UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	)	MDL Docket No. 2738
This Document Relates To All Cases	)	

DEFENDANTS' OPPOSITION TO PLAINTIFFS' STEERING COMMITTEE'S MOTION FOR RECONSIDERATION OF THE COURT'S MARCH 27, 2024 TEXT ORDER ALLOWING A FULL REFILING OF *DAUBERT* MOTIONS

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The PSC seeks to freeze the question of general causation in time, arguing that a *Daubert* ruling issued in 2020 based on expert reports issued in 2018 constitutes law of the case for this entire MDL proceeding. But the law, the science and the record have changed in material respects over the last four years, justifying a fresh look at the reliability of plaintiffs' experts' opinions. Rule 702 has been amended to clarify that fundamental reliability challenges like those at issue here are questions of admissibility, not weight. Moreover, new scientific data have emerged that undercut the reliability of plaintiffs' experts' opinions. This Court appropriately recognized that these circumstances "make a full refiling of *Daubert* motions appropriate" (ECF No. 30260), and the PSC's disagreement with that well-reasoned decision is not a basis for reconsideration.

BACKGROUND

The admissibility of general causation evidence was originally addressed in a ruling issued on April 27, 2020, based on briefing and a scientific record that had been completed in 2019. *See In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Pracs. & Prods. Litig.*, 509 F. Supp. 3d 116 (D.N.J. 2020). Invoking the word "weight" no fewer than 55 times, the *Daubert* decision largely denied defendants' motions, finding that the reliability of plaintiffs' experts' opinions (and, in particular, their application of the "Bradford Hill" methodology) should be decided by jurors on cross-examination. *See, e.g.*, *id.* at 148; *id.* at 167 ("Defendants

may cross-examine the experts on questions of interpretation.").[1] Nonetheless, the ruling recognized that "[b]ecause of talc's alleged carcinogenic properties, studies continue to be conducted by the scientific community" and expressly did not "foreclose the possibility" of revisiting the arguments raised by the parties in light of new data. *Id.* at 129 n.6 ("[I]f such supplemental reports impact my *Daubert* decisions made in this Opinion, I may amend my rulings at a later time.").

Important legal and scientific developments have occurred since the parties initially briefed the question of general causation. Most notably, a pooled study (the largest ever performed on the issue), led by a scientist at the National Institutes of Health, found "no statistically significant association between . . . use of [talcum] powder in the genital area and risk of ovarian cancer."[2] In addition, one of the PSC's

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[1] *See also, e.g.*, *In re Johnson & Johnson*, 509 F. Supp. 3d at 149 ("weaknesses in Dr. Longo's methods, such as" his use of a testing methodology that does not distinguish asbestos particles or asbestiform from cleavage fragments "go to weight rather than to admissibility"); *id.* at 163 ("Defendants' argument with respect to whether the association is 'weak' or 'strong' is one that goes to the weight of the experts' testimony, not the reliability."); *id.* at 166-67 (experts' elevating case-control studies over better quality cohort studies "go[es] to the weight of the experts' testimony"); *id.* at 172 (experts' disregard of inconsistencies between cohort and case-control studies in finding consistency factor satisfied "relate[s] to the weight of their testimony"); *id.* at 175 (the "jury will determine what weight to ascribe to this scientific hypothesis" that talc causes ovarian cancer by inflammation).

[2] O'Brien et al., *Association of Powder Use in the Genital Area with Risk of Ovarian Cancer*, 323(1) JAMA 49, 56 (2020) ("O'Brien 2020") (attached to Cert. of Susan Sharko ("Sharko Cert.") as Ex. 1). This study was published in January 2020, prior to the issuance of the original Rule 702 opinion, but was not addressed

key epidemiologists, Dr. Anne McTiernan, was excluded by another federal court for her use of "result-driven reasoning," *In re Zantac (Ranitidine) Prods. Liab. Litig.*, 644 F. Supp. 3d 1075, 1242 (S.D. Fla. 2022), based on a methodology that she recently admitted was the same one she employed in this litigation. And most recently, on December 1, 2023, three major changes to Rule 702 took effect that: (1) codify the preponderance-of-the-evidence standard into the black letter of Rule 702; (2) specify that "the court"—not a jury—must decide that all four of the substantive criteria for expert admissibility have been met; and (3) clarify that a court's gatekeeping obligation requires it to ensure that all expert testimony satisfies Rule 702's four requirements, especially that the expert's "principles and methods" are reliably applied to the case-specific facts. *See* Fed. R. Evid. 702. The impetus for these changes was the consensus that "in a fair number of cases, the courts . . . essentially treat[] these questions as ones of weight rather than admissibility." *See* Report of the Advisory Committee on Evidence Rules, at 6 (May 15, 2022).

Beyond these legal and scientific developments, plaintiffs have designated two new epidemiologists who were never previously disclosed in this MDL proceeding: Dr. Michele Cote and Dr. Bernard Harlow.[3] (*See* Expert Rep. of

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in the parties' previous expert briefing, which was generally complete by June 2019. (*See generally, e.g.*, ECF Nos. 10029-10043.)

[3] A third epidemiologist, Dr. Kenneth Rothman, was also newly disclosed, but has now been withdrawn.

Michele L. Cote, Nov. 15, 2023; Expert Rep. of Bernard L. Harlow and Kenneth J. Rothman, Nov. 15, 2023.) In addition, several of plaintiffs' original epidemiologists have served new reports that greatly expand their initial opinions regarding Bradford Hill, statistical significance and other scientific concepts. Plaintiffs' "asbestos" expert—Dr. William Longo—now purports to perform asbestos exposure analyses for the bellwether plaintiffs and offers a Polarized Light Microscopy analysis of J&J talc samples using a method developed by the Colorado School of Mines "in the early 1970s" that had not been previously disclosed to defendants.[4] Both the new and previously disclosed experts all purport to address recent literature published after the prior briefing on general causation, including, but not limited to, the O'Brien 2020 study previously discussed.

While the Court denied defendants' motion to strike these new opinions, it reasoned that defendants "could dispute the experts and expert opinions proffered by Plaintiffs through their 2023 Expert Disclosures in future *Daubert* and/or summary judgment motions." (ECF No. 29023, at 10.) On March 27, the Court issued a Text Order, explaining that it "is persuaded that the recent changes to

[4] Beyond the experts identified in text, the PSC also disclosed a new marketing expert, Dr. George Newman, with supposed expertise in "branding and consumer behavior." (Expert Rep. of George E. Newman at 3, Nov. 15, 2023.) In addition, the PSC served a significantly expanded report from Dr. David Kessler, plaintiffs' "regulatory" expert. Neither witness's opinions were addressed in the prior *Daubert* ruling, nor were any opinions regarding specific causation.

Federal Rule of Evidence 702, the emergence of new relevant science, and the language of Chief Judge Wolfson's previous *Daubert* Opinion make a full refiling of *Daubert* motions appropriate." (ECF No. 30260.)

ARGUMENT

As this Court has repeatedly recognized, "[r]econsideration under Local Civil Rule 7.1 is 'an extraordinary remedy' that is rarely granted." *Def. Distributed v. Platkin*, No. 21-9867 (MAS) (TJB), 2023 U.S. Dist. LEXIS 103651, at *4 (D.N.J. June 14, 2023) (Shipp, J.) (citation omitted); *see also Jannarone v. Sunpower Corp.*, No. 18-9612 (MAS) (TJB), 2020 U.S. Dist. LEXIS 76380, at *4, *10 (D.N.J. Apr. 30, 2020) (Shipp, J.) (same). "To succeed on a motion for reconsideration, a movant must show at least one of three factors: '(1) an intervening change in the controlling law; (2) the availability of new evidence that was not available when the court granted [or denied] the motion [at issue]; or (3) the need to correct a clear error of law or fact or to prevent manifest injustice.'" *Def. Distributed*, 2023 U.S. Dist. LEXIS 103651, at *4 (quoting *Max's Seafood Café ex rel. Lou-Ann, Inc. v. Quinteros*, 176 F.3d 669, 677 (3d Cir. 1999)).

The PSC argues that reconsideration of the Court's recent Text Order authorizing plenary *Daubert* briefing is warranted under the third prong both because it "is in clear error" and because it "[w]ould [b]e [m]anifestly [u]njust" for the parties to "re-litigat[e] *Daubert*." (Pls.' Mem. at 1, 7.) As explained below, the

PSC does not come close to satisfying the stringent requirements of "clear error" or "manifest injustice" for reconsidering the Court's order.

I. THE PSC HAS NOT ESTABLISHED ANY CLEAR ERROR OF LAW OR FACT CAPABLE OF JUSTIFYING RECONSIDERATION.

"A court commits clear error of law only if the record cannot support the findings that led to the ruling." *Jannarone*, 2020 U.S. Dist. LEXIS 76380, at *4-5 (citation omitted). Moreover, reconsideration is only proper "when '***dispositive factual matters or controlling decisions of law***' were presented to the court but were overlooked.'" *Def. Distributed*, 2023 U.S. Dist. LEXIS 103651, at *4 (citations omitted) (emphasis added); *see also Jannarone*, 2020 U.S. Dist. LEXIS 76380, at *10 ("Because the Court's decision is supported by precedent, [d]efendant fails to show that the Court's decision was a clear error of law.").

The PSC does not even attempt to identify any "dispositive factual matters or controlling decisions of law" that the Court overlooked. Instead, the gist of the PSC's position is that the original *Daubert* ruling "is the law of the case." (Pls.' Mem. at 1, 9.) This position, not the Court's ruling, misinterprets the law. "Interlocutory orders . . . remain open to trial court reconsideration, and do not constitute the law of the case." *United States ex rel. Petratos v. Genentech Inc.*, 855 F.3d 481, 493 (3d Cir. 2017) (citation omitted); *see also Rimbert v. Eli Lilly & Co.*, 647 F.3d 1247, 1251 (10th Cir. 2011) (declining to apply law of the case to *Daubert* rulings) (cited with approval by Third Circuit in *Petratos*, 855 F.3d. at 493).

But even assuming law of the case did apply, the PSC's own authority recognizes that the "doctrine does ***not*** limit the power of trial judges to reconsider their prior decisions" as long as they "explain on the record why [they are] doing so." (Pls.' Mem. at 6, 10 (emphasis added) (quoting *Pub. Int. Rsch. Grp. of N.J., Inc. v. Magnesium Elektron, Inc.*, 123 F.3d 111, 117 (3d Cir. 1997) (expressly approving of lower court's decision to "reconsider" question of standing based on "new evidence")).) That is exactly what this Court did, explaining "that the recent changes to Federal Rule of Evidence 702, the emergence of new relevant science, and the language of Chief Judge Wolfson's previous *Daubert* Opinion make a full refiling of *Daubert* motions appropriate." (ECF No. 30260.) While the PSC has a different view, "mere disagreement with this Court's decision provides no valid basis for reconsideration." *Cvjeticanin v. United States*, No. 19-549 (MAS), 2022 U.S. Dist. LEXIS 157717, at *1-2, *4 (D.N.J. Aug. 30, 2022) (Shipp, J.) (denying motion for reconsideration). For all of these reasons, discussed further below, the PSC has not demonstrated that the ruling was in "clear error."

A. The Recent Amendments To Rule 702 Support The Court's Decision.

Quoting statements from the Advisory Committee notes on Rule 702, the PSC argues that Rule 702 was merely amended "to ***clarify and emphasize*** that . . . the proponent" of expert testimony must prove its admissibility by a preponderance-of-the-evidence, which the PSC claims has long been "an undeniable part of Rule 702."

(Pls.' Mem. at 7 (quoting Fed. R. Evid. 702 advisory committee's note to 2023 amendment).) The PSC also insists that the Rule 702 ruling "applied a preponderance standard" (*id.* at 11), but the phrase "preponderance of the evidence," appears just three times in the ruling, each time as part of a case parenthetical.[5] And plaintiffs' proffered opinions on biological plausibility (i.e., that talc causes ovarian cancer by inflammation) were deemed admissible because "Defendants ha[d] not introduced any evidence that this theory has been disproven as a matter of science," *In re Johnson & Johnson*, 509 F. Supp. 3d at 175, reflecting a "revers[al] [of] the burden of proof" that is precisely the opposite of what Rule 702 demands. *See In re Onglyza (Saxagliptin) & Kombiglyze (Saxagliptin & Metformin) Prods. Liab. Litig.*, 93 F.4th 339, 345 (6th Cir. 2024) (excluding opinion that the literature "should be interpreted as cause-and-effect unless there is compelling evidence to prove otherwise") (citation omitted).

In any event, the PSC ignores the other key aspects of the recent amendments—namely, that the "court" (rather than a jury) must decide that all four of the substantive criteria for admissibility are satisfied, including that the "expert's opinion reflects a reliable application of the principles and methods to the facts of

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[5] *See In re Johnson & Johnson*, 509 F. Supp. 3d at 148 (quoting *Crowley v. Chait*, 322 F. Supp. 2d 530, 537 (D.N.J. 2004)); *id.* at 187 (quoting *In re Processed Egg Prods. Antitrust Litig.*, 81 F. Supp. 3d 412, 416 (E.D. Pa. 2015)); *id.* at 164 n.37 (quoting *Pick v. Am. Med. Sys., Inc.*, 958 F. Supp. 1151, 1160 (E.D. La. 1997)).

the case." Fed. R. Evid. 702(d). As multiple courts construing these changes both before and after they took effect have explained, "Rule 702's recent amendments were drafted to correct some court decisions incorrectly holding 'that the critical questions of the sufficiency of an expert's basis, and the application of the expert's methodology, are questions of weight and not admissibility.'" *In re Onglyza*, 93 F.4th at 348 n.7 (quoting Fed. R. Evid. 702 advisory committee's note to 2023 amendment); *accord In re Paraquat Prods. Liab. Litig.*, MDL No. 3004, 2024 WL 1659687, at *4 n.9 (S.D. Ill. Apr. 17, 2024) ("The Advisory Committee thus appears to have found that courts had erroneously admitted unreliable expert testimony based on the assumption that the jury would properly judge reliability by assigning appropriate weight to an expert's opinion.").[6]

Defendants respectfully submit that the prior judge's *Daubert* ruling was one

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[6] *See also, e.g.*, *Sardis v. Overhead Door Corp.*, 10 F.4th 268, 279, 284 (4th Cir. 2021) (treating fundamental reliability challenges as "generally questions of weight and not admissibility" is erroneous and constitutes an "abdicat[ion] [of a court's] critical gatekeeping role to the jury") (quoting Advisory Comm. on Evidence Rules, Agenda for Committee Meeting 105, 107 (Apr. 30, 2021)); *James v. Thompson/Ctr. Arms, Inc.*, No. 3:22-cv-01781-JGC, 2024 U.S. Dist. LEXIS 55675, at *6 (N.D. Ohio Mar. 28, 2024) ("This is not merely a question of weight, to be decided by a jury. The expert's proponent bears the burden of demonstrating to *me*, by a preponderance of the evidence, 'the sufficiency of an expert's basis[] and the application of the expert's methodology.'") (quoting Fed. R. Evid. 702 advisory committee's note to 2023 amendment); *In re Acetaminophen - ASD-ADHD Prods. Liab. Litig.*, MDL No. 3043, 2023 U.S. Dist. LEXIS 224899, at *49-50 & n.27, --- F. Supp. 3d ---- (S.D.N.Y. Dec. 18, 2023) ("[O]ne purpose of the amendment was to emphasize that '[j]udicial gatekeeping is essential . . . .'") (citation omitted).

of those incorrect holdings. For example, the decision states that "it is not for the Court to decide" whether plaintiffs' experts properly applied the Bradford Hill considerations such as strength, because doing so "would unnecessarily broaden the scope of this Court's role as a gatekeeper." *In re Johnson & Johnson*, 509 F. Supp. 3d at 164; *see also id* at 171-72 (defendants' criticisms of plaintiffs' experts' approach to consistency factor of Bradford Hill reflected "a battle of the experts" and "relate[s] to the weight of their testimony"); *id.* at 175 ("jury will determine what weight to ascribe to th[e] scientific hypothesis" that talc causes ovarian cancer by inflammation). Courts applying the recently amended Rule 702 have recognized that this is not a proper approach because simply espousing a methodology (i.e., Bradford Hill) does not suffice to withstand a Rule 702/*Daubert* challenge. Rather, "***district courts*** must ensure that '[t]he specific way an expert conducts such an analysis [is] reliable.'" *In re Acetaminophen*, 2023 U.S. Dist. LEXIS 224899, at *56 (emphasis added) (citation omitted) (excluding experts who engaged in similarly unreliable Bradford Hill causation analyses). Accordingly, the caselaw addressing amended Rule 702 makes clear that the kinds of reliability challenges raised by defendants with respect to plaintiffs' general causation experts are admissibility questions for the Court rather than issues of weight to be sorted out by jurors after cross-examination.

