty (27.9%) cases and 48 (22.3%) controls had either used talc for dusting or on napkins but not both. This difference yielded an adjusted relative risk of 1.55, which was of borderline significance ($P = 0.06$). The greatest risk occurred in women who had both exposures (use on the perineum and on napkins) compared to women who had neither exposure. Thirty-two (14.9%) of cases were in this category compared with 13 (6.0%) controls, for an adjusted relative risk of 3.28 ($P < .001$) and 95% confidence limits of 1.68-6.42. The histologic characteristics of tumors developing in women with perineal exposure to talc did not differ significantly from those in women without perineal exposure to talc (Table 5). In addition, the proportion of cases with tumors of borderline malignancy was identical among those with and without perineal exposure to talc. Twenty-two (18%) of 123 cases without the exposure had tumors of bor-

TABLE 4. Relative Risks (RR) for Common Epithelial Ovarian Cancers Associated with Talc Exposure in Perineal Hygiene

	Types of perineal exposure				
	No perineal exposure	Any perineal exposure	As dusting powder but not on napkins	On napkins but not as dusting powder	Both on napkins and as dusting powder
Cases (Total = 215)	123 (57.2%)	92 (42.8%)	43 (20.0%)	17 (7.9%)	32 (14.9%)
Controls (Total = 215)	154 (71.6%)	61 (28.4%)	34 (15.8%)	14 (6.5%)	13 (6.0%)
Crude rr	1	1.89	1.58	1.52	3.08
Adjusted RR*	—	1.92	1.55		3.28
95% confidence limits	—	(1.27-2.89)	(0.98-2.47)		(1.68-6.42)

* Adjusted for parity and menopausal status.

derline malignancy compared to 17 (18%) of 92 with the talc exposure.

Discussion

The argument linking talc and ovarian cancer includes four elements: the chemical relationship between talc and asbestos, asbestos as a cause of pleural and peritoneal mesotheliomas, the possible relation between epithelial ovarian cancers and mesotheliomas, and the ability of talc to enter the pelvic cavity. The mineral talc is a specific hydrous magnesium silicate chemically related to several asbestos group minerals and occurring in nature with them. Generic "talc" is seldom pure and may be contaminated with asbestos, particularly in powders formulated prior to 1976.^{8,9}

Epidemiologic studies have clearly linked lung cancer and pleural and peritoneal mesotheliomas with asbestos exposure.¹⁰ An excess of similar pulmonary lesions has been reported in talc workers and seems to be correlated with the amount of asbestos contamination in the talc deposits worked.¹¹ Graham and Graham¹ were able to induce ovarian neoplasms in guinea pigs with asbestos and suggested that ovarian cancer could be related to asbestos exposure, noting the similarity between mesotheliomas and ovarian cancers. Parmley and Woodruff¹² further emphasized this similarity and popularized the pelvic contamination theory, which proposed that environmental carcinogens might enter the pelvic cavity via the genital tract. Years earlier it had been observed that inert carbon particles placed in the vagina immediately prior to hysterectomy could be recovered from the fallopian tubes.¹³ Although greeted with skepticism, the finding of talc particles embedded in normal and abnormal ovaries suggests that talc is a substance that can enter the pelvic cavity via the vagina.²

Although no consensus concerning the risks of talc has emerged from letters, editorial and articles,^{3,14-16} participants in the discussion have agreed upon the need for epidemiologic studies of ovarian cancer and talc exposure. In this case-control study of ovarian cancer of the epithelial variety, we investigated several sources of potential talc exposure. Among these, the only significant finding was an association between ovarian cancer and hygienic practices involving the use of talc on the perineum. It is especially notable that women who regularly had both dusted their perineum with talc and had used it on sanitary napkins had more than a threefold increase in risk compared to women with neither exposure. Several potential biases must be considered in interpreting this association.

