Personal Use of Hair Dyes and the Risk of Bladder Cancer: Results of a Meta-Analysis

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SYNOPSIS

Objective. This study examined the methodology of observational studies that explored an association between personal use of hair dye products and the risk of bladder cancer.

Methods. Data were pooled from epidemiological studies using a general variance-based meta-analytic method that employed confidence intervals. The outcome of interest was a summary relative risk (RRs) reflecting the risk of bladder cancer development associated with use of hair dye products vs. non-use. Sensitivity analyses were performed to explain any observed statistical heterogeneity and to explore the influence of specific study characteristics of the summary estimate of effect.

Results. Initially combining homogenous data from six case-control and one cohort study yielded a non-significant RR of 1.01 (0.92, 1.11), suggesting no association between hair dye use and bladder cancer development. Sensitivity analyses examining the influence of hair dye type, color, and study design on this suspected association showed that uncontrolled confounding and design limitations contributed to a spurious non-significant summary RR. The sensitivity analyses yielded statistically significant RRs ranging from 1.22 (1.11, 1.51) to 1.50 (1.30, 1.98), indicating that personal use of hair dye products increases bladder cancer risk by 22% to 50% vs. non-use.

Conclusion. The available epidemiological data suggest an association between personal use of hair dye products and increased risk of bladder cancer.

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Bladder cancer represents an important cause of cancer-related morbidity and mortality in the United States, with more than 50,000 cases diagnosed annually, leading to 10,000 deaths per year.[1] Environmental factors are suspected of playing an important role in the development of bladder cancer due to several well recognized epidemiological features, such as the higher incidence among males vs. females (on the order of 3:1), higher incidence among blacks vs. whites and urban vs. rural locations of residence, and association with smoking and certain occupational groups.[2] A number of observational studies have found a possible association between employment as hairdressers, beauticians, and barbers and increased bladder cancer risk, with exposure to hair dyes suggested as the etiological factor.[3]

Hair dyes are widely used in both the United States and Europe. It is estimated that more than one-third of women over age 18 and approximately 10% of men over age 40 use some type of hair dye, with permanent hair dyes constituting the majority of such preparations.[4] In contrast to studies examining workplace exposure to hair dyes, the bladder cancer risk associated with personal use of these products remains more uncertain. In the mid-1970s, Ames et al. demonstrated that some constituents of hair dyes were mutagenic in a bacterial screening system.[5] Prior work also indicates that small amounts of aromatic amines in hair dyes are absorbed percutaneously during normal use of these products, with the aromatic amines being known animal carcinogens.[6] These facts suggest that a hair dye/bladder cancer relationship is biologically plausible.

Due to the limited available data addressing this issue, a meta-analysis was designed to pool all available epidemiological data on this subject. This article provides an overview of the existing data and an analysis of methodological issues that may affect individual study outcomes.

MATERIALS AND METHODS

The methods employed in this analysis have been described previously.[7] Briefly, a study protocol was developed prospectively to outline the purpose and methods of the analysis. Eligibility criteria for studies were determined prospectively, as were the specific data elements to be extracted from each trial. A plan for data analysis was also formulated as part of the study protocol. A data extraction form was designed for recording relevant data from each published study.

Literature retrieval was performed by previously described methods.[8] We conducted a computer search through MEDLINE, Current contents, and the Cochrane database from January 1966 to February 2003 using the terms *hair dyes/adverse effects*, *hair preparations/adverse effects*, *environmental exposure*, *bladder neoplasms*, and *chemically induced*. The reference list of all traced articles and general reviews of this topic were also examined manually. The search included all languages. If a series of papers was published, all data were retrieved from the most recent report.

The initial citations from this literature search (in the form of abstracts) were screened by a physician investigator (oncologist) to exclude those that did not meet protocol-specified inclusion criteria. Rejected formats included animal studies, in vitro studies, review articles, letters to the editor, abstracts, and non-peer reviewed articles. Citations selected from this initial search were subsequently screened for eligibility using the following criteria:

1. observational studies enrolling adult patients 18 years old or older with a diagnosis of "bladder cancer";
2. availability of data on hair dye use;
3. odds ratio or RR of bladder cancer development with a 95% confidence interval for each study or availability of raw data to calculate these parameters.

