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Research Article

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Perineal Use of Talcum Powder and Endometrial Cancer Risk

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Abstract

Background: Several studies have reported a positive association between perineal use of talcum powder among adult women and ovarian cancer risk. However, the relationship between talcum powder use and other gynecologic malignancies such as endometrial cancer has not been examined, and little information is available on nonhormonal risk factors for endometrial cancer.

Methods: Perineal use of talcum powder was assessed in 1982 in the Nurses' Health Study. Approximately 40% of women who responded to the questions about perineal use of talcum powder reported ever use. Cox proportional hazards models were used to estimate the incidence rate ratio of endometrial cancer and 95% confidence interval (CI), adjusted for body mass index and other potential confounders. We evaluated the relationship among all women and stratified by menopausal status.

Results: Our analysis included 66,028 women with 599 incident cases of invasive endometrial adenocarcinoma diagnosed between 1982 and 2004. Although no association was observed overall, the association varied by menopausal status (P interaction = 0.02) and a positive association was observed among postmenopausal women; ever use of talcum powder was associated with a 21% increase in risk of endometrial cancer (95% CI, 1.02-1.44), whereas regular use (at least once a week) was associated with a 24% increase in risk (95% CI, 1.03-1.48). In addition, we observed a borderline increase in risk with increasing frequency of use (P trend = 0.04).

Conclusions: Our results suggest that perineal talcum powder use increases the risk of endometrial cancer, particularly among postmenopausal women.

Impact: Future and larger studies are needed to confirm this association and investigate potential mechanisms. *Cancer Epidemiol Biomarkers Prev; 19(5); 1269–75. ©2010 AACR.*

Introduction

Several studies have reported a positive association between use of talcum powder on the perineal area and ovarian cancer risk (1, 2). In 2006, the IARC classified perineal use of talc as a possible carcinogen (2). In a meta-analysis, data from 16 studies suggested that talc may increase ovarian cancer risk by 30% (1). However, no previous studies have investigated whether talcum powder applied to the perineal area was associated with other gynecologic malignancies such as endometrial cancer. Furthermore, little information is available on factors that influence risk of endometrial cancer, a hormone-responsive cancer (3), through nonhormonal pathways.

Talc is a hydrous magnesium silicate mineral chemically similar to the serpentine class of asbestos (4). In nature, talc is commonly found with other minerals such as chlorite, carbonates, amphiboles, and serpentines (5), in a fibrous or nonfibrous foliated structure (6). Before 1976, talcum powder was commonly contaminated with asbestos due to the proximity of talc and asbestos deposits in nature (7). Guidelines were set thereafter in the United States to ensure that only talc with no detectable levels of asbestos was used in cosmetic products (8). Talc used in powders is finely ground (4, 9); however, it is unknown whether processing of talc makes it more hazardous or increases its potential carcinogenicity (10, 11).

Older studies suggested a link between asbestos exposure in female workers and ovarian cancer incidence (8), which, together with the pathologic similarity between malignant pleural mesothelioma and ovarian tumors and the evidence of talc particles found in ovarian tissue (12), led to the investigation of whether talcum powder increased the risk of ovarian cancer. Although perineal talc use is common among adults—as many as 40% of women in the United States have used talcum powder for feminine hygiene (13, 14)—additional studies are needed to assess other possible health consequences. In this analysis, we used data from the Nurses' Health

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Study (NHS) to assess whether genital use of talcum powder among women confers an increased risk of endometrial cancer.

Materials and Methods

Study population. The NHS is a prospective cohort study established in 1976, when 121,700 married female registered nurses residing in 11 U.S. states and were between the ages of 30 to 55 completed a baseline mailed questionnaire inquiring about various disease exposures and personal health status. Revised questionnaires were mailed biennially to update exposure and disease information. The follow-up rate through 2004, as measured as a percentage of total possible person-years, was 95.5%. Deaths in this cohort were identified by next-of-kin reports, the U.S. Postal Service, or through searches of the National Death Index (15). The Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital, Boston, MA approved this analysis.

For this study, we excluded women who had had a hysterectomy (n = 30,287), had surgical menopause (n = 123), reported endometrial cancer (n = 89), reported any other type of cancer excluding nonmelanoma skin cancer (n = 1,422), or had died (n = 1,203) prior to assessment of talcum powder use in 1982. Women who were missing body mass index (BMI) for at least two consecutive cycles prior to and including the 1982 cycle were temporarily excluded until they reported their weight again. A total of 66,028 women remained for analysis.

