Personal use of permanent hair dyes and cancer risk and mortality in US women: prospective cohort study

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ABSTRACT

OBJECTIVE
To evaluate the associations between personal use of permanent hair dyes and cancer risk and mortality.

DESIGN
Prospective cohort study.

SETTING AND PARTICIPANTS
117 200 women enrolled in the Nurses’ Health Study, an ongoing prospective cohort study of female nurses in the United States. The women were free of cancer at baseline, reported information on personal use of permanent hair dyes, and were followed for 36 years.

EXPOSURE
Status, duration, frequency, and integral use (cumulative dose calculated from duration and frequency) of permanent hair dyes. Age at first use and time since first use of permanent hair dyes.

MAIN OUTCOME MEASURES
Associations of personal use of permanent hair dyes with risk of overall cancer and specific cancers, and cancer related death. Age and multivariable adjusted hazard ratios and 95% confidence intervals were estimated by using Cox proportional hazard models.

RESULTS
Ever users of permanent hair dyes had no significant increases in risk of solid cancers (n=20 805, excluding non-melanoma skin cancers; hazard ratio 0.98, 95% confidence interval 0.96 to 1.01) or hematopoietic cancers overall (n=1807; 1.00, 0.91 to 1.01) compared with non-users. Additionally, ever users did not have an increased risk of most specific cancers (cutaneous squamous cell carcinoma, bladder cancer, melanoma, estrogen receptor positive breast cancer, progestosterone receptor positive breast cancer, hormone receptor positive breast cancer, brain cancer, colorectal cancer, kidney cancer, lung cancer, and most of the major subclasses and histological subtypes of hematopoietic cancer) or cancer related death (n=4860; 0.96, 0.91 to 1.02). Basal cell carcinoma risk was slightly increased for ever users (n=22 560; 1.05, 1.02 to 1.08). Cumulative dose was positively associated with risk of estrogen receptor negative breast cancer, progestosterone receptor negative breast cancer, hormone receptor negative breast cancer, and ovarian cancer. An increased risk of Hodgkin lymphoma was observed only for women with naturally dark hair (based on 70 women, 24 with dark hair), and a higher risk of basal cell carcinoma was observed for women with naturally light hair.

CONCLUSION
No positive association was found between personal use of permanent hair dye and risk of most cancers and cancer related mortality. The increased risk of basal cell carcinoma, breast cancer (estrogen receptor negative, progestosterone receptor negative, hormone receptor negative) and ovarian cancer, and the mixed findings in analyses stratified by natural hair color warrant further investigation.

Introduction
Use of hair dyes is prevalent in modern societies.1 2 In the United States and Europe, an estimated 50-80% of women and 10%-15% of men aged 40 and older use hair dye,1 and the prevalence of hair dye use has remained stable over the past decades.13-1 The World Health Organization’s International Agency for Research on Cancer and the US Food and Drug Administration have continuously monitored data on hair dye safety.13-5 Based on existing epidemiological evidence, animal bioassays, and mechanistic and other relevant data, the International Agency for Research on Cancer classified occupational exposure to hair dyes as a probable carcinogen (group 2A); however, the carcinogenicity resulting from personal use of hair dyes was not classifiable (group 3).1 Nonetheless, public concern remains about the carcinogenic potential of hair dyes.12 4-6 7

Modern hair dyes include oxidative (permanent) dye, direct (semi-permanent or temporary) dye, and natural dye.13 7 Among modern hair dyes, permanent hair dye has a market share of approximately 80% in the US and Europe, and even higher in Asia,1 3 and is the most aggressive and extensively used type that has posed the greatest potential concern.14 7 Permanent hair dye products typically consist of intermediates (para substituted aromatic amines) and couplers (meta...
substituted aromatic amines and other compounds),\textsuperscript{1,7} which can form pigment molecules through chemical reactions in the presence of oxidants.\textsuperscript{1,7} Personal use of permanent hair dyes results in dermal (the main route) and airborne routes of exposure to hair dye chemicals,\textsuperscript{1,7} and exposure to intermediates and couplers is much higher than that to the reaction product during the dyeing process.\textsuperscript{1} The National Toxicology Program led by US government agencies has classified some chemicals that are or were used in hair dyes as reasonably anticipated to be human carcinogens.\textsuperscript{8}

Monitoring the carcinogenic hazard to people from personal use of permanent hair dyes has major public health implications.\textsuperscript{1,5,7,9} However, owing to the limitations of published epidemiological studies, current evidence is far from conclusive.\textsuperscript{1,4,6,7,9-12} The Nurses’ Health Study\textsuperscript{13-16} has detailed assessments of permanent hair dye exposure\textsuperscript{17 18} and validated data on a wide spectrum of potential confounders and cancer outcomes.\textsuperscript{19-24} The study adds high quality human evidence to this field by performing a large prospective cohort study with over 117,000 eligible participants and a 36 year follow-up.

**Methods**

**Study population**

Details of the Nurses’ Health Study cohort have been described elsewhere.\textsuperscript{13-16} The study is an ongoing large prospective cohort study that started in 1976 and has enrolled 121,700 US female nurses aged 30-55 years. Self-administered questionnaires were sent to participants every two or four years (for diet related questions), and a response rate exceeding 90% was achieved for most follow-up cycles. The study protocol was approved by the institutional review board of the Brigham and Women's Hospital (Boston, MA), and those of participating registries as required. Informed consent from participants was implied when they completed and returned the questionnaires. We used 1976 as the baseline, which was when exposure was first assessed. We excluded participants who reported no information on exposure at all assessments, those with a diagnosis of any cancer at baseline, and those who had missing information on age. Our analysis consisted of 117,200 eligible participants.

