Journal of Neuro-Oncology (2005) 72: 133–147
DOI 10.1007/s11060-004-3121-0

Clinical Study

Beauty product-related exposures and childhood brain tumors in seven countries: results from the SEARCH International Brain Tumor Study★

J.T. Efird[1,2], E.A. Holly[2,3], S. Cordier[4], B.A. Mueller[5], F. Lubin[6], G. Filippini[7], R. Peris-Bonet[8], M. McCredie[9,10], A. Arslan[11], P. Bracci[2] and S. Preston-Martin[12]
[1]*John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii at Manoa, USA;* [2]*Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA;* [3]*Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA;* [4]*INSERM U435, Rennes, France;* [5]*Fred Hutchison Cancer Research Center, Seattle, Washington, USA;* [6]*Cancer Epidemiology Unit, Gertner Institute, Chaim Sheba Medical Center, Sackler School of Medicine, Tel-Hashomer, Israel;* [7]*Neuroepidemiology Research Unit, National Neurological Institute 'C Besta', Milan, Italy;* [8]*Registro Nacional de Tumores Infantiles, Instituto Lopez Pinero, CSIC-Universitat de Valencia, Valencia, Spain;* [9]*Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand;* [10]*Previously Epidemiology Research Unit, New South Wales Cancer Council, Sydney, Australia;* [11]*International Agency for Research on Cancer, Lyon, France;* [12]*Department of Preventive Medicine, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, California USA*

Key words: beauty products, childhood brain tumors, foundation face cream, hair color, hair spray, permanent waves

Summary

Data from 1218 cases of childhood brain tumors (CBT) diagnosed between 1976 and 1994 and 2223 matched controls from the general population were included in an analysis of maternal beauty product exposure and beauty-related employment in 9 centers in 7 countries. A 50% increased odds ratio (OR) [95% confidence interval (CI) = 1.0–2.1] for CBT was observed among children of mothers who were exposed via personal use of and/or possible ambient contact with beauty products during the 5 years preceding the index child's birth compared with children of mothers never exposed to beauty products during this time period. Overall maternal personal use of hair-coloring agents in the month before or during the pregnancy of the index child's birth was not associated with CBT (OR = 1.0, CI = 0.83–1.3) or with astroglial (OR = 1.1, CI = 0.85–1.4), PNET (OR = 1.0, CI = 0.71–1.5) and other glial subtypes (OR = 1.0, CI = 0.62–1.0). Similarly, no statistically increased ORs or discernable pattern of risk estimates were observed for period of use or for number of applications per year for maternal personal use of hair-coloring agents overall or by histologic type. Among children born on or after 1980, increased ORs for CBT were associated with maternal non-work-related exposure to any beauty products (OR = 2.6, CI = 1.2–5.9), hair dyes (OR = 11, CI = 1.2–90), and hair sprays (OR = 3.4, CI = 1.0–11). No overall increased OR for CBT was observed among children of mothers employed in beauty-related jobs during the 5 years preceding the index child's birth compared with those who reported no beauty-related employment. In general, other specific beauty product-related exposures were not associated with increased ORs for CBT. Data from our study provide little evidence of an increased risk for CBT with mothers' exposures to beauty products.

Abbreviations: BRONOPOL – *2-bromo-2-nitropropane-1,3-diol;* CBT – childhood brain tumors; CI – confidence intervals; EMF – electromagnetic fields; 4-EMPD – *4-ethoxy-M-phenylenediamine sulfate*; ICD-O – International Classification of Disease-Oncology; ISCO – International Classification of Occupations; 4-MMPD – *4-methoxy-meta-phenylenediamine*; NDELA – *N-nitrosodiethanolamine*; NOC – *N-nitroso* compounds; NOS – not-otherwise-specified; OR – odds ratio; PNET – primitive neuroectodermal tumors; SD – standard deviation; SEARCH – Surveillance of Environmental Aspects Related to Cancer in Humans

Introduction

Brain tumors are the most common solid tumors of childhood and rank second after leukemia as the leading cause of cancer death among children [1]. Established risk factors for childhood brain tumors (CBT) that account for less than 10% of the incidence for CBT include male sex (for medulloblastomas and ependymo-

★ Conducted under the auspices of the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) program of the International Agency for Research on Cancer (IARC).

mas), therapeutic doses of ionizing radiation to the head, and various hereditary conditions (e.g., neurofibromatosis, tuberous sclerosis, naevoid basal-cell syndrome, Turcot syndrome and Li–Fraumeni syndrome) [2]. A few studies have examined maternal beauty product use (e.g., make-up [3–7], hair-color agents [3–7], hair spray [3,5], permanent-wave solution [3]) and employment as a hairdresser/cosmetologist [8–10], as potential risk factors for CBT. Results from these studies have shown no increased odds ratios (OR) or have been inconclusive.

Women worldwide commonly use beauty products [11] and risk frequent exposure to potentially carcinogenic chemicals contained in many of these products. Certain chemical components of beauty products (e.g., coal-tar based and related aromatic amine dyes [12–26], *N-nitroso* compounds (NOC) [14–17,27–30], diethanolamine/triethanolamine [31–34], formaldehyde-releasing preservatives [35–38], phthalates [39–43], cobalt salts [44], lead acetate [45,46], nickel salts [47], and *1,4-dioxane* [46,48]) have been shown to be mutagenic and/or carcinogenic in experimental animals and possibly carcinogenic to humans. Also, some widely used cosmetic ingredients, such as those in the paraben family of preservatives [49,50] and phthalic acid-derived compounds [51,52], are known to mimic estrogen. These estrogen-acting compounds conceivably pose cancer risk in children of mothers exposed preconceptionally [53–56], given that several studies have linked other known xenoestrogens with cancer [57–62] and reproductive problems [63–69] and that estrogens are important in the normal development and function of the CNS [70–83] and in immune programming [84] during embryonic development. Interestingly, women of childbearing age were found to have significantly higher urinary metabolite levels of phthalate compounds, used extensively in perfumes, nail polishes, hair sprays and other cosmetics, compared with other age and sex groups [85].

