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RESEARCH ARTICLE

Absence of mesothelioma risk maintained in an expanded international cohort of cosmetic talc miners and millers

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ABSTRACT

Objectives: Based on novel information for the Vermont cosmetic talc miner/miller cohort, including a reported case of mesothelioma, we sought to update our prior pooled statistical power analyses of mesothelioma incidence among European cosmetic talc miners/millers. With the inclusion of the Vermont cohort, we expanded our pooled analysis by 17,170 person-years of observation.

Methods: Cosmetic talc miner/miller cohort studies conducted in Italy, Norway, France, Austria, and Vermont were pooled. The expected numbers of mesothelioma cases for each cohort as reported in these studies were used. Our statistical power analysis was based on an *a priori* one-sided significance level of 0.05 and Poisson distribution probabilities.

Results: A total of 130,514 person-years of observation was generated across the five cohorts. One case of mesothelioma was observed (in the Vermont cohort), while approximately 3.34 cases (a mid-value estimate) were expected overall. Thus, we found that the pooled cohorts had 59% and 78% power to detect a 2.5-fold or greater and a 3.0-fold or greater increase in mesothelioma, respectively. The work history characteristics of the one mesothelioma case, which included mention of prior asbestos exposure on the case's death certificate, do not support a causal link with cosmetic talc exposure.

Conclusions: Despite the recent finding of one case of mesothelioma in the Vermont cohort (a case unlikely related to talc exposure), we continue to conclude that the epidemiological evidence from the cosmetic talc miner/miller cohort studies does not support the hypothesis that cosmetic talc exposures are associated with an increased risk of pleural mesothelioma.

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Introduction

It has recently been alleged (Emory et al. 2020; Gordon et al. 2014; Moline et al. 2020) that due to the purported presence of trace levels of asbestos, primarily tremolite and anthophyllite fiber types, the inhalation of products containing cosmetic talc (i.e., relatively pure [>95%], platiform talc), such as adult and baby dusting powders and makeups, is capable of causing mesothelioma. This allegation of mesothelioma causation following exposure to cosmetic talc is largely based on recent case series and reports (Emory et al. 2020; Gordon et al. 2014; Moline et al. 2020) that claimed to have identified more than 100 cases of mesothelioma among consumers of cosmetic talcum powder products who reportedly had no other known asbestos exposures.

While some geological talc deposits may indeed contain other silicates, like the amphibole minerals tremolite and anthophyllite (IARC 2010), the habit of these minerals (i.e., asbestiform versus non-asbestiform) must be described to ascertain the risk of disease. For example, amphibole minerals have occasionally been identified in some cosmetic talc source mines, including those located in Italy, Norway, France, Austria, and Vermont, yet numerous investigators (Lightfoot et al. 1972; Pooley 1976; Rubino et al. 1976, 1979; Boundy et al. 1979; Selevan et al. 1979; Parkes 1982; Wegman et al. 1982; Wergeland et al. 1990; Wild et al. 2002; Coggiola et al. 2003; Pira et al. 2017; Wergeland et al. 2017; Fordyce et al. 2019; Pooley [date unknown]) have concluded that these minerals are non-asbestiform and, subsequently, that these deposits do not contain detectable asbestos. This distinction between asbestiform and non-asbestiform is critical because the non-asbestiform types of these minerals do not impart biological activity and are thus not regulated as 'asbestos,' per se (CPSC 1988; ATS 1990; OSHA 1992; Vu 1993; ATSDR 2001; Addison and McConnell 2008; Gamble and Gibbs 2008; Mossman 2008; Williams et al. 2013; Mossman 2018). On the other hand, it has been demonstrated (ATSDR 2001; Finley et al. 2012; Gaffney et al. 2017) that sufficient and prolonged exposures to asbestiform varieties of these minerals may pose an increased risk of asbestos-related disease. Thus, the term 'asbestos' will be used in this paper to denote the asbestiform type of these minerals capable of possessing biological activity.

Despite substantial evidence finding that cosmetic talc source mines do not contain asbestos, the possibility that cosmetic talcum powder products for consumer use may contain trace amounts of asbestos continues to be hotly

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debated, as analytical issues surrounding the proper identification of the amount, type, and habit of asbestos in talc abound (Cralley et al. 1968; USFDA 1971; Lewin 1972; Snider et al. 1972; Caneer 1973; Weissler 1973; Rohl and Langer 1974; Rohl et al. 1976; Krause 1977; Rohl and Langer 1979; Swanson 1986; Addison and Langer 2000; IARC 2010; Gordon et al. 2014; Anderson et al. 2017; Pierce et al. 2017). Regardless of the potential presence of trace asbestos in cosmetic talc, it has been demonstrated that even if one were to assume up to a 0.1% asbestos content for a cosmetic talcum powder product as a 'worst-case' scenario, potential cumulative asbestos exposures and associated health risk at this level are 'orders of magnitude below upper-bound estimates of cumulative asbestos exposure and risk at ambient levels, which have not been associated with increased incidence of asbestos-related disease' (Burns et al. 2019, p. 2272). The United States Food and Drug Administration (FDA) reached a similar conclusion after performing its own risk assessment in the mid-1980s (Brown 1985; Swanson 1986).