Diagnosis of endometrial cancer cases. Information on endometrial cancer diagnoses was collected beginning in 1978 and at each subsequent questionnaire cycle. Women who reported a diagnosis of endometrial cancer were asked for permission to review their medical records. Only cases of invasive type I endometrioid adenocarcinoma (International Classification of Diseases for Oncology-3 histology codes 8380-83) confirmed by medical records were included in this analysis.

Data collection. Use of talcum powder was assessed in 1982. Participants were asked whether they had ever commonly applied talcum, baby, or deodorizing powder to the perineal area (no, less than once a week, one to six times a week, daily), or to sanitary napkins (no, yes).

Age at menarche was collected at baseline in 1976. Menopausal status, age at menopause and type of menopause were collected at baseline and every 2 years thereafter. On each questionnaire, women were asked whether their menstrual periods had ceased permanently [yes, no longer have periods; yes, periods induced by hormones (asked from 1988 onwards); no, unsure]. Women who responded "yes" were classified as postmenopausal and this status was carried forward into all future cycles. Women who responded "no or unsure" were classified as premenopausal. Women missing menopausal status were classified as postmenopausal if they were above a certain age (>54 years for current smokers, >56 years for former or nonsmokers). Nurses were also asked at what age their periods ceased and for what reason (natural, surgery). Age at menopause in the NHS is reported with a high degree of reproducibility and accuracy (16).

Women reported the number of pregnancies lasting 6 months or more and their age at first birth on every questionnaire through 1984. In 1996, they were asked to report their lifetime pregnancy history. These data were used to derive biennially updated variables for parity, age at first birth, and age at last birth.

Postmenopausal hormone (PMH) use and duration of use were first asked in 1976. Beginning in 1978 and at each 2-year follow-up, women were asked whether they currently used PMH, the number of months used during the 24 months prior to the questionnaire, and the type of PMH. Duration of ever hormone use was calculated as the cumulative duration of all types of PMH use reported over the follow-up.

Information on weight, diabetes, and smoking were collected at baseline and updated every 2 years. BMI (kg/m^2) was calculated using height reported in 1976 and weight reported at each cycle. Height and weight are accurately reported in the NHS (17). Because BMI is an important confounder, we carried forward BMI from the prior cycle for women missing weight in one cycle. If BMI was missing for two consecutive cycles, we excluded the person-time for these women until they reported their weight again. Nurses were asked whether they were past or current cigarette smokers and the number of cigarettes smoked per day. Pack-years were calculated by multiplying smoking duration in years by packs of cigarettes smoked per day.

First-degree family history of endometrial cancer was collected only in 1996. Information on oral contraceptive (OC) use and duration of use in months was collected every 2 years until 1982, at which time fewer than 500 women reported using OCs (18).

Statistical analysis. We used multivariate Cox proportional hazards models stratified by age in months at the start of follow-up and calendar year to estimate incidence rate ratios (RR) and 95% confidence intervals (CI). The time scale used was follow-up time in months, which is equivalent to using age in months as the time scale. Participants were followed from the age in months at the date of return of the 1982 questionnaire until the end of the study (June 1, 2004). Women contributed person-time until age in months at death, diagnosis of endometrial cancer, report of any other cancer excluding nonmelanoma skin cancer, report of hysterectomy, report of surgical menopause (one or two ovaries removed), loss to follow-up, or the end of the study, whichever came first. We evaluated the associations among all women and stratified by menopausal status. In the analysis among postmenopausal women, women started contributing person-times after they became menopausal.

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Table 1. Age and age-standardized baseline characteristics according to perineal talc use in 1982 among 66,088 women in the NHS

Characteristics	Ever perineal talc use	
	No (*n* = 40,958)	Yes (*n* = 25,130)
Age	48	48
Age at menarche	12.6	12.5
Nulliparous (%)	6.0	5.6
Parity (mean)*	3.2	3.2
Age at first birth*	25	25
Age at last birth*	31	31
Ever OC use (%)	47	46
OC duration (mo)†	52	51
Postmenopausal (%)	40	40
Age at menopause‡	49	49
Ever PMH use (%)‡	30	29
PMH duration (mo)†,‡	35	34
Ever cigarette smoking (%)	57	56
Pack-years†	22	21
BMI (kg/m^2)	24.2	25.6
BMI (kg/m^2) [%]		
<25	67.9	55.8
25-29	22.6	27.2
≥30	9.5	17.0
Diabetes (%)	0.8	0.9
Family history uterine cancer (%)	3.0	2.9
IUD (%)	2.9	2.8
Diaphragm (%)	4.2	4.4

NOTE: Characteristics adjusted for age in 5-y categories (<45, 45-49, 50-54, 55-59, 60-64, >65).
*Among parous women only.
†Among users.
‡Among postmenopausal women.