Similar to other hormonally dependent cancers, some types of brain tumors possess estrogen/sex steroid receptors [86–89] and respond to the estrogen antagonist drug Tamoxifen [90–93], although the latter effect may be attributable to the inhibition of protein kinase C [91]. Estrogen is known to effectively induce prolactin-secreting pituitary tumors in laboratory animals following prolonged exposure [94]. Additionally, the paraben class agent, *2-Bromo-2-nitropropane-1,3-Diol* (BRONOPOL), is known to act as a nitrosating agent that can result in the formation of the carcinogenic product *N-nitrosodiethanolamine* (NDELA) [11,95]. Potential exposure to the fetus during routine cosmetic use is possible given that many of these compounds are skin permeable [13,96–110], or can enter the body via oral, ocular or inhalation routes [13,85] and thus cross the placenta [111–114]. It also may be that maternal exposure to carcinogenic agents and endocrine disruptors present in beauty products before the birth of the child yield transgenerational effects because they can persist in body fat and/or mother's milk [115,116], or may mutate the germline [117,118].

Among regular clients of beauticians, 93% of women use facial cream/lotion, 53% receive salon permanent waves, 30% use hair color/bleach, 24% use color shampoo, and 6% use at-home permanent-wave products [11]. Annual sales of beauty products by some members of the European community amount to 80% of their market [11]. United States consumers alone purchase more than $3.9 billion of hair and $1.8 billion of skin-care products every year [11]. In some regions of the United States, such as the San Francisco Bay Area, approximately 60% of women between ages 21 and 74 years reported having ever used a hair-coloring product [119]. Given the extensive use of beauty products worldwide, the children of women who are exposed to potentially harmful agents present in these products prior to or during pregnancy, may be at increased risk for cancer.

We investigated the association between CBT and prenatal and preconceptional maternal exposure to beauty products and beauty-related employment. The data were collected from mothers of 1218 cases and 2223 population-based controls who participated in a large international case–control study of CBT that ascertained maternal exposure to hair color, hair spray, permanent-wave solution, foundation face cream, and other beauty products, and employment as a hairdresser or beautician. The study was conducted under the auspices of the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) program of the International Agency for Research on Cancer (IARC).

Methods

Study methods have been published previously [6–8,10,120–134]. Briefly, data were collected from 9 participating centers in seven countries (San Francisco and Los Angeles, California, and Seattle, Washington, in the USA; Israel; Milan, Italy; Valencia, Spain; Sydney, Australia; Paris, France; and Winnipeg, Canada). All centers followed the same international study protocol, including study design and questionnaire use, with minor differences among the participating centers.

Eligible cases were younger than 20 years of age at diagnosis; were diagnosed between 1976 and 1994 with a primary brain [*International Classification of Disease-Oncology* (ICD-O) [135] site code: 191] or cranial nerve [ICD-O:192.0] tumor; and resided in one of the geographic regions covered by each center. Cases were ascertained through population-based cancer registries in Los Angeles, San Francisco, Seattle, Sydney, Valencia and Winnipeg, and through hospital records in Israel, Milan and Paris. If there were no physician-indicated contraindications to contacting the subject, the biological mother of each eligible case was contacted in writing to request participation in the study. A comparison of the expected number of cases (based on published incidence rates) with the rates in each geographic area (not routinely covered by a tumor registry) suggested that case ascertainment was nearly complete [8].

Population-based controls were identified using methods optimal to each geographic region. Telephone directories were used in Winnipeg, electoral rolls in Sydney (where voting is compulsory), census and

telephone directories in Paris, the national population register in Israel, the regional health service in Milan, the municipal census in Valencia and random digit dial in the USA. Matching variables were at least age (ranging from ±3 months to ±4 years) and gender in all centers.

A total of 1627 case and 2950 control children met study eligibility criteria. All interviews were in-person and typically were conducted at the participants' homes. There were 1218 cases (75% response rate; ranging from 69% to 87% between centers) and 2223 controls (75% response rate; ranging from 57% to 87% between centers) who completed interviews. Non-participation of cases and controls was due mainly to an inability to locate or contact families (10% cases, 11% controls), and to refusal by mothers (10% and 13%) [120,130].

Histologic subtypes for CBT were categorized into 5 groups based upon previously defined ICD-O morphology codes [120,135]. In total, there were 621 astroglial, 258 primitive neuroectodermal tumors (PNET), 147 other glial, 178 other histologic type, and 9 not-otherwise-specified (NOS) cases included in these analyses.

Study data were collected from biological mothers via structured interviews using a standardized questionnaire. Mothers were asked to report their occupations (open-ended question coded using *International Standard Classification of Occupations* (ISCO) [136]) in the 5-year period before the birth of the index child. They also were asked about their personal use and/or exposure via ambient contact (e.g., respiratory or dermal) to beauty products at work or outside work during this 5-year period. Work-related beauty-product exposures had to have occurred for a period of 1 month or longer. Non-work-related beauty-product exposures had to have occurred 'at least once a week for 6 months or longer,' or 'for several hours at a time on one or more occasions.' Mothers were asked to select the type of beauty- product exposure from a list that included 'hair dyes,' 'hair sprays,' 'permanent-wave chemicals,' and 'other beauty products.' Additionally, information was obtained about maternal personal use of foundation face cream during pregnancy with the index child, and on maternal personal use of hair-color products in the month before or during pregnancy with the index child. With regard to foundation face cream, mothers were asked: '…did you use foundation cream or liquid on your face during your pregnancy with (child)', and 'for how many days per week did you usually use foundation cream or liquid.' Details asked about mothers' personal use of hair colors included: '… did you use any dyes or coloring agents on your hair;' 'did you use it … during the month before (pregnancy), during the first 3 months, during the second 3 months, during the last 3 months;' 'how many times per week, month or year did you use it;' and 'what type of hair dye was this? Was it … temporary (washes out in one shampoo) … semi-permanent (washes out in 6–10 shampoos) … permanent (leaves a line as it grows out) … or was it a hair darkener (a product used to blend grey with the rest of the hair).' Information about specific types of semi-permanent dyes used (e.g., henna versus synthetic organic dyes) was not collected.

