Published in final edited form as:
Eur J Cancer Prev. 2008 April ; 17(2): 139–146. doi:10.1097/CEJ.0b013e32811080ef.

Perineal Talc Use and Ovarian Cancer: A Critical Review

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Abstract

Talc, like asbestos, is a silicate that has been studied in relation to cancer risk. Several studies conducted over the past 25 years found an association between perineal talc powders and ovarian cancer. The summary relative risk is about 1.3 (95 percent confidence intervals 1.2–1.5) and these data have been interpreted as supporting a causal role. In this review article, we discuss the chemical and morphological features of talc and asbestos, and explain why despite their similar chemical classification talc does not possess asbestos like carcinogenic properties. The heterogeneity in the perineal dusting studies has raised important concerns over the validity of the exposure measurements, and the lack of a consistent dose-response effect limits making causal inferences. Perhaps more importantly, whereas it is unknown whether external talc dust enters the female reproductive tract, measures of internal talc exposure such as talc-dusted diaphragms and latex condoms show no relationship with ovarian cancer risk. In addition, the therapeutic use of high dose cosmetic grade talc for pleurodesis has not been shown to cause cancer in patients receiving these treatment modalities. Talc is not genotoxic. Mechanistic, pathology and animal model studies have not found evidence for a carcinogenic effect. In summary, these data collectively do not indicate that cosmetic talc causes ovarian cancer.

Keywords

Talc; minerology; ovarian cancer; asbestos; epidemiology; inflammation; meta-analysis; bias; pleurodesis

Introduction

The association between perineal talc powder dusting and ovarian cancer was determined in 16 case-control studies (Booth et al., 1989; Chang and Risch, 1997; Chen et al., 1992; Cook et al., 1997; Cramer et al., 1999; Cramer et al., 1982; Godard et al., 1998; Harlow et al., 1992; Harlow and Weiss, 1989; Mills et al., 2004; Ness et al., 2000; Purdie et al., 1995; Rosenblatt et al., 1998; Tzonou et al., 1993; Whittemore et al., 1988; Wong et al., 1999) and the Nurses' Health Study (Gertig et al., 2000; Hankinson et al., 1993). The summary relative risk for these studies in a meta-analysis (excluding Mills et al.) is 1.33 (95% confidence intervals [CI] 1.16–1.45) (Gross and Berg, 1995; Huncharek et al., 2003). Methodological issues such as response rates, validity, reliability, bias, the consistency of dose-response relationships, and causality have been reviewed elsewhere (Muscat and Barish, 1998)

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The use of talc-based powders and their possible health effects has received considerable attention in the print media and in authoritative and consumer oriented web-sites. The basis for these concerns is the increased risks of ovarian cancer associated with perineal dusting. Despite these concerns, a comprehensive review of the talc literature and the conceptual and scientific understanding of how talc could cause ovarian cancer has not been adequately considered in the medical literature. The current review provides a historical context on the origins of the talc and ovarian cancer hypothesis, how certain assumptions on talc carcinogenicity were not properly understood, and describes findings on numerous other data on talc and cancer besides the perineal dusting associations. We conclude with suggestions for new avenues of research in this area.

1. Historical development and public awareness of concerns over talc

The chemical similarity between talc and asbestos provided the rationale in the 1970's for suspecting that the practice of perineal dusting with talc-containing powders could cause ovarian cancer in humans. Supporting this hypothesis was findings that asbestos, which is a human lung and pleural carcinogen, induces ovarian tumors in guinea pigs (Graham and Graham, 1967), and limited human data of elevated standardized mortality rates of ovarian cancer in asbestos manufacturing industries (Acheson et al., 1982; Newhouse et al., 1982; Wignall and Fox, 1982). More recent studies have not confirmed an excess occupational risk (Langseth and Kjaerheim, 2004).

The initial public concerns over talc, however, were not due to its inherent properties but findings of silica minerals in samples of commercial body powders in 1978. It was thought that inhaled powder could cause scarring of lung tissue, mesothelioma or lung cancer (Henderson et al., 1971). About half of the samples contained respirable quartz, a lung carcinogen. There were no concerns raised at that time about ovarian cancer, but in 1982 a case-control study of ovarian cancer that collected information on talc use reported an increased risk with perineal dusting (Cramer et al., 1982). These findings were reported in highly circulated newspapers (1982; Globe, 1982) and subsequent domestic production of cosmetic grade talc steadily declined in the next two decades (Kelly and Matos, 2005). Cosmetic grade talc was nominated to the National Toxicology Program's (NTP) 10th Report on Carcinogens, but the decision was deferred for future consideration. In 2006, the International Agency for Research on Cancer listed cosmetic (perineal) talc application as possibly carcinogenic to humans (e.g. group 2B) (Baan et al., 2006).

2. Minerology of talc and asbestos

Talc and asbestos are both silicate minerals. Minerals are classified according to their anionic structure, and subclasses are defined by chemical composition or structure. Classes and subclasses can be further divided into mineral groups based on atomic structure and chemical similarities. Talc is a magnesium silicate hydroxide, characterized by water molecules trapped between silicate sheets, which belongs to the silicate subclass phyllosilicate and the clay group montmorillonite/smectite. The three other major phyllosilicate clay groups are kaolinite/serpentine, illite, and chlorite.

