ASSOCIATIONS BETWEEN PERSONAL CARE PRODUCT USE PATTERNS AND BREAST CANCER RISK IN THE SISTER STUDY

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ABSTRACT

Kyla Welch Taylor: Associations between Personal Care Product Use Patterns and Breast Cancer Risk in the Sister Study
(Under the direction of Melissa Troester)

Background: Among women in the United States, breast cancer is the second leading cancer-related cause of death. It is hypothesized that certain chemicals in personal care products may increase risk of breast cancer. The primary aims of this study were to use a data-centered approach to classify complex patterns of exposure to personal care products, understand how these patterns vary according breast cancer risk factors, and evaluate whether patterns of beauty, hair, or skin-related personal care products or individual products were associated with breast cancer.

Methods: Limiting the sample to non-Hispanic blacks and whites (N=47,019), latent class analysis (LCA) was used to identify groups of individuals with similar patterns of personal care product use based on responses to survey questions. Personal care products were categorized into three product types (beauty, hair, and skincare products) and separate latent classes were constructed for each type. Adjusted prevalence differences (PD) were calculated to estimate the association between known and suspected breast cancer risk factors and patterns of personal care product use. Multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between product use and breast cancer risk.

Results: Latent class analysis (LCA) was used to reduce data dimensionality across 48 individual personal care product use questions and to identify groups of individuals with similar patterns of product use. Three latent classes were identified for both the beauty and hair product groups; the skincare product group had four classes. Among white women, those classified as 'moderate' and 'frequent' users of beauty products had increased risk of breast cancer relative to 'infrequent users' (HR=1.12; 95% CI: 1.00-1.27 and HR=1.15; 95% CI: 1.02-1.30). 'Frequent' users of skincare products also had increased risk of breast cancer relative to 'infrequent users' (HR=1.13; 95% CI: 1.00-1.29).

Conclusions: Relative to individual product use questions, latent class variables capture complex patterns of personal care product usage. This work generates novel hypotheses for breast cancer risk.

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AIC	Akaike's information criterion
BIC	Bayesian information criterion
BMI	Body Mass Index
BPA	Bisphenol A
BC	Breast Cancer
CDC	Centers for Disease Control
CI	Confidence Interval
EDC	Endocrine Disrupting Chemical
EARTH	Environmental and Reproductive Health Study,
ER	Estrogen Receptor
HT	Hormone Therapy
HR	Hazard Ratio
IRB	Institutional Review Board
LCA	Latent Class Analysis
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
kg	Kilograms
m	Meters
mg	Milligram
MEP	monoethyl phthalate
MBzP	monobenzyl phthalate
MCPP	mono (3-carboxypropyl) phthalate

OC	Oral Contraceptive
OR	Odds Ratio
PD	Prevalence Difference

CHAPTER 1: BACKGROUND

1.1. Breast Cancer Biology and Epidemiology

Breast cancer is the second leading cancer-related cause of death among women in the United States. Only lung cancer accounts for more cancer deaths in women [1, 2]. The American Cancer Society estimates that in 2014 there were approximately 232,670 new cases of invasive breast cancer diagnosed and approximately 40,000 breast cancer-caused deaths [2].

1.1.1. Genetic Risk Factors

It is estimated that 5% to 10% of breast cancer cases are hereditary [3, 4]. Among hereditary breast cancers, 20 to 25% are accounted for by high penetrance BRCA1 and BRCA2 gene mutations [5, 6]. These gene mutations are associated with a 10-fold increase in breast cancer risk but are rare [7]. Intermediate-penetrance genetic mutations in genes involved in DNA repair such as ATM, CHEK2, BRIP1, and PALB2 increase breast cancer risk about 2- to 3-fold [8]. Low-penetrance, common single nucleotide polymorphisms (SNPs) are associated with low personal risk of breast cancer but are prevalent enough in the population to be significant on a public health level (e.g. SNPs found in FGFR2, TNRC9, MAP3K1, or LSP1) [8-10].

Breast cancer risk is higher among women who have one or more first-degree family members with the disease. A woman with one first-degree relative (e.g., mother or sister) with breast cancer has approximately double the risk of breast cancer compared to a woman with no family history of breast cancer [11, 12]. Compared to women without a family history, having two first-degree relatives who have been diagnosed with breast cancer increases a woman’s risk about 3-fold; having three or more first-degree relatives diagnosed with breast cancer increases risk

4-fold. However, the vast majority of women diagnosed with breast cancer, over 85%, do not have a family history [9, 12].

1.1.2. Established Non-Genetic Risk Factors

Established non-genetic risk factors for breast cancer include age, reproductive history (e.g., late age at first birth, nulliparity or low parity, late menopause, early menarche, and little or no lactation), hormone replacement therapy use and recent oral contraceptive use, higher adult body mass index (BMI), and alcohol consumption. The evidence for each of these associations is summarized below.

Age

Breast cancer risk increases significantly with age. As a person grows older, tissue accumulates they experience more opportunities or genetic damage (e.g., mutations) in their bod. According to data from the Surveillance, Epidemiology, and End Results (SEER) Program [13], rates of breast cancer are lowest in women under 40 years. Rates begin to increase after age 40 and are highest in women over age 70 [2]. Between 2006 and 2010, 79% of new cases and 88% of breast cancer deaths occurred in women 50 years of age and older; the median age at the time of breast cancer diagnosis was 61 years [2, 13]. Breast cancer incidence among women ages 80 to 85 years old is 15 times higher than in women ages 30 to 35 years old [14]. Women who are diagnosed with breast cancer at a younger age (≤35-40 years) are more likely to have more aggressive breast cancers that are related to BRCA1 or BRCA2 gene mutations [15].

Race and Ethnicity

In the United States, the highest breast cancer incidence rate of any racial or ethnic group is among non-Hispanic white women [16]. Hormonally responsive, luminal tumors are the predominant breast cancer subtype for non-Hispanic white and African American women in the United States, particularly among postmenopausal women [16]. However, pre-menopausal

African American women have higher incidence before age 40 and have higher prevalence of basal-like breast cancers [17, 18]. African American women are also more likely to die from breast cancer than white women [19]. Hispanic women have lower incidence rates and lower mortality rates than white women and African American women [2]. Asian/Pacific Islander women have the lowest incidence and mortality rates [20]. The reasons for ethnic disparities are not entirely clear, but likely reflect diet, lifestyle, and access to medical care [21].

Reproductive Risk and Protective Factors

Risk of developing breast cancer is strongly linked to reproductive factors, which characterize exposure to sex hormones. Many reproductive risk factors are associated with exposure to estradiol, progesterone, systemic circulating estrogen levels, and other hormones [22, 23]. Reviews of the epidemiologic literature have reported that that early menarche (before age 12), late menopause (after age 55), low parity, late age at first birth (after age 30), and shorter duration of breastfeeding (less than 12 months) are associated with an increased risk of breast cancer [24, 25]. Women who experience risk factors such as early menarche and late menopause may have an increased risk of breast cancer due to a longer lifetime exposure to the hormones estrogen and progesterone [26]. The literature also suggests that the protective effect of earlier first full-term pregnancy and longer duration of breastfeeding may result from the reduced effect of circulating hormones on breast tissue after pregnancy [25] and reduction of a woman's total number of lifetime menstrual cycles [2]. However, reproductive factors have many different effects on biology and lifestyle and therefore the mechanisms are complex and remain uncertain.

Oral Contraceptives and Post-menopausal Hormone Replacement Therapy

Oral contraceptives (OC) and post-menopausal hormone replacement therapy (HRT) are estrogen, progesterone, or estrogen and progesterone combined regimens. The use of OCs is associated with increased breast cancer risk in current and recent users; however the effect diminishes 10 years after stopping use [27]. The use of HRT (estrogen-progesterone) is associated with increased breast cancer risk among post-menopausal women; however the effect diminishes 5 years after cessation of use [28]. A pooled analysis of 51 epidemiologic studies of around 54,000 postmenopausal women [28] reported that the relative risk of breast cancer diagnosis increased in relation to duration of HRT use (2.3% per year; 95% CI: 1.1, 3.5%). Among current or recent users, defined as use within the past 5 years, who had used HRT for 5 or more years, the relative risk of breast cancer was 1.35 (95% CI: 1.21, 1.49). However past users (>5 years since cessation of HRT use) had no significant increase in relative risk of breast cancer that was related to duration of use [28].

Alcohol

Consumption of alcoholic beverages is a well-established risk factor for breast cancer [29]. Meta-analyses report that women who consume one alcohol beverage per day have an increased risk, between 7% and 12%, of breast cancer when compared to non-drinkers [30-32]. Compared with non-drinkers, light drinkers (up to one drink per day, 1.5 units) have a smaller increased risk (5%) [32]. Women who have 2 to 5 drinks a day are 1.5 times more likely to develop breast cancer than non-drinkers [33]. This association may be modified by hormone receptor expression: ethanol and acetaldehyde interfere with estrogen pathways and may trigger the expression of hormone receptors (e.g., estrogen) in breast tumors [34, 35]. However, other mechanisms have also been proposed; alcohol consumption is associated with genetic polymorphisms, such as increased reactive oxygen species through induction of CYP2E1 [36], enhanced mammary gland susceptibility to carcinogenesis, and increased mammary carcinogen DNA damage [37].

Bodyweight

Overweight and obesity, as measured by high body mass index (BMI), moderately increases the risk of breast cancer in postmenopausal women. However obesity is negatively associated with pre-menopausal breast cancer risk [38, 39].The increase in breast cancer risk with increasing BMI among post-menopausal women is largely the result of the associated increase in estrogens [40]. A meta-analysis of 13 studies of post-menopausal women reported that circulating concentrations of sex hormones (e.g., estrogens) were higher in obese women than in women with lower BMI [41]. Higher BMI usually means increased adipose tissue which produces aromatase, an enzyme responsible for a key step in biosynthesis of estrogens [42]. This increased total aromatase activity along with high estrogen levels may explain the increased risk of breast cancer among obese post-menopausal women compared to non-obese post-menopausal women [23, 40, 41, 43]. However, obesity also has effects on many different biological processes, including systemic and local inflammation [44], so mechanisms of obesity are complex.

Geographic Location

In the United States breast cancer rates vary by geographic region. Geographic variation is based on a number of factors including demographics, lifestyle, regional cultures, and access to screening and care [16]. The Centers for Disease Control and Prevention (CDC) reported that the highest incidence rates of breast cancer were in the Northeast followed by the Midwest [45]. These areas are also where the 2015 Annual Report to the Nation on the Status of Cancer reported the highest rates of luminal breast cancers. Authors noted that these areas tend to also have higher mammography screening rates [16]. Rates of triple negative breast cancers were higher in the Southeast; these rates increased with increased percentage of non-Hispanic black women [16]. Death rates from breast cancer are highest in the South, followed by the Midwest, Northeast and West [45].

1.1.3. Non-established Non-Genetic Risk Factors

Tobacco Smoke

The relationship between cigarette smoking and breast cancer risk is unclear. Despite extensive research on smoking and breast cancer there is no scientific consensus, partly because of concern that the association may be confounded by alcohol consumption [46] and because studies have not consistently shown an increase in risk with duration or intensity of smoking [47]. Some studies suggest current smoking to be linked to increased risk of breast cancer through DNA damage mechanisms [48]. However there is also evidence that smoking may decrease ovarian function and therefore endogenous exposure to estrogen, with a resulting protective effect on breast cancer [49]. A meta-analysis of cohort studies and an original cohort analysis on active smoking and breast cancer risk reported increased risk among current smokers, especially when smoking begins at an early age [50]. Data from the Nurses' Health Study suggests that active smoking, especially before the age of 20 or before first birth, may be associated with a modest increase in breast cancer risk. The risk increase for current smokers and former compared to never-smokers was approximately 12% and 9%, respectively [51]. Data from the Women's Health Initiative reported evidence of an association between active and passive smoking and breast cancer risk among postmenopausal women [52].

1.2. Environmental Exposures and Breast Cancer

Breast cancer is a very complex disease because both genetic and environmental factors contribute to its etiology [53]. Environmental exposures, defined in this proposal as environmental pollutants and chemicals, are a potential cause of breast cancer [54]. Over the past few decades, a number of environmental pollutants have been considered, however epidemiologic studies have reported inconsistent or null results [55-57]. Organochlorines are a diverse group of synthetic chemicals that have been widely studied. This group of chemicals includes polychlorinated biphenyls (PCBs), dioxins, and organochlorine pesticides such as dichlorodiphenyl-trichloroethane (DDT), lindane, and hexachlorobenzene. Though use of DDT and PCBs has been banned in the United States since the 1970s, some organochlorine compounds have continued to accumulate and persist in the environment and have been measured in human tissues. Laboratory research provides evidence that a number of persistent organochlorine compounds (e.g., PCBs and DDT) exhibit varying estrogenic and anti-estrogenic activity in biological assays [58]. These compounds can affect the body's estrogen production and metabolism and may contribute to breast cancer risk by damaging DNA, disrupting hormones, promoting tumor growth, or increasing susceptibility by altering mammary gland development [59-61]. The majority of epidemiologic studies studying these chemicals have reported null associations [62], including large prospective cohort studies [63-65], a large case-control study [66] and a meta-analysis of 22 epidemiologic studies [56]. It has been suggested that the null association between organochlorine compounds and breast cancer may reflect a true lack of association or to shared methodological weakness across a large number of studies [67].

In contrast to environmental chemicals, which have typically shown weak or inconsistent associations, environmental ionizing radiation has been strongly linked to breast cancer [68]. Evidence of this comes from studies of women in Hiroshima and Nagasaki when the United States dropped the atomic bombs and women exposed to massive amounts of radiation from the 1986 Chernobyl nuclear reactor accident [69, 70]. The association is not as clear with radiation exposures experienced by the general public or people living in areas that have higher radiation levels (e.g., near industrial accidents or nuclear activities) [71]. Other possible risk factors, such as occupational exposures, electromagnetic fields, light at night, solar radiation, and some environmental chemicals have been indicated by some studies, but the results have been inconclusive [55, 61, 72, 73].

1.3. Methodological Issues

Examining environmental exposures and breast cancer risk in the general population is challenging given a number of methodological issues: exposures are often poorly quantified; it is difficult to find an unexposed group because many environmental contaminants are ubiquitous in the environment; the range of measured exposures may be narrow (with few or no unexposed or highly exposed); small hypothesized relative risks require very large studies for sufficient statistical power; and the timing of measurement may not be etiologically relevant [67, 71]. Exposure measurements made near the time of diagnosis or interview may not represent the appropriate empirical induction period between exposure and development of breast cancer. Latency periods of 8 to 15 years have been reported for breast cancer [67, 74-76]. Therefore, if an environmental exposure were related to breast cancer, empirical induction periods could be at least one to two decades [67]. Another common concern regarding exposure measurement comes from self-report observational studies. Self-reported exposures are subject to multiple sources of error (e.g., recall bias) resulting in misclassification. If the resulting misclassification is non-differential, a small, real effect may not be detected. Therefore another challenge is having a large enough study to have sufficient statistical power [67, 71].

Ideal environmental exposure assessment would provide information about the agent, dose, exposure pathway, timing in relation to the empirical induction period, tumor growth rate, and an unexposed comparison population [67]. However, gathering this kind of detailed data is expensive, time consuming and sometimes not practical. It is also true that low-level environmental exposures are also often associated with small hypothesized relative risks that are difficult to assess statistically in small studies. With the exception of major releases of contaminants due to an industrial accidents or atomic bomb, environmental exposure is challenging to study in the general population [71].

1.4. Personal Care Product Sources and Exposure

The average American woman uses 12 personal care products a day, resulting in daily exposure to an estimated 126 unique chemicals [77]. Because certain chemicals in personal care products are suspected endocrine disrupters (e.g., phthalates, parabens, triclosan) [78, 79], there is concern that exposure to personal care products may be associated with risk of breast cancer and/or may have adverse reproductive health effects. *In vitro* and animal studies have demonstrated that endocrine disrupting chemicals can mimic estrogens [73], alter hormonal signaling, affect developing reproductive systems [80], and/or disrupt normal mammary development [81]. However, there is currently no definitive evidence for the same effects in humans [82-85].

The strongest evidence to support concern for endocrine disrupting chemicals comes from experimental animal studies [85]. However, laboratory animals are usually exposed to individual chemicals over short periods of time (often at higher doses than humans) whereas humans are typically exposed to multiple endocrine disrupting compounds simultaneously over many years. Consequently, there is concern that laboratory animal data have not addressed the patterns of exposure to these complex mixtures which may be most relevant [86, 87]. At the same time, more information is needed to characterize the nature of human exposure in order to design more appropriate animal and *in vitro* studies of complex mixtures as well as validate computational models of predicted exposure. To address the limitations in experimental animal studies and capture the exposure characteristics in human populations, human studies are needed.

Some key challenges have impeded progress in understanding the relationship between personal care product use and health outcomes in humans. First, publically available data on personal care product usage patterns in the United States typically lack large sample populations or include only specific types of product users [88, 89 , 90, 91]. Currently the only population-based studies of personal care product use that have a comparison group of infrequent personal care product users are limited to other countries [92, 93], or small populations within the United States [94]. Second, studies that have collected data on product use have described correlations between use patterns for only a limited numbers of products. Third, studies to date have not placed the personal care product exposures in context of other exposures, particularly those in relevant biological pathways.

