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ORIGINAL ARTICLE

Use of hair products in relation to ovarian cancer risk

Alexandra J.White[1,*], Dale P.Sandler[1], Symielle A.Gaston[1], Chandra L.Jackson[1,2] and Katie M.O'Brien[1]

[1]Epidemiology Branch, National Institute of Environmental Health Sciences, Durham, NC, USA and [2]Intramural Program, Department of Health and Human Services, National Institute on Minority Health and Health Disparities, National Institutes of Health, Bethesda, MD, USA

*To whom correspondence should be addressed. Tel: 984-287-3713; Fax: 301-480-3290; E-mail: alexandra.white@nih.gov

Abstract

We evaluated whether hair products, which may contain carcinogens and endocrine disruptors that can be absorbed into the bloodstream, are related to ovarian cancer incidence in a prospective cohort. After excluding women with a history of ovarian cancer or bilateral oophorectomy, 40 559 Sister Study participants ages 35–74 at enrollment (2003–2009) were included. Participants completed questionnaires on hair product use, including hair dyes, straighteners/relaxers and permanents/body waves, in the past 12 months. Cox regression was used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between hair products and incident ovarian cancer. We assessed associations stratified by tumor type (serous, non-serous). Over a mean follow-up of 10 years, 241 women were diagnosed with ovarian cancer. Ever use of any of the examined hair products during the past year was not associated with ovarian cancer risk. However, frequent use (>4 times/year) of straighteners/relaxers or pressing products in the past year was associated with an increased risk of ovarian cancer (HR = 2.19, 95% CI: 1.12–4.27). Ever use of permanent hair dye was positively associated with non-serous (HR = 1.94, 95% CI 1.12–3.37), but inversely associated with serous (HR = 0.65, 95% CI: 0.43–0.99) tumors (p-for-heterogeneity = 0.002). Our novel findings suggest that frequent use of hair straighteners/relaxers or pressing products, which are primarily used by African American/Black women, and possibly permanent hair dye, may be associated with the occurrence of ovarian cancers.

Introduction

It is estimated that over 21 000 women in the USA will have been diagnosed with ovarian cancer in 2020 (1). Ovarian cancer is responsible for more deaths among US women than any other reproductive cancer (1). Ovarian cancers are hypothesized to have a hormonally driven etiology, however little is known about how exposure to endocrine disruptors may be related to ovarian cancer risk. Studies have supported a potential association between personal care products, including douching products and the application of powder (talc) to the genital area, which can include endocrine disrupting compounds, in relation to ovarian cancer risk (2,3). Widely used chemical hair products are another possibly important source of exposure to carcinogens and endocrine disruptors (4).

Use of chemical hair products is extremely common, with over 50% of women in the USA and Europe, for instance, reporting use of hair dye (5). Recent findings from the Nurses' Health Study observed a 15–20% higher risk of ovarian cancer associated with using permanent hair dye more than 100 times (6). Other studies evaluating the risk of ovarian cancer associated with hair products have been limited (7,8) and have focused on hair dye exposure without consideration of other commonly used hair products such as straighteners/relaxers that are predominately used by African American women. In the Sister Study, we previously observed that both adolescent and adult use of hair products, in particular straighteners/relaxers or pressing products, was associated with a higher risk of developing breast cancer (9,10). In addition to containing endocrine disrupting compounds, (4,11) certain formulations of straighteners release the carcinogen formaldehyde when heated (12).

The aim of this study was to evaluate the association between use of specific hair products during adulthood in relation to incident ovarian cancer in a large prospective cohort of

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Abbreviations

BMI	body mass index
CIs	confidence intervals
HRs	hazard ratios

US women. We hypothesized that women who frequently used these products would have a higher risk of developing ovarian cancer.

Methods

Study population

The Sister Study is a nationwide prospective cohort of 50 884 US women, which was designed to investigate environmental and lifestyle risk factors for cancer (13). Study participants were enrolled between 2003 and 2009. Women were eligible if they were ages 35–74 years, resided in the USA (including Puerto Rico), and had no history of breast cancer themselves, but had a sister who had been diagnosed with breast cancer. At baseline, participants completed structured questionnaires, providing information on their demographics, reproductive history, and lifestyle factors, including personal care product use. A trained examiner measured height and weight at a home visit.