Asbestos is the generic or commercial name for six naturally occurring fibrous minerals including amosite, chrysotile, crocidolite, which have been used in industrial applications, and the fibrous varieties of tremolite, actinolite, and anthophyllite. Asbestos is morphologically distinct from talc and belongs to different silicate mineral groups and subgroups. The serpentine mineral group includes the asbestiform chrysotile, which is the most abundant variety of the serpentine mineral group. It is distinct from the non-asbestiform serpentines in that its brucite and silicate layers bend into tubes that produce clusters of curled fibers that are often entangled. The fibers are bundled but easily separate

out from the host matrix. The inosilicate/amphibole group of minerals is very common in surface rock. There are five asbestiform minerals in the inosilicate/amphibole group, which differ by chemical composition but all form individual rather than bundled needle-like fibers. All asbestos fibers have a high tensile strength and are characterized by an aspect ratio (length to diameter) of 20 to 1,000.

The carcinogenic effects of asbestos have been extensively studied and documented in the medical literature (Huncharek, 1986; Mossman and Gee, 1989). It is clear that the morphologic structure of serpentine asbestos and the fibrous form of amphiboles is responsible for their carcinogenic properties, much more than its atomic constituents (Stanton et al., 1981; Stanton et al., 1977). In contrast, talc which is a member of the montmorillonite/smectite group, rarely occurs in the asbestiform habit (a mineral's fibrous pattern of growth). Even asbestiform talc is not carcinogenic like asbestos because of its dissimilar chemical and physical properties.

The geological classification of minerals is not straightforward and improvements in analytic techniques have led to changes in the nomenclature over time. Minerals are chemically similar but can have substantially different properties. It was noted with levity that the problem with mineralogical analogies can be appreciated by the fact that calcium carbonate constitutes both a pearl and chalk (Krause and Ashton, 1978). However, these critical distinctions have not been recognized in the epidemiologic literature.

3. Proposed mechanisms for talc induced ovarian cancer

Given the dissimilarities between talc and asbestos with regard to their fibrous shapes, the weak but increased associations in the epidemiologic studies could be attributed to other mechanisms assuming that the statistical associations are unbiased and not due to confounding. Asbestos fibers in the lung initiate an inflammatory and scarring process, and it has been proposed that ground talc, as a foreign body, might initiate an inflammatory response (Ness and Cottreau, 1999). However pelvic inflammatory diseases such as endometritis, peritonitis, tubo-ovarian access formation, and salphingo-oophoritis have in general not been associated with an increased risk of ovarian cancer (Risch and Howe, 1995) (Green et al., 1997; Parazzini et al., 1996; Risch et al., 1994). A meta-analysis of studies of anti-inflammatory drug use found no reduction in ovarian cancer risk (Bonovas et al., 2005). Inflammation induces pleural fibrosis (Antony, 2003) but the detection of talc particles in human ovarian surgical specimens was not accompanied by fibrosis in one study (Heller et al., 1996b).

It was suggested that the associations between perineal talc dusting and ovarian cancer might be explained by the induction of ANTI-MUC1 antibodies (Cramer et al., 2005). This idea has been debated on statistical grounds where talcum powder applied to the perineum was associated with increased ANTI-MUC1 expression but the correlation was also observed when talc powder was applied to other body parts. More importantly the simple observation that talc elevates immunoglobulin protein levels in blood, possibly via heat shock proteins seems to have no known direct relevance for ovarian cancer since ANTI-MUC1 is associated with other cancers (Muscat et al., 2005) and because there is no known role of heat shock proteins in ovarian cancer risk.

4. Ecologic data

The domestic sales of cosmetic talc powder in the U.S. declined from 41,000 metric tonnes in 1982 to 5,000 metric tonnes in 2004 (Kelly and Matos, 2005). Sales of other talc products have remained relatively stable indicating that the decline in cosmetic sales is due to decreased demand rather than decreased production capacity. There has been no

corresponding temporal decline in the reported use of perineal talc powder in the epidemiologic studies of ovarian cancer and this discrepancy has not been addressed. The decline in powder sales may have directly resulted from health concerns over talc resulting from study findings and consumer warnings in the print and electronic media. The weak associations reported in the case-control studies could be explained by an increased awareness about the suspected health hazards from talc among case subjects. Alternatively, the decline in sales might be due to temporal changes in feminine hygienic practices, or to demographic changes in population characteristics. We can only speculate about these issues, but the dearth of marketing or epidemiologic data on the characteristics of women who uses talc powders, for what reasons, how they are applied and under what circumstances, and whether these factors have changed over time add to the ambiguities in exposure assessment that is raised by the sales data. Consequently, the question of perineal talc exposure and ovarian cancer risk is only understood from the limited exposure data in case-control studies.

Even this data is somewhat problematic since the terminology used to define exposure varied across studies from “dusting powders,” ”genital powder,” “baby powder,” “talc,” to “talc(genital/rectal and feet,” “bath talc,” “body talc” and “talc use on perineum).” Some studies did not distinguish talcum powder from talc-free, powders, or the location of application was not specified. Where the application was specified, it may not be certain whether the subjects understood the meaning of the words perineum or genital.