The observation by Wynder *et al.*¹⁷ that menstrual characteristics may differ between women with ovarian cancer and controls might suggest that such differences may confound the association between perineal use of

TABLE 5. Characteristics of Ovarian Cancer in Women with and without Perineal Exposure to Talc

	No perineal use of talc	Any perineal use of talc
	No. (%)	No. (%)
Serous	66 (53.7)	45 (48.9)
Mucinous	16 (13.0)	14 (15.2)
Endometrioid and clear cell	32 (26.0)	24 (26.1)
Other and undifferentiated	9 (7.3)	9 (9.8)
Total	123 (100)	92 (100)

talc and ovarian cancer. We found that menstrual characteristics of cases and controls were virtually identical in this study. Fifty-three (24.7%) cases complained of moderate or severe dysmenorrhea compared to 56 (26.0%) controls. Twenty-five (11.6%) cases complained of irregular periods compared to 32 (14.9%) controls. The average numbers (and SEM) of days of flow and cycle length were, respectively, 4.9 (0.1) and 28.9 (0.3) days for cases and 4.9 (0.1) and 29.6 (0.3) days for controls.

Since entry of talc into the pelvic cavity is prevented by hysterectomy or tubal ligation, it might also be argued that the inclusion of subjects with pelvic surgery in the analysis may obviate any association between talc and ovarian cancer. It should be noted that such surgery generally occurred near the end of reproductive life for both cases and controls, probably after most significant talc exposure had already occurred. The exclusion of such subjects from the analysis did not substantially alter the observed associations. For example, the adjusted relative risk for the use of talc both on the perineum and sanitary napkins was 2.79 ($P < 0.003$) in the group without pelvic surgery compared to 3.28 observed for the entire group.

In terms of other confounders, the association persisted after adjustment for menopausal status and parity. We also applied multivariate logistic regression for paired observations.⁶ The maximum likelihood estimate of relative risk associated with any perineal use of talc was 1.61 ($P = 0.03$) with 95% confidence limits of 1.04-2.49 after simultaneous adjustment for religion, marital status, educational level, ponderal index, age at menarche, exact parity, oral contraceptive or menopausal hormone use, and smoking.

Our sample of cases represents more than 50% of ovarian cancer cases diagnosed in Boston residents in the study period. Therefore, it is difficult to conceive of a plausible bias in the selection of cases that would yield this excess use of talc. There is reason for concern that the high refusal rate among the controls may have introduced a selection bias among the controls. But,

when we restricted the analysis to the 121 cases who were matched without a control refusal, we again found a significant association between talc use and ovarian cancer. For women who had used talc both in dusting and on the perineum we found an adjusted relative risk of 2.44 ($P < 0.05$). Interviewer bias is also unlikely to explain the association. Of the 18 women who were initially interviewed as ovarian cancer cases but later excluded as having metastatic tumors to the ovary, only one (5.6%) had both perineal and napkin exposure as compared with 15% in cases and 6% in controls.

Experimental data which might bear on the carcinogenicity of talc come primarily from models using pleural implantation of various minerals in rats.¹⁸ These data suggest that carcinogenicity is dependent primarily upon the shape of the particles with long thin fibers such as those occurring in crocidolite asbestos being most carcinogenic. Talc consists primarily of plates but may contain fibers, although voluntary guidelines to limit the content of asbestiform fibers in consumer talcums were proposed by the cosmetics industry in 1976.¹⁹

If talc is involved in the etiology of ovarian cancer, it is not clear whether this derives from the asbestos content of talc or from the uniqueness of the ovary which might make it susceptible to carcinogenesis from both talc and other particulates. With ovulation entrapment of the surface epithelium of the ovary into the ovarian stroma occurs. If present, talc or other particulates might be incorporated into these inclusion cysts. Apparently implantation of foreign bodies into the lumens of epithelial lined organs provides a favorable environment for carcinogenesis.²⁰ Alternatively, talc might serve to stimulate entrapment of the surface epithelium and act in the same way that "incessant ovulation" has been proposed as an etiologic factor for ovarian cancer.²¹ Given the histologic and clinical diversity of ovarian cancer, talc exposure is unlikely to be the only cause. Undoubtedly, reproductive experiences such as pregnancies and, perhaps, oral contraceptive use play a role in its etiology.²¹⁻²³ The possibility that talc exposure interacts with these variables deserves further investigation.