**Personal use of permanent hair dyes**

The participants reported personal use of permanent hair dyes at baseline (1976), which included current or past use and duration, frequency, and age at first use, with updates every two years.\textsuperscript{17 18} Specifically, on the 1976 questionnaire, the participants reported whether they “had ever used a permanent hair dye (yes or no),” and whether they “have used permanent hair dyes for how many years (in years).” Participants were also asked “At what age did you first use a permanent hair dye? (in years of age)” in the same questionnaire. Additionally, in 1978, 1980, and 1982, the participants provided updated information on permanent hair dye use through questionnaires by answering the question “Do you use a permanent hair dye currently? (yes or no, not including temporary rinses)” and “How often do you currently use permanent hair dyes? (in every how many weeks).” Participants who reported ever use of permanent hair dyes in any of the assessments were classified as ever users, and all others as non-users. Duration of use was calculated using baseline and cumulatively updated assessments of lifetime hair dye use history. Frequency of use was calculated as the average reported at baseline and during regular updates thereafter. Time since first use was determined according to responses and age. To assess an integrated measure of cumulative dose of permanent hair dye use, we multiplied the average frequency of use (times per year) by duration of use (years).

**Cancers and cancer related deaths**

Physician diagnosed incident invasive (with the exception of non-melanoma skin carcinoma) cancers were self-reported every two years on the questionnaires and confirmed by review of medical records and pathology reports (obtained with permission) or by linkage to state cancer registries. More than 96% of deaths were confirmed through next of kin or postal authority reporting, and regular searches of the National Death Index.\textsuperscript{25-26} Investigators reviewed death certificates and medical records to classify the cause of death according to the international classification of diseases (eighth revision).

**Covariates**

We considered age, race, natural hair color, cumulative average body mass index, body mass index at age 18, smoking status, pack years of smoking, and alcohol intake as common confounders in analyses of all cancers. For more complete control of confounding, we also controlled for the following endpoint specific covariates in multivariable analyses of individual cancers and cancer death: physical activity, intake of total calories, total fluid, red or processed meat, fiber, folate, calcium and vitamin D, regular use of aspirin, non-aspirin nonsteroidal anti-inflammatory drugs, use of multivitamins, postmenopausal hormones and oral contraceptives, menopausal status, adolescent body size, age at menarche and first birth, parity, history of breastfeeding, current mammography use, screening colonoscopy or sigmoidoscopy in the previous two years, childhood reaction to sun, lifetime blistering sunburns, number of moles on arms, cumulative ultraviolet flux since baseline,\textsuperscript{27 28} history of hypertension, hypercholesterolemia, diabetes mellitus and breast disease, and family history of colorectal cancer and breast cancer. The validity and reproducibility of these covariates have been described previously.\textsuperscript{19 20-24} The table and supplementary table footnotes list all the covariates in the corresponding models.

Metabolic equivalent of task (MET) scores were assigned to each reported type of common recreational activity, and total physical activity was calculated in MET hours per week. Information on the potential confounding variables was updated throughout follow-
up, except for race, natural hair color, body mass index at age 18, age at menarche, age at first birth, history of breastfeeding, childhood reaction to sun, lifetime blistering sunburns and number of moles on arms. These variables were assessed once and assumed to remain mostly stable over time.

**Statistical analysis**

We calculated person years of follow-up from the date of return of the baseline questionnaire in 1976 until the date of any cancer diagnosis, death, loss to follow-up, or follow-up completion (30 June 2012), whichever was earliest. Age and multivariable adjusted hazard ratios and 95% confidence intervals for outcomes were estimated by using Cox proportional hazard regression models conditioning on age (in months) and questionnaire cycle for each category of a given personal permanent hair dye use characteristic: overall status of use (non-user, ever user); duration of use (non-user, <5 years, 5-9 years, ≥10 years); frequency of use (non-user, every ≥5 weeks, every 1-4 weeks); cumulative dose (non-user, 1-99 times, 100-199 times, ≥200 times); age at first use (non-user, <30 years, ≥30 years); and time since first use (non-user, <30 years, ≥30 years). We calculated P value for trend by using the mid-point values of the following categories: duration and frequency of use, cumulative dose, age at first use, and time since first use. Women who never used permanent hair dyes served as the reference group in most of the analyses, except for analyses of age at first use and time since first use.

To further investigate cumulative dose dependent associations between personal use of permanent hair dye and outcomes, we estimated hazard ratios and 95% confidence intervals for each 50 time increment in analyses among ever users, where the P value for trend was calculated by using the cumulative dose in times as a continuous variable. Dose-response relations were examined by using restricted cubic spline analysis. Tests for linear trend were performed by treating doses as continuous variables in models. We modeled exposures and all time varying covariates as time varying variables. Different sets of covariates were used for each type of cancer. We updated time varying covariates throughout follow-up to leverage the data updated every two years or every four years (for diet related data). To minimize missing information, when values were missing for variables that were repeatedly measured, we carried forward the values once from the most recent follow-up cycle. Additionally, we created missing indicators when necessary and included them in the models for the remaining covariates with missing values, an approach which has been applied in other studies using data from the Nurses’ Health Study.20-33

The outcomes included incident overall cancers and individual cancers, and cancer related deaths. We performed analyses for specific solid cancers, including basal cell carcinoma, cutaneous squamous cell carcinoma, bladder cancer, breast cancer (stratified by hormone receptor status: estrogen receptor and progesterone receptor), brain cancer, melanoma, colorectal cancer, ovarian cancer, kidney cancer, and lung cancer. Separate analyses were also conducted for major subclasses and histological subtypes of hematopoietic cancer, including overall non-Hodgkin lymphoma, overall T cell non-Hodgkin lymphoma (in aggregate), common histological types of B cell non-Hodgkin lymphoma (diffuse large B cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia or small lymphocytic lymphoma), multiple myeloma, Hodgkin lymphoma (in aggregate) and myeloid leukemias (also in aggregate). We conducted further analyses stratified by natural hair color (light—red, blond or light brown; or dark—black or dark brown) for all endpoints. Tests for interaction were performed by adding interaction terms to the models and using log likelihood ratio tests comparing nested models to determine statistical significance.