5. Issues in the case-control literature of talc dusting

5a. Clinical perspectives of talc exposure assessment

One aspect of the epidemiologic literature to date is that the studies have not incorporated a clinical perspective on exposure assessment. While many lifestyle exposures can be determined with reasonable accuracy using a structured questionnaire, the highly personal nature of talc use may require a detailed clinical understanding in order to determine the exact nature of the practice for reducing any possible adverse health effects. The use of genital talc powders could be seasonal and vary by changes in personal history (e.g. changes in marital status, sexual partners, use of contraceptive birth control, parity, occupation etc.). It is unknown whether individual subjects respond differently to questions on genital dusting according to whether undergarments were worn at the time of application, whether dusting occurred before or after sexual intercourse, and whether dusting occurred in combination with douching. The amount of talc introduced into the female genital tract might depend on these hygienic practices, and may vary by lifestyle changes, season, bodyweight and other factors. A typical lifestyle questionnaire also requests respondents to define their practice into a quantifiable frequency, which forces the study subjects to respond into a pattern of regular use that in the case of talc may be unrepresentative of lifetime use, and not reflect cyclical or temporary changes (Muscat and Barish, 1998).

5b. Infant exposure

Epidemiologic studies have not determined whether the internal female genital tract is physically exposed to talc dusts during infancy. Such questions need to consider whether the hymen blocks exposure into the infant genital tract. Clearly, adult women cannot recall their early childhood exposures but the inability to measure this exposure needs to be considered in the overall evaluation of talc carcinogenicity.

5c. Exposure to the adult reproductive tract

Perhaps the most fundamental unanswered question on perineal dusting is whether powder applied to skin surfaces surrounding the external genitalia actually enter the adult female

genital tract. It is uncertain whether dusting contaminates the vagina or cervix and if so under what hygienic conditions. The issue of particle retrograde migration from the cervix to the ovaries assumes that talc particles migrate upwards against both gravity and the downward flow of vaginal mucous and menstrual fluids. The limited number of human experimental studies have found evidence for particle migration in the female reproductive tract, although the interpretation of these findings have been debated (Wehner, 2002). For example, one study found that starch particles from surgical gloves migrated from the vagina into the uterine cavity and fallopian tubes in women undergoing subsequent hysterectomy (Sjosten et al., 2004). The tissue particle count was significantly greater than in women treated with non-powdered gloves. However the starch particles were introduced under routine gynecologic examination that involved the use of a speculum, and the mobility of starch might be different than talc due to its different chemical composition.

Talc particles have been detected in human ovarian surgical specimens. In early studies, it was assumed that the vagina was the route of exposure, although as noted previously occupational studies indicated that inhaled particles could migrate from the lungs to the ovaries. The first study that described the presence of talc particles in ovarian cancer tissue was performed when surgical donning gloves were manufactured with talcum powder or other dusting agents (Henderson et al., 1971). Concerns over contamination led to a second effort that was conducted after manufacturing processes were based on talc-free products. The initial findings were confirmed and contamination was ruled out as an explanation (Henderson et al., 1979). To further explore these issues, a study of normal ovarian tissue obtained from women undergoing oophorectomy was conducted in relation to reported talc use. Some samples that had no measurable talc counts were obtained from women who reported regular talc dusting, whereas other samples with high concentrations were obtained from women who reported no genital talc use. (Heller et al., 1996b). In contrast, the same group reported a correlation between asbestos exposure and asbestos concentrations in ovarian tissue (Heller et al., 1996a). These pathology studies require careful interpretation because of their small sample sizes and limited exposure assessment, but support the notion that ovarian tissue may be contaminated via inhalation and not perineal dusting.

5d. Exposure via diaphragms

Given the uncertainty on whether perineal dusting exposes the internal female genital tract to talc, it seems clinically intuitive that the most valid method for testing the carcinogenic potential of talc is to determine its association with talc-dusted diaphragms or condoms. By definition, the female reproductive tract is exposed to talc containing powders introduced by diaphragms, whereas an exposure route based on perineal dusting requires unproven assumptions about vaginal exposure. The data on talc-dusted contraceptive diaphragms is less extensive than that for talc dusting, but a recent meta-analysis of nine case-control studies found a summary odds ratio of 1.03 (95% CI 0.80–1.33) (Huncharek et al., (in press)). These results suggest that cosmetic talc is not associated with ovarian cancer risk. As with the talc dusting data, the validity of the diaphragm data has not been determined since little is known about the application of talc in female hygienic practices. For example, diaphragms may be used with contraceptive jelly that could potentially inhibit or facilitate the migration of talc into the uterus. The observational studies of ovarian cancer did not collect or report information on the frequency and duration of this practice, but it was acknowledged in one study that the lack of a positive association with talc-dusted diaphragms led to the exclusion of this particular measure in a follow-up study (Cramer et al., 1999). From an epidemiologic perspective it may be argued that the diaphragm and condom data is more valid if not the only valid measure of female reproductive tract talc exposure.