B. New Scientific Evidence Independently Supports The Court's Decision.

Finally, scientific advances since 2020 also support the Court's decision to have plenary *Daubert* briefing. *See, e.g.*, *In re Viagra Prods. Liab. Litig.*, 658 F. Supp. 2d 936, 941-42, 946 (D. Minn. 2009) (vacating prior *Daubert* ruling after "a number of errors in the McGwin Study" relied upon by a general causation expert were discovered); *Bean-Sasser v. Sec'y of Health & Hum. Servs.*, 127 Fed. Cl. 161, 167 (2016) ("As medicine and science continue to advance, so does our understanding about the causes of diseases . . . . When the evidence presented differs [from a prior case], a different result is also plausible."). Even the ruling the PSC claims is law of the case expressly acknowledges that "[b]ecause of talc's alleged carcinogenic properties, studies continue to be conducted by the scientific community" and that the Court "may amend [its] rulings at a later time" based upon new data. *In re Johnson & Johnson*, 509 F. Supp. 3d at 129 n.6.

Over the last several years, additional scientific evidence published by preeminent epidemiologists, including from the National Cancer Institute and the National Institute of Environmental Health Sciences, has further undermined the reliability of plaintiffs' evidence of general causation. Most notably, a recent pooled cohort epidemiological study—the largest epidemiological study ever performed on the issue—found "no statistically significant association between . . . use of [talcum] powder in the genital area and risk of ovarian cancer" in general or for any specific

histological subtype.[7] And a review paper by top government scientists analyzed all the evidence to date and found that "[g]iven the inability to attribute a clear causal factor to the observed associations, the lack of a good experimental model, the lack of a specific biomarker for powder-related carcinogenesis, and the inability to rule out confounding by indication, ***it is difficult to conclude that the observed associations are causal***."[8]

The PSC ignores the latter paper and focuses on one weak finding for one subgroup in the pooled cohort study: women with patent reproductive tracts (HR=1.13, 95% CI 1.01-1.26). The study's authors warned against exactly this interpretation of their data, explaining that the subgroup estimates were prone to false positives and "should be interpreted as exploratory" at best.[9] An editorial accompanying the article was even more explicit that these subgroup findings "should not be selectively highlighted by the statistically unsophisticated reader as evidence of a relationship" between talc and cancer.[10]

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7 O'Brien 2020 at 56.

8 Wentzensen & O'Brien, *Talc, body powder, and ovarian cancer: A summary of the epidemiologic evidence*, 163(1) Gynecol. Oncol. 199, 207 (2021) (emphasis added) (Sharko Cert. Ex. 2); *see also id.* ("Furthermore, given the widespread use of powders and the rarity of ovarian cancer, the case for public health relevance is limited.").

9 O'Brien 2020 at 52.

10 Gossett & del Carmen, *Use of powder in the genital area & Ovarian Cancer Risk*, 323(1) JAMA 29, 30 (2020) (Sharko Cert. Ex. 3).

In any event, the question at this point is not whether the PSC or plaintiffs' experts might ultimately offer a reliable explanation that accounts for the 2020 data. Instead, it is whether the Court should exercise its own judgment based on complete briefing and discovery. The new findings from the largest epidemiological study to date clearly demonstrate that it should. Accordingly, intervening scientific data independently support the Court's decision to permit new *Daubert* briefing on the question of general causation.

II. PROCEEDING WITH NEW *DAUBERT* BRIEFING WOULD NOT RESULT IN MANIFEST INJUSTICE.

The PSC separately argues that it would be "manifestly unjust to require the parties to once again expend substantial time and resources fully re-litigating *Daubert*." (Pls.' Mem. at 7.) Defendants respectfully submit that the opposite is true. In order to "establish manifest injustice, a moving party . . . must show that the . . . Court committed a 'direct, obvious, [or] observable error' and one that is of at least some importance to the larger proceedings.'" *Trs. of B.A.C. Loc. 4 Pension Fund v. Demza Masonry, LLC*, No. 18-17302 (MAS), 2021 U.S. Dist. LEXIS 148298, at *5 (D.N.J. Aug. 6, 2021) (Shipp, J.) (quoting *In re Energy Future Holdings Corp.*, 904 F.3d 298, 312 (3d Cir. 2018)); *see also Shnewer v. United States*, No. 13-3769 (RBK), 2016 U.S. Dist. LEXIS 109830, at *20-21 (D.N.J. Aug. 18, 2016) ("[R]econsideration based on manifest injustice requires that the error be apparent to the point of being indisputable."). As previously discussed, the PSC has

not established any error in the Court's decision, foreclosing this basis for reconsideration.

The PSC's claim of manifest injustice is particularly meritless given its strategic choice to both serve significantly expanded reports from plaintiffs' general causation experts and designate certain new experts altogether—all of whom purport to address the new scientific data that the PSC seeks to dismiss as irrelevant. Defendants have a fundamental right to challenge these new opinions and the experts' treatment of the new scientific data discussed in their reports. *See In re Acetaminophen*, 2023 U.S. Dist. LEXIS 224899, at *55-56 ("[E]ach application [of Bradford Hill] is distinct and should be analyzed for reliability.") (citation omitted). In short, the Court's decision to permit the refiling of *Daubert* briefs would prevent manifest injustice, not cause it.

CONCLUSION

For the foregoing reasons, the Court should deny the PSC's motion for reconsideration.

Dated: April 22, 2024

Respectfully submitted,

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	MDL Docket No. 2738
This Document Relates To All Cases	

CERTIFICATION OF SUSAN SHARKO, ESQ.

SUSAN SHARKO, ESQ., being of full age, certifies as follows:

I am a Partner at Faegre Drinker Biddle & Reath LLP, attorneys for LLT Management, LLC and Johnson & Johnson (together, "Defendants"). I make this Certification based on personal knowledge and in support of Defendants' Opposition to Plaintiffs' Steering Committee's Motion for Reconsideration of the Court's March 27, 2024 Text Order Allowing a Full Refiling of *Daubert* Motions.

1. Attached hereto as Exhibit 1 is a true and correct copy of O'Brien et al., *Association of Powder Use in the Genital Area with Risk of Ovarian Cancer*, 323(1) JAMA 49 (2020).

2. Attached hereto as Exhibit 2 is a true and correct copy of Wentzensen & O'Brien, *Talc, body powder, and ovarian cancer: A summary of the epidemiologic evidence*, 163(1) Gynecol. Oncol. 199 (2021).

3. Attached hereto as Exhibit 3 is a true and correct copy of Gossett & del Carmen, *Use of powder in the genital area & Ovarian Cancer Risk*, 323(1) JAMA 29 (2020).

Dated: April 22, 2024

By: /s/ *Susan M. Sharko*
Susan M. Sharko

EXHIBIT 1

JAMA | Original Investigation

Association of Powder Use in the Genital Area With Risk of Ovarian Cancer

Katie M. O'Brien, PhD; Shelley S. Tworoger, PhD; Holly R. Harris, ScD; Garnet L. Anderson, PhD; Clarice R. Weinberg, PhD; Britton Trabert, PhD; Andrew M. Kaunitz, MD; Aimee A. D'Aloisio, PhD; Dale P. Sandler, PhD; Nicolas Wentzensen, MD, PhD

IMPORTANCE The relationship between use of powder in the genital area and ovarian cancer is not established. Positive associations reported in case-control studies have not been confirmed in cohort studies.

OBJECTIVE To estimate the association between use of powder in the genital area and ovarian cancer using prospective observational data.

DESIGN, SETTING, AND PARTICIPANTS Data were pooled from 4 large, US-based cohorts: Nurses' Health Study (enrollment 1976; follow-up 1982-2016; n = 81 869), Nurses' Health Study II (enrollment 1989; follow-up 2013-2017; n = 61 261), Sister Study (enrollment 2003-2009; follow-up 2003-2017; n = 40 647), and Women's Health Initiative Observational Study (enrollment 1993-1998; follow-up 1993-2017; n = 73 267).

EXPOSURES Ever, long-term (≥20 years), and frequent (≥1/week) use of powder in the genital area.

MAIN OUTCOMES AND MEASURES The primary analysis examined the association between ever use of powder in the genital area and self-reported incident ovarian cancer. Covariate-adjusted hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards models.

RESULTS The pooled sample included 252 745 women (median age at baseline, 57 years) with 38% self-reporting use of powder in the genital area. Ten percent reported long-term use, and 22% reported frequent use. During a median of 11.2 years of follow-up (3.8 million person-years at risk), 2168 women developed ovarian cancer (58 cases/100 000 person-years). Ovarian cancer incidence was 61 cases/100 000 person-years among ever users and 55 cases/100 000 person-years among never users (estimated risk difference at age 70 years, 0.09% [95% CI, −0.02% to 0.19%]; estimated HR, 1.08 [95% CI, 0.99 to 1.17]). The estimated HR for frequent vs never use was 1.09 (95% CI, 0.97 to 1.23) and for long-term vs never use, the HR was 1.01 (95% CI, 0.82 to 1.25). Subgroup analyses were conducted for 10 variables; the tests for heterogeneity were not statistically significant for any of these comparisons. While the estimated HR for the association between ever use of powder in the genital area and ovarian cancer risk among women with a patent reproductive tract was 1.13 (95% CI, 1.01 to 1.26), the *P* value for interaction comparing women with vs without patent reproductive tracts was .15.

CONCLUSIONS AND RELEVANCE In this analysis of pooled data from women in 4 US cohorts, there was not a statistically significant association between use of powder in the genital area and incident ovarian cancer. However, the study may have been underpowered to identify a small increase in risk.

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Supplemental content

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JAMA. 2020;323(1):49-59. doi:10.1001/jama.2019.20079

Some women apply powder to their genitals, either through direct application or on underwear, sanitary napkins, diaphragms or tampons. Most powder products include some mineral talc.[1] Talc was first investigated as a carcinogen based on its relationship to asbestos, which has known carcinogenic effects[2] and may be mined in the same locations. However, all US-based manufacturers of cosmetic talc agreed to ban asbestos in 1976,[3] and the International Agency for Research on Cancer has since concluded there is only "possible" evidence that perineal use of talc-based body powder may be carcinogenic.[1]

This classification was largely based on evidence from observational studies. Case-control studies have reported positive associations between ever use of powder in the genital area and ovarian cancer, with an estimated odds ratio of 1.24 in a pooled analysis[4] and 1.31 in a meta-analysis.[5] However, these findings may be affected by recall bias,[6,7] and a recent surge in talc-related lawsuits and media coverage[8,9] has increased this possibility. Thus, it is crucial to evaluate the talc-ovarian cancer association using prospective data.

To date, 3 large cohort studies have assessed the association between use of powder in the genital area and ovarian cancer risk, with inconsistent results.[10-12] However, ovarian cancer is a rare disease (1.3% lifetime risk in the United States),[13] and individual cohort studies are not sufficiently powered to detect modest associations, particularly if restricted to susceptible subgroups, such as women with patent reproductive tracts (ie, having an intact uterus and no tubal ligation).

To better examine the association between use of powder in the genital area and risk of ovarian cancer, 4 large US cohorts that collected the necessary information were identified: the Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), Sister Study (SIS), and Women's Health Initiative Observational Study (WHI-OS). While associations between genital use of powder and ovarian cancer risk have been reported for 3 of these (NHS, WHI-OS, and SIS),[10-12] the pooled results reported here incorporate updated data, including additional cases and longer follow-up.

Key Points

Question Is use of powder in the genital area associated with the risk of developing ovarian cancer?

Findings In this analysis that pooled data from 4 cohorts with a total of 252 745 women, the hazard ratio for the association between self-reported ever use vs never use of powder in the genital area and incident ovarian cancer was 1.08 (95% CI, 0.99-1.17).

Meaning Among women from 4 prospective cohorts, there was not a statistically significant association between use of powder in the genital area and ovarian cancer, but the study may have been underpowered to identify a small increase in risk.

Methods

Study Sample

The study designs of these 4 US-based cohorts have been described in detail elsewhere.[14-16] Briefly, the NHS (n = 121 700) enrolled registered nurses living in the United States in 1976, and the NHSII (n = 116 429) did the same in 1989. The study protocols were approved by the institutional review boards of the Brigham and Women's Hospital, the Harvard T.H. Chan School of Public Health, and those of participating registries, as required. All participants provided written, informed consent. Although the initial questionnaires did not ask about genital use of powder, participants were queried about powder use on the 1982 NHS and 2013 NHSII questionnaires. We only included follow-up time after the questionnaire about use of powder in the genital area was administered and will refer to the questionnaire that assessed powder use as baseline to maintain consistent language across all 4 studies.

Genital use of powder was assessed at enrollment for SIS between 2003 and 2009 (n = 50 884) and for WHI-OS between 1993 and 1998 (n = 93 676). Women were eligible for SIS if they had a sister previously diagnosed with breast cancer but had no personal diagnosis of breast cancer at enrollment. Eligible participants in WHI-OS were postmenopausal women who resided near one of 40 clinical centers. Both studies were approved by the relevant institutional review boards and all participants provided written, informed consent.

Exposure Assessment

The cohorts differed in how they asked participants about use of powder in the genital area (eAppendix in the Supplement). NHS participants were asked whether they "ever commonly used talcum, baby powder or deodorizing powder" on their "perineal (private) area" (no, <1/week, 1-6 times/week, daily) or on sanitary napkins (yes/no). The NHSII questionnaire asked women to report use only if it occurred at least weekly in the "genital/rectal area or on sanitary napkins, tampons, or underwear" and if so, for how long (<1 year, 1-<10 years, 10-<20 years, 20-<30 years, 30+ years). In SIS, the question specifically focused on use of talcum powder and application to "a sanitary napkin, underwear, diaphragm, or cervical cap, or directly to the vaginal area" in the last year or at the ages of 10 to 13 years. Participants were queried about their frequency of use in the year prior to enrollment (never, <1/mo, 1-3 times/mo, 1-5 times/week, >5 times/week), as well as use during the ages 10-13 (did not use, sometimes, frequently). Women in WHI-OS were asked if they had ever used powder on their "private parts (genital areas)" (yes/no) and for how long they had used it (<1 year, 1-4 years, 5-9 years, 10-19 years, 20+ years), with similar questions for powder use on diaphragms or sanitary pads.