The mortality experience of cosmetic talc miners and millers from around the world provides valuable insight into the potential risk of asbestos-related disease among end-users of cosmetic talc products. These miners and millers are exposed to much greater and more prolonged levels of talc than end-users (Dement et al. 1972; Hildick-Smith 1976; Aylott et al. 1979; Russell et al. 1979; Brown 1985; Swanson 1986; USEPA 1992; Zazenski et al. 1995; Moon et al. 2011; Burns et al. 2019; Rasmussen et al. 2019). Indeed, Rossner et al. (2020) recently concluded that numerous historical average respirable talc dust concentrations measured in Vermont mines and mills, likely including those sites from which the Vermont cohort members were sourced, exceeded occupational exposure limits. Elevated airborne dust measurements have similarly been reported for other cosmetic talc mines, including those located in Italy (Pira et al. 2017), Norway (Wergeland et al. 2017), France (Wild et al. 2002), and Austria (Wild et al. 2002). An increased risk of pneumoconiosis among these cosmetic miners and millers has also been observed, indicating that these workers were indeed exposed to very high levels of mixed dust, including cosmetic talc, silica, among other dusts (Marsh et al. 2019). Therefore, if trace levels of asbestos fibers are truly and consistently present in cosmetic talc at levels sufficient to pose a health risk in end-users, then it would be reasonable to conclude that the cosmetic talc miners and millers are at an even greater risk of developing an asbestos-related disease. However, various international cohort studies of cosmetic talc miners and millers show no increased risk of mesothelioma associated with occupational talc exposures; in fact, up until 2019, no cases of mesothelioma had been reported in any of these cohorts (Rubino et al. 1976, 1979; Selevan et al. 1979; Wergeland et al. 1990; Wild et al. 2002; Coggiola et al. 2003; Pira et al. 2017; Wergeland et al. 2017; Fordyce et al. 2019).

Finley et al. (2017) published the first statistical power calculation of mesothelioma mortality/incidence for the pooled Italian (Rubino et al. 1976, 1979; Coggiola et al. 2003), Norwegian (Wergeland et al. 1990), French (Wild et al. 2002), and Austrian (Wild et al. 2002) cohorts, and determined that 4.0 mesothelioma cases would have been expected following a total of 99,022 person-years of observation. This finding was associated with 67% and 84% statistical power to observe a 2.5-fold or greater and 3.0-fold or greater increase in pleural mesothelioma mortality, respectively. Following the publication of the Finley et al. (2017) analysis, both the Italian (Pira et al. 2017) and Norwegian (Wergeland et al. 2017) cohorts were updated. Marsh et al. (2019) then updated the original statistical power analysis, and determined that 3.0 mesothelioma cases would have been expected following a total of 113,344 person-years of observation. This updated analysis was associated with 62% and 79% power to detect a 2.5-fold or greater and 3.0-fold or greater increased in pleural cancer/mesothelioma, respectively. The discrepancy in the 4.0 vs. 3.0 expected mesotheliomas in the original and updated analyses, respectively, is explained by the background reference rates for mesothelioma used in either study. In the Finley et al. (2017) analysis, these rates were obtained from the available literature, while in the Marsh et al. (2019) updated analysis, expected counts for mesothelioma were reported by the original authors of the underlying cohort studies. We concluded in both of these studies that the epidemiological evidence from the cosmetic talc miner and miller cohort studies does not support the hypothesis that exposure to cosmetic talc is associated with the development of pleural cancer/mesothelioma.

Following the most recent update of our pooled statistical power analysis of mesothelioma mortality/incidence in the cosmetic talc miner and miller cohorts (Marsh et al. 2019), Fordyce et al. (2019) published an update to the Vermont cohort of cosmetic talc miners and millers described originally by Selevan et al. (1979). We chose not to include the Selevan et al. (1979) findings in our earlier power analyses (Finley et al. 2017; Marsh et al. 2019) because the authors did not explicitly report that they assessed mesothelioma as a disease endpoint of interest. Fordyce et al. (2019), on the other hand, applied an expanded set of International Classification of Disease (ICD) codes during their review of death certificates to identify potential mesothelioma deaths among the Vermont cohort. While the authors identified a single case of mesothelioma, the work history characteristics of this case, which included prior asbestos exposure, do not support a causal link with cosmetic talc exposure. Nonetheless, for the purposes of the current study, we have included the Vermont cohort and this single mesothelioma case, and present here an update to our previous power analyses (Finley et al. 2017; Marsh et al. 2019).

Methods

Pooled cohort analysis

In the recent Fordyce et al. (2019) update of the Vermont cohort, the authors did not attempt to calculate the expected number of deaths due to mesothelioma. Rather, the authors estimated that the expected number of mesotheliomas in the Vermont cohort would be approximately equal to the

expected number of pleural cancers (0.60) for the Norwegian cohort (Wergeland et al. 2017), based on the similar sample sizes and follow-up periods of both studies. Subsequently, in a recent letter to the editor, Fordyce et al. (2020) calculated expected number of mesotheliomas based on incidence-based mortality data for the United States from the Surveillance, Epidemiology, and End Results (SEER) 9 database for the period 1975 to 2012. Based on both the minimum and maximum incidence-based age-adjusted mesothelioma death rates for males and a total of 17,170 person-years of observation, the authors calculated a range of 0.17 to 0.34 expected mesotheliomas for the Vermont cohort.