Although individual matching was used in some centers, the conditional and unconditional estimates were essentially the same based on 95% confidence intervals (CI). Thus, unconditional analysis methods were used with the combined data. This allowed us to maximize efficiency by including all available subjects compared with losing some matched units who could not be individually matched if a post-hoc strategy was used to analyze the data. Child's reference age for evaluation of exposures was computed similarly by study centers and corresponded to the method of control selection at each center. Regression models were adjusted for sex, study center and child's age (continuous variable).

Model fit was assessed using deviance-based diagnostic plots [137]. Normal theory was used to compute test-based CIs for estimated ORs. Tests for trend are presented where appropriate and were computed using a likelihood ratio procedure [138]. The least-square means method was used to compare mean values between groups adjusting for study center and sex [139]. Race was mostly homogeneous within the majority of centers and consequently was not a confounder in any model. Regional differences that may not have been controlled for by other variables were addressed via adjustment for study center. Adjustment for mother's education had little or no effect on the magnitude or significance of ORs and CIs and was not included in final models. Sample sizes were too small in some centers to report center-specific estimates reliably or to assess the degree of effect modification across centers. To investigate the effect of changes in product formulations, an *a priori* cutoff year of 1980 was used based upon the declining or discontinued use of several cosmetic chemicals prior to or near 1980 [13]. Continuous variables were categorized into quartiles or tertiles based on the distribution among control participants.

Results

Cases and controls were distributed similarly by child's age and year of birth, maternal age at child's birth and number of years of schooling of the mother [8]. Time from diagnosis (reference) to interview date was not different between cases and controls (cases, adjusted mean time = 3.1 years; controls, adjusted mean time = 2.9 years; $P = 0.20$). The largest proportion of cases were contributed by the USA centers (44%) followed by Israel (25%), Europe (21%), Australia (7%) and Canada (4%) (Table 1).

An OR of 1.5 [95% confidence interval (CI) = 1.0–2.1] for CBT was observed for any use of beauty products (hair dyes, hair sprays, permanent-wave chemicals, and 'other beauty products') among children of mothers who were exposed during the 5 years preceding the index child's birth compared with children of mothers never exposed to beauty products during this time period (Table 2). Within this group, ORs > 2.0 were found for work-related exposure to 'other beauty products'

Table 1. Distribution of cases and controls by study center: IARC SEARCH International Childhood Brain Tumor Study, 1976–1994

Study center	Cases (n = 1218)		Controls (n = 2223)	
	n	%	n	%
United States	540	44	801	36
Los Angeles	304	25	315	14
Seattle	134	11	281	13
San Francisco	102	8	205	9
Israel	300	25	574	26
Europe	251	21	601	27
Milan, Italy	90	7	318	14
Valencia, Spain	86	7	170	8
Paris, France	75	6	113	5
Sydney, Australia	82	7	164	7
Winnipeg, Canada	45	4	83	4

(OR = 2.5, CI = 1.2–5.4, 15 cases, 14 controls, not shown in Table 2) and for non-work-related exposure to hair dyes (OR = 2.3, CI = 0.99–5.5). The 'other beauty products' category was self-defined and included many different types of substances (e.g., bleaches, liquid hair lacquer, nail polish, shampoo, soaps, hair-removing creams, perfumes, deodorant, powder, blusher, beauty creams, make-up products, shaving lather, scalp treatment products, toothpaste, beauty-improvement products). However, few of the mothers reported the same exposures. Maternal non-work-related exposure to hair sprays was associated with a 5.5-fold increased OR (CI = 1.0–29, 5 cases, 2 controls) for CBT among children of mothers living in Sydney, Australia, whereas the OR was 0.95 (CI = 0.45–2.0, 12 cases, 17 controls) in all other sites combined. Among children born before 1980, ORs for CBT were associated with maternal work-related exposure to any beauty products (OR = 1.8, CI = 1.0–3.3) and to 'other beauty products' (OR = 3.4, CI = 1.3–8.7, 11 cases, 8 controls, not shown in Table 2). Among children born in or after 1980, ORs for CBT were associated with maternal non-work-related exposure to any beauty products (OR = 2.6, CI = 1.2–5.9), hair dyes [OR = 11, CI = 1.2–90; mean child's age: 6 cases = 3.2 years (2 from Sydney, 1 from Israel, 2 from Los Angeles, and 1 from Seattle) [± 2.3 standard deviations (SD)], 1 control = 2.2 years (from Sydney)], and hair sprays [OR = 3.4, CI = 1.0–11; mean child's age: 9 cases = 3.8 years (3 from Sydney, 5 from Los Angeles, and 1 from Seattle) (± 2.6 SD), 4 controls = 2.8 years (1 from Sydney, 2 from Winnipeg, and 1 from Los Angeles) (± 2.8 SD)]. Among children born before 1980, all work-related ORs shown in Table 2 were higher than non-work-related ORs, whereas for children born in or after 1980, all non-work-related ORs were higher then work-related ORs.

