COSMETIC INGREDIENT REVIEW

CIR Resource Document

Hair Dye Epidemiology

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BACKGROUND

Hair dyes may be broadly grouped into oxidative (permanent) and direct (semi-permanent) dyes. The oxidative dyes consist of precursors mixed with developers to produce color, while direct dyes consist of preformed colors. Epidemiology studies that seek to determine links, if any, between hair dye use and disease provide broad information and have been considered by the Cosmetic Ingredient Review (CIR) Expert Panel (Panel), although these studies do not specifically address the safety of individual hair dye ingredients.

The Panel reviews new epidemiological studies addressing the personal use of hair dyes as these studies become available. Table 1 summarizes the studies specifically addressing bladder cancer, lymphoma, leukemia, bladder, and breast cancer. Relevant meta-analytical studies included here address glioma and breast cancer, in addition to bladder and blood cancers. Occupation as a hairdresser, barber, or cosmetologist involves exposures to multiple products used during work, making it difficult to use the results of such studies to inform the assessment of the risk, if any, associated specifically with hair dyes. Accordingly, such studies are not summarized here.

The Panel considers that epidemiological studies, when based on better information about exposure, can provide more useful findings than other such studies. According to one study, exposure assessments in hair dye epidemiology studies ranged from minimal information (e.g., ever/never use) to subject-recalled information on type, color, duration and frequency of use.[1] A scale from + to ++++ has been developed to rate the quality of hair dye exposure assessments in hair dye epidemiology studies, as shown below. This scale was used to score the studies that are summarized in Table 1.

+: Assessed ever/never use;
++: Assessed the type of hair dye, *or* dye type plus dye color or duration, *or* with information on two or three other factors (color, frequency, duration), but no information on type;
+++: Assessed dye type, color, *and* frequency *or* duration of use;
++++: Assessed all four critical aspects: hair dye type, color, duration, and frequency of use

An International Agency for Research on Cancer (IARC) working group summarized the relevant epidemiology studies and observations on breast, bladder and hematological cancers.[2,3] The working group concluded that the animal studies provided limited evidence for the carcinogenicity of hair colorants, and the data are of insufficient quality, consistency, or statistical power to establish the presence or absence of a causal link between personal use of hair dyes and cancer. In addition, occupational exposure during work as a hairdresser, barber, or beautician was assessed. The working group found that exposures from these occupations are probably carcinogenic, based on limited evidence of increased risk for bladder cancer in hair dressers and barbers. However, occupational safety is outside the scope of the work of the Panel.

The studies herein result in either an odds ratio or a relative risk, two similar but not synonymous terms. An odds ratio (OR) represents the odds that an outcome (e.g. cancer) will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure; whereas a relative risk (RR) is a measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group.[4,5] In epidemiological research, ORs are most often used in case-control (backward looking) studies, and RRs are used in prospective (forward looking) studies, such as cohort studies and clinical trials. An OR or RR of 1 means there is no difference between two groups in terms of risk following a particular exposure; an OR or RR < 1 means that the exposure may reduce the risk of cancer (possibly protective), while OR or RR > 1 means the exposure may increase the risk of cancer (possibly causal). The 95% confidence interval (CI) is used to estimate the precision of the OR or RR. If a 95% CI for the relative risk includes the null value of 1, then there is insufficient evidence to conclude that the groups are statistically significantly different.

The following provides a brief summary of many relevant epidemiological studies that have been published since about 2010, as well as older epidemiological studies that were included in comprehensive reviews, such as that published by the IARC in 2010[3]. The Panel determines to continue monitoring upcoming epidemiological data on the link between personal use of hair dyes and cancer risk and the conclusion of the document would be re-evaluated based upon the new information on a regular period basis.

STUDY SUMMARY

Bladder Cancer

In a meta-analysis involving 15 case-control and 2 cohort studies, the abstracted information included the variables adjusted and/or used to match control subjects with cases.[6] For example, 12 of the studies clearly adjusted for smoking; adjustment for smoking was not clear in 1 study. The pooled RR of bladder cancer incidence/mortality was 0.93 (95% CI 0.83-1.05) for personal use of any type of hair dye, compared with no use, and similar results were obtained when the subjects were stratified by sex. The RR for personal use of permanent hair dyes from 7 of the studies was 0.92 (95% CI 0.77-1.09). Similarly, no association was found between bladder cancer and the duration or lifetime frequency of use of any type of hair dye or use of permanent hair dyes, compared with never used hair dyes. The RR for the use of dark-color hair dyes was 1.29 (95% CI 0.98-1.71).

In a population-based case-control study conducted in the Netherlands, no association was found between bladder cancer and ever use of permanent hair dyes (OR 0.87; 95% CI 0.65-1.18) or temporary hair dyes (OR 0.77; 95% CI 0.58-1.02).[7] Similarly, no association was observed when hair dye use was defined by type, duration or frequency of use, dye color, or extent of use or when the patients were stratified by aggressive and non-aggressive bladder cancers. The subjects were 246 cases and 2587 controls; all of the subjects for which the analyses were performed were women (less than 5% of the men selected for the study reported ever using hair dyes). All analyses were adjusted for age and smoking status, duration and intensity. Additional adjustment for education level and other variables considered were not included in the final model because they did not change the standardized regression coefficient (β) by more than 10%. The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale.