Citations meeting these criteria were entered onto an "accept" log and copies of full papers were obtained. The key data elements extracted from each trial included number of cases and controls; sex of subjects; type of hair dye used (e.g., permanent, semi-permanent, etc.); dye colors used; duration of use or other dose-response data; factors (if any) used to statistically adjust study odds ratios or relative risks (especially smoking history); and tumor histology, if given. Two researchers performed data extraction. Differences in data extraction forms were resolved by consensus.

Statistical methods

Data analysis was performed according to meta-analysis procedures previously described by Greenland.[8] This meta-analysis method is a general variance-based method employing confidence intervals. Because the variance estimates are based on adjusted measures of effect and on the 95% confidence interval for the adjusted measure, the confidence interval methods do not ignore confounding and are the preferred methodology for observational data.

For each included study, an odds ratio was derived or extracted reflecting the risk of bladder tumor development associated with personal use of hair dyes (as opposed to occupational exposure). Next, the natural logarithm of the estimated odds ratio was determined followed by an estimate of the variance. The 95% confidence interval for each study was used to calculate the variance of each study's measure of effect. The weight for each included data set was calculated as 1/variance followed by a summation of the weights. We then determined the product of the study weight and the natural logarithm of the estimated RR and summed these products. Finally, a summary "odds ratio" (referred to hereafter as a summary relative risk [RRs] by convention[7]) and 95% confidence interval were calculated.

Prior to estimation of a summary relative risk, a statistical test for homogeneity was performed (Q). This procedure tests the hypothesis that the effect sizes are equal in all of the studies.[8] If Q exceeds the upper tail critical value of chi-square ($p<0.10$) at k-1 *df* (where k equals the number of studies analyzed or the number of comparisons made), the observed variance in study effect sizes is significantly greater than what would be expected by chance if all studies shared a common population effect size. If the hypothesis that the studies are homogenous is rejected, the studies are not measuring an effect of the same size. In this instance, calculation of a pooled estimate of effect (i.e., RRs) may be of questionable validity. Study effect sizes may be disaggregated by grouping studies into appropriate categories until Q is not rejected within those categories or regression techniques can be employed. That is, reasons for the observed heterogeneity must be sought. In essence, Q is a diagnostic tool for determining if all the variance in the observed effect sizes is

accounted for. In addition to an analysis for heterogeneity, sensitivity analyses were employed when necessary. These tests assess the robustness of the results to specific methods employed in the conduct of meta-analyses.

Demonstration of a dose-response relationship in observational studies lends support to a suspected causal relationship between exposure and disease. Data permitting, such relationships were analyzed in this study using the methods of Berlin et al.[9]

The potential for publication bias was not examined. Publication bias occurs because published studies are not representative of all studies that have ever been done. The funnel plot method and other statistical adjustments have been constructed in an attempt to address this issue. Unfortunately, these methods lack firm statistical theoretical support and are not generally recommended for medical applications.[6]

RESULTS

Our literature search yielded 10 studies that appeared to meet protocol-specified inclusion criteria, and we obtained full articles for review.[10–19] Further review demonstrated that three of these studies did not meet protocol-specified inclusion criteria.[10–12] Claude et al.[10] did not contain information on hair dye use. Hennekens et al.[11] did not stratify "urinary tract" cancer by site. Therefore it was not possible to determine how many cases were actually bladder tumors vs. cancers at other sites. The 1994 article by Thun et al.[12] was excluded because it represented a preliminary report of the Altekruse et al.[13] study published in 1999. The remaining seven reports met protocol-specified inclusion criteria and form the database for the current meta-analysis.

Even a cursory review of the existing data shows that the available information is extremely limited in both quantity and quality (see Table 1). As stated above, only seven epidemiological studies exist which provide data related to the relationship of interest. Unfortunately, only four[13–15,17] deal specifically with bladder cancer risk and hair dye use, while Stavraky et al.[19] studies hair dye use and risk of cancer at various sites, including urinary bladder. A limitation of this report is that the authors did not stratify "urinary tract" cancers and therefore only presented data for bladder and kidney cancers combined. In addition, there were only a total of 23 bladder cases included in the report, making these data quite limited.

