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Perineal Talc Use and Risk of Endometrial Cancer in Postmenopausal Women

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PERINEAL TALC USE AND RISK OF ENDOMETRIAL CANCER IN POSTMENOPAUSAL WOMEN

A Thesis Presented

by

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ABSTRACT

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May 2011

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Purpose: Endometrial cancer is the most common female reproductive cancer in the United States. Most known risk factors for endometrial cancer are either genetic or related to exposure to unopposed estrogens; less is known about risk due to environmental exposures. While a number of studies have examined the relationship between perineal talcum powder use and ovarian cancer risk, only one study has addressed the relationship with endometrial cancer risk. **Methods:** The Women's Health Initiative Observational Study, a prospective cohort study of 93,676 United States postmenopausal women from 1993-2005, measured perineal powder use at baseline via self-report. Cases of endometrial cancer were self-reported and confirmed by both local and central physician adjudicators. Cox proportional hazards regression was used to examine the association between perineal powder use and endometrial cancer, adjusting for known risk factors. **Results:** Of the 48,912 women in our analysis, 25,181 (52%) reported ever use of perineal powders. There were 452 incident cases of endometrial cancer diagnosed during 366,872 person-years of follow-up. Overall, ever use of

perineal powder was not significantly associated with increased risk of endometrial cancer (hazard ratio 1.05, 95% confidence interval 0.87-1.27). However, use of any perineal powder for 20 or more years was associated with a 30% increase in risk (hazard ratio 1.30, 95% CI 1.01-1.67) compared to never users. Furthermore, use of powder on both a diaphragm and the external perineal area was associated with a 39% increase in risk of endometrial cancer compared to women who never used perineal powder (hazard ratio 1.39, 95% CI 1.00-1.93). **Conclusions:** Cessation of perineal powder use, particularly on a diaphragm, may help reduce the risk of endometrial cancer.

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CHAPTER 1

INTRODUCTION

In the United States, endometrial cancer is the most common female reproductive cancer, with new cases developing in 23.5 women per 100,000 each year.[1] Most cases are diagnosed in women over 50 years old, while cases in women under 40 are very rare. Between 2003 and 2007, the 65-69 age group had the highest incidence in the United States, with 90.8 new cases per 100,000 women.[1] While incidence is highest among white women (24.4 cases per 100,000 women from 2003-2007), black women have the highest mortality (7.2 black women per 100,000 from 2003-2007 vs. 4.1 per 100,000 women of all races).[1] Treatments for endometrial cancer include radiation, surgery, chemotherapy, and endocrine therapy.[2] Five-year survival has ranged from approximately 83-86% from 1992-2002.[1]

Though there are some genetic risk factors, most known risk factors for endometrial cancer are related to exposure to estrogens. Early menarche, late menopause, nulliparity, estrogen-only hormone replacement therapy, and obesity have all been identified as risk factors for endometrial cancer.[3] Oral contraceptives that combine estrogen and progestin have a protective effect against endometrial cancer which persists for many years after oral contraceptive use has ended.[4] Cigarette smoking also has a protective effect; however, the biological mechanism for the protective effect of smoking is still unclear.[5]

One non-hormonal exposure that may increase the risk of endometrial cancer is adult use of talcum powder in the genital and/or perineal area. Talc has been shown to

migrate through the female reproductive tract as far as the ovaries.[6] Talc has also been shown to have an inflammatory effect on human tissues.[7] Talc may therefore contribute to the risk of female reproductive cancers through chronic inflammation, which in turn causes cellular stress and carcinogenic cell damage.[8]

To date, only one epidemiologic study has directly addressed the association of perineal powder use with endometrial cancer and found that perineal powder use led to a 21% increased risk of endometrial cancer in postmenopausal women only.[9] Because this study did not assess duration of powder use, it may have had some misclassification of exposure. In contrast, many epidemiologic studies have examined the risk of perineal powder use in the development of ovarian cancer. A meta-analysis of sixteen observational studies found that ever perineal powder use led to a 33% increase in the risk of ovarian cancer.[10] However, in this meta-analysis the lack of a clear dose-response relationship between increased frequency of powder use and ovarian cancer made this association uncertain.[10] To confirm the association of perineal powder use with increased risk of endometrial cancer in postmenopausal women, it is necessary to replicate the findings of the single previous study in other large cohorts of postmenopausal women.

Because approximately 40% of United States women have used powder for genital and/or perineal hygiene, even a small talc-related increase in the risk of endometrial cancer could contribute significantly to the number of endometrial cancer cases.[9] Therefore, we investigated the association between perineal powder use and endometrial cancer using data from the Women's Health Initiative Observational Study. This large prospective cohort study of United States women contained data on 93,676 postmenopausal women.

CHAPTER 2

REVIEW OF THE LITERATURE

Biological Mechanisms of Perineal Talc Use on Endometrial Carcinogenesis

Unlike most risk factors for endometrial cancer, perineal talc use likely does not increase risk through a hormonal pathway. Instead, talc may increase the risk of endometrial cancer by inducing chronic inflammation, which in turn causes cellular damage and eventual carcinogenesis.

To cause inflammation in the endometrium, talc from powder applied externally to the genitals or perineum must first migrate through the female reproductive tract to the uterus. Although such upward migration goes against gravity and the natural flow of menstrual blood and cervical mucus, several studies have shown that talc particles can migrate through the female reproductive tract as far as the ovaries.[6,11,12] Consistent with these findings, perineal talc use has been associated with an increased risk of ovarian cancer. The fact that some studies have not found this association in women who have had tubal ligation suggests that blocked fallopian tubes may prevent the migration of talc particles to the ovaries.[13,14] Because talc particles must migrate through the uterus to reach the fallopian tubes and ovaries, these studies showing migration of talc to the ovaries imply migration of talc to the uterus.

Once in the uterus, there are two different pathways by which talc can cause inflammation. First, talc, the primary ingredient in talcum powder for cosmetic and hygienic use, is mineralogically similar to asbestos, a known human carcinogen.[15] Because talc deposits in the environment are often found together with asbestos, talcum

powder produced before 1976 was frequently contaminated with asbestos.[16] One of the main mechanisms by which asbestos causes carcinogenesis is through a chronic inflammatory response.[17] Thus, the biological mechanism by which talc may increase endometrial cancer risk may include inflammation caused by asbestos contamination. Second, even when not contaminated by asbestos, talc has been shown to cause granulomas in human tissue.[18] Granulomas are nodules of inflammation caused by immune reaction which can lead to a persistent inflammatory response in the affected tissue.[19]

Inflammation, whether produced by granulomas, asbestos contamination, or direct contact with talc, leads to several mechanisms that cause cellular damage. Oxidants produced by the inflammatory process may damage DNA, particularly the tumor suppressor genes.[20] Chronic inflammation can also lead to the deregulation of cytokine production in cells, which in turn leads to several carcinogenic factors: alteration of cell growth, lessening of normal apotosis, and unfavorable changes in cell differentiation.[21]

In summary, biological evidence supports the hypothesis that perineal talcum powder use may contribute to the risk of endometrial cancer. Talcum powder applied externally migrates through the female reproductive tract, where it can cause chronic inflammatory responses in endometrial and ovarian tissue. This chronic inflammation can then cause several kinds of cellular damage, which in turn can lead to carcinogenesis.

Epidemiology of the Effect of Perineal Talc Use on Endometrial Cancer

To date, there has been only one study of perineal powder use and risk of endometrial cancer.[9] In contrast, epidemiological investigation into the role of talc in the female reproductive system has been almost entirely focused on epithelial ovarian cancer.[8,10,11,13,14,16,18,19,22,23,24] Most of these studies show a small increased risk of ovarian cancer with perineal powder use,[10,11,13,16,18,19,22,23] but some studies have failed to find an association.[8,14,24] One meta-analysis by Huncharek and colleagues of 16 observational studies found a 33% increased risk of ovarian cancer with perineal powder use overall (RR 1.33, 95% CI 1.16-1.45), but the risk in the subset of hospital-based studies was not significantly elevated (RR 1.19, 95% CI 0.99-1.41).[10] Huncharek and colleagues suggested that selection bias or confounding may have influenced the risk estimates of the population-based studies, especially since a dose-response relationship was not observed across studies.[10] In short, although many studies have found an association between perineal powder use and ovarian cancer, the association is weak and not consistently observed.

To our knowledge, Karageorgi and colleagues are the only investigators who have evaluated the association of perineal powder use with endometrial cancer.[9] The authors studied a subset of 66,088 women from the prospective Nurses' Health Study cohort, including 599 incident cases of endometrial cancer. Data on perineal powder use were collected by questionnaire in 1982. Women were asked about their usual use of talcum, baby, or deodorizing powder on the perineal area and on sanitary napkins. Women were also asked to report their frequency of perineal powder use. Data were also collected on known hormonal risk factors for endometrial cancer, such as menstrual and reproductive

history, oral contraceptive use, family history of uterine cancer, and cigarette smoking. Cases of endometrial cancer were assessed by self-report and verified by review of medical records. Women entered the study at a mean age of 48, and were followed for an average of 16 years. The authors found a 13% increase in endometrial cancer risk for all women who had ever used perineal powder compared to women who had never used perineal powder; however, this association was only borderline significant (OR: 1.13, 95% CI 0.96-1.33). In postmenopausal women, the authors found a 21% increase in risk with ever use (OR: 1.21, 95% CI 1.02-1.44) and a 24% increase in risk with use of perineal powder at least once a week (OR 1.24; 95% CI 1.03-1.48).