The Sister Study contacts all participants annually for updates including new diagnoses of cancer. Participants are asked to complete detailed follow-up questionnaires every 3 years to update risk factor information and to report health changes. Response rates have remained approximately 90% throughout follow-up. This report includes follow-up through 23 September 2018 (Data Release 8.1). Informed consent was obtained from all participants. The Sister Study was approved by the institutional review board of the National Institute of Health.

We excluded any women who withdrew from the study (n = 3), who self-reported a diagnosis with ovarian cancer prior to enrollment (n = 201), had uncertain timing of diagnosis relative to baseline (n = 39), were missing data for all questions about hair product use (n = 977), had a history of bilateral oophorectomy (with or without hysterectomy) (n = 8909), or who did not contribute any follow-up time (n = 196). This left 40 559 eligible women.

Outcome assessment

Cases were defined as women who self-reported a diagnosis of incident ovarian, fallopian tube, or peritoneal cancer (n = 241). This number includes 12 deceased women with a next-of-kin report of incident ovarian cancer diagnosis. Beginning several years after enrollment, women who reported ovarian cancer were asked to release their medical records. This delay meant that some incident cases were deceased when we began this effort. Thus, cases were also considered confirmed if a National Death Index search indicated ovarian cancer as a primary cause of death. In total, medical (or death certificate) confirmation was available for 185 cases (77% of all self-reported). Agreement between self-report and medical records was 80%. When medical records data were not available, we used self-reported data. We conducted a sensitivity analysis limiting to ovarian cancer cases that were confirmed by medical record. Among those with medical record confirmation, we evaluated whether associations varied by whether the tumor was considered serous or non-serous (14).

Exposure assessment

At enrollment, study participants completed an extensive personal care product written questionnaire that included information on hair dye and other hair products used in the previous 12 months. Specifically, women were asked questions about their frequency of use of permanent, semi-permanent, and temporary hair dyes, bleach, highlights, hair straighteners/relaxers or pressing products (hereafter referred to as straighteners), hair permanents or body waves (hereafter referred to as perms) (did not use, 1–2 times a year, every 3–4 months, every 5–8 weeks, once a month, >once a month). For permanent and semi-permanent hair dyes they were further asked about colors of hair dye used (dark or light), and total lifetime years of use (did not use, less than 5 years, 5–9 years, 10+ years). We considered a dichotomous variable for use in the past 12 months (ever, never). For the most used products (permanent and semi-permanent dye, straighteners, perms), we considered a collapsed frequency variable (never, ≤4 times/year, >4 times/year). Duration of use of permanent and semi-permanent dyes was collapsed (did not use, <10 years, 10+ years).

Covariate assessment

Demographic and lifestyle factors were assessed as part of the enrollment questionnaires including self-identified race and ethnicity, educational attainment, smoking history, alcohol consumption, reproductive history (age at menarche, parity, oral contraceptive use, hormone therapy use, menopausal status), and history of medical procedures (hysterectomy, oophorectomy, tubal ligation). Body mass index (BMI) (kg/m^2) was calculated from measured height and weight obtained at the baseline home visit.

Statistical analysis

All statistical models were adjusted for an *a priori* list of potential confounders including race/ethnicity (non-Hispanic white, African American/Black including Hispanic/Latina, Hispanic/Latina non-Black, other), educational attainment (high school or less, some college, bachelor's degree, graduate degree), BMI (continuous), age at menarche (continuous), menopausal status (pre, post), parity (nulliparous, 1 birth, 2 births, >2 births), oral contraceptive use duration (none, <5 years, ≥ 5 years), hormone therapy use (none, estrogen alone, estrogen plus progestin), hysterectomy status (yes, no), tubal ligation status (yes, no), smoking status (never, former, current), and alcohol use (never or former, current <1 drink/day, current >1 drink/day).

To evaluate the association between hair product use and ovarian cancer risk we used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% CIs. The time scale for the Cox model was age and women were followed from age at enrollment until age at ovarian cancer diagnosis with censoring at age of bilateral oophorectomy, loss to follow-up, or the end of follow-up. The proportional hazards assumption was evaluated using a Wald test of hair product-by-time interaction term(s). For the associations with frequency of use variables, we estimated a p-for-trend using a chi-square test for an ordinal characterization of the exposure variable.