While Altekruse et al.[13] dealt with the cancer risk/hair dye use association, this large cohort study concerned primarily hematopoietic cancer rather than bladder cancer specifically. Of the 202 bladder cancer deaths included, only 48 subjects used hair dyes. The major limitation of this report from the American Cancer Society is that, as compared to all others included in this meta-analysis, it used cancer mortality as the endpoint. Despite the fact that this is a large cohort study with 12 years of follow-up, it is likely that mortality is not the optimum endpoint to use in evaluating the hair dye/bladder cancer risk association. Bladder cancer is a heterogeneous neoplasm, with the majority of cases (75% to 85%) presenting with superficial disease, i.e. non-invasive papillary disease (Ta), tumor limited to the subepithelial connective tissue (T1), or carcinoma in situ (Tis).[20] As in most solid tumors, survival is directly related to stage of disease. Superficial bladder cancer is often non-fatal, although recurrences are not uncommon. Although a percentage of patients progress to muscle-invasive disease (which has a much higher likelihood of mortality, approximately 50% within five years of diagnosis), this process is not universal and is dependent on tumor grade, stage (Ta vs. T1 vs. Tis), and treatment. Also, some patients with recurrent superficial disease unresponsive to intravesical or other therapy may undergo cystectomy with a high likelihood of cure. Altekruse et al.[13] abstracted information from death certificates using the ICD-9 code for bladder cancer (i.e., 188). This does not allow for any evaluation of stage of disease and therefore no distinction is possible between patients with superficial vs. muscle-invasive tumors. Such cases will therefore not be reflected in a mortality study and may lead to a spurious finding of no relationship between hair dye use and bladder cancer since cancer *incidence* is not being examined.

Howe et al.[16] presented very limited data in that the study looked at multiple possible etiologies of bladder cancer with only 16 subjects reporting exposure to hair dyes. Such a small number of cases makes interpretation of the study results difficult and the risk estimates uncertain. Likewise, Ohno et al.[18] enrolled primarily male patients among whom hair dye use is known to be far less frequent than among females. Out of 293 patients enrolled, only 86 were female. Of these, only 42 were exposed to hair dyes. The report by Nomura et al.[17] is also a small study, with only 66 women enrolled. The majority of subjects were male. Also, the authors combined tumors of the lower urinary tract without further stratification. Although 90% were bladder tumors, tumors of the renal pelvis and ureter were also included. Given the small sample size, inclusion of non-bladder neoplasms could potentially bias study results.

Bearing these caveats in mind, the data in Tables 1 and 2 were reviewed in order to develop a strategy for pooling information to calculate a summary estimate of effect reflecting the risk of bladder cancer development associated with hair dye use. As seen in Table 2, few investigators made any attempt to stratify data by hair dye type (i.e., permanent, semi-permanent, or temporary-rinse). This distinction is important, since many permanent and semi-permanent dye product formulations have been shown to be mutagenic in vitro and account for approximately 75% of the market.[5,14] Also, only three studies provided information on frequency of use.[14,15,18] A dichotomous exposure classification of ever vs. never does not allow for any detailed analysis of a dose-response relationship and is obviously a crude measure of exposure. Lack of such detail is problematic, since dose-response information could provide further insight into the strength, or lack thereof, of a causal relationship between hair dye use and bladder cancer, and is an important criterion for the establishment of causality using observational data.[21]

Data were therefore initially pooled in the following manner. Since Gago-Dominguez et al.[14] stratified on sex and type of dye used, the initial summary relative risk was calculated using the odds ratio and 95% confidence interval for use of *any* hair dye among both sexes combined (i.e., 1.0 [0.7, 1.4]). Hartge et al.[15] stratified use as ever vs. never by sex and

Table 1. Overview of included study designs

Author	*Study design*	*Number of cases or cohort size*	*Number of controls*	*Type of hair dye specified*	*Dye color specified*	*Adjustment for smoking*	*Information on duration of use*	*ICD code specified*	*Histologies specified*
Altekruse	cohort	547,586 (202 bladder cancer deaths)[a]	na	permanent	y	y	y	y	n
Gago-Dominguez	case-control	897[b]	897	permanent,	n semi-permanent, temporary	y	y	n	n
Hartge	case-control	2,982[c]	3,313	n	y	y	y	n	n
Howe	case-control	630[d]	630[d]	n	n	y	n	n	n
Nomura	case-control	261[e]	261[e]	n	n	y	y	n	y
Ohno	case-control	293[f]	589	n	n	y	y	n	y
Stavraky	case-control	392[g]	784	permanent semi-permanent	n	y	n	n	n

