HAIR DYE EPIDEMIOLOGY – through July, 2014

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 a preformed color.

Epidemiology studies that seek to determine links, if any, between hair dye use and disease provide broad information and have been considered by the CIR Expert Panel, although these studies do not specifically address the safety of individual hair dye ingredients.

The following provides a brief summary of the 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 International Agency for Research on Cancer (IARC) in 2010[1].

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, based on the lack of strength of the associations and inconsistency of the findings. In addition, the Panel noted that there was no consistent pattern of genotype/phenotype influence on hair dye epidemiology findings.

Background

The CIR Expert Panel reviews selected, new epidemiological studies addressing the personal use of hair dyes as these studies become available. Table 1 summarizes these studies specifically addressing bladder cancer, lymphoma, and leukemia. Occupation as a hairdressers, 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 CIR Expert Panel considers that epidemiological studies based of better information about exposure, compared with other such studies, can provide more useful findings. Rollison et al. (2006)[2] noted that 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. These authors developed a scale from + to ++++ to score the quality of hair dye exposure assessments in hair dye epidemiology studies. This scale was used to score the studies that are summarized in Table 1.

An IARC working group summarized the relevant epidemiology studies and observations on bladder cancer and hematological concerns.[1,3] The working group concluded that 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. They also concluded that the animal studies provided limited evidence for the carcinogenicity of hair colorants. Occupational exposure during work as a hairdresser, barber, or beautician was also 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.

Bladder Cancer

Turati et al. (2014) performed a meta-analysis of 15 case control and 2 cohort studies.[4] The pooled relative risk (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).

Ros et al. (2012)[5] performed a population-based case-control study of hair dye use and bladder cancer in the Netherlands. 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). The hair dye exposure assessment

was ++++ on the Rollison et al. (2006) scale. 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). 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.

Koutros et al. (2011)[6] conducted a population-based case-control study in Maine, Vermont, and New Hampshire. The subjects were 1193 cases of urinary bladder cancer diagnosed from 2001 to 2004 (911 male and 282 female), and 1418 controls (1039 male and 379 female). The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale.

No association was found between ever/never use of hair dyes and bladder cancer – the odds ratio (OR) and associated 95% confidence interval (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).

Shakhssalim et al. (2010)[7] reported a population-based case-control study of bladder cancer in Iran with 692 cases and 692 controls. 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 1.99 (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.

Lymphoma and Leukemia

Wong et al. (2009)[8] reported a hospital-based case-control study of acute myeloid leukemia (AML) in Shanghai, China. There were 722 cases and 1444 controls, and the evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. The study found no increase in the risk of AML and personal use of hair dyes; OR of 0.98 (95% CI 0.8 – 1.2).

Lv et al. (2010)[9] conducted a hospital-based case-control study of myelodysplastic syndromes (MDS) in China. 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 MDS was 1.46 (95% CI 1.03 – 2.07). In a multivariate analysis, the OR was 1.31 (95% CI 0.88 – 1.93).

Wong et al. (2010)[10] conducted a hospital-based case-control study in Shanghai of non-Hodgkin's lymphoma (NHL). There were 649 cases and 1298 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 chronic lymphocytic leukemia (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).

Chang et al. (2010)[11] re-evaluated tissue samples from a NHL case-control study in males from Iowa and Minnesota using FISH (fluorescence *in situ* hybridization) cytogenetic technique to evaluate both *t*(14;18)-positive and *t*(14;18)-negative NHL subtypes. The evaluation of hair dye exposure scored + on the Rollison et al. (2006) scale. An association between ever/never use of hair dyes and *t*(14;18)-negative NHL was reported, but no association was found with *t*(14;18)-positive NHL.

Glioma

Shao et al. (2013)[12] performed a meta-analysis of 4 case-control and 2 cohort studies of personal hair dye use and the incidence of gliomas. Summary relative risks (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.

NAT1, NAT2, GSTM1, and GSTT1 Genotype/Phenotype

The study by Koutros et al. (2011)[6] is the latest in a series of studies that have examined the influence of genotype and phenotype of liver enzymes that may activate or inactivate potential carcinogens.

NAT1 and NAT2 genes encode arylamine *N*-acetyltransferases that can function to activate or deactivate 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.

Koutros et al. (2011)[6] performed genotyping for NAT2, NAT1, GSTM1, and GSTT1. 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, 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 use and bladder cancer.

Gago-Dominguez et al. (2003)[13] 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) compared to individuals with the NAT2 rapid acetylator phenotypes (OR 1.3; 95% CI 0.6 – 2.8). 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).

Kogevinas et al. (2006)[14] evaluated the association of hair dye use with bladder cancer among females in a case-control study that also examined the effect of hair dye use among genetic subgroups. 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).[13]

Morton et al. (2007)[15] conducted a U.S. population-based case-control study of NHL. Women with the NAT2 slow acetylator phenotype or who had no copies of the NAT1*10 allele and used intense-tone permanent hair dyes before 1980 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), but women with the NAT2 rapid/intermediate acetylator phenotype or 1 or 2 copies of the NAT1*10 allele did exhibit a potential increased NHL risk (OR 3.3; 95% CI 1.3 - 8.6 and OR 2.5; 95% CI 0.9 - 7.6, respectively).

Zhang et al. (2009)[16] re-evaluated data from a case-control study of NHL in Connecticut (Zhang et al. 2004)[17] to consider NAT1 and NAT2 genotype/phenotype and other single nucleotide polymorphisms (SNPs). None of the different individual genes was associated with a significant change in the risk of NHL overall or for any of the NHL subtypes considered. The finding that the NAT2 rapid/intermediate acetylator phenotype or the presence of copies of the NAT1*10 allele in this study was not associated with an increase of NHL is not consistent with the findings of Morton et al. (2007),[15] but the finding in this study that the NAT2 slow acetylator phenotype is not associated with and increased risk of NHL is consistent with the findings of Morton et al (2007).[15]

Table 1. Recent Original 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. Exposure assessment was on the Rollison et al. (2006) scale.	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)[5]
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. Exposure assessment ++++ on the Rollison et al. (2006) scale.	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 degree women were stratified by education – this was based on 15 cases and 6 controls.	Koutros, et al. (2011)[6]
Population-based case-control study of bladder cancer in Iran with 692 cases and 692 controls (identified using the Iranian cancer registry). Exposure assessment was a + on the Rollison et al. (2006) scale.	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)[7]
Lymphoma and Leukemia		
Hospital-based case-control study of acute myeloid leukemia (AML) in Shanghai, China. There were 722 cases and 1,444 controls. Evaluation of hair dye exposure that was a ++ on the Rollison et al. (2006) scale.	No increase in the risk of AML and personal use of hair dyes with an OR of 0.98 (95% CI 0.8 – 1.2).	Wong et al. (2009)[8]
Hospital-based case-control study of myelodysplastic syndromes (MDS) in China. There were 403 cases and 806 controls. Evaluation of hair dye exposure that was a ++ on the Rollison et al. (2006) scale.	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)[9]
Hospital-based case-control study in Shanghai of non-Hodgkin's lymphoma (NHL). There were 649 cases and 1298 controls Evaluation of hair dye exposure that was a ++ on the Rollison et al. (2006) scale.	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)[10]

Re-evaluated tissue samples from a non-Hodgkin's lymphoma 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. The evaluation of hair dye exposure that was a + on the Rollison et al. (2006) scale.	An association between ever/never use of hair dyes and *t*(13:18)-negative NHL was reported, but no association was found with *t*(14:18)-positive NHL.	Chang et al. (2010)[11]

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