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Hair dye use and risk of human cancer

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1. ABSTRACT

Over 50% of the adult population will use hair dyes at some point in their lifetimes. Hair dyes consist of various chemicals and the composition of these chemicals vary by hair dye types. Chemicals p-phenylenediamine and aminophenyl have been suggested as possible carcinogens or mutagens in experimental studies. The scientific community has been interested in this potential public health impact and the results of published epidemiological studies are summarized here. The current evidence provides limited evidences on the association between personal hair dye use and human cancer risk, except for the possibility of hematopoietic cancers and to a lesser extent, bladder cancer. Risk appears to be affected by time period of use and by specific genetic polymorphisms. Future studies should investigate potential gene and environment interaction to assess possible genetic susceptibility. Several methodological issues should also be considered in future studies including completed hair dye use information such as on timing, duration, frequency and type of hair dye product use.

2. INTRODUCTION

It is estimated that the hair-coloring product sales worldwide is about $12 billion per year and that up to 50% of the adult population of high-resource countries use hair colorants (1). Hair-coloring products include permanent, semipermanent and temporary dyes that vary by chemical formulation and are distinguished mainly by how long they last and whether they penetrate the hair shaft. Permanent dyes represent about 80% of the hair color market (1). Some compounds in hair dyes have been reported to be mutagenic or carcinogenic in bioassay systems (2). Many oxidative dye products were reformulated in the early 1980s to eliminate ingredients that produced tumors in experimental bioassay studies. Although it is unclear whether the current compounds have carcinogenic effects or can affect overall immune response, paraphenylenediamine (PPD), a major arylamine currently used in most hair dyes, has been suggested as a putative carcinogen (3). In addition, it has been found that many permanent hair dyes are contaminated with 4-

aminobiphenyl (4-ABP), a recognized human carcinogen (4).

During the past three decades, the general public and the scientific community have shown great interest in the potential health impact from personal use of hair dyes. Epidemiological studies have been conducted to investigate the relationship between hair dye use and human cancer risk. The reported results, however, have been inconsistent and the relationship is varied by cancer type. The purpose of this review is to summarize the current understanding of the relationship between personal hair dye use and risk of human cancer by specific cancer types.

3. BLADDER CANCER

A total of 11 case-control studies (5-15) and three cohort studies (16-18) have investigated the relationship between personal hair dye use and risk of bladder cancer (Table 1). These investigations assessing hair dye use and risk of bladder cancer have produced inconsistent results. Many of the studies involved small population sizes and/or incomplete hair dye usage information.

One large population-based case-control study including 2,982 cases and 5,782 controls reported an increased risk of bladder cancer associated with ever using black hair dye product for both men and women (OR=1.4, 95% CI: 1.0,1.9) (8). Another population-based case-control study involving 897 cases and equal number of controls found a two-fold increased risk of bladder cancer among women who had used permanent hair dyes at least once a month, and the risk increased to 3.3-fold (95% CI: 1.3,8.4) for women who were regular (at least monthly) users for at least 15 years (15). The cohort studies generally reported no association between bladder cancer and hair dye use (16-20)

Three meta-analysis studies have been published since 2005 assessing risk of bladder cancer and exposure to hair dyes (21-23). A study by Huncharek and Kupelnick (21), which had significant exclusion criteria (which limited the meta-analysis to a mere seven studies) and a unique weighted method of analyzing the data, suggested that there is a relative risk between 1.22 (95% CI: 1.11, 1.51) and 1.50 (95% CI: 1.30, 1.98). Another two meta-analysis studies by Takkouche *et al.* (22) and Kelsh *et al* (23) found no association between bladder cancer and hair dye use.

To date, very few studies have investigated whether genetic susceptibility modify the relationship between personal hair dye use and risk of bladder cancer. Gago-Dominguez *et al.* (15) examined permanent hair dyes and bladder cancer risk by N-acetyltransferase-2 (NAT2) phenotype among female in the Los Angeles Bladder Cancer Study. Among NAT2 slow acetylators, exclusive use of permanent hair dyes was associated with 2.7-fold increased risk of bladder cancer (95% CI: 1.0,7.2), and the risk appeared to increase with increasing duration and frequency of use of hair dye products. Hair dye use was not associated with bladder cancer risk among NAT2 fast acetylators (OR=1.1, 95%CI: 0.4,2.7). In 2003, Gago-Dominguez *et al.* (3) also examined the effects of several other potential arylamine-metabolizing genotypes/phonetypes (*GATM1, GSTT1, GSTP1, CYP1A2*). The study found a 2.5-fold increased risk of bladder cancer associated with permanent hair dye use among women exhibiting CYP1A2 'slow' phenotype but not among women exhibiting CYP1A2 'rapid' phenotype. No such modifying effects were observed for *GSTT1, GSTM1*, and *GSTP1* genotypes. Another study reported no such increase in risk by any *NAT1, NAT2, GSTM1, GSTM3, GSTP1, GSTT1, or CYP1A2* genotype (13).