[a]all females

[b]203 females

[c]733 females

[d]152 female cases and controls, 16 exposed cases

[e]66 female cases and control

[f]86 females

[g]23 bladder cancer cases

dye color. The initial pooling used the odds ratio for ever vs. never use, both sexes combined (i.e., 1.0 [0.9, 1.0]). Nomura et al.[17] provided data stratified by sex and frequency of use (i.e., ever vs. never), without further elaboration. Therefore, data for women users was utilized. Ohno et al.[18] included only female subjects and stratified on frequency of use (see Table 2). Initially, data on patients using hair dyes more than once a month were included in the pooled summary estimate of effect.

Combining the above-outlined data yielded an RRs of 1.01 with a 95% confidence interval of 0.92, 1.11, a statistically non-significant result suggesting no relationship between hair dye use and bladder cancer risk. Calculation of Q for this meta-analysis resulted in a value of 2.79. With six degrees of freedom, this yielded a *p* value of 0.85, also a non-significant result, demonstrating that the data are homogeneous and can be statistically pooled. Due to the limitations of the available data previously discussed, the finding of a non-significant RRs is not surprising. A number of additional sensitivity analyses were performed to determine how the above-noted limitation could possibly contribute to a spurious negative result.

The reports by Gago-Dominguez et al.[14] and Hartge et al.[15] stratified data by sex and type/color of dye used. These distinctions are important, since permanent and semi-permanent dyes (particularly black) are considered to pose a greater risk to the consumer than other types of hair coloring products.[5] Examining the information in Table 2, it is clear that the data provided in Gago-Dominguez[14] and Hartge[15] show differing odds ratios when use of permanent or black hair dye among women is compared with *any* hair dye use or when sexes are combined. A second meta-analysis

Table 2. Individual study data on risk of bladder cancer associated with personal hair dye use

Author	*OR or RR (95% confidence interval)*	*Dose-response data*
Altekruse	1.0 (0.7, 1.4) ever vs. never	0.9 (0.6, 1.6) 1–9 years 1.1 (0.7, 1.8) 10–19 years 0.9 (0.5, 1.6) 20+ years
Gago-Dominguez	1.0 (0.7, 1.4) regular use of ANY type of hair dye-both sexes combined	1.1 (0.5, 2.5) +15 yrs permanent dye
	1.3 (0.8, 2.2) regular use of ANY type of hair dye, women only	1.7 (0.8, 3.6) 15–30yrs permanent dye
	1.4 (0.9, 2.2) exlcusive use of permanent hair dyes-both sexes combined	3.7 (1.2, 11.2) 30+ yrs permanent dye
	1.8 (1.1, 3.3) exclusive use of permanent hair dyes-women only	1.6 (0.8, 2.9) less than 12 times per year
	0.6 (0.3, 1.4) any use of semi-permanent hair dye-women only	2.1 (1.0, 4.7) more than 12 times per year
	1.1 (0.5, 2.2) any use of temporary rinse-women only	3.3 (1.3, 8.4) 15+ yrs AND 12+ times per year
Hartge	1.0 (0.9, 1.0) ever vs. never, both sexes 0.9 (0.8, 1.1) ever vs. never, women 1.1 (0.9, 1.4) ever vs. never, men	no effect on OR with duration of use for females
	1.4 (1.0, 1.9) black dye, both sexes 0.9 (0.7, 1.1) brown dye, both sexes 1.3 (0.8, 2.1) black dye, women 1.5 (0.9, 2.3) black dye, men	
Howe	0.7 (0.3, 1.4) ever vs. never, women No exposed controls, men	none
Nomura	1.5 (0.8, 2.9) ever vs. never, women	2.4 (1.0, 6.0) 1–5 years 1.2 (0.6, 2.4) 6+ years
	1.3 (0.6, 2.8) ever vs. never, men	2.1 (0.9, 4.8) 1–5 years 0.7 (0.2, 2.4) 6+ years
Ohno	no data on males 1.31 (0.64, 2.71) use less than once per month 1.70 (0.82, 3.52) use more than once per month (based on only 12 cases and controls combined)	(see data in OR column)
Stavraky	1.1 (0.4, 2.8)[a]	none

[a]Combined both renal and bladder cancers without stratification; only 23 bladder cancer cases included

OR = odds ratio

RR = relative risk

was therefore performed using the odds ratio from Gago-Dominguez[14] for "exclusive use of permanent hair dyes by women only" (i.e., 1.8 [1.1, 3.3]) and the odds ratio for "black hair dye used by females" as recorded by Hartge et al.[15] (i.e., 1.3 [0.8, 2.1]). The resultant RRs was 1.22 with a 95% confidence interval of 1.11, 1.51, a statistically significant result. When this adjustment is made, this suggests that hair dye use is associated with a 22% increase in bladder cancer risk vs. non-use.