Karageorgi and colleagues represented a very strong preliminary evaluation of the risk of endometrial cancer associated with perineal powder use. However, this study did have some limitations. Women were asked about their usual powder use, which may not be consistent over time. and therefore lead to nondifferential misclassification of exposure. Also, the authors lacked data on duration of powder use, and so were unable to evaluate a possible dose-response relationship between duration of powder use and risk of endometrial cancer.

Mills and colleagues examined the association of perineal powder use with risk of ovarian cancer in a population-based case-control study conducted from 2000-2001 in 22 counties in central California.[19] Cases in this study had a mean age at interview of 56.6 years, and controls had a mean age at interview of 55.0 years. A total of 256 incident cases were identified by hospital tumor registrars. Controls were defined as women 18 years or older with at least one intact ovary and no prior diagnosis of ovarian cancer. Controls were selected by random-digit dialing in the same geographic area and

frequency matched by race/ethnicity and age. Powder use was assessed in a telephone questionnaire conducted by trained interviewers for both cases and controls. Overall, the authors observed an odds ratio of 1.37 for ever use of perineal powder (95% CI 1.02-1.85) compared to never perineal powder use. However, stratifying the results by tubal ligation status changed the risk estimates considerably: powder-using women with tubal ligation had a non-significant 12% decrease in ovarian cancer risk (OR 0.88, 95% CI 0.45-1.68), compared to powder-using women with no tubal ligation who had a 54% increase in ovarian cancer risk (OR 1.54, 95% CI 1.10-2.16).

One strength of this study is that it measured both frequency (in times per month or week) and duration (in number of years) of perineal powder use. Also, stratification of results by tubal ligation points to a possible protective mechanism in which the passage of talc from the genital area to the ovaries is interrupted by ligation of the fallopian tubes. Limitations of the study include a small sample size and low participation rates (40% of eligible cases and 57% of eligible controls) which may have led to selection bias. Furthermore, results were not stratified by menopausal status, so an odds ratio for postmenopausal women only was not calculated.

Gertig and colleagues evaluated the association of perineal powder use with risk of ovarian cancer in 78,630 women, aged 30-55 at baseline, from the prospective Nurses' Health Study cohort.[14] The methodology of this study was similar to Karageorgi and colleagues as discussed above: perineal powder use was assessed at baseline by questionnaire, and cases were ascertained by self-report confirmed by medical records. The authors found no significant association of ever perineal powder use with ovarian cancer compared to never use (RR 1.09, 95% CI 0.86-1.37). Risk did not significantly

increase with increased frequency of powder use (RR 1.12, 95% CI 0.82-1.55), nor was risk increased in women who had tubal ligation compared to women with no tubal ligation (RR 0.97, 95% CI 0.71-1.32). The only borderline significant finding in this study was a small increase in risk of invasive serous ovarian cancer in ever perineal powder users compared to never users (RR 1.40, 95% CI 1.02-1.91).

As with Karageorgi and colleagues' analysis of the Nurses' Health Study cohort, Gertig and colleagues benefitted from the large sample size, which gave them adequate statistical power to detect even a relatively small increase in risk. The prospective nature of the study also eliminated possible recall bias in the measurement of exposure. However, as with Karageorgi and colleagues, this study was limited by a single assessment of powder use and no information on duration of powder use. Results were not stratified by menopausal status, so there is no estimate of ovarian cancer risk from perineal powder use among postmenopausal women.

In summary, the majority of studies examining perineal powder exposure as a risk factor for female reproductive cancer have focused on epithelial ovarian cancer. These studies have tended to find that perineal powder use leads to a small but significant increase in risk of ovarian cancer, possibly modified by tubal ligation. Only one study has explored perineal powder use as a risk factor for endometrial cancer. This previous study had many strengths, but lacked data on duration of perineal powder use. Additional study is needed to further evaluate the risk of endometrial cancer associated with perineal talc use in postmenopausal women.

Summary

Endometrial cancer affects more women in the United States than any other cancer of the female reproductive system. Most research on endometrial cancer has focused on hormonal risk factors; many of these factors, such as age at menarche or menopause, are not possible for women to modify. As many as 40% of women in the United States are current or past users of powder on the perineal area; this represents an easily modifiable non-hormonal risk factor which, if eliminated, could reduce the burden of endometrial cancer in the Untied States.

Perineal talcum powder use may increase the risk of endometrial cancer through several inflammatory pathways. Previous studies have shown that externally applied talc can migrate through the female reproductive tract as far as the ovaries; [6,11,12] this migration would necessarily involve talc exposure of the endometrium. In the past, talc has been contaminated with asbestos, a known carcinogen that produces an inflammatory response in human tissues.[15, 16, 17] Even pure talc has been shown to cause granulomas in female reproductive tissues; in turn, granulomas can lead to chronic inflammation.[18, 19] Inflammation interferes with cellular cytokine production, which can then cause several carcinogenic changes in the cell.[21]

Epidemiologic data have long suggested an association between perineal powder use and ovarian cancer, potentially caused by a chronic inflammatory response to talc in ovarian tissue. Most epidemiologic data on endometrial cancer relate to the risk of hormonal factors, rather than environmental exposures such as talc. Existing data, while limited, suggest an association between perineal powder use and endometrial cancer. More data are needed to further study this association.

Therefore, our study examined perineal powder use as a risk factor for endometrial cancer among postmenopausal women from the large Women's Health Initiative Observational Study cohort.

CHAPTER 3

METHODS

Study Hypothesis

Specific Aim: We proposed to evaluate the association between perineal powder use and the risk of endometrial cancer in postmenopausal United States women.

Hypothesis: Among United States postmenopausal women, adult perineal use of powder is associated with an increased risk of endometrial cancer.

Study Design and Population

This study examined the association between perineal powder use and endometrial cancer using the publicly available data set from the National Heart, Lung, and Blood Institute's Women's Health Initiative Observational Study, a prospective cohort study conducted in the United States from 1993 to 2005.

The Women's Health Initiative Observational Study enrolled a cohort of 93,676 ethnically diverse women from 40 clinical centers in 24 states and the District of Columbia.[25] Enrollment began on October 1, 1993 and continued until December 31, 1998. This cohort consisted of women who had initially been screened for one or more of the Women's Health Initiative clinical trials, but who were ineligible or unwilling to participate in the clinical trials. At baseline, women were eligible for inclusion in the Observational Study if they were between 50 and 79 years old, postmenopausal, and planning to reside in the same area for at least 3 years. Women were excluded if they were participating in another clinical trial, were unlikely to survive 3 years due to

medical conditions, or had conditions such as dementia, drug dependency, or alcoholism that could interfere with study participation.

At baseline, study participants had a screening visit at which physical measurements and blood samples were collected.[26] Participants also completed several questionnaires at baseline to assess family history, medical history, reproductive history, quality of life, and lifestyle/behavioral factors. An additional baseline questionnaire measured various exposures of potential interest, such as physical activity, early life exposures, and occupational exposures. After baseline data collection, participants were mailed questionnaires annually to update their exposure information and to report medical outcomes of interest. Participants had another physical examination and blood collection approximately 3 years after enrollment in the study. Participants were followed prospectively for 6 to 10 years, depending on their time of enrollment, until March 2005. At the end of the study, 6.1% were deceased and 4.1% were otherwise lost to follow-up. The annual follow-up rate was at least 94% for each year.

In our study, we excluded women with hysterectomy at baseline (n=39,429) because they are not at risk of endometrial cancer. We also excluded women with a history of cancer other than nonmelanoma skin cancer (n=5,355), as well as women who had both hysterectomy and history of cancer at baseline (n=6,720), leaving 49,172 eligible postmenopausal women. Of these women, we excluded those with missing follow-up time in the Women's Health Initiative data set (n=260), leaving 48,912 women in the final analysis.

Exposure Assessment

Perineal powder use was assessed at baseline by self-report on the Observational Study Questionnaire.[27] Women were asked three questions about their perineal powder use. The first question was "Have you ever used powder on your private parts (genital area)?" Women who answered yes were asked to specify duration of use: less than 1 year, 1-4 years, 5-9 years, 10-19 years, or 20 or more years. The second question was "Did you ever use a diaphragm (a birth control device that fits over the opening of your womb)?" Women who answered yes were asked "Did you ever use powder on your diaphragm?" and, if yes, were asked to specify duration of use with the same categories. Finally, women were asked "Did you ever use powder on a sanitary napkin or pad?" Women who answered yes were asked to specify the duration of use with the categories above. In this study, each of these ever/never variables was analyzed dichotomously, with duration of use analyzed categorically to evaluate a possible dose-response relationship. Women were also categorized according to how many different ways they had used perineal powders externally and/or internally; duration of use for this variable was assigned according to the maximum duration of use across all categories. Assessing the exposure at baseline ensured that exposure to perineal powder occurred before the development of endometrial cancer.

The baseline questionnaires of the Women's Health Initiative Observational Study asked about "powder" use, and not all cosmetic powders contain talc. As such, the measurements of powder use in this study were considered surrogate measurements for talc use.

