Editorial Commentary

Evidence that cosmetic talc is a cause of ovarian cancer

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O'Brien *et al.* (2020) published a meta-analysis of four cohorts of 252,745 women and concluded "there was not a statistically significant association between use of powder in the genital area and incident ovarian cancer (1)." We have published on the many erroneous assumptions that plagued talc-ovarian cancer cohort studies; however, these problems persisted in O'Brien *et al.* (2).

(I) Inadequate understanding of the asbestos content of talc powders.

Contrary to O'Brien *et al.*, neither the U.S government nor the talc industry ever banned the presence of asbestos in "cosmetic" talc (2). In fact, since the 1950s and as recently as October 2019, talc manufacturing companies and the FDA have found asbestos in cosmetic talc products and ores (2). During perineal and other body applications of cosmetic talc, users inhale talc and asbestos (3,4). Inhaled asbestos transmigrates through the lymphatic system to the peritoneum ovary and adjacent tissues (5,6). Exposures during cosmetic talc use are high enough to cause talcosis in some users (7).

(II) Similarities between ovarian cancer and asbestos-caused mesothelioma.

Inhaled asbestos is an established cause of mesothelioma, ovarian and lung cancers (2,8). Peritoneal mesotheliomas and serous ovarian cancer are histologically similar and often difficult to distinguish (9-11). The peritoneum, pleura, ovary and fallopian tubes all originate in the mesoderm and their tumors are "histologically and clinically" similar (2,12,13). Mesothelioma and serous ovarian cancer frequently exhibit p53 chromosomal deletions (11). Asbestos has been shown to induce p53 deletions in vitro (14). Gordon *et al.* (2019) found that cosmetic talc contained asbestos and was "a causative agent in the development of mesotheliomas, lung tumors, gastrointestinal tumors, and ovarian tumors (7)."

(III) Asbestos has been found in ovarian tumor tissue of talc users.

Steffen *et al.* (2020) reported tissue analysis of ovarian tumors removed from ten talc users: asbestos was detected in in tissue samples from eight cases and fibrous talc was detected in all ten cases (4). Similarly, Emory *et al.* (2020) found asbestos in the lymph nodes and ovary of a cosmetic talc user who only had inhalation exposure (15,16). The specific combination of asbestos fiber types, tremolite and anthophyllite, found in tumor tissue is a "fingerprint" that is unique to fiber types present in "cosmetic" talc ores and products (4). Findings "fingerprints" of asbestos found in talc in ovarian cancer tissue is evidence that asbestos exposures from cosmetic talc use are sufficient to cause ovarian cancer.

(IV) Misclassification issues in ovarian cancer-talc epidemiology studies:

(i) Inadequate characterization of exposure.

O'Brien *et al.* only considered perineal exposure in adults (1,5) (*Table 1*). However, most female inhalation exposures occur during diapering and adult upper body use (4). Johnson & Johnson (J&J) estimated that

Table 1 Questions related to use of powder/talc in the genital area in each of the 4 cohorts

