DOI:10.1093/jnci/dju260
First published online September 11, 2014

EDITORIAL

Talc Use and Ovarian Cancer: Epidemiology Between a Rock and a Hard Place

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With over 14000 deaths in the United Stated 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. So far, no epidemiologic study has demonstrated a dose-response relationship between talc use and ovarian cancer risk.

In addition to the difficulties of talc exposure assessment, ovarian cancer is a challenging outcome because of its rarity and heterogeneity (12). There is increasing evidence supporting the hypothesis that ovarian cancers may derive from different cells of origin. For example, some serous ovarian cancers supposedly originate in the fallopian tubes, while some endometrioid cancers may originate in ectopic or orthotopic endometrial tissue (13). Reports of a stronger association of talc use with serous ovarian cancers compared with other subtypes (8) might suggest that talc exposure to the fallopian tubes plays a role in carcinogenesis. However, the associations with serous cancers are not consistent, and experimental data are lacking. Even larger sample sizes and high-quality subtype data are needed to establish subtype-specific associations.

Based on the evidence from epidemiologic studies, in 2006 the International Agency for Research on Cancer (IARC) classified genital talc use as possibly carcinogenic to humans (carcinogen group 2B) (14). The limited evidence for this recommendation was based primarily on the case-control studies that showed increased risk of ovarian cancer. From a regulatory perspective, cosmetic products do not require review by the US Food and Drug Administration (FDA), but the FDA can act on evidence of harm related to cosmetic products. While the FDA is currently monitoring potential health effects of cosmetic talc use, the activities have mainly focused on assuring that cosmetic talc products are asbestos-free (15). Helpful recommendations

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 to be an independent, more objective data source that could be used to assess talc exposure. With the current evidence, it 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 that can improve food frequency assessment or physical activity (16). These technologies could improve quantification of talc use, providing detailed data on dose, frequency, and duration in cohort study participants. Meanwhile, cosmetic talc use has substantially decreased in the United States between 1982 and 2004 (17). While the reasons are not clear, it is possible that consumers already react to reports of potential harms, despite the lack of clear evidence.

References

1. American Cancer Society. Cancer Facts and Figures 2012.
2. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA*. 2011;305(22):2295–2303.
3. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst*. 1999;91(17):1459–1467.
4. Trabert B, Ness RB, Lo-Ciganic WH, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst*. 2014;106(2):djt431 doi:10.1093/jnci/djt431.
5. Cramer DW, Welch WR, Berkowitz RS, Godleski JJ. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obstet Gynecol*. 2007;110(2 Pt 2):498–501.
6. Cramer DW, Titus-Ernstoff L, McKolanis JR, et al. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14(5):1125–1131.
7. Houghton SC, Reeves K, Hankinson SE, et al. Perineal powder use and risk of ovarian cancer. *J Natl Cancer Inst*. 2014;(9):dju208 doi:10.1093/jnci/dju208.
8. Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital talc exposure and risk of ovarian cancer. *Int J Cancer*. 1999;81(3):351–356.
9. Muscat JE, Huncharek MS. Perineal talc use and ovarian cancer: a critical review. *Eur J Cancer Prev*. 2008;17(2):139–146.
10. Terry KL, Karageorgi S, Shvetsov YB, et al. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res (Phila)*. 2013;6(8):811–821.
11. Gertig DM, Hunter DJ, Cramer DW, et al. Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst*. 2000;92(3):249–252.
12. Yang HP, Trabert B, Murphy MA, et al. Ovarian cancer risk factors by histologic subtypes in the NIH-AARP Diet and Health Study. *Int J Cancer*. 2012;131(4):938–948.
13. Sherman ME, Guido R, Wentzensen N, Yang HP, Mai PL, Greene MH. New views on the pathogenesis of high-grade pelvic serous carcinoma with suggestions for advancing future research. *Gynecol Oncol*. 2012;127(3):645–650.
14. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Talc Not Containing Asbestiform Fibres. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Volume 93: Carbon Black, Titanium Dioxide, and Talc. 2010:277–412.
15. FDA. Talc. Food and Drug Administration Homepage. 2014.
16. Rusin M, Arsand E, Hartvigsen G. Functionalities and input methods for recording food intake: a systematic review. *Int J Med Inform*. 2013;82(8):653–664.
17. Kelly TD, Matos GR. Historical Statistics for Mineral and Material Commodities in the United States. April 9, 2014.

Notes

The authors report no conflict of interest.

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