It is hoped that this report will stimulate further study of talc exposure in relation to ovarian cancer. Animal studies would be helpful to determine whether and under what circumstances ovarian tumors may be induced by various talc preparations. Epidemiologic studies should focus on opportunities for excessive vaginal contamination with talc such as when it is repeatedly used in perineal dusting powders or sprays and in or on tampons, sanitary napkins, or other products intended for

intravaginal use. More precise details on the exact nature and frequency of the exposure and the amount and specific brand of powder used are essential. Opportunities for talc exposure are widespread and pervasive,²⁴ but that should not discourage epidemiologists from studying this potentially important exposure in relation to ovarian cancer.

REFERENCES

- Graham J, Graham R. Ovarian cancer and asbestos. *Environ Res* 1967; 1:115-128.
- Henderson WJ, Joslin CAF, Turnbull AC, Griffiths K. Talc and carcinoma of the ovary and cervix. *J Obstet Gynaecol Br Commonw* 1971; 78:266-272.
- Longo DL, Young RC. Cosmetic talc and ovarian cancer. *Lancet* 1979; ii:349-351.
- Scrovo SF, Scully RE, Sobin LH. International Histological Classification of Tumours, No. 9. Histological Typing of Ovarian Tumours. Geneva, World Health Organization, 1973.
- Rothman KJ, Boice JD. Epidemiologic analysis with a programmable calculator. NIH Publication No. 79-1649, 1979.
- Breslow NE, Day NE, Halvorsen KT, Prentice RL, Sabai C. Estimation of multiple relative risk functions in matched case-control studies. *Am J Epidemiol* 1978; 108:299-307.
- Henderson WJ, Hamilton TC, Griffiths K. Talc in normal and malignant ovarian tissue. *Lancet* 1979; i:499.
- Cralley LJ, Key MM, Groth DH, Lainhart WS, Ligo RM. Fibrous and mineral content of cosmetic talcum products. *Am Ind Hyg Assoc J* 1968; 350-354.
- Rohli AN, Langer AM, Selikoff IJ, Tordini A, Klimentidis R. Consumer talcums and powders: Mineral and chemical characterization. *J Toxicol Environ Health* 1976; 2:255-284.
- Selikoff IJ, Hammond EC (eds.). Health hazards of asbestos exposure. *Ann NY Acad Sci*. 1979; 330:1-179.
- Kleinfeld M, Messite J, Zaki MH. Mortality experiences among talc workers: A follow-up study. *J Occup Med* 1974; 16:345-349.
- Parmley TH, Woodruff JD. The ovarian mesothelioma. *Am J Obstet Gynecol* 1974; 120:234-241.
- Egli GE, Newton M. The transport of carbon particles in the human female reproductive tract. *Fertil Steril* 1961; 12:151-155.
- Anonymous. Cosmetic talc powder. *Lancet* 1977; i:1348.
- Newhouse ML. Cosmetic talc and ovarian cancer. *Lancet* 1979; ii:528.
- Roe FJC. Controversy: Cosmetic talc and ovarian cancer. *Lancet* 1979; ii:744.
- Wynder EL, Dodo H, Barber HRK. Epidemiology of cancer of the ovary. *Cancer* 1969; 23:352-370.
- Stanton MF, Layard M, Tegeris A, et al. Relation of particle dimension to carcinogenicity in amphibole asbestos and other fibrous minerals. *J Natl Cancer Institute* 1981; 67:965-975.
- C.T.F.A. Specification. Talc, cosmetic: Cosmetic, toiletry, and fragrance association, Inc. Issue 10-17, 1976.
- Brand KG, Johnson KH, Buoen LC. Foreign body tumorigenesis. *CRC Crit Rev Toxicol* 1976; 4(Oct):353-394.
- Casagrande JT, Pike MC, Ross RK, Louie EW, Roy S, Henderson BE. Incessant ovulation and ovarian cancer. *Lancet* 1979; ii:170-172.
- Newhouse ML, Pearson RM, Fullerton JM, Boesen EAM, Shannon HS. A case control study of carcinoma of the ovary. *Br J Prev Soc Med* 1977; 31:148-153.
- McGowan L, Parent L, Lednar W, Norris HJ. The woman at risk for developing ovarian cancer. *Gynecol Oncol* 1979; 7:325-344.
- Blejer JP, Arlon R. Talc: A possible occupational and environmental carcinogen. *J Occup Med* 1973; 15:92-97.