An increased OR for PNET [OR = 2.7, CI = 1.3–5.4; mean child's age: 11 cases = 7.0 years (± 5.3 SD) (1 from Sydney, 2 from Israel, 1 from Paris, 2 from Milan, 4 from Los Angeles, and 1 from Seattle), 40 controls = 8.0 years (± 4.9 SD) (4 from Sydney, 4 from Israel, 2 from Winnipeg, 1 from Paris, 8 from Milan, 5 from Valencia, 4 from Los Angeles, 9 from San Francisco, and 3 from Seattle)] was observed among children of mothers exposed to hair sprays at work during the 5 years preceding the index child's birth, compared with children of mothers never exposed to beauty products during this time period (Table 3). However, the non-work-related OR for hair-spray exposure was 0.35, which should generate caution in interpreting this result. Maternal exposure at work to the highly variable category of 'other beauty products' was associated with an increased OR for astroglial CBT (OR = 3.7, CI = 1.6–8.6). Non-work-related maternal exposure to hair dyes was associated with an increased OR for other glial CBT [OR = 6.5, CI = 1.6–26; mean child's age: 3 cases = 8.6 years (± 5.6 SD) (1 from Los Angeles, 1 from San Francisco, and 1 from Seattle), 10 controls = 10.2 years (± 4.2 SD) (3 from Sydney, 1 from Winnipeg, 1 from Milan, 1 from Los Angeles, and 4 from San Francisco)].

Overall maternal personal use of hair-coloring agents (e.g., temporary, semi-permanent, permanent, hair darkener) in the month before or during the pregnancy with the index child was not associated with CBT (OR = 1.0, CI = 0.83–1.3, 163 cases, 283 controls) compared with children of mothers who never used any hair-coloring agents during this time period (Table 4). Similarly, personal use of any hair-coloring agents was not associated with astroglial (OR = 1.1, CI = 0.85–1.4), PNET (OR = 1.0, CI = 0.71–1.5) and other glial (OR = 1.0, CI = 0.62–1.7) subtypes (Table 5). No statistically increased ORs or discernable pattern of risk estimates were observed for 'period of use' or 'applications per year' for maternal personal use of hair-coloring agents overall (Table 4) or by histologic type (Table 5). Among children in Israel, maternal personal use of semi-permanent hair color was associated with an increased OR for CBT (OR = 3.0, CI = 1.1–7.9, 11 cases, 7 controls, not shown in Table 4) compared with Israeli children whose mothers never used any hair-coloring agents. However, the OR for CBT at all other study centers was 0.86 (CI = 0.47–1.6, 17 cases, 35 controls).

A decreased OR for CBT (OR = 0.86, CI = 0.73–1.0, 354 cases, 698 controls, not shown in tables) was observed among children of mothers who used foundation face cream or liquid during pregnancy, compared with mothers who did not use these products. An increasing number of applications per week of foundation face cream or liquid was not associated with a consistently decreasing OR for CBT (never used during pregnancy: OR = 1.0; 1–6 applications per week: OR = 0.81, CI = 0.65–1.0); > 6 applications per week: OR = 0.87, CI = 0.71–1.1).

There was no association between CBT and mothers' history of employment in beauty-related jobs during the 5 years preceding the index child's birth (ever versus never; OR = 1.2, CI = 0.69–1.9, 25 cases, 42 controls, result not shown in Tables). A 2.8-fold OR for PNET (CI = 0.81–9.4, 4 cases, 9 controls) was observed among children of mothers ever employed as beauticians. However, the risk estimate did not statistically differ from unity.

Table 2. Adjusted odds ratios for CBT by maternal exposures to beauty products during the 5 years preceding the index child's birth: SEARCH International Brain Tumor Study, 1976–1994[a]

Maternal exposure to beauty products[b] during the 5 years preceding the index child's birth	Combined birth years		Birth year <1980		Birth year ≥1980	
	Cases/controls	OR [95% CI][c]	Cases/controls	OR [95% CI][c]	Cases/controls	OR [95% CI][c]
Never exposed[d]	1153/2143	1.0 Referent	574/1102	1.0 Referent	579/1041	1.0 Referent
Ever exposured	65/80	1.5 [1.0–2.1]	33/48	1.2 [0.77–2.0]	32/32	1.8 [1.0–2.9]
Work-related[e,g]	37/48	1.5 [0.99–2.4]	22/25	1.8 [1.0–3.3]	15/23	1.2 [0.64–2.4]
Non-work–related[f,g]	28/34	1.3 [0.77–2.2]	11/24	0.66 [0.31–1.4]	17/10	2.6 [1.2–5.9]
Hair dyes	38/47	1.6 [1.0–2.5]	22/28	1.5 [0.86–2.8]	16/19	1.6 [0.81–3.2]
Work-related[e,g]	26/38	1.3 [0.80–2.3]	16/20	1.6 [0.80–3.1]	10/18	1.1 [0.49–2.4]
Non-work-related[f,g]	12/10	2.3 [0.99–5.5]	6/9	1.3 [0.44–3.6]	6/1[h]	11 [1.2–90]
Hair sprays	46/58	1.4 [0.93–2.1]	25/34	1.2 [0.71–2.1]	21/24	1.5 [0.84–2.8]
Work-related[e,g]	29/40	1.4 [0.85–2.3]	17/20	1.6 [0.83–3.2]	12/20	1.1 [0.54–2.3]
Non-work-related[f,g]	17/19	1.3 [0.68–2.6]	8/15	0.70 [0.28–1.7]	9/4[i]	3.4 [1.0–11]
Permanent-wave chemicals	33/47	1.3 [0.81–2.0][j]	16/22	1.3 [0.69–2.6]	17/25	1.2 [0.64–2.3]
Work-related[e,g]	23/36	1.2 [0.71–2.1]	14/17	1.6 [0.76–3.3]	9/19	0.90 [0.40–2.0]
Non-work-related[f,g]	10/13	1.2 [0.52–2.8]	2/6	0.51 [0.10–2.6]	8/7	1.8 [0.64–5.1]

[a] Year of diagnosis for children with brain tumors included in this study.
[b] Hair dyes, hair sprays, permanent–wave chemicals, 'other beauty products.'
[c] Adjusted for child's age, sex and center.
[d] Reference group for all exposures were mothers who never were exposed to beauty products on or off the job during the 5 years preceding the index child's birth.
[e] Personal use and/or ambient contact (e.g., inhaling it or getting it on skin or clothes) for a period of 1 month or longer.
[f] Personal use and/or ambient contact (e.g., inhaling it or getting it on skin or clothes) at least once a week for a period of 6 months or longer, or for several hours at a time on one or more occasions.
[g] Work- and non-work-related exposures may not be mutually exclusive.
[h] Mean child's age: 6 cases (2 from Syndey, 1 from Israel, 2 from Los Angeles, and 1 from Seattle) = 3.2 years (±2.3 SD), 1 control (from Sydney) = 2.2 years.
[i] Mean child's age: 9 cases (3 from Sydney, 5 from Los Angeles, and 1 from Seattle) = 3.8 years (±2.6 SD), 4 controls (1 from Sydney, 2 from Winnipeg, and 1 from Los Angeles) = 2.8 years (±2.2 SD).
[j] OR = 0.95 (CI = 0.45–2.0) for all geographic sites except Sydney, AU where OR = 5.5 (CI = 1.0–29, 5 cases, 2 controls).