4. BREAST CANCER

A total of 11 case-control studies (7, 24-34) and four cohort studies (16, 18-20, 35) have investigated the relationship between personal hair dye use and risk of breast cancer (Table 2). Nearly all of the studies have yet to suggest a conclusive no association between breast cancer risk and exposure to hair dyes with the exception of one case-control study (34).

No association between breast cancer and hair dye use was noted in most case-control studies (7, 24-26, 28-33). When some of these studies estimated frequency, duration, or dose-response relationships, no significant results exists for most studies. Moreover, several studies lacked information critical to performing some of these analyses (31, 34).

When assessing for duration of use and type of hair dye use, positive associations sometimes were seen. In a study by Cook *et al* (32), 2.5-fold (95% CI: 1.6, 3.9) increased risk was found among women who reported using any hair dye products after bleaching. A significantly increased risk was also observed for women who reported using any rinse (OR=1.7, 95% CI: 1.2, 2.5) and any frosting/tipping (OR=1.5, 95% CI: 1.2, 2.0) before applying hair dye products. Among women who reported using two or more types of hair dye products, a 3.1-fold (95%CI: 1.6, 6.1) increased risk of breast cancer was observed for those used hair dyes for 90 or more total episodes during their lifetime. In the Zheng *et al.* study (33) individuals using exclusively semi-permanent types of hair coloring products, some ORs were elevated. Also, an increase in risk was noted for women who changed hair colors multiple times (28)

The one study which suggested a strong association is the Petro-Nustas *et al.* (34) case-control study in Jordan women. They reported that women who had ever used hair dye products experienced an 8.6-fold (95 CI: 3.3, 22.3) increased risk of breast cancer compared to those who had never used hair dye products. However, this study had several limitations, including a convenience sample of controls, lack of detailed information on hair dye use, and most importantly, is based on a very small sample size.

5. NON-HODGKIN LYMPHOMA

Fourteen case-control studies and three cohort studies (18, 20, 36) relating hair dye use and non-Hodgkin lymphoma (NHL) have been published (37-52)(Table 3).

Table 1. Summary of the published literature on the relationship between personal use of hair dyes and risk of bladder cancer

Authors (Ref)	Year of the report	Study Design	Country	Study Population	Disease Outcome	Findings
Cohort Studies						
Henneckens *et al.*(16)	1979	Retrospective cohort, 4 yrs of follow-up, 1972-76	USA	Cohort: 120,557; cases 5	Incidence	Female: Permanent hair dyes, RR=0.6, no trend with duration
Thun *et al.* (20); Altekruse *et al.* (19); Henley *et al.* (17)	1994; 1999; 2001	Prospective cohort, 7 yrs of follow-up, 1982-89; 12 yrs follow-up, 1994; and 15 yrs follow-up, 1998	USA	Cohort: 537,369; cases=336	Mortality	Female: Permanent hair dyes, RR=0.6-1.1, no trend with duration
Mendelsohn *et al.* (18)	2009	Prospective cohort, 5-9 yrs of follow-up 1996-2005	China	Cohort: 75,221; cases: 32	Incidence	Female: OR=1.1; adjusted for smoking
Case-Control Studies						
Jain *et al.* (5)	1977	Hospital-based	Canada	Cases: 107; controls: 107	Incidence	All hair dyes OR=1.1, not adjusted for smoking
Neutel *et al.* (6)	1978	Hospital-based	Canada	Cases: 50; controls: 50	Incidence	Female, all hair dyes OR=0.9, not adjusted for smoking
Howe *et al.* (9)	1980	Population-based,1974-76	Canada	Cases: 480(M) 152 (F); controls: 1:1	Incidence	All hair dyes, female: OR=0.7; male: no exposed controls; unknown for control for smoking
Stavraky *et al.* (7)	1981	Population-based, 1976	Canada	Cases: 23; controls: 46	Incidence	All hair dyes OR=1.1, unknown for control for smoking
Hartge *et al.* (8)	1982	Population-based,1977-78	USA	Cases: 2249(M) 733(M); controls: 4282(M) 1500(F)	Incidence	All hair dyes OR=0.9-1.1, no trend with frequency and duration; OR=1.4 for dark color hair dyes; adjusted for smoking
Ohno *et al.* (10)	1985	Population-based	Japan	Cases: 293; controls: 589	Incidence	All hair dyes OR=1.5; adjusted for smoking
Nomura *et al.* (14)	1989	Population-based, 1977-86	USA	Cases: 195(M) 66(F); controls: 2:1	Incidence	All hair dyes OR=1.3-1.5, no trend with duration; adjusted for smoking
Gago-Dominguez *et al.* (15,3)	2001; 2003	Population-based, 1987-96	USA	Cases: 694(M) 203(F); controls: 1:1	Incidence	All hair dyes, no association for male; female: OR=1.9* for permanent users and increasing trend with frequency & duration; OR=2.9*, 2.5*, 6.8* for NAT2 slow phenotype, CYP1A2 slow phenotype and non-NAT1*10 genotype, respectively, with increasing trend; adjusted for smoking
Andrew *et al.* (11)	2001	Population-based, 1994-98	USA	Cases: 495; controls: 665	Incidence	Male: all hay dyes OR=0.5; Female: permanent hair dyes OR=1.5, no trend with frequency & duration; adjusted for smoking
Lin *et al.* (12)	2006	Hospital-based, 1999-2001	USA	Cases: 712; controls: 712	Incidence	Female: all hair dyes OR=0.9; male: all hair dyes OR=0.7; adjusted for smoking
Kogevinas *et al.* (13)	2006	Hospital-based, 1998-2001	Spain	Cases: 128; controls: 131	Incidence	Female: all hair dyes OR=0.8; no significant association after stratify by NAT1, NAT2, GSTM1, GSTM3, GSTP1, GSTT1, and CYP1A2; adjusted for smoking