Cohort	Question(s)
Nurses' Health Study (1976): 1982 questionnaire	Have you ever commonly used talcum, baby powder or deodorizing powder to:
	a. Apply to perineal (private) area?
	Options: No; Daily; 1–6 times a week; less than once a week
	b. Apply to sanitary napkins?
	Options: No; Yes
Nurses' Health Study II (1989): 2013 questionnaire	Have you ever used talcum, baby or deodorizing powder AT LEAST WEEKLY in the genital/rectal area or on sanitary napkins, tampons, or underwear?
	Options: Never; Less than 1 year; 1 to <10 years; 10–<20 years; 20–<30 years; 30+ years
Sister Study: Baseline Questionnaire	During the ages of 10–13, about how often did you apply talcum powder to a sanitary napkin, underwear, diaphragm, cervical cap, or directly to your vaginal area? (Mark one)
	Options: Did not use; Sometimes; Frequently; Don't Know
	In the past 12 months, how frequently have you applied talcum powder to a sanitary napkin, underwear, diaphragm, cervical cap, or directly to your vaginal area? (Mark one)
	Options: Did not use; Less than once a month; 1–3 times per month; 1–5 times per week; More than 5 times per month
	In the past 12 months, what types of talcum powder have you usually used on a sanitary napkin, underwear, diaphragm, cervical cap, or your vaginal area? (Mark all that apply)
	Options: Did not use; Powder, Spray
Women's Health Initiative: Observational Study Baseline Questionnaire	Have you ever used powder on your private parts (genital areas)?
	Options: No; Yes
	For how many years?
	Options: Less than 1 year; 1–4 years; 5–9 years; 10–19 years; 20 or more years
	Did you ever use a diaphragm (a birth control device that fits over the opening of your womb)?
	Options: No, Yes
	Did you ever use powder on your diaphragm?
	Options: No; Yes
	For how many years did you use powder on your diaphragm?
	Options: Less than 1 year; 1–4 years; 5–9 years; 10–19 years; 20 or more years
	Did you ever use powder on a sanitary napkin or pad?
	Options: No; Yes
	For how many years did you use powder on sanitary pads?
	Options: Less than 1 year; 1–4 years; 5–9 years; 10–19 years; 20 or more years

over 130 million babies born prior to 1992 were diapered with talc and "75% of teen girls and 80% of women use a talc (2,17)." O'Brien *et al.* ignore many other uses that result in inhalation exposure including application to the upper body, sheets and pillows; dry shampoo; and pet flea powders. For example, Glickman *et al.* attributed a statistically significant 11-fold increase in mesothelioma in dogs whose owners used talc

Table 2 O'Brien *et al.* (2020)'s classification of exposures

Cohort	Ever	Frequent	Long-term
Nurses' Health Study (1976): 1982 questionnaire	"Using ever on perineal area (a) or on sanitary napkins (b)"	"Use on perineal area at least once per week."	"Not assessed"
Nurses' Health Study II (1989): 2013 questionnaire	"Using at least weekly for any time period"	"Using at least weekly for any time period"	"Using at least weekly for >20 years"
Sister Study: Baseline Questionnaire	"Use in 12 months prior to baseline or at ages 10–13"	"Use at least once per week (in the last 12 months) or 'frequently' during ages 10–13."	"Perineal use at ages 10–13 and in the last 12 months"
Women's Health Initiative: Observational Study Baseline Questionnaire	"'Yes' to any of 3 'ever use' questions"	"Not assessed"	"Use for 20 or more years on any of 3 'years used' questions"

flea powders (18)." By focusing exclusively on perineal exposure, O'Brien *et al.* randomly misclassified and underestimated talc and asbestos exposure.

(ii) Conflating Cornstarch and Talc.

O'Brien *et al.* (2020) claimed "to evaluate the talc-ovarian cancer association using prospective data (1)." However, three of the four included cohort studies conflated cornstarch and talc powder use (2). For example, the Women's Health Initiative only asked "Have you ever used powder on your private parts (genital areas)?" without specifying the type of powder that was used (*Table 1*). Thus, exposures in O'Brien *et al.* (2020) are seriously misclassified in a way that diminishes associations (2). Such misclassification—the inclusion of un-exposed cases in the exposure group—introduces bias towards the null.

(iii) Misclassification of perineal exposures.

O'Brien *et al.* (2020) claimed to compare "Ever, long-term (20 years), and frequent (1/week) use of powder in the genital area." However, neither the Nurses' Health Studies nor O'Brien 2013 questionnaires asked subjects if they ever used talc (1). For example, the Nurses' Health Study asked their participants "Have you ever *commonly* used talcum, baby powder or deodorizing powder." (See *Table 1*) Furthermore, O'Brien *et al.* (2020)'s criteria for "ever," "frequent" and "long term" talc use are inconsistent. (See *Table 2*) In addition, the underlying studies only evaluated talc exposure at a single point in time. It is likely that talc use changed after it was assessed, as some use was associated with application during menstruation (2).

