TITLE

Association between Body Powder Use and Ovarian Cancer: the African American Cancer Epidemiology Study (AACES)

RUNNING TITLE

Body Powder Use and Ovarian Cancer in African Americans

KEYWORDS

Body powder, African American, ovarian cancer, case-control study, inflammatory response

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CONFLICT OF INTEREST

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ABSTRACT

Background. Epidemiologic studies indicate increased ovarian cancer risk among women who use genital powder, but this has not been thoroughly investigated in African American (AA) women, a group with a high prevalence of use. We evaluate the relationship between use of genital powder and non-genital powder in invasive epithelial ovarian cancer (EOC).

Methods. Subjects are 584 cases and 745 controls enrolled in the African American Epidemiology Cancer Study, an ongoing, population-based case-control study of EOC in AA women in 11 geographic locations in the U.S. AA controls were frequency matched to cases on residence and age. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between genital and non-genital powder exposure and EOC risk, controlling for potential confounders.

Results. Powder use was common (62.8 % of cases and 52.9% of controls). Genital powder was associated with an increased risk of EOC (OR = 1.44, 95% CI: 1.11, 1.86) and a dose-response relationship was found for duration of use and number of lifetime applications ($p < 0.05$). Non-genital use was also associated with EOC risk, particularly among non-serous EOC cases (OR = 2.28; 95% CI: 1.39, 3.74). An association between powder use and upper respiratory conditions suggests an enhanced inflammatory response may explain the association between body powder and EOC.

Conclusion. In a study of AA women, body powder use was significantly associated with EOC risk.

Impact. The results support that body powder is a modifiable risk factor for EOC among AA women.

INTRODUCTION

Genital powder use may be a modifiable risk factor for epithelial ovarian cancer (EOC), the most deadly of all gynecologic cancers. (1) In 2010, the International Agency for Research on Cancer (IARC) classified perineal (genital) use of non-asbestos containing, talc-based body powder as 'possibly' carcinogenic to humans. (2) Although particles of asbestos have been found in older body powder formulations, particularly prior to 1976, (3) more recent body powder formulations no longer contain asbestos. (4,5) However, the relationship between genital powder use and ovarian cancer appears to persist. (6) It has been proposed that talc-containing powders may promote cancer development through local inflammation, increased rates of cell division and DNA repair, increased oxidative stress and increased cytokine levels. (7)

A recent pooled analysis of eight population-based case-control studies demonstrated an elevated odds ratio of 1.24 for the association between genital powder use and EOC. (6) Some (7–15) but not all (6,8,16) previously published studies of talc and ovarian cancer reported a dose-response relationship with genital powder use for frequency, duration or number of applications. Additionally, some studies reported a stronger association among the most common serous histologic subtype (4,10,14,16,17) although the pooled analysis did not confirm this finding. (6) Only one prospective study (17) found a significant association with ever genital talc use and invasive serous EOC (RR = 1.40, 95% CI: 1.02, 1.91), although no overall association with EOC was found. The Women's Health Initiative (WHI) (18) did not detect an association with genital talc use and EOC. Neither prospective study found evidence of a dose-response relationship.

Previous studies of genital powder use have included mostly white women. However, two studies reported analyses stratified by race and both found an increased EOC risk among African American (AA) women who used genital talc. (14,15) One study reported a non-significant association between one or more years of talc use and risk of ovarian cancer, odds ratio (OR) = 1.56, (95% confidence interval (CI): 0.80, 3.04) among a small sample of 128 AA EOC cases and 143 AA controls, who were shown to have higher prevalence of talc use compared to whites. (14) A second study reported an imprecise, but significant association with genital talc use with an OR of 5.08 (95% CI: 1.32, 19.6) among a very small sample of 16 cases and 17 controls. (15) In this report, we present analyses of the relationship between both genital powder and non-genital powder exposure from the African American Cancer Epidemiology Study (AACES), an ongoing, multi-center case-control study of invasive EOC in AA women.