Table 3. Adjusted odds ratios for CBT by maternal exposures to beauty products during the 5 years preceding the index child's birth – Histology: SEARCH International Brain Tumor Study, 1976–1994[a]

Maternal exposure to beauty products[b] during the 5 years preceding the index child's birth	Astroglial		PNET		Other glial	
	Cases/controls	OR [95% CI][c]	Cases/controls	OR [95% CI][c]	Cases/controls	OR [95% CI][c]
Never exposed[d]	587/2143	1.0 Referent	246/2143	1.0 Referent	141/2143	1.0 Referent
Ever exposured	36/80	1.5 [1.0–2.3]	13/80	1.4 [0.75–2.6]	7/80	1.4 [0.61–3.1]
Work-related[e,g]	19/48	1.5 [0.89–2.7]	11/48	2.2 [1.1–4.4]	4/48	1.4 [0.50–4.1]
Non-work-related[f,g]	17/34	1.4 [0.78–2.6]	2/34	0.39 [0.09–1.7]	3/34	1.2 [0.35–4.1]
Hair dyes	18/47	1.5 [0.83–2.6]	9/47	1.9 [0.89–3.9]	6/47	2.2 [0.90–5.3]
Work-related[e,g]	13/38	1.4 [0.71–2.6]	8/38	2.0 [0.90–4.4]	3/38	1.3 [0.38–4.3]
Non-work-related[f,g]	5/10	1.7 [0.55–5.0]	1/10	1.2 [0.14–9.3]	3/10[h]	6.5 [1.6–26]
Hair sprays	21/58	1.2 [0.69–2.0]	12/58	1.8 [0.93–3.4]	7/58	1.9 [0.83–4.3]
Work-related[e,g]	12/40	1.1 [0.55–2.1]	11/40[i]	2.7 [1.3–5.4]	4/40	1.7 [0.60–5.0]
Non-work-related[f,g]	9/19	1.3 [0.56–2.9]	1/19	0.35 [0.05–2.6]	3/19	2.1 [0.59–7.7]
Permanent-wave chemicals	16/47	1.2 [0.66–2.1]	9/47	1.6 [0.77–3.4]	5/47	1.7 [0.65–4.4]
Work-related[e,g]	10/36	1.1 [0.51–2.2]	8/36	2.1 [0.93–4.6]	3/36	1.3 [0.39–4.4]
Non-work-related[f,g]	6/13	1.3 [0.48–3.4]	1/13	0.46 [0.06–3.7]	2/13	2.4 [0.50–12]

[a] Year of diagnosis for children with brain tumors included in this study.
[b] Hair dyes, hair sprays, permanent–wave chemicals, 'other beauty products.'
[c] Adjusted for child's age, sex and center.
[d] Reference group for all exposures were mothers who never were exposed to beauty products on or off the job during the 5 years preceding the index child's birth.
[e] Personal use and/or ambient contact (e.g., inhaling it or getting it on skin or clothes) for a period of 1 month or longer.
[f] Personal use and/or ambient contact (e.g., inhaling it or getting it on skin or clothes) at least once a week for a period of 6 months or longer, or for several hours at a time on one or more occasions.
[g] Work-and non-work-related exposures may not be mutually exclusive.
[h] Mean child's age: 3 cases (1 from Los Angeles, 1 from San Francisco, and 1 from Seattle) = 8.6 (± 5.6 SD), 10 controls (3 from Sydney, 1 from Winnipeg, 1 from Milan, 1 from Los Angeles, and 4 from San Francisco) = 10.2 (± 4.2 SD).
[i] Mean child's age: mean child's age: 11 cases (1 from Sydney, 2 from Israel, 1 from Paris, 2 from Milan, 4 from Los Angeles, and 1 from Seattle) = 7.0 years (± 5.3 SD), 40 controls (4 from Sydney, 4 from Israel, 2 from Winnipeg, 1 from Paris, 8 from Milan, 5 from Valencia, 4 from Los Angeles, 9 from San Francisco, and 3 from Seattle) = 8.0 years (± 4.9 SD).

Table 4. Adjusted odds ratios for CBT by maternal personal use of hair dyes or coloring agents in the month before or during the pregnancy of the index child's birth: SEARCH International Brain Tumor Study, 1976–1994[a]