A population-based case-control study was conducted in Maine, Vermont, and New Hampshire.[8] The subjects were 1,193 cases of urinary bladder cancer diagnosed from 2001 to 2004 (911 male and 282 female), and 1418 controls (1,039 male and 379 female). The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. The hair dye models were adjusted for age, race, sex, and smoking status.

No association was found between ever/never use of hair dyes and bladder cancer – the OR and associated 95% CI for women was 0.7 (95% CI 0.5-1.0), and for men 0.7 (95% CI 0.4-1.0). Because of the excellent exposure assessment, the authors were able to examine subsets of the population studied. Women who used red hair colors, for example, exhibited an OR of 0.4 (95% CI 0.2- 0.8), suggesting a significantly lower risk of bladder cancer associated with the use of such hair dyes. A similar lower risk of bladder cancer was reported for women who used hair dyes for a duration between 10 and 19 years (OR 0.5; 95% CI 0.27-0.79). As the data were further analyzed, the authors considered women with and without college degrees. Women without college degrees who used permanent hair dyes exclusively, for example, had a significantly lower risk of bladder cancer (OR 0.5; 95% CI 0.4- 0.7). Exclusive use of permanent hair dyes by women with college degrees was associated with a significantly higher risk of bladder cancer (OR 4.9; 95% CI 1.7-14.6). No statistically-significant interactions with hair-dye use were found when the data were stratified by state of residence, hair-dye product type, smoking, age at diagnosis/interview, or disease aggressiveness in the female subjects.

To investigate risk factors for bladder cancer in Iran, a population-based case-control dataset with 692 cases and 692 controls was analyzed.[9] Cases were identified using the Iranian cancer registry. The hair dye exposure assessment was a + on the Rollison et al. (2006) scale. The OR for hair dye use and bladder cancer was 1.81 (95% CI 1.08-3.06). After adjustment for cigarette smoking, the OR was 1.99 (95% CI 1.02-3.82). When women and men were analyzed separately, no significant association with hair dye use and bladder cancer was found.

Prostate Cancer

A hospital-based case-control study was conducted among prostate cancer cases in Taiwan, involving 296 cases with newly diagnosed prostate cancer and 296 age-, ethnicity-, and hospital-matched controls. Information on hair dye use was obtained through a standardized questionnaire.[10] The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale. The prevalence of hair dye use was higher in the cases than the controls (95/296 = 32.1% vs. 64/296 = 21.6%, $p < 0.05$), and the hair dye users had increased odds of prostate cancer when compared with the non-users (adjusted OR 2.15; 95% CI 1.32–3.57). The study found personal hair dye use increased risk of prostate cancer with a dose-response effect. Meanwhile, to determine the rate of prostate cancer survival, another 608 incident prostate cancer cases were investigated. Of the 608 cases, 26.4% (161/608) reported having used hair dyes. The use of hair dye did not affect cumulative incidence estimates of prostate cancer-specific deaths (p=0.753).

This report was the first to show a positive association between personal hair dye use and risk of prostate cancer, revealing a dose-response relationship assessed by duration and frequency; however, cumulative exposure dose, a critical

indicator to estimate a dose-response effect, was not assessed. The external validity of this study has been questioned.[11] Other studies targeted on hairdressers observed no increased risk of prostate cancer.[12] While Tai et al.'s findings are limited and do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted.

Lymphoma and Leukemia

A meta-analysis of 20 case-control studies of leukemia has been performed in 2017.[13] The RRs for the associated risk of leukemia were: with permanent hair dye use RR = 1.19 (95% CI 1.07–1.33), with dark hair dye use RR = 1.29 (95% CI 1.11–1.50), with hair dye use among males RR = 1.42 (95% CI: 1.01–2.00), with hair dye use pre-1980 RR = 1.49 (95% CI: 1.21–1.83), and with hair dye use for longer than 15 years RR = 1.35 (95% CI: 1.13–1.62). Overall, findings suggest that ever use of hair dye is not a significant risk factor for leukemia.

A population-based case-control study was conducted to evaluate whether the hair dye use influenced the risk of leukemia and non-Hodgkin's lymphoma (NHL) in Italy.[14] The analysis was restricted to women in the population studies because too few of the men reported any hair dye use. There were 161 cases (120 lymphoid and 41 myeloid) and 84 controls among the women. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale, because only duration of hair dye use < 15 years vs. ≥ 15 years was evaluated. In a multivariate analysis, the OR was 2.3 (95% CI 1.0-4.9), with p = 0.036 for a trend, for NHL in women using hair dye for at least 15 years. No association was found between lymphoid malignancies and tobacco smoking or the consumption of alcoholic beverages in this study.

A meta-analysis of 19 case-control studies of NHL subtypes was conducted, focusing on follicular lymphoma (FL).[15] No associations between FL and hair dye use type, duration, or frequency were found in this study, except for a modest increase in women who used hair dyes before 1980 (OR = 1.4; 95% CI 1.10-1.78). Many oxidative hair dye products were reformulated in the early 1980s in the US to eliminate ingredients that produced tumors in animal bioassays.[16] In comparison, the risk of FL in women was associated with current cigarette smoking, trending higher with increasing duration of smoking.