1.5. Data Collection in Epidemiological Studies

Wu et al [94] used a telephone interview to collect information on the frequency of use of ~30 types of personal care products from 604 Californian participants. Participants were recruited in three age groups: children, their parents, and adults age 55 years or older. Manová et al [93] used a postal questionnaire survey to examine patterns of personal care product use in three Western European countries: Switzerland, Germany, and the Netherlands. A self-administered questionnaire asked participants to recall their use of eight personal care product categories (face cream, body lotion, aftershave, hand cream, makeup foundation, lipstick, lip care, and sunscreen) over the past year. The third study used a digital questionnaire to collect information on the use of 32 different personal care products among 516 men and women living in the Netherlands [92]. In the sections that follow, the main findings from these three studies are summarized.

Prevalence

Lotion/cream products had the overall highest prevalence of use. Manová et al [93] reported that among adult females the prevalence of use was highest for face lotion (95.9%) and hand lotion (95.3%). Biesterbos et al [92] reported that a high percentage of respondents (70-95%) used a combination of two skin care products (e.g., day cream and night cream). A majority of users (>50%) indicated that they used deodorant, day cream, night cream, make-up remover, mascara, eye pencil and eye brow pencil once a day [92]. The California study [94] found that the different hygiene products (e.g., body lotion and hand lotion, shampoo and conditioner) were strongly correlated with each other. The use of different skincare products were moderately correlated with each other and the use of some cosmetics were correlated (e.g., foundation and mascara were correlated). Foundation and mascara were also correlated with hair styling and face cleaning products [94]. In all three studies personal care product use patterns varied by socio-demographic factors including age, race, education [92-94] and by climatic region in the California study (e.g., northern vs. southern California) [94].

Age/Region

Younger female adults in northern California had a higher prevalence of a wider range of personal care product use than older female adults in central California [94]. Younger females had higher use frequencies of shampoo, conditioner and hair mousse compared to older female adults. The older female adults reported a higher prevalence of hair spray, permanent hair treatment, ear and nasal care products, foundation, mascara, nail polish and hair dye [94]. In Europe, younger adults were heavier users of personal care products such as foundation, lip care, and sunscreen [93]. Female participants in the oldest age group, 66 years and older, had the highest prevalence of lipstick use (72.6%).

Race/Ethnicity

According to a study in California [94] race/ethnicity was an important factor among younger women in determining personal care products use. Compared to younger non-Hispanic white women, younger African American women were more likely to have their hair treated permanently (including chemical straightening or relaxing). However this study was based on a very small number of African American women (N=10) compared to non-Hispanic white women (N=206) so comparison may be subject to small sample biases [94]. An analysis of 2,540 samples collected from participants of the National Health and Nutrition Examination Survey 1999-2000 found that African American women had higher urinary levels of monoethyl phthalate, a phthalate found in personal care products, compared to non-Hispanic white women[84]. The authors speculated that these differences are likely due to differences in hair texture and cultural practices [94].

The European studies did not specify race/ethnicity, however participants from Netherlands, Switzerland, and Germany were categorized by self-reported skin type: very fair, fair, light brown, medium brown, dark brown, and black [93]. The prevalence of use of face cream, body lotion, hand cream, makeup foundation, lipstick, lip care, and sunscreen was higher among those with very fair, fair, and light brown skin compared to those with medium brown, dark brown, and black skin [93]. This study did not look at hair products, an important category when considering race/ethnicity because African American women are more likely to use hair products that contain endocrine disrupting compounds [95, 96].

Education

In the US, educational attainment influenced choices of products, particularly for products where awareness of a healthy lifestyle could be considered a factor (e.g., more frequent use of sunscreen) or where higher income might play a role (e.g., more use of professional services for nails) [94]. Manová et al [93] reported that education had an influence on the prevalence of use of body lotion, hand cream, makeup foundation, lipstick, and sunscreen. The prevalence of use of body lotion and hand cream decreased as education increased and the prevalence of sunscreen use increased as education increased. The largest proportion of sunscreen users were university graduates (92.4%). For cosmetics (i.e., makeup foundation and lipstick) the prevalence of use was highest among the participants who completed the European equivalent of high-school [93].

Patterns of Co-use

Manová et al [93] reported that most (64.8%) adult females reported using two or more personal care products concurrently and regularly. The most common combination of products that adult females used was sunscreen, face cream, and body lotion. A similar pattern was reported in the U.S. Wu et al. [94] found moderately positive correlations between the use of face moisturizer and body lotion among California residents. In the Netherlands, Biesterbos et al.[92] also reported co-use of products. Most products within the hair care, skin care, or cosmetic product groups were correlated. Day cream was often used by the same people who used night cream (kappa=0.49) and the use of powder was likely among people who used foundation (kappa=0.67). Among those who applied nail polish, 93% also used nail polish remover (kappa=0.95), 82.5% of all users who applied eye shadow also used mascara (kappa=0.62). Surprisingly, not all products that seem to be associated were used simultaneously.

For example, out of 499 respondents who use shampoo, only 173 used conditioner as well (kappa=0.03) [92].

Currently, there are no studies that have examined a large, diverse sample population to evaluate exposure patterns for a wide range of personal care products. In addition, the previous studies used Cohen's Kappa coefficients and Spearman correlation coefficient to describe patterns of co-use. To advance public health knowledge about the health effects of personal care product use, there is a need to more comprehensively describe patterns of use.

1.6. Personal Care Products and Breast Cancer

There is concern that use of personal care products may be associated with breast cancer risk [67]. It has been hypothesized that chemicals in personal care products (e.g., parabens and phthalates) may act as endocrine disrupting chemicals (EDCs) [79, 97] possibly mimicking the effects of carcinogenic effects of estrogenic exposures [98, 99]. *In vitro* and animal studies have demonstrated that these chemicals can mimic estrogens [73], alter hormonal signaling, affect developing reproductive systems [80], and/or disrupt normal mammary development [81]. However, there is currently no definitive evidence for the same effects in humans [82-85]. There have been studies showing associations between personal care product use and increased phthalate or paraben exposure. A cross-sectional analysis of controls from a population based case-control study of women in northern Mexico reported increasing numbers of personal care products used were associated with higher urinary concentrations of monoethyl phthalate (MEP), a phthalate that is commonly used in certain personal care products [100]. The Environmental and Reproductive Health [EARTH] Study, a cohort study of women ages 18 to 45 years, showed evidence of a monotonic dose-response relationship between total number of products used and urinary paraben and phthalate metabolite concentrations [101].

Very few studies have evaluated risk of breast cancer in association with components of personal care products or individual products and those studies have not strongly supported increasing risk of breast cancer in association with personal care product use in humans [102]. A possible relationship between phthalate exposure and breast cancer has been investigated in several studies but has yielded mixed results. A population based case-control study of women residing in northern Mexico, with 233 histopathologically confirmed breast cancer cases and 221 age-matched controls studied exposure to several phthalates found in a wide range of personal care products. This study reported that urinary concentrations of monobenzyl phthalate (MBzP) and mono (3-carboxypropyl) phthalate (MCPP)) were negatively associated with breast cancer (MBzP: OR= 0.46, 95% CI: 0.27–0.79; MCPP: OR= 0.44, 95% CI:0.24–0.80). However, MEP and mono-2-ethyl-5-carboxypentyl phthalate (MECPP), a metabolite of DEHP, were significantly associated with increased breast cancer risk (MEP: OR =2.20, 95% CI: 1.33–3.63; MECPP: OR=1.68, 95% CI: 1.01–2.78) [102]. The odds ratio for MECPP was weak and borderline significant and other metabolites of DEHP were not significantly different between cases and controls [102].

Epidemiologic research related to personal care products has mostly emphasized specific component ingredients in deodorants/ antiperspirants and hair dye. It has been suggested that aluminum compounds and other ingredients (e.g., parabens) in deodorant and antiperspirant could be related to breast cancer because they have estrogen-like effects [103] and are applied frequently to an area near the breast [103, 104]. However, epidemiological studies of the relationship between deodorants/antiperspirants and breast cancer have reported conflicting or inconclusive results [88-90]. A 2002 population-based case-control study of 813 women diagnosed with breast cancer and 793 controls reported no increased risk for women who reported using underarm deodorant or antiperspirant [89]. A 2003 retrospective case-only study of 437 females diagnosed with breast cancer reported that age of breast cancer diagnosis was significantly earlier in women who used deodorant/antiperspirant more frequently [90]. In 2006, a study of hospital patients in Iraq compared 54 women with breast cancer and 50 women without breast cancer; they reported no association between antiperspirant use and the risk of breast cancer [88].

Personal use of hair dye and breast cancer risk has been widely studied. Meta-analyses of hair dye products conclude that there is no consistent evidence for these products increasing breast cancer risk [91, 105]. A meta-analysis of 12 case-control studies and 2 cohort studies published between 1977 and 2002 that examined the association between hair dye and breast cancer concluded that use of hair dyes does not increase breast cancer risk in women [91]. However, some sub-populations with more exposure may be at increased risk [106]. A 2009 meta-analysis reported that compared to other occupations, hairdressers and salon workers have a slightly increased risk of breast cancer [106].

1.7. Conclusions

This project seeks to describe personal care product use patterns among women in the United States and to estimate the associations between product use patterns and breast cancer risk. Exposure to personal care products is common in the general U.S. population, however measuring this exposure is complex. Currently, to the best of our knowledge, there are no other studies that have evaluated personal care product use patterns among a large, diverse sample population. Personal care product exposure is difficult to characterize because each product is a complex mixture and multiple products are often used in combination by one person. Also, many individual product exposures are correlated, making it difficult to measure the health effects of any single exposure. To better characterize patterns of personal care product use and the risk associated with usage, this project will use detailed personal care product use information, together with latent class analysis (LCA), to create latent classes that describe exposure to broad patterns of personal care product use. LCA can be used to address these limitations by identifying latent classes which describe variability among multiple, correlated, and observed variables [107 714].

After identifying classes of personal care product use, this project will identify how these classes are related to other important breast cancer risk factors and to breast cancer risk. If patterns of personal care product use are associated with breast cancer or breast cancer risk factors, results from this study may help inform prevention strategies.

CHAPTER 2: METHODS

2.1. Specific Aims and Hypotheses

Specific Aim 1. Objective: Identify groups of personal care product users among United States women and describe the prevalence of these product use subgroups within strata defined by race/ethnicity. Hypothesis: There are latent classes of personal care product use that vary according to race/ethnicity. Approach: Using data from the NIEHS Sister Study's Personal Care Questionnaire, latent class analysis (LCA), a data reduction tool, will be used to identify classes of personal care product users based on broad patterns of exposure. Latent classes will be constructed for three product categories: (1) beauty products, (2) hair products, and (3) skincare products. Characteristics of participants will be described by race/ethnicity.

Specific Aim 2. Objective: Estimate the association between personal care product latent class membership and breast cancer risk factors. Hypothesis: Personal care product varies according to known and suspected breast cancer risk factors. Approach: Stratified logistic regression will be used to estimate prevalence differences (PDs) and 95% confidence intervals (CIs) to examine the association between personal care product latent class (Aim 1) and breast cancer risk factors among women in the Sister Study. These risk factors include age, age at menarche, parity, age at first pregnancy, duration of breastfeeding, OC or HRT use, adult BMI, smoking, alcohol use, geographic region, education, and family history.

Specific Aim 3. Objective: Estimate the associations between personal care product use classes and breast cancer risk within strata defined by race, controlling for appropriate confounders. Hypothesis: Personal care product latent classes will be associated with breast cancer risk in multivariable models. Approach: We will use Cox proportional hazards regression to estimate breast cancer risk in association with personal care product latent classes defined in Aim 1, adjusting for confounders and stratifying by race/ethnicity.

2.2. Study Design

2.2.1. NIEHS Sister Study

The Sister Study is a large prospective cohort study directed at identifying environmental and genetic risk factors for breast cancer. The study consists of 50,884 women who had at least one sister diagnosed with breast cancer but were cancer-free themselves at time of enrollment. Study enrollment began in 2003 and ended in 2009; eligible women were 35-74 years of age. Participants were recruited nationally through health professionals, breast cancer advocates, the Internet, trained recruitment volunteers, and a national advertising campaign. Baseline enrollment activities included a computer-assisted telephone interview and self-administered questionnaires that collected information about environmental and genetic risk factors for breast cancer. The Sister Study was approved by the institutional review boards at the National Institute of Environmental Health Sciences and Copernicus Group. Written informed consent was provided by study participants. The present analysis was limited to non-Hispanic white (n=42,558, 84% of participants) and non-Hispanic black (n=4,462, 9% of participants) women; there were too few Hispanic (5%) and Other (3%) participants to include in this analysis.

2.2.2. Data acquisition

Permission to use the data was obtained from the Principal Investigator of the Sister Study, Dr. Dale P. Sandler, at the National Institutes of Environmental Health Sciences in Research Triangle Park, North Carolina. IRB approval was obtained from the UNC IRB for analyzing the data.

2.3. Data Analysis

2.3.1. Exposure assessment and categorization

Detailed self-reported use of 48 personal care products was collected during the baseline phase of the study (Table A.4). Frequency of use (5-level-response option) during the previous 12 months was reported. Because performing LCA of such a large data matrix (almost 50,000 participants, with 48 questions per participant and 5 response categories per question) is too computationally challenging for the SAS program PROC LCA, we employed a variety of data reduction steps. First, using histograms to examine the distribution of exposure responses, we condensed the number of response categories from five into three (Table A.5). Second, we separated the different product types into three different product categories and separate latent classes were constructed for each category: (1) beauty products, (2) hair products, and (3) skincare products (Table A.5). Finally, to further reduce dimensionality, and improve interpretability of the model we used a method based on Dean et al. [108] to select the variables that were most useful for distinguishing among latent classes (i.e., ≥10% difference in posterior probabilities between classes) (Table A.5). Variables that were determined not to contribute to the distinction between latent classes were removed from the model. Within each product category, latent classes were described and considered as exposure variables (Table 3.1).

2.3.2. Breast cancer assessment

Participants reported breast cancer diagnoses on annual and biennial health questionnaires, or by calling the Sister Study helpline. Women who reported an incident breast cancer during follow-up were asked to authorize release of pertinent medical records. Response rates were >94% over follow-up [109]. Among participants in our sample population, 2,328 breast cancers were reported during 299,689 person-years (average follow-up ~5.4 years). By the time of the present analysis, pathology reports or medical records had been obtained for >80% of these cases (n=1,923). Confirmation of self-reported breast cancer diagnoses by medical record was very high [positive predictive value (PPV)=99.5%] [110]. After medical record review, self-reported ER status information was confirmed for 99% of ER positive cases, and 85% of ER negative cases. Therefore, we used self-reported tumor.

2.3.3. Effect modification

All models were stratified by race. Race/ethnicity was based on self-report at baseline. The two race/ethnicities included in this analysis were non-Hispanic white and non-Hispanic black women. In analyses investigating associations by menopausal status at the time of breast cancer diagnosis, women who became postmenopausal during the follow-up period were censored at the time of menopause and the person-time that accumulated after menopause contributed to postmenopausal person-time at risk. Menopausal status was self-reported by the participant at enrollment and during follow-up. Women who reported that they had undergone natural menopause, hysterectomy, bilateral oophorectomy, irradiation to the ovaries, or otherwise reported cessation of menstruation were classified as post-menopausal; women who reported that they were still cycling were classified as pre-menopausal. Women who did not know if they had undergone menopause (N=16) or had never had their period (N=4) were excluded. In sensitivity analyses among post-menopausal white women only, models were stratified by ER status (ER positive or ER negative according to the clinical record), and breast cancer type (in situ or invasive).

2.3.4. Confounding

To identify possible confounders, we considered the association between latent classes and breast cancer risk factors (Table 2.1). The following covariates, measured at baseline, were included in adjusted models: menopausal status (pre-menopausal or post-menopausal), education (< high school or ≥high school), age at first birth (nulliparous, <26 years, or ≤26 years), parity (nulliparous, 1-2 children, or ≥3 children) , duration of breastfeeding (<12 months or ≥12 months), oral contraceptive (OC) use (ever or never), post-menopausal hormone therapy (HT) use among women >50 years (ever or never), alcohol consumption (never drinker, former drinker, currently drink <1 drink/day or currently drink ≥1 drink/day), adult body mass index (BMI) (<25kg/m^2, 25 to <30kg/m^2, or ≥30 kg/m^2), family history (having one sister with breast cancer or ≥1 sister and/or a mother with breast cancer), smoking status (never smoker, past smoker, current smoker), and age at menarche (<12 years or ≥12 years), and region (West, South, North, East). In sensitivity analyses, models were stratified by ER status and breast cancer subtype. More details on measurement and definition of potential confounders are listed in Table 2.1.

2.3.5. Statistical methods

Latent classes

LCA was used to identify groups of individuals with similar patterns of personal care product use. LCA is a data reduction tool that describes variability among multiple, correlated, observed variables in terms of a fewer number of unobserved variables called latent classes. It has been used for identifying patterns of exposure when the exposure is a complex combination of separate factors [107]. Personal care products were categorized into three product categories and separate latent classes were constructed for each category: (1) beauty products, (2) hair products, and (3) skincare products.