MATERIALS AND METHODS

Study population

AACES is an ongoing, population-based, case-control study of invasive EOC in AA women in 11 locations (Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas). Institutional review board approval was obtained from all participating institutions. Methods have been described in detail elsewhere.(19) Briefly, cases include AA women 20 to 79 years of age with newly diagnosed EOC. With a goal of enrolling an equal number of cases and controls, controls were AA women identified through random digit dialing, with at least one intact ovary and no history of ovarian cancer, and frequency matched to cases on

region of residence and 5-year age categories. Participants complete a baseline telephone interview, which includes detailed questions on demographic characteristics; reproductive, gynecologic and medical history; hormone therapy (HT) and oral contraceptive (OC) use; cancer family history and lifestyle characteristics including smoking, alcohol consumption, and physical activity. In an effort to obtain information from as many women as possible, a short version of the questionnaire is offered to those who would otherwise refuse to participate in the study. Accrual began in December 2010 and as of August 31, 2015, 593 cases and 750 controls were enrolled. Eligibility for this analysis was restricted to participants for whom data on body powder use and all covariates were available, resulting in a final sample size of 584 cases and 745 controls; of these, 49 cases and 16 controls completed the short questionnaire.

Exposure to body powder and talc

In the baseline interview, participants were asked if they had ever regularly used talc, cornstarch, baby or deodorizing powders. Participants were considered "regular users" if they reported using any of these powders at least one time per month for at least 6 months, and "never users" if they did not. Regular users were asked about their frequency and duration of use, age at first use, and whether they applied powders to genital areas (including on underwear or sanitary napkins, or on birth control devices like diaphragms) and/or non-genital areas. Participants were categorized according to their type of application as non-genital use only, genital use only, or genital and non-genital use. Lifetime number of applications was calculated by multiplying the number of body

powder applications per month by the number of months used. Occupational exposure to talc (yes, no) was available only for subjects completing the long baseline survey.

Statistical analysis

The prevalence of demographic characteristics was calculated and t-tests and chi-square tests were performed to compare distributions between cases and controls. Due to the relatively small number of women who reported having only used genital powder (43 cases and 44 controls), we merged this exposure category with those who reported use of both non-genital and genital powder, creating an exposure category of 'any' genital powder use. Unconditional multivariable logistic regression was performed to calculate ORs and 95% CIs for the associations between body powder exposure ('only' non-genital use, and 'any' genital use) and risk of EOC. Body powder exposure was further examined by frequency of use (less than 30 times per month, daily), duration of use categorized as less than the median or the median and greater among the controls (<20 years, ≥20 years), and lifetime number of applications categorized as less than the median or the median and greater among controls (<3,600, ≥3,600 lifetime applications). Trend tests for frequency, duration and lifetime applications of powder use by route of exposure were conducted separately in two subsamples: only non-genital users plus never users and any genital users plus never users. For each subsample, each of the above variables was entered into a logistic regression as multiple indicator variables representing three levels and two degrees of freedom (i.e. for frequency of use: no exposure, less than daily, daily), adjusting for confounders. Trends were evaluated by statistical tests for the association between frequency/duration/lifetime applications with EOC risk, using Wald tests to

simultaneously test the equality of parameter estimates with zero.. Because experimental data suggest a relationship between inhaled inert particles and asthma, (20) a logistic regression analysis was conducted to determine the association between body powder use and upper respiratory conditions (yes, no), controlling for EOC case/control status.