5e. Exposure via barrier condoms

A similar argument may be made for talc-dusted condoms. In seven studies that gathered information on condom use, none of these including the Nurses Health Study found an increased risk with ovarian cancer (Table 1). Information on frequency and duration of use was not collected in these studies. Latex condoms have been manufactured with a wide variety of dusting powders including talc, starch, silica and other minerals. The density of talc particles differes substantially by brands (Kasper and Chandler, 1995). Condom sales increased substantially in 1975, rising by about 10% annually until 1980 (Castleman, 1980). Similarly, the use of condoms was reported to increase significantly by consumers in the National Surveys of Family Growth, i.e. from 13% in 1988 to 19% in 1995 in women (Bankole et al., 1999; Piccinino and Mosher, 1998). This increase was attributed to a greater awareness of the health risks associated with older formulations of oral contraceptives and protection against sexually transmitted diseases including HIV infection. It was predicted in 1995 that the increase in condom use would increase the incidence of ovarian cancer in the United States if the talc in condoms was carcinogenic (Kasper and Chandler, 1995). The annual −0.9% decline in the age-adjusted SEER incidence of ovarian cancer since 1987 would appear to indicate that talc is not an ovarian carcinogen. Talc has been the preferred dusting powder used to manufacture latex condoms, but since 1995 talc has fallen into disfavor as a dry lubricants and newer products are manufactured with cornstarch.

6. Asbestos contamination and confounding

Cosmetic talcum powder contains greater than 95%–99% pure talc, while other dusting powders are typically composed of talc, cornstarch and other additives. Cosmetic grade talc is asbestos-free and has been for several decades, but some baby powders manufactured in the 1970's contained small amounts of tremolite or quartz silica (Rohl et al., 1976). The X-ray analytic methods to determine the concentration of these contaminants have been questioned (Krause, 1977) and the diffraction patterns did not distinguish between fibrous and nonfibrous minerals. In the epidemiologic studies of ovarian cancer that distinguished dates of exposure, the magnitude of the odds ratios for perineal dusting did not vary significantly between early and later exposure periods. The overall odds ratios in these studies was also fairly consistent regardless of whether the studies were conducted during the 1970's or decades later, suggesting that crystalline quartz or other silicates in talc powder were not confounders.

7. Clinical detection, treatment and management of ovarian cancer

Ovarian cancer ordinarily presents with few distinctive symptoms. The most common indication of ovarian cancer is ascites, which is excess fluid accumulation in the abdomen that causes abdominal swelling. Other indications include abdominal/pelvic discomfort or pressure, back or leg pain, bloating, changes in bowel function or urinary frequency, fatigue, gastrointestinal problems, malnourishment, jaundice, anemia, nausea or loss of appetite and menorrhagia or excess vaginal bleeding. Menorrhagia is menstruation with excessive flow and duration and is a common complaint in premenopausal women. The World Health Organization reported that 18 million women aged 30–55 years perceive their menstrual bleeding to be exorbitant but that only 10% of these women experience blood loss severe enough to be defined clinically as menorrhagia. In a study of 187 patients with ovarian carcinoma, 24% reported excessive vaginal bleeding or menorrhagia (Munnell, 1952), a symptom that might lead to a temporary increase in talc use. A recent review found that vaginal bleeding was one of the most reported symptoms of ovarian cancer (Bankhead et al., 2005).

Meta-analysis uncovers heterogeneity in studies and is a powerful tool for exploring possible biases, particularly since it does not rely on subjective assumptions about study quality. A meta-analysis of the talc dusting studies showed that risk estimates varied by study design (e.g. hospital vs. population based) (Huncharek et al., 2003). The relative risk was 1.38 (1.25–1.52) for population-based studies and 1.19 (0.99–1.41) for hospital-based studies. Conventional wisdom suggests that this difference is due to a non-representative exposure rate in hospital controls, and that the results from population-based studies are more accurate. However the proportion of controls dusting with talc powder was the same in both groups, i.e. 32%. One explanation is that case subjects in population-based studies had the opportunity to review literature about the causes of ovarian cancer after discharge but before the interview, whereas hospital-based case subjects did not have this opportunity. Additionally, clinicians may recognize a “treatment effect” among population-based cases since many were interviewed months after discharge. Study questionnaires may specify talc use prior to diagnosis, but patients in population-based studies may not always make the distinction between pre-diagnosis and post-treatment use. In contrast, hospital-based studies ascertain exposure information at the time of discharge and reported talc use is not influenced by post-diagnostic treatment. The reasons why post-diagnostic talc use might be important is that approximately 60% of incident ovarian cancers are stage III or IV (metastatic) disease, which is characterized by a low 5 year survival rate (~10%). Patients with advanced cancer usually undergo chemotherapy, and possibly debulking surgery whereas early stage disease is usually treated with surgery, whole abdominal radiation, or intraperitoneal radioactive phosphorus. Population based studies may contain a disproportionately high numbers of early stage patients due to their favorable prognosis. Radiation treatment in early stage patients often induces radiation dermatitis in the lower abdomen, a side effect that can be partly alleviated by talc dusting. Other disease symptoms such as bloating from ascites may also prompt talc use. Early stage patients may also subsequently relapse and undergo radiation therapy prompting further talc use.