For each product category we fit a sequence of LCA models starting with two classes and increasing the number of classes for each model (up to six). To identify an optimal but minimal number of classes, Akaike's information criterion (AIC), the Bayesian information criterion (BIC), and entropy were considered [107]. A smaller AIC and BIC and higher entropy for a particular model suggests a better model fit [107]. A summary of the fit statistics and entropy are shown in Table 3.1. The classes were described and labeled based on item-response probabilities [108] and ability to identify which variables were driving each class [107].

To assign participants class membership, we used a common classify-analyze approach referred to as the *maximum-probability assignment rule*, where individuals are assigned to the class in which they have the highest posterior probability of membership [111]. Item-response probabilities provided the basis on which each latent class was interpreted [112]. The correlation among use patterns for the three product types was evaluated by Spearman correlation coefficients of the item response variables' posterior probabilities.

Association between latent classes and potential confounders

Logistic regression stratified by race was used to estimate age-adjusted prevalence differences and 95% confidence intervals for potential confounders and latent class membership for the three different product categories (Table A.6). Covariates that were considered as potential confounders are listed in Table 2.1.

Association between latent classes and breast cancer risk

Multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between the personal care product latent classes and breast cancer risk. Statistical models used age as the time scale, where participants entered the analysis at their baseline age (left-truncation) and exited at their event/censoring age; person-time was accrued from enrollment. Follow-up extended until breast cancer diagnosis (event) or the date of last follow-up (censored). All models were stratified by race and adjusted for potential confounders.

Table 2.1. Measurement and definition of potential confounders

Variables	Measurement	Code in statistical analysis
Age at baseline	Self-administered form	5 year age categories
Age at menarche	Self-administered form	<12 years or ≥12 years
Menopausal status[a]	Self-administered form	Pre-menopausal or post-menopausal
Education	Self-administered form	< high school or ≥high school
Age at first live birth	Self-administered form	Nulliparous, <26 years, or ≤26 years
Parity	Self-administered form	Nulliparous, 1-2 children, or ≥3 children
Duration of breastfeeding	Self-administered form	<12 months or ≥12 months
Oral contraceptive use	Self-administered form	Ever or never
Post-menopausal hormone therapy use	Self-administered form	Ever or never (among women >50 years)
Alcohol consumption	Self-administered form	Never drinker, former drinker, currently drink <1 drink/day or currently drink ≥1 drink/day
Adult body mass index	Examiner form	<25kg/m^2, 25 to <30kg/m^2, or ≥30 kg/m^2
Family history	Self-administered forms	Having one sister with breast cancer or ≥1 sister and/or a mother with breast cancer
Smoking status	Self-administered forms	Never smoker, past smoker, current smoker
Geographic location	Self-administered forms	West, Midwest, Northeast, and South

[a]The definition of menopause was described in 2.2.4.

CHAPTER 3: ASSOCIATIONS AMONG PERSONAL CARE PRODUCT USE PATTERNS AND EXOGENOUS HORMONE USE IN THE SISTER STUDY

3.1. Overview

Background: It is hypothesized that certain chemicals in personal care products may alter risk of adverse health outcomes. The primary aim of this study was to use a data-centered approach to classify complex patterns of exposure to personal care products and to understand how these patterns vary according to use of exogenous hormone exposures, oral contraceptives (OCs) and postmenopausal hormone therapy (HT).

Methods: The NIEHS Sister Study is a prospective cohort study of 50,884 U.S. women. Limiting the sample to non-Hispanic blacks and whites (N=47,019), latent class analysis (LCA) was used to identify groups of individuals with similar patterns of personal care product use based on responses to survey questions. Personal care products were categorized into three product types (beauty, hair, and skincare products) and separate latent classes were constructed for each type. Adjusted prevalence differences (PD) were calculated to estimate the association between exogenous hormone use, as measured by ever/never OC or HT use, and patterns of personal care product use.

Results: Latent class analysis (LCA) was used to reduce data dimensionality across 48 individual personal care product use questions and to identify groups of individuals with similar patterns of personal care product use. Three latent classes were identified for both the beauty and hair product groups; the skincare product group had four classes. There were strong differences in latent class distribution by race, particularly for hair care products. For both blacks and whites,

exogenous hormone exposures were associated with higher levels of product use, especially beauty and skincare products.

Discussion: Relative to individual product use questions, latent class variables capture complex patterns of personal care product usage. These patterns differed by race and were associated with ever OC and HT use. Future studies should consider personal care product exposures with other exogenous exposures when modeling health risks.

3.2. Introduction

The average American woman uses 12 personal care products a day, resulting in daily exposure to an estimated 126 unique chemicals [77]. Because certain chemicals in personal care products are suspected endocrine disrupters (e.g., phthalates, parabens, triclosan) [78, 79], there is concern that exposure to personal care products may be associated with risk of breast cancer and/or may have adverse reproductive health effects. *In vitro* and animal studies have demonstrated that endocrine disrupting chemicals can mimic estrogens [73], alter hormonal signaling, affect developing reproductive systems [80], and/or disrupt normal mammary development [81]. However, there is currently no definitive evidence for the same effects in humans [82-85].

The strongest evidence to support concern for endocrine disrupting chemicals comes from experimental animal studies [85]. However, laboratory animals are usually exposed to individual chemicals over short periods of time (often at higher doses than humans) whereas humans are typically exposed to multiple endocrine disrupting compounds simultaneously over many years. Consequently, there is concern that laboratory animal data have not addressed the patterns of exposure to these complex mixtures which may be most relevant [86, 87]. At the same time, more information is needed to characterize the nature of human exposure in order to design more appropriate animal and in vitro studies of complex mixtures as well as validate computational models of predicted exposure. To address the limitations in experimental animal studies and capture the exposure characteristics in human populations, human studies are needed.

The objective of the current study was to use data from 47,019 women in the NIEHS Sister Study to characterize patterns of personal care product use across a wide range of products. We hypothesized that individuals would be classifiable according to broad patterns of personal care product usage, with patterns differing by race. We also hypothesized that personal care product use would be correlated with other exposures, notably other exogenous estrogens (e.g., OC and HT use) potentially associated with disease risk. To test these hypotheses, we used latent class analysis (LCA) to identify groups of women by patterns of product use and compared these patterns with in terms of past exogenous estrogen use.

3.3. Methods

3.3.1. Study population

The Sister Study is a large prospective cohort study directed at identifying environmental and genetic risk factors for breast cancer. The study consists of 50,884 women who had at least one sister diagnosed with breast cancer but were cancer-free themselves at time of enrollment. Study enrollment began in 2003 and ended in 2009, and eligible women were 35-74 years of age. Baseline enrollment activities included a computer-assisted telephone interview and self-administered questionnaires that elicited information about environmental and genetic risk factors for breast cancer. The Sister Study was approved by the institutional review boards at the National Institute of Environmental Health Sciences and Copernicus Group. Written informed consent was provided by study participants. The present analysis was limited to non-Hispanic white (n=42,558, 84% of participants) and non-Hispanic black (n=4,462, 9% of participants) women (Table 3.1); there were too few Hispanic (5%) and Other (3%) participants to include in this analysis.

3.3.2. Personal care product assessment

Detailed self-reported use of 48 personal care products (Table A.4) was collected during the baseline phase of the study by inquiring about frequency of use (5-level-response options) during the previous 12 months. The five response options varied according to intended use of the product. For example, the response options for a product intended to be used regularly (e.g., hand lotion) included: (1) did not use, (2) used less than once a month, (3) used 1-3 times per month, (4) 1-5 times per week, (5) more than 5 times per week. Response options for products that are used less often (e.g., hair dye) included : (1) did not use, (2) 1-2 times a year, (3) every 3-4 months, (4) every 5-8 weeks, (5) once a month or more. To identify latent classes of personal care product use, each of three product categories were analyzed separately to identify latent classes for each category: (1) beauty products (e.g., lipstick, mascara, nail polish), (2) hair products (e.g., hair spray, hair relaxers), and (3) skincare products (e.g. facial lotion, hand lotion).

3.3.3. Latent classes

LCA was used to identify groups of individuals with similar patterns of personal care product use. LCA is a data reduction tool that describes variability among multiple, correlated, observed variables in terms of a fewer number of unobserved variables called latent classes. It has been used for identifying patterns of exposure when the exposure is a complex combination of separate factors [107]. Personal care products were categorized into three product categories [94], and separate latent classes were constructed for each category: (1) beauty products, (2) hair products, and (3) skincare products. To reduce dimensionality, improve interpretability of the model, and improve classification and precision we used a method based on Dean et al. [108] to select the variables that were most useful for distinguishing among latent classes (i.e., ≥10% difference in posterior probabilities between classes). Variables that were determined not to contribute to the distinction between latent classes were removed from the model.

We fit a sequence of LCA models starting with two classes and increasing the number of classes for each model (up to six). To identify an optimal but minimal number of classes, Akaike's information criterion (AIC), the Bayesian information criterion (BIC), and entropy were considered [107]. A smaller AIC and BIC and higher entropy for a particular model suggests a better model fit [107]. A summary of the fit statistics and entropy are shown in Table 3.2. The classes were described and labeled based on item-response probabilities [108] and ability to identify which variables were driving each class [107].

To assign participants class membership, we used a common classify-analyze approach referred to as the *maximum-probability assignment rule*, where individuals are assigned to the class in which they have the highest posterior probability of membership [111]. Item-response probabilities provided the basis on which each latent class was interpreted [112]. The correlation among use patterns for the three product categories was evaluated by Spearman correlation coefficients of the item response variables' posterior probabilities.

3.3.4. Statistical analysis describing association between personal product use and exogenous hormone use

We examined associations between personal product use and OC use (ever, never) for the entire sample and the association between personal care product use and HT use (never/ever) among women >50 years. We used logistic regression stratified by race to estimate age-adjusted prevalence differences and 95% confidence intervals in exogenous hormone use associated with latent class membership for the three different product types. We considered education as a covariate but did not include it in the final model because it did not substantially change the age-adjusted associations.

3.4. Results

3.4.1. Latent class descriptions

Based on fit statistics and parsimony (Table 3.2), three latent classes were identified as optimal for both the beauty and hair product groups; the skincare product group had four classes. Figure 3.1 indicates the specific personal care products and the item response probabilities for each product. Analysis of fourteen initial beauty product usage items resulted in three latent classes (<u>infrequent users; moderate users; frequent users</u>) with nine contributing product items: mascara, lipstick, foundation, nail polish, perfume, eye shadow, eye liner, blush, and makeup remover (Figure 3.1, Table 3.4). Analysis of fifteen hair product usage items resulted in three latent classes (<u>infrequent users of hair products other than shampoo/conditioner; users of pomade and hair straightener; Frequent users of hair spray/hair gel</u>) with six contributing product items: pomade, hair straightener, conditioner, hair spray, hair gel, and shampoo. Finally, analysis of nineteen skincare product usage items resulted in four latent classes (<u>infrequent users; moderate users; frequent users; talcum powder users</u>) with nine contributing product items: cleansing cream, anti-aging cream, body lotion, hand lotion, face cream, foot cream, petroleum jelly, talcum powder applied under arms, and talcum powder applied elsewhere. Short descriptions of the classes were created based on the item-response probabilities.

3.4.2. Product use patterns by race

Among non-Hispanic women in our study population, 91% were white and 9% were black (Table 3.3). Race was most strongly associated with differences in haircare product classes; only 3% of white women were in the "users of pomade and hair straightener" group, while over two-thirds (67%) of black women were. There were also some differences in beauty product classes: white women were more frequent users than black women. The frequent lotion user category was the most common skin care class among both black and white women users (Table 3.3). Because of racial differences in population distribution across product classes, we report results separately by race in the subsequent analyses.

3.4.3. Patterns of class membership across product categories (beauty, hair, skin)

After considering the three different categories of personal care products in separate classification schemas, we also evaluated whether product usage class in one category (e.g. hair products) predicted use in another category (e.g. beauty products). As shown in Figure 3.2, the product categories for whites tended to be correlated, i.e., frequent users of one product category tended to be frequent users of the other product categories, but correlation coefficients were modest. The highest correlation of posterior probabilities of class membership was between infrequent users of beauty and skincare products (r=0.45). The next strongest correlations were between frequent beauty product users and frequent users in both the hair (r=0.39) and skincare (r=0.34) categories. For black women the correlations among usage patterns for the different product categories were low except for skin and beauty (r=0.39).

3.4.4. Exogenous hormonal exposures and product use

The prevalence of OC use history was 85% for whites and 86% for blacks; the prevalence of HT among women over age 50 was 66% for whites and 48% for blacks. Product use showed strong associations with exogenous hormonal exposures (Figure 3). White and black women who were "moderate" or "frequent" users of beauty products were more likely to have ever taken OCs. Among white women, compared to "infrequent" users of beauty products, the age-adjusted differences in prevalence of ever using OCs for “moderate” users and “frequent” users was 7% and 8%, respectively. Among black women, compared to “infrequent users”, the age-adjusted prevalence differences of ever using OCs were 8% for “moderate” users and 10% for “frequent” users of beauty products. White women over age 50 who were “moderate” users and “talcum powder” users were more likely to have ever used HT compared to “infrequent” users of skincare products; the age-adjusted difference in prevalence of ever receiving HTs for “moderate” users and “talcum powder” users was 12% and 11%, respectively. Among black women, the age-adjusted difference in prevalence of ever using HTs for “moderate” users compared to “infrequent” users of skincare products was 10%.

3.5. Discussion

We found that use of LCA could identify a relatively small number of subgroups of women with distinct personal care product use and that personal care product use varied by race. We also showed that the women with the highest use of personal care products are more likely to have used the common exogenous hormone medications, OC or HT. Previous studies have examined correlation structure between specific personal care products [92-94], but such studies were not aimed at reducing the complexity of individual product usage patterns, nor did these studies evaluate associations between personal care product use and other exposures.

Some key challenges have impeded progress in understanding the relationship between personal care product use and health outcomes in humans. First, publically available data on personal care product usage patterns in the United States typically lack large sample populations or include only specific types of product users [88, 89 , 90, 91]. Currently the only population-based studies of personal care product use that have a comparison group of infrequent personal care product users are limited to other countries [92, 93], or small populations within the United

States [94]. Second, studies that have collected data on product use have described correlations between use patterns for only a limited numbers of products. Third, studies to date have not placed the personal care product exposures in context of other exposures, particularly those in relevant biological pathways.

Our analysis addresses some of these challenges. First, we used a large, nationwide study of personal care product use and other environmental exposures to study patterns of exposure. Second, we took a broad approach to characterizing exposure, incorporating information on 24 different personal care products included in the Sister Study's personal care questionnaire. Finally, we used LCA to identify exposure patterns in the context of other, relevant exposures. However, with currently available data we cannot specify a commonality of chemical exposures, only a commonality of which products tend to be used together by different groups of women. Information about specific chemicals or ingredients in personal care products was not captured in the questionnaire.

The use of LCA was a key strength of our analysis. As opposed to a variable centered-approach that considers how variables are related to each other, LCA is a data-centered approach that considers how variables are grouped within individuals. LCA can reduce and organize large, multifaceted data sets and create manageable categorical data elements to summarize complex patterns [107]. LCA has been used to capture complex exposures in a variety of research settings. For example, it has been used to organize and describe subgroups of weight loss strategies and disordered eating among women [112] and to identify subgroups of emerging sexual behaviors among adolescents [113]. LCA has also been used to identify substance use behavior among adolescents to inform programs that could be targeted for or tailored to the different population subgroups that are expected to show the strongest response [114].

Our results were consistent with some previous studies. We observed race-related patterns of hair product use similar to those observed in previous smaller studies [84, 95, 115, 116]. The class that was characterized by use of pomade and hair straightener contained the majority of black women, but only 3% of white women. In a small study with ten black and 206 white participants from California [94] African American women were more likely to have their hair treated permanently (including chemical straightening or relaxing). Although the National Health and Nutrition Examination Survey (NHANES) 1999-2000 did not collect questionnaire information on frequency of product use, a NHANES analysis of 2,540 participant samples found that compared to non-Hispanic white women, African American women had higher urinary levels of monoethyl phthalate, a phthalate found in personal care products [84]. The authors of the NHANES suggest that these differences were likely due to differences in hair texture and cultural practices. While our analyses did not link product exposure with specific internal dose markers, future application of LCA approaches, or the patterns identified here, could be used to link specific exposure biomarkers with self-reported exposure information.

To consider personal care product use in association with health outcomes, it is important to integrate these exposures with other biologically relevant and risk-related exposures. Having observed correlation within personal care product use classes (e.g. between heavy users of hair care products and heavy users of beauty products), we tested whether personal care product categories are associated with other relevant exposure patterns. OC and HT are examples of key exposures to exogenous estrogens. There were statistically significant associations between beauty and skincare product latent classes and OC and HT. Therefore, when personal care product use is being evaluated as a potential risk factor for hormonally-mediated conditions, we encourage researchers to consider possible confounding by OC and HT use.