We considered a series of sensitivity analyses. Firstly we performed 6, 10, 16, and 20 year latency analyses (by assuming follow-up starts 6, 10, 16, and 20 years after assessments of exposures stopped in 1982) for overall cancer, basal cell carcinoma, breast cancer, and ovarian cancer. Secondly, to explore the potential timing of associations, we repeated analyses for these endpoints by restricting follow-up to the first 10 and 20 years after exposure assessments stopped. Given a proportion of participants (9.09%) who were never users at baseline reported their first time of hair dye use in subsequent assessment cycles (1978, 1980, and 1982), we also conducted analyses by using baseline exposure information only. Statistical analyses were conducted by using SAS software (version 9.4 for UNIX; SAS Institute, Cary, NC, USA). All tests were two sided and P values less than 0.05 were considered statistically significant.

**Patient and public involvement**

Participants were not involved in setting the research question or the outcome measures, nor were they involved in the design or implementation of the study. No participants were asked to advise on interpretation or writing up of the manuscript. The participants are updated on findings and developments of the Nurses’ Health Study cohort through annual newsletters and the official website (https://www.nurseshealthstudy.org).

**Results**

**Population characteristics**

During 36 years of follow-up, a total of 20805 solid cancers (not including major non-melanoma skin cancers), 1807 hematopoietic cancers, 22560 basal cell carcinomas, and 2792 cutaneous squamous cell carcinomas were reported. Additionally, 4860 cancer related deaths were documented. Women whose natural hair color was blond or light brown were more likely to use permanent hair dyes, and those whose natural hair color was dark brown, black, and red were less likely to use permanent hair dye. Ever users were more likely to be smokers and consumed more alcohol than those reporting no history of personal permanent
Hair dye use. We did not observe any other major variations across self-reported personal permanent hair dye use (table 1).

Personal use of permanent hair dyes and cancer risk
In multivariable analyses, we observed no significant association between status, duration, frequency, or cumulative dose and cancer mortality. Multivariable analyses showed no significant association between status, duration, frequency, or cumulative dose and cancer related death, and stratified by natural hair color. The spline analysis showed no statistically significant nonlinear relation between cumulative dose and cancer related death, and stratified by natural hair color. The results remained similar, although we observed a possible increased ovarian cancer risk with longer latency among women with naturally light hair (supplementary table 48). Assumptions of various latencies did not materially change the main findings for the aggregated and site specific cancer endpoints, except for a possible increased ovarian cancer risk with longer latency among women with naturally light hair (supplementary tables 30-37). Similarly, we did not observe any major variation in the associations when follow-up was restricted to the first 10 and 20 years after exposure assessments stopped. However, there was a possible decreased breast cancer risk with longer follow-up among women with naturally light hair (all remained statistically significant), and a decreased ovarian cancer risk among women whose natural hair color was black (remained statistically significant within the first 20 years; supplementary tables 38-45). In analyses that used baseline exposure information only, the results remained similar, although we observed minor variations (supplementary table 46).

Table 1: Age and age adjusted characteristics of study population in the Nurses’ Health Study (n=117 200, 1976) across self-reported status of personal use of permanent hair dye. Data are percentages (numbers) unless indicated otherwise

| Characteristic | Status of personal permanent hair dye use |
|----------------|------------------------------------------|
|                | Non-user | Ever user |
| No of participants (%) | 79.430 (67.77) | 37.770 (32.23) |
| Age (mean (SD)) | 42.65 (7.22) | 43.23 (7.19) |
| Race            |           |          |
|                  | White   | Black   | Other |
|                  | 96.27 (76.464) | 2.95 (2027) | 1.18 (939) |
|                  | 97.81 (36.941) | 1.54 (581) | 0.66 (248) |
| Natural hair color |         |          |
|                  | Black    | Dark brown | Red |
|                  | 3.62 (2878) | 34.32 (27259) | 3.65 (2899) |
|                  | 2.56 (968) | 29.56 (11166) | 2.24 (846) |
|                  | Light brown | Blond | Body mass index (mean (SD))* |
|                  | 27.62 (21942) | 8.02 (6366) | 23.83 (3.22) |
|                  | 32.45 (12256) | 10.41 (3930) | 32.62 (1256) |
| Smoking status   |           |          |
|                  | Never smoked | Past smoker | Current smoker (>25 cigarettes/day) |
|                  | 47.33 (37.595) | 21.85 (17.357) | 22.54 (17.906) |
|                  | 36.37 (13.737) | 25.99 (9816) | 26.83 (10.132) |
|                  | 21.37 (3.03) | 21.29 (3.96) | 10.81 (4.085) |
| Pack years of smoking |   |           |
|                  | 48.42 (38.458) | 37.61 (14.204) |
|                  | 11.30 (8974) | 12.76 (4811) |
|                  | 14.84 (11786) | 17.50 (6610) |
|                  | 25.45 (2021) | 32.15 (12145) |
|                  | 5.89 (10.17) | 7.35 (11.24) |

Participants with a previous diagnosis of any cancer before or at baseline, or participants who reported no information on personal use of permanent hair dyes were excluded. Denominators for percentage calculations are of non-missing values. Percentages may not sum to 100% after rounding.