There are no published data on the specific treatments and medical management of the study subjects in these studies and it is unknown whether the above biases are present and to what degree. However, these alternative explanations for the observed increased risks have not been considered and ruled out as possible explanations for the weak case-control findings. The lack of an increased risk in the prospective Nurses Health cohort study suggests that such biases may be present in the case control data.

Another factor in the clinical management of ovarian cancer that is relevant to the epidemiology concerns the association in women who have underwent tubal ligation or hysterectomy. These procedures block the environmental contamination of the ovaries, and after excluding women with bilateral oopohorectomy, studies that reported on whether the risk was modified by hysterectomy or tubal ligation have not found consistent differences. The interpretation of these data are complicated by evidence indicating that there are other possible hormonal/biological explanations for the reduced risks associated with tubal ligation besides ovarian occlusion. For example, the reduced risk of ovarian cancer associated with hysterectomy could be an artifact resulting from an increased risk of ovarian cancer associated with menopausal hormonal therapy in women with an intact uterus (Glud et al., 2004). An increased risk associated with talc dusting in women who had these surgical procedures could also be biased in the talc studies by the failure to exclude women who underwent unilateral oophorectomy. Theoretically, the lower risk of ovarian cancer associated with hysterectomy in these women is reduced because 50% of their ovarian tissue was removed.

8. Talc and other reproductive tract cancers

Genital exposure to talc dust was first hypothesized as not only a possible risk factor for ovarian tumors but also cervical and endometrial cancer. It might be expected that the cervix is at greater risk than the ovaries due to the build up of talc particles on the uterine cervix, which serves as a barrier to uterine contamination. This association has not been studied, but such data would be informative.

9. Therapeutic uses of talc

Cosmetic grade talc is used therapeutically to treat nonmalignant and malignant pulmonary disease. Talc insufflation causes adhesions between the parietal and visceral pleura, and is used in the treatment of bronchopleural fistulas, malignant pleural effusions, and pneumothorax (a collapse of the lung from changes in intrapleural pressure in the chest cavity). The procedure involves the application of chemical agents such as cosmetic grade talc into the pleural space, causing a pleuritis that seals the air leak. The use of carcinogens for medical treatment is not uncommon (e.g. tamoxifen), however talc pleurodesis has been used as an effective treatment for several decades without concerns about its carcinogenic potential. Talc slurry is directly applied to the pulmonary pleura in concentrations equivalent to experimentally injected doses in animals on a per weight basis. If human bronchial or pleural tissue were treated with 5 g of asbestos instead of talc, it might be reasonably hypothesized that the treatment would significantly increase the rate of mesothelioma or lung cancer in these patients. However there have been no case reports of lung or pleural cancer following pulmonary pleurodesis.

The safety of talc pleurodesis has been clinically recognized anecdotally for many decades but also supported by clinical studies. In a group of 70 patients medically treated with talc pleurodesis, none developed subsequent malignancies after follow-up for outcomes (Honma et al., 1963). In 99 patients undergoing thoroscopy and asbestos-free talc pleurodesis for spontaneous pneumothorax between 1954–1964 (Lange et al., 1988), none developed malignant mesothelioma as of 1985. In 210 patients treated with talc (or kaolin) primarily for pneumothorax between 1956–1960, there were no reported cases of mesothelioma after 15–40 years follow-up (1979), and no excess number of lung cancers. The mean talc particle size and exact method of application may vary between treatment centers (Ferrer et al., 2001), but the pleurodesis studies are consistent with animal experiments that found a lack of tumor induction following pleural implantation of talc (Wagner et al., 1975).

Talc pleurodesis is also used palliatively for the treatment of malignant pleural effusions in patients with advanced breast, lung and other cancers. Because life expectancy is limited in patients treated for malignant pleural effusions, the long-term carcinogenic potential of talc pleurodesis is not a significant medical concern, particularly as many of these patients suffer from recurrent malignant pleural effusions. A meta-analysis of 36 randomized controlled trials with 1,499 subjects found no evidence that talc pleurodesis for malignant pleural effusions increased short-term mortality relative to controls (Shaw and Agarwal, 2004). However because the latency for asbestos-induced malignancies can be lengthy, these clinical findings are less relevant than the pneumothorax data with regard to talc carcinogenicity.

Pleural growth alterations have not been found in tissue specimens obtained from talc-treated patients with malignant and benign pleural effusions (Krismann et al., 1998). Therapeutic concentrations of talc significantly increased apoptosis in human malignant mesothelioma cell lines relative to control cells. No apoptotic effect was found in normal pleural mesothelioma cells (Nasreen et al., 2000).

10. Heterogeneity in the talc-dusting and ovarian cancer associations

A sensitivity analysis of the perineal dusting studies revealed interesting differences by study design. The summary odds ratio was 1.19 (95% CI 0.99–1.41) for hospital-based studies and 1.38 (95% CI 1.25–1.52) for population-based studies. Although traditional dogma suggests that population-based studies are less biased, we have noted that because of a poor prognosis, women enrolled in population-based studies after hospital discharge are more likely to be early stage cases with a history of radiation and treatment for skin irritation, or may have had the opportunity to become more familiar with known and suggested risk factors. In addition, many of the studies of perineal dusting and ovarian cancer included information on dose of talc exposure in terms of duration, frequency and cumulative use. However, few found a positive dose-response relationship and an inverse relationship was found in some.