Maternal personal use of hair dyes or coloring agents in the month before or during the pregnency of the index child's birth[b]	Combined birth years		Birth year < 1980		Birth year ≥ 1980	
	Cases/controls	OR [95% CI][c]	Cases/controls	OR [95% CI][c]	Cases/controls	OR [95% CI][c]
Never used[d]	1037/1913	1.0 Referent	510/993	1.0 Referent	527/920	1.0 Referent
Ever used	163/283	1.0 [0.83–1.3]	87/142	1.1 [0.83–1.5]	76/141	0.91 [0.67–1.2]
Applications per year						
1–2	45/97	0.81 [0.56–1.2]	15/39	0.90 [0.39–1.3]	30/58	0.86 [0.54–1.4]
3–6	63/93	1.2 [0.86–1.7]	39/49	1.5 [0.95–1.1]	24/44	0.92 [0.55–1.5]
>6	55/93	1.1 [0.75–1.5]	33/54	1.1 [0.68–1.7]	22/39	0.99 [0.58–1.7]
Period of use						
Month before pregnancy	107/170	1.1 [0.87–1.5]	65/91	1.3 [0.93–1.9]	42/79	0.91 [0.61–1.4]
1st trimester	113/198	1.0 [0.80–1.3]	73/107	1.2 [0.88–1.7]	40/91	0.77 [0.52–1.1]
2nd trimester	116/196	1.0 [0.81–1.3]	73/101	1.3 [0.93–1.8]	43/95	0.77 [0.52–1.1]
3rd trimester	118/191	1.1 [0.87–1.4]	71/102	1.2 [0.89–1.7]	47/89	0.93 [0.63–1.4]
Type of product used						
Temporary (washes out in 1 shampoo)	12/16	1.4 [0.65–3.0]	4/8	1.1 [0.31–3.6]	8/8	1.7 [0.61–4.6]
Semi-permanent (washes out in 6–10 shampoos)	28/42	1.2 [0.73–2.0]	15/18	1.5 [0.73–3.0]	13/24	0.98 [0.49–2.0]
Permanent (leaves a line as it grows in)	129/223	1.0 [0.81–1.3]	69/118	1.1 [0.77–1.5]	60/105	0.96 [0.68–1.4]
Hair darkener (used to blend grey with rest of hair)	7/7	1.8 [0.63–5.3]	4/2	4.5 [0.82–25]	3/5	0.94 [0.22–4.1]

[a] Year of diagnosis for children with brain tumors included in this study.
[b] Complete exposure information unavailable for 18 cases and 27 controls.
[c] Adjusted for child's age, sex and center.
[d] Reference group for all exposures were mothers who never personally used hair dye or coloring agents in the month before or during the pregnancy of the index child's birth.

Table 5. Adjusted odds ratios for CBT by maternal personal use of hair dyes or coloring agents in the month before or during the pregnancy of the index child's birth – Histology: SEARCH International Brain Tumor Study, 1976–1994[a]

Maternal personal use of hair dyes or coloring agents in the month before or during the pregnancy of the index child's birth[b]	Astroglial		PNET		Other glial	
	Cases/controls	OR [95% CI][c]	Cases/controls	OR [95% CI][c]	Cases/controls	OR [95% CI][c]
Never used[d]	524/1913	1.0 Referent	219/1913	1.0 Referent	129/1913	1.0 Referent
Ever used	90/283	1.1 [0.85–1.4]	35/283	1.0 [0.71–1.5]	19/283	1.0 [0.62–1.7]
Applications per year						
1–2	21/97	0.77 [0.47–1.3]	15/97	1.2 [0.70–2.2]	4/97	0.59 [0.21–1.6]
3–6	35/93	1.3 [0.89–2.0]	11/93	0.99 [0.51–1.9]	6/93	1.0 [0.42–2.4]
>6	34/93	1.3 [0.84–1.9]	9/93	0.87 [0.43–1.8]	9/93	1.6 [0.78–3.3]
Period of use						
Month before pregnancy	60/170	1.2 [0.91–1.7]	19/170	0.97 [0.59–1.6]	13/170	1.3 [0.71–2.4]
1st trimester	62/198	1.1 [0.81–1.5]	26/198	1.2 [0.74–1.8]	13/198	1.1 [0.58–1.9]
2nd trimester	69/196	1.2 [0.89–1.6]	20/196	0.87 [0.66–1.2]	15/196	1.2 [0.66–2.1]
3rd trimester	69/191	1.3 [0.95–1.7]	20/191	0.90 [0.55–1.5]	13/191	1.1 [0.60–2.0]
Type of product used						
Temporary (washes out in 1 shampoo)	7/16	1.7 [0.69–4.3]	4/16	2.1 [0.67–6.5]	1/16	0.84 [0.11–6.6]
Semi-permanent (washes out in 6–10 shampoos)	19/42	1.7 [0.96–3.0]	3/42	0.67 [0.20–2.2]	3/42	1.0 [0.31–3.5]
Permanent (leaves a line as it grows in)	71/223	1.1 [0.82–1.5]	28/223	1.0 [0.68–1.6]	14/223	1.0 [0.56–1.8]
Hair darkener (used to blend grey with rest of hair)	5/7	2.7 [0.85–8.8]	0/7	–	1/7	2.0 [0.22–17]

[a] Year of diagnosis for children with brain tumors included in this study.
[b] Complete exposure information unavailable for 18 cases and 27 controls.
[c] Adjusted for child's age, sex and center.
[d] Reference group for all exposures were mothers who never personally used hair dye or coloring agents in the month before or during the pregnancy of the index child's birth.

Discussion

There were few statistically significant associations and no clear patterns were observed between CBT and maternal exposure to beauty products before or during pregnancy in this study. A borderline 1.5-fold OR for CBT was observed among children of mothers who were exposed to any beauty products during the 5 years preceding the index child's birth. Some increased ORs were reported for work-related maternal exposure to 'other beauty products' and for non-work-related maternal exposure to hair dyes. The OR for CBT was increased for children born in or after 1980 whose mothers reported non-work-related exposure to hair dyes but the number of subjects was small and the CI was wide. In Israel, children of mothers who personally used semi-permanent hair color in the month before or during pregnancy had an increased OR for CBT, but this was not found for all other countries.

Mothers who use or work with beauty products may risk exposure to many potentially carcinogenic agents [12–48]. These compounds may enter the bloodstream via dermal, oral, ocular or inhalation routes [96–103]. and during pregnancy may affect the fetus [111–114]. The immature nervous system of the fetus is characterized by rapid cell growth and division, and exposure during gestation may occur at a vulnerable time when the fetal blood-brain barrier, nervous system and immune response are less developed and possibly more susceptible to cancer [140], and brain tumors are known to occur *in utero* [141,142]. Beauty-product exposures or employment should be evaluated carefully to determine the timing of the exposure before or during pregnancy, the calendar year and the country of exposure. Chemical ingredients vary considerably among seemingly similar products and by country [11]. For example, in the USA coal-tar hair dyes specifically are exempt from regulation [48]. Furthermore, manufacturers frequently change product formulations.