Another meta-analysis of 19 case-control studies of NHL subtypes was performed, focusing on diffuse large B-cell lymphoma (DLBCL).[17] There were no overall and sex- or age-specific associations between DLBCL and hair dye use, based on the basic adjusted model results of this study. The OR for mediastinal DLBCL was 4.97 (95% CI 1.63-15.15) for use of hair dyes for at least 20 years, compared with never used hair dyes. Using hair dyes for at least 20 years was not associated with DCBCL at other anatomical sites, including the central nervous system (CNS), testis, gastrointestinal tract, and skin. Use of hair dyes for less than 20 years was not associated with DLBCL at any site. In comparison, smoking was associated with CNS, testicular and cutaneous DLBCLs in this study.

A hospital-based case-control study was conducted to investigate the hair dye use in the etiology of leukemia and lymphoma in Egypt.[18] There were 130 cases, including 23 cases of chronic lymphocytic leukemia (CLL) and 107 cases of NHL, and 130 age- and sex-matched controls. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale. In a univariate analysis, no statistically significant association was found between these lymphoproliferative disorders and history of using hair dyes, family history of cancer, exposure to X-rays, or smoking (χ^2, $p>0.05$).

A hospital-based case-control study of myelodysplastic syndromes (MDSs) was performed in China.[19] There were 403 cases and 806 controls, and the evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. In a univariate analysis, the OR for hair dye use (≥ 2 times per year) and all MDSs was 1.46 (95% CI 1.03-2.07). In a multivariate analysis performed to adjust for potential confounding factors, the OR was not statistically significant (OR 1.31; 95% CI 0.88-1.93). In comparison, smoking was associated with the development of MDSs in the univariate analysis and with refractory anemia with excess blasts (RAEB) in both the univariate and multivariate analyses.

A hospital-based case-control study was conducted on 649 NHL cases in Shanghai.[20] The analysis included 1,298 controls and the evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. No increased risk of NHL was reported (OR 0.93; 95% CI 0.75-1.16). For CLL and small lymphocytic lymphoma (SLL), the authors reported a significantly lower risk associated with hair dye use (OR 0.37; 95% CI 0.18-0.76). In comparison, alcohol consumption and cigarette smoking were not associated with NHL in this study, although smoking ≤ 20 years (but not > 20 years) was associated with precursor B-cell neoplasms.

Tissue samples from a NHL case-control study in males from Iowa and Minnesota were subjected to re-evaluation using FISH (fluorescence in situ hybridization) cytogenetic technique to examine both *t*(14;18)-positive and *t*(14;18)-negative NHL subtypes and IHC (immunohistochemistry) assays to evaluate expression of the anti-apoptotic protein bcl-2.[21] There were 8 *t*(14;18)-positive, 12 *t*(14;18)-negative, 20 bcl-2 positive, and 4 bcl-2 negative NHL cases and 58 control subjects in the subpopulation tested (i.e., men having used hair dye at least once a month for at least one year, or occupational

exposure to hair dyes on any job held for at least a year). The evaluation of hair dye exposure scored + on the Rollison et al. (2006) scale. Adjusting for age, state and proxy status (i.e., whether or not next-of-kin proxies were interviewed), a statistically-significant association between ever/never use of hair dyes and *t*(14;18)-negative NHL (OR 2.9; 95% CI 1.6-5.0) and bcl-2 positive NHL (R 2.2; 95% CI 1.4-3.4), but not with *t*(14;18)-positive NHL (OR 1.3; 95% CI 0.6-2.6) or bcl-2 negative NHL (OR 1.4; 95% CI 0.5-3.8). Similarly, smoking was associated with *t*(14;18)-negative NHL, but not clearly associated with *t*(14;18)-positive NHL, bcl-2 negative NHL, or bcl-2 positive NHL in this study.

A hospital-based case-control study of acute myeloid leukemia (AML) was conducted in Shanghai.[22] The investigation consisted of 722 newly diagnosed AML cases and 1444 individually gender-age-matched patient controls at 29 hospitals in Shanghai. The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. There was no increase in the risk of AML and personal use of hair dyes; The OR was 0.98 (95% CI 0.8-1.2). In contrast, there was an association between AML and smoking, particularly among the male subjects, as well as alcohol consumption and a low level of education in this study.

Glioma

A meta-analysis including 4 case-control and 2 cohort studies of personal was conducted to investigate the hair dye use and the incidence of gliomas.[23] Matching or adjustment for age and sex was performed in all 6 studies included in this meta-analysis, and for smoking in 2 of the 6 studies. The most adjusted risk estimates were included, and the raw data were used when adjusted estimates were not available. Summary RRs for ever use of any hair dyes were 1.132 (95% CI 0.887-1.446) for all studies, 1.291 (95% CI 0.937-1.777) for case-control studies, and 0.903 (95% CI 0.774-1.054) for cohort studies. Similar results were obtained when the subjects were stratified by geographic regions and sex. No significant associations were found among the studies that evaluated permanent hair dye use and duration of any hair dye use.