*95% confidence interval excludes null value

Table 2. Summary of the published literature on the relationship between personal use of hair dyes and risk of breast cancer

Authors (Ref)	Year of the report	Study Design	Country	Study Population	Disease Outcome	Findings
Cohort Studies						
Henneckens *et al.*(16)	1979	Retrospective cohort, 4 yrs of follow-up, 1972-76	USA	Cohort: 120,557; cases 270	Incidence	Permanent hair dyes RR=1.1; RR=1.5 for those used for more than 20 years
Green *et al.* (35)	1987	Prospective cohort, 6 yrs of follow-up, 1976-82	USA	Cohort: 118,404; cases 353	Mortality	Permanent hair dyes RR=1.1, no trend with frequency & duration
Thun *et al.* (20); Altekruse *et al.* (19)	1994; 1999	Prospective cohort, 7 yrs of follow-up, 1982-89; 12 yrs of follow-up, 1994	USA	Cohort: 537,369; cases: 2676	Mortality	Permanent hair dyes RR=0.9-1.0, no trend with duration
Mendelsohn *et al.* (18)	2009	Prospective cohort, 5-9 yrs of follow-up 1996-2005	China	Cohort: 75,221; cases: 592	Incidence	All hair dyes RR=0.9, no trend with duration
Case-Control Studies						
Kinlen *et al.* (24)	1977	Hospital-based, 1975-76	UK	Cases: 191; controls 561	Incidence	Permanent hair dyes OR=0.1, no trend with duration
Shore *et al.* (25)	1979	Hospital-based, 1964-76	USA	Cases: 129; controls 193	Incidence	All hair dyes OR=1.0, permanent hair dyes significant association with cumulative exposure
Stavraky *et al.* (26, 7)	1979; 1981	Hospital-based/population-based, 1976-79	UK, Canada	Cases: 85; controls 170	Incidence	Permanent hair dyes OR=1.1-1.3
Nasca *et al.* (28)	1980	Population-based, 1975-76	USA	Cases: 118; controls 233	Incidence	Permanent or semi-permanent hair dyes OR=1.1, no trend with frequency or latency; OR=3.1* for use hair dyes to change hair color
Wynder & Goodman (29)	1983	Hospital-based, 1979-81	USA	Cases: 401, controls 625	Incidence	All hair dyes OR=1.0, no dose response
Koenig *et al.* (30)	1991	Hospital-based, 1977-81	USA	Cases: 398, controls 790	Incidence	All hair dyes OR=0.8, no trend with frequency or duration
Nasca *et al.* (27)	1992	Population-based, 1982-84	USA	Cases: 1617; controls 1617	Incidence	All hair dyes OR=1.0, no trend with duration or age at first use, and total applications
Boice *et al.* (31)	1995	Population-based, 1987-96	USA	Cases: 528, controls 2628	Prevalence	All hair dyes OR=1.1
Cook *et al.* (32)	1999	Population-based, 1983-90	USA	Cases: 844; controls 960	Incidence	OR=1.1 for exclusive use of any one hair dye products, OR=1.9* for us of two or more of the following methods: rinses, semi-permanent or permanent dyes, as well as bleaching then dyeing or frosting their hair
Zheng *et al.* (33)	2002	Hospital/population-based, 1994-97	USA	Cases: 608; controls 609	Incidence	All hair dyes OR=0.8, no trend with frequency or duration
Petro-Nustas *et al.* (34)	2002	Population-based, 1996	Jordan	Cases: 100; controls 100	Incidence	All hair dyes OR=8.6*