We considered whether associations for these hair products varied by whether the tumor was serous or non-serous. Here, we calculated heterogeneity P-values using Wald tests of subtype-by-hair-product interaction terms from a joint Cox proportional hazards model (15). As an exploratory analysis, we estimated HRs for non-Hispanic White and African American/Black women separately, comparing estimates via Wald tests of race-by-hair-product interaction terms. We did not estimate associations among women who were classified as non-Black Hispanic/Latina or other race/ethnicity due to limited sample size.

In sensitivity analyses, we evaluated whether the observed associations were similar when we limited the analysis to the ovarian cancers that were medically confirmed. These analyses were limited to the more frequently used hair products (permanent and semi-permanent dyes, straighteners, hair perms) due to sample size limitations. To address the possibility of misclassification of straightener and perm use due to interchangeable use of the terms within the African American/Black community, we also conducted a sensitivity analysis considering use of either of those products.

Results

With an average of 10 years of follow-up, 241 women were diagnosed with ovarian cancer. On average, at baseline, women who went on to develop ovarian cancer were older, more likely to be non-Hispanic White, have lower education attainment, and a higher BMI than women in the full cohort (Table 1). In addition, women with ovarian cancer were more likely to be postmenopausal, have used hormone therapy and to have undergone a hysterectomy (with retention of one or both ovaries) compared to the full cohort.

Overall, we observed little to no increase in risk of ovarian cancer associated with ever use in the past 12 months of most

Table 1. Baseline characteristics of Sister Study participants (2003–2009)[a]

	Full cohort	Ovarian cancer cases
	(*N* = 40 559)	(*N* = 241)
Age; Mean (std)	54.9 (9.0)	57.6 (8.6)
Follow-up time; Mean (std)	10.2 (2.7)	5.7 (3.4)
Age at menarche; Mean (std)	12.7 (1.5)	12.7 (1.5)
Race/ethnicity; *N* (%)		
Non-Hispanic White	34 044 (84)	209 (87)
African American/Black	3418 (8)	22 (9)
Hispanic/Latina non-Black	1847 (5)	8 (2)
Other	1247 (3)	4 (2)
Educational attainment; *N* (%)		
High school or less	5873 (14)	44 (18)
Some college	13 190 (33)	86 (36)
Bachelor's degree	11 330 (28)	63 (26)
Graduate degree	10 160 (25)	48 (20)
Body mass index (BMI); *N* (%)		
<25.0 kg/m^2	16 519 (41)	81 (34)
25–<30 kg/m^2	12 654 (31)	75 (31)
≥30 kg/m^2	11 375 (28)	85 (35)
Postmenopausal; *N* (%)	24 113 (59)	164 (68)
Parity; *N* (%)		
Nulliparous	7506 (19)	50 (21)
1 birth	5843 (14)	35 (15)
2 births	14 981 (37)	83 (35)
>2 births	12 203 (30)	72 (30)
Oral contraception use; *N* (%)		
None	5798 (14)	37 (15)
<5 years	13 611 (34)	97 (40)
≥5 years	20 936 (52)	106 (44)
Hormone therapy use; *N* (%)		
None	26 495 (66)	125 (52)
Estrogen alone	4447 (11)	50 (21)
Estrogen plus Progestin	9509 (24)	66 (27)
Hysterectomy; *N* (%)	6841 (17)	64 (27)
Tubal ligation; *N* (%)	11 663 (29)	61 (25)
Smoking status; *N* (%)		
Never	22 996 (57)	125 (52)
Former	14 306 (35)	99 (41)
Current	3248 (8)	17 (7)
Alcohol use; *N* (%)		
Never or former	7204 (18)	55 (23)
Current, <1 drink/day	27 638 (68)	161 (67)
Current ≥1 drink/day	5652 (14)	25 (10)

[a]Excluding those with pre-baseline breast or ovarian cancer, pre-baseline bilateral oophorectomy, inconsistent information on ovarian cancer diagnosis or age at diagnosis, or if did not complete the survey about use of personal care products.
Missing: race/ethnicity (3 overall), childhood socioeconomic status (87 overall), education (6 overall), relative weight age 10 (121 overall, 1 case), parity (26 overall, 1 case), hormonal contraceptive use (214 overall, 1 case), hormone therapy (108 overall), hysterectomy (23 overall), tubal ligation (16 overall), smoking (9 overall), alcohol (65 overall).

hair products. This included permanent, semi-permanent and temporary dyes, bleach, highlights, and perms (Table 2). We did observe an imprecise but positive association between ever use of straighteners and incident ovarian cancer (HR = 1.29, 95% CI: 0.70–2.38).