Our analysis has several key strengths. LCA provides an objective method of distinguishing between groups of women on the basis of their patterns of personal care product use and, thus, potential chemical exposures. The number of latent classes is determined, in part, by data-based metrics, and is small relative to the number of product use items. The component product-use probabilities are complex and objectively discerning overall product-use data from casual inspection would be difficult. The NIEHS Sister Study provided a large dataset for this purpose.

LCA provides an objective means of reducing data dimensionality; however, there are some limitations. For example, the classes can be difficult to interpret. Labels were assigned to different classes based on our observation and interpretation of the probability based weights for class membership. Although there is some subjectivity in choosing the shorthand label descriptors for different classes, the precise item response probabilities are provided in supplemental tables (Tables A1-A3). Another limitation was that we could not consider them all of the personal care products together; due to the large number of variables we had to break LCA into three different product category models: beauty, hair and skin products. Also, the categories we identified with LCA may not be generalizable to other populations. Therefore it is important that these methods are replicated in other populations. Finally, our models only adjusted for age and not for other possible confounders of the personal care product use and exogenous estrogen association. However, the goal of this research was not to quantify the independent effects of personal care product use on estrogen exposure, but rather to illustrate a method for identifying important covariates for future studies of personal care product-health outcome associations.

3.6. Conclusion

One active area of environmental health research is the investigation of associations between personal care product use and health outcomes [117-119]. This necessitates a thorough understanding of how exposures vary within a population and co-vary with other exposures. We identified patterns of personal care product use among a nationwide group of women and found that for white women, those with the highest level of exposure to personal care products also tended to have used exogenous hormone medications. Understanding and accounting for such relationships is critical as researchers explore associations between personal care product use and health outcomes.

Table 3.1. Descriptive characteristics of sample population

	N	%
Race/ethnicity		
Non-Hispanic White	42453	91%
Non-Hispanic Black	4452	9%
Menopausal status		
Missing	264	0.6%
Pre-menopausal	16550	35%
Post-menopausal	30091	64%
Highest level of education completed		
Missing	4	0
<High school	369	0.8%
HS or equivalent	6574	14%
Some college but no degree	9185	20%
Associate, technical or, Bachelor’s degree	19323	41%
More than Bachelor’s	11450	24%
Oral contraceptive use		
Missing	36	0.1%
Never	7161	15%
Ever	39708	85%
Post-menopausal hormone therapy (HT)		
Missing	155	0.3%
Never	23545	50%
Ever	23205	49%
Geographic location		
Missing	34	0.1%
Northeast	8165	17%
Midwest	13234	28%
South	15574	33%
West	9906	21%

Table 3.2. Indicators of fit for latent class analysis

	AIC	BIC	Entropy
Beauty classes			
2	78666	78993	0.77
3	35717	36210	0.83
4	29716	30378	0.79
5	24355	25184	0.74
6	22393	23390	0.71
Hair classes			
2	14239	14459	0.96
3	7936	8271	0.67
4	5237	5686	0.61
5	3416	3980	0.64
6	2046	2725	0.67
Skin classes			
2	48055	48381	0.72
3	38337	38831	0.71
4	30150	30812	0.73
5	26769	27598	0.69
6	24092	25089	0.67

AIC: Akaike information criterion
BIC: Bayesian information criterion

Table 3.3. Latent class distribution by race

	Class descriptor	White N (%)	Black N (%)	Total N (%)
Beauty Products				
Total		42558	4461	47019
Beauty A	Infrequent users	9231 (22%)	1282 (29%)	10513 (22%)
Beauty B	Moderate users	16010 (38%)	2156 (48%)	18166 (39%)
Beauty C	Frequent users	16762 (39%)	746 (17%)	17508 (37%)
Missing		555 (1%)	277 (6%)	832 (2%)
Hair Products				
Total		42558	4461	47019
Hair A	Infrequent users of hair spray	20950 (49%)	1011 (23%)	21961 (47%)
Hair B	Users of pomade and hair straightener	1182 (3%)	2989 (67%)	4171 (9%)
Hair C	Frequent users of hair spray and hair gel	19659 (46%)	173 (4%)	19832 (42%)
Missing		767 (2%)	288 (6%)	1055 (2%)
Skincare Products				
Total		42558	4461	47019
Skin A	Infrequent users	7954 (19%)	812 (18%)	8766 (19%)
Skin B	Moderate users	18617 (44%)	2192 (49%)	20810 (44%)
Skin C	Frequent users	10271 (24%)	551 (12%)	10822 (23%)
Skin D	Talcum powder users	5158 (12%)	628 (14%)	5786 (12%)
Missing		558 (1%)	278 (6%)	836 (2%)

Table 3.4. Latent class descriptions by product category

Category/class		Label	Description
Beauty product classes	A	Infrequent users	Infrequent use of eye shadow, eyeliner, mascara, foundation, and blush; relatively (to the other classes) infrequent use of make-up remover, perfume, and lipstick.
	B	Moderate users	Intermediate use of eye shadow, ner, mascara, foundation, blush, make-up ver, perfume and lipstick (relative to the classes).
	C	Frequent users	Frequent use of eye shadow, eyeliner, mascara, foundation, blush, make-up remover, nail polish, and lipstick.
Hair product classes	A	Infrequent users of hair spray	Relatively infrequent use of hair spray, hair gel compared to Hair-C (similar to class Hair-B); frequent use of shampoo, conditioner; infrequent use of pomade and hair straightener
	B	Users of pomade and hair straightener	Infrequent use of shampoo, hair gel; intermediate use of pomade, hair straightener, and hair spray
	C	Frequent users of hair spray and hair gel	Frequent use of hair spray, hair gel, shampoo, conditioner; infrequent use of pomade and hair straightener
Skincare product classes	A	Infrequent users	Infrequent use of lotions, creams, talcum powder
	B	Moderate users	Intermediate use of lotions, creams; infrequent use of talcum powder
	C	Frequent users	Frequent use of face creams and lotions; infrequent use of talcum powder
	D	Talcum powder users	Second most frequent use of lotions; most frequent use of talcum powder

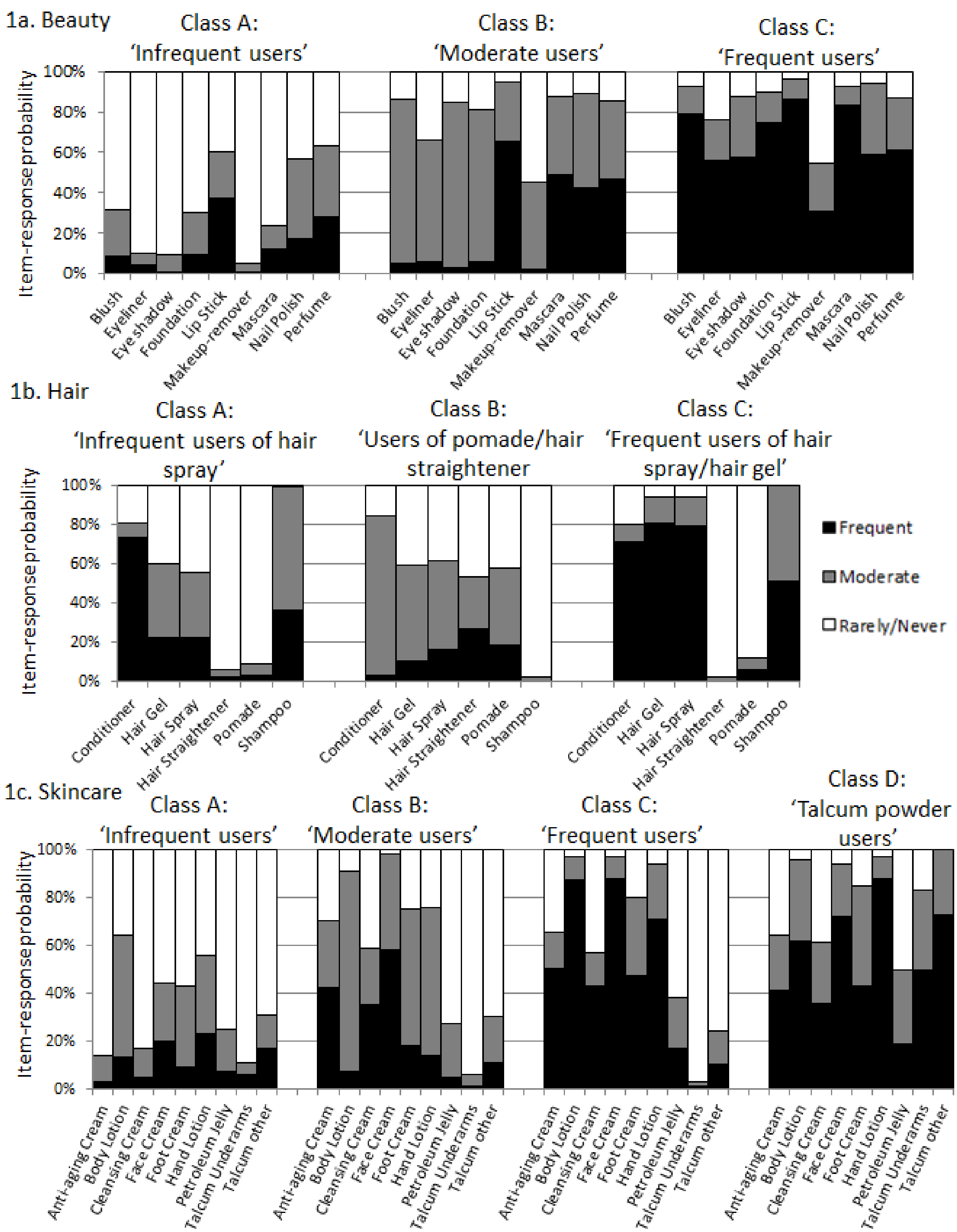


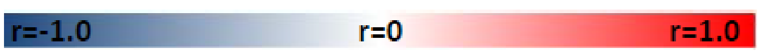
Figure 3.1. Item-response probabilities for frequency of personal care product use, conditional on class membership

A. White women

	Hair A	Hair B	Hair C	Skin A	Skin B	Skin C	Skin D
Beauty A	0.34	0.19	-0.37	0.45	0.00	-0.15	-0.26
Beauty B	0.08	0.10	-0.09	0.07	0.18	0.05	-0.13
Beauty C	-0.36	-0.22	0.39	-0.42	-0.08	0.13	0.34
Hair A				0.24	0.04	-0.10	-0.17
Hair B				0.17	0.07	0.00	-0.17
Hair C				-0.26	-0.04	0.10	0.20

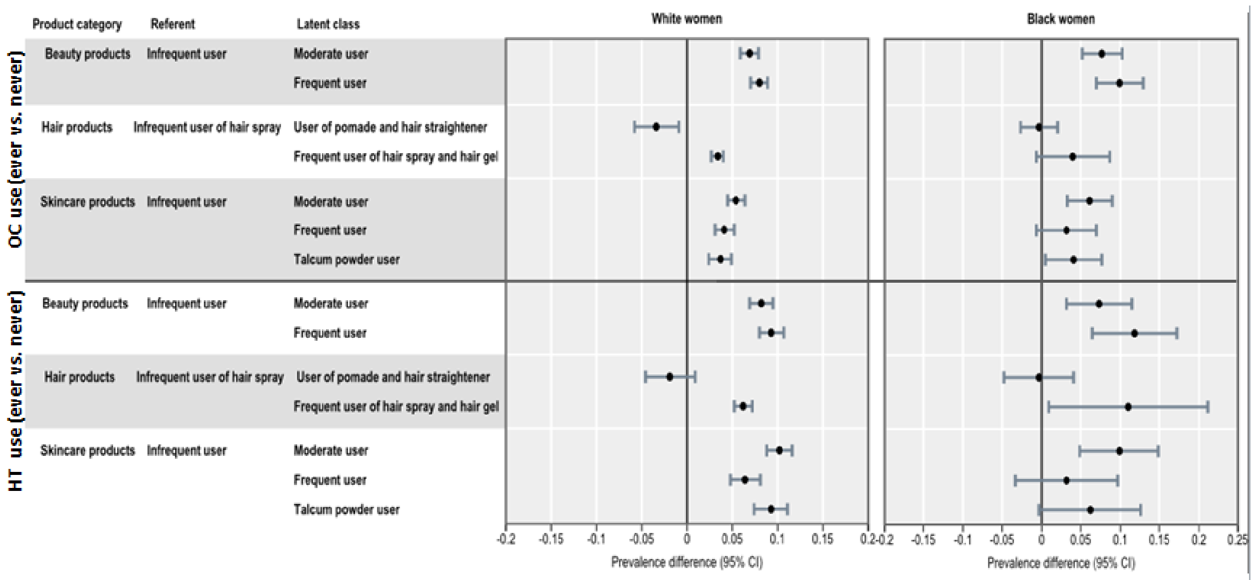
B. Black women

	Hair A	Hair B	Hair C	Skin A	Skin B	Skin C	Skin D
Beauty A	-0.01	0.03	-0.09	0.39	-0.02	-0.11	-0.20
Beauty B	-0.02	0.03	0.00	-0.11	0.14	0.09	0.00
Beauty C	0.03	-0.05	0.10	-0.35	-0.07	0.08	0.25
Hair A				-0.06	-0.02	-0.01	0.05
Hair B				0.07	0.02	0.00	-0.05
Hair C				-0.11	-0.03	0.05	0.06



r= Spearman Correlation Coefficient

Figure 3.2. Spearman correlation coefficients of posterior probabilities of latent class membership for beauty products, hair products, and skincare products among (A) white and (B) black women



OC: Oral contraceptives
HT: Post-menopausal hormone therapy
Statistically significant results are those where the 95% CI excludes a prevalence difference of zero

Figure 3.3. Difference in prevalence of ever use of OCs and HTs by latent class membership

CHAPTER 4: ASSOCIATION BETWEEN PERSONAL CARE PRODUCT USE PATTERNS AND BREAST CANCER RISK IN THE SISTER STUDY

4.1. Overview

Background: It is hypothesized that certain chemicals in personal care products may increase risk of breast cancer. The primary aim of this study was to evaluate whether patterns of beauty, hair, or skin-related personal care products, or individual products, were associated with breast cancer.

Methods: We evaluated data from non-Hispanic black and white women (N=46,905) in The Sister Study, a national prospective cohort study of breast cancer risk due to environmental and genetic exposures. Latent class analysis (LCA) was used to identify groups of individuals with similar patterns of personal care product use at cohort enrollment in 2003-2009. Multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between product use and breast cancer risk.

Results: A total of 2,328 women developed breast cancer during follow-up (average follow-up= 5.4 years). Among white women, those classified as 'moderate' and 'frequent' users of beauty products had increased risk of breast cancer relative to 'infrequent users' (HR=1.13; 95% CI: 1.00-1.27 and HR=1.15; 95% CI: 1.02-1.30, respectively). 'Frequent' users of skincare products also had increased risk of breast cancer relative to 'infrequent users' (HR=1.13; 95% CI: 1.00-1.29). Numbers for black women were too sparse for most analyses. None of the hair product classes were associated with increased breast cancer risk in either black or white women. In stratified analyses, the associations were more apparent in post-menopausal white women.

Conclusions: This work generates novel hypotheses about personal care product use and breast cancer risk. Users of specific classes of personal care products appear to differ in their breast cancer risk. Whether these results are due to specific chemicals to other correlated behaviors needs to be evaluated.

Conclusions: Users of specific classes of personal care products appear to differ in their breast cancer risk. Whether this difference is due to specific chemicals in these products or to other correlated behaviors should be evaluated.

4.2. Introduction

There is concern that use of personal care products (e.g., cosmetics, lotions, and fragrances) may be associated with breast cancer risk [67]. These products are a possible source of human exposure to endocrine disrupting chemicals, such as phthalates, parabens, and phenols [79, 97, 101, 120]. These chemicals have been linked to risk of reproductive and other endocrine-related cancers [121-124], and have been hypothesized to mimic the carcinogenic effects of estrogenic exposures [98, 99].

Women are the primary consumers of many personal care products and are disproportionately exposed to these chemicals [125]. A survey of more than 2,300 women reported that the average adult woman uses approximately 12 individual personal care products each day and that more than a quarter of all women use at least 15 products daily [77]. A cross-sectional analysis of women in northern Mexico reported that increased personal care product use was associated with higher urinary concentrations of monoethyl phthalate (MEP) [100]., a phthalate used in a range of personal care products [126]. The Environmental and Reproductive Health [EARTH] Study, a cohort study of women ages 18 to 45 years**,** reported evidence of a monotonic dose-response relationship between number of products used and urinary paraben and phthalate metabolite concentrations [101]**.** However, few studies have evaluated the association between individual personal care products, or components of products, and breast cancer risk. Studies of deodorant/antiperspirant and hair dye have not strongly supported an association between personal care product use and increasing risk of breast cancer [88-91, 102, 105, 106]**.** However, a population based case-control study of women residing in northern Mexico, with 233 histopathologically confirmed breast cancer cases and 221 age-matched controls, reported that exposure to MEP may be associated with increased risk of breast cancer [102]. However, the same study also reported that exposure to other phthalates used in personal care products (i.e., monobenzyl phthalate (MBzP) and mono (3-carboxypropyl) phthalate (MCPP)) was inversely associated with breast cancer [102].