*95% confidence interval excludes null value

Table 3. Summary of the published literature on the relationship between personal use of hair dyes and risk of haematopoietic neoplasms

Authors (Ref)	Year of the report	Study Design	Country	Study Population	Disease Outcome	Findings
NON-HODGKIN LYMPHOMA						
Cohort Studies						
Grodstein *et al.* (36)	1994	Prospective cohort, 8 yrs of follow-up, 1982-90	USA	Cohort: 99,067; cases 144	Incidence	Permanent hair dyes RR=1.1 for NHL overall; OR=1.5 for follicular lymphoma, no trend with duration or frequency
Thun *et al.* (20); Altekruse *et al.* (19)	1994, 1999	Prospective cohort, 7 yrs of follow-up 19892-89, and 12 yrs of follow-up 1994	USA	Cohort: 537,369; cases 763	Mortality	Black permanent hair dyes RR=2.5* for using 10-19 years and 2.1 for more than 20 years
Mendelsohn *et al.* (18)	2009	Prospective cohort, 5-9 yrs of follow-up 1996-2005	China	Cohort: 75,221; cases: 51	Incidence	RR=1.1 for ever use any hair dyes
Case-Control Studies						
Cantor *et al.* (37)	1988	Population-based, 1980-83	USA	Cases: 622; controls 1245	Incidence	All hair dyes OR=2.0* for NHL overall, OR=2.8* for follicular lymphoma
Zahm *et al.* (40)	1992	Population-based, 1980-86	USA	Cases: 441; controls 1432	Incidence	Female: permanent hair dyes OR=1.7* for NHL overall, OR=2.0* for follicular lymphoma, no trend with frequency or duration; Male: no association
Markovic-Denic *et al.* (46)	1995	Hospital-based	Yugoslavia	Cases:130; controls 130	Incidence	OR=2.0* for chronic lymphocytic leukemia ever use
Holly *et al.* (38)	1998	Population-based, 1991-95	USA	Cases: 1593; controls 2515	Incidence	Female: no association; Male: semi-permanent hair dyes OR=2.0* for NHL overall, OR=2.4* for large cell lymphoma, no trend with frequency or duration
Miligi *et al.* (49, 50)	1999, 2005	Population-based, 1991-93	Italy	Cases: 611; controls 828	Incidence	All hair dyes OR=1.0, permanent hair dyes OR=1.1, black hair dyes for CLL OR=3.0*.
Schroeder *et al.* (51)	2002	Population-based, 1980-83	USA	Cases: 182; controls 1245	Incidence	All hair dyes OR=1.8 for t(14;18)-positive NHL, OR=2.0* for t(14;18)-negative NHL
Zhang *et al.* (41, 42)	2004, 2009	Population-based, 1996-2000	USA	Cases: 601; controls 717	Incidence	Hair dyes users started before 1980, OR=1.3* for NHL overall, OR=1.9* for follicular lymphoma ever use permanent hair dyes; OR=2.9* for carriers of CYP2C9 Ex3-52C>T TT/CT genotypes, OR=2.0* for carriers of CYP2E1 -332T>A AT/AA genotypes, OR=2.3* for a homozygous or heterozygous 3-base-pair deletion in intron 6 of GSTM3, OR=1.8* for GSTP1 Ex5-24A>G AA genotypes (OR = 1.8, 95% CI: 1.1, 2.9), and OR=1.6* for NAT2 genotypes conferring intermediate/rapid acetylator status, and the observed gene-hair dye-NHL associations were mainly seen for follicular lymphoma; No association for hair dyes users started after 1980
Chiu *et al.* (47)	2004	Population-based, 1980-83	USA	Cases: 807; controls 1926		All hair dyes OR=1.4 for NHL overall, no data on subtype
Tavani *et al.* (45)	2005	Hospital-based, 1985-97	Italy	Cases: 446; controls 1295	Incidence	All hair dyes OR=1.0 for NHL overall, no data on NHL subtype