Talcum powder use was modeled as ever use (no, yes), regular use (at least once a week), frequency of use (0, less than once a week, one to six times a week, daily use), and indirect use on sanitary napkins (no, yes). To test for trend, we weighted the categories of frequency of perineal talc use as 0, 2, 15.5, and 30 days of use per month and calculated the Wald test. The final model was adjusted for age at menarche, age at menopause, parity, age at last birth, PMH use duration, OC use duration, BMI, smoking pack-years, report of diabetes, and family history of endometrial cancer. All variables in the model were entered as time-dependent and updated biennially at the date in months of return of each questionnaire, with the exception of talcum powder use, age at menarche, and family history of endometrial cancer, which were collected at a single time point (in 1982, 1976, and 1996, respectively) and were entered as baseline variables. Other than BMI, which was modeled continuously, all exposures and covariates were categorized and an indicator variable was created for each category (see tables for categories). For covariates with missing data, a missing indicator was included in the model.

Results

Our analysis included 66,028 women with 599 incident cases of confirmed endometrial cancer diagnosed between 1982 and 2004. A total of 1,069,130 person-years were accumulated over 22 years of follow-up. The mean age at the start of follow-up was 48 years, and women were followed for an average of 16 years. Ever users of perineal talc and never users were similar in terms of their baseline characteristics, except for BMI (Table 1). Women who reported ever using talcum powder were more likely to be obese than never users (17% versus 10%), and talc users had a higher mean BMI (25.6 versus 24.2 kg/m^2). In addition, users were less likely to be nulliparous (5.6% versus 6.0%).

After control for confounding, ever use of perineal talcum powder was associated with a borderline significant 13% increase in endometrial cancer risk among all

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Table 2. Incidence RRs and 95% CIs for ever and regular talc use and endometrial cancer risk among all women and stratified by menopausal status in the NHS

Women	Ever perineal talc use		Regular perineal talc use (at least once a week)	
	No	Yes	No	Yes
All women				
Cases	334	265	397	202
Person-years	687,327	420,106	806,391	301,041
RR (95% CI)*	1.00	1.13 (0.96-1.33)	1.00	1.17 (0.99-1.40)
Postmenopausal				
Cases	287	242	344	185
Person-years	461,381	281,958	538,227	205,113
RR (95% CI)*	1.00	1.21 (1.02-1.44)	1.00	1.24 (1.03-1.48)
Premenopausal				
Cases	47	23	53	17
Person-years	204,180	125,414	242,419	87,176
RR (95% CI)†	1.00	0.69 (0.40-1.19)	1.00	0.77 (0.42-1.39)
P interaction‡		0.02		0.07

*Adjusted for age, parity (0, 1, 2, 3, 4+), age at last birth (nulliparous, <30, 30-34, 35-39, ≥40), age at menarche (≤11, 12, 13, ≥14), age at menopause (premenopausal, <45, 45-49, 50-54, ≥55), OC duration (never, ≤12 mo, 13-36 mo, 37-72 mo, >72 mo), PMH duration (premenopausal/never, past <5 y, past 5+ years, current <5 y, current 5+ y), BMI (continuous), smoking pack-years (0, 1-20, 21-40, 40+), diabetes (no, yes), and family history of uterine cancer (no, yes); also adjusted for menopausal status (premenopausal, postmenopausal) among all women only.

†Adjusted for age, parity (0, 1, 2, 3, 4+), age at last birth (nulliparous, <30, 30-34, 35-39, ≥40), age at menarche (≤11, 12, 13, ≥14), OC duration (never, ≤12 mo, 13-36 mo, 37-72 mo, >72 mo), BMI (continuous), smoking pack-years (0, 1-20, 21-40, 40+), diabetes (no, yes), and family history of uterine cancer (no, yes).