*Calculated as weight in kilograms divided by height in meters squared.

Personal use of permanent hair dyes and cancer mortality
We explored the association between personal use of permanent hair dyes and cancer mortality. Multivariable analyses showed no significant association between status, duration, frequency, or cumulative dose and cancer related death, and stratified by natural hair color. The spline analysis showed no statistically significant nonlinear relation between cumulative dose and cancer related death, and stratified by natural hair color. The specific cancers, except for T cell lymphoma. Supplementary figures 1-28 present the results.

Personal use of permanent hair dyes and cancer risk and mortality (sensitivity analyses)
Assumptions of various latencies did not materially change the main findings for the aggregated and site specific cancer endpoints, except for a possible increased ovarian cancer risk with longer latency among women with naturally light hair (supplementary tables 30-37). Similarly, we did not observe any major variation in the associations when follow-up was restricted to the first 10 and 20 years after exposure assessments stopped. However, there was a possible decreased breast cancer risk with longer follow-up among women with naturally light hair (all remained statistically significant), and a decreased ovarian cancer risk among women whose natural hair color was black (remained statistically significant within the first 20 years; supplementary tables 38-45). In analyses that used baseline exposure information only, the results remained similar, although we observed minor variations (supplementary table 46).
Table 2 | Cox proportional hazard ratios (95% confidence intervals) for overall and specific cancer incidence and cancer related deaths among women in the Nurses’ Health Study according to personal use of permanent hair dyes and natural hair color

| Type of cancer | Any hair color | Dark hair color | Light hair color | P value for interaction |
|---------------|---------------|----------------|----------------|------------------------|
| All cancers*  | 22,612        | 0.96 (0.96 to 1.01) | 8,389          | 1.00 (0.96 to 1.05) | 9,417 | 0.98 (0.94 to 1.02) | 0.42 |
| All solid cancers* | 20,805        | 0.96 (0.96 to 1.01) | 7,648          | 0.99 (0.95 to 1.04) | 8,708 | 0.98 (0.94 to 1.02) | 0.69 |
| Basal cell carcinoma† | 22,560 | 1.05 (1.02 to 1.08) | 7,737          | 1.01 (0.96 to 1.06) | 11,334 | 1.06 (1.02 to 1.11) | 0.21 |
| Cutaneous squamous cell carcinoma§ | 27,922 | 1.00 (0.93 to 1.09) | 9,595          | 1.02 (0.89 to 1.16) | 13,751 | 0.95 (0.85 to 1.06) | 0.36 |
| Melanoma†‡ | 1,198         | 1.01 (0.89 to 1.16) | 386           | 0.93 (0.75 to 1.16) | 580   | 1.00 (0.84 to 1.19) | 0.62 |
| Breast cancer† | 9,252         | 1.02 (0.98 to 1.07) | 3,565         | 1.06 (0.99 to 1.13) | 3,902  | 1.02 (0.96 to 1.09) | 0.38 |
| Breast cancer (ER+)>§ | 5,905 | 1.00 (0.95 to 1.05) | 2,388         | 1.01 (0.93 to 1.10) | 2,595  | 1.01 (0.93 to 1.09) | 0.61 |
| Breast cancer (ER–)>§ | 15,211 | 1.02 (0.92 to 1.16) | 6,100         | 1.16 (0.98 to 1.37) | 6,491  | 1.00 (0.85 to 1.17) | 0.12 |
| Breast cancer (PR+)>§ | 4,826 | 0.97 (0.92 to 1.03) | 1,933         | 0.99 (0.90 to 1.08) | 2,148  | 0.96 (0.88 to 1.05) | 0.48 |
| Breast cancer (PR–)>§ | 23,797 | 1.05 (0.97 to 1.15) | 9,777         | 1.13 (0.99 to 1.29) | 10,003 | 1.09 (0.96 to 1.24) | 0.48 |
| Breast cancer (ER+/PR+)†§ | 4,634 | 0.97 (0.91 to 1.03) | 1,848         | 0.98 (0.89 to 1.07) | 2,079  | 0.96 (0.88 to 1.06) | 0.58 |
| Breast cancer (ER−/PR−)†§ | 1,086 | 1.09 (0.97 to 1.26) | 4,595         | 1.11 (0.92 to 1.35) | 4,441  | 1.20 (0.99 to 1.45) | 0.67 |
| Breast cancer (ER−/PR+)†§ | 1,287 | 1.03 (0.92 to 1.15) | 5,17           | 1.15 (0.96 to 1.38) | 5,612  | 1.02 (0.86 to 1.21) | 0.19 |
| Ovarian cancer†‡ | 1,215 | 1.09 (0.97 to 1.22) | 449           | 1.21 (1.00 to 1.47) | 5,09   | 1.06 (0.89 to 1.27) | 0.54 |
| Colorectal cancer** | 2,394 | 1.05 (0.97 to 1.16) | 858           | 1.07 (0.91 to 1.23) | 991    | 1.03 (0.91 to 1.18) | 0.97 |
| Bladder cancer†† | 596 | 1.05 (0.90 to 1.24) | 227           | 1.06 (0.81 to 1.38) | 260    | 1.05 (0.85 to 1.39) | 0.81 |
| Kidney cancer | 477 | 1.03 (0.85 to 1.23) | 184           | 0.99 (0.73 to 1.34) | 190    | 1.13 (0.84 to 1.51) | 0.42 |
| Lung cancer | 2,623 | 0.94 (0.87 to 1.01) | 908           | 0.81 (0.70 to 0.93) | 1,017  | 0.97 (0.85 to 1.10) | 0.06 |
| Brain cancer | 277 | 0.72 (0.56 to 0.93) | 100           | 0.91 (0.60 to 1.37) | 1,00    | 0.53 (0.35 to 0.82) | 0.08 |
| All hematopoietic cancers | 1,807 | 1.00 (0.91 to 1.10) | 714           | 1.06 (0.91 to 1.26) | 790    | 0.94 (0.81 to 1.10) | 0.14 |
| All non-Hodgkin lymphomas | 1,277 | 0.94 (0.84 to 1.05) | 529           | 0.99 (0.81 to 1.18) | 510    | 0.92 (0.77 to 1.09) | 0.52 |
| Melanoma†§§ | 51     | 1.26 (0.71 to 2.27) | 25            | 0.88 (0.38 to 2.04) | 15     | 1.64 (0.56 to 4.75) | 0.26 |
| Diffuse large B cell lymphoma | 190 | 1.06 (0.79 to 1.42) | 76            | 1.16 (0.72 to 1.84) | 79     | 0.87 (0.55 to 1.37) | 0.45 |
| Follicular lymphoma | 204 | 1.20 (0.91 to 1.59) | 83            | 1.45 (0.93 to 2.25) | 87     | 1.12 (0.73 to 1.72) | 0.33 |
| Chronic lymphocytic leukemia or small lymphocytic lymphoma | 227 | 0.69 (0.53 to 0.89) | 122           | 0.78 (0.54 to 1.14) | 111    | 0.62 (0.41 to 0.92) | 0.35 |
| Hodgkin lymphoma†‡ | 70     | 1.32 (0.82 to 2.13) | 24            | 3.89 (1.61 to 9.40) | 31     | 0.70 (0.33 to 1.49) | 0.004 |
| Multiple myeloma†‡ | 274 | 1.10 (0.86 to 1.40) | 113           | 1.07 (0.73 to 1.56) | 108    | 1.13 (0.77 to 1.67) | 0.85 |
| Myeloid leukemias | 476 | 0.99 (0.72 to 1.36) | 59            | 1.17 (0.69 to 1.97) | 64     | 0.90 (0.55 to 1.50) | 0.46 |
| Cancer related death§§ | 4860 | 0.96 (0.91 to 1.02) | 1661          | 1.00 (0.91 to 1.11) | 1801   | 0.94 (0.85 to 1.03) | 0.32 |