Benavente *et al.* (43)	2005	Hospital-based, 1998-2002	Spain	Cases: 574; controls 616	Incidence	OR=1.2 for ever use of any hair dyes for NHL overall, OR=1.3 for those use permanent hair dyes, OR=2.3* for chronic lymphocytic leukemia for use any hair dyes.
de Sanjose *et al.* (44)	2006	Hospital/population-based, 1998-2002	Europe	Cases: 2302; controls 2417	Incidence	OR=1.2* for ever use any hair dyes, OR=1.4* for users started using hair dyes before 1980. (The study was conducted in six countries: Czech Republic, France, Germany, Ireland, Italy, and Spain)
Morton *et al.* (39)	2007	Population-based, 1998-2000	USA	Cases: 1321; controls 1057	Incidence	Female: OR=1.2 for ever use any hair dyes; women started using hair dyes before 1980: OR=1.6 for use of permanent, intense tone (black, dark brown, dark blonde) products, OR=3.3* for those had the rapid/intermediate NAT2 phenotype; no increased risk among women who began hair dye use after 1980 or among men
Chiu *et al.* (48)	2007	Population-based, 1983-1986	USA	Cases: 385; controls: 1432	Incidence	No association
Wong *et al.* (52)	2010	Hospital-based, 2003-08	China	Cases: 649; controls 1298	Incidence	OR=0.9 for ever use any hair dyes, OR=1.6 for follicular lymphoma
Zhang *et al.* (53)	2008	Pooled analysis	Europe and USA	Cases: 4461; controls 5799	Incidence	Women who began using hair dye before 1980, OR=1.3* for NHL overall, OR=1.4* for follicular lymphoma (FL) and OR=1.5* for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); Women who began using hair dye in 1980 or afterward, OR=1.5* for FL for users of dark-colored dyes; no association for men
HODGKIN'S DISEASE						
Cohort Studies						
Grodstein *et al.* (36)	1994	Prospective cohort, 8 yrs of follow-up, 1982-90	USA	Cohort: 99,067; cases 24	Incidence	All hair dyes RR=0.9 for ever use
Thun *et al.* (20)	1994	Prospective cohort, 7 yrs of follow-up, 1982-89	USA	Cohort: 537,369; cases 31	Mortality	RR=0.6 for ever use
Case-Control Studies						
Zahm *et al.* (40)	1992	Population-based, 1983-86	USA	Cases: 70; controls 1432	Incidence	Female: OR=1.7 for ever use any hair dyes, OR=3.0* for ever use permanent hair dyes; Male: OR=1.7 for ever use any hair dyes
Miligi *et al.* (50)	1999	Population-based, 1991-93	Italy	Cases: 165; controls 828	Incidence	OR=0.7 for ever use any hair dyes or ever use permanent hair dyes
Tavani *et al* (45)	2005	Hospital-based, 1985-97	Italy	Cases: 158; controls: 1295	Incidence	OR=0.7 for ever use any hair dyes, OR=1.1 for ever use permanent hair dyes
MULTIPLE MYELOMA						
Cohort Studies						
Grodstein *et al.* (36)	1994	Prospective cohort, 8 yrs of follow-up, 1982-90	USA	Cohort: 99,067; cases 32	Incidence	RR=0.4* for ever use