A challenge facing epidemiologic studies of personal care products lies in the fact that individual chemical exposures or personal care product usage may not capture overarching patterns of use across multiple products. We have previously observed that there are unique patterns of personal care product use, and these patterns were associated with breast cancer risk factors [127]. In this current work, we evaluated patterns of beauty, hair, and skin -related personal care product use in association with breast cancer risk.

4.3. Methods

4.3.1. Study Design and Population

The Sister Study is a prospective cohort directed at identifying environmental and genetic risk factors for breast cancer and enrolled 50,884 women in the continental United States and Puerto Rico during 2003-2009. Eligible women were 35-74 years of age and had at least one sister diagnosed with breast cancer but were cancer-free themselves at enrollment. Enrollment activities included a computer-assisted telephone interview and self-administered questionnaires that elicited information about environmental and reproductive exposures. The Sister Study was approved by the institutional review boards at the National Institute of Environmental Health Sciences and Copernicus Group. All study participants provided written informed consent.

4.3.2. Breast cancer ascertainment

Participants reported breast cancer diagnoses on annual and biennial health questionnaires, or by calling the Sister Study helpline. Women who reported an incident breast cancer during follow-up were asked to authorize release of pertinent medical records. Response rates were >94% over follow-up [109]. Among participants in our sample population, 2,328 breast cancers were reported during 304,034 person-years (average follow-up ~5.4 years). By the time of the present analysis, pathology reports or medical records had been obtained for >80% of these cases (n=1,923). Confirmation of self-reported breast cancer diagnoses by medical record was very high [positive predictive value (PPV)=99.5%] [110]. After medical record review, self-reported ER status information was confirmed for 99% of ER positive cases, and 85% of ER negative cases. Because agreement between self-reported and medical abstracted data was high, we used self-reported tumor information when medical records were not available.

4.3.3. Personal care product exposure

Self-reported use of 48 personal care products was collected during the baseline phase of the study (Table A.4) by inquiring about frequency of use (5-level-response option) during the previous 12 months. To identify latent classes of personal care product use, responses were categorized according to three product types, with separate latent classes within each type: (1) beauty products, (2) hair products, and (3) skincare products [127]. To reduce dimensionality, improve interpretability of the model, and improve classification and precision we selected the personal care products that were most useful for distinguishing between latent classes (i.e., ≥10%

difference in posterior probabilities between classes) Dean et al. [108]. Variables that did not contribute to the distinction between latent classes were removed from the model. Within each product category, latent classes were described and considered as exposure groups with the labels described in Table 1.

Starting with 48 individual personal care product use questions, we reduced data dimensionality by identifying fourteen initial beauty product types. These were further reduced to nine contributing product items (Supplemental Table 1) and three latent classes. Analysis of fifteen hair product types was reduced to six contributing products and three latent classes. Finally, analysis of nineteen skincare product types was reduced to nine contributing products and four latent classes.

4.3.4. Statistical Analyses

The present analysis was limited to non-Hispanic white (n=42,453, 91%) and non-Hispanic black (n=4,452, 9%) women (Table 2). Multivariable Cox proportional hazards models were used to estimate adjusted hazard ratios (adjHR) and 95% confidence intervals (CI) for the association between the personal care product latent classes and breast cancer risk. Statistical models used age as the time scale, where participants entered the analysis at their enrollment age (left-truncation) and accrued person-time until they exited at their cancer diagnosis or were administratively censored at their age at last follow-up. In analyses investigating associations by menopausal status at the time of breast cancer diagnosis, women who became postmenopausal during the follow-up period were censored at the time of menopause and the person-time that accumulated after menopause contributed to postmenopausal person-time at risk. The proportional hazards assumption was visually assessed using ln-ln survival plots; there was no suggestion of time-variant associations.

All models were stratified by race. Women who reported that they had undergone natural menopause, hysterectomy, bilateral oophorectomy, irradiation to the ovaries, or otherwise reported cessation of menstruation were classified as post-menopausal; women who reported that they were still cycling were classified as pre-menopausal. The following covariates, measured at baseline, were included in adjusted models: menopausal status at baseline (pre-menopausal or post-menopausal), age at menarche (<12 years or ≥12 years), age at first birth (nulliparous, <26 years, or ≥26 years), parity (nulliparous, 1-2 children, or ≥3 children) , duration of breastfeeding (<12 months or ≥12 months), oral contraceptive (OC) use (ever or never), post-menopausal hormone therapy (HT) use among women >50 years (ever or never), education (< high school or ≥high school), alcohol consumption (never drinker, former drinker, currently drink <1 drink/day or currently drink ≥1 drink/day), adult body mass index (BMI) (<25kg/m^2, 25 to <30kg/m^2, or ≥30 kg/m^2), family history (having one sister with breast cancer or ≥1 sister and/or a mother with breast cancer), smoking status (never smoker, former smoker, current smoker), and current region of residence (West, South, North, East). In sensitivity analyses among post-menopausal white women only, models were stratified by ER status (ER positive or ER negative according to the clinical record), and breast cancer type (in situ or invasive).

We also explored HRs for individual product types, using Bonferroni correction to adjust for multiple comparisons (p-value ≤ 0.001) . For all analyses, results are presented that included at least 20 exposed breast cancer cases. All analyses were performed using SAS statistical software (version 9.3; SAS Institute Inc, Cary, NC).

4.4. Results

During the 304,034 person-years contributed by 46,905 women, 2,328 breast cancers were diagnosed (average follow-up ~5.4 years). We recognize that the latent classes shown in

Table 1 reflect complex patterns of exposure that may appear oversimplified by the label; however these labels are used to improve clarity of presentation. Cohort characteristics along with the complete profile associated with these labels has been reported previously [127] and is described briefly here:

Among the 24 beauty products considered, nine contributed to the latent classes. Compared to the 'infrequent' beauty product user latent class, women in the 'frequent' user class were more likely to report the most frequent use of all nine products: eye shadow, eyeliner, mascara, foundation, make-up remover, nail polish perfume, blush, and lipstick. Women in the 'moderate' beauty user class reported the second most frequent use of the same products, excluding blush. Among the original nineteen skincare products, there were nine products that contributed to the latent classes. Compared to the other latent classes, women in the 'frequent user' skincare latent class were most likely to be frequent users of cleansing cream, anti-aging cream, body lotion, face cream, and foot cream. These women had moderate use (relative to other latent classes) of hand lotion and petroleum jelly and were the most infrequent users of talcum powder (underarms and 'other').

Among white women, 'moderate users' and 'frequent users' of beauty products had increased risk of breast cancer relative to 'infrequent users' (adjHR= 1.13; 95% CI, 1.00-1.27 and adjHR=1.15 (1.02, 1.30) (Table 3.2). Among white women, 'frequent users' of skincare products had increased risk of breast cancer relative to infrequent use (adjHR= 1.13; 95% CI, 1.00-1.29. The associations were not significantly nor appreciably elevated among black women; however, there were only 165 breast cancer cases among blacks (Table 3.2). Neither beauty nor skincare product use appeared to be associated with increased breast cancer risk among black women.

In analyses that were restricted to white women and stratified by menopausal status, HRs for breast cancer associated with frequent (compared to infrequent) use of beauty or skincare products were slightly higher among post-menopausal women (adjHR=1.18 and 1.12, respectively) than pre-menopausal women (adjHR = 1.01 and 1.06, respectively) but were not statistically different (p-interaction >0.3) (Table 3.3). Other latent class membership did not appear to be associated with breast cancer risk.

In sensitivity analyses ER status was available for 89% (N=1,467) of white post-menopausal women. In this group, ‘moderate’ and ‘frequent’ users (compared to infrequent users) of beauty products did not appear to differ substantially between ER+ (adjHR=1.05; 95% CI: 0.90-1.23 and adjHR=1.10; 95% CI: 0.94-1.28) and ER- (adjHR=1.03; 95% CI: 0.69-1.54 and adjHR=0.72; 95% CI: 0.47-1.10). When stratified by breast cancer type, white post-menopausal ‘moderate’ and ‘frequent’ users of beauty products had increased risk of in situ (adjHR=1.41; 95% CI: 1.06-1.89 and adjHR=1.38; 95% CI: 1.03-1.85) but not invasive breast cancer (adjHR=1.09; 95% CI: 0.94-1.27 and adjHR=1.13; 95% CI: 0.97-1.32). We also conducted exploratory analyses of the 24 individual products included in LCA. However, after adjusting for Bonferroni criteria (p-value ≤ 0.001) none were associated with breast cancer (Table A.7).

4.5. Discussion

Our findings from this large, prospective study with detailed self-report of personal care product use suggest that membership in the ‘moderate’ and ‘frequent’ users of beauty products latent class was associated with an approximately 10-15% increased risk of developing breast cancer compared to ‘infrequent’ users. Among post-menopausal women the increase in risk was slightly greater. ‘Frequent users’ of beauty products can be broadly categorized as women who report using a combination of beauty products on a weekly basis (e.g., mascara, foundation, and lipstick). ‘Moderate’ users were more likely to report using these same products at least monthly or up to several times a month. One latent class of skincare product, ’frequent users’, was also associated with an approximate 13% increased risk of breast cancer. ‘Frequent users’ were more likely to report at least weekly use of a combination of skincare products, such as lotions and creams. Like the beauty product latent classes, when compared to pre-menopausal women, the magnitude of the association for ‘frequent’ users of skincare products was stronger among post-menopausal women.

The hypothesis that personal care products are associated with increased breast cancer risk is primarily based on animal and laboratory studies. In these settings, chemicals found in a wide variety of personal care products (e.g., parabens and phthalates) mimic estrogens [73], alter hormonal signaling, affect developing reproductive systems [80], and/or disrupt normal mammary development [81]. We found the association between both beauty and skincare latent classes and breast cancer risk to be slightly stronger among post-menopausal women. This is consistent with the hypothesis that weak estrogenic effects might be more impactful during the post-menopausal period as women with lower endogenous estrogen levels are more susceptible to exogenous estrogenic exposures. Post-menopausal women are older on average than pre-menopausal women, so it is also likely that they have accumulated exposure or longer duration of exposure to personal care products. However, because associations are stronger for in situ and not invasive breast cancer, it is possible that the results for in situ are driving the associations for overall breast cancer risk. These results may also suggest that increased risk of breast cancer among beauty product users is driven more by behavioral factors than chemical exposure. For example, women who are more frequent users of beauty products may be more likely to undergo more frequent screenings and mammograms and thus be more likely to have a carcinoma in situ detected.

Personal care product exposure is difficult to characterize because each product is a complex mixture and multiple products are often used in combination by one person. Co-occurring exposures may have additive or interacting effects or may result in confounding. For example, a chemical that does not show estrogenic activity could be a marker for other chemicals that are estrogenic. Products that include chemicals that can be estrogenic may show either estrogenic or anti-estrogenic effects in specific tissues [128]. Previous studies have examined correlation structure between specific personal care products [92-94], but these studies did not evaluate associations between personal care product use and health outcomes.

Our study addressed the idea that combinations and patterns of exposure may be especially important in relation to risk. The large sample size of white women, detailed self-report of personal care product use, prospective identification of breast cancer, multivariable analysis, and inclusion of both the aggregated and individual exposure data strengthen our study.

This work should be interpreted in light of some limitations. First, we had limited power to examine associations among black women. The Sister Study questionnaire did not capture information on specific brands of personal care products or the individual components of these products. However, even if product brand information were available, manufacturers are not required to disclose all chemical ingredients in consumer products [118]. Chemical composition of products change over time and across batches and chemicals (e.g., BPA) can leach from containers into the product [129]. Thus, individual chemical exposures are not feasible to ascertain from the questionnaire data.

Although information on product ingredients was not available, the personal care questionnaire measured current exposure, defined as patterns within the last twelve months. This information is most useful if exposure is relatively constant over time. In our study, the average follow-up was ~5.4 years, and therefore, it is likely that exposure was reasonably well captured over shorter intervals. We did not have information on duration of use of specific products. If the relevant time window is years in the past, it is not clear that current patterns will be relevant. However, since the use classes are quite broad, it seems reasonable to assume that they are a general approximation of adult behavior patterns.

Confounding by indication should be considered when interpreting the exposure patterns in this study. Underlying or latent biological factors may determine certain patterns of use. The goal of LCA is to capture groups of people with shared behaviors or traits that may not be measured or observed in the data. Thus, it is possible that a latent class may capture individuals with a shared, unmeasured characteristic that increases susceptibility to breast cancer or it could capture early, undiagnosed breast cancer. For example, it is possible that frequent use of skincare products or beauty products represent a latent class that shares a common set of skin conditions, along with use of medications for those skin conditions. There have been studies suggesting that certain skin conditions associated with hormone imbalance (e.g., acne or rosacea) may be associated with breast cancer risk [130-133]. Acne is suspected to be a result of high levels of circulating androgens which have been associated with breast cancer in prospective studies [130, 131]. Other indicators for skin conditions should also be considered. Radiotherapy treatment for acne and other skin conditions has also been positively associated with breast cancer [134, 135]. Antibiotics, often used to treat acne and other skin conditions, have also been associated with increased risk of breast cancer [132, 136, 137]; though other studies of antibiotic use and breast cancer have found no association [138-140]. We have previously shown that frequent use of beauty and skincare products is associated with exogenous hormone exposure [127]. While a number of covariates were included in this analysis, underlying skin conditions were not available.

4.6. Conclusion

The results from this study generate novel hypotheses concerning the relationship between use of personal care products and risk of female breast cancer. Users of specific classes of personal care products appear to differ in their breast cancer risk. Whether this is due to specific chemicals in the products or to other correlated behaviors, such as early and/or frequent breast cancer screenings, needs to be evaluated. Future studies are needed to replicate these findings and examine biological pathways by which these complex exposures influence breast cancer risk. For example, future studies might address medication used to treat skin conditions. Future work should also address duration of exposure and how product use patterns vary over time, perhaps by re-administering the same questionnaire on personal care product use among to a sample of the Sister Study population at additional follow-up intervals.

Table 4.1. Latent class descriptions by product category

Category/class		Label	Description
Beauty product classes	A	Infrequent users	Infrequent use of eye shadow, eyeliner, mascara, foundation, and blush; relatively (to the other classes) infrequent use of make-up remover, perfume, and lipstick.
	B	Moderate users	Intermediate use of eye shadow, eyeliner, mascara, foundation, blush, make-up remover, perfume and lipstick (relative to the other classes).
	C	Frequent users	Frequent use of eye shadow, eyeliner, mascara, foundation, blush, make-up remover, nail polish, and lipstick.
Hair product classes	A	Infrequent users of hair spray	Relatively infrequent use of hair spray, hair gel compared to Hair-C (similar to class Hair-B); frequent use of shampoo, conditioner; infrequent use of pomade and hair straightener
	B	Users of pomade and hair straightener	Infrequent use of shampoo, hair gel; intermediate use of pomade, hair straightener, and hair spray
	C	Frequent users of hair spray and hair gel	Frequent use of hair spray, hair gel, shampoo, conditioner; infrequent use of pomade and hair straightener
Skincare product classes	A	Infrequent users	Infrequent use of lotions, creams, talcum powder
	B	Moderate users	Intermediate use of lotions, creams; infrequent use of talcum powder
	C	Frequent users	Frequent use of face creams and lotions; infrequent use of talcum powder
	D	Talcum powder users	Second most frequent use of lotions; most frequent use

Table 4.2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between personal care product latent classes and overall breast cancer risk among white and black women

	White				Black			
Beauty Classes	**Person-years**	**BC Events**	**HR (95% CI)[a]**	**HR (95% CI)[b]**	**Person-years**	**BC Events[*]**	**HR (95% CI)[a]**	**HR (95% CI)[b]**
Infrequent user	60483	448	1	1	7066	53	1	1
Moderate user	104790	816	1.13 (1.01, 1.27)	1.13 (1.00, 1.27)	11782	86	1.00 (0.71, 1.40)	0.95 (0.66, 1.36)
Frequent user	111191	859	1.12 (1.00, 1.26)	1.15 (1.02, 1.30)	4171	26	0.85 (0.53, 1.36)	0.86 (0.53, 1.39)
Totals	276464	2123			23019	165		
Hair Classes								
Infrequent users of hair spray	137672	1059	1	1	5615	42	1	1
Users of pomade and hair straightener	7686	61	0.91 (0.70, 1.18)	0.91 (0.70, 1.19)	16333	118	0.93 (0.65, 1.32)	0.90 (0.63, 1.28)
Frequent users of hair spray and hair gel	129205	997	1.01 (0.93, 1.10)	1.02 (0.93, 1.11)	998	5	--	--
Totals	274563	2117			22946	165		
Skincare Classes								
Infrequent user	52506	404	1	1	4310	39	1	1
Moderate user	123010	930	1.00 (0.89, 1.12)	1.03 (0.91, 1.17)	12124	88	0.76 (0.52, 1.11)	0.75 (0.51, 1.10)
Frequent user	66346	548	1.12 (0.98, 1.27)	1.13 (1.00, 1.29)	3032	23	0.82 (0.49, 1.38)	0.79 (0.47, 1.34)
Talcum powder user	34582	242	0.90 (0.77, 1.06)	0.92 (0.78, 1.08)	3543	15	--	--
Totals	276444	2124			23009	165		