Breast Cancer

In a case-control study conducted in the metropolitan New York City area and in ten counties in New Jersey (NJ), involving both African Americans and White women, breast cancer cases were identified by multiple sources, including hospital charts and NJ cancer registry.[24] The subjects were 1508 African American and 772 European American cases (52±10.7 and 52.0±10.0 years old, respectively) and 1290 African American and 715 European American age- and county-matched control subjects (50.9±10.3 and 49.8±8.7 years old, respectively). The evaluation of hair dye exposure was ++++ on the Rollison et al. (2006) scale. Final OR estimates were adjusted by age, education, body mass index, family history of breast cancer, and oral contraceptive use. In the control group, about 30% of African Americans and 58% of Whites reported regular use of hair dyes. Overall, ever use of hair dyes and duration of use were not significantly associated with increased cancer risk in both African Americans and Whites. Among African Americans, an increased risk of breast cancer was documented for the use of dark hair dye shades, and for salon application of dyes, adjusted OR being 1.51 (95% CI, 1.20-1.9) and 1.26 (95% CI, 1.00-1.58), respectively. In Whites, an increased risk was documented for dual use of relaxers and hair dyes with OR 2.40 (95% CI 1.35-4.27), the wide CI reflecting the limited number of exposed women. When considering the estrogen receptor status of cancer, the risk of estrogen positive breast cancer was increased in African Americans with a higher frequency of hair dye use (OR 1.36, 95% CI 1.01-1.84) and in Whites with the use of dark hair dye shades (OR 1.54, 95% CI, 1.01-2.33). These differences in risk profile between African Americans and Whites are not easy to reconcile. They may reflect different patterns of use, or represent chance effects due to multiple testing. In this study, women who started using hair dyes before 1980 were not distinguished from women who started in 1980 or thereafter. Replication of results by an independent study is needed. Ideally, such a study should be able to ascertain the type of hair dye product used and its timing of use.

A population based case-control study in Finland recruited a total of 6,567 breast cancer patients diagnosed between 2000 and 2007 and 21,598 age-matched controls.[25] The evaluation of hair dye exposure was a +++ on the Rollison et al. (2006) scale. The recruitment of patients was based on a nation-wide cancer registry covering almost 100% of solid tumors. The exposure of primary interest was the use of hair dyes with detailed information on the cumulative lifetime number of hair dye episodes, age at first use, and the types of dyes used. When calculating ORs, potential confounding factors, namely parity, age at first birth, family history of breast cancer, menarche age, use of hormonal contraceptives, physical activity, alcohol use, body mass index and education, were included in a stepwise regression model. Bias-adjusted ORs were calculated as well. A large proportion of women reported ever use of hair dye products, with rates increasing from 84% in women born before 1950 up to 92% in women born in or after 1960. The odds of breast cancer were significantly increased when comparing ever vs never users of hair dyes (OR 1.23, 95% CI: 1.11–1.36).

Early age at first dye (20 - 29 years) was associated with higher odds of breast cancer when compared to late age at first dye (40 years or later) (OR 1.14, 95% CI: 1.05–1.25). When considering ever use vs. non-use, the ORs were increased

with all the different types of hair dyes, the highest estimates being obtained for women who reported to have used temporary and/or semi-permanent dyes, ORs being 1.32 (95% CI: 1.16 - 1.52) and 1.31 (95% CI: 1.17 - 1.46), respectively. Latency of effect was suggested by the fact that the OR for cumulative hair dye use was the highest among women born between 1950 and 1959. When considering the cumulative number of hair dye episodes, the OR ranged from 1.07 (1 - 2 dye episodes) to 1.28 (10 - 34 dye episodes) and 1.31 (35 - 89 dye episodes), and then decreased to 1.25 (≥ 90 dye episodes). The ORs did not change when smoking was included in the multivariate analysis.

One meta-analysis summarized results of studies conducted from 1966 up to 2005,[12] and included 12 case-control studies, which involved a total of 5019 cases and 8486 controls, and 2 cohort studies which recruited a total of 1135 incident cases of breast cancer. The pooled RR of breast cancer was 1.06 (95% CI 0.95-1.18) and nonsignificant when comparing ever use vs. never use of hair dyes. No significant increased risk was documented when considering intensive exposure or restricting analyses to the use of permanent dyes only. It is noted that, giving the largely prevalent use of hair dyes in the population, frequency of use rather than simple distinction between users and nonusers, would be relevant to consider.

In a cohort study conducted in the framework of the Shanghai Women's Health Study, a total of 75221 women completed a baseline survey between 1996 and 2000 and were followed up to 2005.[26] A total of 358 incident cases of breast cancer were identified. In the sample, 29076 women (39.6%) reported ever using hair dye and a total of 358 incident cases of breast cancer were identified. The average number of person years was 7.31. The RR for breast cancer in hair dye users vs non-users, adjusted by age, education and smoking, was 0.93 (95% CI 0.78-1.09). No relation was documented between duration of hair dye use and risk of cancer. Stratification by menopausal status indicated no association between breast cancer and hair dye use in either pre- or post-menopausal women. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale.