Validity of Exposure Assessment

To test the reliability of self-administered questionnaires, a Measurement Precision Study was performed in a subset of subjects in the Observational Study.[28] In this substudy, women were asked to repeat 4 of the 8 self-administered baseline questionnaires approximately 3 months after enrollment. Of the 2,045 women selected for the substudy, 1,092 repeated their questionnaires. Kappa statistics were calculated to measure the reliability of subjects' responses over time. However, a kappa statistic for the questions on perineal powder use was not reported in the Measurement Precision Study results, as the questionnaire including powder use was not one of the questionnaires that was repeated. Measured kappa statistics ranged from as low as 0.44 for reported history of congestive heart failure to 1.00 for reported history of colorectal cancer. Overall, the authors of the Measurement Precision Study stated that "most risk factors were reliably reported."[29] No behavioral variables similar to powder use were measured in the Measurement Precision Study. We are not aware of any other validation or reproducibility studies for perineal powder use.

Outcome Assessment

Endometrial cancer was one of the five main cancer outcomes of interest in the Women's Health Initiative study.[30] Participants in the Observational Study were mailed an annual questionnaire by which they self-reported clinical outcomes of interest. For all reports of new diagnoses of endometrial cancer, the physician adjudicator at the subject's local clinic confirmed the diagnosis and sent relevant pathology reports and other medical

record information to the WHI's Clinical Coordinating Center. In this study, endometrial cancer was analyzed as a dichotomous variable.

Validity of Outcome Assessment

Tumor registry coders at the Clinical Coordinating Center coded information about each endometrial cancer case.[30] Coding was supervised by a physician and a cancer epidemiologist.[30] Trained cancer coders at the Clinical Coordinating Center also reviewed self-reported cases whose diagnosis was denied by the local physician adjudicator. In at least 94% of endometrial cancer diagnoses, locally reported cases were confirmed centrally.[30] Both local and centralized adjudicators were blinded to exposure status to avoid bias.[30]

Covariate Assessment

Data on family history, medical history, demographics, and other exposures were collected by self-report on the Women's Health Initiative Observational Study baseline questionnaires.[31] Physical measurements and blood samples were taken at baseline in-clinic by certified staff. In this study, we considered covariates that are known protective or risk factors for endometrial cancer: age, race, body mass index, number of live births, age at menopause, oral contraceptive use, postmenopausal hormone use, and smoking status (Table 1).[9]

Statistical Analysis

We used multivariate Cox proportional hazards regression models to estimate the association of categories and duration of perineal powder use with endometrial cancer. Follow-up time was measured in days. Women contributed person-time for analysis until diagnosis of endometrial cancer, death, hysterectomy, loss to follow-up, or the end of the study, whichever happened first.

The Women's Health Initiative Observational Study data set contained data on three separate categories of perineal powder use: genital, sanitary napkin, and diaphragm. In addition, duration of use was measured separately within each of these categories. For this study, we first considered a simple ever/never model of perineal powder use (Table 6). Any woman who had ever used perineal powder in any of the three categories was considered an ever user. Because different exposures to perineal powder may have been associated with different risk, we also modeled risk of endometrial cancer according to type of use. Within each category of use, we estimated the risk associated with different durations of use (Table 7). For women who used powder on a diaphragm, we repeated the analysis of duration of use restricted only to women who had ever used a diaphragm.

Many women used perineal powder in more than one way, such as on both genitals and diaphragm. Such combined uses may have led to increased exposure to powder, and potentially to increased risk of endometrial cancer. As such, we modeled risk of women's total powder exposure across all categories in two different ways. In one analysis, we estimated risk associated with using talc powder only externally, only internally, or both externally and internally (Table 8). In an additional analysis, we estimated risk associated with the duration of powder use across all categories of use

(Table 9). In this analysis, each woman was categorized according to her maximum duration of powder use; for example, if she used powder on sanitary napkins for five years and on a diaphragm for ten years, she was categorized as having ten years of exposure.

To address potential confounding, we included covariates that have been identified in previous studies as known risk and/or protective factors for endometrial cancer. Age was included as a continuous variable. Because of the relatively small number of cases among subcategories of nonwhite women, race was included as a categorical variable of white and other. Similarly, because of the relatively small number of cases among underweight women and women of normal weight, body mass index was included as a categorial variable with three levels: underweight/normal (BMI < 25kg/m^2), overweight (BMI 25-30 kg/$m^{2)}$, and obese (BMI > 30kg/m^2). Number of live births was included as a categorical variable: 0, 1-2, and 3 or more. Age at menopause was included categorically and based on quartiles of women in the data set: age 48 or younger, age 49-50, age 51-53, and age 54 and over. Because the protective effects of oral contraceptive use have been shown to endure for many years after cessation of use, oral contraceptive use was included as an ever/never categorical variable.[4] Postmenopausal hormone use was included categorically according to current status: never used, past user, and current user. Smoking was also included categorically according to current status: never smoked, past smoker, and current smoker. For each of these covariates except age, we estimated the association with endometrial cancer using Cox proportional hazards regression to approximate age-adjusted hazard ratios with 95% confidence intervals (Table 5).

Variables as listed above were evaluated for inclusion in each model as potential confounders, using backward selection based on changes in the coefficients of interest. All covariates with a p-value of <0.25 were included in the preliminary multivariable models, as well as variables of clinical interest. After each preliminary model was fit, covariates were removed one at a time, and models with and without each covariate were compared to determine if removal of the covariate changed the coefficient of the powder variable by more than 15%. After removing nonsignificant variables from the preliminary model, variables that had initially been excluded from the preliminary model were reintroduced and similarly checked for significance (p-value < 0.10). Finally, we added interaction terms to the models to assess possible effect modification. Interaction terms with a p-value of >0.05 were removed. To assess possible effect modification, models were stratified by age category and BMI category and evaluted for a 15% or greater change in the coefficient of the powder variable.

In the final, fully adjusted multivariate models, we estimated hazard ratios and 95% confidence intervals for ever vs. never perineal powder use, for different combinations of use, and for different durations of use both within and across categories of use. Final models were adjusted for age, race, BMI, number of live births, age at menopause, oral contraceptive use, postmenopausal hormone use, and smoking status. For each model, the proportional hazards assumption was tested based on weighted Schoenfeld residuals, and goodness-of-fit was assessed by plotting the Nelson-Aalen cumulative hazard estimate for Cox-Snell residuals.

All analyses were performed using Stata v. 11.1 (StataCorp, College Station, TX). When data were missing, analyses were performed on available data without imputation.

P-values of <0.05 were considered statistically significant; no adjustment was made for multiple comparisons.

CHAPTER 4

RESULTS

The final analysis included 48,912 women with 452 confirmed diagnoses of endometrial cancer during the follow-up period between 1993 and 2005. Over 12 years of follow-up, a total of 366,872 person-years were accumulated. At baseline, the average age of all participants was 63 years, and approximately 85% of the women reported their race as white. Of the 48,912 women in the final analysis, 25,181 (52%) reported ever use of powder on genitals, sanitary napkin, and/or diaphragm (Table 1). Ever users of perineal powders were on average one year younger than never users (mean age of 62.7 versus 63.7). Ever users were also slightly more likely to be white (87% versus 84%), and more likely than never users to be obese (26% versus 21%). Ever users of perineal powders reported more ever use of oral contraceptives (44% versus 39%). Ever users of perineal powders were also slightly more likely to be past or current users of postmenopausal hormones (51% versus 49%) and to have ever smoked (52% versus 47%). Ever and never users of perineal powders were similar in their number of live births and age at menopause.

Tables 2, 3, and 4 present a more detailed breakdown of perineal powder use by category of use (genital, sanitary napkin, and diaphragm) and duration of use, ranging from never use to 20 or more years of use. A comparison of the most extreme category of duration of use (20 or more years) to the never use category in each of the types of perineal powder use showed a distribution similar to the overall ever/never use distribution described above. Some notable differences occurred in the category of

women who reported 20 or more years of use of powder on a diaphragm compared to women who never used powder on a diaphragm (Table 4). Women in this extreme category of diaphragm powder use were on average older than never users (67 years versus 63 years), more likely to be white (94% versus 85%), less likely to be obese (18% versus 24%), more likely to have had at least one live birth (96% versus 85%), less likely to have used oral contraceptives (21% versus 41%), less likely to have used postmenopausal hormones (45% versus 49%), and less likely to have never smoked (47% versus 51%).

To examine the role of potential confounding factors, we estimated the age-adjusted hazard ratios for known risk or protective factors for endometrial cancer: race, BMI, number of live births, age at menopause, oral contraceptive use, postmenopausal hormone use, and smoking status. Table 5 presents the age-adjusted bivariate hazard ratios with 95% confidence intervals for each of these covariates. Women who reported belonging to a race category other than white had a significantly lower risk of endometrial cancer (HR 0.47; 95% CI 0.33-0.68). Obese women also had a higher risk of endometrial cancer compared to women who were of normal weight or underweight (HR 1.52; 95% CI 1.24-1.89). Past use of postmenopausal hormones was associated with an increased risk of endometrial cancer (HR 1.43; 95% CI 1.07-1.90) and current use of postmenopausal hormones further increased risk (HR 1.95; 95% CI 1.59-2.40). In age-adjusted bivariate models, number of live births, age at menopause, ever oral contraceptive use, and smoking status were not statistically significantly associated with differences in risk of endometrial cancer (Table 5). However, because of the clinical significance of each of these factors, all multivariate powder use models were fully

adjusted for age, race, BMI, number of live births, age at menopause, oral contraceptive use, postmenopausal hormone use, and smoking status.