To account for the uncertainties in the expected number of mesothelioma cases associated with the Vermont cohort, we conducted our statistical power analysis using all three estimates (0.17, 0.34, and 0.60) provided by Fordyce et al. (2019, 2020). The expected values of mesothelioma for the Italian, Norwegian, French, and Austrian cohort were calculated and reported by the original study authors (Table 1). These values were used in the current analysis to estimate the total number of expected mesotheliomas in the pooled cohort.

Statistical power analysis

We followed the same methodology for our pooled statistical power analysis as utilized in both Finley et al. (2017) and Marsh et al. (2019) to address the question of whether the pooled cosmetic talc miner and miller cohort studies provided sufficient power to detect a statistically significant elevated risk of mesothelioma among these workers. As we noted previously (Marsh et al. 2019), because a reduced risk of mesothelioma resulting from exposure to cosmetic talc is an implausible event, our power analysis focused on detecting only elevated mesothelioma risks. Thus, we entered into our pooled analysis with the *a priori* alternative hypothesis (H_A) that the relative risk (RR; estimated using standardized mortality or incidence ratios) for mesothelioma among cosmetic talc miners and millers would be greater than that expected in the corresponding general reference populations (i.e., H_A: RR $>$ 1.0), and used a 5% one-sided significance test to test the null hypothesis (H_0) of no excess risk (i.e., H_0: RR $=$ 1.0). Power calculations were based on exact Poisson distribution probabilities as described by Breslow and Day (1987). In a companion paper, we describe the methods and results of a confidence interval function analysis using data from the five pooled cosmetic talc miner and miller cohorts (Marsh and Ierardi, 2020).

Results

Pooled analysis

In the recently updated evaluation of the Vermont cohort, the total number of cohort members was expanded by 35 workers, the total follow-up period by 37 years, and the total length of observation by 9,487 person-years from the original study conducted by Selevan et al. (1979), resulting in a total of 427 workers who contributed a total of 17,170 person-years of observation (Fordyce et al. 2019). Therefore, with the addition of the Vermont cohort, the total observation time for the five pooled cosmetic talc cohort studies is now 130,514 person-years (Table 1).

Upon a thorough review of the death certificates for the Vermont cohort of talc miners and millers, Fordyce et al. (2019) identified one case of mesothelioma, representing the first case of mesothelioma in any of the cohort studies included in our pooled analyses (Finley et al. 2017; Marsh et al. 2019). However, the authors reported that '[t]his worker was employed in the talc industry for less than 5 years and death occurred 30 years following employment, leaving open the possibility of exposure to asbestos in other occupations and/or possible exposure to ionizing radiation. The death certificate explicitly mentioned exposure to asbestos' (Fordyce et al. 2019, p. 922). As such, it is unlikely that this case of mesothelioma was directly related to the worker's employment in the Vermont talc industry.

Total expected counts for mesothelioma across the five pooled cohort studies were 3.17, 3.34, or 3.60, depending on the expected value used as reported by Fordyce et al. (2019, 2020) (Table 2). Based on this range of expected values and the observed value of one mesothelioma, standardized mortality ratios (SMR) of 0.315 (95% CI: 0.016, 1.50), 0.299 (95% CI: 0.015, 1.42), and 0.278 (95% CI: 0.014, 1.32) were calculated for the pooled cohort (Table 1). None of these SMRs was elevated above the null value of 1.00.

Statistical power analysis

For various SMRs of interest, Table 2 shows the statistical power based on the one observed mesothelioma case (Fordyce et al. 2019) and the range of expected numbers of mesothelioma cases for the combined European and Vermont cohorts. Table 2 also shows that the statistical power to detect 1.5- to 3.0-fold elevations in mesothelioma risk were similar for each of the expected number of cases and are generally higher than those reported by Marsh et al. (2019) (based on 3.0 expected mesotheliomas) due to the inclusion of the expected cases from the Vermont cohort (Fordyce et al. 2019). Using the mid-value estimate of 3.34 for the expected number of mesothelioma cases, the combined studies now had 59% and 78% power to detect a 2.5-fold or greater and a 3.0-fold or greater increase in mesothelioma, respectively (Table 2). We note also that the irregular pattern in some power values with increasing SMRs of interest and across the three expected numbers stems from the small number of events and the discrete nature of the Poisson probability distribution as noted previously by Marsh et al. (2019).

Further, with 3.17 expected mesotheliomas, 7 or more mesotheliomas (or an SMR of 7/3.17 = 2.21 or greater) would need to be observed across the pooled cohort studies to reject at the 0.05 significance level the null hypothesis of no association (i.e., SMR $=$ 1.0) between exposure to cosmetic talc and mesothelioma. For both 3.34 and 3.60

Table 1. Most recent cohort studies included in an expanded pooled analysis of pleural cancers/mesotheliomas associated with employment as a cosmetic talc miner or miller.