Factors influencing the level of exposure to beauty products include wearing protective gloves and masks, using the products in a well-ventilated area, avoiding eating or drinking during exposure, and frequently taking breaks during prolonged periods of exposure. The absorption of beauty-product chemicals into the bloodstream also may be altered by humidity, temperature and pH, as well as skin damage or irritation [13]. Chemicals in some beauty products, such as hair dyes/lighteners/straighteners and permanent-wave lotions that enhance the penetration of these products into the hair shaft may facilitate the absorption of carcinogens into the scalp [13]. Furthermore, the carcinogenic effect of certain beauty products may be influenced by genetic variability of enzymes involved in chemical detoxification and/or acetylation (e.g., NAT1, NAT2, GSTM1, GSTT1, GSTP1, CYP1A2) [143]. Heterogeneity of these enzymes could mask underlying risk associations in study populations [144].

The association between beauty-product-related exposures or beauty-related employment and CBT risk has been examined in few studies unrelated to our SEARCH CBT series. A pediatric oncology cooperative group study conducted in the USA and Canada among 33 hospitals and their affiliates [3] included 155 astrocytic glioma and 166 PNET cases, diagnosed before 6 years of age in 1986–1989. Controls were selected via random-digit dial and individually matched to cases on race, birth year, and telephone area code and prefix. No increased ORs (>1.2) for astrocytoma or PNET were observed for children of mothers who used hair spray, hair color, hair permanent-wave product or make-up during pregnancy. Their hair color results were similar to the USA portion of the SEARCH CBT study [7]. Neither maternal employment as a hairdresser nor maternal exposure to beauty products in the preconceptual period were examined in this study [3]. Also similar to our USA results [7], a Los Angeles area study of 209 CBT cases individually matched to friend controls of the same age between 1972 and 1977 [5] examined maternal use of face make-up and permanent hair dyes during the index pregnancy. A 30% increased OR for CBT was observed among children of mothers who used permanent hair dye, but the estimate was not statistically significant. Maternal use of face make-up was associated with a significantly increased OR of 1.6 ($P = 0.02$) for CBT with 91 discordant case–control pairs. Use of other beauty products and beauty-related employment were not examined in this study. In another USA case–control study of astrocytoma that included 163 pairs of children under 15 years of age at diagnosis in 1980–1986, children whose mothers had worked as hairdressers were observed to have nonsignificant increased ORs for astrocytoma (before conception: OR = 2.5, CI = 0.4–26; during pregnancy: OR = 1.5, CI = 0.2–18; and after pregnancy of the index child: OR = 3.0, CI = 0.2–157) [9]. However, risk estimates were imprecise, numbers were small and all confidence intervals overlapped unity. In a separate analysis of the same participants, personal use of hair-coloring products (OR = 0.9, CI = 0.4–1.8) or facial make-up (OR = 0.7, CI = 0.4–1.2) during pregnancy with the index child were not associated with astrocytoma [4].

Similar to previous studies, [3,4,5], our results from analysis of the SEARCH CBT study data did not show an increased OR for CBT, including astrocytoma and PNET separately, among children of mothers who personally used hair-coloring agents in the month before or during pregnancy. Our results showed increased ORs for CBT among children of mothers who had non-work-related exposure to hair dyes during the 5 years preceding the index child's birth, particularly when exposure occurred in 1980 or later. Several factors may explain this increase. Chance is likely to have occurred given the broad range of ORs and small numbers in the subgroups. Contact with hair dyes at home may largely account for the difference between non-work-related and work-related exposures. The contact may be via self-application of hair-color products, applying the product to other family members or friends, or as a family member or friend exposed in the home of someone else who used these products. Exposure at home may differ from salon exposure on several levels. Exposure may take place in a poorly ventilated area. Product application also may occur without the use of

protective gloves. The increased OR associated with exposure during or after 1980 may reflect changes in product formulations over time. Use of carcinogenic agents *2,4-diaminotoluene* (*4-methyl-meta-phenylenediamine*), *2,4-diaminoanisole* (*4-methoxy-meta-phenylenediamine,* 4-MMPD), *4-amino-2-nitrophenol* (*o-nitro-p-aminophenol, p-aminonitrophenol*), and HC Blue No. 1 were regulated out of use by the early 1980s (although nitrophenol compounds remained in the European market until 1990) and were replaced with *O*- and *N-hydroxy*-alkyl derivatives and certain isomers of the parent compounds, such as *4-ethoxy-M-phenylenediamine sulfate* (4-EMPD) [13,26]. However, 4-EMPD is structurally similar to 4-MMPD and is a potential mutagen based on positive results of the *Salmonella* plate assay [145]. Other compounds with carcinogenic potential have been introduced over time to maintain the range of colors in hair dye products [13]. Nonetheless, the above effect was based on small numbers in a subset analysis, and is opposite to our *a priori* hypothesis that predicted a reduced OR for hair dye exposure after 1980 relative to before 1980 due to agents regulated out of use.

Although no statistically significant association was found between CBT and overall maternal personal use of temporary, semi-permanent, or permanent hair-coloring products in this study, a 3-fold increased OR for CBT was found among Israeli children whose mothers personally used semi-permanent hair color during the index pregnancy. However, caution should be used in interpreting this result as the OR for the remainder of the study participants was below unity. Unlike permanent dyes that contain oxidizing agents that allow the dye to irreversibly bind to the hair shaft [144], semi-permanent hair-coloring products typically achieve their coloring action via the use of various solvents (e.g., alcohols and ethylene glycol ethers)[13]. Semi-permanent color may penetrate the scalp more efficiently than permanent dyes [13], as the oxidation process of permanent dyes generally lowers skin absorption of specific aromatic amines [144]. Greater direct skin contact also occurs when using semi-permanent dyes since they are applied as a foam, rinse and/or surfactant solution [13]. In particular, surfactant solutions tend to facilitate uptake by the skin [13]. Semi-permanent hair-coloring products also typically contain nitro derivatives of phenylenediamines or aminophenols, azo dyes and aminoanthraquinone dyes [13] and *N-nitroso* compounds have been shown to be transplacental neurocarcinogens in rodents [146].