Covariates included reference age in years (age at diagnosis for cases and age at baseline interview for controls); study site (Alabama, Louisiana, New Jersey, North Carolina, Ohio, South Carolina, Texas, Michigan and Illinois [combined due to sample size and regional similarities], Georgia and Tennessee [combined due to sample size]); education ($\leq$high school, some post-high school training, college or graduate degree); parity (0, 1, 2, 3+); duration of oral contraceptives (never, <60 months, $\geq$60 months); history of tubal ligation (yes/no); family history of breast or ovarian cancer in a first degree relative (yes/no); smoking (ever/never); and body mass index (BMI <25, 25-29.9, $\geq$30 kg/m^2). Two class action lawsuits were filed in 2014 (21) concerning possible carcinogenic effects of body powder, which may have influenced recall of use. Therefore, year of interview 2014 or later (yes/no) was included as a covariate in the logistic regression models. To assess potential reporting bias, we also examined whether there were differences in prevalence of reported powder use by interview year (before 2014, 2014 and later) for cases and controls as well as whether interview year was an effect modifier of the relationship between powder use and EOC risk.

Analyses by the histologic subtype versus all controls were also conducted and heterogeneity of risk estimates was tested by seemingly unrelated regression. (22) Due to missing data for histology, 48 cases were omitted from these analyses. Through stratified analyses we also assessed possible effect modification of the association with powder use

and ever use of HT among postmenopausal women using logistic regression. Experimental data show that the inflammatory response is enhanced in the presence of estrogen and progesterone and we therefore tested for interaction of the association with body powder use by menopausal status. (20) Logistic regression and trend analyses were performed using SAS version 9.4 (Cary, North Carolina).

RESULTS

Descriptive statistics for cases and controls are presented in Table 1. Cases were older than controls and had lower educational achievement. Although this study was designed to match controls to cases by 5-year age group, the difference in the age at diagnosis/age at interview may, in part, be because the study is actively enrolling subjects. However, age ranges of cases (20-79 years) and controls (20-79 years) overlap. Significant differences in the distributions of well-established risk factors, including a shorter duration of oral contraceptive use, and lower prevalence of tubal ligation in cases as compared to controls, were as expected. As expected, parity was lower among cases compared to controls, but the difference was not significant. Additionally, cases were more likely to report a family history of breast or ovarian cancer. No significant difference in the median years of use of body powder or occupational exposure of talc in cases compared to controls was observed.

Table 2 shows the results of logistic regression models examining the relationship between any use of body powder (either ‘only’ non-genital powder or ‘any’ genital powder) as well as the use of body powder by type of application: ‘only’ non-genital powder use or ‘any’ genital powder use. Adjusting for potential confounders, we

observed a significant positive association between any powder use and EOC (OR = 1.39, 95% CI: 1.10, 1.76). The OR for the association with 'any' genital powder use was 1.44 (95% CI: 1.11, 1.86). An OR of 1.31 (95% CI: 0.95, 1.79) for the measure of association between 'only' non-genital powder use and EOC was only slightly lower in magnitude compared to the association when 'any' genital use was reported, but not statistically different from one another (p = 0.56). In 2014 and later, we observed an increase in any powder use of 12% and 6% of cases and controls, respectively. Although increased, these exposure prevalences were not significantly different from those interviewed before 2014 (p = 0.30). For those interviewed in 2014 or later, we observed an OR for 'any' genital powder use of 2.91 (95% CI: 1.70, 4.97) compared to 1.19 (95% CI: 0.87, 1.63) before 2014. We observed a weaker OR of 1.26 (95% CI: 0.69, 2.32) for 2014 and later compared to 1.40 (95% CI: 0.96, 2.03) before 2014 for those who reported 'only' non-genital use. A test for effect modification by year of interview was statistically significant (p = 0.005).

The ORs for the association between daily use of powder for either 'only' non-genital' powder use (OR=1.53, 95% CI: 1.00, 2.35) or 'any' genital powder use (OR=1.71, 95% CI: 1.26, 2.33) with EOC were larger in magnitude than ORs for less than daily use compared to never use but the test for trend was significant for only 'any' genital powder use (Table 2). There is a moderately stronger association for ≥20 years of 'any' genital powder use (OR=1.51, 95% CI: 1.11, 2.06) compared to <20 years of use (OR = 1.33, 95% CI: 0.95, 1.86; P for trend = 0.02). No dose-response with years of use was detected for 'only' non-genital powder use. The ORs for the number of lifetime applications of body powder at or above and below the median support a dose-response

with 'any' genital powder use (P for trend <0.01) but not for non-genital powder use (P for trend = 0.14).