(V) Inadequate follow-up and latency.

The Nurses' Health Study II began in 1989 but did not collect information on talc use (1). In 2013, O'Brien created a retrospective questionnaire about talc use for the Nurses' Health Study II (1). As a result, O'Brien only analyzed 76 ovarian cases that occurred after the 2013 questionnaire. O'Brien *et al.* (2020)'s analysis of the "updated" Nurses' Health Study II only had, on average, 3.8 years follow-up time even though pre-2013 talc use would have influenced the result if talc exposure caused ovarian cancer (1). For example, O'Brien's analysis omits all of the 287 patients who may have used talc between 1989 and 2013 but were diagnosed with ovarian cancer before the 2013 questionnaire. O'Brien *et al.* (2020)'s overall average follow-up time is 11.2 (3.9–21.0) years (1). The latency for ovarian cancer is from 25 years to "several decades (19,20)."

(VI) Recall Bias as an explanation for the different findings in cohort and case-control studies.

O'Brien *et al.* argued that previous case-control results "may be affected by recall bias." However, recall bias cannot explain the inconsistent association between talc use and different ovarian cancer sub-types. Berge *et al.* (2018), a meta-analysis of case-control and cohort studies, found that the association between talc use and

ovarian cancer varied by histologic type, with no evidence of association for mucinous and clear cell carcinomas (21).” Similarly, Penninkilampi *et al.* (2018) reported that an increased risk of serous and endometrioid, but not mucinous or clear cell subtypes (22).” Recall bias, if it existed, would have operated across all histologic types (21).

(VII) “Nonsignificant” conclusion.

O’Brien *et al.* observed a “nonsignificant” risk increase of (HR, 1.08; 95% CI, 0.99–1.17). This does not represent affirmative evidence that talc is not a cause of ovarian cancer. In fact, the study fails to reject the null hypothesis that there is a 17% increased risk. Furthermore, under any reasonable prior, the posterior probability that that true risk exceeds 1 is greater than 95%. This “nonsignificance” reflects the study’s low power for detecting risk increases, and is unsurprising, as power depends on the number of ovarian cancer cases, not the number of patients enrolled. O’Brien *et al.* reported 2,168 ovarian cancer cases while Taher *et al.* (2019) reported 15,063 ovarian cancer cases from case-control studies (23). Therefore, the number of enrolled patients (252,745 women) does not per se indicate that the cohort meta-analysis was more powered to find a statistical significant result than that found in the case-control studies which have more ovarian cancer cases. Etikan *et al.* (2016) stated “Computationally, both approaches lead to the same result but the case control study has a greater statistical power than cohort studies, which must often wait for a ‘sufficient’ number of disease events to accumulate (24).”

Non-statistically significant results do not establish an absence of risk. A meta-analysis of epidemiological case-control studies reported a relative risk of 1.35 (95% CI, 1.27–1.43) for talc usage and ovarian cancer (22). A meta-analysis of cohort studies found a statistically significant association between talc use and invasive serous type ovarian cancer (OR, 1.25; 95% CI, 1.01–1.55) (22).

(VIII) Applying Hill’s Considerations to the Question of the Relationship between Talc Use and Ovarian Cancer.

In 1965, to rebut tobacco company arguments on the safety of cigarette smoke, Sir Bradford Hill published a set of considerations to be used to access the carcinogenicity of an environmental or occupational exposure (25). These considerations are: strength of association, specificity, temporality, consistency, biological gradient, plausibility, coherence, experimental evidence, and analogy (25).

We apply these considerations to evaluate the question, “Does asbestos and fibrous talc as found in cosmetic talc contribute to the development of ovarian cancer?”

Strength of association

IARC 100c “examined 11 cohort studies that examined the association between asbestos exposure and ovarian cancer in 13 populations, ten with occupational exposure to asbestos and three with community-based or residential exposure (26).” For each of these studies the Standardized Mortality Ratio (SMR) ranged from 1.26 to 5.35. IARC determined a causal link between inhalation of asbestos and ovarian cancer (26). This causal link in turn applies to cosmetic talc which contains asbestos.