In both age-adjusted and multivariate-adjusted models, ever perineal powder use was not statistically significantly associated with increased risk of endometrial cancer (Table 6). This analysis included any category of perineal powder use as ever use: genital powder, sanitary napkin powder, and /or diaphragm powder. This analysis did not consider duration of perineal powder use.

Because the Women's Health Initiative baseline questionnaire measured three kinds of perineal powder use, we estimated risk of endometrial cancer associated with each kind of use: genital use, sanitary napkin use, and diaphragm use. We also estimated risk associated with different durations of each kind of perineal powder use in order to determine a possible dose-response relationship. Table 7 presents a more detailed breakdown of age-adjusted and multivariate-adjusted hazard ratios for endometrial cancer associated with each category of perineal powder use and duration of use within these categories. Genital powder use and sanitary napkin powder use were not statistically significantly associated with increased risk of endometrial cancer, regardless of duration of use, suggesting that for these categories of use there was no dose-response relationship. However, diaphragm powder use of 20 or more years was associated with a threefold risk of endometrial cancer compared to women who never used powder on a diaphragm (multivariate-adjusted HR 3.02; 95% CI 1.97-4.63).

Use of perineal powder in more than one way may represent an increase in total talc exposure. To examine risk associated with multiple uses of perineal powder, we categorized women according to their different combinations of perineal powder use.

Table 8 presents age-adjusted and multivariate-adjusted hazard ratios for endometrial cancer associated with different combinations of perineal powder use, regardless of duration of use. Using powder externally on genitals only, sanitary napkin only, or on both genitals and sanitary napkins was not associated with an increased risk of endometrial cancer. Use of powder internally on a diaphragm only was associated with a nonsignificant increase in risk of endometrial cancer compared to women who never used perineal powder (multivariate-adjusted HR 1.24; 95% CI 0.85-1.81). However, women who used powder on both a diaphragm and genitals and/or sanitary napkins (i.e. both internally and externally) had a borderline significant 39% increased risk of endometrial cancer compared to never users of perineal powder (multivariate-adjusted HR 1.39; 95% CI 1.00-1.93).

We also assessed the risk associated with total duration of all perineal powder use by categorizing women according to their maximum duration of any perineal powder use. Table 9 presents age-adjusted and multivariate-adjusted hazard ratios for endometrial cancer associated with the maximum duration of powder use across all categories of use. Use of any kind of perineal powder for less than 19 years was not associated with increased risk of endometrial cancer. Women who had used any kind of perineal powder for at least 20 years had a borderline significant 30% increased risk of endometrial cancer compared to never users of perineal powder (multivariate-adjusted HR 1.30, 95% CI 1.01-1.67).

To test for possible effect modification by BMI or post-menopausal hormone use, all analyses were repeated to estimate strata-specific hazard ratios for each category of BMI and postmenopausal hormone use status. Effect estimates within strata of BMI and

hormone use status were not substantially different from pooled estimates. Furthermore, we repeated each analysis excluding cases occurring within two years of baseline, to control for the possibility that women may have begun or increased perineal powder use in response to symptoms of endometrial cancer. Analyses excluding cases within two years of baseline yielded similar results to analyses of the entire study cohort. Finally, effect estimates were consistent when both category of powder use and duration of use were included in a single model.

The proportional hazards assumption was tested in each model using weighted Schoenfeld residuals. Global tests for each model yielded p-values of <0.05 for all but the model of duration of diaphragm powder use ($p=0.08$), showing that the proportional hazards assumption may not be met for these models overall. However, testing the proportional hazards assumption within each model for each individual powder-related variable consistently yielded p-values >0.05, showing that the proportional hazards assumption is satisfied for these variables. Plots of the Nelson-Aalen cumulative hazard estimate for Cox-Snell residuals of each model showed adequate goodness-of-fit.

CHAPTER 5

DISCUSSION

The purpose of this analysis was to evaluate the association of perineal powder use with risk of endometrial cancer in postmenopausal women. Overall, we found that the risk of endometrial cancer differed depending on category and duration of perineal powder use. Among women who used powder only on the genitals or sanitary napkins, we found no significant increase in risk of endometrial cancer regardless of duration of talc use. However, use of powder on genitals and/or sanitary napkins in combination with diaphragm powder use was associated with a 39% increase in risk of endometrial cancer. When duration of powder use was evaluated across categories of use, women who used any perineal powder for 20 or more years showed a 30% increase in risk of endometrial cancer. Furthermore, women who used powder on a diaphragm for 20 or more years showed a threefold increase in risk of endometrial cancer. These associations of endometrial cancer with duration of powder use were only evident in the highest category of duration, and did not suggest a dose-response effect.

It is possible that perineal powder use is only associated with certain subtypes of endometrial cancer. In a previous study, Reeves and colleagues classified the subtypes of endometrial cancer in the Women's Health Initiative Observational Study data set according to the World Health Organization and International Society of Gynecological Pathology guidelines outlined by Creasman and colleagues.[32,33] The majority of cases were of the endometrioid type. There were not enough cases of other types of

endometrial cancer to permit an analysis of risk by endometrial cancer subtype in our study.

One limitation of this study is the potential for nondifferential misclassification of exposure. Women reported their perineal powder use on a written questionnaire at baseline; they may have misreported their perineal powder use for various reasons. The questionnaire states that the questions relate to talc, baby powder, and deodorant powder. It is possible that some women reporting perineal powder use did not use powders containing talc, or used talc products only some of the time. Women may have underreported their perineal powder use if they felt embarrassed about such use, or over-reported their use if they felt that powder was necessary for genital hygiene. Some embarrassment may have been avoided by using a written questionnaire in which women did not have to speak about their perineal powder use to an interviewer. Also, the questions on perineal powder use represented just a few personal questions in a lengthy questionnaire that asked many personal questions; as such, these questions did not stand out as particularly intrusive. A more likely source of misclassification of exposure is that women may not accurately recall the duration of their perineal powder use, and therefore report a greater or lesser exposure than their true exposure. Another likely source of misclassification of exposure is that women may have changed their perineal powder use over the course of follow-up; thus, their exposure at baseline may not reflect their current level of powder use. Any of these nondifferential misclassifications of exposure, if present, would have biased our results toward the null, reducing our estimate of the risk of perineal powder use on endometrial cancer.

Nondifferential misclassification of outcome was less likely to have affected our study findings. Cases of endometrial cancer were ascertained first through self-report on annual questionnaires. All reported cases were verified both by local study physicians and trained adjudicators at the Women's Health Initiative Clinical Coordinating Center. Because of this extensive professional verification, it is unlikely that any false cases of endometrial cancer were included in the analysis. It is possible that some cases were missed, most likely because they were asymptomatic or because women had not yet sought medical care for their symptoms. Missed cases occurring equally among the exposed and unexposed would be a nondifferential misclassification of outcome, and would bias our results toward the null. Such misclassification is only likely to have occurred in a very small percentage of participants.

Selection bias in this study is possible, but unlikely to have significantly affected our results. In this prospective cohort study, information on perineal powder exposure was collected before any cases of endometrial cancer had occurred; therefore, selection bias at the time of participant selection was not an issue. Selection bias due to loss to follow-up is possible. Overall, the follow-up rates for the Women's Health Initiative Observational Study were high.[34] The annual questionnaire response rate was over 94% each year. At the end of the follow-up period, only 4.1% of participants had ended their participation or otherwise been lost to follow-up. An additional 6.1% of study participants were deceased at the end of the follow-up period; however, information on the cause of death was collected for most participants either through local study physicians or through the National Death Index. If participants lost to follow-up or missed as cases differed significantly in both exposure and outcome status, then selection

bias may have occurred. For example, if women who were both powder users and had endometrial cancer were most likely to stop participating in the study, we would have underestimated the association between powder use and endometrial cancer. Because the percentage of women lost to follow-up was relatively small and participation rates are unlikely to differ by both exposure and outcome status, the effects of selection bias from loss to follow-up should have been minimal.

Effects of potential information bias should have been similarly minimal. If women who used perineal powders were less likely to seek medical care for reproductive system related symptoms, then they would not be counted among cases and our results would have been attenuated. Conversely, if perineal powder users paid more attention to their genital areas and were therefore more likely to seek medical care for reproductive system related symptoms, they would be more likely to be diagnosed as cases and our results would have shown an exaggerated risk of perineal powder use. Neither of these situations seems likely to have occurred on a scale large enough to have influenced our results significantly. To further reduce the possibility of information bias, both local and central adjudicators who reviewed cases were blinded to exposure status.

The Women's Health Initiative Observational Study data set contained information on all of the major risk factors for endometrial cancer recognized in previous literature, including exposures related to reproductive history and hormone use. We adjusted for potential confounders that we found to be significant from our bivariate and multivariate analyses, as well as factors known to increase or decrease risk of endometrial cancer. Despite our efforts to adjust for confounders, it is possible that one or more confounding factors was measured insufficiently, or that we have missed an unknown

confounder. For example, socioeconomic status may be related both to powder use and risk of endometrial cancer, and this variable was not included in our analysis. If women of a lower socioeconomic status were more likely to use perineal powder, and women of lower socioeconomic status were also more likely to develop endometrial cancer (perhaps due to lesser access to health care), then we would have seen a false association between powder use and endometrial cancer. Confounding that we have not adequately adjusted for could have caused us to over- or underestimate the risk of endometrial cancer from perineal powder use, depending on how the confounding variable affects this association. Because we have adjusted for a comprehensive set of variables that includes all major known risk factors for endometrial cancer, we do not think that any residual confounding significantly affected our results.