Discussion

In this large prospective cohort study of US women, we observed no increase in risk of most cancers or cancer related mortality among personal users of permanent hair dyes, with the exception of basal cell carcinoma, breast cancer (estrogen receptor negative, progesterone receptor negative, and hormone receptor negative), and ovarian cancer. We observed mixed findings for some endpoints (Hodgkin lymphoma and basal cell carcinoma) in analyses stratified by natural hair color.

Comparison with other studies

Hematopoietic cancer, bladder cancer, breast cancer, and lung cancer are among the cancers most frequently investigated in relation to hair dye use.4 Our results differ from reports of a slightly increased
relative risk of overall hematopoietic cancer (especially among people who use permanent hair dye, and ever users of hair dyes before 1980).

Our findings update the first prospective cohort study of hematopoietic cancer among women who use permanent hair dye conducted in 1994 with participants from the Nurses’ Health Study.

WHO classification of hematological cancers (therefore subgroup specific findings might not be directly comparable). The observation of higher Hodgkin lymphoma risk among women who were presumed to use dark colored permanent hair dye is novel and warrants cautious interpretation. This finding is based on a limited number of women and we had insufficient histological subtype information to restrict the analysis to classic Hodgkin lymphoma types, which might have a different cause from non-classical types. Additionally, we cannot rule out an influence of residual or otherwise uncontrolled confounding, for
example, by factors for which we lacked information (such as history of oncogenic infections).

Our study corroborates the null evidence on higher risk of bladder cancer among personal users of hair dyes with any hair colors reported by prior meta-analyses,6 but is inconsistent with the previously reported elevated risk of bladder cancer among dark colored dye users11 and the reported null finding for breast cancer among any colored dye users.6 11 Evidence from these previous meta-analyses6 10-12 is not conclusive and might have been influenced by the following factors: not discriminating between personal and occupational exposure11; an inability to distinguish between use of permanent and non-permanent hair dyes11; the design of the included studies (predominantly case control studies with relatively limited power)9 10-12; non-evaluation of several critical domains of exposure history (eg, duration, frequency, and cumulative dose of use) owing to lowest common denominator of the evaluated studies9 10-12; and diagnostic challenges.12

African Americans have higher risks of presenting with estrogen receptor negative and progesterone receptor negative breast cancer than non-Hispanic white people in the US.35 36 Interestingly, a recent US cohort study observed considerably higher breast cancer risk in black women and a borderline increased use of permanent and non-permanent hair dyes11; the design of the included studies (predominantly case control studies with relatively limited power)9 10-12; non-evaluation of several critical domains of exposure history (eg, duration, frequency, and cumulative dose of use) owing to lowest common denominator of the evaluated studies9 10-12; and diagnostic challenges.12