Study	Employment	Follow-up period	Location	Sample size	ICD version	Person-years	Reference population for expected deaths or incident cases	Observed mesotheliomas	Expected mesotheliomas reported by authors	Observed pleural cancers	Expected pleural cancers reported by authors	Combined expected cancers reported
Pira et al. (2017)	1946 to 1995	1 January 1946 to 31 March 2013	Italy	Miners = 1,166 Millers = 556	9	59,339	Regional and National[a]	0	NA	0	2.0	2.0
Wergeland et al. (2017)	1944 to 1972	1 January 1953 to 31 December 2011	Norway	Miners = 94 Millers = 296	7	15,687	National[b]	0	NA	0	0.6	0.6
Wild et al. (2002)	1945 to 1994	1 January 1945 to 31 December 1996	France	Miners and Millers = 1,070	8 and 9	28,849	Regional and National[c]	0	0.3	NA	NA	0.3
	1972 to 1995	1 January 1973 to 31 December 1995	Austria	Miners and Millers = 542	8 and 9	9,469	Regional[d]	0	0.1	NA	NA	0.1
Fordyce et al. (2019)	1930 to 1983	1 January 1940 to 31 December 2012	Vermont, USA	Miners and Millers = 427	5, 6, 7, 8, 9, and 10	17,170	Regional and National[e]	1	0.34[f]	NA	NA	0.34
Total				4,151		130,514		1	0.74	0	2.6	3.34

[a]Regional rates were used for the period 1970 to 2013; national death rates were used for the period 1950 to 1969. Rates were not available for the period 1946 to 1949, for which 1950 to 1954 national rates were used.
[b]National rates were used, as these were recorded in the same national cancer registry used to identify pleural cancer incident cases.
[c]Local (département de l'Ariège) and national mortality rates were used. Local mortality rates were only available since 1968.
[d]Regional rates of the federal state of Styria were exclusively used.
[e]Both United States national rates and rates for the state of Vermont were used. However, in accordance with confidentiality and privacy restrictions, Fordyce et al. (2019) only reported SMRs using United States national rates.
[f]Based on the mid-value estimate of the expected number of mesotheliomas for the Vermont cohort reported by Fordyce et al. (2019, 2020). The lower- (0.17) and upper-bound (0.60) values of the expected number of mesotheliomas for the Vermont cohort were included in a sensitivity analysis (Table 2). The total number of expected cancers would therefore be 3.17 or 3.60 if either the lower- or upper-bound estimates, respectively, were used in the pooled analysis.
NA: Not applicable

Table 2. Statistical power for pooled cosmetic talc miner/miller cohorts calculated after study completion[a].

Expected number of mesothelioma cases[b]	SMR	95% CI	Minimum detectable relative risk (SMR > 1.0)[c]			
			1.5	2	2.5	3
3.17	0.315	(0.016, 1.50)	0.20	0.45	0.68	0.84
3.34	0.299	(0.015, 1.42)	0.13	0.35	0.59	0.78
3.60	0.278	(0.014, 1.32)	0.18	0.43	0.68	0.84

[a]Based on one observed mesothelioma case from Fordyce et al. (2019).
[b]Based on values provided in Marsh et al. (2019) for European cohorts (3.0) plus those provided by Fordyce et al. (2019) (0.60) and Fordyce et al. (2020) (0.14, 0.34).
[c]Statistical power to detect SMR of interest with one-sided significance level of 0.05.
SMR: Standardized Mortality Ratio
CI: Confidence Interval

expected mesotheliomas, 8 or more mesotheliomas (or SMRs of 8/3.34 = 2.40 or greater, or 8/3.60 = 2.22 or greater) would need to be observed to reject the null hypothesis of no association at $p < 0.05$.

Discussion

The updated findings of our statistical power analysis suggest that the pooled cohort studies had a 59% and 78% chance of resulting in a statistically significant ($p < 0.05$) SMR of 2.5 or 3.0, respectively, using the mid-value estimate of 3.34 expected mesotheliomas. However, we know that based on the identification of one reported case of mesothelioma across the pooled cohorts of cosmetic talc miners and millers, such SMR estimates were not found (Table 2). In fact, none of these SMRs was elevated above the null value of 1.00. This provides further support for our conclusion that exposure to cosmetic talc is not associated with an elevated risk of mesothelioma.

We were unable to update the previous latency analysis we performed for these cohorts (Marsh et al. 2019) due to a lack of adequate information that would allow us to reliably perform such an analysis for the Vermont cohort. However, based on the findings of our prior analysis, we expect that those individuals belonging to the older age groups (i.e., age 50+) in the Vermont cohort would be the primary drivers of the total number of expected mesotheliomas for this cohort. This is because 'mesothelioma rates increase in an exponential fashion with age, being very low and relatively constant up to about age 50 when they begin to increase dramatically and continue to increase throughout life' (Moolgavkar et al. 2009, 2017; Boffetta et al. 2018; Marsh et al. 2019, p. 215).

We note that Fordyce et al. (2019, 2020) reported a range of values (0.17, 0.34, and 0.60) for the expected number of mesothelioma cases associated with the Vermont cohort. Based on United States national and Vermont state-specific age-adjusted background mesothelioma rates as reported by Henley et al. (2013), who also used SEER data to calculate mesothelioma incidence in the United States by state, we calculate that the expected number of mesotheliomas for the Vermont talc cohort would range from approximately 0.14 to 0.35, using 17,170 person-years of observation. We therefore concur with the range provided by Fordyce et al. (2019, 2020) and believe that the use of the mid-value estimate (0.34) for our statistical power analysis represents an appropriate estimate of the true expected number of mesotheliomas for this cohort.