The results of our study should be generalizable to all post-menopausal women in the United States who are at risk for endometrial cancer. The biological mechanisms by which talc exposure can cause endometrial cancer may be modified by genetic variation that increases or reduces risk; however, our large cohort represents a genetically diverse population. Internationally, the results should be generalizable in areas in which cosmetic talc composition is similar to United States cosmetic talc (i.e. no contamination with asbestos).

In our analysis, we found that 52% of women had reported ever perineal powder use, which is higher than the approximately 40% reported in other studies.[9,35] However, this percentage is high because it includes more than one category of powder use. In our analysis, the highest percentage of women reported genital powder use; at approximately 39% of study participants, this finding is consistent with prior literature.

To date, only one other study has examined the risk of endometrial cancer associated with perineal powder use.[9] Karageorgi and colleagues studied this association in the Nurses' Health Study cohort, which consisted of both pre- and post-menopausal women. Karageorgi and colleagues reported a small but significant increase in risk among postmenopausal women (21% for ever vs. never use; 24% for regular use vs. never use).[9] Their study measured use of powder on the genitals and on sanitary napkins, but not on diaphragms. Their study also measured frequency of powder use, but not total duration of powder use. Because Karageorgi and colleagues measured frequency of powder use and our study measured duration of powder use, it is not possible to exactly compare the measures of associated risk. However, the strength of the association found in both studies is similar. The strength of association that we report is also comparable to the reported association between perineal powder use and risk of ovarian cancer from several previous studies.[10,11,13,16,18,19,22,23]

One important finding in this study was the increased risk of endometrial cancer associated with use of powder on a diaphragm, especially for durations of diaphragm powder use of 20 or more years. There are two possible explanations for this finding. First, use of powder containing talc on a diaphragm introduces the talc directly into the reproductive tract, where the talc is then physically closer to the endometrium. Talc thus introduced directly into the reproductive tract has a shorter distance to migrate to the endometrium, compared to talc which is applied to the genitals externally. With a shorter migration distance and closer physical contact, talc used on a diaphragm may thus have a greater inflammatory and/or carcinogenic impact on the endometrium. Second, a duration of 20 or more years measured at baseline in 1993 suggests that women with

especially long durations of use were using perineal powder prior to 1976, the year in which asbestos contamination of talcum powder ended in the United States. Prior to 1976, cosmetic talc was often contaminated with the known carcinogen asbestos, possibly rendering pre-1976 talcum powders more carcinogenic than talcum powders produced after that date.[16]

In summary, we found a small but significant increase in risk of endometrial cancer associated with diaphragm powder use and with any perineal powder use of 20 or more years. While these findings are mostly consistent with prior research, further study is needed to evaluate both the diaphragm-specific risk of powder use and the exact biological mechanisms of the association. Because approximately 40% of United States women have used powder for perineal hygiene, even a small talc-related increase in risk may contribute significantly to the number of endometrial cancer cases. The results of this study help clarify the relationship of powder use with endometrial cancer, and point to a risk factor that is easily modified to reduce risk of a common reproductive cancer. Furthermore, if the association of pre-1976 powder use with endometrial cancer is indeed linked with asbestos contamination, our study suggests that further efforts to remove asbestos from cosmetic talc may be necessary in areas in which this contamination may still persist.

APPENDICES

APPENDIX A

HUMAN SUBJECT PROTECTION

All data were collected from participants by the Women's Health Initiative Observational Study. At the time of enrollment, all participants signed two separate informed consent forms: one for the Women's Health Initiative study in general, and another specifically for the Observational Study arm. These forms both contained explanations of the purpose of the study, the role of participants, potential benefits and risks, confidentiality, and the right to withdraw.

Our study used only de-identified data from the Women's Health Initiative Observational Study, and as such no additional participant consent was required. Because the data contains no personally identifiable information, no security measures were necessary to protect participant confidentiality. Additionally, this specific analysis plan was approved by the University of Massachusetts Institutional Review Board.

APPENDIX B

PERMISSION TO ACCESS DATA

Permission to access data is was granted by the National Heart, Lung, and Blood Institute on November 24, 2010. A copy of the permission to access data follows. Signed copies are on file at the University of Massachusetts and the National Heart, Lung, and Blood Institute.

NHLBI Research Materials Distribution Agreement (RMDA)

Introduction and Definitions

The National Heart, Lung, and Blood Institute (NHLBI), the RECIPIENT Organization (RECIPIENT) and the Principal Investigator (PI) hereby enter into this Research Materials Distribution Agreement (RMDA) as of the effective date specified on the final signature page .

The Research Materials and Research Plan covered by this RMDA are:

- Name of Clinical Study: WHIOS
- Title of Research Plan: Endometrial Cancer Risk in post menopausal women: Coffee,Tea and talc use
- Research Materials Requested: Data
- Name of Principal Investigator: Dr. Katherine W. Reeves
- Name of Other Users: Dr. Susan Sturgeon, Ms. Lori Crawford & Mr. Ayush Giri

The Research Materials are provided through the Biologic Specimen and Data Repository Information Coordinating Center. The Center was established by the NHLBI to develop and maintain the infrastructure necessary to facilitate and maximize access to Research Materials from NHLBI-sponsored studies in accordance with NHLBI approved procedures

The Research Materials were collected as part of the above clinical study, hereafter referred to as "STUDY". They constitute a unique scientific resource and the NHLBI is committed to making them available in a timely manner, on appropriate terms and conditions, to the largest possible number of qualified investigators who wish to analyze the materials in a secondary study designed to enhance the public health benefit of the original work. The RECIPIENT and PI acknowledge responsibility for ensuring the review of and agreement to the terms within this RMDA and the appropriate research use of the Research Materials, subject to applicable laws and regulations.

The RECIPIENT and PI acknowledge that other researchers are entitled to access to the Research Materials on the same terms as RECIPIENT so that duplication of research may occur. RECIPIENT and PI also recognize that the STUDY Investigators have made a substantial long-term contribution in establishing the Research Materials and the NHLBI encourages appropriate collaborative relationships by outside investigators with the STUDY Investigators and proper acknowledgement of their contributions.

The NHLBI believes that the confidentiality and privacy of the STUDY participants can best be assured by requiring all who are interested in accessing the Research materials to acknowledge their review of this RMDA and agree to adhere to its provisions. Violation of its confidentiality provisions could lead to legal action on the part of STUDY participants, their families, or the U.S. Government.

Note: RECIPIENT requests access to NHLBI Research Materials for its PI at its sole risk.

For the purpose of this agreement

"RECIPIENT" is any organization that is seeking access to STUDY Research Materials, and may be a: Public/State Controlled Institution of Higher Education; Private Institution of Higher Education; Nonprofit organization with 501(c)(3) IRS Status (Other than Institution of Higher Education); Nonprofit Organization without 501(c)(3) IRS Status (Other than Institution of Higher Education); Small Business; For-Profit Organization (Other than Small Business); State Government; Government of a U.S. Territory or Possession; Non-domestic (non-U.S.) Entity (Foreign Organization); or Eligible Agency of the U.S. Government.

"Principal Investigator (PI)" is an individual judged by the RECIPIENT to have the appropriate level of authority and responsibility to lead the scientific investigation proposed in the Research Plan using the requested materials, oversee the supporting staff who are provided access to the Research Materials and contribute to the analytic effort and public disclosure of STUDY results, and assume responsibility for all team members' compliance with the terms and conditions of this RMDA.

"APPROVED USERS" are all individuals specifically identified in the Research Plan, including the PI. Only individuals listed in the Research Plan may have access to the Research Materials.

"Research Plan" is a description of the proposed research that includes the identities of the investigators participating in the research effort. The Research Plan must include the project title, the RECIPIENT's name, the PI's name, the name of other APPROVED USERS, and the proposed research protocol with the research objectives and design. For plans including biospecimens, the biospecimen material type, number, minimum volume, and required characteristics needed to meet the objectives of the protocol must also be included.

"Research Materials" are the requested materials covered by this RMDA and may include STUDY data, defined as clinical or epidemiologic subject data, and/or STUDY biospecimens. STUDY biospecimens may have associated characterization data. Characterization data serve to describe STUDY biospecimens only and are not considered to be STUDY data; they are exempt from STUDY data requirements that may be described elsewhere in this RMDA.

"STUDY"is the clinical study that collected the Research Materials described in this RMDA.

"STUDY Investigator" is a research investigator with a current or previous grant, contract or consulting agreement with the NHLBI, or one of its contractors, to work on the STUDY.

Terms of Access

1. **Research Use**

   The RECIPIENT and APPROVED USERS agree that they will use the Research Materials solely in connection with the research project described in the Research Plan named in this RMDA. Substantive modifications to the research project will require submission of a revised RMDA.

2. **Institutional and Approved User Responsibilities**

   RECIPIENT and APPROVED USERS acknowledge that the conditions for use of STUDY data and "coded" biospecimens are not exempt from review and have been approved by the RECIPIENT's Institutional Review Board (IRB) operating under an Office of Human Research Protections (OHRP) - approved Assurance and in accordance with Department of Health and Human Services regulations at 45 CFR Part 46. RECIPIENT and APPROVED USERS agree to comply fully with all such conditions.