| Type of cancer                      | No of events | Non-user 1-99 times | 100-199 times | ≥200 times | P value for trend† | Per 50 time increment | P value for trend‡ |
|-------------------------------------|--------------|---------------------|---------------|------------|-------------------|-----------------------|-------------------|
| Breast cancer (ER–/PR–)             | 517          | 1                   | 1.18 (0.99 to 1.39) | 1.14 (0.93 to 1.38) | 1.17 (0.96 to 1.40) | 0.01                  | 1.00 (0.99 to 1.01) |
| Breast cancer (ER+/PR+)             | 1848         | 1                   | 0.98 (0.86 to 1.15) | 0.99 (0.84 to 1.14) | 0.99 (0.83 to 1.14) | 0.003                 | 1.00 (0.99 to 1.01) |
| Breast cancer (PR+)                 | 1933         | 1                   | 1.11 (0.91 to 1.36) | 1.16 (0.94 to 1.40) | 1.14 (0.91 to 1.41) | 0.004                 | 1.00 (0.99 to 1.01) |
| Breast cancer (ER–)                 | 610          | 1                   | 1.00 (0.70 to 1.23) | 1.05 (0.68 to 1.61) | 1.02 (0.57 to 1.85) | 0.01                  | 1.00 (0.99 to 1.01) |
| Bladder cancer §                    | 227          | 1                   | 1.22 (0.99 to 1.46) | 1.14 (0.84 to 1.54) | 1.12 (0.72 to 1.43) | 0.01                  | 1.00 (0.99 to 1.01) |
| Bladder cancer §§                   | 858          | 1                   | 1.04 (0.67 to 1.37) | 0.98 (0.54 to 1.36) | 0.97 (0.50 to 1.83) | 0.004                 | 1.00 (0.99 to 1.01) |
| Bladder cancer §§§                  | 517          | 1                   | 1.18 (0.96 to 1.47) | 1.07 (0.70 to 1.66) | 1.14 (0.74 to 1.67) | 0.01                  | 1.00 (0.99 to 1.01) |
| Colon cancer§                       | 449          | 1                   | 1.12 (0.99 to 1.26) | 1.04 (0.73 to 1.49) | 1.05 (0.64 to 1.54) | 0.01                  | 1.00 (0.99 to 1.01) |
| Colon cancer §§§                    | 83           | 1                   | 1.22 (0.84 to 1.71) | 1.06 (0.59 to 2.01) | 1.07 (0.51 to 1.99) | 0.01                  | 1.00 (0.99 to 1.01) |
| Chronic lymphocytic leukemia & small lymphocytic lymphoma | 122 | 1 | 0.86 (0.53 to 1.38) | 0.54 (0.26 to 1.12) | 0.91 (0.49 to 1.69) | 0.38                  | 0.95 (0.87 to 1.04) |
| Hodgkin lymphoma §§§                | 24           | 1                   | 3.16 (1.14 to 8.77) | 5.90 (1.83 to 19.10) | 4.06 (0.97 to 16.90) | 0.01                  | 1.13 (1.00 to 1.29) |
| Multiple myeloma§                   | 113          | 1                   | 1.09 (0.90 to 1.39) | 1.01 (0.80 to 1.27) | 1.03 (0.73 to 1.43) | 0.009                 | 1.00 (0.98 to 1.02) |
| Myeloid leukemias §                  | 59           | 1                   | 1.22 (1.00 to 1.45) | 1.12 (0.84 to 1.49) | 1.12 (0.78 to 1.66) | 0.002                 | 1.00 (0.98 to 1.02) |
| Myeloid leukemia §§                  | 1661         | 1                   | 1.07 (0.95 to 1.22) | 0.95 (0.78 to 1.19) | 0.97 (0.82 to 1.15) | 0.50                  | 1.00 (0.98 to 1.01) |

†P value for trend was calculated by using the mid-point of each category of cumulative dose in times.
‡P value for trend was calculated by using cumulative dose in times as continuous variable.
§Models were additionally adjusted for childhood reaction to sun, lifetime blistering sunburns, number of males on arms, and cumulative ultraviolet flux since baseline.
¶Models were additionally adjusted for menopausal status, postmenopausal hormone use, family history of colorectal cancer, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the previous two years, regular use of aspirin, regular use of non-aspirin non-steroidal anti-inflammatory drugs, multivitamin use, total calorie intake, red or processed meat intake, and intake of fiber, folate, calcium, and vitamin D.
††Models were additionally adjusted for total fluid intake.
‡‡Models were additionally adjusted for regular use of aspirin.
***Models were additionally adjusted for physical activity, menopausal status, postmenopausal hormone use, parity, regular use of aspirin, regular use of non-aspirin non-steroidal anti-inflammatory drugs, multivitamin use, total calories intake, history of hypertension, history of hypercholesterolemia, and history of diabetes mellitus.
*Not including basal cell carcinoma and cutaneous squamous cell carcinoma.
+‡‡‡P value for trend was calculated by using cumulative dose in times as continuous variable.
Risk among white women who used permanent hair dyes, which is largely consistent with our findings among US women with predominantly European ancestry. In particular, this recent study detected potential differences by estrogen receptor status; the risk associated with permanent hair dye appeared to be specifically increased for estrogen receptor negative breast cancer compared with estrogen receptor positive breast cancer. Our study, which was based on a larger number of women with breast cancer and more refined confounding control, observed similar findings for estrogen receptor negative breast cancers. Additionally, our study performed stratification analyses according to progesterone receptor status, and risk was similarly increased for progesterone receptor negative and hormone receptor negative breast cancer.