We found little evidence that more frequent use of permanent hair dye in the previous 12 months was associated with a higher risk of ovarian cancer compared to never use (>4 times/year, HR = 1.07, 95% CI: 0.79–1.45, *p*-for-trend = 0.64) (Table 3). Similarly, HRs were similar for light (HR = 0.95, 95% CI: 0.71–1.27) and dark (HR = 1.09, 95% CI: 0.82–1.45) permanent hair dyes. For semi-permanent hair dye, frequent use (>4 times/year) was possibly associated with higher ovarian cancer risk, when compared to never use (HR = 1.33, 95% CI:0.87–2.04), with little evidence of a dose–response trend (*p*-for-trend = 0.23) or for differences by dye color.

Notably, frequent use (>4 times/year) of straighteners was strongly associated with ovarian cancer, compared to never use (HR = 2.19, 95% CI: 1.12–4.27; *p*-for-trend = 0.03). Frequent use of perms was rare (*N* = 6 exposed cases), but also corresponded to a possible elevation in risk compared to never use (*N* = 1.77, 95% CI: 0.75–4.19; *p*-for-trend = 0.53).

Overall, findings were similar when we limited to the ovarian cancer cases that were confirmed by medical record (Supplemental Table 1, available at *Carcinogenesis* Online). When we considered whether the associations varied by serous versus non-serous ovarian tumors, we observed that ever use in the past 12 months of permanent hair dye was positively associated with non-serous ovarian cancer (HR = 1.94, 95% CI: 1.12–3.37) but inversely associated with serous tumors (HR = 0.65, 95% CI: 0.43–0.99) (*p*-for-heterogeneity = 0.002) (Table 4). The positive association between frequent use of straighteners and ovarian cancer may be limited to non-serous ovarian cancer (HR = 4.35, 95% CI: 1.10–17.2) rather than serous tumors (HR = 1.13, 95% CI: 0.49–2.57) (*p*-for-heterogeneity = 0.25). Associations for semi-permanent hair dye and perms did not substantially vary by serous versus non-serous tumor status.

The associations estimated for ever or frequent use of hair products tended to be higher for African American/Black women than for non-Hispanic White women (Table 5). Specifically, among African American/Black women, HR were elevated for frequent use of semi-permanent hair dye (e.g. frequent vs. never semi-permanent hair dye, HR = 3.06, 96% CI: 1.08–8.63), and ever use of straighteners (HR = 1.28, 95% CI: 0.46–3.52) or perms (HR = 1.80, 95% CI: 0.74–4.36). Estimates for combined use of either straighteners or perms were imprecise but elevated among African American/Black women (Supplemental Table 2, available at *Carcinogenesis* Online). In general, we had limited power to detect differences by race/ethnicity as part of this exploratory analysis, and the confidence intervals were overlapping.

Discussion

In this large prospective cohort of US women, we report the findings from a novel investigation into the role of a range of hair products and ovarian cancer incidence. In this first study to consider the impact of straighteners/relaxers on ovarian cancer risk, we observed that frequent adult use of straighteners/relaxers or pressing products was associated with approximately twice the risk of developing ovarian cancer. Although we saw little consistent evidence to suggest hair dye, including permanent, semi-permanent or temporary dye, was associated with ovarian cancer overall, we did observe opposite associations between permanent hair dye use and non-serous versus serous ovarian tumors. These findings are relevant for public health due to the widespread use of hair products and the lack of established modifiable risk factors for ovarian cancer.