As described in the Marsh et al. (2019) analysis, Lamm and Starr (1990) reported a case of mesothelioma in 'one Vermont talc man' in a published National Institute for Occupational Health and Safety (NIOSH) conference proceeding (Lamm and Starr 1990, p. 1577). Notably, Fordyce et al. (2019) were unable to verify or identify this case after an extensive and thorough review of the death certificates for the Vermont cohort. The authors explained that the mesothelioma death they identified occurred after 1975, and therefore after the follow-up period of the initial Selevan et al. (1979) evaluation, which ended 31 December 1975. Similarly, mortality follow-up in the Lamm and Starr (1990) evaluation was continued through 1975, thereby precluding the mesothelioma case reported by Fordyce et al. (2019) from being the same case of mesothelioma potentially identified by Lamm and Starr (1990). Thus, we believe that both this alleged mesothelioma case in the Vermont cohort, as well as the previously alleged case in the Italian cohort (Mirabelli 2018) have now been sufficiently scrutinized (Pira et al. 2018; Fordyce et al. 2019, 2020) and we maintain that the only reported case of mesothelioma from any of the cosmetic talc miner/miller cohorts investigated herein is the single case reported by Fordyce et al. (2019).

The lack of a significantly increased risk of mesothelioma among cosmetic talc miners and millers from five pooled cohorts is consistent with the fact that these talc mines are free from detectable asbestos (Lightfoot et al. 1972; Pooley 1976; Rubino et al. 1976, 1979; Boundy et al. 1979; Selevan et al. 1979; Parkes 1982; Wegman et al. 1982; Wergeland et al. 1990; Wild et al. 2002; Coggiola et al. 2003; Pira et al. 2017; Wergeland et al. 2017; Fordyce et al. 2019; Pooley [date unknown]). With regard to the Vermont mine specifically, it is interesting to note that Boundy et al. (1979) measured airborne fiber concentrations of approximately 0 to 60 f/cc by phase contrast microscopy (PCM), but ultimately concluded that they did not identify any asbestos among the samples that were analyzed. The authors explained that PCM 'may suffice in an asbestos environment, but the resolution limitations of optical microscopy and the inability to distinguish rolled talc particles and talc "shards" from actual asbestos fibers will allow only a crude determination of the total fiber exposure' (Boundy et al. 1979, p. 377). Thus, further testing must be performed in order to confirm initial analytical findings of detectable

airborne fiber levels measured by PCM in talc environments, such as during the personal use of cosmetic talcum powder products.

Our finding of no association between cosmetic talc exposures and an increased risk of pleural mesothelioma in the cosmetic talc miner and miller cohorts directly contradicts the claimed causal relationship between this specific exposure and disease outcome as reported in prior case series and reports (Emory et al. 2020; Gordon et al. 2014; Moline et al. 2020). These case series and reports, however, are not informative of causation. Rather, they are limited by their lack of a comparison population, which is present in all of the cohort studies described above, resulting in the inability to calculate risk estimates with associated confidence intervals (e.g., SMRs and 95% CIs).

To support their conclusion of causation, the authors (Emory et al. 2020; Gordon et al. 2014; Moline et al. 2020) claimed to have identified anthophyllite, tremolite, and/or chrysotile fibers in lung tissue samples analyzed for a select subset of the cases they described. However, Roggli et al. (2020) recently noted that 'the mere identification of talc or tremolite in lung tissue samples provides no useful information regarding the causation of mesothelioma' and found that in one case of mesothelioma who had cosmetic talc exposure, 'both talc and tremolite were present in concentrations [of lung tissue] within … background range' (Roggli et al. 2020, p. 5, 6). Additionally, amosite was identified in one case evaluated by Emory et al. (2020); the authors did not comment on this finding in their paper and instead reported that '[s]tudies have confirmed that the most common types of asbestos present in cosmetic talc are tremolite, anthophyllite, and chrysotile. Industrial asbestos products used in the United States generally contained chrysotile, amosite, and/or crocidolite, and anthophyllite and tremolite were rarely present' (Emory et al. 2020, p. 2). Moline et al. (2020) further noted that '[t]esting results of talcum powders have failed to show the presence of commercial amphiboles' (Moline et al. 2020, p. 14). The finding of amosite in at least one of these cases indicates that the individual likely experienced exposure to commercial amphiboles that she was not aware of or did not recall, and discredits the assertion that these individuals were only exposed to asbestos through their use of cosmetic talcum powder products. Thus, these limitations effectively render the case series and reports as being incapable of concluding a causal relationship between cosmetic talc use and mesothelioma, and we maintain that no association exists between cosmetic talc exposures and an increased risk of pleural mesothelioma.

Conclusion

In the current pooled cohort analysis, a total of 130,514 person-years of observation was generated across the Italian, Norwegian, French, Austrian, and Vermont cohorts. We found that the five pooled cohorts had 59% and 78% power to detect a 2.5-fold or greater and a 3.0-fold or greater increase in mesothelioma, respectively, when the mid-value estimate of 3.34 for the expected number of mesothelioma cases was used. The power values calculated using the other two estimates of expected number of mesotheliomas (3.17 and 3.60) were slightly higher than the mid-point estimate, and all of the power values generated in the current study were similar to the power values calculated in early iterations of the statistical power analysis (Finley et al. 2017; Marsh et al. 2019). Thus, despite the recent finding of one case of mesothelioma in the Vermont cohort (a case likely unrelated to talc exposure), we continue to conclude that the epidemiological evidence from the cosmetic talc miner and miller cohort studies does not support the hypothesis that cosmetic talc exposures are associated with an increased risk of pleural mesothelioma.