Thun *et al.* (20); Altekruse *et al.* (19)	1994, 1999	Prospective cohort, 7 yrs of follow-up, 1982-89; 12 yrs of follow-up, 1994	USA	Cohort: 537,369; cases: 460	Mortality	RR=1.1 for ever use, RR=3.1* for more than 20 years of use dark permanent hair dyes
Mendelsohn *et al.* (18)	2009	Prospective cohort, 5-9 yrs of follow-up 1996-2005	China	Cohort: 75,221; cases: 18	Incidence	RR=0.8 for ever use any hair dyes
Case-Control Studies						
Zahm *et al.* (40)	1992	Population-based, 1983-86	USA	Cases: 72; controls 1432	Incidence	Female: OR=1.8 for ever use any hair dyes, OR=2.8* for ever use permanent; Male OR=1.8 for ever use any hair dyes
Brown *et al.* (54)	1992	Population-based, 1981-84	USA	Cases: 173; controls 650	Incidence	Male: OR=1.9* for ever use any hair dyes, OR=4.3 for used more than one year and at least once a month
Herrinton *et al.* (55)	1994	Population-based, 1977-81	USA	Cases: 689; control 1681	Incidence	Female: OR=1.1 for ever use any hair dyes; Male: OR=1.3 for ever use any hair dyes
Miligi *et al.* (50)	1999	Population-based, 1991-93	Italy	Cases: 134; controls 828	Incidence	Female: OR=0.8 for ever use any hair dyes, OR=1.0 for ever use permanent hair dyes
Tavani *et al* (45)	2005	Hospital-based, 1985-97	Italy	Cases: 141; controls: 1295	Incidence	OR=1.2 for ever use any hair dyes, OR=1.3 for ever use permanent hair dyes
Koutros *et al.* (56)	2009	Population-based, 1996-2000	USA	Cases: 175; controls 679	Incidence	OR=0.8 for every use any hair dyes, no association by type and color of hair dyes.
LEUKEMIA						
Cohort Studies						
Grodstein *et al.* (36)	1994	Prospective cohort, 8 yrs of follow-up, 1982-90	USA	Cohort: 99,067; cases 44	Incidence	RR=0.6 for chronic lymphocytic leukemia ever use, RR=0.8 for acute and chronic myelocytic leukemia and acute lymphocytic leukemia
Thun *et al.* (20); Altekruse *et al.* (19)	1994, 1999	Prospective cohort, 7 yrs of follow-up, 1982-89; 12 yrs of follow-up, 1994	USA	Cohort: 537,369; cases: 718	Mortality	RR=1.1 for ever use, RR=1.3 for more than 20 years of use with significant trend of duration, RR=1.5 for more than 20 years of use of brown color
Mendelsohn *et al.* (18)	2009	Prospective cohort, 5-9 yrs of follow-up 1996-2005	China	Cohort: 75,221; cases: 29	Incidence	RR=0.7 for ever use any hair dyes
Case-Control Studies						
Cantor *et al.* (37)	1988	Population-based, 1980-83	USA	Cases: 577; controls 1245	Incidence	OR=1.8* for leukemia (all types) ever use
Mele *et al.* (57)	1994	Hospital-based, 1986-90	Italy	Cases: 252 (acute myeloid leukemia) 100 (acute lymphocytic leukemia) 156 (chronic myeloid leukemia); conrtols 1161	Incidence	Female : OR=1.6 for acute myeloid leukemia use >10 yrs; OR=2.0 for acute lymphocytic leukemia use > 10 yrs; OR=0.8 for chronic myeloid leukemia use>10 yrs; Male: OR=1.6 for acute myeloid leukemia ever use dark color hair dyes; OR=2.1 for chronic myeloid leukemia ever use dark color hair dyes
Miligi *et al.* (50)	1999	Population-based, 1991-93	Italy	Cases: 260; controls 828	Incidence	OR=0.9 for ever use any hair dyes, OR=2.0 for ever use dark permanent hair dyes
Bjork *et al.* (58)	2001	Population-based, 1976-93	Sweden	Cases: 226; controls 251	Incidence	OR=0.4* for chronic myeloid leukemia ever use any hair dyes

Rauscher *et al.* (59)	2004	Population-based, 1986-89	USA and Canada	Cases: 769; controls 623	Incidence	OR=1.5* for acute leukemia ever use of permanent dyes, OR=1.8* for use 15 or more years, OR=2.4 for use 15 or more years up to six times per year
MYELODYSPLASTIC SYNDROMES						
Ido *et al.* (60)	1996	Hospital-based, 1992-93	Japan	Cases: 116; controls 116	Incidence	Female: OR=2.5 for ever use any hair dyes; Male: OR=1.2 for ever use any hair dyes
Nagata *et al.* (61)	1999	Hospital-based, 1995-96	Japan	Cases: 111; controls 830	Incidence	Both gender: OR=2.0* for ever use any hair dyes, trend with frequency or duration; Female: OR=2.9* for ever use any hair dyes, trend with frequency or duration

*95% confidence interval excludes null value

hese studies have varying conclusions, but the majority of case-control studies suggest a potential for elevated risk of NHL with hair dye use and cohort studies are somewhat mixed.

A pooled analysis by Zhang *et al* (53), which included studies (38, 39, 41, 43, 44) that have collected detailed information on personal hair dye use, noted a significantly increased risk of NHL in women who used hair dyes before 1980 (OR=1.3, 95% CI: 1.1, 1.4). Analyses by NHL subtype showed increased risk associated with follicular lymphoma (OR=1.4, 95% CI: 1.1, 1.9) and chronic/small lymphocytic leukemia (CLL/SLL) (OR=1.5, 95% CI: 1.1, 2.0) with a significant trend in risk with duration of use. No association was observed for other NHL subtypes. For women who began using the products in 1980 or after, an increased risk of follicular lymphoma was limited to users of dark-colored hair dyes (OR=1.5, 95%CI: 1.1,2.0). The results indicate that personal hair dye use may play a role in the risk of follicular lymphoma and CLL/SLL in women who started use before 1980 and that an increase in risk of follicular lymphoma in women starting use in 1980 or after cannot be excluded. The pooled analysis did not find an association among men.