Products that are used to straighten or relax hair texture have been found to contain a range of endocrine disrupting compounds that are potentially of concern, including phthalates, parabens, cyclosiloxanes, and metals, in addition to formaldehyde (4,11,12). Both hair dyes and hair perm/waving

Table 2. Associations between ever use of hair products in the 12 months prior to baseline and incident invasive ovarian cancer in the Sister Study

	Person-time[a]	Non-cases; *n* = 39 648 N (%)[a]	Ovarian cancer cases; *n* = 238 N (%)[a]	Age-adjusted hazard ratio (95% CI)	Age and race/ethnicity-adjusted hazard ratio (95% CI)	Multivariable adjusted hazard ratio (95% CI)[b]
Permanent hair dye						
Never	181 362	17 548 (44)	108 (46)	1.00	1.00	1.00
Ever	222 792	21 892 (56)	129 (54)	1.04 (0.80, 1.34)	1.06 (0.82, 1.38)	1.07 (0.82, 1.39)
Semi-permanent hair dye						
Never	324 911	31 669 (80)	185 (79)	1.00	1.00	1.00
Ever	78 968	7745 (20)	50 (21)	1.17 (0.85, 1.60)	1.16 (0.85, 1.59)	1.17 (0.85, 1.60)
Temporary hair dye						
Never	370 448	36 088 (92)	219 (93)	1.00	1.00	1.00
Ever	33 481	3331 (8)	16 (7)	0.80 (0.48, 1.33)	0.76 (0.45, 1.28)	0.75 (0.45, 1.26)
Bleach						
Never	356 936	34 780 (88)	210 (89)	1.00	1.00	1.00
Ever	46 646	4608 (12)	25 (11)	0.94 (0.62, 1.42)	0.95 (0.63, 1.44)	0.92 (0.61, 1.40)
Highlights						
Never	276 382	26 996 (68)	166 (70)	1.00	1.00	1.00
Ever	128 442	12 513 (32)	72 (30)	1.04 (0.79, 1.38)	1.07 (0.80, 1.42)	1.10 (0.82, 1.46)
Straightener/relaxers						
Never	369 104	35 713 (90)	213 (90)	1.00	1.00	1.00
Ever	35 463	3769 (10)	24 (10)	1.37 (0.89, 2.10)	1.26 (0.69, 2.30)	1.29 (0.70, 2.38)
Hair permanents/ body waves						
Never	354 978	34 649 (88)	200 (84)	1.00	1.00	1.00
Ever	49 461	4825 (12)	38 (16)	1.18 (0.83, 1.68)	1.15 (0.81, 1.65)	1.06 (0.74, 1.52)

Missing: permanent dye (203 non-cases, 1 case), semi-permanent dye (229 non-cases, 3 cases), temporary dye (224 non-cases, 3 cases), semi-permanent dye (229 non-cases, 3 cases), bleach (255 non-cases, 3 cases), highlights (134 non-cases), straighteners/relaxers adult (161 non-cases, 1 case), hair permanents/waves adult (169 non-cases).

[a]Among participants with complete covariate information.

[b]Hazard ratio compares ever versus never use and is adjusted for race/ethnicity, education, BMI, age at menarche, menopausal status, parity, oral contraceptive use, hormone therapy use, hysterectomy status, tubal ligation status, smoking, and alcohol use.

products have been found to contain aromatic amines, which are carcinogens capable of binding to DNA (16–18). Compounds arising from hair dye have been found to bind to DNA to form adducts in breast epithelial cells (16) suggesting that the chemicals from hair products can circulate throughout the body.

In our population, self-reported frequent adult use of hair straighteners was associated with a higher risk of ovarian cancer. This association was more pronounced for non-serous ovarian cancer, a heterogeneous group of histologic subtypes. Frequent use of straighteners has been previously associated with breast cancer risk, in both this study population as well as in others (9,10,19,20). To the best of our knowledge, there have been no previous studies considering how straighteners are associated with the incidence of ovarian cancer or any other cancer types aside from breast cancer.

Black women are much more likely to use products to straight or relax hair than non-Hispanic white women (21–23). Although Black women are less likely than other racial/ethnic groups to be diagnosed with ovarian cancer, they have disproportionately lower survival rates after diagnosis (24,25). Differences in personal care product use patterns, including more frequent use of straighteners, has been hypothesized to contribute to the higher body burden of endocrine disrupting compounds in non-Hispanic Black women compared to non-Hispanic white women (26–28). In our study, the estimated associations between frequent straightener/relaxer use and ovarian cancer risk did not appear to substantially differ by race/ethnicity. However, because ovarian cancer is rare, we had very limited power to detect any differences. Although the observed associations did not significantly vary by race/ethnicity, given the much higher prevalence of use of these products, the impact of these results is more relevant for African American/Black women (29). Future research is needed in larger and more diverse populations with greater representation of racial/ethnic minorities to evaluate how hair straighteners or other products used by particular racial/ethnic groups might contribute to ovarian cancer risk and survival.