Several additional sensitivity analyses of this second meta-analysis were performed to address some of the previously noted deficiencies in the available data. The study by Stavraky et al.[19] did not directly address the issue of hair dye use and bladder cancer risk, but rather looked at its relationship to cancers of various sites. The authors also combined bladder tumors and neoplasms of the kidney without stratification. In addition, the study enrolled only 23 patients with cancer of the bladder and therefore had very limited statistical power to detect an effect of exposure on disease risk. A sensitivity analysis was performed by dropping this study from the pooled analysis and recalculating an RRs. This produced an RRs of 1.23, showing a slight increase in the summary estimate of effect with exclusion of this study. Given that Stavraky et al.[19] only accounted for 4% of the summed weights of all included studies (see Table 3), this marginal effect on RRs is not surprising.

Altekruse et al.[13] is the only cohort study included in the analysis. As previously discussed, this report also used bladder cancer mortality as the endpoint of interest, in contrast to all other included analyses. Altekruse[13] suggests that bladder cancer *mortality* is not related to permanent hair dye use (i.e., odds ratio of 1.0). A sensitivity analysis was performed by excluding these data and recalculating a summary estimate of effect. This resulted in an RRs of 1.36 with a 95% confidence interval of 1.05, 1.75, a statistically significant result suggesting a 36% greater risk of bladder cancer among hair dye users compared with non-users. These results suggest that inclusion of this cohort study may spuriously attenuate the magnitude of the RRs. If both Altekruse[13] and Stavraky[19] are excluded, the RRs is further increased to 1.38 (1.06–1.79). Howe et al.[16] presents very limited data, in that the study looked at multiple possible etiologies of bladder cancer with only 16 subjects reporting exposure to hair dyes. Such a small number of cases makes interpretation of the study results difficult and the risk estimates uncertain. A pooled analysis excluding Altekruse, Howe, and Stavraky resulted in an RRs of 1.50 with a 95% confidence interval of 1.30–1.98.

Table 3. Study weights used in calculation of second pooled RRs

Study	*Weight*[a]
Altekruse	30.3
Gago-Dominguez	15.9
Hartge	16.4
Howe	5.35
Nomura	9.71
Ohno	7.52
Stavraky	3.76
Sum	88.9

[a]Weight equals 1/variance

RRs = summary relative risk

The protocol for this meta-analysis allowed for exploration of dose-response data. Demonstration of a dose-response relationship would lend additional weight to a suspected cause-effect relationship.[21] As shown in Table 2, only three studies provided any type of dose-response information.[13,14,17] Although the data presented by Gago-Dominguez et al.[14] suggest increasing risk with increased exposure measured as years of hair dye use, the available information is inadequate for any meaningful analysis of this relationship. A dose-response analysis as described by Berlin et al.[9] was therefore not possible.

The sensitivity analyses described above demonstrate that hair dye use is associated with an increased risk of bladder cancer. Multiple study design limitations of the existing epidemiological literature have resulted in the spurious attenuation of risk estimates in individual observational studies.

DISCUSSION

Although transitional cell carcinoma of the bladder is not an uncommon tumor in the United States, few risk factors other than cigarette smoking and occupational exposure to arylamines and polycyclic aromatic hydrocarbons are associated with this neoplasm.[22] Cigarette smoking seems to represent the most important risk factor, believed to contribute to about 50% of the tumors in men and a third of the cancers in women.[23] Smoking appears to increase bladder cancer risk on the order of two- to four-fold. A number of occupational groups may also be at increased risk for bladder cancer. These include aluminum workers,[24] manufacturers of polychlorinated biphenyls,[25] and hairdressers, barbers, and beauticians.[3] Increased bladder cancer risk among the latter occupational groups is documented in numerous prior studies.[3] This finding prompted speculation that personal use of hair dyes could also pose a bladder cancer risk. The existence of such a relationship is of public health importance due to the widespread use of personal hair dye products among both the female and male general population of the United States and Europe. It is estimated that one-third of American women and 10% of men over the age of 40 use hair dyes, with permanent hair dyes accounting for approximately three-quarters of the world market.[14] The fact that some hair dye products and their constituents are mutagenic in vitro and carcinogenic in experimental animal systems[5] provides further support for a causal association.