To harmonize across the 4 studies, we defined women as ever vs never users of powder on genital areas. For SIS, ever use included use in the last year or at ages 10 to 13 years. We were also able to examine long-term use, which we defined as use of powder on genitals for at least 20 years (NHSII and WHI-OS) or use at ages 10 to 13 years and also in the last year (SIS). Frequent users were those who reported use of powder in the

genital area at least once per week (NHS, NHSII), at least once per week in the last year, or "frequently" during ages of 10 to 13 years (SIS).

Outcome Assessment

For NHS and NHSII, follow-up questionnaires were distributed every 2 years, at which point participants were asked to report recent cancer diagnoses. Those reporting incident cancers were asked to grant access to their medical records, which were reviewed for confirmation of the diagnosis and disease details. Additional cases were identified from among deceased participants via National Death Index searches. The protocol for SIS was similar, except follow-up questionnaires were collected annually and most participants provided pathology reports rather than complete medical records. Participants in WHI-OS were also asked to self-report cancers on annual questionnaires, but only medically confirmed cases were counted. All 4 studies categorized tumors originating in the ovary, peritoneum, and fallopian tubes as ovarian cancers.

For NHS, NHSII, and SIS, delays in the confirmation process and incomplete retrieval of medical records meant that not all self-reported cases could be medically confirmed. We ran sensitivity analyses limited to medically confirmed cases but included all self-reported diagnoses in our main analyses. Subtype analyses were limited to medically confirmed cases.

Covariates

All 4 studies had substantial covariate data, which we harmonized into a common set of potential confounders or effect modifiers. The following data were included: age at baseline (continuous), race (white, black, other), education (≤high school, some college, completed college), body mass index (BMI [calculated as weight in kilograms divided by height in meters squared], restricted cubic spline), parity (nulliparous, 1 birth, 2 births, ≥3 births), smoking status (never, former, current), oral contraceptive use (ever/never), hormone therapy use (ever/never), tubal ligation status (yes/no), hysterectomy status (yes/no), and menopausal status (premenopausal/postmenopausal). Race was self-reported by the participant, based on provided categories. It was considered to be an important confounder because both ovarian cancer rates[13] and genital powder use vary by race/ethnicity. Only baseline levels of these covariates were considered as confounders, though we did consider post-baseline changes in menopausal status when assessing effect modification.

Statistical Analyses

We used Cox proportional hazards models with age as the primary time scale to estimate hazard ratios (HRs) and 95% CIs measuring the association between genital use of powder and incident ovarian cancer, adjusting for potential confounders. We selected potential confounders using a directed acyclic graph framework,[17] considering covariates that were possibly related to use of powder in the genital area and also ovarian cancer risk.

We excluded women who had ovarian cancer or a bilateral oophorectomy prior to baseline, or who were missing information on powder use or age at ovarian cancer diagnosis. For regression analyses, we additionally excluded women with missing data for 1 or more covariates. Women underwent follow-up from age at baseline until ovarian cancer diagnosis, with censoring at bilateral oophorectomy, end of follow-up, or death from causes other than ovarian cancer. An exception was made for WHI-OS because postbaseline oophorectomy data were not collected. Participants in SIS and WHI-OS who were no longer actively responding to follow-up requests were censored at age of last contact, although their follow-up continued via linkage to the National Death Index.

To better control for differences across studies, we allowed the baseline hazard function to vary across cohorts by implementing study-stratified Cox models. We tested for study heterogeneity by conducting likelihood ratio tests comparing models with and without study × powder interaction terms. For the primary analysis of ever vs never powder use and ovarian cancer risk, we additionally calculated the effect estimate and the *P* value for heterogeneity from a random-effects meta-analysis.[18] Proportional hazards assumptions were tested via likelihood ratio tests of powder × time interaction terms.

Because patency is required for there to be a direct physical pathway between the powder application area and the ovaries, we hypothesized a priori that women with patent reproductive tracts would be more susceptible to the effects of powder use in the genital area on ovarian cancer. We therefore conducted analyses restricted to this subgroup. When estimating the effects of duration of powder use on ovarian cancer risk, we compared long-term (≥20 years) and non-long-term users with never users. Similarly, we compared frequent users (≥1/week) and nonfrequent users with never users. We conducted trend tests using the ordinal forms of these variables.

We also conducted exploratory analyses to examine whether the association between powder use in the genital area and ovarian cancer varied by subgroup. These categorizations were selected based on the existing literature or hypotheses about potential biological mechanisms and included age, race/ethnicity, menopausal hormone therapy use, BMI, and parity. We also considered time-varying menopausal status and follow-up time as effect modifiers and more formally compared subgroups defined by hysterectomy, tubal ligation and patency status. We evaluated heterogeneity across strata of each potential effect modifier by conducting likelihood ratio tests of the interaction between that factor and powder use in the genital area.

For analyses limited to medically confirmed cases of ovarian cancer, we censored unconfirmed cases at their self-reported age of diagnosis. For type-specific analyses, the medically confirmed cases were further divided by invasiveness status (invasive vs borderline), tumor location (epithelial ovarian, peritoneal, or fallopian tube), or histotype (serous, endometroid, mucinous, clear-cell, or other). For an alternative histotype analysis, we defined high-grade

Table 1. Description of Participating Cohorts[a]

	Nurses' Health Study[b]	Nurses' Health Study II[c]	Sister Study[d]	Women's Health Initiative[e]	Total
Sample size	81 869	61 261	40 647	73 267	257 044
Included study period	1982-2016	2013-2017	2003-2017	1993-2017	1982-2017
Follow-up time, median (IQR), y	33.2 (20.0-34.0)	3.8 (3.5-3.9)	9.6 (8.4-11.1)	17.4 (8.7-19.9)	11.2 (3.9-21.0)
Age range at assessment for use of powder in the genital area, y	35-62	48-68	35-77	49-81	35-81
Age, median (IQR), y	48 (42-55)	58 (54-62)	55 (48-61)	63 (57-69)	57 (50-62)
All ovarian cancer cases	1258	76	220	659	2213
Medically confirmed ovarian cancer cases	1055	37	172	659	1923
Powder use in genital area, %					
Ever	41	26	27	53	39
Long-term		6	6	16	10
Frequent	27	26	7		22

Abbreviation: IQR, interquartile range.

[a] More detailed descriptions of the Nurses' Health Study and the Nurses' Health Study II can be found in Bao et al[14]; in Sandler et al[15] for the Sister Study; and in Anderson et al[16] for the Women's Health Initiative.

[b] Powder use in the genital area was assessed in the 1982 follow-up questionnaire, not at study baseline. Participants were excluded if they did not respond to the question regarding use of powder in the genital area (n = 28 584), had ovarian cancer prior to responding to the 1982 questionnaire (n = 174), underwent a bilateral oophorectomy at the time of the 1982 questionnaire (n = 10 896), or did not contribute any person-time after the 1982 questionnaire (n = 4). Frequent use was defined as use of powder in the genital area at least once per week. Women who underwent bilateral oophorectomy during follow-up were censored at age of oophorectomy. Follow-up was complete through June 1, 2016.

[c] Use of powder in the genital area was assessed in the 2013 follow-up questionnaire, not at study baseline. Participants were excluded if they did not respond to the question regarding use of powder in the genital area (n = 41 141), had ovarian cancer prior to 2013 (n = 287), underwent a bilateral oophorectomy at the time of the 2013 questionnaire (n = 13 739), or did not contribute any person-time after the 2013 questionnaire (n = 1). Frequent use was defined as use of powder in the genital area at least once per week. Long-term use was defined as use of powder in the genital area for 20 years or longer. Because data were reported in 2-year cycles, we did not censor for oophorectomy that occurred after 2013. Follow-up was complete through June 1, 2017.

[d] Participants were excluded if they withdrew from the study (n = 2), had ovarian cancer prior to baseline or unclear ovarian cancer status at baseline (n = 225), underwent a bilateral oophorectomy prior to baseline (n = 9009), or did not respond to any of the questions regarding use of powder in the genital area (n = 1001). Ever powder use was defined as use of powder in the genital area during the 12 months prior to baseline or at ages 10 to 13 years. Long-term use was defined as use of powder in the genital area at ages 10 to 13 years and within the last 12 months. Frequent use was defined as use of powder in the genital area at least once per week (during the last 12 months) or *frequently* (as termed in the questionnaire) between ages 10 and 13 years. Women who underwent a bilateral oophorectomy during follow-up were censored at age of oophorectomy. Follow-up was complete through September 15, 2017.

[e] Participants were excluded if they did not complete the questionnaire regarding use of powder in the genital area (n = 342), had ovarian cancer before baseline (n = 641) or unknown cancer status before baseline (n = 890), underwent a bilateral oophorectomy at baseline (n = 18 183), or had no follow-up information (n = 353). Long-term use was defined as use of powder in the genital area for 20 years or longer. Postbaseline oophorectomies were not recorded. Follow-up was complete through February 28, 2017.

serous as grades 2 to 4 serous or grades 3 to 4 endometroid tumors.[19] We estimated the HRs for each set of subtypes using joint Cox proportional hazards models,[20] utilizing likelihood ratio tests to compare model fit for models that did and did not allow the main-effect estimates to differ by subtype. These test results are reported as *P* values for heterogeneity.

In a sensitivity analysis, we attempted to isolate participants who were possibly exposed to asbestos-contaminated talc by limiting analysis to women in WHI-OS and NHS, most of whom were born before 1945. In the age-adjusted and fully adjusted models, we additionally estimated cumulative risk of ovarian cancer by age 70 years and assessed differences in absolute risk among ever vs never users of powder in the genital area using the Breslow method.[21]

Statistical tests were 2-sided, and a *P* value less than .05 was considered statistically significant. Because of the potential for type I error due to multiple comparisons, findings from subgroup and sensitivity analyses should be interpreted as exploratory. All analyses were conducted in SAS 9.4.

Results

After initial exclusions, we had data from 257 044 women, including 2213 who developed incident ovarian cancer (**Table 1**). Use of powder in the genital area was common overall (39%) but varied by cohort with 53% of participants reporting ever use in WHI-OS, 41% in NHS, 27% in SIS, and 26% in NHSII. Long-term use was reported by 16% in WHI-OS and by 6% in both SIS and NHSII; frequent use was reported by 27% in NHS, 26% in NHSII, and 7% in SIS.

After further excluding women with missing covariates (<3% of all participants), 2168 participants with ovarian cancer (1884 medically confirmed) and 250 577 without ovarian cancer remained. Most NHS and WHI-OS participants were born between 1915 and 1944 and most NHSII and SIS participants were born in 1945 or later (eTable 1 in the Supplement), and there appeared to be a generational trend in use of powder in the genital area, with older cohorts more

Table 2. Study-Specific and Pooled Risk Differences, Hazard Ratios, and 95% CIs for the Association Between Ever Use of Powder in the Genital Area and Risk of Ovarian Cancer

Cohort	Person-Years, No. at Risk[a]	No. Without Ovarian Cancer[a]	No. With Ovarian Cancer[a]	Incidence per 100 000 Person-Years[a]	Prevalence of Powder Use in the Genital Area, %[a]		Age-Adjusted RD (95% CI), %[a]	Adjusted RD (95% CI), %[a,b]	Adjusted HR (95% CI)[a,b]
					Without Ovarian Cancer	With Ovarian Cancer			
Ever Used Powder in the Genital Area, All Women									
NHS	2 130 797	79 055	1224	57	41	42	0.06 (−0.07 to 0.20)	0.09 (−0.06 to 0.24)	1.07 (0.95 to 1.20)
NHSII	220 658	60 464	76	34	26	24	−0.10 (−0.44 to 0.24)	−0.15 (−0.49 to 0.20)	0.81 (0.47 to 1.38)
SIS	376 212	40 193	219	58	27	29	0.14 (−0.28 to 0.56)	0.03 (−0.39 to 0.45)	1.02 (0.76 to 1.38)
WHI-OS	1 038 039	70 865	649	63	53	56	0.09 (−0.05 to 0.23)	0.09 (−0.05 to 0.24)	1.11 (0.95 to 1.30)
Pooled estimate[c]	3 765 706	250 577	2168	58	38	44	0.08 (−0.03 to 0.19)	0.09 (−0.02 to 0.19)	1.08 (0.99 to 1.17)[d]
Ever Used Powder in the Genital Area, Women With Patent Reproductive Tracts[e]									
NHS	1 408 991	52 191	850	60	41	44	0.22 (0.03 to 0.40)	0.22 (0.02 to 0.42)	1.16 (1.01 to 1.33)
NHSII	140 534	38 503	51	36	26	27	0.06 (−0.39 to 0.51)	−0.01 (−0.46 to 0.43)	0.98 (0.52 to 1.83)
SIS	226 866	24 080	116	51	25	23	−0.13 (−0.63 to 0.37)	−0.21 (−0.72 to 0.31)	0.84 (0.55 to 1.31)
WHI-OS	614 280	41 928	367	60	51	56	0.12 (−0.08 to 0.32)	0.11 (−0.08 to 0.30)	1.13 (0.92 to 1.39)
Pooled estimate[c]	2 390 672	156 702	1384	58	37	45	0.15 (0.01 to 0.30)	0.15 (0.01 to 0.29)	1.13 (1.01 to 1.26)[f]

Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RD, risk difference; SIS, Sister Study; WHI-OS, Women's Health Initiative Observational Study.

[a] Data are reported among participants with complete covariate information. Includes all self-reported cases.

[b] Referent group is never users. Effect estimates and HRs for women with patency were adjusted for race/ethnicity (white, black, other), education (≤ high school, some college, ≥college graduate), body mass index (calculated as weight in kilograms divided by height in meters squared, [restricted cubic spline]), parity (0, 1, 2, ≥3 births), ever use for oral contraceptives, tubal ligation (yes or no), hysterectomy status (yes or no), menopausal status (premenopausal or postmenopausal), and ever use of hormone therapy. Only effect estimates were adjusted for tubal ligation status (yes or no) and for hysterectomy status (yes or no). All covariates indicate status at time of assessment for use of powder in the genital area. RDs were calculated based on estimated cumulative incidence of ovarian cancer by age 70 years.

[c] Pooled estimates were calculated using Cox proportional hazards models, stratified by study to allow for the baseline hazard functions to vary by cohort, and adjusted for the same covariates as the study-specific models.

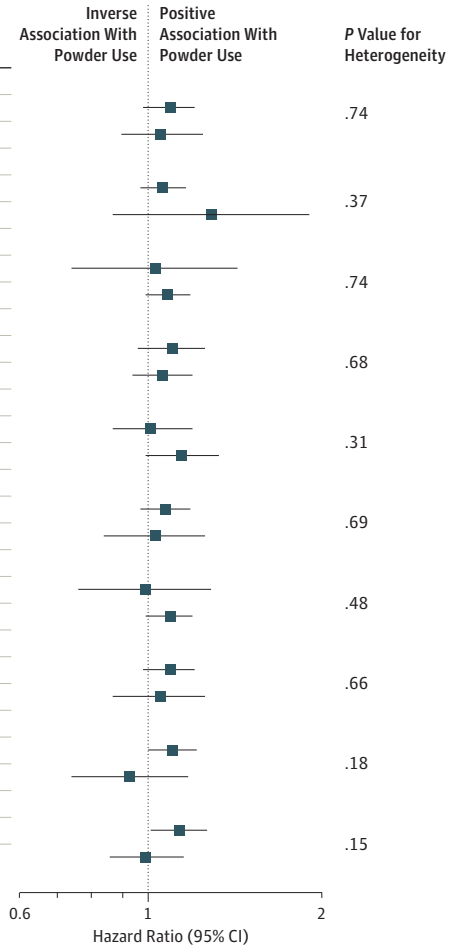
[d] The *P* value for heterogeneity between studies was .81 and was calculated using the likelihood ratio test for study by main-effects interaction term.