A case-control study was conducted, including 191 breast cancer patients interviewed in a hospital in 1975 - 1976 in Oxford, UK, with 561 aged matched controls without cancer (within three years), marital status, and social class.[27] The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. Seventy-three cases and 213 controls had used permanent or semi-permanent hair dyes, giving an RR of 1.01. There was no evidence of an increasing risk for breast cancer with increasing duration of use of hair dyes or with use beginning more than four or more than nine years before diagnosis.

A case-control study consists of 50 breast cancer patients at a cancer treatment center with 100 hospitalized controls in London, Ontario, and 35 breast cancer cases with 70 neighborhood controls in Toronto, Ontario.[28] The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. The RRs for breast cancer from use of permanent hair dyes (at any time) were 1.3 (95% CI 0.6-2.5) in London and 1.1 (0.5-2.4) in Toronto. Further statistical analyses, allowing for smoking habits, family history of cancer and age at first birth, showed no significant relationship between hair-dye use and breast cancer incidence.

A case control study was performed among 398 breast cancer patients at a screening center between 1977 and 1981 in New York City, with 90 randomly selected, age matched controls.[29] The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. The OR for breast cancer from use of permanent hair dyes (at any time) was 0.8 (95% CI 0.6-1.1). There was also no evidence of a trend in risk with increasing number of hair dye uses (38% of the subjects had used hair dye at least 100 times, while 77% had used hair dyes at least once). An analysis of breast cancer risk from 5 or more years of work as a beautician was also compared. Although personal hair dye use was unrelated to breast cancer risk, the OR for beauticians was 3.0 (95% CI 1.1-7.8).

A hospital-based case-control study of breast cancer was conducted on 1052 women in Iran.[30] The evaluation of hair dye exposure was + on the Rollison et al. (2006) scale. There were 526 newly diagnosed breast cancer cases, with 526 age-matched controls randomly selected in Namazi Hospital between November 2014 and March 2016. The study showed that multiple factors were associated with the risk of breast cancer, such as hair coloring, age at first delivery, stress, and smoking. The OR of breast cancer from hair dye use on a regular basis compared to no use was 1.93 (95% CI, 1.41-2.62). However, the design of the study was not able to confirm a causal association between any investigated variables and breast cancer.

A meta-analysis was performed to investigate the association between hair dye use and breast cancer, including 8 case-control studies published between 1980 and 2017 with a total of 38037 participants.[31] Of the 24 studies initially considered relevant, only 8 were considered to meet the authors' selection criteria, including the five prospective studies that did not show any association between hair dye use and breast cancer. The prospective studies were excluded for various reasons: hazard ratio (HR) instead of an OR/RR was used, the death rate instead of cancer incidence was recorded, no information on the number of controls was provided, and the study had a high focus on other types of cancer. Using a random effects model the pooled RR for women using hair dyes was 1.18 (95% CI 1.03-1.37), which indicates an 18.8% increased risk of future development of breast cancer among hair dye users. However, the authors also stated that the reliability of this systematic analysis had decreased due to the large number of excluded prospective studies. Importantly, the

limited exposure information in the eight analyzed studies did not allow for any conclusion related to dose-response (either duration or frequency of use), or type of hair dye.

Genetic Polymorphisms

NAT1, NAT2, GSTM1, and GSTT1 Genotype/Phenotype

Altered genotype and phenotype of liver enzymes may activate or inactivate potential carcinogens.[8] NAT1 and NAT2 genes encode arylamine *N*-acetyltransferases that can deactivate (or, less commonly, potentially activate) arylamine and hydrazine chemicals. Polymorphisms in these genes determine, in part, the liver-function phenotypes. Human populations segregate into rapid, intermediate, and slow acetylator phenotypes. *N*-acetylation is a major route of biotransformation of aromatic amine compounds, including those found in hair dyes. The GSTM1 gene encodes a cytoplasmic glutathione *S*-transferase that belongs to the μ class, which functions in the detoxification of electrophilic compounds (including carcinogens, therapeutic drugs, environmental toxicants, and products of oxidative stress) through conjugation with glutathione. The GSTT1 gene encodes the glutathione *S*-transferase that belongs to the θ class, which catalyzes the conjugation of reduced glutathione to a variety of electrophilic and hydrophobic compounds. Genetic polymorphisms in GSTM1 and GSTT1 also may affect the metabolism of the constituents of hair dyes.

In one study, the association between hair dye use and effect modification by NAT1, NAT2, GSTM1, and GSTT1 genotypes was evaluated among patients with bladder cancer.[8] The hair dye models were adjusted for age, race, sex, and smoking status. An increased risk of bladder cancer was reported primarily among exclusive users of permanent dyes who had NAT2 slow-acetylation phenotypes, compared to never users of dye with NAT2 rapid/intermediate-acetylation phenotypes. This increase was observed in females with a college degree, but the difference was not statistically significant. The authors concluded that NAT1, GSTM1, and GSTT1 genotypes did not appear to be important modifiers of the association between ever, permanent, or exclusive permanent hair dye use and bladder cancer.