The true relationship between personal hair dye use and bladder cancer has remained uncertain. Although some in the scientific community suggest that no causal association exists,[26] there is a clear lack of consensus[14] and persistent public interest. This analysis was designed to address the current uncertainty and provide a systematic, quantitative, and qualitative evaluation of existing data.

Our analysis highlights several important limitations of the existing medical literature addressing hair dyes and bladder cancer risk. The first is that only seven observational studies exist that met protocol-specified inclusion criteria.

The majority of the studies did not directly address the hair dye/bladder cancer association, leading to overall small numbers of bladder cancer cases enrolled in many analyses. Small sample sizes limit the statistical power to detect an effect if one exists. In addition, the vast majority of reports did not specify or stratify the various types of hair dyes (i.e., permanent, semi-permanent, or temporary). This information is of crucial importance, since the different types of preparations differ in their chemical make-up, including type and level of suspected carcinogenic chemicals.[10] Support for the importance of such stratification was demonstrated by Gago-Dominguez et al.,[14] as seen in Table 2. Failure to differentiate product type may lead to attenuation of the study estimate of effect (i.e., the odds ratio). This will also affect a summary estimate of effect in a pooled analysis as seen in the present meta-analysis. Lack of stratification on dye type also complicates dose-response data. Few studies provided such information, as seen in Table 2. Of those that did provide some information, use in terms of number of years was often used. Gago-Dominguez[14] also used frequency of use (i.e., times per year), while Ohno et al.[18] used less than or more than once per month. Frequency of use may lead to a spurious negative association between exposure and disease risk if product type is not specified. This will arise because temporary dyes may be used more frequently than permanent or semi-permanent dyes, but may also pose a lesser risk due to their particular chemical composition.

An additional problem uncovered by our meta-analysis concerns the report by Altekruse et al.[13] This cohort study from the American Cancer Society database used cancer mortality as the endpoint of interest in contrast to the use of incident cases among all other included studies. Cancer mortality may represent an inappropriate end point for studying this exposure-disease relationship. As discussed earlier, 70% to 80% of all bladder neoplasms are superficial in nature (i.e., do not invade the bladder muscle or perivesical tissues). As opposed to muscle-invasive disease, the natural history of superficial bladder cancer can be long and often non-fatal. Such tumors can be cured by cystectomy or managed with intravesical immunotherapy or intravesical chemotherapy. Although some superficial tumors can progress to invade the bladder wall, the majority of tumors do not. Using bladder cancer death as the endpoint of interest may drastically underestimate the magnitude of a cause-effect relationship between hair dye use and bladder cancer or may even mask an effect that does, in fact, exist. Furthermore, data from the Surveillance, Epidemiology, and End Results (SEER) database shows that while bladder cancer incidence rates have increased somewhat (i.e., on the order of 1% or so annually), death rates have decreased by several percentage points over the same time period.[2] This SEER data overlaps the period of time from which the Altekruse et al.[13] study data were drawn. The increasing incidence and decreasing death rate could be due to earlier diagnosis and improved treatment. Therefore, a mortality study may lead to spurious findings, since the vast majority of bladder cancer cases would not be evaluated and a decreasing death rate could be partially accounted for by a treatment effect.

In summary, the present meta-analysis suggests that personal use of hair dyes is a risk factor for carcinoma of the bladder and that prior suggestions to the contrary are due to a multitude of study design limitations and uncontrolled confounding. Although it is likely that the summary relative risk associated with hair dyes and bladder cancer is less than 2 (i.e., less than doubling of the bladder cancer risk), permanent hair dye products should be used cautiously until more definitive data are available. Additional well designed studies are needed that take into account product type, duration and frequency of use, and the natural histories of both superficial and muscle-invasive bladder cancer.

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