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Disclosure statement

Both of the authors are employed by Cardno ChemRisk, a consulting firm that provides scientific advice to the government, corporations, law firms, and various scientific/professional organizations. GMM is also Professor of Biostatistics and Director and Founder, Center for Occupational Biostatistics and Epidemiology at the University of Pittsburgh, Graduate School of Public Health. This manuscript was prepared and written exclusively by the authors, and no external funding was received for this study. No organizations other than Cardno ChemRisk were aware of the preparation of this manuscript, and no other organizations other than Cardno ChemRisk reviewed any part of this manuscript prior to its submission for publication. Both AMI and GMM have been retained as defense experts in cosmetic talc-related litigation.

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References

Addison J, Langer AM. 2000. Draft comments on the NTP draft report on carcinogens background document for talc asbestiform and non-asbestiform. Yorkshire: John Addison Consultancy.

Addison J, McConnell EE. 2008. A review of carcinogenicity studies of asbestos and non-asbestos tremolite and other amphiboles. Regul Toxicol Pharmacol. 52(1 Suppl):S187–S199.

Anderson EL, Sheehan PJ, Kalmes RM, Griffin JR. 2017. Assessment of health risk from historical use of cosmetic talcum powder. Risk Anal. 37(5):918–929.

[ATS] American Thoracic Society. 1990. Health effects of tremolite. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, June 1990. Am Rev Respirat Dis. 142(6 Pt 1):1453–1458.

[ATSDR] Agency for Toxic Substances and Disease Registry 2001. Toxicological profile for asbestos. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Aylott RI, Byrne GA, Middleton JD, Roberts ME. 1979. Normal use levels of respirable cosmetic talc: Preliminary study. Int J Cosmet Sci. 1(3):177–186.

Boffetta P, Malvezzi M, Pira E, Negri E, La Vecchia C. 2018. International analysis of age-specific mortality rates from mesothelioma on the basis of the International Classification of Diseases, 10th revision. J Glob Oncol. 4:1–15.

Boundy MG, Gold K, Martin K, Jr. Burgess WA, Dement JA. 1979. Occupational exposures to non-asbestiform talc in Vermont. In: Lemen R, Dement JM, editors. Dusts and disease. Park Forest South, IL: Pathotox Publisher Inc.; p. 356–378.

Breslow NE, Day NE. 1987. Statistical methods in cancer research. Volume II–The design and analysis of cohort studies. IARC Sci Publ. (82):1–406. https://pubmed.ncbi.nlm.nih.gov/3329634/

Brown R. 1985. Memo from QRAC (Quantitative Risk Assessment Committee) to W. Gary Flamm, Ph.D. (Director, Office of Toxicological Sciences – Food and Drug Administration), RE: Asbestos in Talc. Dated June 6, 1985.

Burns AM, Barlow CA, Banducci AM, Unice KM, Sahmel J. 2019. Potential airborne asbestos exposure and risk associated with the historical use of cosmetic talcum powder products. Risk Anal. 39(10):2272–2294.

Caneer WT. 1973. Internal Memo from W. T. Caneer (Colorado School of Mines Research Institute) to W. H. Ashton (Colorado School of Mines Research Institute), RE: Meeting with Bowling Green State University Geological Staff. Dated June 8, 1973.

Coggiola M, Bosio D, Pira E, Piolatto PG, La Vecchia C, Negri E, Michelazzi M, Bacaloni A. 2003. An update of a mortality study of talc miners and millers in Italy. Am J Ind Med. 44(1):63–69.

[CPSC] Consumer Product Safety Commission 1988. Briefing package of the CPSC office of the secretary on a petition to ban play sand with non-asbestiform tremolite. Washington, D.C.: U.S. Product Safety Commission.

Cralley LJ, Key MM, Groth DH, Lainhart WS, Ligo RM. 1968. Fibrous and mineral content of cosmetic talcum products. Am Ind Hyg Assoc J. 29(4):350–354.

Dement JM, Shuler PJ, Zumwalde RD. 1972. Preliminary Report: Fiber Exposure During Use of Baby Powders. Cincinnati, OH: Environmental Investigations Branch, Division of Field Studies and Clinical Investigations, National Institute for Occupational Safety and Health.

Emory TS, Maddox JC, Kradin RL. 2020. Malignant mesothelioma following repeated exposures to cosmetic talc: a case series of 75 patients. Am J Ind Med. 63(6):484–489.

Finley BL, Benson SM, Marsh GM. 2017. Cosmetic talc as a risk factor for pleural mesothelioma: A weight of evidence evaluation of the epidemiology. Inhal Tox. 29(4):179–185.

Finley BL, Pierce JS, Phelka AD, Adams RE, Paustenbach DJ, Thuett KA, Barlow CA. 2012. Evaluation of tremolite asbestos exposures associated with the use of commercial products. Crit Rev Toxicol. 42(2):119–146.

Fordyce TA, Leonhard MJ, Mowat FS, Moolgavkar SH. 2019. A 37-year update on mortality patterns in an expanded cohort of Vermont talc miners and millers. J Occup Env Med. 61(11): 916–923.

Fordyce TA, Leonhard MJ, Mowat FS, Moolgavkar SH. 2020. Letter to the Editor: Egilman et al.'s misrepresentation of the Fordyce et al. (2019) Vermont talc miners and millers cohort study update. J Occup Env Med. 62(1):e19–e21.

Gaffney SH, Grespin M, Garnick L, Drechsel DA, Hazan R, Paustenbach DJ, Simmons BD. 2017. Anthophyllite asbestos: state of the science review. J Appl Toxicol. 37(1):38–49.