BC: Breast cancer
[a] adjusted for age
[b] adjusted for menopausal status, parity, age at first live birth, duration of breastfeeding, Adult BMI, alcohol use, oral contraceptive use, post-menopausal hormone therapy use, education, family history, region of residence, age at menarche, and smoking status
[*]Did not report if <20 BC events

Table 4.3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between latent classes and breast cancer risk among post-menopausal and pre-menopausal women white women

	Post-menopausal				Pre-menopausal			
Beauty Classes	**Person-years**	**BC Events**	**HR (95% CI)[a]**	**HR (95% CI)[b]**	**Person-years**	**BC Events[*]**	**HR (95% CI)[a]**	**HR (95% CI)[b]**
Infrequent user	53247	372	1	1	6834	74	1	1
Moderate user	84289	632	1.16 (1.02, 1.32)	1.16 (1.12, 1.19)	19586	177	0.99 (0.75, 1.30)	0.98 (0.74, 1.30)
Frequent user	90181	656	1.14 (1.00, 1.29)	1.18 (1.14, 1.21)	19861	191	1.01 (0.77, 1.33)	1.01 (0.76, 1.33)
Totals	227717	1659			46281	442		
Hair Classes								
Infrequent users of hair spray	115014	841	1	1	21377	208	1	1
Users of pomade and hair straightener	7190	56	0.90 (0.68, 1.18)	0.76 (0.71, 0.81)	442	4	--	--
Frequent users of hair spray and hair gel	103825	757	0.99 (0.90, 1.10)	1.03 (1.01, 1.06)	24276	229	1.07 (0.89, 1.29)	1.04 (0.86, 1.25)
Totals	226029	1654			46095	441		
Skincare Classes								
Infrequent user	43793	324	1	1	8266	76	1	1
Moderate user	101807	721	0.98 (0.86, 1.12)	1.08 (1.05, 1.12)	20031	200	1.09 (0.84, 1.42)	1.06 (0.81, 1.39)
Frequent user	52621	420	1.13 (0.98, 1.30)	1.12 (1.09, 1.16)	13152	122	1.07 (0.80, 1.42)	1.06 (0.79, 1.42)
Talcum powder user	29453	195	0.91 (0.76, 1.09)	1.03 (0.99, 1.07)	4853	44	0.88 (0.61, 1.29)	0.84 (0.57, 1.23)
Totals	227674	1660			46302	442		

BC: Breast cancer
[a] adjusted for age
[b] adjusted for menopausal status, parity, age at first live birth, duration of breastfeeding, Adult BMI, alcohol use, oral contraceptive use, post-menopausal hormone therapy use, education, family history, region of residence, age at menarche, and smoking status
[*] Did not report if <20 BC events

CHAPTER 5: DISCUSSION

5.1. Brief summary of findings

Using data from a large study of United States women, we identified subgroups of women with distinct personal care product use exposure. Personal care product exposure is difficult to characterize because each product is a complex mixture and multiple products are often used in combination by one person. These co-occurring exposures may have additive or interacting effects or may result in confounding. Latent class analysis addresses these limitations by identifying latent classes which describe variability among multiple, correlated, and observed variables [107 714]. Three latent classes were identified for beauty products; four classes were identified for skincare products; and three classes were identified for hair care products. Our results suggest that relative to individual product use questions, latent class variables capture different dimensions of product use or other latent characteristics associated with product use.

In Chapter 3 we emphasize the association between latent classes and exogenous hormone use (OC use and post-menopausal HT use among women >50 years). Having observed correlation within personal care product use classes (e.g. between frequent users of hair and beauty products), we tested whether personal care product categories are associated with OC and HT, examples of key exposures to exogenous estrogens. We found that the women with the highest use of personal care products are more likely to have used these common exogenous hormone medications. Therefore, when personal care product use is being evaluated as a potential risk factor for hormonally-mediated conditions, we encourage researchers to consider possible confounding by OC and HT use. However, OC and HT use are only two examples; a wide range of associations between latent classes and other breast cancer risk factors (Table 2.1) were also considered (Table A.6). While the LCA approach addresses complex exposure patterns within personal care products, it is also important to integrate product use patterns with other biologically relevant and risk-related exposures.

The overall goal of this analysis was to examine personal care product use in association with breast cancer risk. Chapter 4 provides some evidence that certain classes of beauty product and skincare product users may be at increased risk of breast cancer. However, we cannot distinguish whether the association is related to specific chemical components in the products or if it is due to a characteristic or correlated behavior of the women in the latent classes themselves. The goal of LCA is to capture groups of people with shared behaviors or traits that may not be measured or observed in the data. Thus, it is possible that a latent class may capture individuals with a shared, unmeasurable biological characteristic that itself increases susceptibility to breast cancer. Therefore, confounding by indication should be considered when interpreting the exposure patterns in this study. For example, it is possible that frequent use of skincare products or beauty products represent a latent class that shares a common set of skin conditions, along with use of medications for those skin conditions.

5.2. Biological plausibility

The concern that use of personal care products may be associated with breast cancer risk is based on the hypothesis that chemicals in personal care products (e.g., parabens and phthalates) may act as endocrine disrupting chemicals (EDCs) [67, 79, 97, 103, 104], possibly mimicking the carcinogenic effects of estrogenic exposures [98, 99]. One product can be a source of many chemicals and use of multiple products can result in exposure to an even larger number of chemicals [79]. We found the association between both beauty and skincare latent classes and breast cancer risk to be slightly stronger among post-menopausal women. However, among pre-menopausal women, we found no association. This is consistent with, though not confirmative of, the hypothesis that weak estrogenic effects might be more impactful during the post-menopausal period as women with low estrogenic levels are more susceptible to estrogenic exposures. Because they are older on average than pre-menopausal women, is also likely that post-menopausal women have more accumulated exposure to personal care products due to longer duration of use. These results may also suggest that increased risk of breast cancer among beauty product users is driven more by behavioral factors than chemical exposure. For example, women who are more frequent users of beauty products may be more likely to undergo more frequent screenings and mammograms and thus be more likely to have an early breast cancer detected.

Although the Sister Study's questionnaire did not have information on duration of exposure, we were able to examine detailed information on the frequency of use of 48 personal care products. The questionnaire measured current exposure, defined as product use over the past twelve months. Among white women in our sample population, the average follow-up is ~5.4 years, and therefore, it is likely that exposure was reasonably well captured over shorter intervals. However, if exposure varies over shorter intervals, exposure may have been misclassified. However, if we assume that the mechanisms of action for personal care products involve tumor growth/maintenance rather than initiation, the timing of exposure is likely to be relevant.

5.3. Significance and future direction

To our knowledge, this was the first study to do two things: (1) use LCA to categorize exposure to personal care products, and (2) examine the association between aggregate personal care product use and breast cancer. Previous studies have examined the co-use of personal care products [92-94], but these studies were not aimed at reducing the complexity of individual product usage patterns. Nor did these studies examine how product use relates to other exposures or health outcomes. Surprisingly, this study was the first to examine the association between overarching patterns of personal care product use and breast cancer. When considering personal care product use in association with a health outcome, it is important to integrate these exposures with other biologically relevant and risk-related exposures. We observed correlation within personal care product use classes (e.g. between heavy users of hair care products and heavy users of beauty products) and examined how product use relates to other relevant exposures. Understanding and accounting for such relationships is critical as researchers explore associations between personal care product use and health outcomes. Future studies of other health outcomes measured in the Sister Study that have a suspected link to personal care product use (e.g., other cancers, asthma, etc.) should consider these latent classes.

In addition to considering latent classes as potential covariates for other relevant health outcomes, future work should also address how product use patterns vary over time. The exposure measured by the questionnaire is most useful in relation to evaluating health outcomes with longer empirical induction periods if it captures exposure that is relatively constant over time. This could be examined in the Sister Study by re-administering the same questionnaire on personal care product use among to a sample of the Sister Study population at additional follow-up intervals. Another issue regarding exposure as measured by the questionnaire relates to the validity of the questionnaire. Information collected from the personal care questionnaire provides extensive data related to the frequency and pattern of personal care product use. However, because the information was self-reported, a limitation of the personal care questionnaire includes potential recall bias. In addition, chemical-specific exposures cannot be ascertained from the questionnaire data. To address these limitations we are currently developing a study at the National Toxicology Program to evaluate the effectiveness of the personal care questionnaire by jointly assessing product use via daily diary, product photographs, and biomonitoring.

The results from this study generate novel hypotheses for breast cancer risk. Our results suggest that relative to individual product use questions, latent class variables capture different dimensions of product use or other latent characteristics associated with product use. Users of specific classes of personal care products appear to differ in their breast cancer risk. Whether this is due to specific chemicals in the products or to other correlated behaviors, such as early and/or frequent breast cancer screenings, needs to be evaluated. Future studies are needed to replicate these findings and examine biological pathways by which these complex exposures influence breast cancer risk. For example, future studies might address medication, or additional product types, used to treat skin conditions. LCA is a valuable tool as it identifies groups of people with shared behaviors or traits that may not be measured or observed in the data. Therefore, rather than assuming that the observable data used to create a latent class is etiologically relevant to an associated health outcome, results of LCA must be interpreted with the knowledge that a latent class may instead be capturing individuals with a shared, unmeasurable biological characteristic that itself increases susceptibility to disease.

APPENDIX A: TABLES

Table A.1. Item response probabilities for beauty product latent classes (3 class model)

Class prevalence	**Beauty A** Infrequent user 23%	**Beauty B** Moderate user 40%	**Beauty C** Frequent user 38%
Mascara			
Never	0.7667	0.1243	0.0698
<once a month to 1-3 times a month	0.1154	0.3885	0.0970
1 to 5+ times a week	0.1179	0.4872	0.8331
Lip Stick			
Never	0.3967	0.0524	0.0405
<once a month to 1-3 times a month	0.2336	0.2925	0.0998
1 to 5+ times a week	0.3697	0.6551	0.8597
Foundation			
Never	0.6976	0.1876	0.1001
<once a month to 1-3 times a month	0.2077	0.7498	0.1499
1 to 5+ times a week	0.0947	0.0626	0.7500
Nail Polish			
Never	0.4344	0.1112	0.0573
<once a month	0.3917	0.4721	0.3500
1-3 times a month or more	0.1740	0.4167	0.5927
Perfume			
Never	0.3746	0.1461	0.1272
<once a month to 1-3 times a month	0.3482	0.3872	0.2626
1 to 5+ times a week	0.2772	0.4667	0.6102
Eye shadow			
Never	0.9041	0.1514	0.1240
<once a month to 1-3 times a month	0.0816	0.8169	0.3025
1 to 5+ times a week	0.0143	0.0316	0.5735
Eyeliner			
Never	0.8962	0.3394	0.2383
<once a month to 1-3 times a month	0.0632	0.6043	0.2045
1 to 5+ times a week	0.0406	0.0563	0.5572
Blush			
Never	0.6850	0.1404	0.0682
<once a month to 1-3 times a month	0.2290	0.8071	0.1401
1 to 5+ times a week	0.0861	0.0529	0.7916
Makeup-remover			
Never	0.9480	0.5417	0.4562
<once a month to 1-3 times a month	0.0406	0.4347	0.2371
1 to 5+ times a week	0.0113	0.0237	0.3068

Table A.2. Item response probabilities for hair product latent classes (3 class model)

	Hair A Infrequent user of hair styling products	Hair B Infrequent user of shampoo	Hair C Frequent user of hair styling products
Class prevalence	48%	43%	9%
Pomade			
Never	0.9074	0.8803	0.4235
<once a month to 1-3 times a month	0.0588	0.0602	0.3930
1 to 5+ times a week	0.0338	0.0594	0.1836
Hair Straightener			
Never	0.9442	0.9782	0.4797
<once a month to 1-3 times a month	0.0390	0.0170	0.2638
1 to 5+ times a week	0.0167	0.0048	0.2565
Conditioner			
never to <once a month	0.1897	0.1991	0.1572
1-3 times a month	0.0770	0.0865	0.8163
1 to 5+ times a week	0.7334	0.7144	0.0265
Hair Spray			
Never	0.4463	0.0606	0.3835
<once a month to 1-3 times a month	0.3387	0.1529	0.4532
1 to 5+ times a week	0.2151	0.7865	0.1604
Hair Gel			
Never	0.4001	0.0602	0.4089
<once a month to 1-3 times a month	0.3766	0.1279	0.4946
1 to 5+ times a week	0.2233	0.8119	0.0964
Shampoo			
Never to 1-3 times a month	0.0094	0.0040	0.9802
1 to 5 times a week	0.6337	0.4857	0.0198
>5 times a week	0.3569	0.5102	0.0000

Table A.3. Item response probabilities for skincare product latent classes (4 class model)

	Skin A Infrequent users	**Skin B** Moderate users	**Skin C** Frequent users	**Skin D** Talcum powder users
Class prevalence	19%	73%	24%	14%
Cleansing Cream				
Never	0.8336	0.4264	0.4084	0.3908
<once a month to 1-3 times a month	0.1197	0.1448	0.2367	0.2500
1 to 5+ times a week	0.0467	0.4287	0.3549	0.3592
Anti-aging Cream				
Never	0.8576	0.3407	0.3000	0.3619
<once a month to 1-3 times a month	0.1090	0.1540	0.2750	0.2291
1 to 5+ times a week	0.0334	0.5053	0.4250	0.4090
Body Lotion				
Never to <once a month	0.3630	0.0270	0.0932	0.0410
<once a month to 1-5 times a week	0.5054	0.1015	0.8378	0.3386
>5 times per week	0.1316	0.8716	0.0690	0.6204
Hand Lotion				
Never to 1-3 times a month	0.4356	0.0282	0.2447	0.0626
1 to 5 times a week	0.3320	0.0907	0.6111	0.2269
>5 times a week	0.2324	0.8811	0.1442	0.7105
Face Cream				
Never to <once a month	0.5550	0.0343	0.0180	0.0587
<once a month to 1-5 times a week	0.2441	0.0911	0.4005	0.2191
>5 times per week	0.2009	0.8746	0.5815	0.7222
Foot Cream				
Never	0.5705	0.1980	0.2505	0.1528
<once a month to 1-3 times a month	0.3374	0.3350	0.5682	0.4172
1 to 5+ times a week	0.0921	0.4671	0.1813	0.4300
Petroleum Jelly				
Never	0.7518	0.6196	0.7344	0.5065
<once a month to 1-3 times a month	0.1773	0.2129	0.2178	0.3053
1 to 5+ times a week	0.0708	0.1675	0.0478	0.1882
Talcum powder Underarms				
Never	0.8918	0.9643	0.9376	0.1672
Once a month	0.0512	0.0216	0.0507	0.3371
1-3 times a month or more	0.0570	0.0142	0.0117	0.4957
Talcum powder other				
Never	0.6896	0.7568	0.7024	0.0000
Once a month	0.1369	0.1395	0.1925	0.2725
1-3 times a month or more	0.1735	0.1037	0.1051	0.7275

Table A.4. Initial product types and final product types by category: beauty, hair, skincare products

Initial personal care products from personal care questionnaire by category (beauty, hair, and skin)		
Beauty (14)	**Hair (15)**	**Skin (19)**
Mascara	Shampoo	Cleansing cream
Eyeshadow	Conditioner	Face cream
Eyeliner	Hair spray	Face mask
Lip moisturizer	Hair gel	Shaving cream
Lip stick	Pomade	Anti-aging cream
Foundation	Hair dye-permanent	Age spot remover
Blush	Hair dye-semi permanent	Self-tanner
Makeup remover	Hair highlighter	Baby oil
Nail polish	Hair straightener	Petroleum Jelly
Nail polish remover	Hair color rinse	Body lotion
Artificial nails	Hair food	Hand lotion
Artificial nails (other)	Hair bleach	Foot cream
Perfume	Hair perm	Deodorant
Cuticle cream	Rogaine	Talcum underarms
	Hair straightener (other)	Talcum other
		Talcum vaginal
		Bath gel
		Skin lightener
		Blemish cream

Reduced personal care products used in the latent class analyses by category (beauty, hair, and skin)		
Beauty (9)	**Hair (6)**	**Skin (9)**
Mascara	Shampoo	Cleansing cream
Eyeshadow	Conditioner	Anti-aging cream
Eyeliner	Hair spray	Body lotion
Lip Stick	Hair gel	Hand lotion
Foundation	Pomade	Foot cream
Blush	Hair straightener	Face cream
Makeup remover		Petroleum Jelly
Nail polish		Talcum underarms
Perfume		Talcum other