[e] Patency indicates having a uterus (ie, no hysterectomy) and no tubal ligation.

[f] The *P* value for heterogeneity between studies was .73 and was calculated using the likelihood ratio test for study by main-effects interaction term.

Figure. Subgroup Analyses for the Association Between Ever Use of Powder in the Genital Area and Risk of Ovarian Cancer, Pooled Hazard Ratios (HRs) and 95% CIs[a]

Characteristic	Participants With Ovarian Cancer, No.[b]	Hazard Ratio (95% CI)	P Value for Heterogeneity
Age, y			
<60	1533	1.09 (0.98-1.20)	.74
≥60	635	1.05 (0.90-1.24)	
Race/ethnicity			
Non-Hispanic white	2061	1.06 (0.97-1.16)	.37
Other	107	1.28 (0.87-1.90)	
Menopause status[c]			
Premenopausal	730	1.03 (0.74-1.42)	.74
Postmenopausal	1438	1.08 (0.99-1.18)	
Follow-up time, y			
0-10	954	1.10 (0.96-1.25)	.68
≥10	1214	1.06 (0.94-1.19)	
Hormone therapy[d]			
Never	654	1.01 (0.87-1.19)	.31
Ever	784	1.14 (0.99-1.32)	
Body mass index[e]			
<30	1757	1.07 (0.97-1.18)	.69
≥30	411	1.03 (0.84-1.25)	
Parity			
Nulliparous	252	0.99 (0.76-1.28)	.48
Parous	1916	1.09 (0.99-1.19)	
Hysterectomy			
No	1658	1.09 (0.98-1.20)	.66
Yes	510	1.05 (0.87-1.25)	
Tubal ligation			
No	1840	1.10 (1.00-1.21)	.18
Yes	328	0.93 (0.74-1.17)	
Patency			
Patent	1384	1.13 (1.01-1.26)	.15
Not patent	784	0.99 (0.86-1.15)	



[a] Adjusted for study, race/ethnicity (white, African American, other), education (<high school, some college, ≥college graduate), body mass index (BMI [calculated as weight in kilograms divided by height in meters squared], restricted cubic spline), parity (0, 1, 2, ≥3 births), ever use of oral contraceptives, tubal ligation (yes or no), hysterectomy (yes or no), menopausal status (premenopausal or postmenopausal), ever hormone therapy use. When estimating HRs within a strata of a variable, that variable was not included in the adjustment set.

[b] Numbers include only participants with complete covariate information.

[c] Effect estimate based on menopausal status updated throughout follow-up. Of the 2168 cases, 165 were diagnosed while the participant was premenopausal and 2003 occurred after menopause.

[d] Among women who were postmenopausal at baseline.

[e] Calculated as weight in kilograms divided by height in meters squared.

likely to report use. Overall, this was a highly educated group (most completed college) and most participants were white (84%-98% of each cohort). Compared with never users, ever users of powder in the genital area were more likely to be black (6% vs 3%; eTable 2 in the Supplement), to be obese (26% vs 19%), or to have had a hysterectomy (22% vs 18%), and less likely to have used oral contraceptives (57% vs 64%).

A total of 2168 women developed ovarian cancer (58 cases per 100 000 person-years; **Table 2**). Consistent with mean age at enrollment, incidence was highest in WHI-OS (63 cases per 100 000 person-years) and lowest in NHSII (34 cases per 100 000 person-years). In the pooled sample, estimated crude cumulative incidence of ovarian cancer at age 70 years was 1.3%, with higher risk among participants in NHS (1.3%) and SIS (1.4%) than in NHSII (0.7%) or WHI-OS (0.9%).

Considering all 4 cohorts, the estimated incidence of ovarian cancer was 61 per 100 000 person-years among ever users and 55 among never users. The estimated adjusted cumulative risk of ovarian cancer by age 70 years among unexposed participants was 1.16%, with an estimated covariate-adjusted risk difference of 0.09% (95% CI, −0.02% to 0.19%) comparing with those who were exposed. The HR for the association between ever powder use and incident ovarian cancer was 1.08 (95% CI, 0.99 to 1.17; Table 2). There was no evidence of heterogeneity across cohorts (*P* value for heterogeneity = .81) and no evidence of a proportional hazards assumption violation (*P* > .99). The estimated HR from the random-effects model was 1.07 (95% CI, 0.98 to 1.17; *P* value for heterogeneity = .71).

When restricted to women with patent reproductive tracts at baseline, the HR was 1.13 (95% CI, 1.01 to 1.26) and the estimated covariate-adjusted risk difference was 0.15% (95% CI, 0.01% to 0.29%). Among women without patent reproductive tracts, the estimated HR was 0.99 (95% CI, 0.86 to 1.15) and the *P* value for heterogeneity comparing the result for women with patency vs without was .15 (**Figure**). The remaining stratified analyses are also presented in the Figure and in eTable 3 in the Supplement.

The covariate-adjusted risk difference for long-term (≥20 years) vs never use was 0.01% (95% CI, −0.21% to 0.24%), and the HR was 1.01 (95% CI, 0.82 to 1.25; *P* value for trend = .57; **Table 3**). The covariate-adjusted risk difference for frequent use (≥1/week) vs none was 0.10% (95% CI, −0.05% to 0.25%), and the HR was 1.09 (95% CI, 0.97 to 1.23; dose-response

Table 3. Study-Specific and Pooled Risk Differences, Hazard Ratios, and 95% CIs for the Association Between Duration and Frequency of Powder Use in the Genital Area and Risk of Ovarian Cancer

Powder Use in the Genital Area	Person-Time at Risk[a]	Noncases[a]	Ovarian Cancer Cases[a]	Incidence per 100 000 Person-Years[a]	Prevalence of Powder Use[a], %		Age-Adjusted RD (95% CI), %[a]	Adjusted RD (95% CI), %[a,b]	Adjusted HR (95% CI)[a,b]	*P* Value for Heterogeneity[c]	*P* Value for Trend[d]
					Noncases	Cases					
All Women											
Long-term use[e]											
NHSII	220 658	60 464	76	34	6	5	−0.11 (−0.71 to 0.49)	−0.18 (−0.77 to 0.41)	0.76 (0.27 to 2.10)		
SIS	376 212	40 193	219	58	6	5	−0.07 (−0.85 to 0.70)	−0.21 (−0.95 to 0.53)	0.85 (0.46 to 1.57)		
WHI-OS	1 034 453	70 598	649	63	16	15	0.04 (−0.16 to 0.24)	0.05 (−0.15 to 0.26)	1.06 (0.85 to 1.34)		
Pooled estimate[f]	1 631 323	171 255	944	58	10	12	0.01 (−0.24 to 0.25)	0.01 (−0.21 to 0.24)	1.01 (0.82 to 1.25)	.90	.49
Used powder ≥1/wk											
NHS	2 130 797	79 055	1224	57	27	29	0.12 (−0.04 to 0.28)	0.14 (−0.04 to 0.31)	1.11 (0.97 to 1.26)		
NHSII	220 658	60 464	76	34	26	24	−0.10 (0.44 to 0.25)	−0.15 (−0.49 to 0.20)	0.81 (0.47 to 1.38)		
SIS	376 212	40 193	219	58	7	9	0.52 (−0.32 to 1.35)	0.35 (−0.46 to 1.15)	1.25 (0.78 to 2.00)		
Pooled estimate[f]	2 727 667	179 712	1519	56	22	26	0.11 (−0.05 to 0.26)	0.10 (−0.05 to 0.25)	1.09 (0.97 to 1.23)	.65	.20
Women With Patent Reproductive Tracts[g]											
Long-term use[e]											
NHSII	140 534	38 503	51	36	6	4	−0.20 (−0.91 to 0.51)	−0.30 (−0.94 to 0.35)	0.59 (0.14 to 2.47)		
SIS	226 866	24 080	116	51	5	5	−0.04 (−1.05 to 0.97)	−0.14 (−1.14 to 0.85)	0.89 (0.39 to 2.05)		
WHI-OS	612 086	41 770	367	60	15	15	0.05 (−0.24 to 0.33)	0.05 (−0.22 to 0.33)	1.06 (0.78 to 1.44)		
Pooled estimate[f]	979 486	104 353	534	54	9	12	0.01 (−0.31 to 0.32)	0.00 (−0.29 to 0.30)	1.00 (0.76 to 1.32)	.81	.66
Used powder ≥1/wk											
NHS	1 408 991	52 191	850	60	27	31	0.28 (0.06 to 0.49)	0.29 (0.05 to 0.52)	1.21 (1.04 to 1.41)		
NHSII	140 534	38 503	51	36	26	27	0.06 (−0.39 to 0.51)	−0.01 (−0.46 to 0.43)	0.98 (0.52 to 1.83)		
SIS	226 866	24 080	116	51	6	8	0.33 (−0.74 to 1.41)	0.20 (−0.84 to 1.25)	1.15 (0.58 to 2.31)		
Pooled estimate[f]	1 776 391	114 774	1017	57	22	28	0.25 (0.04 to 0.46)	0.22 (0.02 to 0.42)	1.19 (1.03 to 1.37)	.69	.03

Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RD, risk difference; SIS, Sister Study; WHI-OS, Women's Health Initiative Observational Study.

[a] Data are reported among participants with complete covariate information. Includes all self-reported cases.

[b] Referent group is never users. Effect estimates are adjusted for race/ethnicity (white, black, other), education (≤high school, some college, ≥college graduate), body mass index (calculated as weight in kilograms divided by height in meters squared, [restricted cubic spline]), parity (0, 1, 2, ≥3 births), ever use of oral contraceptives, tubal ligation (yes or no), hysterectomy status (yes or no), menopausal status (premenopausal or posmenopausal), and ever use of hormone therapy. All covariates indicate status at time of assessment for use of powder in the genital area. RDs were calculated based on estimated cumulative incidence of ovarian cancer by age 70 years.

[c] Likelihood ratio test for study by main-effects interaction term.

[d] A test of the β coefficient for considering frequency (no use, nonfrequent use, frequent use) or duration (no use, non–long-term use, long-term use) of powder as an ordinal variable.

[e] See eAppendix in the Supplement for study-specific definitions of long-term use.

[f] Pooled estimates were calculated using Cox proportional hazard models, stratified by study to allow for the baseline hazard functions to vary by cohort, and adjusted for the same covariates as the study-specific models.

[g] Patency indicates having a uterus (ie, no hysterectomy) and no tubal ligation.

Table 4. Pooled Hazard Ratios and 95% CIs Among Medically Confirmed Cases Overall and by Tumor Invasiveness, Location, and Histotype

	No. of Cases[a]	Hazard Ratio (95% CI)		
		Ever Use[b]	Long-term Use[b]	Frequent Use[b]
All medically-confirmed cases	1884	1.05 (0.96-1.16)	1.03 (0.83-1.28)	1.05 (0.92-1.20)
Invasiveness level				
Invasive only	1538	1.07 (0.97-1.19)	1.08 (0.85-1.37)	1.08 (0.93-1.25)
Borderline	139	1.09 (0.79-1.52)	1.31 (0.59-2.92)	0.98 (0.60-1.60)
P value for heterogeneity[c]		.90	.41	.31
Tumor location				
Epithelial ovarian	1536	1.08 (0.97-1.19)	1.08 (0.85-1.37)	1.09 (0.94-1.27)
Fallopian tube	52	1.19 (0.69-2.08)	2.18 (0.46-10.3)	1.35 (0.69-2.65)
Peritoneal	103	1.12 (0.76-1.65)	1.18 (0.33-4.16)	0.76 (0.44-1.31)
P value for heterogeneity[c]		.92	.58	.02
Histotype				
Serous	1038	1.10 (0.97-1.25)	1.02 (0.75-1.38)	1.07 (0.90-1.28)
Endometroid	157	1.15 (0.83-1.58)	1.14 (0.49-2.63)	1.17 (0.76-1.79)
Mucinous	102	1.03 (0.69-1.54)	1.35 (0.58-3.15)	1.27 (0.73-2.22)
Clear Cell	68	1.17 (0.73-1.89)	1.01 (0.35-2.95)	1.11 (0.55-2.24)
Other	357	0.97 (0.79-1.20)	1.24 (0.79-1.94)	0.93 (0.68-1.27)
P value for heterogeneity[c]		.86	.97	.76
Histotype II[d]				
High-grade serous	732	1.08 (0.93-1.25)	0.99 (0.70-1.40)	1.05 (0.84-1.31)
Low-grade serous	29	1.41 (0.70-2.82)	1.25 (0.17-9.25)	0.70 (0.23-2.09)
Other	601	1.01 (0.86-1.19)	1.19 (0.84-1.69)	1.04 (0.82-1.32)
P value for heterogeneity[c]		.64	.78	.31

[a] Includes ever-use analysis; limited to women with complete covariate information.

[b] Referent group is never users. Adjusted for study, race/ethnicity (white, African-American, other), education (≤high school, some college, ≥college graduate), body mass index (calculated as weight in kilograms divided by height in meters squared, [restricted cubic spline]), parity (0, 1, 2, ≥3 births), ever use of oral contraceptives, tubal ligation (yes or no), hysterectomy status (yes or no), menopausal status (premenopausal or postmenopausal), ever use of hormone therapy.

[c] From competing risks model: likelihood ratio test of model that allows effect estimate to vary by subtype compared with a model that does not.

[d] High-grade serous indicates grades 2 to 4 serous or grades 3 to 4 endometroid; low-grade serous indicates grade 1 serous.

P value for trend =.20). The covariate-adjusted risk difference for the association between frequent powder use and ovarian cancer among women with patent reproductive tracts was 0.22% (95% CI, 0.02% to 0.42%), and the HR was 1.19 (95% CI, 1.03 to 1.37; *P* value for trend = .03).

When the outcome was limited to medically confirmed cases, the HR was attenuated (**Table 4**; HR, 1.05 [95% CI, 0.96 to 1.16] for ever use vs never use). There were no notable differences in estimates by invasive status, tumor location, or histotype. This was also true for analyses limited to women with patent reproductive tracts (eTable 4 in the Supplement). When limited to the older cohorts (NHS and WHI-OS), the estimated pooled HR was 1.09 (95% CI, 0.99 to 1.19) for ever use vs never use. The estimated HR from the young cohorts (NHSII and SIS) was 0.97 (95% CI, 0.75 to 1.26).

Discussion

In this pooled analysis of 4 large US cohorts, there was no statistically significant association between self-reported use of powder in the genital area and risk of ovarian cancer. There were no clear dose-response trends for duration and frequency of powder use in the genital area in relation to ovarian cancer risk. Although the study was underpowered to detect small changes in risk, this is, to our knowledge, the largest study of this topic to date, and it is believed that no other large prospective cohorts have collected data on powder exposure in the genital area.