One study reported that individuals with the NAT2 slow-acetylator phenotype who exclusively used permanent hair dyes had an increased risk of bladder cancer (OR 2.9; 95% CI 1.3-7.5) after adjustment for cigarette smoking, compared to individuals with the NAT2 rapid-acetylator phenotypes (OR 1.3; 95% CI 0.6-2.8).[32] The NAT*10 allele contains an altered polyadenylation signal that has been associated with elevated DNA adduct levels and greater risk of bladder cancer in other studies. Individuals with a NAT1*10 genotype who were non-smokers and used permanent hair dyes exclusively had an OR of 1.0 (95% CI 0.2-4.3), and those with a non-NAT1*10 genotype had an OR of 6.8 (95% CI 1.7-27.4) in this study.

A case-control study that evaluated the association of hair dye use with bladder cancer among females also examined the effect of hair-dye use among genetic subgroups.[33] ORs were estimated after adjustment for age, region, and smoking. No statistically significant differences in bladder cancer incidence were noted as a function of any of the genotypes examined, including those with slow- or intermediate/rapid-NAT2 acetylator phenotypes. For NAT2 slow-acetylator phenotypes, the OR was 0.6 (95% CI 0.3-1.4), and for NAT2 rapid/intermediate phenotypes, the OR was 0.9 (95% CI 0.3-2.6). Individuals with a NAT1*10 genotype had an OR of 2.9 (95% CI 0.7-11.6), and those with non-NAT1*10 had an OR of 0.6 (95% CI 0.2-1.6). These findings were directionally opposite to those of Gago-Dominguez et al. (2003).[32]

A population-based case-control study was conducted to explored the relationship between hair dye use and the incidence of NHL.[34] The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale. Subjects were identified among residents of 4 Surveillance Epidemiology and End Results (SEER) registries (Iowa, Los Angeles County, and metropolitan Detroit and Seattle). There were 101 cases and 98 control subjects reporting no use of hair coloring products and 509 cases and 413 control subjects among the women reporting use of such products, in the population studied. There were 317 cases and 269 control subjects reporting the use of hair dyes before 1980 and 192 cases and 148 controls reporting hair dye use in 1980 or thereafter. The risk estimates were adjusted for age, sex, race and SEER area; education, smoking status, history of farming, having a first-degree relative with a history of NHL or lymphoproliferative malignancy were excluded from the final models because these factors did not materially alter (> 10%) the parameter estimates.

Among the women who started using permanent, intense-tone hair dyes before 1980, those with the NAT2 slow-acetylator phenotype (23 cases/14 controls) or who had no copies of the NAT1*10 allele (26 cases/16 controls) did not have an increased risk of NHL (OR 1.5; 95% CI 0.6-3.6 and OR 1.5; 95% CI 0.7-3.3, respectively). Likewise, women in this subpopulation with 1 or 2 copies of the NAT1*10 allele (22 cases/10 controls) did not have an increased NHL risk (OR 2.5; 95% CI 0.9-7.6, respectively). However, women with the NAT2 rapid/intermediate-acetylator phenotype who started using such dyes before 1980 (25 cases/11 controls) did exhibit a potentially increased NHL risk (OR 3.3; 95% CI 1.3-8.6). There was no evidence of increased risk among women who began using hair dyes after 1980.

One study re-evaluated data from a case-control study of NHL in Connecticut to consider NAT1 and NAT2 genotype/phenotype and 17 other single nucleotide polymorphisms (SNPs).[35,36] The subjects, including 461 cases and 535 control subjects, were identified from the Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource (RCASR). Potentially confounding variables included in the final model were age and race. Adjustment for cigarette smoking, alcohol consumption, and farming history were not included in the final models because these factors did not materially alter the parameter estimates. The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale.

With the exception of FL, none of the different individual genes examined was associated with a statistically-significant change in the risk of NHL for any of the NHL subtypes considered. The exception was a statistically-significant increase in the risk of FL in women with rapid/intermediate NAT2 phenotypes who started to use hair dye before 1980, compared with women who never used hair dye (OR 2.8; 95% CI 1.1-7.2; 24 rapid/intermediate acetylator cases vs. 79 control subjects). In women who carried the CYP2C9 allele (TT or CT genotypes) and started to use hair dyes before 1980, there was an increased risk of NHL in general (OR 2.9; 95% CI 1.4-6.1; 58 cases, 43 control subjects) and the follicular lymphoma subtype specifically (OR 6.3; 95% CI 1.6-24.7; 20 cases, 43 control subjects), compared with women who never used hair dyes and women who started using hair dyes in 1980 or thereafter. No association evident in women who carried the CYP2C9 allele (TT or CT genotypes) and started using hair dyes in 1980 or thereafter (23 cases, 46 control subjects), compared with women who carried this allele and never used hair dyes (OR 1.0; 95% CI 0.4-2.3; 23 cases, 46 control subjects).