Table A.5. Re-categorization of original response options by product

	New categories	Original categories (1=did not use; 2=<once a month; 3=1-3 times a month; 4=1-5 times a week; 5=> 5 times a week
Skincare Products		
Body Lotion	Never to <once a month	1,2
	Multiple times a month to 1-5 times a week	3,4
	>5 times per week	5
Hand Lotion	Never to 1-3 times a month	1,2,3
	1 to 5 times a week	4
	>5 times a week	5
Face Cream	Never to <once a month	1,2
	Multiple times a month to 1-5 times a week	3,4
	>5 times per week	5
Cleansing Cream	Never to <once a month	1,2
	1-3 times a month	3
	1 to 5+ times a week	4,5
Anti-age cream	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4,5
Foot cream	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4,5
Baby oil	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4, 5
Petroleum Jelly	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4,5
Cuticle Cream	Never	1
	<once a month	2
	1-3 times a month or more	3, 4, 5
Hair Products		
Hair Spray	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4,5
Hair Gel	Never	1
	<once a month to 1-3 times a month	2,3

	1 to 5+ times a week	4,5
Conditioner	Never to <once a month	1,2
	1-3 times a month	3
	1 to 5+ times a week	4,5
Pomade	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4,5
Hair Straightener	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4,5
Beauty Products		
Mascara	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4,5
Foundation	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4,5
Lipstick	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4,5
Lip moisturizer	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4,5
Nail Polish	Never	1
	<once a month	2
	1-3 times a month or more	3, 4, 5
Perfume	Never	1
	<once a month to 1-3 times a month	2,3
	1 to 5+ times a week	4,5

Table A.6. Age-adjusted prevalence differences (PDs) and 95% confidence intervals (CIs) for associations between breast cancer risk factors and latent classes within each product category

Variable	**Comparison**	**Latent class**	**Class labels**	**PD (95% CI)** White women	**PD (95% CI)** Black women
Menopausal status	Pre- vs. Post-meno (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.11 (0.10, 0.12)	0.09 (0.06, 0.12)
		Beauty C	Frequent users	0.11 (0.10, 0.12)	0.06 (0.01, 0.10)
	Pre- vs. Post-meno (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	-0.05 (-0.05, -0.04)	-0.05 (-0.08, -0.02)
		Hair C	Frequent users of hair spray/hair gel	0.02 (0.01, 0.03)	-0.01 (-0.05, 0.03)
	Pre- vs. Post-meno (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	0.02 (0.01, 0.03)	-0.03 (-0.06, 0.00)
		Skin C	Frequent users	0.06 (0.05, 0.08)	-0.02 (-0.07, 0.03)
		Skin D	Talcum powder users	-0.01 (-0.03, 0.01)	-0.02 (-0.07, 0.03)
Age at menarche	<12 years vs ≥12 years (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	-0.01 (-0.03, 0.00)	0.00 (-0.04, 0.04)
		Beauty C	Frequent users	-0.02 (-0.03, 0.00)	-0.03 (-0.08, 0.01)
	<12 years vs ≥12 years (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.00 (0.00, 0.01)	0.02 (-0.01, 0.05)
		Hair C	Frequent users of hair spray/hair gel	0.00 (-0.01, 0.01)	0.02 (-0.03, 0.06)
	<12 years vs ≥12 years (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	-0.02 (-0.03, 0.01)	-0.03 (-0.06, 0.01)
		Skin C	Frequent users	-0.03 (-0.04, -0.01)	-0.06 (-0.12, 0.00)
		Skin D	Talcum powder users	0.01 (-0.01, 0.03)	0.00 (-0.05, 0.06)

Parity	1-2 Children vs. Nulliparous (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.08 (0.07, 0.10)	0.01 (-0.04, 0.05)
		Beauty C	Frequent users	0.14 (0.13, 0.16)	0.00 (-0.06, 0.05)
	3+ Children vs. Nulliparous (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.08 (0.06, 0.10)	-0.02 (-0.07, 0.03)
		Beauty C	Frequent users	0.12 (0.10, 0.13)	-0.11 (-0.18, -0.05)
	1-2 Children vs. Nulliparous (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	-0.01 (-0.02, 0.00)	0.01 (-0.03, 0.05)
		Hair C	Frequent users of hair spray/hair gel	0.07 (0.05, 0.08)	-0.05 (-0.11, 0.00)
	3+ Children vs. Nulliparous (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.00 (-0.01, 0.00)	0.03 (-0.01, 0.08)
		Hair C	Frequent users of hair spray/hair gel	0.05 (0.03, 0.06)	-0.05 (-0.12, 0.02)
	1-2 Children vs. Nulliparous (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	0.06 (0.04, 0.07)	-0.06 (-0.1, -0.02)
		Skin C	Frequent users	0.06 (0.04, 0.08)	-0.04 (-0.12, 0.03)
		Skin D	Talcum powder users	0.04 (0.02, 0.06)	-0.06 (-0.13, 0.01)
	3+ Children vs. Nulliparous (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	0.02 (0.01, 0.04)	-0.08 (-0.10, -0.03)
		Skin C	Frequent users	0.06 (0.03, 0.08)	0.01 (-0.08, 0.09)
		Skin D	Talcum powder users	0.03 (0.00, 0.05)	-0.05 (-0.13, 0.03)

Age at first live birth	≤26 years vs. Nulliparous (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.09 (0.07, 0.11)	-0.02 (-0.06, 0.03)
		Beauty C	Frequent users	0.15 (0.13, 0.16)	-0.05 (-0.11, 0.01)
	>26 years vs. Nulliparous (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.07 (0.05, 0.09)	0.04 (-0.01, 0.09)
		Beauty C	Frequent users	0.11 (0.10, 0.13)	0.01 (-0.06, 0.08)
	≤26 years vs. Nulliparous (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.00 (-0.01, 0.00)	0.02 (-0.01, 0.06)
		Hair C	Frequent users of hair spray/hair gel	0.08 (0.07, 0.10)	-0.06 (-0.11, 0.00)
	>26 years vs. Nulliparous (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	-0.01 (-0.02, 0.00)	-0.01 (-0.05, 0.04)
		Hair C	Frequent users of hair spray/hair gel	0.02 (0.00, 0.03)	-0.05 (-0.11, 0.02)
	≤26 years vs. Nulliparous (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	0.04 (0.03, 0.06)	-0.07 (-0.11, -0.04)
		Skin C	Frequent users	0.06 (0.04, 0.08)	-0.03 (-0.1, 0.04)
		Skin D	Talcum powder users	0.05 (0.02, 0.07)	-0.05 (-0.13, 0.01)
	>26 years vs. Nulliparous (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	0.05 (0.03, 0.06)	-0.05 (-0.10, 0.00)
		Skin C	Frequent users	0.06 (0.04, 0.08)	-0.02 (-0.11, 0.07)
		Skin D	Talcum powder users	0.02 (-0.01, 0.04)	-0.05 (-0.14, 0.03)
Duration of breastfeeding	<12 vs. ≥12 months (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.05 (0.04, 0.06)	-0.05 (-0.1, 0.00)
		Beauty C	Frequent users	0.11 (0.09, 0.12)	0.01 (-0.06, 0.08)

	<12 vs. ≥12 months (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.01 (0.00, 0.02)	0.00 (-0.05, 0.04)
		Hair C	Frequent users of hair spray/hair gel	0.10 (0.09, 0.11)	0.04 (-0.02, 0.10)
	<12 vs. ≥12 months (ref)	Skin A (ref)	Infrequent users	1	
		Skin B	Moderate users	0.02 (0.01, 0.04)	-0.01 (-0.06, 0.04)
		Skin C	Frequent users	0.01 (-0.01, 0.03)	-0.01 (-0.09, 0.07)
		Skin D	Talcum powder users	0.02 (0.00, 0.04)	0.01 (-0.07, 0.09)
OC use	Ever vs. never (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.12 (0.10, 0.14)	0.15 (0.10, 0.2)
		Beauty C	Frequent users	0.14 (0.12, 0.16)	0.17 (0.12, 0.23)
	Ever vs. never (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	-0.01 (-0.02, 0.00)	0.00 (-0.04, 0.04)
		Hair C	Frequent users of hair spray/hair gel	0.07 (0.06, 0.08)	0.05 (0.00, 0.11)
	Ever vs. never (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	0.10 (0.08, 0.12)	0.11 (0.06, 0.16)
		Skin C	Frequent users	0.09 (0.07, 0.11)	0.06 (-0.01, 0.13)
		Skin D	Talcum powder users	0.07 (0.05, 0.09)	0.07 (0.00, 0.14)
HRT use	Ever vs. never (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.09 (0.08, 0.11)	0.09 (0.08, 0.11)
		Beauty C	Frequent users	0.10 (0.09, 0.12)	0.11 (0.06, 0.16)
	Ever vs. never (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.00 (-0.01, 0.01)	0.00 (-0.04, 0.03)
		Hair C	Frequent users of hair spray/hair gel	0.08 (0.07, 0.09)	0.07 (0.01, 0.12)
	Ever vs. never (ref)	Skin A (ref)	Infrequent users	1	1

		Skin B	Moderate users	0.10 (0.09, 0.12)	0.08 (0.04, 0.12)
		Skin C	Frequent users	0.07 (0.05,0.09)	0.04 (-0.04, 0.11)
		Skin D	Talcum powder users	0.11 (0.09,0.13)	0.06 (-0.01, 0.13)
BMI	25 to <30kg vs <25kg (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.01 (-0.01, 0.02)	0.01 (-0.03, 0.06)
		Beauty C	Frequent users	-0.03 (-0.04, -0.02)	-0.08 (-0.15, -0.01)
	≥30kg vs <25kg (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	-0.03 (-0.04, -0.01)	-0.07 (-0.12, -0.03)
		Beauty C	Frequent users	-0.14 (-0.16, -0.13)	-0.19 (-0.25, -0.13)
	25 to <30kg vs <25kg (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.00 (0.00, 0.01)	0.05 (0.01, 0.10)
		Hair C	Frequent users of hair spray/hair gel	0.02 (0.01, 0.03)	0.09 (0.04, 0.14)
	≥30kg vs 1<25kg (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.01 (0.00, 0.01)	0.06 (0.02, 0.10)
		Hair C	Frequent users of hair spray/hair gel	-0.02 (-0.04, -0.01)	0.04 (-0.01, 0.09)
	25 to <30kg vs <25kg (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	0.10 (0.06, 0.14)	-0.16 (-0.43, 0.11)
		Skin C	Frequent users	0.06 (-0.01, 0.13)	-0.04 (-0.35, 0.28)
		Skin D	Talcum powder users	-0.05 (-0.13, 0.04)	-0.15 (-0.45, 0.14)
	≥30kg vs 1<25kg (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	0.01 (-0.01, 0.02)	0.08 (0.04, 0.11)
		Skin C	Frequent users	0.04 (0.03, 0.06)	0.08 (0.02, 0.14)

		Skin D	Talcum powder users	0.01 (0.00, 0.03)	0.04 (-0.02, 0.10)
Alcohol	< 1 day vs never (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.06 (0.02, 0.10)	0.09 (0.01, 0.17)
		Beauty C	Frequent users	-0.01 (-0.04, 0.03)	0.02 (-0.06, 0.09)
	Former vs. never (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.20 (0.17, 0.24)	0.25 (0.18, 0.32)
		Beauty C	Frequent users	0.18 (0.14, 0.21)	0.21 (0.13, 0.29)
	1 or more/day vs. never (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.23 (0.2, 0.27)	0.23 (0.13, 0.33)
		Beauty C	Frequent users	0.23 (0.19, 0.26)	0.27 (0.16, 0.39)
	< 1 day vs never (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.03 (0.01, 0.06)	0.00 (-0.06, 0.06)
		Hair C	Frequent users of hair spray/hair gel	-0.04 (-0.07, -0.01)	-0.08 (-0.15, 0.00)
	Former vs. never (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.01 (0.00, 0.02)	0.03 (0.00, 0.06)
		Hair C	Frequent users of hair spray/hair gel	-0.06 (-0.08, -0.05)	-0.02 (-0.07, 0.03)
	1 or more/day vs. never (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.00 (-0.01, 0.00)	-0.04 (-0.11, 0.02)
		Hair C	Frequent users of hair spray/hair gel	0.01 (-0.01, 0.02)	0.02 (-0.07, 0.11)
	< 1 day vs never (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	-0.17 (-0.2, -0.14)	-0.08 (-0.15, -0.01)
		Skin C	Frequent users	-0.18 (-0.22, -0.14)	-0.18 (-0.28, -0.07)
		Skin D	Talcum powder users	-0.15 (-0.19, -0.11)	-0.17 (-0.28, -0.06)

	Former vs. never (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	-0.13 (-0.15, -0.12)	-0.13 (-0.16, -0.09)
		Skin C	Frequent users	-0.13 (-0.15, -0.11)	-0.14 (-0.20, -0.08)
		Skin D	Talcum powder users	-0.10 (-0.12, -0.08)	-0.10 (-0.16, -0.05)
	1 or more/day vs. never (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	0.04 (0.03, 0.06)	0.00 (-0.07, 0.07)
		Skin C	Frequent users	0.02 (0.00, 0.04)	-0.05 (-0.17, 0.08)
		Skin D	Talcum powder users	0.01 (-0.02, 0.04)	0.00 (-0.12, 0.12)
Smoking	Past smoker vs never (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.07 (0.06, 0.08)	0.03 (-0.01, 0.07)
		Beauty C	Frequent users	0.07 (0.05, 0.08)	0.02 (-0.02, 0.07)
	Past smoker vs never (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.00 (-0.01, 0.00)	-0.03 (-0.06, 0.00)
		Hair C	Frequent users of hair spray/hair gel	0.01 (0.00, 0.02)	-0.03 (-0.08, 0.02)
	Past smoker vs never (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	0.04 (0.03, 0.05)	-0.03 (-0.06, 0.01)
		Skin C	Frequent users	0.04 (0.03, 0.06)	-0.02 (-0.08, 0.04)
		Skin D	Talcum powder users	0.04 (0.02, 0.06)	-0.03 (-0.09, 0.03)
	Current smoker vs never (ref)	Beauty A (ref)	Infrequent users	1	
		Beauty B	Moderate users	0.08 (0.06, 0.10)	0.01 (-0.04, 0.06)
		Beauty C	Frequent users	-0.01 (-0.03, 0.01)	-0.03 (-0.10, 0.04)
	Current smoker vs never (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.02 (0.01, 0.03)	0.00 (-0.04, 0.05)
		Hair C	Frequent users of hair spray/hair gel	-0.02 (-0.04, -0.01)	-0.01 (-0.08, 0.06)
	Current smoker vs	Skin A (ref)	Infrequent users	1	1

	never (ref)				
		Skin B	Moderate users	-0.04 (-0.06, -0.02)	-0.10 (-0.15, -0.04)
		Skin C	Frequent users	0.01 (-0.01, 0.04)	-0.02 (-0.10, 0.06)
		Skin D	Talcum powder users	0.00 (-0.03, 0.03)	-0.01 (-0.09, 0.07)
Education	Degree vs no degree (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.04(0.03, 0.05)	-0.07 (-0.11, -0.04)
		Beauty C	Frequent users	0.04 (0.03, 0.05)	-0.12 (-0.16, -0.07)
	Degree vs no degree (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.02 (0.01, 0.02)	0.03 (0.01, 0.00)
		Hair C	Frequent users of hair spray/hair gel	0.07 (0.01, 0.06)	0.00 (0.02, -0.05)
	Degree vs no degree (ref)	Skin A (ref)	Infrequent users	1.00	1.00
		Skin B	Moderate users	0.00 (-0.01, 0.01)	-0.10 (-0.13, -0.06)
		Skin C	Frequent users	0.01 (-0.01, 0.01)	-0.09 (-0.15, -0.04)
		Skin D	Talcum powder users	0.02 (0.01, 0.04)	-0.09 (-0.15, -0.04)
Family History	More than 1 sister or 1 sister & mom vs 1 sister, no mom (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	0.01 (-0.01, 0.02)	0.00 (-0.04, 0.03)
		Beauty C	Frequent users	0.01 (0.00, 0.03)	0.03 (-0.01, 0.08)
	More than 1 sister or 1 sister & mom vs 1 sister, no mom (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	0.00 (0.00, 0.01)	-0.01 (-0.04, 0.02)
		Hair C	Frequent users of hair spray/hair gel	0.01 (0.00, 0.02)	0.03 (-0.01, 0.08)
	More than 1 sister or 1 sister &	Skin A (ref)	Infrequent users	1	1

	mom vs 1 sister, no mom (ref)				
		Skin B	Moderate users	0.01 (0.00, 0.02)	0.02 (-0.02, 0.06)
		Skin C	Frequent users	0.01 (-0.01, 0.03)	0.00 (-0.06, 0.06)
		Skin D	Talcum powder users	0.01 (-0.01, 0.03)	0.08 (0.02, 0.14)
Geographic Region	Midwest vs. South (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	-0.05 (-0.07, 0.71)	0.01 (-0.03, 0.05)
		Beauty C	Frequent users	-0.05 (-0.06, -0.03)	-0.03 (-0.08, 0.03)
	Midwest vs. South (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	-0.01 (-0.02, -0.01)	0.02 (-0.01, 0.05)
		Hair C	Frequent users of hair spray/hair gel	0.04 (0.03, 0.06)	0.04 (-0.01, 0.09)
	Midwest vs. South (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	-0.02 (-0.03, 0.00)	-0.02 (-0.03, 0.00)
		Skin C	Frequent users	-0.03 (-0.04, -0.01)	-0.05 (-0.11, 0.02)
		Skin D	Talcum powder users	-0.07 (-0.09, -0.05)	0.00 (-0.06, 0.07)
	Northeast vs. South (ref)	Beauty A (ref)	Infrequent users	1	1
		Beauty B	Moderate users	-0.09 (-0.11, -0.08)	-0.05 (-0.11, 0.01)
		Beauty C	Frequent users	-0.13 (-0.14, -0.11)	-0.10 (-0.16, -0.03)
	Northeast vs. South (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
		Hair B	Users of pomade and hair straightener	-0.02 (-0.03, -0.01)	-0.01 (-0.06, 0.04)
		Hair C	Frequent users of hair spray/hair gel	-0.06 (-0.07, -0.04)	0.07 (-0.01, 0.14)
	Northeast vs. South (ref)	Skin A (ref)	Infrequent users	1	1
		Skin B	Moderate users	-0.06 (-0.08, -0.05)	-0.06 (-0.08, 0.00)