Evidence remains inadequate for other cancers. Individual or pooled relative risks were increased for several specific brain cancers, basal cell carcinoma, ovarian cancer, lung cancer, prostate cancer, cancer of the salivary glands, and neuroblastoma in offspring in previous studies, but not for cervical cancer and melanoma. However, these studies had similar limitations to those discussed above. Our current study, overcoming most of the major limitations in previous investigations, reported no positive association between ever personal use of permanent hair dyes and risk of cutaneous squamous cell carcinoma.
squamous cell carcinoma, melanoma, ovarian cancer, colorectal cancer, kidney cancer, lung cancer, and brain cancer, but it found a slightly increased risk of basal cell carcinoma. Larger cumulative dose was also not associated with higher risk of most of these specific cancer subtypes in our analyses, except for breast cancer and ovarian cancer. Our results among US women conflict with previous reports on brain cancer and lung cancer but are consistent with studies on basal cell carcinoma, ovarian cancer, and melanoma. The possibility of a spurious finding for ovarian cancer cannot be ruled out given the sensitivity analyses. Our study examined permanent hair dye use in relation to risk of cutaneous squamous cell carcinoma, colorectal cancer, and kidney cancer. We found no positive association between personal use of permanent hair dyes and cancer related death, which confirms the findings in previous reports.

We observed potentially lower risks of lung cancer, brain cancer, and chronic lymphocytic leukemia or small lymphocytic lymphoma among ever users of permanent hair dyes and those who used larger cumulative doses. These observations are difficult to account for and warrant re-evaluation in other investigations. We encourage caution when interpreting these findings owing to uncertainty about their biological plausibility.

We observed mixed findings for several endpoints when examining non-users versus ever users and cumulative dose of hair dyes in analyses stratified by natural hair color. One plausible assumption (among several) linking natural hair color with the color of hair dyes used could be that, especially in the birth cohorts specific to the Nurses’ Health Study, women tended to use hair dye products with the same color as their natural hair color. We do not have data to directly assess this assumption or other plausible assumptions. However, if this assumption holds, women with naturally dark hair who presumably used dark colored permanent hair dyes experienced an increased risk of Hodgkin lymphoma. Possible explanations could be that shades of permanent hair dyes are associated with the concentration of ingredients, with darker colors having higher concentrations. However, we also reported that women with naturally light colored hair who presumably dyed their hair using light colored permanent hair dyes had a higher risk of basal cell carcinoma, which remains difficult to explain. Until these findings can be confirmed in other large populations and mechanisms elucidated, they require cautious interpretation. More research is needed to identify the specific chemical constituents that might be contributing to these increased risks.

Strengths and limitations of study

Our study had several noteworthy strengths. Firstly, it was a large study (comprising over 117,000 eligible participants, with more than 47,000 incident cancers and over 4800 cancer related deaths documented during 36 years of follow-up), and the prospective design and high follow-up rates (exceeding 90% in most questionnaire cycles, including the cycles when information on hair dye exposure was assessed) minimized the potential for bias. Secondly, we had validated, time varying information on a wide spectrum of known or plausible confounders, which allowed relatively rigorous control for confounding throughout follow-up for every specific cancer, even though our exposure information was not updated after the first six years. Thirdly, we measured diverse major domains of exposure (overall status, duration and frequency of use, cumulative dose, age at first use, and time since first use), presenting an important advantage which has not been addressed by most previous studies. Although a study validating measurements of hair dye exposure and certain confounding variables has not been performed (eg, body mass index at age 18, childhood reaction to sun, which involved participants recalling information from long before the baseline), we have confidence in the reliability of our exposure assessments and in the retrospectively assessed variables because a wide range of measurements on anthropometrics, lifestyle, diet, and medical history have previously been shown to be valid in the Nurses’ Health Study cohort. Fourthly, the availability of detailed medical records and pathology reports enabled us to examine heterogeneity across major cancer subtypes, including some individual lymphoid malignancies and several individual breast cancer subtypes according to hormone receptor status. Finally, the high homogeneity of our study participants (all trained health professionals) minimized underreporting or misreporting of cancer diagnoses before final confirmation by study investigators through medical record confirmation and cancer registry linkages, further ensuring high quality data, minimal socioeconomic confounding, and enhanced internal validity.

This study has several limitations. Firstly, our cohort was not randomly sampled from US women, but enrolled only healthcare professionals and more than 96% of the women had European ancestry. Therefore, although racial or ethnical disparities in the association between personal permanent hair dye use and risk of certain cancers (eg, breast cancer) have been suggested in previous studies, we were not able to investigate heterogeneity across race or ethnicity in cancer risk and mortality in this cohort, limiting the generalizability of our findings. Additionally, compared with the general population, nurses might be more adept at taking precautions while applying hair dyes (eg, following directions, using gloves, keeping track of time, rinsing the scalp thoroughly with water after use), which could limit the generalizability of our findings. Secondly, although we performed extensive multivariate analyses to address confounding, the possibility of residual unmeasured confounding remains. For example, we lacked information on exposure to oncogenic infections, family history of hematopoietic cancer, and exposure to pesticides and other putative environmental risk factors in analyses of hematopoietic cancers, or information on skin tone in
analyses of cutaneous cancers. Other examples include the lack of information on use of other hair dye and
hair straightening products in addition to permanent
hair dyes. Women who use hair dye products might
also use other cosmetics more commonly, which
could also contain a wide spectrum of effective chemicals; confounding from this exposure could
not be addressed. Moreover, information about the
localization of cutaneous cancers was also unavailable.