‡Wald test for interaction term between talc use and menopausal status.

women, and a statistically significant 21% increase in risk among postmenopausal women (95% CI, 1.02-1.44; Table 2). There was no evidence of an association among premenopausal women, although the confidence interval was wide due to the small number of premenopausal cases. Because of significant differences in the results by menopausal status (*P* interaction = 0.02), as well as the small number of premenopausal cases, further detailed analyses of talc and risk were conducted among postmenopausal women only (Table 3). When we examined the association between frequency of perineal talc use and risk among postmenopausal women, there was a borderline trend of increasing risk with increasing frequency of use (*P* trend = 0.04; Table 3); in addition, the risks associated with perineal talc use one to six times a week or daily were elevated and borderline statistically significant. Regular use of talcum powder, defined as use at least once a week, was associated with a 24% increase in risk among postmenopausal women (95% CI, 1.03-1.48). The difference between the age-adjusted and multivariate results was due to confounding by BMI. Indirect use on sanitary napkins was not associated with risk. We further restricted the analyses to a group of postmenopausal women at low risk for endometrial cancer (19), consisting of normal-weight women with no history of PMH use (n = 27 cases). The association with regular use of talcum powder was maintained in this low-risk group despite decreased power (BMI < 25 never PMH users, cases = 27: RR, 2.44; 95% CI, 1.02-5.80; BMI ≥ 25 never PMH users, cases = 157: RR, 1.52; 95% CI, 1.09-2.12; BMI < 25 ever PMH users, cases = 139: RR, 0.90; 95% CI, 0.59-1.36; BMI ≥ 25 ever PMH users, cases = 170: RR, 1.27; 95% CI, 0.92-1.75; data not shown).

Discussion

We report for the first time an association between perineal use of talcum powder and endometrial cancer risk. In this large prospective study, we found a significant although modest increase in risk for endometrial cancer among postmenopausal women with a history of perineal use of talcum powder. The presence of an association among postmenopausal but not premenopausal women may be attributed to a longer duration of exposure or an increased latency in postmenopausal women, or to pathologic differences between premenopausal and postmenopausal endometrial cancer. The strength of the association is comparable with that reported between talc and ovarian cancer risk, a relationship investigated since the early 1980s (1, 20). In addition, some studies have

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reported a positive association between talc and the serous (21) or endometrioid histologic subtype of ovarian cancer (22, 23), the latter of which resembles endometrial carcinoma, providing additional support for our findings.

We observed a borderline increase in risk with increasing frequency of talc use, indicating a possible dose-response. In addition, the association with regular talc use was slightly stronger than the association for ever use. If regular users recall use more accurately than non-regular users, regular use of talcum powder may be a more precise classification of exposure. Alternatively, regular use may be necessary to cause an adverse effect, if there is a threshold level of exposure below which carcinogenicity is not evident. To adequately address a dose-response relationship, the exposure needs to incorporate information regarding frequency of use, duration of use, and intensity of exposure (24). In this study, information was available only on frequency of use. Studies for ovarian cancer have been inconsistent in establishing a dose-response relationship, partly due to the difficulty of accurately quantifying exposure (25).

Our results suggest a possible role of inflammation in the development of endometrial cancer, as talc is a known inflammatory agent (26). Talc may increase endometrial cancer risk by inducing local and/or systemic inflammation. A local inflammatory response would entail activation of macrophages and cytokine production, increased production of reactive oxygen species, increased cell proliferation, DNA damage, and finally, malignant transformation of cells (6). Talc has been shown to produce such responses *in vivo* and *in vitro* (26, 27). The local inflammation mechanism would require talc to reach the uterus. Although few studies are available, there is some evidence of retrograde transport of inert particles through the genital tract (28, 29). Talc particles have been found in human ovarian tissue (12) and human pelvic lymph nodes (30), and an increased risk of ovarian cancer has been noted with talc use before compared with after tubal ligation (22, 23). In addition, talc is a poorly soluble chemical; it is estimated that a 1-μm spherical talc particle in the lung would take 8 years to dissolve (31). These data support the contention that talc particles can migrate and persist in distant organs; furthermore, the uterus is a more accessible site than the ovaries. Exposure of the external genital area to talcum powder may also activate a systemic inflammatory response. Users of talcum powder have lower plasma levels of anti-MUC1 antibodies than nonusers (32). MUC1 is a protein highly expressed by ovarian, breast, and endometrial tumors, and low levels of anti-MUC1 antibodies are associated with poorer prognosis (32, 33). Reducing immunity to MUC-1 may be one mechanism by which talc increases endometrial cancer risk.