	Skin C	Frequent users	-0.05 (-0.07, -0.03)	-0.07 (-0.16, 0.01)
	Skin D	Talcum powder users	-0.03 (-0.05, 0.00)	0.01 (-0.08, 0.09)
West vs. South (ref)	Beauty A (ref)	Infrequent users	1	1
	Beauty B	Moderate users	-0.07 (-0.09, -0.05)	0.01 (-0.06, 0.07)
	Beauty C	Frequent users	-0.10 (-0.11, -0.08)	0.02 (-0.06, 0.10)
West vs. South (ref)	Hair A (ref)	Infrequent users of hair spray	1	1
	Hair B	Users of pomade and hair straightener	-0.01 (-0.02, -0.01)	-0.03 (-0.09, 0.02)
	Hair C	Frequent users of hair spray/hair gel	-0.06 (-0.07, -0.05)	-0.02 (-0.09, 0.06)
West vs. South (ref)	Skin A (ref)	Infrequent users	1	1
	Skin B	Moderate users	0.03 (0.01, 0.04)	0.03 (0.01, 0.04)
	Skin C	Frequent users	-0.02 (-0.05, 0.00)	0.05 (-0.06, 0.16)
	Skin D	Talcum powder users	-0.05 (-0.08, -0.03)	0.05 (-0.06, 0.16)

Table A.7. Age-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between individual personal care products and breast cancer risk by race

	White women		Black women	
	N(%)	HR (95% CIs)*	N(%)	HR (95% CIs)*
Beauty products				
Mascara				
Infrequent	9376 (23%)	1	1668 (41%)	1
Moderate	8312 (20%)	1.00 (0.78, 1.22)	1217 (30%)	1.01 (0.54, 1.94)
Frequent	23149 (57%)	1.07 (0.89, 1.28)	1218 (30%)	1.10 (0.59, 2.06)
Eyeshadow				
Infrequent	12621 (31%)	1	1609 (39%)	1
Moderate	18251 (44%)	1.02 (0.87, 1.22)	2121 (51%)	0.86 (0.50, 1.48)
Frequent	10224 (25%)	0.96 (0.78, 1.17)	407 (10%)	--
Eyeliner				
Infrequent	17523 (43%)	1	1962 (48%)	1
Moderate	13071 (32%)	1.07 (0.92, 1.3)	1553 (38%)	0.94 (0.53, 1.65)
Frequent	10368 (25%)	1.11 (0.94, 1.36)	590 (14%)	--
Lip Moisturizer				
Infrequent	5236 (13%)	1	678 (16%)	1
Moderate	12990 (32%)	1.06 (0.81, 1.29)	1184 (29%)	0.78 (0.36, 1.66)
Frequent	22812 (56%)	1.01 (0.77, 1.2)	2251 (55%)	0.87 (0.44, 1.72)
Lip Stick				
Infrequent	5244 (13%)	1	497 (12%)	1
Moderate	8321 (20%)	1.02 (0.79, 1.35)	941 (23%)	0.90 (0.33, 2.45)
Frequent	27450 (67%)	1.06 (0.82, 1.31)	2655 (65%)	1.17 (0.5, 2.77)
Foundation				
Infrequent	10892 (27%)	1	1340 (33%)	1
Moderate	15750 (38%)	1.14 (0.94, 1.36)	2023 (49%)	1.11 (0.61, 1.99)
Frequent	14310 (35%)	1.07 (0.88, 1.29)	742 (18%)	0.85 (0.37, 1.92)
Blush				
Infrequent	8835 (22%)	1	1750 (43%)	1
Moderate	17027 (42%)	1 (0.84, 1.24)	1906 (46%)	0.97 (0.55, 1.71)
Frequent	15133 (37%)	1.04 (0.87, 1.29)	455 (11%)	1.02 (0.44, 2.38)
Makeup remover				
Infrequent	24639 (61%)	1	2579 (63%)	1
Moderate	10624 (26%)	1.11 (0.9, 1.26)	1232 (30%)	0.83 (0.45, 1.5)
Frequent	5420 (13%)	1.05 (0.85, 1.31)	270 (7%)	--
Nail polish				
Infrequent	7201 (17%)	1	349 (8%)	1
Moderate	16994 (41%)	0.97 (0.79, 1.19)	1668 (41%)	1.08 (0.42, 2.75)

Frequent	17305 (42%)	0.96 (0.79, 1.19)	2099 (51%)	0.87 (0.34, 2.2)
Nail polish remover				
Infrequent	7757 (19%)	1	399 (10%)	1
Moderate	17821 (43%)	0.99 (0.82, 1.22)	1717 (42%)	0.73 (0.33, 1.61)
Frequent	15947 (38%)	1.01 (0.82, 1.23)	1995 (49%)	0.63 (0.29, 1.4)
Artificial nails				
Infrequent	35014 (86%)	1	3064 (75%)	1
Moderate	1873 (5%)	1.13 (0.75, 1.5)	475 (12%)	--
Frequent	3811 (9%)	1.08 (0.85, 1.39)	562 (14%)	0.89 (0.4, 1.97)
Artificial nails (other)				
Infrequent	39412 (99%)	1	3919 (96%)	1
Moderate	215 (0.5%)	1.61 (0.62, 3.62)	98 (2%)	--
Frequent	122 (0.3%)	0.85 (0.21, 3.96)	47 (1%)	--
Perfume				
Infrequent	8492 (21%)	1	377 (9%)	1
Moderate	14120 (34%)	1.01 (0.84, 1.26)	1119 (27%)	1.14 (0.42, 3.09)
Frequent	18493 (45%)	1.02 (0.86, 1.27)	2618 (64%)	1.10 (0.43, 2.82)
Cuticle cream				
Infrequent	21509 (53%)	1	1547 (38%)	1
Moderate	12541 (31%)	1.11 (0.94, 1.31)	1557 (38%)	1.02 (0.57, 1.81)
Frequent	6854 (17%)	1.07 (0.87, 1.31)	996 (24%)	0.70 (0.34, 1.44)
Hair products				
Shampoo				
Infrequent	1188 (3%)	1	2945 (72%)	1
Moderate	21751 (54%)	1.12 (0.67, 1.58)	1031 (25%)	1.05 (0.57, 1.9)
Frequent	17525 (43%)	1.22 (0.73, 1.76)	119 (3%)	--
Conditioner				
Infrequent	8350 (21%)	1	450 (11%)	
Moderate	4022 (10%)	0.95 (0.71, 1.24)	2562 (63%)	1.24 (0.5, 3.08)
Frequent	28245 (70%)	0.97 (0.79, 1.13)	1081 (26%)	1.16 (0.43, 3.14)
Hair spray				
Infrequent	10449 (25%)	1	1755 (43%)	1
Moderate	10099 (25%)	1.07 (0.87, 1.3)	1806 (44%)	0.99 (0.57, 1.72)
Frequent	20561 (50%)	0.94 (0.79, 1.13)	553 (13%)	--
Hair gel				
Infrequent	9420 (23%)	1	1738 (42%)	1
Moderate	10615 (26%)	1.07 (0.83, 1.25)	1696 (41%)	1.08 (0.62, 1.89)
Frequent	20717 (51%)	1.07 (0.88, 1.27)	671 (16%)	0.75 (0.32, 1.72)
Pomade				
Infrequent	36510 (91%)	1	1139 (28%)	1
Moderate	2022 (5%)	0.97 (0.7, 1.4)	1816 (44%)	0.91 (0.48, 1.73)

Frequent	1411 (4%)	0.89 (0.63, 1.46)	1158 (28%)	1.08 (0.55, 2.13)
Permanent hair dye				
Infrequent	17898 (48%)	1	21461 (49%)	1
Moderate	9425 (26%)	1.06 (0.86, 1.27)	11518 (26%)	1.31 (0.71, 2.42)
Frequent	9633 (26%)	1.09 (0.86, 1.26)	10781 (25%)	1.97 (0.92, 4.2)
Semi-permanent hair dye				
Infrequent	33792 (84%)	1	2645 (67%)	1
Moderate	2538 (6%)	1.02 (0.74, 1.37)	560 (14%)	1.46 (0.72, 2.98)
Frequent	3681 (9%)	0.85 (0.63, 1.1)	717 (18%)	1.01 (0.49, 2.09)
Hair highlighter				
Infrequent	27156 (67%)	1	3689 (91%)	1
Moderate	5791 (14%)	1.05 (0.81, 1.26)	302 (7%)	--
Frequent	7765 (19%)	1.04 (0.86, 1.26)	82 (2%)	--
Hair straightener				
Infrequent	38806 (98%)	1	1045 (29%)	1
Moderate	718 (2%)	1.03 (0.59, 1.92)	1189 (33%)	1 (0.48, 2.06)
Frequent	84 (0%)	--	1345 (38%)	1.15 (0.57, 2.33)
Hair straightener (other)				
Infrequent	39518 (99%)	1	3156 (79%)	1
Moderate	224 (0.6%)	--	475 (12%)	1.35 (0.62, 2.91)
Frequent	70 (0.2%)	--	342 (9%)	--
Hair color rinse				
Infrequent	38324 (95%)	1	2929 (75%)	1
Moderate	1181 (3%)	--	465 (12%)	--
Frequent	846 (2%)	--	500 (13%)	--
Hair food				
Infrequent	39221 (98%)	1	2610 (64%)	1
Moderate	297 (1%)	0.7 (0.35, 2.18)	755 (18%)	1.23 (0.64, 2.34)
Frequent	252 (1%)	0.74 (0.28, 2.25)	745 (18%)	0.75 (0.35, 1.63)
Hair bleach				
Infrequent	35201 (88%)	1	3846 (95%)	1
Moderate	1851 (5%)	0.93 (0.69, 1.42)	146 (4%)	--
Frequent	3000 (7%)	1.02 (0.71, 1.27)	54 (1%)	--
Hair perm				
Infrequent	36128 (87%)	1	3120 (78%)	1
Moderate	2885 (7%)	0.91 (0.7, 1.24)	220 (5%)	--
Frequent	2435 (6%)	0.92 (0.71, 1.29)	664 (17%)	1.3 (0.68, 2.49)
Rogaine				
Infrequent	39066 (98%)	1	3960 (97%)	1
Moderate	106 (0.3%)	--	25 (1%)	--

Frequent	532 (1%)	0.87 (0.54, 1.88)	78 (2%)	--
Skincare products				
Cleansing cream				
Infrequent	21018 (51%)	1	1688 (41%)	1
Moderate	6738 (16%)	1.07 (0.86, 1.29)	995 (24%)	0.76 (0.37, 1.52)
Frequent	13185 (32%)	0.96 (0.78, 1.1)	1439 (35%)	1.01 (0.56, 1.81)
Blemish				
Infrequent	31716 (77%)	1	3002 (73%)	1
Moderate	4256 (10%)	1.10 (0.89, 1.44)	406 (10%)	--
Frequent	5147 (13%)	1.24 (0.97, 1.51)	699 (17%)	1.04 (0.5, 2.15)
Face cream				
Infrequent	5168 (13%)	1	938 (23%)	1
Moderate	8283 (20%)	1.06 (0.8, 1.34)	1220 (29%)	0.86 (0.4, 1.82)
Frequent	27885 (67%)	1.05 (0.79, 1.22)	1980 (48%)	1.04 (0.54, 1.99)
Face mask				
Infrequent	26043 (63%)	1	2372 (58%)	
Moderate	11789 (29%)	1.08 (0.91, 1.26)	1156 (28%)	0.91 (0.5, 1.66)
Frequent	3340 (8%)	1.08 (0.78, 1.36)	588 (14%)	1 (0.47, 2.13)
Shaving cream				
Infrequent	22273 (55%)	1	2408 (59%)	1
Moderate	5724 (14%)	1.00 (0.80, 1.24)	794 (19%)	1 (0.51, 1.97)
Frequent	12871 (31%)	1.00 (0.84, 1.17)	886 (22%)	0.94 (0.46, 1.88)
Anti-aging cream				
Infrequent	17038 (42%)	1	2669 (65%)	1
Moderate	7542 (19%)	1.00 (0.82, 1.24)	671 (16%)	0.84 (0.39, 1.8)
Frequent	16151 (40%)	1.08 (0.9, 1.24)	771 (19%)	1.09 (0.57, 2.07)
Age spot remover				
Infrequent	35111 (87%)	1	3465 (84%)	1.00 (0.43, 2.07)
Moderate	4174 (10%)	0.95 (0.78, 1.27)	526 (13%)	0.94 (0.09, 4.05)
Frequent	910 (2%)	0.67 (0.38, 1.23)	117 (3%)	--
Self-tanner				
Infrequent	28688 (70%)	1	3940 (96%)	1
Moderate	6762 (17%)	0.98 (0.8, 1.2)	90 (2%)	--
Frequent	5363 (13%)	0.91 (0.72, 1.14)	62 (2%)	--
Baby oil				
Infrequent	31752 (77%)	1	1715 (42%)	1
Moderate	6796 (17%)	1.02 (0.85, 1.26)	1387 (34%)	0.62 (0.33, 1.17)
Frequent	2623 (6%)	0.84 (0.59, 1.13)	1019 (25%)	0.79 (0.41, 1.5)
Petroleum Jelly				
Infrequent	28273 (69%)	1	1392 (34%)	1
Moderate	8465 (21%)	0.93 (0.76, 1.11)	1465 (36%)	1.12 (0.60, 2.10)

Frequent	4345 (11%)	1.00 (0.8, 1.26)	1269 (31%)	1.15 (0.61, 2.18)
Body lotion				
Infrequent	4679 (12%)	1	259 (6%)	1
Moderate	16445 (40%)	1.03 (0.77, 1.23)	1125 (27%)	0.80 (0.30, 2.10)
Frequent	19522 (48%)	0.96 (0.73, 1.15)	2718 (66%)	0.63 (0.25, 1.57)
Hand lotion				
Infrequent	7016 (17%)	1	371 (9%)	1
Moderate	11838 (29%)	0.99 (0.78, 1.2)	929 (23%)	0.64 (0.25, 1.63)
Frequent	22109 (54%)	0.90 (0.73, 1.08)	2808 (68%)	0.64 (0.29, 1.44)
Foot cream				
Infrequent	12034 (30%)	1	680 (17%)	1
Moderate	16837 (41%)	1.02 (0.85, 1.2)	1351 (33%)	0.89 (0.42, 1.86)
Frequent	11893 (29%)	0.89 (0.74, 1.08)	2082 (51%)	0.75 (0.37, 1.51)
Deodorant				
Infrequent	3347 (8%)	1	134 (3%)	1
Moderate	4406 (11%)	1.02 (0.67, 1.33)	354 (9%)	--
Frequent	33720 (81%)	1.15 (0.82, 1.41)	3651 (88%)	1.44 (0.27, 7.67)
Infrequent	34014 (84%)	1	3430 (83%)	1
Talcum underarms				
Moderate	3074 (8%)	0.87 (0.69, 1.22)	354 (9%)	--
Frequent	3496 (9%)	0.81 (0.65, 1.12)	333 (8%)	--
Talcum other				
Infrequent	25798 (63%)	1	2541 (62%)	1
Moderate	7107 (17%)	0.97 (0.81, 1.2)	614 (15%)	0.79 (0.37, 1.7)
Frequent	8086 (20%)	0.91 (0.77, 1.12)	969 (24%)	0.73 (0.37, 1.41)
Talcum vaginal				
Infrequent	34746 (86%)	1	3318 (81%)	1
Moderate	2618 (6%)	0.87 (0.59, 1.13)	280 (7%)	--
Frequent	3158 (8%)	0.93 (0.76, 1.31)	522 (13%)	0.93 (0.42, 2.06)
Bath gel				
Infrequent	12111 (30%)	1	483 (12%)	1
Moderate	12304 (30%)	1.11 (0.9, 1.31)	1158 (28%)	1.27 (0.51, 3.16)
Frequent	16551 (40%)	1.07 (0.85, 1.21)	2464 (60%)	1.12 (0.48, 2.63)
Skin lightener				
Infrequent	38467 (96%)	1	3400 (83%)	1
Moderate	524 (1%)	1.24 (0.79, 1.27)	221 (5%)	--
Frequent	922 (2%)	0.94 (0.56, 1.58)	476 (12%)	--

*Confidence intervals adjusted for Bonferroni criteria (p-value<0.001)

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