Because our questionnaire focused on the use of permanent hair dye in the year prior to enrollment rather than estimating cumulative use of hair products our results are not directly comparable to those of a recent Nurses' Health Study publication, which concluded there was a 15–20% higher risk of ovarian cancer associated with >100 uses of permanent hair dye (6). Although we did not observe a higher risk for permanent hair dye with overall ovarian cancer, we did find that permanent dye use was associated with non-serous ovarian tumors. This may suggest etiologic heterogeneity by tumor type or simply be due to chance given the small case numbers available. The Nurses' Health Study did not consider histologic type so it is unclear whether these particular findings are consistent (6).

Our prospective study design eliminates the possibility of recall bias. However, there is possible recall error or misclassification, particularly by frequency of use or type of product used. We classified frequency of use in broad categories (≤4, >4 times/year) and focused on use in the past 12 months, which should minimize the impacts of these recall errors.

Table 3. Associations between hair product use frequency, dye color or duration, and incident invasive ovarian cancer in the Sister Study

	Person-time[a]	Non-cases; *n* = 39 648 *N* (%)[a]	Ovarian cancer cases; *n* = 238 *N* (%)[a]	Adjusted hazard ratio[b] (95% CI)
Permanent hair dye				
Frequency of use in 12 months prior to baseline				
Never	181 362	17 551 (44)	108 (46)	1.00
≤4 times/year	93 855	9242 (23)	53 (22)	1.06 (0.76, 1.48)
>4 times per year	128 938	12 652 (32)	7 (32)	1.07 (0.79, 1.45)
p-for-trend				0.64
Color used in the 12 months prior to baseline				
Never	181 362	17 551 (44)	108 (46)	1.00
Light colors[c]	20 345	11 743 (54)	68 (53)	0.95 (0.71, 1.27)
Dark colors[c]	31 465	12 158 (56)	72 (56)	1.09 (0.82, 1.45)
Duration of use, lifetime				
Never	145 914	14 099 (36)	91 (39)	1.00
0–<10 years	129 513	12 624 (32)	60 (26)	0.80 (0.58, 1.12)
≥10 years	127 856	12 638 (32)	84 (36)	1.06 (0.78, 1.43)
p-for-trend				0.75
Semi-permanent hair dye				
Frequency of use in 12 months prior to baseline				
Never	324 911	31 670 (80)	185 (79)	1.00
≤4 times/year	47 188	4657 (12)	26 (11)	1.05 (0.69, 1.59)
>4 times per year	31 779	3092 (8)	24 (10)	1.33 (0.87, 2.04)
p-for-trend				0.23
Color used in the 12 months prior to baseline				
Never	324 911	31 670 (80)	185 (79)	1.00
Light colors[c]	21 427	2838 (37)	13 (26)	0.72 (0.42, 1.23)
Dark colors[c]	29 393	5168 (67)	35 (70)	1.27 (0.88, 1.82)
Duration of use, lifetime				
Never	283 620	27 696 (70)	169 (73)	1.00
0–<10 years	89 434	8651 (22)	53 (22)	0.79 (0.56, 1.12)
≥10 years	30 197	3004 (8)	76 (32)	1.17 (0.76, 1.82)
p-for-trend				0.90
Straighteners/relaxers, frequency of use in 12 months prior to baseline				
Never	369 104	35 717 (90)	213 (90)	1.00
≤4 times/year	16 532	1780 (5)	4 (2)	0.50 (0.17, 1.44)
>4 times per year	18 931	1990 (5)	20 (8)	2.19 (1.12, 4.27)
p-for-trend				0.03
Hair permanents/body waves, frequency of use in 12 months prior to baseline				
Never	354 978	34 654 (88)	200 (84)	1.00
≤4 times/year	44 864	4345 (11)	32 (13)	0.98 (0.67, 1.44)
>4 times per year	4597	480 (1)	6 (3)	1.77 (0.75, 4.19)
p-for-trend				0.53

[a]Among participants with complete covariate information.
[b]Hazard ratio is adjusted for race/ethnicity, education, BMI, age at menarche, menopausal status, parity, oral contraceptive use, hormone therapy use, hysterectomy status, tubal ligation status, smoking, and alcohol use.
[c]Hair color is non-exclusive: participants could be both light and dark users. Percents of color users are calculated based on % of ever users who reported using that color, with some participants reporting using neither (126 non-case semi-permanent users; 3 case semi-permanent users; 201 non-case permanent users) and some missing data for color (37 non-case semi-permanent users; 68 non-case permanent users). In regression models we adjust for use of the opposing color.