Gamble JF, Gibbs GW. 2008. An evaluation of the risks of lung cancer and mesothelioma from exposure to amphibole cleavage fragments. Regul Toxicol Pharmacol. 52(1 Suppl):S154–S186.

Gordon RE, Fitzgerald S, Millette J. 2014. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. Int J Occup Environ Health. 20(4):318–332.

Henley SJ, Larson TC, Wu M, Antao VC, Lewis M, Pinheiro GA, Eheman C. 2013. Mesothelioma incidence in 50 states and the District of Columbia, United States, 2003-2008. Int J Occup Environ Health. 19(1):1–10.

Hildick-Smith GY. 1976. The biology of talc. Br J Ind Med. 33(4): 217–229.

[IARC] International Agency for Research on Cancer 2010. IARC monographs on the evaluation of carcinogenic risks to humans Vol. 93. Carbon Black, Titanium Dioxide, and Talc. Lyon, France: International Agency for Research on Cancer.

Krause JB. 1977. Mineralogical characterization of cosmetic talc products. J Toxicol Environ Health. 2(5):1223–1226.

Lamm SH, Starr JA. 1990. Similarities in lung cancer and respiratory disease mortality of Vermont and New York State talc workers. In: NIOSH, editor. Proceedings of the VIIth International Pneumoconioses Conference, August 23-26, 1988, Pittsburgh, Pennsylvania Publication No 90–108, 1990 Nov; (Part II). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health; p. 1576–1581.

Lewin SZ. 1972. Memo from Seymour Z. Lewin (Professor of Chemistry, New York University) to Dr. Alfred Weissler (Acting Director, Division of Colors and Cosmetics Technology, Office of Product Technology, Food and Drug Administration), RE: Lewin's Final Analytical Results on the Mineral Compositions of 102 Examples of Standard, Commercial Products Containing Talc (With Attachment). Dated August 3, 1972.

Lightfoot J, Kingston GA, Pooley FD. 1972. An examination of italian mine samples and Relevant powders. Cardiff, (UK): Cardiff University.

Marsh GM, Ierardi AM. 2020. Confidence interval function analysis to evaluate the risk of mesothelioma among an expanded international cohort of cosmetic talc miners and millers. Regul Toxicol Pharmacol. doi:10.1016/j.yrtph.2020.104696.

Marsh GM, Ierardi AM, Benson SM, Finley BL. 2019. Occupational exposures to cosmetic talc and risk of mesothelioma: An updated pooled cohort and statistical power analysis with consideration of latency period. Inhal Tox. 31(6):213–223.

Mirabelli D. 2018. Letter on: "Mortality of Talc Miners and Millers From Val Chisone, Northern Italy. J Occup Env Med. 60(1):e72.

Moline J, Bevilacqua K, Alexandri M, Gordon RE. 2020. Mesothelioma associated with the use of cosmetic talc. J Occup Env Med. 62(1): 11–17.

Moolgavkar SH, Chang ET, Mezei G, Mowat FS. 2017. Chapter 3, Epidemiology of mesothelioma. In: Testa JR, editor. Asbestos and mesothelioma current cancer research. Cham, Switzerland: Springer; p. 43–72.

Moolgavkar SH, Meza R, Turim J. 2009. Pleural and peritoneal mesotheliomas in SEER: age effects and temporal trends, 1973–2005. Cancer Causes Control. 20(6):935–944.

Moon MC, Park JD, Choi BS, Park SY, Kim DW, Chung YH, Hisanaga N, Yu IJ. 2011. Risk assessment of baby powder exposure through inhalation. Toxicol Res. 27(3):137–141.

Mossman BT. 2008. Assessment of the pathogenic potential of asbestiform vs. nonasbestiform particulates (cleavage fragments) in in vitro (cell or organ culture) models and bioassays. Regul Toxicol Pharmacol. 52(1 Suppl):S200–S203.

Mossman BT. 2018. Mechanistic in vitro studies: what they have told us about carcinogenic properties of elongated mineral particles (EMPs). Tox Appl Pharm. 361:62–67.

[OSHA] Occupational Safety and Health Administration. 1992. 29 CFR Parts 1910 and 1926: occupational exposure to asbestos, tremolite, anthophyllite and actinolite; final rule. Fed Reg. 57(110): 24310–24331.

Parkes WR. 1982. Occupational lung disorders. 2nd ed. Boston: Butterworths.

Pierce JS, Riordan AS, Miller EW, Gaffney SH, Hollins DM. 2017. Evaluation of the presence of asbestos in cosmetic talcum products. Inhal Toxicol. 29(10):443–456.

Pira E, Coggiola M, Ciocan C, Romano C, La Vecchia C, Pelucchi C, Boffetta P. 2017. Mortality of talc miners and millers from Val Chisone, Northern Italy: an updated cohort study. J Occup Environ Med. 59(7):659–664.

Pira E, Coggiola M, Ciocan C, Romano C, La Vecchia C, Pelucchi C, Boffetta P. 2018. Response to letter to the editor on the mortality of talc miners and millers from Val Chisone, Northern Italy. J Occup Env Med. 60(1):e73.

Pooley FD. [date unknown]. Report of the examination of rock sampels from the vermont mine. UK: Department of Mineral Exploitation, Cardiff University.