   RECIPIENT and APPROVED USERS agree to report promptly to the NHLBI any proposed change in the Research Plan and any unanticipated problems involving risks to subjects or others. Changes to the Research Plan include changes in the APPROVED USERS list. This RDMA is made in addition to, and does not supersede, any of RECIPIENT's institutional policies or any local, State, and/or Federal laws and regulations that provide additional protections for human subjects.

   Evidence of local IRB approval from an expedited or convened review to conduct the Research Plan with the requested STUDY data must be included in a supplemental Adobe PDF document that will be uploaded during the application process and attached to the RMDA form.

3. **Public Posting of Approved User's Research Use Statement**

The RECIPIENT and PI agree that information about the proposed research use can be posted on a public web site that describes the project(s) included in the RESEARCH PLAN. The information will include the PI's name, RECIPIENT institution, project title, and a brief summary of the research. In addition, citations resulting from the use of Research Materials may be posted on the Biologic Specimen and Data Repository Information Coordinating Center Website.

4. **Non-Identification**

The PI agrees not to use the Research Materials, either alone or in concert with any other information, to identify or contact individual STUDY subjects without specific approval to contact STUDY subjects obtained from the IRB(s) responsible for the STUDY.

5. **Non-Transferability of Research Materials**

The RECIPIENT and PI agree to retain control over the Research Materials, and further agree not to release or distribute Research Materials in any form to any entity or individual unless required by NHLBI policies. The RECIPIENT and PI agree to store Research Material data on a computer with adequate security controls (see Section 6), and to maintain appropriate control over the Research Materials at all times. Research Materials data containing individual-level information, in whole or in part, may not be sold to any entity or individual at any point in time for any purpose.

The PI agrees that if his or her relationship with the RECIPIENT terminates and a relationship with a different RECIPIENT is established during the period of the RMDA, a new RMDA from the second RECIPIENT will be submitted and approved before the PI resumes use of the Research Materials. Any versions of Research Material data stored at the first RECIPIENT will be destroyed and their destruction documented. However, if advance written notice and approval by the NHLBI Program Office is obtained to transfer responsibility for the approved Research Plan to a different PI with a relationship with the first RECIPIENT, the Research Material data may not need to be destroyed.

6. **Security of Research Materials**

The RECIPIENT and PI agree to store Research Material data on a computer with security controls adequate to protect sensitive or identifiable information, to ensure that only approved, supervised persons have access to the data, and to maintain appropriate control over the Research Materials at all times. Hard copies of any Research Material must similarly be stored under conditions sufficiently secure to avoid inappropriate access, and shredded prior to discarding.

This RMDA will be in effect for a period of three (3) years from its effective date for the requested STUDY data set. At the end of the three (3) year period, the RECIPIENT and PI agree to destroy all copies of the STUDY data, and all derivatives that contain individual-level information. Characterization data associated with the STUDY biospecimens are exempt from this requirement.

An extension of this RMDA may be permitted by the NHLBI upon submission by the PI and RECIPIENT of evidence of IRB approval for the extended period.

7. **Intellectual Property**

By requesting access to the STUDY Research Materials, the REQUESTER and APPROVED USERS acknowledge the intent of the NHLBI to see that anyone authorized for research access through the attached Research Plan, follow the intellectual property principles within the NIH GWAS Policy for Data Sharing as summarized below:

Achieving maximum public benefit is the ultimate goal of Research Material distribution through the NHLBI Biological and Data Repository Information Coordinating Center. The NIH believes that Research Materials, such as these covered by this RMDA, should be considered as pre-competitive, and urges APPROVED USERS to avoid making IP claims derived directly from the STUDY Research Materials. However, the NIH also recognizes the importance of the subsequent development of IP on downstream discoveries, especially in therapeutics, which will be necessary to support full investment in products to benefit the public.

It is expected that these NHLBI-provided data, and conclusions derived there from, will remain freely available, without requirement for licensing. The NIH encourages broad use of shared Research Materials coupled with a responsible approach to management of intellectual property derived from downstream discoveries in a manner consistent with the NIH's Best Practices for the Licensing of Genomic Inventions and the NIH Research Tools Policy.

8. **Acknowledgement of BioLINCC Research Resources**

RECIPIENT agrees to acknowledge the contribution of the STUDY in all oral and written presentations, disclosures, or publications resulting from any analyses conducted on the STUDY Research Materials.

If the Research Plan involves collaboration with STUDY Investigators, then the APPROVED USERS will comply with all policies established by the STUDY's publications committee. In addition, the APPROVED USERS will acknowledge the source of the data by including language similar to the following either in the acknowledgment or in the text of the manuscript: "This manuscript was prepared using WHIOS Research Materials obtained from the NHLBI".

If the Research Plan does not involve collaboration with STUDY Investigators or the STUDY has ended, the RECIPIENT will acknowledge the source of the data by including language similar to the following either in the acknowledgment or in the text of the manuscript: "This Manuscript was prepared using WHIOS Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the WHIOS or the NHLBI." Manuscripts and abstracts resulting from the Research Plan should not use the name of the STUDY in the title of the manuscript/abstract unless the title clearly denotes the source of the Research Materials as being from the NHBLI Biologic Specimen and Data Repository Information Coordinating Center (e.g., "...An investigation using the WHIOS Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center"). The purpose is to delineate manuscripts from the Research PI and APPROVED USERS from manuscripts from the STUDY and STUDY Investigators.

The RECIPIENT and PI agree to ensure that all APPROVED USERS will not include in any manuscripts derived from Research Materials any case studies that describe the characteristics of individual participants, or a small number or groups of participants.

9. **Research Use Reporting**

Prompt publication or other public disclosure of the results of the Research Plan is encouraged.

When requested by the NHLBI, the APPROVED USERS agree to provide general comments regarding topics such as the effectiveness of the NHLBI Biological Specimen and Data Repository Information Coordinating Center Research Material access process (ease of access and use; appropriateness of STUDY data format; challenges in following the policies; suggestions for improving research material access; or the program in general).

10. **Non-Endorsement, Indemnification**

The RECIPIENT and PI acknowledge that although all reasonable efforts have been taken to ensure the accuracy and reliability of Research Materials, the NHLBI, and STUDY Investigators do not and cannot warrant the results that may be obtained by using any Research Materials included therein. The NHLBI and all contributors to these Research Materials disclaim all warranties as to performance or fitness of the Research Materials for any particular purpose.

No indemnification for any loss, claim, damage or liability is intended or provided by any party under this agreement. Each party shall be liable for any loss, claim, damage, or liability that said party incurs as a result of its activities under this agreement, except that the NIH, as an agency of the United States, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. 2671 et seq.

11. **Termination and Violations**

The NHLBI may terminate this agreement if RECIPIENT or APPROVED USERS are in default of any of its conditions and such default has not been remedied within 30 days after the date of written notice of such default by an authorized representative of the NHLBI. Past violations will be taken into consideration by the NHLBI for future requests from the RECIPIENT and APPROVED USERS to access NHLBI Research Materials.

12. **Amendments**

Amendments to this Agreement must be made in writing and signed by authorized representatives of all parties..

Signatures Page

By submission of the RMDA, the RECIPIENT and PI attest to the APPROVED USERS qualifications for access to and use of STUDY Research Materials and certify their agreement to the NHLBI principles, policies, and procedures for the use of Research Materials as articulated in this document.

This Agreement is entered into as of: 11/24/10 (effective date)

BY RECIPIENT:

Name of RECIPIENT Institution: University of Massachusetts, Amherst
Name and Title of RECIPIENT's Authorized Institutional Business Official:
Robert C. Holub
Chancellor
Signature and Date of RECIPIENT's Authorized Institutional Business Official: 11/13/10

BY PRINCIPAL INVESTIGATOR:

Name and Title:
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(413) 577-4298
Fax Number:
(413) 545-1645
Signature and Date:
Katherine Reeves 11/10/10

BY NHLBI Authorized Representative:

Name and Title: Sean Coady P.O. Data Distribution
Signature and Date: 11/24/10

"Authorized Institutional Business/Signing Official" is an individual with the authority to enter into business transactions on behalf of the RECIPIENT.

APPENDIX C

TABLES

Table 1. Distribution of covariates by perineal powder use status (n=48,912): Women's Health Initiative Observational Study, 1993-2005.

Characteristic	Never perineal powder use N=23,346 N	%	Mean ± SD	Ever perineal powder use N=25,181 N	%	Mean ± SD
Age at baseline, years	23,346		63.7 ± 7.5	25,181		62.7 ± 7.2
Race						
White	19,464	83.6		21,776	86.7	
Other	3,808	16.4		3,332	13.3	
BMI category						
<25 kg/m^2	10,813	46.3		10,219	40.6	
25-<30 kg/m^2	7,668	32.9		8,314	33.0	
≥30 kg/m^2	4,865	20.8		6,648	26.4	
Number of live births						
0	3,346	14.4		3,281	13.1	
1-2	7,935	34.4		9,147	36.6	
3 or more	11,894	51.3		12,568	50.3	
Age at menopause, years						
≤48	6,452	27.6		6,784	26.9	
49-50	5,183	22.2		5,591	22.2	
51-53	5,108	21.9		5,677	22.6	
54+	6,603	28.3		7,129	28.3	
Ever oral contraceptive use						
no	14,337	61.4		14,158	56.2	
yes	9,009	38.6		11,023	43.8	
Postmenopausal hormone use						
Never	11,968	51.3		12,330	49.0	
Past	3,004	12.9		3,311	13.2	
Current	8,350	35.8		9,522	37.8	
Smoking status						
Never	12,224	53.1		12,012	48.3	
Past	9,301	40.4		11,375	45.8	
Current	1,507	6.5		1,462	5.9	

Abbreviations: BMI, body mass index; SD, standard deviation
NOTE: Total numbers may not sum to total n due to missing data.