A potential limitation is that our questionnaire asked about use of hair straighteners/relaxers or pressing products. Pressing hair is a more temporary method of hair straightening that uses a heated comb or flatiron. It can be done in combination with some type of hair product, although this would be distinct from products used for chemical straightening/relaxing of hair. Therefore, some women who are categorized as being exposed to straightening products may have used products that are less harsh than chemical straighteners/relaxers. Thus, the effect estimates reported here may underestimate the true association.

Ovarian cancer is a rare disease, and even with a large cohort of over 50 000 US women who may have enhanced risk for ovarian cancer because of their family history of breast cancer (30) and more than 10 years of follow-up, we had only 241 ovarian cancer cases. As such, we were unable to consider ovarian cancer histologic subtypes in more detail and instead only compared serous and non-serous tumors. Because the non-serous group includes clear cell, endometrioid, and mucinous carcinomas, as well as several other histologic types with potentially divergent etiologies, the subtype-stratified analyses are difficult to interpret.

An important strength of this study is that we had detailed information on frequency of adult use for many commonly used hair products. Previous studies have only considered exposure to permanent hair dye, whereas we were able to additionally consider straighteners/relaxers and perms/body waving products. Identifying more specific chemicals of concern remains an ongoing challenge. We did not ask about specific formulations,

Table 4. Associations between hair products used in the 12 months prior to baseline and incident invasive ovarian cancer by tumor type

	Medically confirmed ovarian cancer cases[a]	*N* (%) cases who are ever users	Ever vs. never	*N* (%) cases who are frequent users	Frequent vs. never	
			HR (95% CI)		HR (95% CI)	*p*-for-trend
Permanent hair dye						
Serous ovarian	95	41 (43)	0.65 (0.43, 0.99)	21 (22)	0.56 (0.33, 0.94)	0.02
Non-serous ovarian	59	40 (68)	1.94 (1.12, 3.37)	24 (41)	1.90 (1.03, 3.51)	0.002
p-heterogeneity[c]			*0.002*		*0.008*	
Semi-permanent hair dye						
Serous ovarian	95	23 (24)	1.49 (0.94, 2.38)	10 (11)	1.47 (0.76, 2.84)	0.12
Non-serous ovarian	57	9 (16)	0.83(0.41, 1.68)	6 (11)	1.32 (0.57, 3.06)	0.30
p-heterogeneity			*0.18*		*0.29*	
Straighteners/relaxers						
Serous ovarian	95	6 (6)	1.33 (0.68, 2.62)	4 (4)	1.13 (0.49, 2.57)	0.89
Non-serous ovarian	58	5 (9)	1.49 (0.42, 5.33)	4 (7)	4.35 (1.10, 17.2)	0.12
p-heterogeneity			*0.87*		*0.25*	
Hair permanents/ body waves						
Serous ovarian	95	16 (17)	1.18 (0.66, 2.09)	2 (2)	1.91 (0.49, 7.39)	0.49
Non-serous ovarian	59	5 (8)	0.50 (0.19, 1.31)	0 (0)	---[b]	
p-heterogeneity			*0.13*		---[b]	

Hazard ratio is adjusted for race/ethnicity, education, BMI, age at menarche, menopausal status, parity, oral contraceptive use, hormone therapy use, hysterectomy status, tubal ligation status, smoking, and alcohol use.

Note: 88 of 95 (93%) of serous cases were non-Hispanic white and 6 (6%) were African American/Black; 54 of 59 (92%) of non-serous cases were non-Hispanic white and 2 (3%) were African American/Black.

[a]29 medically confirmed cases are missing information about histotype.

[b]Not estimable as there were no non-serous ovarian cancer cases who reported frequently getting hair permanents/body waves.

[c]P-value for heterogeneity by tumor type calculated using Wald tests of subtype-by-hair-product interaction terms from a joint Cox proportional hazards model.