One of the primary drivers of research on genital use of talc-based products and ovarian cancer has been the potential link between talc and asbestos, which can occur together in nature. In an analysis limited to the older cohorts in which women may have started using powder before the asbestos ban of 1976, the estimated effect remained consistent, with no association observed in the younger cohorts. However, it was recently suggested that some products may have contained asbestos after 1976, meaning that there may not be a clearly defined time period in which talc-based products did or did not contain asbestos.[22] Further, although most cosmetic powder products include some quantity of mineral talc,[1] the percentage varies widely,[23] and exposure to asbestos (through talc) would also depend on the type of product used and the method of application (eg, underwear vs diaphragm).

By irritating epithelial ovarian tissue or fallopian tubes[24] directly, powder could induce an inflammatory response even in the absence of asbestos. This could set off a cascade of increased oxidative stress levels, DNA damage, and cell division, all of which could contribute to carcinogenesis.[25] In this analysis, there was a possible positive association among women with patent reproductive tracts (no history of hysterectomy or tubal ligation), although because the association was not significantly different from that observed in women with nonpatent reproductive tracts, this finding should be considered only exploratory and hypothesis generating. This observation lends support to the hypothesis that powder with or without asbestos could irritate and inflame the reproductive

tract, as patency is required for there to be a direct physical path between the genitals and the fallopian tubes or ovaries.[26] The positive relationships between pelvic inflammatory disease and ovarian cancer[27] and chlamydia infection and ovarian cancer[28] also support an inflammation-mediated mechanism, as does the inverse association between regular aspirin use and ovarian cancer.[29]

One of the main concerns about previous case-control studies on this topic is the possibility for recall bias, which would result if case participants were more likely to report using powder than control participants. As highlighted by Trabert,[7] the African American Cancer Epidemiology Study[6] found evidence supporting this phenomenon. Based on the timing of the first major talc lawsuits,[30] Schildkraut et al[6] stratified their results by year of interview (earlier than 2014 vs 2014 or later), observing that among women interviewed earlier, ever use of powder in the genital area was less-strongly associated with ovarian cancer (odds ratio [OR], 1.19 [95% CI, 0.87 to 1.63]) than among women interviewed later (OR, 2.91 [95% CI, 1.70 to 4.97]). This difference was driven by an increase in the reported prevalence of powder use among case participants (36.5% vs 51.5% of women interviewed early vs later), while self-reported use in the control partcipants remained stable (34.0% vs 34.4%). However, most of the case-control studies that have examined this association recruited well before 2014, and a large pooled analysis published in 2013 reported an OR of 1.24 (95% CI, 1.15 to 1.33).[4] For the current analysis, recall bias was avoided by excluding those with preexisting ovarian cancer.

The strengths of this study were large sample size and long follow-up time. The main analysis included 2168 ovarian cancer cases that developed over 3.8 million person-years. This far exceeds a previous meta-analysis of the published NHS, SIS, and WHI-OS results (890 cases over 182 000 person-years).[5] However, power to investigate links to peritoneal or fallopian tube cancers or histotypes other than serous was still low. Improvements in the classification of tumor types may contribute new insights, especially for fallopian tube cancers, which may be the true point of origin for most serous ovarian cancers.[24] This and other subtype-specific associations should be better examined in the future.

Limitations

This study has several limitations. First, the included cohorts varied widely in how they assessed exposure, particularly the duration and frequency of powder use. There was no evidence of between-study heterogeneity for either the pooled or meta-analysis models of ever use vs never use, but because the 2 largest studies were missing information on duration (NHS) and frequency (WHI-OS) of powder use, the dose-response analyses are underpowered compared with the main results and thus difficult to interpret. Second, use of powder in the genital area could not be assessed as a time-varying factor, as none of the 4 studies collected data on use after baseline.

Third, specific exposure windows could not be examined, nor could type of powder used or patency status at time of powder use. As previously noted, information on powder exposure is typically more limited in cohort studies compared with case-control studies, particularly with respect to dose and duration of use.[31] Therefore, ongoing or future cohort studies should collect detailed information on these topics.

Fourth, as with all observational studies, residual confounding is possible. All 4 included studies recorded detailed information on many potential confounders, which were harmonized across cohorts and adjusted for in multivariable models. However, residual confounding may still be present if the harmonized covariates did not adequately capture the relationship or if any key confounders were missing.

Fifth, the study may have limited generalizability. All 4 cohorts included predominately white, well-educated women, approximately half of whom had a BMI of less than 25, which could raise concerns about generalizability, especially since these factors may be related to powder use. However, these studies have high retention rates and accurate self-reported data, increasing internal validity.

Sixth, confounding by indication is another potential limitation, and it would occur if women with other underlying conditions that were associated with ovarian cancer were also more likely to use powder in the genital area. It is also possible that if powder use is associated with increased risk of other gynecologic conditions (eg, fibroids, ovarian cysts), it can affect whether women receive oophorectomies, hysterectomies, or tubal ligations and alter their risk of developing ovarian cancer. Seventh, because tests to confirm patency were not performed, it is possible that not all women categorized as having a patent reproductive tract in this analysis had truly patent tubes.

Conclusions

In this analysis of pooled data from women in 4 US cohorts, there was not a statistically significant association between self-reported use of powder in the genital area and incident ovarian cancer. However, the study may have been underpowered to identify a small increase in risk.

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Invited Review

Talc, body powder, and ovarian cancer: A summary of the epidemiologic evidence

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HIGHLIGHTS

- Genital powder use shows a weak association with ovarian cancer risk.
- The increase in absolute risk of ovarian cancer is very small.
- Body powders have different ingredients that can be hard to quantify.
- The causal mechanism underlying the observed associations is not clear.

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ABSTRACT

Many women apply powder to the genital area as a drying agent. Talc, an inert mineral with a high capacity to absorb water, has historically been a major component of body powders. Due to its similarity and co-occurrence with asbestos, the association of body powder/talc use and gynecological cancer risk, specifically ovarian cancer risk, has been a long-standing research question. Retrospective case-control studies have shown associations between genital powder use and ovarian cancer risk, with summary relative risk estimates from meta-analyses and pooled analyses ranging from 1.24 to 1.35 for ever versus never use. In contrast, prospective cohort studies have not shown a statistically significant association until recently, when a pooled analysis of four large cohorts demonstrated a weak, but statistically significant association among women with patent reproductive tracts (hazard ratio 1.13). Taken together, the epidemiological data from case-control studies and cohort studies suggest that there may be a small, positive association between genital powder use and ovarian cancer. The causal factors underlying this association are not clear. Proposed factors include talc, other minerals, such as asbestos or quartz, that are known carcinogens and may contaminate talc products, or other powder ingredients that could cause inflammation of the reproductive tracts. Given the rarity of ovarian cancer in the general population, the small increase in relative risk translates to a very low increase in absolute risk. Further research is needed to understand the underpinnings of the observed association between genital powder use and ovarian cancer risk.

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1. Introduction

Talc is a soft and inert mineral with a high capability to absorb water and organic matter. It is used in a wide range of products, including paper, plastics, paint, rubber, agricultural products, pharmaceuticals, and cosmetics [1]. Because of its capacity to bind water, talc powder has been used in baby powders and feminine hygiene products as a drying agent. Notably, talc shares chemical features and often co-occurs with asbestos, a long-established carcinogen [2]. Due to the similarity with asbestos, talc has been evaluated for its carcinogenic potential [1]. Powder application to the genital area has been fairly common, but body powders contain varying levels of talc, including some labeled as talc-free [3]. Historically, there has been great interest in whether there is a link between genital talc use and cancers of the female reproductive tract.

The assessment of the carcinogenic potential of a biological or chemical agent is based on multiple lines of evidence from diverse studies, including epidemiological studies, mechanistic studies, cancer bioassays, and animal experiments. This review focuses on epidemiological data, particularly on studies evaluating the association between body powder/talc and ovarian cancer.

In 1971, Henderson et al. showed talc particles in 10 out of 13 ovarian cancer tissue samples, as well as in a low number of endometrial and cervical cancer tissues [4]. In 1979, Longo and Young summarized the evidence available at the time for a role of talc in ovarian cancer and laid out what studies would be needed to better assess the relationship [5]. In 1982, Cramer et al. published the first epidemiological study evaluating the association between genital talc use and ovarian cancer [6]. In a case-control study conducted in the Boston area, the authors reported an increased risk of ovarian cancer (OR 1.92; 95% CI 1.27–2.89) for any perineal exposure to talc. Since then, several case-control studies evaluating the association between talc or body powder and ovarian cancer have been published that showed positive associations, while evaluations in prospective cohort studies have shown only weak or no associations (summarized in Table 1). Associations between talc use and uterine cancer have also been investigated in several case-control and cohort studies.

In 2010, IARC published volume 93 of their Monograph series on "Evaluation of Carcinogenic Risks to Humans" that included the assessment of carcinogenicity of carbon black, titanium dioxide, and talc [1]. Based on the summary of the biological and epidemiological data at the time, the IARC group classified talc as a possible carcinogen (2B), which means that there is some evidence that a substance can cause cancer in humans, but that the evidence was not conclusive. Since the 2010 IARC carcinogenicity assessment, several epidemiological studies have been published that expand the state of knowledge about talc's possible carcinogenicity. In this review, we evaluate the epidemiological evidence on whether there is an association between body powder use and ovarian cancer risk. If the evidence suggests an association between powder use and ovarian cancer, it is important to understand underlying causal factors and the potential clinical and public health relevance.

2. Chemical properties of talc in body powder

Talc may either refer to mineral talc itself, or to cosmetic products that contain mineral talc in varying proportions, often in combination with corn starch. Talc is a metamorphic mineral composed of magnesium silicate (generalized chemical formula $Mg_3Si_4O_{10}(OH)_2$). Mineral talc is commonly platy, i.e. it occurs in flaky layers or sheets, but it can also occur as asbestiform fibers. Talc is the softest known mineral. Solid talc minerals are crushed into a white powder referred to as talcum powder that has great ability to absorb both watery and oily substances. This form of talc is the focus of the current review.

Talc can be contaminated with a variety of other minerals. Most important are contaminations with asbestos or quartz, both class 1 carcinogens according to IARC (which means that there is enough evidence to conclude that these substances can cause cancer in humans), which frequently co-occur naturally with talc [7]. Early cosmetic talc products were found to be contaminated with asbestos to various extent [8]. More stringent quality control introduced in talc production in 1976 led to a steep reduction in asbestos contamination. While talc products since the 1980s have been considered asbestos-free, recent reports have suggested that low-level contamination of talc with asbestos fibers may have persisted in some cosmetic products. To systematically assess the presence of asbestos in cosmetic products, the US FDA recently conducted extensive testing of cosmetic talc products and identified several products with asbestos contaminations that have subsequently been recalled from the market [9]. It cannot be excluded that other ingredients of body powders, such as corn starch, may also have biological effects, e.g. by causing irritation or inflammation of the female reproductive tract.

3. Biological properties of talc and carcinogenicity studies

The number of biologic and animal studies evaluating the carcinogenic potential of talc is limited. In autopsy studies, talc particles have been found in the lungs of occupationally exposed individuals [10]. Pathology studies have shown talc particles in various cancer tissues including stomach tumors and gynecological tumors, suggesting that talc can reach various parts of the body through inhalation, deposition, and even retrograde movement in the female genital tract [1]. Potential toxic effects of talc may depend on the route and dose of administration. When conducting carcinogenicity assessment, it is important to distinguish effects caused by other contaminating minerals such as asbestos or quartz, from talc-specific effects. This distinction is only possible when highly pure substances are studied.

The carcinogenicity of talc has been evaluated in few animal studies, summarized in the IARC monograph [1]. For example, mice were

Table 1
Reported estimates of the association between ever (versus never) powder use and ovarian cancer, including summary estimates from published meta- and pooled analyses.

Author	Year	OR (95% CI)	Meta-analyses			Pooled analyses			Comments
			Penninkilampi 2018	Berge 2018	Taher 2019	Terry 2013	O'Brien 2020[a]	Davis 2021[b]	
Overall summary estimates			1.31 (1.24–1.39)	1.22 (1.13–1.3)	1.28 (1.2–1.37)	1.24 (1.15–1.33)	1.08 (0.99–1.17)	1.32 (1.17–1.48)[c]	
Case control summary estimates			1.35 (1.27–1.43)	1.26 (1.17–1.35)	1.32 (1.24–1.40)	1.24 (1.15–1.33)			
Cramer	1982	1.92 (1.27–2.89)	X	X	X				
Hartge	1983	2.5 (0.7–10)	X	X	X				Meta-analyses used different subgroup estimates
Whittemore	1988	1.4 (1.98–2)	X	X	X				
Booth	1989	1.3 (0.94–1.8)	X	X					
Harlow	1989	1.1 (0.7–2.1)	X	X	X				
Chen	1992	3.9 (0.9–10.6)	X	X					
Harlow	1992	1.5 (1–2.1)		X	X				
Rosenblatt	1992	1 (0.2–4)	X	X	X				Meta-analyses used different subgroup estimates
Tzonou	1993	1.05 (0.28–3.98)	X	X	X				
Purdie	1995	1.27 (1.04–1.54)	X	X					
Shushan	1996	2 (1.11–3.6)	X						
Green	1997	1.3 (1.06–1.6)	X		X				
Chang	1997	1.42 (1.08–1.86)	X	X	X	X			
Cook	1997	1.5 (1.1–2)	X	X	X				
Godard	1998	2.49 (0.94–6.6)	X	X	X				
Wong	1999	0.92 (0.24–3.57)	X	X	X				
Ness	2000	1.5 (1.1–2)	X	X	X				
Mills	2004	1.37 (1.02–1.85)	X	X	X				
Goodman	2008	0.99 (0.7–1.41)		X		X			Abstracted numbers from Terry 2013
Merritt	2008	1.17 (1.01–1.36)	X	X	X	X			
Gates	2008	1.06 (0.89–1.28)			X				Data updated by Gates 2010 and Cramer 2016
Moorman	2009	1.37 (1.05–1.8)		X	X	X		X	Abstracted numbers from Terry 2013
Rosenblatt	2011	1.27 (0.97–1.66)	X	X	X	X			
Lo-Ciganic	2012	1.34 (1.07–1.66)		X		X			Abstracted numbers from Terry 2013
Kurta	2012	1.4 (1.16–1.69)	X		X				
Wu	2015	1.46 (1.27–1.69)	X	X	X	X		X	
Cramer	2016	1.33 (1.16–1.52)	X	X	X	X			Update of Gates 2010
Schildkraut	2016	1.44 (1.11–1.86)	X	X	X			X	
Cohort summary estimates			1.06 (0.9–1.25)	1.02 (0.85–1.2)	1.06 (0.9–1.25)		1.08 (0.99–1.17)		
Gertig	2000	1.09 (0.86–1.38)	X		X		X		Updated in Gates 2010, updated numbers in O'Brien 2020
Gates	2010	1.06 (0.89–1.28)		X			X		
Houghton	2014	1.12 (0.92–1.36)	X	X	X		X	X	Updated numbers in O'Brien 2020
Gonzalez	2016	0.73 (0.44–1.21)	X	X	X		X		Updated numbers in O'Brien 2020

[a] Additionally includes data from the Nurses' Health Study II (talc data unpublished)
[b] Additionally includes data from the Cook County Case-Control Study (talc data previously unpublished).
[c] OR = 1.22 (95% CI: 0.97–1.53) in African-American women; OR = 1.36 (95% CI: 1.19–1.57) in White women.

subjected to inhalation, as well as subcutaneous, intraperitoneal, and intrathoracic injection. Generally, no increase in tumor incidence was observed in mice. Rats were subjected to oral administration, inhalation, as well as intraperitoneal, intrathoracic, or intrapleural injection, and ovarian implantation. In some studies, incidences of alveolar and bronchial carcinomas were increased after talc inhalation. An increase in pheochromocytomas was also observed, but the IARC group did not consider that pheochromocytomas are causally related to talc. Hamsters were subjected to inhalation and intratracheal injection; no tumors were observed in these studies. A study conducted in rats that evaluated intravaginal and perineal talc application did not observe any neoplastic changes, but inflammatory reactions in the fallopian tubes and other areas of the genital tract [11]. However, the limited follow-up time may have precluded development of tumor endpoints.