Conclusion

The causes of ovarian cancer are poorly understood but ongoing research will likely uncover important genetic determinants of this disease. In this review, we have discussed that the findings on perineal dusting powders in case-control studies of ovarian cancer are only part of a larger body of relevant literature and perspectives that have not been adequately considered with regard to talc and ovarian cancer. It may be argued that the overall null findings associated with talc-dusted diaphragms and condom use is more convincing evidence for a lack of a carcinogenic effect, especially given the lack of an established correlation between perineal dusting frequency and ovarian tissue talc concentrations and the lack of a consistent dose-response relationship with ovarian cancer risk. The absence of mesotheliomas in patients treated with therapeutic concentrations would appear to demonstrate a high degree of safety.

The biological rationale for talc carcinogenicity has been misunderstood in terms of its chemical and physical properties, and other suggested mechanisms such as inflammation have not been supported by epidemiologic data. Talc is not fibrous and not genotoxic (Endocapron et al., 1993), and lifetime whole body exposure experiments in female laboratory rats found that ovarian tissue was not contaminated with talc and that ovarian tumor incidence was not increased (Boorman and Seely, 1995).

In addition, inhaled talc in mining and milling operations is not associated with increased pulmonary tumors. IARC classified inhaled talc that does not contain asbestos fibers as a group 3 carcinogen (e.g. inadequate evidence in humans), and the likelihood that talc could selectively induce ovarian cancer and not lung cancer, and at exposure concentrations presumably orders of magnitude lower than that in occupational settings needs to be weighed. We suggest that future research efforts in this area should include determining the validity and reliability of reported perineal talc exposure from dusting and other sources, more detailed assessment of historical usage patterns, determining the influences of disease symptomology and treatment on reported talc use, and determining the risk for other female reproductive tract cancers.

Acknowledgments

Supported by a contract from Crowell Moring, Inc. and Public Health Service Grant K07-CA104231. The authors express their appreciation to Lemar Wheeler for editorial assistance.

References

A survey of the long-term effects of talc and kaolin pleurodesis. Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit. 1979; 73:285–288.

TALCUM COMPANY CALLS STUDY ON CANCER LINK INCONCLUSIVE. New York Times. 1982:D.23. (ed.,

Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. Br J Ind Med. 1982; 39:344–348. [PubMed: 6291580]

Antony VB. Immunological mechanisms in pleural disease. Eur Respir J. 2003; 21:539–544. [PubMed: 12662014]

Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Cogliano V. Carcinogenicity of carbon black, titanium dioxide, and talc. Lancet Oncol. 2006; 7:295–296. [PubMed: 16598890]

Bankhead CR, Kehoe ST, Austoker J. Symptoms associated with diagnosis of ovarian cancer: a systematic review. Bjog. 2005; 112:857–865. [PubMed: 15957984]

Bankole A, Darroch JE, Singh S. Determinants of trends in condom use in the United States, 1988–1995. Fam Plann Perspect. 1999; 31:264–271. [PubMed: 10614516]

Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. Br J Clin Pharmacol. 2005; 60:194–203. [PubMed: 16042673]

Boorman GA, Seely JC. The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. Regul Toxicol Pharmacol. 1995; 21:242–243. [PubMed: 7644712]

Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. Br J Cancer. 1989; 60:592–598. [PubMed: 2679848]

Castleman M. A consumer's guide to the condom comeback. Med Self Care. 1980:35–37. [PubMed: 12339697]

Chang S, Risch HA. Perineal talc exposure and risk of ovarian carcinoma. Cancer. 1997; 79:2396–2401. [PubMed: 9191529]

Chen Y, Wu PC, Lang JH, Ge WJ, Hartge P, Brinton LA. Risk factors for epithelial ovarian cancer in Beijing, China. International Journal of Epidemiology. 1992; 21:23–29. [PubMed: 1544753]

Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. American Journal of Epidemiology. 1997; 145:459–465. [see comment][erratum appears in Am J Epidemiol 1998 Aug 15;148(4):410]. [PubMed: 9048520]

Cramer DW, Liberman RF, Titus-Ernstoff L, Welch WR, Greenberg ER, Baron JA, Harlow BL. Genital talc exposure and risk of ovarian cancer. International Journal of Cancer. 1999; 81:351–356.