Table 5. Associations between hair products used in the 12 months prior to baseline and incident invasive ovarian cancer by race/ethnicity [33 545 non-Hispanic Whites (206 cases)], 3329 African Americans/Blacks [22 cases]

	N (%) cases who are ever users	*N* (%) non-cases who are ever users	Ever vs. never	*N* (%) cases who are frequent users	*N* (%) non-cases who are frequent users	Frequent vs. never	
			HR (95% CI)			HR (95% CI)	*p*-for-trend
Permanent hair dye							
Non-Hispanic White	116 (57)	18 545 (56)	1.14 (0.86, 1.52)	70 (34)	11 003 (33)	1.14 (0.83, 1.57)	0.39
African American/ Black	7 (32)	1382 (42)	0.63 (0.25, 1.55)	4 (18)	462 (14)	0.92 (0.30, 2.85)	0.57
p-heterogeneity[b]			*0.22*			*0.36*	
Semi-permanent hair dye							
Non-Hispanic White	35 (17)	5728 (17)	1.02 (0.71, 1.47)	16 (8)	2298 (7)	1.10 (0.66, 1.83)	0.81
African American/ Black	11 (52)	1178 (36)	2.05 (0.86, 4.88)	6 (29)	413 (13)	3.06 (1.08, 8.63)	004
p-heterogeneity			*0.15*			*0.22*	
Straighteners/relaxers							
Non-Hispanic White	4 (2)	1004 (3)	0.89 (0.33, 2.40)	3 (1)	416 (1)	1.55 (0.49, 4.86)	0.86
African American/ Black	17 (77)	2417 (74)	1.28 (0.46, 3.52)	14 (64)	1454 (44)	1.82 (0.64, 5.18)	0.15
p-heterogeneity			*0.59*			*0.94*	
Hair permanents/body waves							
Non-Hispanic White	30 (15)	3830 (12)	0.98 (0.65, 1.47)	0 (0)	128 (0)	---[a]	
African American/ Black	8 (36)	706 (22)	1.80 (0.74, 4.36)	6 (27)	333 (10)	2.97 (1.12, 7.88)	0.06
p-heterogeneity			*0.21*			---[a]	

Hazard ratio compares and is adjusted for education, BMI, age at menarche, menopausal status, parity, oral contraceptive use, hormone therapy use, hysterectomy status, tubal ligation status, smoking, and alcohol use.

Missing data: permanent hair dye (1 non-Hispanic White case, 146 non-Hispanic White non-cases, 31 African American/Black non-cases); semi-permanent hair dye (2 non-Hispanic White cases, 164 non-Hispanic White non-cases, 1 African American/Black case, 43 African American/Black non-cases); straighteners/relaxers (1 non-Hispanic White case, 100 non-Hispanic White non-case, 39 African American/Black non-cases); hair permanent/body wave (99 non-Hispanic White non-cases).

[a]Not estimable as there were no non-Hispanic white ovarian cancer cases who reported frequently getting hair permanents/body waves.

[b]P-value for heterogeneity by race/ethnicity calculated using Wald tests of subtype-by-hair-product interaction terms from a joint Cox proportional hazards model.

brands, or ingredients of products that were used and thus are unable to hypothesize about the effects of individual chemicals. However, even if we had collected this information, product labels may not accurately list all the chemicals within personal care products (4). Further, formulations change over time and those being used during the Sister Study enrollment period (2003–2009) may not be on the market now. For example, Brazilian keratin hair straightening/relaxing products were widely used the early 2000s, but these products have now largely been removed due to concerns regarding exposure to formaldehyde (12).

In this large US prospective cohort, we provide the first evidence of a possible relationship between frequent adult use of straightener/relaxers or pressing products and ovarian cancer risk. In addition, we observed that permanent hair dye use may be associated with ovarian cancer risk differentially by histologic type. Given the novelty of these findings, more research is needed to confirm our results and identify constituents of these products that may be driving risk. It is particularly important for future studies to be conducted in racially/ethnically diverse populations and inclusive of a wider variety of hair care products to help us better understand their role in determining ovarian cancer risk among US women.

Supplementary Material

Supplementary data are available at *Carcinogenesis* online.

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Data Availability

The data underlying this article is available upon reasonable request, as described https://sisterstudy.niehs.nih.gov/English/data-requests.htm

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