A report of any occupational talc exposure, for those completing the long baseline questionnaire, was found to be positively, but not statistically significantly, associated with EOC (OR=1.31; 95% CI: 0.88, 1.93) (data not shown).Table 3 shows an OR of 1.38 (95% CI: 1.03, 1.85) for the association in serous cases with 'any' genital powder use. Among serous cases, the OR for 'only' non-genital powder use was lower in magnitude and not significant (OR=1.10; 95% CI: 0.76, 1.58). Compared to serous cases, larger and statistically significant ORs are found for the associations with type of powder application in non-serous EOC cases; ORs were 1.63 (95% CI: 1.04, 2.55) and 2.28 (95% CI: 1.39, 3.74), for 'any' genital powder use and 'only' non-genital powder use, respectively (Table 3). A comparison of adjusted odds ratios between serous and non-serous histologic subtypes and powder use, detected a difference in 'only' non-genital powder use (P = 0.008), but did not detect significant differences in association for 'any' genital powder use (P = 0.50).

The stratified results by menopausal status (Table 4) suggest differences in the association for exposure to 'only' non-genital powder use among pre-menopausal where no association is seen for 'only' non-genital powder use while the associated with the risk of EOC and 'any' genital use is elevated. Among postmenopausal women, we observed positive associations of similar magnitude for both the association between EOC and 'only' non-genital powder use (OR=1.49; 95% CI: 1.04, 2.15) and 'any' genital powder use (OR= 1.41, CI: 1.03, 1.92). However, tests of interaction indicate no evidence for interaction by menopausal status for either route of exposure. Among menopausal

women, analyses stratified by HT use suggest a stronger association among users compared to non-users of HT for both routes of applications, although we detected a borderline, non-significant interaction for the associations with 'any' genital body powder by HT use (P = 0.06). The test for interaction for non-genital body powder by HT use was not significant (P=0.76)

To further consider the underlying mechanism for the relationship between use of body powder and the risk of EOC we calculated the association between both 'only' non-genital powder use and 'any' genital powder use and having an upper respiratory condition. Controlling for case-control status, age at diagnosis/interview, study site, education, smoking and BMI, we found ORs of 1.35 (95% CI: 0.89, 2.05) and 1.45 (95% CI: 1.03, 2.05) for 'only' non-genital and 'any' genital powder use, respectively in relation to a reported respiratory condition, respectively (data not shown). A non-significant, but elevated OR of 1.26 (95% CI: 0.77, 2.06) was observed with occupational exposure to talc and respiratory conditions (data not shown).

DISCUSSION

In the largest EOC case-control study in AA women to date, we observed a positive association between regular use of powder and EOC regardless of the route of application. Users of genital powder were shown to have greater than a 40% increased risk of EOC compared to an increased risk of more than 30% among those who used only non-genital powder. The OR for the association with genital powder use in the current study is consistent with the association reported in AA women by Wu et al. (14) Of note, a high proportion of EOC cases (63%) and controls (53%) reported any use of body

powder. A dose-response trend was evident for median years of use or greater as well as median number or greater of lifetime applications of 'any' genital powder but not for use of 'only' non-genital powder. Our results support that the association with 'any' genital powder use is similar in pre- and post-menopausal women while there appears to be an association with use of 'only' non-genital powder use among post-menopausal but not pre-menopausal women. Associations were found among non-serous EOC cases and among postmenopausal users of HT exposed to either genital or non-genital powder.