Other mechanistic factors that may come into play include chronicity of inflammation (34) and timing of exposure with regard to the phases of the uterine cycle. Any inflammation initiated by genital application of talc

Table 3. Incidence RRs and 95% CIs for talc use and endometrial cancer risk among postmenopausal women in the NHS

	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR* (95% CI)
Ever perineal talc use				
No	287	461,381	1.00	1.00
Yes	242	281,958	1.38 (1.16-1.64)	1.21 (1.02-1.44)
Frequency of perineal talc use				
No use	287	461,381	1.00	1.00
Less than once a week	57	76,845	1.22 (0.91-1.62)	1.09 (0.81-1.45)
One to six times a week	87	97,793	1.40 (1.10-1.79)	1.28 (1.00-1.63)
Daily	98	107,320	1.49 (1.18-1.87)	1.24 (0.98-1.56)
P trend†			<0.001	0.04
Regular perineal talc use (at least once a week)				
No	344	538,227	1.00	1.00
Yes	185	205,113	1.40 (1.17-1.68)	1.24 (1.03-1.49)
Sanitary napkin talc use				
No	403	587,317	1.00	1.00
Yes	67	94,233	1.04 (0.80-1.35)	0.98 (0.75-1.27)

*Adjusted for age, parity (0, 1, 2, 3, 4+), age at last birth (nulliparous, <30, 30-34, 35-39, ≥40), age at menarche (≤11, 12, 13, ≥14), age at menopause (<45, 45-49, 50-54, ≥55), OC duration (never, ≤12 mo, 13-36 mo, 37-72 mo, >72 mo), PMH duration (never, past <5 y, past 5+ y, current <5 y, current 5+ y), BMI (continuous), smoking pack-years (0, 1-20, 21-40, 40+), diabetes (no, yes), and family history of uterine cancer (no, yes).

†*P* trend for categories of frequency of perineal talc use weighted as 0, 2, 15.5, and 30 d of use per month.

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is likely to be sustained because studies indicate that women start using talcum powder at an early age (35) and continue using it for decades (14). The endometrial tissue is highly proliferative and regenerates with every menstrual cycle. Chronic inflammation following long duration of use of talcum powder may be sufficient to cause carcinogenesis despite the monthly shedding of the endometrial lining. Certain phases of the uterine cycle may also represent windows of particular susceptibility to exposure. For example, exposure during the proliferative phase of the uterine lining may be more likely to cause DNA damage and propagation. On the other hand, the inflammatory response is a natural process in the uterus during the late secretory and menstrual phase. During this period of tissue disintegration, inflammatory cells infiltrate the region, cytokines, prostaglandins, and cyclooxygenase-2 are released, and NF-κB is activated (36). Use of talcum powder during menstruation may interfere with normal immune processes in the uterus and prevent complete shedding of the lining. The inflammation hypothesis as a mechanism for the carcinogenic effects of talc is supported by recent evidence that the risk of ovarian cancer associated with talc is modified by variation in detoxification genes (35), emphasizing that clearance mechanisms are important in reducing risk. Studies show a reduction in risk for endometrial cancer following use of nonsteroidal anti-inflammatory drugs, especially among high-risk individuals (37, 38), supporting the role of inflammation in endometrial cancer.

The strengths of this study include prospectively collected data and adjustment for known risk factors for endometrial cancer, some of which are associated with talc use, such as obesity (39). We adjusted for BMI continuously to reduce confounding, and to minimize potential residual confounding, we secondarily restricted the analysis to normal-weight women. We additionally restricted our analysis to never users of PMH because both BMI and PMH use are strong enough risk factors for endometrial cancer to obscure a modest association with talc, and are linked to chronic systemic inflammation and changes in levels of inflammatory markers (40), respectively. The availability of a single assessment of talc use is a limitation of this study, as this may have resulted in some exposure misclassification during follow-up; however, talc use was assessed when women in the study were above 36 years of age (mean age, 48 years), when never users are unlikely to start using talc, reducing potential exposure misclassification (35). Furthermore, we were unable to explore a dose-response with duration of talc use because information on duration of use was not available.

In summary, we noted a modest positive association between genital use of talcum powder and endometrial cancer risk among postmenopausal women. However, this association needs to be replicated in future and larger studies. Mechanistic studies also are needed to elucidate the process by which talc may increase the risk of carcinogenesis and to provide additional support for this relationship. Studies may include assessing differences in inflammatory markers between talc users and nonusers or *in vitro* studies of the response of endometrial cells to talc particles. In addition, identifying genetically susceptible populations might offer insight into potential mechanisms. Future studies addressing the association between talcum powder use and endometrial cancer risk may provide further evidence for the role of inflammation in endometrial cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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