Several studies also investigated effect modifications of genetic variation on the relationship between personal hair dye use and risk of NHL (39, 42, 48, 51) Schroeder *et al* (51) classified NHL by presence of t(14;18) translocation and found a significant risk for hair dye use in t(14;18)-negative translocation NHL (OR=2.1, 95%CI: 1.3,3.4) but not in t(14;18)-positive translocation NHL (OR=1.8, 95%CI: 0.9,3.7). Another study by Chiu *et al* (48), however, did not find an association by t(14;18) translocation in either men or women.

Morton *et al.* (39) examined the association by NAT1 and NAT2 genotype/phenotypes in a population-based multi-center case-control study involving 1,321 cases and 1,057 controls. They found an increased risk among women who used permanent intense tone hair dye products before 1980 if they had the rapid intermediate NAT2 phenotype (OR=3.3, 95%CI: 1.3,8.6) or the NAT1 10 allele (OR=2.5, 95%CI: 0.9,7.6), but not if they were slow NAT2 acetylators or had no copies of the NAT1 10 allele. NHL risk was not increased among women who began hair dye use after 1980 or among men.

A population-based case-control study among Connecticut women was conducted to test whether genetic variation in xenobiotic metabolic pathway genes modifies the relationship between hair dye use and risk of NHL (42). No effect modifications were found for women who started using hair dyes in 1980 or after. For women who started before 1980 compared to never users, a significantly increased risk of NHL overall was found for carriers of *CYP2C9 Ex3-52C>T* TT/CT genotypes (OR=2.9, 95%CI:1.4,6.1), *CYP2E1 -332T>A* AT/AA genotypes (OR=2.0, 95%CI:1.2,3.4), a homozygous or heterozygous 3bp deletion in intron 6 of *GSTM3* (OR=2.3, 95%CI:1.3,4.1), *GSTP1 Ex5-24A>G* AA genotypes (OR=1.8, 95%CI:1.1,2.9), or *NAT2* genotypes conferring intermediate/rapid acetylator status (OR=1.6, 95%CI: 1.0,2.7). The observed risks were strengthened and mainly observed for follicular lymphoma. In contrast, no significant increased risk was observed for hair dye users starting before 1980 relative to never users among women who were homozygous wild-type for the *CYP2C9*, *CYP2E1*, or *GSTM3* polymorphisms, women carrying one or two copies of the variant *GSTP1* allele, or women who were slow *NAT2* acetylators.

6. HODGKIN'S DISEASE

Three case-control studies (40, 45, 50) and two cohort studies (20, 36) have investigated the relationship between hair dye use and risk of Hodgkin's disease. All of them have reported a non-significant inverse association except for one case-control study (40), which reported a three-fold increased risk of Hodgkin's disease associated with permanent hair dye use.

7. MULTIPLE MYELOMA

Two case-control studies suggested an increased risk of multiple myeloma associated with personal hair dye use (40, 54), while four studies found no association (45, 50, 55, 56)(Table 3). Brown reported a 1.9-fold increased risk of multiple myeloma among ever users based on 14 exposed cases. Zahm *et al.* (40) found that users of

permanent hair dyes had about 3-fold increased risk of multiple myeloma.

The cohort studies provided inconsistent results linking hair dye use and risk of multiple myeloma (18-20, 36). Grodstein *et al.* (36) reported a reduced risk of multiple myeloma associated with personal hair dye use. Thun *et al.* (20) found a three-fold increased risk associated with dark permanent hair dye use. Mendelsohn *et al.* (18) noted no association between hair dye use and risk of multiple myeloma.

8. LEUKEMIA

Most studies suggested no association between leukemia risk and personal use of hair dyes (18, 20, 36, 50, 57), , while others suggested an inverse association (58) or positive association (37, 59). Study that examined the association by leukemia subtypes found no association with any subtype of leukemia (57).

In studies with a positive association of hair dye use and risk of leukemia, there is a possibility for increasing risk with darker and/or permanent hair dyes and longer duration of use. Miligi *et al.* (50) reported an increased risk of leukemia among women who reported using dark permanent hair dyes (OR=2.0, 95% CI: 1.1,3.8), although the study lacked information on time and duration of using hair dye products. Rauscher *et al* (59) reported an increased risk of leukemia associated with permanent hair dye use and the highest risk was found for women who used for 15 or more years up to six times per year of use.

Caution is necessary interpreting the inverse association noted in the Bjork *et al* (58) study. Information on use of hair dyes were obtained by proxy interview in 81% of cases and 14% of controls and no information on type, color, frequency or duration of hair coloring products was collected.

9. MYELODYSPLASTIC SYNDROMES

Ido *et al.* (60) conducted a hospital-based case-control study in Japan from 1992-93 to investigate the risk factors for myelodysplastic syndromes. No information on type or color of hair dyes, frequency or duration of use was collected in this study. A non-significant 2.5-fold increased risk (95% CI: 0.97, 6.41) was observed among women who had ever used hair dyes.