A meta-analysis by Camargo *et al.* (2011) reported a pooled rate of 1.77 (95% CI, 1.37–2.28) based on 20 occupational cohort studies (27).” Camargo *et al.* reaffirmed that “Our study supports the IARC conclusion that exposure to asbestos is causally associated with increased risk of ovarian cancer.” Penninkilampi *et al.* (2018) conducted a meta-analysis of 31 ovarian cancer epidemiologic studies that examined the relationship between perineal talc application and ovarian cancer (22). Researchers in the underlying studies Penninkilampi *et al.* (2018) reviewed did not consider inhalation exposure or exposure during diapering and thus suffered from systematic misclassification of exposed and control cases and underestimations of exposure both of which bias the results toward the null (2). Nonetheless Penninkilampi *et al.* (2018) found that any perineal talc use was associated with increased risk of ovarian cancer (OR, 1.31; 95% CI, 1.24–1.39). An association with ever use of talc was found in case-control studies (OR, 1.35; 95% CI, 1.27–1.43), but not cohort studies (OR, 1.06; 95% CI, 0.90–1.25).” Penninkilampi *et al.* (2018) evaluation of cohort studies, “found an association between talc use and invasive serous type ovarian cancer (OR, 1.25; 95% CI, 1.01–1.55). Penninkilampi *et al.* (2018) concluded, “there is a consistent association between perineal talc use and ovarian cancer (22).” Overall the studies show a 30% increase in cases with exposure. This is in the same range of various risk factors that are accepted causes of

cardiovascular disease (28).

Consistency

Studies demonstrate consistency across subjects, location, circumstance and time. Camargo *et al.* (2011) reported only three results included in their meta-analysis had an SMR point estimate less than one (27). Camargo and IARC respectively found that 85% and 93% of studies analyzed revealed an increased risk of ovarian cancer with asbestos exposure (27). Camargo *et al.* reported studies of populations in the UK, Australia, Italy, Germany, Denmark, Finland, Iceland, Norway and Sweden that have found an elevated risk of ovarian cancer in women exposed to asbestos (27). IARC identified 14 studies on asbestos and ovarian cancer and only one (Reid *et al.* 2009) had an SMR below one (29).

Specificity

Specificity is not reliable as a causal factor since many carcinogens cause multiple cancers and non-malignant diseases (26). For example, smoking causes cancer of the lung, larynx, esophagus, mouth, lip, and stomach, as well as heart disease, strokes, Buerger's disease, ulcers and other diseases (30). In this case, inhaled asbestos causes mesothelioma, ovarian cancer, and other types of cancer.

Temporality

Temporality is met in all studies because exposure to talc always preceded the outcome—ovarian cancer (27).

Biologic gradient (dose-response)

Wignall *et al.* found that the "some exposure" group of talc users had a SMR of 2.78 while the "heavy exposure" group had a SMR of 14.81 for asbestos and ovarian cancer (31). Berry found an increasing non-statistically significant increase in ovarian cancer rates comparing "low/moderate" exposure to "severe" exposure (>2 years) (32). Penninkilampi *et al.* (2018) conducted a meta-analysis of 31 ovarian cancer epidemiologic studies that examined the relationship between perineal talc application and ovarian cancer (22). They found a dose response relationship and elevated risk, "Higher use (> than 3,600 lifetime applications had an OR, 1.42; 95% CI, 1.25–1.61 were slightly more associated with ovarian cancer than <3,600 (OR, 1.32; 95% CI, 1.15–1.50)."