Several lines of evidence suggest that talc causes inflammatory reactions. Animal studies have shown release of cytokines, chemokines and growth factors from pleural mesothelial cells after injection with talc. Similarly, in human tissue, intrapleural talc injection has led to inflammation and pleural fibrosis. In patients with documented perineal talc use, talc particles can be found in multiple sites along the female reproductive tract [12]. Talc use was shown to have an inverse association with MUC1 antibodies in healthy women, but the biologic process underlying this association is not understood [13]. One study found a higher risk of ovarian cancer associated with powder use among women with variations in the GSTM1 and GSTT1 genes [14], but to our knowledge, no other studies have examined potential gene-by-environment interactions.

4. Important considerations for epidemiological studies of talc use and gynecological cancer risk

4.1. Etiologic heterogeneity of ovarian cancer

Ovarian cancer is characterized by profound heterogeneity that can be observed in site of origin, genetic susceptibility, somatic mutations, molecular pathways, risk factor associations and morphologic differences [15–17]. In aggregate, these data suggest that there are several etiologically distinct types of cancers that manifest in the ovaries. It has been proposed that a majority of high-grade serous carcinomas arise from the fallopian tubes, while endometrioid carcinomas may arise from orthotopic or ectopic endometrial tissue, including endometriosis tissue [15]. Many ovarian cancer risk factors and exposures are specific to certain subtypes [16]. Demonstrating a subtype-specific association can, theoretically, point to a specific carcinogenic effect.

Further, there is similarity between subtypes of ovarian and endometrial cancers [18]. Serous ovarian and endometrial carcinomas have similar molecular features and may originate from the same cells in the fallopian tube. Similarly, endometrioid ovarian carcinomas share risk factors and molecular features with endometrioid endometrial carcinomas [16,19,20]. Therefore, comparisons of subtype-specific associations across gynecologic cancer sites can inform the carcinogenic process.

4.2. Study designs

Epidemiological studies of talc exposure have been conducted in special populations, like talc miners and pulp and paper industry workers who are exposed to high doses of talc over an extended time period. These occupational studies allow for the assessment of very high levels of exposure that are typically not found in the general population, with possibilities for detailed studies of dose-response effects (duration and frequency). However, due to the possible contamination of talc with co-existing minerals in mines and in industrial talc products, evaluating talc-specific effects remains a challenge. Ovarian cancer is particularly difficult to study in occupational settings, as high-exposure jobs are typically male-dominated.

In the general population, epidemiological studies of talc use and gynecological cancer risk include case-control studies and prospective cohort studies. A case-control study is an observational study consisting of a group of cases who experienced a specific outcome, such as ovarian cancer, as well as controls without that outcome [21,22]. These are compared to see if there are differences in exposure patterns between the two groups. Controls for case-control studies should be sampled from the base population from which the cases arise. Incompatibility between the controls and the true source population can lead to bias, as discussed further below. In contrast, cohort studies are observational studies that follow an initially non-diseased population to see who develops the outcome(s) of interest [23]. Cohort studies are typically much larger than case-control studies and require long-term follow-up, especially for rare outcomes.

These study designs have different advantages and disadvantages. The major difference between case-control studies and cohort studies is that case-control studies assess exposures at the time of or just after a cancer diagnosis, which can lead to differential reporting of exposures by cases and controls. In contrast, exposure assessment in cohort studies occurs before the cancer diagnosis. Case-control studies typically focus on a single disease of interest, like ovarian cancer, and are specifically designed to evaluate the exposures of interest for that specific disease. Therefore, case-control studies tend to have more detailed information on specific exposures. In contrast, cohort studies generally evaluate a wide range of disease outcomes. Exposure assessment is much broader and usually does not go as deep into specific exposures. For genital powders, this means studies will typically have less information on mode of application, dose, and duration. Further, when exposure assessment is not re-assessed at later follow-up times in cohort studies, the exposure assessment may refer to a time period that was many years, if not decades, prior to disease development, thereby opening the possibility to non-differential misclassification.

For rare diseases, cohort studies must be of sufficient size and duration to allow for well-powered assessment of potential risk factors. Most individual prospective cohort studies have not observed meaningful associations between talc use and ovarian cancer risk. However, many cohort studies have few cases and may not be sufficiently powered to detect a small increase in risk at statistically significant levels. It is important to be transparent about study power and the lower limit of detectable associations when reporting study results.

Both case-control studies and cohort studies typically report relative risk measures, including odds ratios or hazard ratios. These relative risks indicate how much the risk of an outcome is increased due to a specific exposure in one group compared to another. Measures of absolute risk of disease may have greater clinical relevance but are often difficult to assess using these standard study designs. Disease prevalence is a key factor here: the rarer the disease, the smaller the absolute risk increase for a given relative risk increase [24]. Accordingly, for a rare disease like ovarian cancer, even a large relative increase may not translate to an increase in absolute risk that is considered clinically meaningful.

4.3. Bias and confounding

In contrast to randomized trials, which are designed to achieve unbiased assessment of specific exposures, drugs, or interventions, observational studies are at risk of bias. In epidemiology, bias is defined as an error in the study design or conduct that leads to results that are systematically different from the truth [25]. Key forms of bias including selection bias, information bias, and confounding. Selection bias is introduced when there is a systematic difference between study participants and the base population, or a systematic difference between cases and non-cases. Information bias may occur when data on exposure or outcomes is systematically different between cases and non-cases. This includes recall bias, discussed in further detail below, and survivor bias, which could occur if talc use affected survival time. Survivor bias is a potentially important source of bias for retrospective studies of diseases with high fatality rates, such as ovarian cancer, as cases need to live long enough to be included. If cases are not interviewed soon after their diagnosis, the sample may include a disproportionate number of women with less severe disease.

Confounding occurs when an exposure is associated with an outcome, but the causal association is driven by a different factor that is correlated with both the exposure and the outcome. If the confounding factor is well-measured, bias due to confounding can be mitigated by adjusting for or stratifying on that variable using multivariable regression models. As an example, the association between genital powder use and uterine cancer is strongly confounded by body mass index (BMI), which is both a risk factor for uterine cancer and a strong predictor of genital powder use. As shown by O'Brien et al., while crude estimates of the genital powder use- uterine cancer relationship indicated a strong positive association, models adjusted for BMI indicated there was no independent relationship between body powder use and uterine cancer [26].

4.4. Assessment and quantification of talc exposure

Since talc use is not documented in medical or pharmacy records, assessment of talc exposure relies purely on self-report [27]. Cosmetic talc products are typically not easily recognizable without studying the list of ingredients. Body powders have a wide range of ingredients with different talc content, including some talc-free varieties. Since many study participants may not know whether they used talc, questionnaires in epidemiologic studies often ask about body powder use. Some case-control studies include questions about the mode of application. Body

powder may be applied to the genital area directly or via application to sanitary napkins or diaphragms [1].

When evaluating associations between exposures and disease outcomes in epidemiological studies, establishing a dose-response relationship can be important to support a causal association. Due to the varying talc content of body powders and the different modes of application, it is difficult to estimate the actual talc dose applied to the genital area.

Despite these limitations, some case-control studies have assessed the frequency and duration of genital powder use. This allows researchers to distinguish groups with potentially higher and lower exposure, even when the absolute talc exposure level cannot be quantified. Cohort studies typically have collected less information on dose and frequency of application than case-control studies.

4.5. Recall bias

Since exposure assessment in case-control studies is conducted at the time of diagnosis, there is a risk of differential recall bias, a type of information bias. This occurs when reporting of an exposure is influenced by the diagnosis and affected individuals are more likely to report a specific exposure or are likely to report a higher dose or duration of exposure compared to control individuals. This differential recall bias may result in an association of an exposure with disease outcome when there is truly none, or it may lead to overestimation of a truly small association.

Differential recall bias has been observed in case control studies for a wide range of exposures, but there are specific and well-documented concerns that differential recall bias underlies some of the associations in case-control studies of talc use and ovarian cancer risk. For example, in a large case-control study of African American women conducted in North Carolina Schildkraut et al. reported a strong association between talc use and ovarian cancer [28,29]. However, they only observed a significant association between genital powder use and ovarian cancer in participants interviewed after 2014 (adjusted OR, 2.91; 95% CI, 1.70–4.97), a benchmark for when a possible talc–ovarian cancer association began being widely discussed in the media as a result of ongoing litigation. Prior to 2014, the association was weaker and not statistically significant (OR, 1.19; 95% CI, 0.87–1.63; P interaction by time period = 0.005). Importantly, the prevalence of genital powder use among controls was the same across the two time periods, whereas the proportion of cases reporting "any" genital powder use increased among those interviewed during the later time period. This suggests that differential recall of body powder use may explain at least some of the observed associations.

4.6. Confounding by indication

Confounding by indication is a concern in epidemiological studies evaluating drugs and other exposures. It can occur when an underlying cause of the outcome also causes changes to exposure. An example relevant to the powder-ovarian cancer association is if a hormone-related condition was a risk factor for ovarian cancer, and also altered the vaginal environment in a way that made women more or less likely to apply genital powder. Such a relationship would induce a non-causal association between talc use and ovarian cancer. Most studies do not collect data on the underlying reason for talc use, which may be wide ranging. Without this knowledge, we cannot rule out confounding by indication.

4.7. Timing of exposure

Talc/body powder may be used over a wide age range, or only during a short period in life. The biologic effect of body powder on the cells at risk of ovarian cancer may differ depending on the timing of exposure. With the example of ovarian and other cancers, the disease latency period may be quite long, meaning that use several decades prior could be associated with disease risk. On the other extreme, recent use could also be relevant, including as a promoter of pre-cancerous cells into tumors, or by accelerating the growth of existing tumors. Few studies have collected information on talc/body powder dose and duration during specific time windows or across the lifespan. Depending on how talc/body powder exposure is assessed, many studies may not evaluate the relevant exposure window.

5. Summary of the data for genital powder use and ovarian cancer risk

5.1. Overall associations reported in systematic reviews, meta-analyses, and pooled analyses

Over the last 15 years, several systematic reviews and meta-analyses evaluating the association between body powder or talc use and ovarian cancer have been published. Three recent meta-analyses and three pooled analyses are summarized in Table 1 [30–34]. A total of 32 papers were included in at least one of the meta-analyses and pooled analyses spanning articles from 1982 to 2016 [6,14,28,35–62]. There were some differences with regard to inclusion of studies and specific estimates which resulted in differences of the reported associations between the meta-analyses and the pooled analyses.

Penninkilampi and Eslick summarized 23 case-control studies and 3 cohort studies via meta-analysis [33]. 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 the meta-analysis of 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). The systematic review also evaluated lifetime applications of talc to assess whether there is a dose-response relationship. Subjects with more than 3600 lifetime applications (OR = 1.42; 95% CI: 1.25–1.61) had a slightly higher risk of ovarian cancer compared to those with <3600 applications (OR = 1.32; 95% CI: 1.15–1.50).

Berge et al. summarized 24 case-control studies and 3 cohort studies via meta-analysis [30]. The overall summary relative risk (RR) for ever use of genital talc and ovarian cancer was 1.22 (95% CI: 1.13–1.30). The RR for case-control studies was 1.26 (95% CI: 1.17–1.35) and for cohort studies was 1.02 (95% CI: 0.85–1.20, P-for-heterogeneity by study design = 0.007). There was a weak trend in RR with duration and frequency of genital talc use.

Taher et al. summarized 21 case-control studies and 3 cohort studies [31]. This was the most recently published meta-analysis, and the authors included a detailed comparison of included studies in their supplemental materials, with the main differences being the exclusion of studies that did not report talc use as main effect estimates in their original publication. A positive association between perineal use of talc powder and ovarian cancer was found (OR = 1.28; 95% CI: 1.20–1.37). They noted significant risks in Hispanic and White women, in women applying talc to underwear, in pre-menopausal women, and in post-menopausal women receiving hormonal therapy.

Terry et al. published a large pooled analysis from the Ovarian Cancer Association Consortium (OCAC) [34]. This pooled analysis included eight case-control studies that are included in the previously discussed meta-analyses. In contrast to meta-analyses, pooled analyses make use of the original data, with the ability to harmonize exposure categories and covariates across studies. Based on data from 8525 cases and 9859 controls, Terry et al. found that genital powder use was associated with a statistically significant increase in risk of ovarian cancer (OR = 1.24, 95% CI: 1.15–1.33). There was limited evidence of a dose-response trend across categories of lifetime number of applications (p-for-trend = 0.17).

O'Brien et al. pooled data from the four large prospective cohorts known to have information on genital powder use [32]. This included updated data from three previously published cohorts [14,40,42,48] as well as previously unpublished data from the Nurses' Health Study II. Ever use of genital powder was associated with a small but not

statistically significant increase in ovarian cancer risk (HR = 1.08, 95% CI: 0.99–1.17). There was no evidence that more frequent or long-term use was associated with further increases in risk.

Most recently, Davis et al. published results from a pooled analysis of 5 studies (4 population-based case-control, 1 prospective cohort) participating in the Ovarian Cancer in Women of African Ancestry Consortium (OCWAA) [63]. They observed a positive association between genital powder use and ovarian cancer in both African-American women (OR = 1.22, 95% CI: 0.96–1.55) and White women (OR = 1.34, 95% CI: 1.16–1.56 in White women), with a combined estimate of OR = 1.31 (95% CI: 1.15–1.48) overall. There were no clear dose-response trends.

5.2. Associations of genital powder use and ovarian cancer risk by histotype

As discussed previously, ovarian cancers encompass several different histotypes, which may have different cells of origin and unique risk factors. The identification of subtype-specific associations could strengthen the argument for the existence of a causal relationship. Most studies published since 1997 have included histotype-specific estimates, with serous ovarian cancers (sometimes restricted to high grade serious or invasive serous) being the most common (Table 2). In the previously published meta-analyses, Penninkilampi and Eslick reported that ever talc use was positively associated with serous carcinomas (OR = 1.32, 95% 1.22–1.43), including among cohort studies only (OR = 1.25, 95% CI: 1.01–1.55) [33]. Talc use was also positively associated with endometroid tumors (OR = 1.35, 95% CI: 1.14–1.60), and possibly mucinous (OR = 1.12, 95% CI: 0.94–1.33), but not clear cell (OR = 1.02, 95% CI: 0.75–1.39).

The Berge et al. meta-analysis reported similar findings, including a positive association between talc use and serous carcinoma (RR: 1.24; 95% CI: 1.15–1.34) and to a lesser extent endometroid carcinoma (RR: 1.15, 95% CI: 0.91–1.39), but not mucinous (RR = 0.96, 95% CI:

Table 2
Reported estimates of the association between ever (versus never) powder use and ovarian cancer by histotype, including summary estimates from published meta- and pooled analyses.