Most previous case-control studies have not found an association between non-genital powder use and ovarian cancer, including a large pooled analysis by Terry et al. who reported an adjusted OR of 0.98 (95% CI: 0.89, 1.07). (6,16) No prospective studies have evaluated non-genital powder use, nor has any study examined these associations by histologic subtype.(17,18) In the current study the overall association with non-genital use and EOC was similar to that for genital powder use though it did not reach statistical significance possibly due to small numbers and random variation. However, we also did not find a dose-response relationship with frequency, duration, or lifetime applications of 'only' non-genital powder use. Furthermore, we did not detect a significant association with use of 'only' non-genital powder among serous cases, while the OR for the association with use of 'only' non-genital powder showed over a 2-fold significant increased risk for non-serous EOC. In fact, we found a statistically significant difference between associations by subtype for 'only' non-genital use. Given the inconsistency with previous published findings it is also reasonable that underreporting genital powder use, such as abdominal powder use that reaches the genital area, may have led to a spurious result. Another possible explanation for our finding may be that there is a higher

inflammatory response in AAs compared to whites. (23–25) Our results also suggest that the route of powder exposure may have different effects by histologic subtype. As most high grade serous EOC, but not non-serous subtypes, arise in the fallopian tubes, (26) it is possible that direct exposure through the genital tract specifically affects this disease subtype. The association with any genital powder use and non-serous cases may be due to the overlap between genital and non-genital powder use (83% of cases and 83% of controls). We were unable to examine associations with 'only' genital powder users due to sample size considerations. In contrast, non-genital powder use may be related to inhalation of the exposure through the lungs. Several large pooled analyses have demonstrated risk factor associations with inflammatory-associated exposures, such as smoking (27), endometriosis (28), and obesity (29) with non-serous histologic subtypes of ovarian cancer but not high grade serous EOC, providing a plausible theoretical basis for differences we found in associations by histologic subtype.

Akin to talc powders, titanium dioxide (TiO_2) is another inert particle that induces an inflammatory response upon inhalation and has been considered to be 'possibly carcinogenic to humans' by IARC. (2) Experimental evidence of enhanced inflammation due to exposure to inert environmental particulates of TiO_2 showed inhibition of phagocytic activity of alveolar macrophages in pregnancy, and was found to be associated with increased asthma risk in the offspring of BALB/c mice exposed to TiO_2. In this study, elevated estrogen levels during pregnancy were found to contribute to the resulting asthma risk. (20) Our findings also support that enhanced airway inflammation is due to exposure to inert particles. Consistent with a recent study (15) where an association with powder use and asthma was reported, the relationship between body

powder use and respiratory conditions likely reflects an enhanced inflammatory response due to powder use, suggesting a mechanism by which EOC risk is increased. Therefore, lung inhalation of powder could be a biologically plausible mechanism for the association between non-genital body powder use and increased EOC risk, particularly in non-serous EOC cases.

To further explore whether estrogen influences the inflammatory response we performed stratified analyses by menopausal status. We did not see a difference in the association with pre- compared to post-menopausal use of 'any' genital powder use, which is not consistent with a recent report (15) where an association with pre-menopausal use but not post-menopausal use was found. However, consistent with this report, we found a stronger association between 'any' genital powder use and EOC among post-menopausal women who reported HT use compared to non-users. This finding is also consistent with experimental data showing that in the presence of estrogen and/or estrogen and progesterone, the ability of macrophages to clear inert particulates is altered, enhancing the inflammatory response leading to the development of asthma in mouse offspring. (20) It has also been proposed that chronic inflammation, resulting from exposure to body powder, whether through inhalation or through a transvaginal route, may exert a suppressive effect on adaptive immunity, leading to increased risk of EOC. (30) These findings suggest that AA women may be particularly susceptible to exposure to body powder due to having higher endogenous estrogen levels compared to white women. (31,32) Due to the limited sample size, we were not able to evaluate associations with the timing or duration of HT use or the concurrent effects of both HT

and powder use. Tests for interaction of the associations in the stratified analyses by HT use were not significant and our findings should be considered exploratory.