Cramer DW, Titus-Ernstoff L, McKolanis JR, Welch WR, Vitonis AF, Berkowitz RS, Finn OJ. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2005; 14:1125–1131. [PubMed: 15894662]

Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. Cancer. 1982; 50:372–376. [PubMed: 7083145]

Endocapron S, Renier A, Janson X, Kheuang L, Jaurand MC. Invitro Response of Rat Pleural Mesothelial Cells to Talc Samples in Genotoxicity Assays (Sister Chromatid Exchanges and DNA-Repair). Toxicology in Vitro. 1993; 7:7–14. [PubMed: 20732166]

Ferrer J, Villarino MA, Tura JM, Traveria A, Light RW. Talc preparations used for pleurodesis vary markedly from one preparation to another. Chest. 2001; 119:1901–1905. [PubMed: 11399721]

Gertig DM, Hunter DJ, Cramer DW, Colditz GA, Speizer FE, Willett WC, Hankinson SE. Prospective study of talc use and ovarian cancer. Journal of the National Cancer Institute. 2000; 92:249–252. [PubMed: 10655442]

Globe, B. Boston Globe. Boston: 1982. Study Links Talc Use To Ovarian Cancer.

Glud E, Kjaer SK, Thomsen BL, Hogdall C, Christensen L, Hogdall E, Bock JE, Blaakaer J. Hormone therapy and the impact of estrogen intake on the risk of ovarian cancer. Arch Intern Med. 2004; 164:2253–2259. [PubMed: 15534163]

Godard B, Foulkes WD, Provencher D, Brunet JS, Tonin PN, Mes-Masson AM, Narod SA, Ghadirian P. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. American Journal of Obstetrics & Gynecology. 1998; 179:403–410. [PubMed: 9731846]

Graham J, Graham R. Ovarian cancer and asbestos. Environ Res. 1967; 1:115–128. [PubMed: 5628974]

Green A, Purdie D, Bain C, Siskind V, Russell P, Quinn M, Ward B. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. 1997; 71:948–951.

Gross AJ, Berg PH. A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer. Journal of Exposure Analysis and Environmental Epidemiology. 1995; 5:181–195. [PubMed: 7492905]

Hankinson SE, Hunter DJ, Colditz GA, Willett WC, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE. Tubal ligation, hysterectomy, and risk of ovarian cancer. A prospective study. 1993; 270:2813–2818.

Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. Obstetrics & Gynecology. 1992; 80:19–26. [PubMed: 1603491]

Harlow BL, Weiss NS. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. Am J Epidemiol. 1989; 130:390–394. [PubMed: 2750733]

Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. American Journal of Industrial Medicine. 1996a; 29:435–439. [PubMed: 8732916]

Heller DS, Westhoff C, Gordon RE, Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. American Journal of Obstetrics & Gynecology. 1996b; 174:1507–1510. [PubMed: 9065120]

Henderson WJ, Hamilton TC, Griffiths K. Talc in normal and malignant ovarian tissue. Lancet. 1979; 1:499. [PubMed: 85089]

Henderson WJ, Joslin CA, Turnbull AC, Griffiths K. Talc and carcinoma of the ovary and cervix. J Obstet Gynaecol Br Commonw. 1971; 78:266–272. [PubMed: 5558843]

Honma N, Hiratsuka T, Kozawa E, Watanabe A, Saijo K, Shimizu K. Clinical Aspects of Spontaneous Pneumothorax. Origin and Results of Treatment in 70 Cases. Chiryo. 1963; 45:2169–2174. [PubMed: 14103580]

Huncharek M. The biomedical and epidemiological characteristics of asbestos-related diseases: a review. Yale J Biol Med. 1986; 59:435–451. [PubMed: 3532578]

Huncharek M, Geschwind JF, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. Anticancer Research. 2003; 23:1955–1960. [PubMed: 12820486]

Huncharek M, Muscat JE, Onitilo A, Kupelnick BA. Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: A meta-analysis of nine observational studies. Eur J Cancer Prevention. (in press).

Kasper CS, Chandler PJ Jr. Possible morbidity in women from talc on condoms. Jama. 1995; 273:846–847. [PubMed: 7869551]

Kelly T, Matos G. Historical statistics for mineral and material commodities in the United States. U.S. Geological Survey. 2005; vol. 2005 (ed.

Krause, J.; Ashton, W. United States. National Bureau of Standards. Misidentification of asbestos in talc. In: Gravatt, CC.; LaFleur, PD., editors. Proceedings of a Workshop on Asbestos: Definitions and Measurement Methods : held at the National Bureau of Standards; July 18–20, 1977; Gaithersburg, Maryland. Washington: U.S. Dept. of Commerce, National Bureau of Standards; 1978. p. 339-352.

Krause JB. Mineralogical characterization of cosmetic talc products. J Toxicol Environ Health. 1977; 2:1223–1226. [PubMed: 864791]

Krismann M, Pieper K, Muller KM. Pleural reaction pattern after talc pleurodesis. Pathologe. 1998; 19:214–220. [PubMed: 9648147]

Lange P, Mortensen J, Groth S. Lung function 22–35 years after treatment of idiopathic spontaneous pneumothorax with talc poudrage or simple drainage. Thorax. 1988; 43:559–561. [PubMed: 3212753]

Langseth H, Kjaerheim K. Ovarian cancer and occupational exposure among pulp and paper employees in Norway. Scandinavian Journal of Work, Environment & Health. 2004; 30:356–361.

Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. International Journal of Cancer. 2004; 112:458–464.