Author	Year	Serous	Endometroid	Mucinous	Clear cell	Meta-analyses			Pooled analyses		
						Penninkilampi 2018	Berge 2018	Taher 2019	Terry 2013[a]	O'Brien 2020[b]	Davis 2021[c]
Case control studies											
Harlow	1992	1.4 (0.9–2.2)	2.8 (1.2–6.4)	1.2 (0.6–2.5)	1.6 (0.8–3.3)		X	X			
Chang	1997	1.34 (0.96–1.85)	1.7 (1.00–2.79)	1.585 (0.97–2.58)		X	X	X	X		
Cook	1997	1.7 (1.1–2.5)	1.2 (0.6–2.3)	0.7 (0.4–1.4)	1.8 (1.1–2.8)	X	X	X			
Wong	1999	1.2 (0.7–2.1)	1.4 (0.7–2.7)	1.5 (0.6–4.0)	1.6 (0.6–4.3)	X	X	X			
Mills	2004	1.77 (1.12–2.81)	1.28 (0.62–2.62)	2.56 (0.89–7.39)	0.63 (0.15–2.64)	X	X	X			
Goodman	2008	1.29 (0.82, 2.03)	0.49 (0.20–1.18)	0.82 (0.29–2.30)	1.29 (0.82–2.03)		X		X		
Merritt	2008	1.21 (1.03–1.44)	1.18 (0.81–1.70)	1.10 (0.80–1.52)	1.08 (0.68–1.72)	X	X	X	X		
Gates	2008	1.60 (1.26–2.02)	1.41 (0.97–2.05)	1.28 (0.85–1.92)				X			
Moorman	2009	1.56 (1.13–2.15)	1.19 (0.69–2.06)	0.87 (0.27–1.84)	1.03 (0.52–2.03)		X	X	X		X
Rosenblatt	2011	1.01 (0.69–1.47)	1.53 (0.91–2.57)	1.78 (0.98–3.23)		X	X	X	X		
Lo-Ciganic	2012	1.12 (0.83–1.52)	1.32 (0.74–2.35)	3.03 (1.28–7.16)	1.75 (0.86–3.55)		X		X		
Cramer	2016	1.42 (1.19, 1.69)	1.38 (1.06–1.80)	0.87 (0.53, 1.44)	1.01 (0.65–1.57)	X	X	X	X		
Schildkraut	2016	1.38 (1.03–1.85)				X	X	X			X
Cohort studies											
Gertig	2000	1.26 (0.94–1.69)	0.91 (0.49–1.87)	0.93 (0.53–1.66)		X		X		X	
Gates	2010	1.06 (0.84–1.35)	1.06 (0.66–1.69)	1.50 (0.84–2.66)			X			X	
Houghton	2014	1.16 (0.88–1.53)	1.29 (0.64–2.61)	1.03 (0.47–2.27)	1.04 (0.70–1.54)	X	X	X		X	X
Pooled/meta-analyzed estimates											
Penninkilampi	2018	1.32 (1.22–1.43)	1.35 (1.14–1.60)	1.12 (0.94, 1.33)	1.02 (0.75, 1.39)						
Berge	2018	1.24 (1.15–1.34)	1.15 (0.91–1.39)	0.96 (0.73–1.18)	0.98 (0.72–1.23)						
Taher	2019	1.35 (1.21–1.50)		1.17 (0.82–1.67)							
Terry	2013	1.20 (1.09–1.32)	1.22 (1.04–1.43)	1.09 (0.84–1.42)	1.24 (1.01–1.52)						
O'Brien	2020	1.10 (0.97–1.25)	1.15 (0.83–1.58)	1.03 (0.69–1.54)	1.17 (0.73–1.89)						
Davis, African Americans	2021	1.30 (1.00–1.68)									
Davis, Whites	2021	1.32 (1.13–1.56)									

[a] Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62].
[b] Additionally includes data from the Nurses Health Study II (talc data previously unpublished) and the Sister Study [42].
[c] Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62] and the Cook County Case-Control Study (talc data previously unpublished).

0.73–1.18) or clear cell (RR = 0.98; 95% CI: 0.72–1.23) [30]. A positive association with serous tumors was again demonstrated in the Taher et al. meta-analysis (OR = 1.35, 95% CI: 1.21–1.50) [31]. Taher et al. observed an elevated but not significant risk associated with mucinous tumors (OR = 1.17, 95% CI: 0.82–1.67). In the Terry et al. pooled analysis, ever genital powder use was associated with serous (OR = 1.20, 95% CI: 1.09–1.32), endometroid (OR = 1.22, 95% CI: 1.04–1.43) and clear cell (OR = 1.24, 95% CI:1.01–1.52) carcinomas, but not mucinous (OR = 1.09, 95% CI: 0.84–1.42) [34].

In the pooled analysis that included updated data from the prospective cohorts, O'Brien et al. observed an elevated but not statistically significant hazard ratio for the association between ever genital powder use and serous ovarian cancers (HR = 1.10, 95% CI: 0.97–1.25) [32]. Estimates were also elevated for endometroid (HR = 1.15, 95% CI: 0.83–1.58) and clear cell (HR = 1.17, 95% CI: 0.73–1.89) carcinomas, but not statistically significant. Ever genital powder use was not associated with mucinous tumors (HR = 1.03, 95% CI: 0.69–1.54). The Davis et al. pooled analyses also reported elevated risk for serous tumors in both African American (OR = 1.30, 95% CI: 1.00–1.68) and white women (OR = 1.32, 95% CI: 1.13–1.56). The other histotypes were not separately evaluated [63].

Overall, these results consistently demonstrate that there is a positive association between talc use and serous ovarian cancers, and possibly also endometroid tumors. The relationship between talc use and the rarer mucinous or clear cell tumor histotypes is more ambiguous, though it is not clear whether this is due to true etiologic differences or because their rarity makes them more difficult to study.

5.3. Associations of genital powder use and ovarian cancer risk by tubal ligation and hysterectomy status

Another key factor in understanding the potentially causal relationship between talc use and ovarian cancer is the concept of patency, defined here as having an unobstructed physical pathway between the genital area and ovaries. The proposed carcinogenic mechanism suggests that talc particles must travel up the reproductive tract (through the vagina, cervix, and uterus) to reach the fallopian tubes and ovaries. As such, it would make sense that women who did not have uteri (i.e. had had a hysterectomy) and/or those who had blocked fallopian tubes (via tubal ligation), would have a markedly reduced risk of developing the disease as a direct consequence of talc use. As described below, many of the existing studies have attempted to look at this in some way. However, most were unable to do so with a clear temporal sequence between hysterectomy/tubal ligation and powder use. For example, it may not be possible to know whether talc was used prior to hysterectomy/tubal ligation or what a woman's combined patency

Table 3
Reported estimates of the association between ever (versus never) powder use and ovarian cancer stratified by hysterectomy and tubal ligation (TL) status, including summary estimates from published meta- and pooled analyses.

Author	Year	Association for ever vs. never talc use		Notes	Taher 2019 meta-analysis	Terry 2013 pooled[a]	O'Brien 2020[b] pooled
		Patent women (no hysterectomy or tubal ligation)	Women with hysterectomy and/or tubal ligation (non-patent)				
Case control studies							
Cramer	1982	2.79 ($p < 0.003$)		compared to 3.28 overall	X		
Whittemore	1988	1.33 (0.88, 2.01)	1.42 (0.75, 2.68)	non-patent estimate based on crude numbers	X		
Harlow	1992	1.7 (1.0–3.0) for 10,000 applications versus none		compared to 1.8 (1.0, 3.0) overall	X		
Rosenblatt	1992	2.4 (1.0–5.8)	0.15 (0.027–0.88)	tubal ligation only; patency estimates based on talc use prior to tubal ligation/ never tubal ligation, non-patent estimate based on time after tubal ligation	X		
Green	1997	1.3 (1.0–1.7)	0.6 (0.5–0.84)	patency estimates based on talc use prior to surgery/ never surgery, non-patent estimate based on time after surgery	X		
Chang	1997	1.11 (0.99–1.24)	1.03 (0.82–1.29)		X	X	
Cook	1997			estimates unchanged after excluding those who used powder after hysterectomy/tubal ligation	X		
Wong	1999	1.2 (0.8–1.6)	0.8 (0.5–1.2)		X		
Mills	2004	1.54 (1.10–2.16) no TL; 1.33 (0.95–1.87) no hyst	0.88 (0.46–1.68) TL; 1.79 (0.91–3.52) hyst		X		
Merritt	2008	>25 years vs. none: 1.29 (1.04–1.58), p-trend =0.02	>25 years vs. none: 1.00 (0.64–1.51); p-trend = 0.61	patency estimates based on talc use prior to surgery/ never surgery, non-patent estimate based on time after surgery	X	X	
Rosenblatt	2011	1.23 (0.93–1.64)		compared to 1.27 (0.97, 1.66) overall	X	X	
Cramer	2016	1.22 (1.04, 1.43)	1.73 (1.31, 2.27)		X	X	
Cohort studies							
Gertig	2000	1.16 (1.01–1.33)	1.07 (0.94–1.20)	updated study-specific results from O'Brien et al.	X		X
Houghton	2014	1.13 (1.01–1.26)	1.11 (0.95–1.30)	updated study-specific results from O'Brien et al.	X		X
Gonzalez	2016	0.85 (0.92–1.39)	1.02 (0.76–1.38)	updated study-specific results from O'Brien et al.	X		X
Pooled/Meta-analyzed estimates							
Taher	2019		1.06 (0.78, 1.42)	compared to 1.06 (0.90–1.25) overall			
Terry	2013	Q5 vs. Q1 of cumulative applications: 1.36 (1.18–1.57)		Limiting analysis to those exposed prior to surgery (or never surgery) made "no substantive difference" in results			
O'Brien	2020	1.13 (1.01–1.26)	0.99 (0.86–1.15)				
Davis[c]	2021	1.27 (1.09–1.48)	1.42 (1.17–1.72)				

[a] Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62]; the Hawaii Ovarian Cancer Study [43]; the North Carolina Ovarian Cancer Study [53]; the Hormones and Ovarian Cancer Prediction Study [50].
[b] Additionally includes data from the Nurses Health Study II (talc data previously unpublished) and the Sister Study [42].
[c] Includes only Women's Health Initiative [48] from table. Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62], the Cook County Case-Control Study (talc data previously unpublished), North Carolina Ovarian Cancer Study [53] and the African-American Cancer Epidemiology Study [28].

and talc use status was during key windows of susceptibility (e.g. menopause).

In their pooled analysis of 8 case-control studies, Terry et al. found that after excluding those who first started using genital powder after hysterectomy or tubal ligation, results were similar to the overall analysis (Table 3; OR = 1.36, 95% CI: 1.18–1.57 for the 4th versus 1st quartile of cumulative number of lifetime talc applications; compared to original overall estimate OR = 1.32, 95% CI: 1.16–1.52) [34]. The only meta-analysis to explore this issue was Taher et al., who reported an inverse association between talc and ovarian cancer among those who had had tubal ligation (OR = 0.64, 95% CI: 0.45–0.92) [31]. When they examined studies that reported estimates from participants with a history of either hysterectomy or tubal ligation, the meta-analyzed estimate was close to null (OR = 1.06, 95% CI: 0.78–1.42). Davis et al. reported similar estimates when analyses were restricted to women with patent reproductive tracts (OR = 1.27, 95% CI: 1.09–1.48) versus those with a history of tubal ligation or hysterectomy (OR = 1.42, 95% CI: 1.17–1.72; p-for-heterogeneity = 0.31) [63].

The prospective studies did not systematically collect details on timing of genital powder use relative to the age at which women underwent hysterectomy or tubal ligation [32]. However, in those who had patent reproductive tracts at enrollment, a history of genital powder use was associated with an increased risk of developing incident ovarian cancer (HR = 1.13, 95% CI: 1.01–1.26). This association was null among women who did not have patent reproductive tracts at enrollment (HR = 0.99, 95% CI: 0.86–1.15).

Given the difficulties with establishing a clear sequence of events in the genital powder use relative to hysterectomy or tubal ligation, especially in the case-control studies, the interpretation of these findings is quite difficult. However, the results of the prospective studies support the hypothesis that the positive association between genital powder use and ovarian cancer may be limited to women with patent reproductive tracts.

5.4. Associations of genital powder use and ovarian cancer risk in diverse populations

As previously mentioned, Davis et al. conducted a pooled analysis examining the association between genital powder use and ovarian cancer in the OCWAA consortium [63], which only included studies with large samples of African-American women. Consistent with previously observed trends, African American women in the included studies were more likely to report ever having used genital powder (34% of African-American non-cases versus 31% of White non-cases), but effect estimates were similar between the two racial groups (OR = 1.22, 95% CI: 0.97–1.53 in African American women and OR = 1.37, 95% CI: 1.1–1.57 in White women). In analyses limited to high grade serous tumors, Davis et al. reported elevated associations for both African American (OR = 1.30. 95% CI: 1.00–1.68) and White (OR = 1.32, 95% CI: 1.13–1.56) women. Non-serous tumors were positively associated with powder use in White women (OR = 1.38, 95% CI: 1.15–1.66), but not African American women (OR = 1.08. 95% CI: 0.78–1.51).

5.5. Association of genital powder use and uterine cancer

The shared etiology of ovarian and uterine cancer subtypes warrant evaluation of presumed and established ovarian cancer risk factors in uterine cancer studies. Genital powder has easier access to the uterine lining compared to the fallopian tubes and the ovarian surface. On the other hand, menstruation could clear genital powder from the surface of the uterus, thereby mitigating its influence. Several studies have evaluated the association of genital powder use and uterine cancer, including one case-control study [64] and three cohort studies [65–67]. Updated data from the three cohorts plus the Nurses' Health Study II were combined in a uterine-cancer specific pooled analysis [26].

The case-control study reported no association between perineal talc use and endometrial cancer (OR = 0.88, 95% CI: 0.68–1.14) [64]. Findings from the pooled analysis were also null (HR = 1.01, 95% CI: 0.94–1.09), except for a possible increased risk among long-term users (>20 years; HR = 1.12, 95% CI: 0.96–1.31). There was no evidence for heterogeneity by endometrial cancer subtype.

6. Conclusion

When assessing the complex relationship between genital powder use and ovarian cancer, three important related questions need to be addressed: 1. Is there an association between genital powder and ovarian cancer risk? 2. If there is an association, what is the underlying causal factor? 3. If there is an association, what is the clinical and public health relevance? The epidemiological data on the association between powder use and ovarian cancer risk have varied by study type. Recent systematic reviews and meta-analyses that included case-control data reported elevated ovarian cancer risk among powder users relative to non-users, with odds ratios ranging from 1.22 to 1.32. Concern has been raised that this association could be at least somewhat attributable to recall bias, which would occur if ovarian cancer patients were more likely to report body powder use compared to controls [29].

Because cohort studies assess exposure before disease occurs, they are not subject to recall bias. Individual cohort studies have not shown statistically significant associations between powder use and ovarian cancer risk, but many cohort studies are limited by low ovarian cancer case numbers and limited exposure assessments. In a recent pooled cohort analysis with a large number of cases, ever use of genital powder was positively associated with ovarian cancer, but the hazard ratio did not reach statistical significance. However, a pre-specified sub-analysis limited to women who had not had a hysterectomy or tubal ligation showed a statistically significant positive association (HR = 1.13). Taken together, the epidemiological data from case-control studies and cohort studies suggest that there may be a small, positive association between genital powder use and ovarian cancer, which may be limited to women with patent reproductive tracts. Data from a large case-control study suggested that associations between talc use and ovarian cancer risk were largely confined to premenopausal women and postmenopausal women who used hormone therapy [39]. This could indicate that estrogen may be an effect modifier of the talc-ovarian cancer association.