Table 2. Distribution of covariates by duration of genital powder use (n=48,912): Women's Health Initiative Observational Study, 1993-2005.

	Genital powder use												
	Never		<1 year		1 - 4 years		5 - 9 years		10 - 19 years		20+ years		
	N=29,837		N=5,128		N=3,307		N=2,245		N=2,131		N=5,868		p-value
	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	
Age at baseline, years	29,837	63.7±7.3	5,128	61.8±7.2	3,307	61.8.±7.2	2,245	62.2±7.1	2,131	62.3±7.1	5,868	63.4±7.2	<0.01
Race													0.06
White	25,202 (84.7)		4,393 (85.9)		2,794 (84.8)		1,963 (87.6)		1,832 (86.2)		5,048 (86.3)		
Other	4,542 (15.3)		721 (14.1)		502 (15.2)		279 (12.4)		293 (13.8)		799 (13.7)		
BMI category													<0.01
<25 kg/m^2	14,035 (47.0)		2,087 (40.7)		1,322 (40.0)		864 (38.4)		784 (36.8)		1,954 (33.3)		
25-30 kg/m^2	9,766 (32.7)		1,699 (33.1)		1,057 (32.0)		737 (32.8)		709 (33.2)		1,998 (34.1)		
>30 kg/m^2	6,036 (20.3)		1,342 (26.2)		928 (28.0)		644 (28.8)		638 (30.0)		1,916 (32.6)		
Number of live births													<0.01
0	4,137 (14.0)		721 (14.1)		485 (14.8)		290 (13.0)		287 (13.6)		689 (11.8)		
1-2	10,318 (34.9)		1,827 (35.9)		1,193 (36.3)		863 (38.8)		759 (35.9)		2,117 (36.3)		
3 or more	15,155 (51.1)		2,543 (50.0)		1,605 (48.9)		1,073 (48.2)		1,070 (50.5)		3,023 (51.9)		
Age at menopause, years													0.57
48 and under	8,136 (27.3)		1,394 (27.2)		908 (27.5)		610 (27.2)		579 (27.2)		1,589 (27.1)		
49-50	6,619 (22.2)		1,142 (22.3)		741 (22.4)		483 (21.5)		459 (21.5)		1,337 (22.8)		
51-53	6,555 (22.0)		1,197 (23.3)		770 (23.3)		512 (22.8)		484 (22.7)		1,265 (21.6)		
54 and over	8,527 (28.5)		1,395 (27.2)		888 (26.8)		640 (28.5)		609 (28.6)		1,677 (28.5)		
Ever oral contraceptive use													<0.01
No	18,104 (60.7)		2,715 (52.9)		1,790 (54.1)		1,212 (54.0)		1,189 (55.8)		3,469 (59.1)		
Yes	11,733 (39.3)		2,413 (47.1)		1,517 (45.9)		1,033 (46.0)		942 (44.2)		2,399 (40.9)		
Postmenopausal hormone use													<0.01
Never	15,028 (50.4)		2,370 (46.3)		1,595 (48.3)		1,102 (49.1)		1,047 (49.2)		3,148 (53.7)		
Past	3,884 (13.0)		685 (13.4)		440 (13.3)		289 (12.9)		278 (13.0)		742 (12.7)		
Current	10,894 (36.6)		2,068 (40.3)		1,269 (38.4)		854 (38.0)		804 (37.8)		1,977 (33.6)		
Smoking status													<0.01
Never	15,439 (52.5)		2,434 (48.1)		1,609 (49.3)		1,060 (47.8)		1,003 (47.6)		2,682 (46.3)		
Past	12,137 (41.2)		2,335 (46.2)		1,471 (45.0)		1,065 (48.1)		989 (46.9)		2,685 (46.3)		
Current	1,852	(6.3)	288	(5.7)	187	(5.7)	91	(4.1)	117	(5.5)	429	(7.4)	

Abbreviations: BMI, body mass index; SD, standard deviation
NOTE: Total numbers may not sum to total n due to missing data.

Table 3. Distribution of covariates by duration of sanitary napkin powder use (n=48,912): Women's Health Initiative Observational Study, 1993-2005.

	Sanitary napkin powder use												
	Never N=38,046		<1 year N=2,939		1 - 4 years N=2,443		5 - 9 years N=1,595		10 - 19 years N=1,603		20+ years N=1,917		p-value
	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	
Age at baseline, years	38,046	63.4±7.4	2,939	61.8±7.1	2,443	61.8±6.9	1,595	62.5±6.9	1,603	63.6±6.9	1,917	64.1±7.1	<0.01
Race													
White	25,202 (84.7)		2,567 (87.5)		2,148 (88.3)		1,371 (86.1)		1,336 (83.7)		1,493 (78.1)		<0.01
Other	4,542 (15.3)		367 (12.5)		285 (11.7)		221 (13.9)		260 (16.3)		418 (21.9)		
BMI category													<0.01
<25 kg/m^2	16,690 (43.9)		1,314 (44.7)		1,043 (42.7)		655 (41.1)		659 (41.1)		676 (35.2)		
25-30 kg/m^2	12,512 (32.9)		940 (32.0)		807 (33.0)		547 (34.3)		545 (34.0)		624 (32.6)		
>30 kg/m^2	8,844 (23.2)		685 (23.3)		593 (24.3)		393 (24.6)		399 (24.9)		617 (32.2)		
Number of live births													0.19
0	5,062 (13.4)		408 (14.0)		379 (15.7)		261 (16.5)		226 (14.3)		282 (14.8)		
1-2	13,309 (35.2)		1,041 (35.7)		896 (37.1)		583 (36.8)		591 (37.3)		679 (35.6)		
3 or more	19,407 (51.4)		1,464 (50.3)		1,141 (47.2)		6,741 (46.7)		768 (48.4)		947 (49.6)		
Age at menopause, years													0.03
48 and under	10,368 (27.3)		738 (25.1)		662 (27.1)		489 (30.7)		457 (28.5)		519 (27.1)		
49-50	8,493 (22.3)		647 (22.0)		533 (21.8)		344 (21.6)		365 (22.8)		405 (21.1)		
51-53	8,416 (22.1)		702 (23.9)		541 (22.1)		339 (21.2)		353 (22.0)		429 (22.4)		
54 and over	10,769 (28.3)		852 (29.0)		707 (29.0)		423 (26.5)		428 (26.7)		564 (29.4)		
Ever oral contraceptive use													<0.01
No	22,553 (59.3)		1,572 (53.5)		1,281 (52.4)		926 (58.1)		949 (59.2)		1,216 (63.4)		
Yes	15,493 (40.7)		1,367 (46.5)		1,162 (47.6)		669 (41.9)		654 (40.8)		701 (36.6)		
Postmenopausal hormone use													<0.01
Never	19,144 (50.4)		1,330 (45,3)		1,085 (44.4)		764 (47.9)		871 (54.4)		1,097 (57.3)		
Past	4,893 (12.9)		390 (13.3)		342 (14.0)		220 (13.8)		221 (13.8)		255 (13.3)		
Current	13,975 (36.7)		1,217 (41.4)		1,015 (41.6)		610 (38.3)		510 (31.8)		562 (29.4)		
Smoking status													<0.01
Never	19,048 (50.7)		1,509 (51.9)		1,221 (50.6)		747 (47.5)		786 (49.8)		925 (48.9)		
Past	16,130 (43.0)		1,240 (42.7)		1,070 (44.3)		730 (46.5)		701 (44.5)		820 (43.4)		
Current	2,357	(6.3)	156	(5.4)	124	(5.1)	94	(6.0)	90	(5.7)	146	(7.7)	

Abbreviations: BMI, body mass index; SD, standard deviation
NOTE: Total numbers may not sum to total n due to missing data.

Table 4. Distribution of covariates by diaphragm powder use (n=48,912): Women's Health Initiative Observational Study, 1993-2005.