DNA Repair-Enzyme Genes

One study investigated the interaction between polymorphisms in DNA repair genes and hair dye use with NHL in a population-based case-control study in Connecticut.[37] The study population from which the subjects were drawn was the same as that of Zhang et al. (2009)[36] study summarized above, including 461 cases and 535 control subjects identified from the Yale Comprehensive Cancer Center's RCASR. The subjects included 518 NHL cases and 597 age-matched controls. All subjects were genotyped for 24 single nucleotide polymorphisms (SNPs) in 16 DNA repair-enzyme gene polymorphisms. The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. All of the models were adjusted for age, race, and smoking status. The risk of FL, but not DLBCL, was statistically-significantly elevated in women with any one of 10 of the 24 SNPs and who used hair dye before 1980, compared to those who never used hair dyes; the ORs ranged from 1.93 (95% CI 1.00-3.72; 15 cases and 70 control subjects with EECC1rs3212961 CC) to 3.28 (95% CI 1.27-8.50; 7 cases and 110 control subjects with BRCA2rs144848 AC+CC). In addition, there was a statistically-significant interaction between hair dye use before 1980 and NHL in women with one of these 10 SNPs (1.88 (95% CI 1.26-2.80; 146 cases and 100 control subjects with WRNrs1346044 TT). There was no association between NHL, FL, or DLBCL in women who began using hair dyes after 1980.

CONCLUSION

The CIR Expert Panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer.

Table 1. Hair Dye Epidemiology Studies considered by the CIR Expert Panel.

Study Type/Methodology	Results	Reference
Bladder Cancer		
Population-based case-control study in the Netherlands. Cases diagnosed between 1975 and 2009 for a total of 246 female cases with 2587 female controls; Analyses were not performed for the men selected for the study because less than 5% reported ever using hair dyes.	No association between bladder cancer and ever/never use of permanent hair dyes – permanent OR 0.87 (95% CI 0.65-1.18); temporary OR 0.7 (95% CI 0.58-1.02) No association between bladder cancer and duration of use, number of times used per year, total number of times used over a lifetime, dying all the hair or only part of the hair, or dye color (none of the subjects reported use of black dye). No association found when patients stratified by aggressiveness of the cancer.	Ros et al (2012)[7]

Population-based case-control study in Maine, Vermont, and New Hampshire. Cases diagnosed 2001 to 2004 for a total of 1193 cases (911 male and 282 female) with 1418 controls (1039 male and 378 female). Genotyping done for NAT2, NAT1, GSTM1, and GSTT1.	No association between ever/never use of hair dyes and bladder cancer – women OR 0.7 (95% CI 0.5-1.0); men OR 0.7 (95% CI 0.4-1.0). No association between hair dye use, NAT2 phenotype or NAT1 genotype and bladder cancer risk. Increased risk of bladder cancer with permanent hair dye use in a subgroup of women with a college degree, but no dose-response for color, duration of use, or total lifetime uses. NAT2 phenotype was associated with a suggestive, but not statistically significant, increased risk when college-degreed women were stratified by education – this was based on 15 cases and 6 controls.	Koutros, et al. (2011)[8]
Population-based case-control study of bladder cancer in Iran with 692 cases and 692 controls (identified using the Iranian cancer registry).	Overall (male and female) OR for hair dye use and bladder cancer was 1.99 (95% CI 1.02-3.82). When women and men were analyzed separately, no significant association with hair dye use and bladder cancer was reported.	Shakhssalim et al. (2010)[9]
Prostate Cancer		
Hospital-based case-control study of prostate cancer in Taiwan with 296 cases and 296 controls Another 608 incident prostate cancer cases were investigated to determine the rate of prostate cancer survival.	The prevalence of hair dye use was higher in the cases than the controls (95/296 = 32.1% vs. 64/296 = 21.6%, $p < 0.05$), and the hair dye users had increased odds of prostate cancer when compared with the non-users (adjusted OR 2.15; 95% CI 1.32–3.57). Personal hair dye use increased risk of prostate cancer with a dose-response effect. Of the 608 cases, 26.4% (161/608) reported having used hair dyes. The use of hair dye did not affect cumulative incidence estimates of prostate cancer-specific deaths (p=0.753).	Tai et al. (2016)[10]
Lymphoma and Leukemia		
Cohort or case-control study of leukemia in North America, Europe and Asia.	Mutivariate analysis: Based on 20 studies, ever use of any type of personal hair dye was associated with a non-statistically significant increased risk of leukemia, when compared to no use of hair dye (meta-RR=1.09; 95% CI 0.97–1.22). A model restricted to case-control studies yielded a statistically significant increased RR of 1.13 (95% CI 1.00–1.28), while a model including cohort studies yielded an RR of 1.00 (95% CI 0.85–1.19). When restricted to studies that adjusted for smoking history, use of any hair dye was not associated with leukemia (RR= 0.99; 95% CI 0.76–1.29).	Towle et al. (2017)[13]
Population-based case-control study of leukemia and non-Hodgkin's lymphoma (NHL) in Italy. There were 161 cases (120 lymphoid and 41 myeloid) and 84 randomly-selected controls among women in the population studied.	Multivariate analysis: Hair dye use for at least 15 years was associated with NHL (OR=2.3; 95% CI 1.0-4.9), but hair dye use for less than 15 years was not associated with NHL (OR=1.4; 95% CI 0.6-3.1). Leukemia was not associated with using hair dye for at least 15 years (OR=2.7; CI 0.9-7.9) or for less than 15 years (OR=2.7; CI 0.9-8.4).	Parodi et al. (2016)[14]
Hospital-based case-control study of lymphoproliferative cancers in Egypt. There were 130 cases (107 NHL and 23 chronic lymphocytic leukemia) and 130 age- and sex-matched controls.	Multivariate analysis: No increase in the risk of lymphoproliferative disorders with history of using hair dyes (χ^2, $p>0.05$).	Salem et al. (2014)[18]
Hospital-based case-control study of myelodysplastic syndromes (MDS) in China. There were 403 cases and 806 controls.	Univariate analysis: OR for hair dye use (≥2 times per year) and all MDS was 1.46 (95% CI 1.03-2.07). Multivariate analysis: OR was 1.31 (95% CI 0.88-1.93).	Lv et al. (2010)[19]