The results of the present study showed that genital powder use was associated with ovarian cancer risk in AA women and are consistent with localized chronic inflammation in the ovary due to particulates that travel through a direct transvaginal route. The dose-response observed for duration of genital powder use provides further evidence for the relationship between genital powder and overall EOC risk. Our data suggest that the increased risk due to use of genital powder applies to both serous and non-serous histologic subtypes of EOC. Use of 'only' non-genital powder was not found to be associated with the serous subtype, but our data suggest a relationship with non-serous EOC. The association with serous EOC is consistent with several previous studies. (4,6,14–17) Only the pooled analysis found associations with the endometrioid and clear cell subtypes. (6) The association with any occupational talc exposure and EOC (OR= 1.31) (data not shown), though not statistically significant, is also consistent with the results for 'only' non-genital powder use and suggest other routes of exposure, aside transvaginal, may effect EOC risk.

A recent publication of data from the WHI, which did not find an association with genital talc use and ovarian cancer (18), was accompanied by an editorial that emphasized the challenges in assessing the exposure to talc due to the reliance on self-report.(33) This limitation in the measurement of the exposure variables in the current study needs to be considered when interpreting our results. The possibility of differential misclassification exists in a case-control study such as AACES, especially due to heightened awareness of the exposure as a result of two recent class action lawsuits.(21)

Due to such publicity, we adjusted for date of interview in the analysis. However, there is still a possibility that recall bias may have caused some inflation of the ORs. Although our findings suggest that the publicity of the class action lawsuits may have resulted in increased reporting of body powder use, our data do not support that recall bias alone before 2014 versus 2014 or later would account for the associations with body powder use and EOC. It is possible that the lawsuits sharpened memories of body powder use and improved the accuracy of reported use for both cases and controls interviewed in 2014 or later. As the association with non-genital body powder use is not consistent with the published literature, the possibility of misclassification of exposure, residual confounding, or a chance finding cannot be ruled out as an explanation for the associations with non-genital powder use.

In summary, we found that the application of genital powder is associated with serous and non-serous EOC in AA women, a novel observation in this population that is consistent with some large studies in whites. Our data are consistent with the notion that localized chronic inflammation in the ovary caused by exposure to genital powder contributes to the development of EOC. Although associations with non-genital powder use and EOC have not been previously reported, we cannot rule out the possibility that this relationship may be specific to AA women. The high prevalence of exposure to both genital and non-genital body powder among AA women compared to the mostly white subjects (41%), as in the large pooled analysis,(6) underscores the importance of the study's findings. The results of the current study suggest that the use of body powder is an especially important modifiable risk factor for EOC in AA women.

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Table 1. Characteristics of Ovarian Cancer Cases and Controls in the African American Cancer Epidemiology Study.