Mossman BT, Gee JB. Asbestos-related diseases. N Engl J Med. 1989; 320:1721–1730. [PubMed: 2659987]

Munnell EW. Ovarian carcinoma; predisposing factors, diagnosis and management. Cancer. 1952; 5:1128–1133. [PubMed: 12998019]

Muscat J, Huncharek M, Cramer DW. Talc and anti-MUC1 antibodies. Cancer Epidemiol Biomarkers Prev. 2005; 14:2679. author reply 2680. [PubMed: 16284398]

Muscat JE, Barish M. Epidemiology of talc exposure and ovarian cancer. A critical assessment. 1998; 6:327–335.

Nasreen N, Mohammed KA, Dowling PA, Ward MJ, Galffy G, Antony VB. Talc induces apoptosis in human malignant mesothelioma cells in vitro. Am J Respir Crit Care Med. 2000; 161:595–600. [PubMed: 10673205]

Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. Journal of the National Cancer Institute. 1999; 91:1459–1467. [see comment]. [PubMed: 10469746]

Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, Morgan M, Schlesselman JJ. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology. 2000; 11:111–117. [see comment]. [PubMed: 11021606]

Newhouse ML, Berry G, Skidmore JW. A mortality study of workers manufacturing friction materials with chrysotile asbestos. Ann Occup Hyg. 1982; 26:899–909. [PubMed: 6295251]

Parazzini F, La Vecchia C, Negri E, Moroni S, dal Pino D, Fedele L. Pelvic inflammatory disease and risk of ovarian cancer. Cancer Epidemiol Biomarkers Prev. 1996; 5:667–669. [PubMed: 8824371]

Piccinino LJ, Mosher WD. Trends in contraceptive use in the United States, 1982–1995. Fam Plann Perspect. 1998; 30:4–10. 46. [PubMed: 9494809]

Purdie D, Green A, Bain C, Siskind V, Ward B, Hacker N, Quinn M, Wright G, Russell P, Susil B. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. 1995; 62:678–684.

Risch HA, Howe GR. Pelvic inflammatory disease and the risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev. 1995; 4:447–451. [PubMed: 7549798]

Risch HA, Marrett LD, Howe GR. Parity, contraception, infertility, and the risk of epithelial ovarian cancer. Am J Epidemiol. 1994; 140:585–597. [PubMed: 7942759]

Rohl AN, Langer AM, Selikoff IJ, Tordini A, Klimentidis R, Bowes DR, Skinner DL. Consumer talcums and powders: mineral and chemical characterization. J Toxicol Environ Health. 1976; 2:255–284. [PubMed: 1011287]

Rosenblatt KA, Mathews WA, Daling JR, Voigt LF, Malone K. Characteristics of women who use perineal powders. Obstetrics & Gynecology. 1998; 92:753–756. [PubMed: 9794663]

Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database of Systematic Reviews. 2004 [see comment]. CD002916.

Sjosten AC, Ellis H, Edelstam GA. Retrograde migration of glove powder in the human female genital tract. Hum Reprod. 2004; 19:991–995. [PubMed: 15033954]

Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl Cancer Inst. 1981; 67:965–975. [PubMed: 6946253]

Stanton MF, Laynard M, Tegeris A, Miller E, May M, Kent E. Carcinogenicity of fibrous glass: pleural response in the rat in relation to fiber dimension. J Natl Cancer Inst. 1977; 58:587–603. [PubMed: 839555]

Tzonou A, Polychronopoulou A, Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. International Journal of Cancer. 1993; 55:408–410.

Wagner JC, Berry G, Cooke TJ, Hill RJ, Pooley FD, Skidmore JW. Animal experiments with talc. Inhaled Part. 1975; 4 Pt 2:647–654. [PubMed: 1236243]

Wehner AP. Cosmetic talc should not be listed as a carcinogen: comments on NTP's deliberations to list talc as a carcinogen. Regulatory Toxicology & Pharmacology. 2002; 36:40–50. [PubMed: 12383717]

Whittemore AS, Wu ML, Paffenbarger RS Jr, Sarles DL, Kampert JB, Grosser S, Jung DL, Ballon S, Hendrickson M. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. American Journal of Epidemiology. 1988; 128:1228–1240. [PubMed: 3195564]

Wignall BK, Fox AJ. Mortality of female gas mask assemblers. Br J Ind Med. 1982; 39:34–38. [PubMed: 7066218]

Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstetrics & Gynecology. 1999; 93:372–376. [see comment]. [PubMed: 10074982]

Table 1

Summary of studies with data on latex condom use and ovarian cancer risk

Study	Cases *N* (% exposed)	Controls N (% exposed)	Crude relative risk	95% CI
Chen	112 (35.7%)	224 (41.1)	0.79	.05–1.27
Cook	313 (2.2%)	256 (4.5%)	0.49	0.2–1.17
Cramer	169 (11.2%)	191 (15.7%)	0.68	0.37–1.26
Booth	213 (49.3%)	420 (51.1%)	0.92	0.67–1.29
Hankinson	150 (14%)	NA	0.78	0.49–1.23[a]
Ness	767 (8%)	1367 (9%)	1.0	0.7–1.4
Rosenblatt	72 (48.6%)	43 (51.1%)	0.9	0.42–1.92

Nurses' Cohort data.

[a]The relative risk and 95% confidence interval (CI) are adjusted for age.