Hospital-based case-control study in Shanghai of NHL. There were 649 cases and 1298 controls	No increased risk of NHL, with an OR of 0.93 (95% CI 0.75-1.16). For chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), the authors reported a significantly lower risk associated with hair dye use with an OR of 0.37 (95% CI 0.18-0.76).	Wong et al. (2010)[20]
Re-evaluated tissue samples from an NHL case-control study in males from Iowa and Minnesota using FISH (fluorescence in situ hybridization) cytogenetic technique to evaluate both *t*-positive and *t*-negative NHL subtypes.	An association between ever/never use of hair dyes and t(14;18)-negative NHL (OR 2.9; 95% CI 1.6-5.0) and bcl-2 positive NHL (R 2.2; 95% CI 1.4-3.4), but not with t(14;18)-positive NHL (OR 1.3; 95% CI 0.6-2.6) or bcl-2 negative NHL (OR 1.4; 95% CI 0.5-3.8).	Chang et al. (2010)[21]
Hospital-based case-control study of acute myeloid leukemia (AML) in Shanghai, China. There were 722 cases and 1,444 controls.	No increase in the risk of AML with personal use of hair dyes; OR = 0.98 (95% CI 0.8-1.2).	Wong et al. (2009)[22]
Breast Cancer		
Population-based case-control study of breast cancer in African American and European American women in New York city and 10 counties in New Jersey. There were 1508 African American and 772 European American cases and 1290 African American and 715 European American frequency-matched (by age and county of residence) control subjects.	Increase in the odds of breast cancer in African American women who reported using dark permanent hair dyes (1.52; 95% CI 1.21-1.91), African American women who typically had their hair dyed in a salon (1.30; 95% CI 1.03-1.63), and European American women who had a history of both hair dyes and chemical hair relaxers (2.21; 95% CI 1.26-3.86). Women who started using hair dyes before 1980 were not distinguished from women who started in 1980 or thereafter.	Llanos et al. (2017)[24]
Population-based case-control study of breast cancer in Finland. There were 6,567 cases and 21,598 age-matched controls.	Increase in the odds of breast cancer in women who ever used hair dyes, compared with those who never used hair dyes (OR=1.28; 95% CI 1.10-1.48). Statistically significant trend in ORs for cumulative use of hair dyes (1.07 and 1.31 for 1-2 episodes and 35-89 episodes, respectively). In comparison, the OR decreased from 1.28 (10 - 34 dye episodes) and 1.31 (35 - 89 dye episodes) to 1.25 ($\geq$ 90 dye episodes).	Heikkinen et al. (2015)[25]
Breast Cancer (continued)		
Prospective population-based cohort study of breast cancer in China. Cases of breast cancer include 234 hair dye users and 358 non-users.	No increase in the relative risk of breast cancer in women who ever used hair dyes, compared with never used hair dyes (RR=0.93; 95% CI 0.78-1.09). Stratification by menopausal status indicated no association between breast cancer and hair dye use in either pre- or post-menopausal women.	Mendelsohn et al. (2009)[26]
Hospital based case-control study in the UK. There were 191 cases and 561 age matched controls. 73 cases and 213 controls had ever used hair dyes.	A non-statistically significant increase in the relative risk of breast cancer in women who ever used hair dyes, compared with never used hair dyes (RR=1.01). There was no evidence of an increasing risk for breast cancer with increasing duration of use of hair dyes or with use beginning more than four or more than nine years before diagnosis.	Kinlen et al. (1977)[38]
Hospital based case-control study in Canada and London. There were 85 cases and 170 controls, both over two locations.	A non-statistically significant increase in the odds of breast cancer in women who ever used hair dyes, compared with never used hair dyes (London: RR=1.3; 95% CI, 0.6-2.50 and Toronto, Ontario: RR=1.1; 95% CI, 0.5-2.4). Further statistical analyses, allowing for smoking habits, family history of cancer and age at first birth, showed no significant relationship between hair-dye use and breast cancer incidence.	Stavraky et al. (1979)[28]
Hospital based case-control study in New York City with 398 cases and 90 randomly selected, age-matched controls.	No increase in the odds of breast cancer in women who ever used hair dyes, compared with never used hair dyes (OR=0.8; 95% CI 0.6-1.1). There was also no statistically significant difference between those who report using hair dyes at least once and those who reported more than 100 uses.	Koenig et al. (1991)[29]

Hospital-based case-control study in Iran with 526 newly diagnosed breast cancer cases and 526 randomly selected, age-matched controls.	Multiple factors contribute to the risk of breast cancer, such as hair coloring, stress, and smoking. The OR of breast cancer from hair dye use on a regular basis compared to no use was 1.93 (95% CI, 1.41-2.62).	Dianatinasab et al. (2017)[30]

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