	Cases (n=584) n (%)	**Controls** (n=745) n (%)	**p-value**
Age (years)			<0.01
<40	31 (5.3)	80 (10.7)	
40-59	299 (51.21)	398 (53.4)	
60+	254 (43.5)	267 (35.8)	
Range (years)	20-79	20-79	
Education			0.02
High school or less	262 (44.9)	278 (37.3)	
Some post high school training	145 (24.8)	210 (28.2)	
College or graduate degree	177 (30.3)	257 (34.5)	
Body Mass Index (kg/m^2)			0.09
<24.9 (under- and normal weight)	86 (14.7)	140 (18.8)	
25-29.9 (overweight)	148 (25.3)	197 (26.4)	
≥30 (obese)	350 (59.9)	408 (54.8)	
Parity (# of live births)			0.06
0	105 (18.0)	96 (12.9)	
1	113 (19.4)	141 (18.9)	
2	136 (23.3)	198 (26.6)	
3+	230 (39.4)	311 (41.6)	
Tubal Ligation			0.02
Yes	201 (34.4)	302 (40.5)	
No	383 (65.6)	443 (59.5)	
Oral Contraceptive Use			<0.01
Never	180 (30.8)	155 (20.8)	
<60 months	230 (39.4)	334 (44.8)	
≥60 months	174 (29.8)	256 (34.4)	
First Degree Family History of Breast or Ovarian Cancer			<0.01
Yes	149 (25.5)	132 (17.7)	
No	435 (74.5)	613 (82.3)	
Menopausal Status			0.31
Premenopausal	158 (27.2)	221 (29.7)	
Postmenopausal	423 (72.8)	522 (70.3)	
Hormone Therapy			0.10
Ever use	118 (20.3)	125 (16.8)	
Never use	463 (79.7)	618 (83.2)	
Smoking			0.48
Ever	257 (44.0)	313 (42.0)	
Never	327 (56.0)	432 (58.0)	
Hysterectomy[a]			0.43
Yes	141 (24.1)	166 (22.3)	
No	443 (75.9)	579 (77.7)	
Body Powder Use (median years)[b]	20	20	0.48
Occupational Talc Exposure[c]			0.16
Yes	58 (10.8)	62 (8.5)	
No	477 (89.2)	667 (91.5)	
Histologic Subtype[d]			
Serous	393 (73.2)		
Mucinous	24 (4.5)		
Endometrioid	72 (13.4)		
Clear cell	13 (2.4)		
Other	35 (6.5)		

[a] Defined as hysterectomy 2 years prior to diagnosis for cases and 2 years prior to interview for controls.
[b] Among body powder ever users only.
[c] Data not available for participants who completed the short questionnaire (49 cases and 16 controls).
[d] Data missing on histologic subtype for 47 cases.

Table 2. Adjusted Odds Ratios for the Associations Between Mode, Frequency and Duration of Body Powder Use and Ovarian Cancer in the African American Cancer Epidemiology Study (AACES).

Exposure	Cases (n=584) n (%)	Controls (n=745) n (%)	OR[a]	95% CI
Body powder use				
Never use	217 (37.2)	351 (47.1)	1.00	Referent
Ever use	367 (62.8)	394 (52.9)	1.39	1.10, 1.76
Body powder use by location				
Never use	217 (37.2)	351 (47.1)	1.00	Referent
Only non-genital use	119 (20.4)	140 (18.8)	1.31	0.95, 1.79
Any genital use	248 (42.5)	254 (34.1)	1.44	1.11, 1.86
Interview date <2014	***(n=351)***	***(n=571)***		
Never use	147 (41.9)	286 (48.4)	1.00	Referent
Only non-genital use	76 (21.7)	104 (17.6)	1.40	0.96,2.03
Any genital use	128 (36.5)	201 (34.0)	1.19	0.87,1.63
Interview date ≥2014	***(n=233)***	***(n=154)***		
Never use	70 (30.0)	65 (42.2)	1.00	Referent
Only non-genital use	43 (18.4)	36 (23.3)	1.26	0.69,2.32
Any genital use	120 (51.5)	53 (34.4)	2.91	1.70,4.97
Frequency of use				
Never use	217 (37.3)	351 (47.2)	1.00	Referent
Only non-genital use				
Less than daily	61 (10.5)	82 (11.0)	1.15	0.78, 1.71
Daily	58 (10.0)	58 (7.8)	1.53	1.00, 2.35
p-for-trend				0.09
Any genital use				
Less than daily	88 (15.1)	119 (16.0)	1.12	0.80, 1.58
Daily	158 (27.2)	134 (18.0)	1.71	1.26, 2.33
p-for-trend				<0.01
Duration of use				
Never use	217 (37.4)	351 (47.4)	1.00	Referent
Only non-genital use				
<20 years	59 (10.2)	68 (9.2)	1.37	0.91, 2.07
≥20 years	60 (10.3)	70 (9.5)	1.28	0.85, 1.93
p-for-trend				0.13
Any genital use				
<20 years	101 (17.4)	118 (15.9)	1.33	0.95, 1.86
≥20 years	144 (24.8)	134 (18.1)	1.52	1.11, 2.07
p-for-trend				0.02
Lifetime body powder applications				
Never use	217 (37.4)	351 (47.4)	1.00	Referent
Only non-genital use				
Below median (<3600 applications)	60 (10.3)	72 (9.7)	1.35	0.90, 2.03
Above median (≥3600 applications)	59 (10.2)	66 (8.9)	1.30	0.86, 1.97
p-for-trend				0.14
Any genital use				
Below median (<3600 applications)	92 (15.9)	119 (16.1)	1.16	0.83, 1.63
Above median (≥3600 applications)	152 (26.2)	133 (17.9)	1.67	1.23, 2.26
p-for-trend				<0.01