The inability to differentiate between different types of powder and their respective ingredients in epidemiological studies makes it challenging to identify factors responsible for the observed associations. Since talc is a major component in many body powders, it has long been proposed as a causal factor. However, the experimental and animal carcinogenicity data for talc are limited and inconclusive, and there are currently no good animal or experimental models of ovarian carcinogenesis that could be used to more directly test biological effects of talc [1]. Asbestos contamination of talc was proposed as an explanation for some of the initially observed associations between powder use and ovarian cancer, and recent findings of asbestos contamination in cosmetic products suggest that asbestos could have continued to play a role. Data on other possibly carcinogenic contaminants of talc, such as quartz, are very scarce. Other components of body powder, including corn starch, could also possibly play a role in carcinogenesis by inducing inflammation in the reproductive tract, but carcinogenicity data are lacking. Confounding by indication may explain some of the observed associations. This would occur if women with hormonal or inflammatory exposures or conditions that are associated with ovarian cancer were also more likely to use powder in the genital area. However, there is currently no data supporting such an effect. In summary, we currently do not understand the causal factors that underly the observed weak associations between genital powder use and ovarian cancer risk.

Independent of the underlying cause, the association between powder use and ovarian cancer risk is weak. The low relative risk translates to a very low absolute risk increase, given the rarity of ovarian cancer. In the pooled cohort analysis by O'Brien et al., the estimated increase in ovarian cancer risk by age 70 was 0.09% (95% CI: −0.02-0.19%) for all users of body powder and 0.22% (95% CI: 0.02–0.42%) for body powder users with patent reproductive tracts [32]. Given the inability to attribute a clear causal factor to the observed associations, the lack of a good experimental model, the lack of a specific biomarker for powder-related carcinogenesis, and the inability to rule out confounding by indication, it is difficult to conclude that the observed associations are causal. Furthermore, given the widespread use of powders and the rarity of ovarian cancer, the case for public health relevance is limited.

Future work on understanding the association of powder use and ovarian cancer risk should focus both on existing data and new studies. Given that the association from case-control studies may be exaggerated by recall bias and the association from cohort studies may be underestimated because of limited exposure information and attenuation in effects over time since exposure assessment, the association probably lies between these estimates. A systematic bias assessment could attempt to account for these biases and lead to a more accurate risk estimate. Existing studies may have collected more detailed exposure information, particularly on timing of powder use and brand names that could allow investigators to revisit the role of possible asbestos contamination of cosmetic talc products. Further, data on additional medical conditions that may be related both to ovarian cancer risk and powder use may be available in these studies, allowing for further evaluation of confounding by indication. Future studies should expand on the assessment of body powder use, with an extended focus that captures data on different formulations, including talc-free brands and improved exposure quantification. Ideally, this would also include careful consideration of differences in product use across different racial/ethnic groups, given the observed higher use of genital powder among African American women [63]. Biological and experimental studies on potential mechanisms of powder-related carcinogenesis should also focus more on extra-ovarian cells of origin, particularly in the fallopian tubes. Further, biological studies should evaluate other components of body powders, such as corn starch, that may cause inflammatory reactions in the genital tract and the fallopian tubes. Despite the limitations of current experimental and animal models that complicate evaluating the full carcinogenic process, the effects of body powder components on inflammation in various areas of the genital tract could provide important data on intermediate endpoints that could explain potential carcinogenic mechanisms.

Use of talcum powder has decreased substantially in the US over the last decades [68]. Following the recent reports on asbestos contamination of talc products, the cosmetic industry has moved away from using talc in their products and major brands of talcum powder have been removed from the market. Given the weak observed associations and the uncertainty of the underlying causes, current recommendations about body powder use remain vague. For example, the American Cancer Society states that “Until more information is available, people concerned about using talcum powder may want to avoid or limit their use of consumer products that contain it.” [69] Given the uncertainty about the role of other powder ingredients in the observed associations and continued widespread use of body powder around the world, we should continue to evaluate the health effects of genital powder use, as well as the public health messaging related to powder use.

Author contributions

Nicolas Wentzensen: Conceptualization; Data curation; Investigation; Methodology; Writing - original draft, review & editing. *Katie O'Brien*: Conceptualization; Data curation; Investigation; Methodology; Writing - original draft, review & editing.

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Declaration of Competing Interest

The authors do not report a conflict of interest.

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EXHIBIT 3

EDITORIAL

Use of Powder in the Genital Area and Ovarian Cancer Risk
Examining the Evidence

Dana R. Gossett, MD, MSCI; Marcela G. del Carmen, MD, MPH

Women have used powders for genital hygiene for decades to absorb odor and moisture. While rates of powder use in the genital area have declined over the last 50 years,[1] it remains a routine practice for some women. Commonly used products typically include talc, cornstarch, or some combination of both. Women may apply powders directly to the perineum or onto sanitary napkins, tampons, diaphragms, or underwear. Investigations of an association between the use of talc-containing powders for genital hygiene and epithelial ovarian cancer risks have provided inconsistent results to date and resulted in ongoing controversy. Since 1971, peer-reviewed articles have documented the possible association between talc use and the development of ovarian cancer. However, a PubMed search covering the last 5 decades identified only 17 primary or secondary studies and 36 other articles that were reviews, commentaries, meta-analyses, or letters to the editor.[1-4] In short, while some investigations have been reported, the majority of publications were opinion and discussion articles.

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Several case-control studies identified an increased risk of ovarian cancer with relatively small effect sizes—odds ratios (ORs) of 1.24 to 1.6.[5-8] In a 2018 meta-analysis that included 24 case-control studies and 3 cohort studies, any use of talc in the perineal region was associated with an increased risk of developing epithelial ovarian cancer, with a statistically significant association in case-control studies (OR, 1.35 [95% CI, 1.27-1.43]), and a non-statistically significant association in cohort studies (OR, 1.06 [95% CI, 0.90-1.25]).[2] These studies have been criticized for likely recall bias among patients with cancer, which could increase reported talc use among these patients compared with controls and inflate the calculated association. Cohort studies, such as the Women's Health Initiative (WHI), have not demonstrated the same associations between talc use and ovarian cancer.[9] Since a minority of women in the United States use powder in the genital area, these studies may have lacked power to detect a true association given the relative rarity of epithelial ovarian cancer. Despite this lack of consistency in the primary literature, review articles cited "the robustness of the association between perineal exposure to talc and ovarian cancer."[10-13]

This lack of clarity, as well as recent high-profile litigation regarding the risks of ovarian cancer among users of talc products, prompted O'Brien and colleagues to investigate the question with a larger study population, as reported in this issue of *JAMA*.[14] The authors conducted a pooled analysis of 4 large prospective cohort studies—the Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), Women's Health Initiative Observational Study (WHI-OS), and the Sister Study (SIS). Investigators from 3 of these 4 cohort studies had previously published findings regarding talc use and ovarian cancer risk.[9,15,16] The authors pooled data from all 4 studies to create a cohort of more than 252 745 women, of whom 2168 developed ovarian cancer during the study periods. This is the largest reported investigation to date.

Each of the 4 studies used slightly different measures for powder or talc exposure; 3 of the 4 queried women about duration of use (NHSII, SIS, WHI-OS), and 3 of the 4 queried women about frequency of use (NHS, NHSII, SIS). Thus, the authors of the current investigation performed 2 different dose-response analyses with these 2 subgroups of study participants, one for duration and the other for frequency. The authors identified a decrease in use of powder in the genital area over time, with the oldest cohort (the WHI-OS participants) most likely to report use of powder (53%) and younger participants reporting lower rates of use (NHSII, 26% and SIS, 27%).

Given the varying ages of the participants and the varying duration of exposure and follow-up, the investigators calculated an estimated risk of ovarian cancer by the age of 70 in both the exposed and unexposed groups and found a hazard ratio (HR) of 1.08 (95% CI, 0.99-1.17) between ever users and never users of powder in the genital area. This estimate did not reach statistical significance, although it is important to note the CIs. Examination of duration and frequency of powder use in the genital area yielded similar results, with no evidence of a significant dose-response relationship identified in the study population. However, when the analysis was restricted to women with patent reproductive tracts (in situ uterus and fallopian tubes), the HR among ever users of powder was 1.13 (95% CI, 1.01-1.26). For "frequent" use of powder in the genital area vs non-use among women with patent reproductive tracts, the HR was 1.19 (95%CI, 1.03-1.37; *P* value for trend = .03).

The putative etiologic mechanism for talc as a causative agent in epithelial ovarian cancer is via uptake into the vagina, through the cervix and uterus, and through the fallopian tubes into the peritoneal cavity. The evidence of talc in ovarian specimens lends credence to a transgenital transit mechanism.[17-19] Once in contact with the fallopian tubes, ovaries, and peritoneum, it is posited that talc causes local inflammation and triggers a carcinogenic process.[20] Talc has structural similarities to asbestos and is often found in the same mines from which asbestos is obtained. Whether inflammation occurs in response to mineral talc alone or occurs only when talc is contaminated with asbestos remains

an area of controversy. Data regarding rates of asbestos contamination in talc products are scarce and there are public accusations that companies manufacturing talc powder have manipulated or hidden such data.[21,22] Whether the carcinogenic agent is hypothesized to be talc or asbestos, in either case, the agent would need direct access to the fallopian tubes, ovaries, and peritoneum. Thus, the patency of the reproductive tract during the time of exposure is of paramount interest. If a woman has had a hysterectomy or a tubal ligation, then talc applied to the vulva or vagina will have no means of ingress and could not cause inflammation of the fallopian tubes or ovaries.

Given this putative mechanism of exposure, the subgroup analysis of women with patent reproductive tracts is of particular interest. However, it is not possible to equate a patent reproductive tract with exposure and a nonpatent reproductive tract with nonexposure. Women who undergo tubal ligation or hysterectomy (nonpatent) and use powders in the genital area cannot be assumed to have started using them only after their surgeries—in fact, this is highly unlikely as women often begin use of powder in the genital area during adolescence. Thus, the stratification of the groups as patent and nonpatent does not clearly group women into exposed and nonexposed categories. The fact that there are no significant differences in the HRs in the patent (HR, 1.13 [95% CI, 1.01-1.26]) and nonpatent subgroups (HR, 0.99 [95% CI, 0.86-1.15]; *P* value for heterogeneity comparing these subgroups of .15) confirms the overall conclusion that there is no demonstrable statistically significant association between use of powder in the genital area and ovarian cancer risk. This is the key finding of the study. The subgroup analysis suggesting that women with intact reproductive tracts who used powder in the perineal area developed ovarian cancer more frequently than nonusers is below the effect size that epidemiologists generally consider important and should not be selectively highlighted by the statistically unsophisticated reader as evidence of a relationship. In addition, the investigators conducted multiple subgroup analyses increasing the risk of a type I error or a finding that reaches statistical significance but results from chance alone. The fact that this subgroup finding barely achieves statistical significance is further evidence that it is does not represent a true association. The conclusions of the authors, supported by tests of heterogeneity across subgroup HRs, are that there was no evidence of a statistically significant association between use of powder in the genital area and ovarian cancer.

The study by O'Brien et al represents the largest cohort to date to examine whether an association exists between powder use in the genital area and ovarian cancer risk, and the findings are overall reassuring. Yet, despite 3.8 million person-years of observation in the study population, the number of ovarian cancer cases was small, and it is possible that the study was underpowered to detect small increases or decreases in ovarian cancer rates. Future analyses would be strengthened by focusing on women with intact reproductive tracts, with particular attention to timing and duration of exposure to powder in the genital area. Accumulation of such data will take many years, and given the low rates of current powder use among US women, may not be feasible. Nonetheless, the rigorously conducted study by O'Brien et al contributes important and timely data about the potential link between use of powder in the genital area and risk of ovarian cancer.

ARTICLE INFORMATION

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Can an Evidence-Based Approach Improve the Patient-Physician Relationship?

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The importance of the patient-physician relationship has been recognized for millennia.[1,2] Concern that this special relationship is threatened has likely existed nearly as long, although more recently time constraints, insurer demands, novel technologies, and documentation burdens have intensified these worries.[3,4] In their Special Communication in this issue of *JAMA*, Zulman et al report a novel study that proposes a limited number of evidence-based practices that may lead to more meaningful connections between patients and physicians.[5]

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The novelty of this study is the approach the authors used to identify, group, and distill their suggested practices. The authors first performed a literature search that identified 73 studies of evidence-based, interpersonal interventions that could potentially improve practice in 4 domains: patient experience, clinician experience, population health, and health care utilization and cost. Next, a diverse group of physicians, chosen for their exceptional interpersonal skills, were observed in 27 distinct patient encounters. Patients and physicians were debriefed after the interview to identify successful strategies used by the clinicians. Then, nonmedical professionals from 7 professions whose jobs involve intense interpersonal interactions were interviewed to identify cross-disciplinary practices thought to foster human connection.

Through these steps, the research team identified potentially useful clinical approaches that were perceived to contribute to physician "presence," defined by the authors as a purposeful practice of "awareness, focus, and attention with the intent to understand and connect with patients." These practices were rated by patients and clinicians on their likely effects and feasibility in practice. A Delphi process was used to condense 13 preliminary practices into 5 final recommendations, which were (1) prepare with intention, (2) listen intently and completely, (3) agree on what matters most, (4) connect with the patient's story, and (5) explore emotional cues. Each of these practices is complex, and the authors provide detailed explanations, including narrative examples and links to outcomes, that are summarized in the article and included in more detail in the online supplemental material.

If implemented in practice, these 5 practices suggested by Zulman and colleagues are likely to enhance patient-physician relationships, which ideally could help improve physician satisfaction and well-being, reduce physician frustration, improve clinical outcomes, and reduce health care costs. Importantly, the authors also call for system-level interventions to create an environment for the implementation of these practices. Although the patient-physician interaction is at the core of most physicians' activities and has led to an entire genre of literature and television programs, very little is actually known about what makes for an effective relationship. In part, this is because the patient-physician interaction occurs in private, making its study difficult.[6] Efforts to identify effective practices, measure their effectiveness, and learn to teach them are uncommon. The authors' methods of searching for strategies that have some evidentiary support, enhancing their search with clinical experiences and nonclinical expertise, and then synthesizing this information into potentially usable strategies are impressive. They also emphasize the importance of culturally sensitive care and caution against assumptions based on race, ethnicity, gender, socioeconomic status, or past encounters.

However, there are challenges in considering the results of the study. One reason might be the lack of a clear connection between the evidence and the recommendations. A report that focused on motivational interviewing in nursing practice was used to bolster the recommendation to "connect with the patient's story."[7] While the advice to prepare and listen to a patient would be advised by most practicing clinicians without reading this Special Communication, "listen intently and completely" and "explore emotional cues" are such broad and generic recommendations that physicians might as well be advised to be attentive and kind.

The recommendations are on strongest ground in linking the 5 recommended practices to the domains of improved patient and clinician satisfaction. It is less clear if following the recommended practices will actually lead to improved clinical outcomes. For example, in support of the "explore emotional cues" recommendation, Zulman et al cited the "population health" benefit of a study that showed an association between an intervention enhancing clinician empathy and a reduction of common cold symptoms from 7 days to 5.9 days.[8]

CERTIFICATION OF SERVICE

I hereby certify that on April 22, 2024, a true and correct copy of the foregoing documents was filed electronically. Notice of this filing will be sent by operation of the Court's electronic filing system to all parties indicated on the electronic filing receipt. Parties may access this filing through the Court's system.

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