	Diaphragm powder use												
	Never N=42,332		<1 year N=1,020		1 - 4 years N=1,831		5 - 9 years N=1,260		10 - 19 years N=1,145		20+ years N=780		p-value
	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	N(%)	Mean ±SD	
Age at baseline, years	42,332	63.2±7.4	1,020	62.2±6.8	1,831	62.0±6.4	1,260	63.6±6.4	1,145	65.0±6.1	780	67.1±6.1	<0.01
Race													<0.01
White	35,637 (84.5)		873 (85.8)		1,648 (90.1)		1,148 (91.2)		1,061 (93.0)		731 (94.2)		
Other	6,564 (15.5)		144 (14.2)		180 (9.9)		111 (8.8)		80 (7.0)		45 (5.8)		
BMI category													0.06
<25 kg/m^2	18,080 (42.7)		468 (46.0)		861 (47.0)		616 (48.9)		564 (49.3)		380 (48.7)		
25-30 kg/m^2	14,009 (33.1)		316 (31.0)		582 (31.8)		415 (32.9)		346 (30.2)		263 (33.7)		
>30 kg/m^2	10,243 (24.2)		236 (23.0)		388 (21.2)		229 (18.2)		235 (20.5)		137 (17.6)		
Number of live births													<0.01
0	6,186 (14.7)		99 (9.8)		147 (8.1)		92 (7.4)		61 (5.4)		28 (3.6)		
1-2	14,607 (34.8)		384 (37.9)		767 (42.1)		514 (41.1)		434 (38.2)		329 (42.4)		
3 or more	21,222 (50.5)		531 (52.3)		907 (49.8)		645 (51.5)		640 (56.4)		419 (54.0)		
Age at menopause, years													0.03
48 and under	11,781 (27.8)		258 (25.3)		423 (23.1)		294 (23.3)		297 (25.9)		143 (18.3)		
49-50	9,378 (22.2)		216 (21.2)		416 (22.7)		289 (22.9)		253 (22.1)		185 (23.7)		
51-53	9,333 (22.0)		218 (21.4)		428 (23.9)		307 (24.4)		249 (21.8)		202 (25.9)		
54 and over	11,840 (28.0)		328 (32.1)		554 (30.3)		370 (29.4)		346 (30.2)		250 (32.1)		
Ever oral contraceptive use													<0.01
No	25,192 (59.5)		510 (50.0)		795 (43.4)		613 (48.7)		684 (59.7)		616 (79.0)		
Yes	17,140 (40.5)		510 (50.0)		1,036 (56.6)		647 (51.3)		461 (40.3)		164 (21.0)		
Postmenopausal hormone use													<0.01
Never	21,602 (51.1)		462 (45.4)		709 (38.7)		524 (41.6)		500 (43.7)		427 (54.8)		
Past	5,430 (12.8)		160 (15.7)		265 (14.5)		175 (13.9)		165 (14.4)		90 (11.6)		
Current	15,264 (36.1)		396 (38.9)		856 (46.8)		561 (44.5)		479 (41.9)		262 (33.6)		
Smoking status													<0.01
Never	21,464 (51.4)		448 (44.6)		849 (46.8)		540 (43.3)		509 (45.0)		363 (47.3)		
Past	17,615 (42.2)		486 (48.4)		880 (48.5)		660 (52.9)		580 (51.3)		375 (48.9)		
Current	2,685 (6.4)		70 (7.0)		84 (4.7)		47 (3.8)		41 (3.7)		29 (3.8)		

Abbreviations: BMI, body mass index; SD, standard deviation
NOTE: Total numbers may not sum to total n due to missing data.

Table 5. Risk factors related to endometrial cancer (n=48,912): Women's Health Initiative Observational Study, 1993-2005.

Variable		Number of cases	Person-years	Age-adjusted hazard ratio	95% CI
Race	White	417	312936	1.00	
	Other	32	52431	0.47	0.33-0.68
BMI category	<25 kg/m^2	192	160485	1.00	
	25-30 kg/m^2	104	120363	0.71	0.56-0.90
	>30 kg/m^2	155	85536	1.52	1.24-1.89
Number of live births	0	68	50474	1.00	
	1 - 2	166	129341	0.96	0.72-1.27
	3+	215	183831	0.82	0.63-1.08
Age at menopause (years)	<48	113	99494	1.00	
	49-50	87	81587	0.93	0.70-1.23
	51-53	105	81781	1.15	0.88-1.50
	54+	146	103523	1.21	0.94-1.54
Ever oral contraceptive use	No	276	213250	1.00	
	Yes	175	153134	1.07	0.87-1.32
Postmenopausal hormone use status	Never	174	183625	1.00	
	Past	65	47547	1.43	1.07-1.90
	Current	211	134900	1.95	1.59-2.40
Smoking status	Never	240	183336	1.00	
	Past	190	155931	0.95	0.78-1.15
	Current	17	22096	0.63	0.38-1.03

Abbreviations: BMI, body mass index; SD, standard deviation
NOTE: Total numbers may not sum to total n due to missing data.

Table 6. Hazard ratios and 95% CIs for ever vs. never perineal powder use and endometrial cancer (n=48,912): Women's Health Initiative Observational Study, 1993-2005.

	All perineal powder use		
	Never	Ever	p-value*
All women			
Number of cases	207	241	
Person-years	174,127	189,459	
Age-adjusted HR (95% CI)	1.00 (ref)	1.11 (0.92-1.34)	<0.001
Multivariate-adjusted HR (95% CI)†	1.00 (ref)	1.05 (0.87-1.27)	<0.001

Abbreviations: HR hazard ratio; CI confidence interval

* P-value of likelihood ratio test comparing nested models

† Adjusted for age, race, body mass index category, number of live births, age at menopause, oral contraceptive use, postmenopausal hormone use status, and smoking status.

Table 7. Hazard ratios and 95% CIs for duration of perineal powder use and endometrial cancer, by category of powder use (n=48,912): Women's Health Initiative Observational Study, 1993-2005.

	Duration of powder use						
	Never	<1 year	1 - 4 years	5 - 9 years	10 - 19 years	20+ years	p-value*
Genital powder use							
Number of cases	283	49	28	15	18	59	
Person-years	223,409	38,604	24,739	16,886	15,963	44,079	
Age-adjusted HR (95% CI)	1.00 (ref)	1.07 (0.79-1.45)	0.95 (0.65-1.41)	0.74 (0.44-1.25)	0.94 (0.58-1.51)	1.07 (0.81-1.42)	<0.001
Multivariate-adjusted HR (95% (	1.00 (ref)	1.02 (0.75-1.39)	0.89 (0.60-1.32)	0.70 (0.42-1.18)	0.89 (0.55-1.44)	1.02 (0.76-1.35)	<0.001
Sanitary napkin powder use							
Number of cases	340	36	17	18	22	17	
Person-years	284,736	22,039	18,483	11,995	12,021	14,315	
Age-adjusted HR (95% CI)	1.00 (ref)	1.45 (1.03-2.04)	0.82 (0.50-1.3)	1.30 (0.81-2.09)	1.53 (0.99-2.36)	0.98 (0.60-1.59)	<0.001
Multivariate-adjusted HR (95% (	1.00 (ref)	1.35 (0.95-1.92)	0.79 (0.49-1.29)	1.30 (0.81-2.09)	1.62 (1.05-2.50)	1.03 (0.63-1.67)	<0.001
Diaphragm powder use							
Number of cases	371	11	13	15	13	23	
Person-years	317,591	7,653	14,011	9,495	8,654	5,889	
Age-adjusted HR (95% CI)	1.00 (ref)	1.27 (0.70-2.32)	0.83 (0.48-1.44)	1.34 (0.80-2.25)	1.23 (0.71-2.14)	3.01 (1.97-4.59)	<0.001
Multivariate-adjusted HR (95% (	1.00 (ref)	1.29 (0.71-2.35)	0.79 (0.46-1.38)	1.30 (0.77-2.18)	1.09 (0.61-1.93)	3.02 (1.97-4.63)	<0.001

Abbreviations: HR hazard ratio; CI confidence interval

* P-value of likelihood ratio test comparing nested models

† Adjusted for age, race, body mass index category, number of live births, age at menopause, oral contraceptive use, postmenopausal hormone use status, and smoking status.

Table 8. Hazard ratios and 95% CIs for categories of perineal powder use and endometrial cancer (n=48,912): Women's Health Initiative Observational Study, 1993-2005.

	Categories of perineal powder use				
	No talc use	Genital and/or sanitary napkin	Diaphragm only	Diaphragm + genital and/or napkin	p-value*
All perineal powder use					
Number of cases	207	163	32	44	
Person-years	174,127	141,821	20,552	25,468	
Age-adjusted HR (95% CI)	1.00 (ref)	1.01 (0.82-1.24)	1.31 (0.91-1.90)	1.49 (1.07-2.06)	<0.001
Multivariate-adjusted HR (95'	1.00 (ref)	0.96 (0.77-1.18)	1.24 (0.85-1.81)	1.39 (1.00-1.93)	<0.001

Abbreviations: HR hazard ratio; CI confidence interval

* P-value of likelihood ratio test comparing nested models

† Adjusted for age, race, body mass index category, number of live births, age at menopause, oral contraceptive use, postmenopausal hormone use status, and smoking status.

Table 9. Hazard ratios and 95% CIs for maximum duration of perineal powder use across categories and endometrial cancer (n=48,912): Women's Health Initiative Observational Study, 1993-2005.

	Maximum duration of all powder use						
	Never	<1 year	1 - 4 years	5 - 9 years	10 - 19 years	20+ years	p-value*
All perineal powder use							
Number of cases	207	44	43	30	35	88	
Person-years	174,127	41,615	38,056	26,934	26,588	55,031	
Age-adjusted HR (95% CI)	1.00 (ref)	0.95 (0.69-1.32)	1.02 (0.73-1.42)	0.97 (0.66-1.43)	1.14 (0.80-1.63)	1.35 (1.05-1.73)	<0.001
Multivariate-adjusted HR (95% C	1.00 (ref)	0.89 (0.63-1.24)	0.96 (0.68-1.34)	0.93 (0.63-1.37)	1.06 (0.74-1.53)	1.30 (1.01-1.67)	<0.001

Abbreviations: HR hazard ratio; CI confidence interval

* P-value of likelihood ratio test comparing nested models

† Adjusted for age, race, body mass index category, number of live births, age at menopause, oral contraceptive use, postmenopausal hormone use status, and smoking status.

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