A hospital-based case-control study in Japan in 1995-96 investigated the association between hair dye use and risk of myelodysplastic syndromes (61). Ever use of hair dyes was significantly associated with the risk of myelodysplastic syndromes in both men and women (OR=2.0, 95%CI: 1.2,3.4) and in women only (OR=2.9, 95% CI: 1.4,6.0). The risks increased with increasing duration and number of hair dye uses. The study, however, provided no information on type or color of hair dye products used.

10. CANCERS AT OTHER SITES

A working group assessment by the Internal Agency for Research on Cancer (IARC) in 1993 assessed the risk of cancers of the cervix (7), ovary (7), lung (7), kidney (7), brain (62), salivary gland (63), and malignant melanoma (64, 65). Too few studies were available on those cancer sites to allow reviewers to make a conclusion whether personal hair dye use is associated with the risk of these cancer sites. More recently, however, a significant two-fold increased risk of ovarian cancer was observed for women who reported using hair dyes greater than 4 times per year and the risk increased with increasing frequency of hair dye use (P=0.007) (66). In one study of brain tumors, glioma risk was increased 1.7-fold (95% CI: 1.0, 2.9), and those who used permanent dye, a 2.4-fold increased risk (95% CI: 1.3, 4.5) (67). However, a large portion of cases were proxy interviews. In another brain tumor study no consistent association with any brain tumors (glioma, meningioma, and acoustic neuroma) was noted (68). Exposure assessment did not heavily rely on proxy interview as in the Heineman *et al* study (<18%)(67).

11. CHILDHOOD CANCERS

An investigation of Wilms Tumor risk, a childhood kidney tumor, was non-significantly increased with maternal use of hair dye products during pregnancy (OR=1.4, 95% CI: 0.7, 2.9) (69). Maternal use of hair dye products was not associated with the risk of childhood brain tumors in two studies (70, 71). But one study on maternal use of hair dyes and the risk of neuroblastoma in children identified an increased risk (OR=1.6, 95% CI: 1.2, 2.2) (72).

12. CONCLUSIONS

Epidemiological studies so far have provided limited evidence to support the hypothesis that personal use of hair dyes is associated with human cancer risk (73). However, a possible association between certain type or color of hair dye products, such as permanent dark color hair dyes, and certain subtype of cancers, such as bladder cancer and hematopoietic neoplasms, cannot be ruled out. Susceptible subgroups in the population may exist, such as certain functional polymorphisms in genes involved in arylamine activation or detoxification, which modify the association between hair dye use and human cancer risks.

Hematopoietic cancers appear to have a possible elevated risk associated with hair dye use. The strongest association appears to be with non-Hodgkin lymphoma where various studies have estimated the risk of up to 100% and even as high as 230% elevated risk for specific subtypes of NHL. Out of a total of 17 studies, 12 had significant results of elevated risk of NHL with hair dye use, while five other studies had elevated risk, though not statistically significant. Increased risk of NHL may be subtype specific. In several studies, when assessed by subtype, follicular lymphoma and CLL/SLL subtypes were elevated. Due to the different etiologies of most NHL, future studies should investigate NHL subtype and genetic polymorphisms in greater detail to better elucidate higher risk populations.

While a relationship between hair dye exposure and human cancer risk is biologically plausible, the results from epidemiological studies assessing hair dye use to human cancer risks have been inconsistent for nearly all cancer sites investigated. The major methodological challenge is exposure assessment. In most studies, hair dyes were just one of many exposure variables on which information was collected. In a few studies, only a few questions were asked to collect history regarding lifetime hair dye uses. This limited scope of exposure assessment diminishes an adequate characterization of exposure in terms of type or color of hair dyes, frequency or duration of use, time period of use, age during each period of use.

To further improve the value of epidemiologic research with regard to hair dye use will be an improvement in the methodology of both study design and exposure assessment. Prospective cohort studies have the importance of being able to several disease outcomes and to address temporal relationship. However, the published studies lacked complete information on timing, duration, frequency and type of hair dye product use, and this information is crucial to determining if intensity, total dose, type, and time period of hair dye use is most important in assessing risk.

In conclusion, the current evidence do not support a significant association between hair dye use and human cancer risk, except for the possibility of hematopoietic cancers. Given the complicated use patterns of hair dye products, the heterogeneity of many cancer sites, and the potential gene-environmental interactions, well-designed, large population-based studies could clarify the relationship between hair dyes and human cancer risks. Based on several recent studies, this relationship appears to be affected by specific genetic polymorphisms and future studies should investigate potential gene and environment interaction to assess possible genetic susceptibility.

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