Biologic plausibility

It is well established that inhaled asbestos is the main cause of peritoneal mesothelioma in asbestos exposed populations (33-36). Several studies have demonstrated the ability of asbestos and talc to migrate to the ovaries after inhalation. In 1971, Henderson *et al.* reported the incidence of talc and asbestos in a case series of patients with cervical or ovarian cancer (37). They found talc particles in 10/13 ovarian tumors and 12/21 cervical tumors (37). J&J obtained the ovarian tissue from Henderson and sent it to Dr. Langer at Mount Sinai for evaluation. Langer found asbestos and talc in Henderson's ovarian cancer tissue (38). Henderson *et al.* demonstrated that talc migrated to the ovaries from the vagina (39). Heller *et al.* found "significant asbestos fiber burdens" in the ovaries of 9 out of 13 women with household asbestos exposure (6,40,41). Other studies by Werebe *et al.* and Cramer *et al.* confirm the finding of talc and asbestos in ovarian tissue (26,42,43). As noted above Steffen *et al.* (2020) reported tissue analysis of ovarian tumors removed from ten talc users and found tremolite and/or anthophyllite in their ovarian tissue samples in addition to talc (4). Talc was present in tumor tissue in all cases. Talc is the only commercial product that contains both tremolite and anthophyllite. The singular presence of these two asbestos fiber types is a finger print for talc exposure. These cases provide more evidence of the causal link between asbestos, talc, and ovarian cancer and indicate that asbestos is present in consumer talc products at a level sufficient to cause disease.

Serous ovarian cancer and mesothelioma are histologically and clinically similar (44). Mutations are a cause of ovarian cancer, and asbestos induces P53 mutations and 80% of serous ovarian cancers have P53 mutations (14,45-48). The ovary and peritoneum have the same embryologic mesodermal origin (44,49).

Coherence

The data is coherent based on consistency, biologic plausibility and strength of association. The data is not inconsistent with any known biologic models or theories.

Analogy

There are no other known fibers that have been evaluated as possible causes of ovarian cancer. A case-control study of mesothelioma in domestic dogs concluded that there

was an association between the incidence of mesothelioma and asbestos exposure; the source of exposure of the dogs was from the use of talc containing flea powders and/or the owner's asbestos-related occupations (hobbies) (18).

Experiment

In 1967, Graham and Graham published their series of experiments on asbestos and ovarian cancer in animals (50). Graham and Graham injected tremolite into the peritoneum of mice, hamsters, guinea pigs, and rabbits over 18 weeks. Animals were killed in 1-4-week intervals and ovaries were examined upon autopsy. Graham and Graham observed surface abnormalities "reminiscent of changes seen in early ovarian lesions in humans" on the ovaries of 2 of 10 exposed rabbits and 2 of 16 exposed guinea pigs; no ovarian abnormalities were observed among the controls.

There are no other experimental studies directly evaluating the risk of ovarian cancer in animals exposed to asbestos. However, several studies have evaluated the incidence of ovarian cancer in animals exposed to talc, which likely contained asbestos as an accessory mineral. These did not find an increase in ovarian cancer (51,52). Wehner *et al*. (1977) lacked sufficient latency (53).

Conclusions

Based on Hill's considerations, there is sufficient evidence that cosmetic talc products cause or contribute to the development of serous ovarian cancer.

In 1974, J&J told the FDA that, "…if the results of any scientific studies show any question of safety of talc, Johnson & Johnson will not hesitate to take it off the market (2)." Studies like O'Brien *et al.*, which are based on post-hoc hypotheses and mining of flawed data, fail to answer the question of the safety of talc. For those readers who (erroneously) believe statistical significance is a key measure of effect, one analysis in the study supports the inference that talc exposure increases the risk of ovarian cancer. O'Brien *et al*. (2020) reported a statistically significant ovarian cancer risk increase in women who used cosmetic talc with no history of tubal ligation (HR, 1.10; 95% CI, 1.00–1.21) (1). Thus "cosmetic" talc should be avoided, for it has no medical benefit and cornstarch is a safe substitute. We agree with J&J: cosmetic talc should not be sold. On May 19, 2020, J&J stopped selling talc containing baby powder in the United States and Canada.

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