The third limitation of our study pertains to potential
misclassification of hair dye use. Specifically, owing
to a lack of questions on participants’ history of non-
permanent hair dye use, some users of non-permanent
hair dyes might have misunderstood and inadvertently
misclassified themselves as permanent hair dye
users. Further, given that exposure assessments ceased relatively early during cohort follow-up,
exposure domains might be underestimated, which
could bias our results towards the null. Moreover,
given the potential for non-differential recall, the
baseline exposure assessment might have been more
misclassified than subsequent assessments because of
the longer time frame. Another potential concern
is whether exposure measurements were less relevant
30 years later than they were in the shorter term.
However, it is relatively rare that effects of genotoxic
agents are immediate. A latency of even decades might exist before the effect of genotoxic agents could be
observed. By restricting follow-up to the first 10 and
20 years of follow-up, we reported no material variation of the observed associations under this assumption
for most of the endpoints. Finally, the potential of
chance findings owing to multiple comparisons merits
consideration. However, considering that we used only
five distinct exposure scales in our analyses, all of
which related to hair dye use and were complementary
to each other because they allowed different aspects of
causality to be assessed, we were conservative in our
adjustments for multiple comparisons.

Other challenges relating to human evidence of the
carcinogenicity of permanent hair dye use should be
mentioned. Firstly, our data collection on permanent
hair dyes might not exactly represent exposure today or
in the past 10 years. Hair dyes might contain hundreds
of chemicals, with ingredients that have changed over
time. Whereas there was little innovation in the components of permanent hair dyes between the
1930s and 1970s, the cosmetic industry has made
several changes in the composition of permanent hair
dyes since the 1980s. These changes were in response
to the US Food and Drug Administration warning on the
safety of permanent hair dyes that contain 4-methoxy-
m-phenylenediamine (2,4-diaminoanisole), or its
sulfate. Additionally, several new oxidative substances were introduced during the same period.
In this study, we could not conduct a stratified analysis of permanent hair dye use before or after 1980
because not enough women reported first use of
permanent hair dye after 1980 (1890/117 200). This
lack of use could be because our study participants
are all health professionals, which might have made
them more sensitive than the general population to
the cautionary label that appeared on permanent
hair dye packaging from 1980 onwards. However,
considering that most of the frequently used modern
permanent hair dye ingredients (including para
phenylenediamine, resorcinol, 2,5-diaminotoluene,
para and meta aminophenol, 4-amino-2-hydroxytoluene, 4-amino-meta-cresol, and 2-methyl-5-
hydroxyethylaminophenol) have been on the market
since the 1930s, our findings should still be relevant
to current day exposure regardless of type and shade of
color (they are regulated according to their ingredients regardless of the shade) and therefore have public
health implications.

Secondly, the carcinogenic potential of dark colored
permanent hair dyes are of greatest concern. Permanent hair dyes consist of dye intermediates
(alkyl amines) and couplers, which can react with each other to form pigment molecules. The
shades of color are approximately proportional to the concentration of ingredients (a clear estimate cannot be made because of the complexity of ingredients)—
darker hair dyes tend to contain higher concentrations of ingredients, whereas lighter shades contain lower
concentrations. Additionally, lead acetate based dark
colored products can still be found on the international
market. Previous studies have particularly noted a
potential increase in cancer risk for users of dark colored
permanent hair dyes. However, in our study, we
lacked information on the color of permanent hair dyes
used, instead conducting analyses stratified by natural
hair color to explore the question of heterogeneous
effects only indirectly (presuming that participants
would use dyes of a similar color to their natural hair
color). Thirdly, the reported increase in using natural
(eg, henna or its pure dye ingredient) or direct (semi-
permanent or temporary) dye in combination with
permanent hair dye should be noted, and their safety
warrants further investigations. Fourthly, attention
should be paid to differences relating to permanent
hair dye use in personal and occupational exposure
settings. Although the chemical composition of hair
dye products for occupational use is similar to that for
home use, the cumulative dose of dermal and airborne
exposure for hairdressers or beauticians could be
higher (prolonged time with higher frequency) than
that of consumers.

Finally, legislation and regulation of ingredients
in hair dye formulations differ by country, adding
further complexity. In the US, permanent hair dyes
do not require premarket approval by the US Food
and Drug Administration manufacturers are
responsible for the safety of ingredients. However,
the US Food and Drug Administration continues to
monitor safety concerns about these products. Additionally, Europe, but not the US, has banned a
number of individual hair dye ingredients that were
considered putatively carcinogenic during the 1980s
and 2000s. The most restrictive regulation of hair
dyes exists in Japan where cosmetic products are
considered equivalent to drugs.
Conclusion and public health implications

This prospective cohort study among mostly white US women offers some reassurance against concerns that personal use of permanent hair dyes might be associated with increased cancer risk or mortality. However, we did find a positive association for risk of some cancers, including basal cell carcinoma, breast cancer (estrogen receptor negative, progesterone receptor negative, hormone receptor negative) and ovarian cancer. Additionally, mixed results were found in analyses stratified by natural hair color for some endpoints (increased risk of Hodgkin lymphoma was observed only among women with naturally dark hair; higher risk of basal cell carcinoma was observed specifically among women with naturally light hair). The generalizability of current findings is limited to white US women and might not extend to other populations. Our findings warrant further prospective validation in diverse populations and nations, various susceptibility genotypes (e.g., N-acetyltransferases, NAT1 or NAT2), cancers of various genotypes and molecular genetic phenotypes, different exposure settings (personal use vs occupational exposure), different timings, and colors of permanent hair dyes used (dark vs light colored). Additionally, exposure assessments should be more refined and interpreted in the light of the totality of evidence.

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Ethical approval: The study protocol was approved by the institutional review board at Brigham and Women’s Hospital (1999-P-011114), and those of participating registries as required. Consent from participants was indicated by the completion and return of the questionnaires.

Data sharing: Data, the statistical code, questionnaires, and technical processes are available from the corresponding author at angela.schenhammer@channing.harvard.edu.

The lead author (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We plan to disseminate the results to study participants. This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

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