Pooley FD. 1976. Letter from Dr. F.D. Pooley, Department of Mineral Exploitation, University College, Cardiff, to Dr. R.E. Shapiro, Ph.D., Epidemiology Unit, HFF-108, Department of Health, Education & Welfare, Public Health Service, Food and Drug Administration, Washington, D.C. Dated March 9, 1976. Cardiff: University College.

Rasmussen PE, Levesque C, Niu J, Gardner HD, Nilsson G, Macey K. 2019. Characterization of airborne particles emitted during application of cosmetic talc products. IJERPH. 16(20):3830.

Roggli VL, Carney JM, Sporn TA, Pavlisko EN. 2020. Talc and mesothelioma: mineral fiber analysis of 65 cases with clinicopathological correlation. Ultrastruct Pathol. 44(2):211–218.

Rohl AN, Langer AM. 1974. Identification and quantitation of asbestos in talc. Environ Health Perspect. 9:95–109.

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

Rohl AN, Langer AM. 1979. Fibrous mineral content of consumer talc-containing products. In: Lemen R, Dement JM, editors. Dusts and disease. Park Forest South (IL): Pathotox Publishers; p. 393–403.

Rossner A, Williams PRD, Mellas-Hulett E, Arifur Rahman M. 2020. Analysis of historical worker exposures to respirable dust from talc mining and milling operations in Vermont. Ann Work Expo Health. 64(4):416–429.

Rubino GF, Scansetti G, Piolatto G. 1979. Mortality and morbidity among talc miners and millers in Italy. In: Lemen R, Dement JM, editors. Dusts and disease: proceedings of the conference on occupational exposures to fibrous and particulate dust and their extension into the environment. Park Forest South (IL): Pathotox Publishers; p. 357–363.

Rubino GF, Scansetti G, Piolatto G, Romano CA. 1976. Mortality study of talc miners and millers. J Occup Med. 18:186–193.

Russell RS, Merz RD, Sherman WT, Sivertson JN. 1979. The determination of respirable particles in talcum powder. Food Cosmet Toxicol. 17(2):117–122.

Selevan SG, Dement JM, Wagoner JK, Froines JR. 1979. Mortality patterns among miners and millers of non-asbestiform talc: preliminary report. J Environ Pathol Toxicol. 2(5):273–284.

Snider DW, Pfeiffer DE, Mancuso JJ. 1972. Asbestosform impurities in commerical talcum powders. Compass of Sigma Gamma Epsilon. 49:65–67.

Swanson JW. 1986. Memo from J.W. Swanson (Acting Associate Commissioner for Regulatory Affairs – U.S. Food and Drug Administration) to Mr. Phillippe Douillet, RE: Docket Number 1982P-404, Denying a November 8, 1983, Petition Requesting that Cosmetic Talc be Labeled with an Asbestos Warning Statement (Includes Enclosures/Talc Documents). Dated July 11, 1986.

[USEPA] U.S. Environmental Protection Agency 1992. Health assessment document for talc. EPA-600/8-91/217. Washington, (DC).: Office of Reseach and Development, U.S. Environmental Protection Agency.

[USFDA] U.S. Food and Drug Administration 1971. FDA Meeting Minutes- Asbestos in Cosmetic Talc. August 3, 1971 – Washington, (DC).

Vu VT. 1993. Chapter 19, Regulatory approaches to reduce human health risks associated with exposures to mineral fibers. In: Guthrie Jr. GD, Mossman BT, editors. Health effects of mineral dusts Vol 28. Washington, D.C.: Mineralogical Society of America; p. 545–554.

Wegman DH, Peters JM, Boundy MG, Smith TJ. 1982. Evaluation of respiratory effects in miners and millers exposed to talc free of asbestos and silica. Br J Ind Med. 39(3):233–238.

Weissler A. 1973. Internal Memo from Alfred Weissler Ph.D. (Acting Director- Division of Color Technology, U.S. Food and Drug Administration) to Dr. Robert M. Schaffner (Director – Office of Technology, U.S. Food and Drug Administration), RE: Summary and Comments on Prof. Lewin's Analytical Results for Asbestos in Talc (Enclosures Included – Final Report: X-Ray Powder Diffraction Analyses of Commerical Cosmetic Powders). Dated July 31, 1973.

Wergeland E, Andersen A, Baerheim A. 1990. Morbidity and mortality in talc-exposed workers. Am J Ind Med. 17(4):505–513.

Wergeland E, Gjertsen F, Vos L, Grimsrud TK. 2017. Cause-specific mortality and cancer morbidity in 390 male workers exposed to high purity talc, a six-decade follow-up. Am J Ind Med. 60(9): 821–830.

Wild P, Leodolter K, Refregier M, Schmidt H, Zidek T, Haidinger G. 2002. A cohort mortality and nested case-control study of French and Austrian talc workers. Occup Environ Med. 59(2):98–105.

Williams C, Dell L, Adams R, Rose T, Van Orden D. 2013. State-of-the-science assessment of non-asbestos amphibole exposure: is there a cancer risk? Environ Geochem Health. 35(3):357–377.

Zazenski R, Ashton WH, Briggs D, Chudkowski M, Kelse JW, MacEachern L, McCarthy EF, Nordhauser MA, Roddy MT, Teetsel NM. 1995. Talc: occurrence, characterization, and consumer applications. Regul Toxicol Pharmacol. 21(2):218–229.