[a] Adjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first degree family history of breast or ovarian cancer, and interview year.

Table 3. Adjusted Odds Ratios for the Associations Between Talc Use and Serous/Non-serous EOC.

Histologic Subtype[a]	Cases n (%)	Controls n (%)	OR[b]	95% CI
Serous (n=392)				
Never use	156 (39.8)	351 (47.1)	1.00	Referent
Only non-genital use	71 (18.1)	140 (18.8)	1.10	0.76, 1.58
Any genital use	165 (42.1)	254 (34.1)	1.38	1.03, 1.85
Non-serous (n=144)				
Never use	44 (30.6)	351 (47.1)	1.00	Referent
Only non-genital use	42 (29.2)	140 (18.8)	2.28	1.39, 3.74
Any genital use	58 (40.3)	254 (34.1)	1.63	1.04, 2.55

Abbreviations: epithelial ovarian cancer (EOC).

[a] Test for interaction for association with powder use by serous and non-serous histologic subtype and route of body powder exposure was p=0.008 for 'only' non-genital powder use and p=0.50 for 'any' genital powder use.

[b] Adjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first degree family history of breast or ovarian cancer, and interview year.

Table 4. Adjusted Odds Ratios for the Association Between EOC Risk and Body Powder by Menopausal Status and Hormone Therapy Use.

	Pre-menopause				Post-menopause			
Exposure	**Cases (n=158) n (%)**	**Controls (n=221) n (%)**	**OR[a]**	**95% CI**	**Cases (n=423) n (%)**	**Controls (n=522) n (%)**	**OR[a]**	**95% CI**
Body Powder Use[b]								
Never use	59 (37.3)	103 (46.6)	1.00	Referent	157 (37.1)	247 (47.3)	1.00	Referent
Only non-genital use	22 (13.9)	42 (19.0)	0.90	0.44, 1.84	97 (22.9)	98 (18.8)	1.49	1.04, 2.15
Any genital use	77 (48.7)	76 (48.7)	1.50	0.87, 2.57	169 (40.0)	177 (33.9)	1.41	1.03, 1.92
HT Ever/Never Use[c,d,e]								
HT Ever Use								
Never use					34 (32.1)	55 (48.7)	1.00	Referent
Only non-genital use					23 (21.7)	23 (20.4)	1.74	0.77, 3.92
Any genital use					49 (46.2)	35 (31.0)	2.68	1.33, 5.40
HT Never Use								
Never use					122 (38.9)	191 (46.9)	1.00	Referent
Only non-genital use					73 (23.3)	75 (18.4)	1.51	0.99, 2.29
Any genital use					119 (37.9)	141 (34.6)	1.24	0.87, 1.79

Abbreviations: epithelial ovarian cancer (EOC); hormone therapy (HT).

[a] Adjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first degree family history of breast or ovarian cancer, and interview year.

[b] Test for interaction between menopausal status and route of body powder exposure was non-significant for only non-genital use (p=0.21) and any genital use (p=0.85) compared with never use.

[b] Restricted to post-menopausal women.

[d] Test for interaction between HT use and only non-genital use was non-significant (p=0.76).

[e] Test for interaction between HT use and any genital use was non-significant (p=0.06).

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