Talc Use and Ovarian Cancer: Epidemiology Between a Rock and a Hard Place
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With over 14,000 deaths in the United States each year, ovarian cancer is the most lethal gynecologic cancer (1). Most ovarian cancers are detected at late stage and have poor prognoses. Given the failure at prevention of death by screening for ovarian cancer using CA-125 and transvaginal ultrasound (2), finding potential preventive interventions has greatest promise of reducing ovarian cancer mortality.

Ample epidemiologic evidence suggesting that inflammation plays an important role in ovarian carcinogenesis include associations of incessant ovulation, endometriosis, and pelvic inflammatory disease with increased ovarian cancer risk (3) and reduced risks observed for regular aspirin users (4).

Evidence on perineal talc use as a risk factor for ovarian cancer is more equivocal. Talc, a metamorphic mineral composed of magnesium silicate that absorbs water, is a common component of genital powders. Naturally, talc has similarities to and co-occurs with asbestos; although early studies hypothesized that asbestos contamination of talc may have a causal role in ovarian carcinogenesis, later case-control studies reporting use after cosmetic products became asbestos-free in the United States continued to show associations.

The biological basis of possible talc carcinogenicity is not understood. Direct physical contact of talc with ovarian epithelium may cause chronic inflammation; some studies have suggested retrograde transport of talc particles through the reproductive tract (5). A mechanism that would not require direct contact of talc with the tissue at risk is reduction of anti-MUC1 antibodies, which are associated with lower risk of ovarian cancer (6).

In this issue of the Journal, Houghton and colleagues report on the association between perineal powder use and ovarian cancer risk from the observational arm of the Women's Health Initiative (WHI) (7). Although several case-control studies have reported associations between talc use and ovarian cancer risk (8–10), the only previous prospective evaluation of talc use and ovarian cancer risk did not find an association with ovarian cancer overall, but with serous ovarian cancer, the most common and most lethal subtype (11). With over 400 cases, the new study was well powered to confirm previously reported effect sizes (7). However, the authors found neither an association between perineal powder use with ovarian cancer overall nor with specific subtypes.

Assessing the association between talc use and ovarian cancer risk poses several challenges: First and foremost, assessment of talc exposure relies purely on self-report. Talc use is not documented in medical or pharmacy records that could be used to confirm or supplant self-reported use. Therefore, reporting bias is of great concern in case-control studies. Previous studies have argued that a stronger association observed for certain ovarian cancer subtypes speaks against reporting bias (8). However, the clinical presentation and prognosis of ovarian cancer, which varies by ovarian cancer subtype, may differentially affect cases’ reporting.

Further, the quantification of talc dose is very difficult: Cosmetic perineal powders vary in talc content. Talc can be applied as spray or powder, either directly to the genital region, using swabs, or by application on diaphragms. The amount of talc applied or making contact with the ovary may vary substantially by mode of application. Particularly the cohort studies suffer from very limited exposure information: The Nurses’ Health Study which previously reported on talc use collected only information on frequency of talc use per week (11), whereas the Women's Health Initiative (7) only collected information on duration of use, not on frequency.
to women will need to weigh the benefits of perineal talc use against the potential harms and the effective alternative products for reducing moisture absorption to prevent chafing and rashes; no evaluation of long-term use of alternative products has been undertaken.

How do the results from Houghton et al. (7) change the assessment of harm related to perineal talc use? Overall, the evidence regarding carcinogenicity of talc use remains inconclusive. While reporting bias may explain the positive associations reported from case-control studies, the limitations of cohort studies regarding exposure assessment still do not completely eliminate the possibility that talc use is associated with ovarian cancer risk. So where do we go from here? Ideally, we would want to have high-quality exposure data on talc use in a cohort setting, with periodic updates on exposure. These data are currently not available. Ovarian cancer is rare, and collecting these data prospectively will take time.

Behavioral exposures such as cosmetic talc use are very difficult to assess, even though they are important for etiology and possibly public health. Cohort studies need attentive participants, long follow-up, detailed histology, and large sample size to be helpful. Case-control studies must avoid differential misclassification. There does not seem likely that additional conventional epidemiological studies will strengthen the evidence for or against talc carcinogenicity. Other exposures face similar challenges of misclassification and reporting bias, such as diet and physical activity. One possible long shot for exposure assessment might be phone apps similar to those reporting bias, such as diet and physical activity. One possible long shot for exposure assessment might be phone apps similar to those

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Notes
The authors report no conflict of interest.

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