In contrast to the null results for personal hair spray use in the pediatric oncology cooperative group study [3], our SEARCH CBT study data showed a 2.7-fold increased OR for PNET among children of mothers who were exposed to hair spray at work during the 5 years preceding the index child's birth. However, the OR for the non-work-related hair-spray exposure of mothers was 0.35 in our study population of PNET patients, and it is unlikely that hair spray could have a differential effect. Further, these 'work-related' hair-spray exposures were not confined to occupations where hair spray was routinely used, but included all work-related exposures to hair spray. ORs for astroglial tumors corresponding to hair spray exposure in our SEARCH CBT study were similar to the pediatric oncology cooperative group study, [3]. The different results observed for PNET between these studies may indicate a greater frequency of work-related exposure in our SEARCH CBT study compared with the personal use of hair spray in the pediatric oncology cooperative group study, or may be a chance finding. Overall maternal exposure to hair permanent wave products was not significantly associated with CBT risk in either of these studies.

Similar to previous studies [3,4], our results showed no positive association between CBT and mothers'use of face make-up (e.g., foundation cream or liquid) during pregnancy with the index child. However, in an earlier study, a significantly increased OR for CBT was observed among children in Los Angeles whose mothers had used face make-up [5]. The difference in results may be explained partly by the earlier study time period of 1972–1977 in the Los Angeles study.

Several factors common to case–control studies should be considered when interpreting these observations. All exposures in this study were self-reported, were collected retrospectively and may have been influenced by disease status. However, because little is known about risk factors for CBT, differential reporting of risk factors by cases or controls is less likely. The heterogeneity of odds ratio estimates across exposures suggests that recall bias was not a major source of bias in our study, except for the self-defined exposures given in the 'other beauty products' category. As in all case–control studies, case mothers may have been more likely than control mothers to try to recall all prior exposures.

Although control selection differed by center (e.g., regional health services, census data, telephone directories and random-digit dial), the variety in control selection is likely to have been an asset because bias associated with particular selection methods would have been diluted in the combined sample. Only Winnipeg exclusively relied upon telephone directories to identify study controls, and the possibility exists that some homes with unlisted telephone numbers would have been missed. However, Winnipeg had the smallest number of study participants, and any potential bias most likely would have had a nominal influence on study results. In Paris, telephone directories were used to supplement census data to identify eligible controls. However, since cases and controls were contacted by telephone and only one case family did not have a number listed in the phone book, this would not have been likely to have introduced a difference in selection between cases and controls [127]. The most recent census data corresponding to the study recruitment period was used to identify controls in Paris and Valencia (in combination with telephone directories), and some potentially eligible controls may have been undetected by this method. Some eligible controls also may have been missed in Milan by using the regional health-service records to identify potential control participants. However, this number is likely to have been small given the socialized medical care system in Italy. Overall, possible selection bias was diminished as cases and controls resided in the same general geographic region

served by each center and the participation rates for cases and controls were equivalent (i.e., 75%).

Detailed information about control recruitment was not collected for some of the study centers. In Paris, for example, study investigators were unable to reach 20% of homes, even after several phone calls at different times and days of the week [127]. This figure is comparable with the multicenter case-control study of Hartge et al. (1984) [147] that reported initial non-contact rates of 15–20% when using random-digit dial. Nevertheless, the inability to establish telephone contact with potentially eligible controls would not influence study results unless beauty-product exposures are believed to differ between the contacted and non-contacted controls.

Our results may have been influenced by unmeasured potential confounders. However, no maternal environmental exposure other than ionizing radiation has been firmly established as a potential risk factor for CBT and this exposure is rare. Also, exposures examined in this study may be surrogate measures for other exposures conceivably related to CBT but not collected in this study. For example, mothers exposed to hair dyes, permanent waves, and hair sprays also may be exposed to electromagnetic fields (EMF) from electric hair dryers. However, studies of maternal exposure to EMF have consistently reported no increased risk for CBT [130,143,148,149].

The scope of our study did not permit the use of more detailed methods to collect data on the frequency, duration, or quantity of specific beauty product chemical exposures, or to estimate exposures based on a job-exposure matrix. Although questionnaires tend to be imprecise when used to capture exposure to specific potential carcinogens, our questionnaire was largely designed to measure a general class of exposures rather than precise carcinogens. Occupational data that was coded using the ISCO may have been subject to misclassification or residual confounding. We considered the occupational groups to provide a more precise description of beauty-product-related tasks than categories of economic activity (e.g., International Standard Industrial Classification of All Economic Activities [150]. Thus, our main interpretation is based on occupation groups.

The increased risk estimates observed in the SEARCH CBT study must be interpreted with substantial caution as the number of mothers exposed to some beauty products was small, and differential misclassification of a few responses could account for the observed differences between cases and controls. Further, small numbers prevented conducting more detailed analyses of effect modification among study variables. Results also may be due to chance given the large number of comparisons made in this analysis. This effect was minimized by testing hypotheses for a group of beauty products specified *a priori*, and by investigating specific periods of maternal exposure, as suggested by previous work. Nevertheless, some results were found that were the opposite of our *a priori* hypotheses.

The advantages of this international study are its large combined size, heterogeneity of participants by country and culture, a low refusal rate for eligible cases and controls, and the use of a standardized questionnaire and relatively consistent methodology across centers. Furthermore, this represents the largest number of CBT cases that has been published to date and improves our ability to detect risk factor associations.

In general, our results do not lend strong support to the hypothesis that maternal exposure to beauty products may be associated with CBT occurrence in offspring. The specific exposures examined were not, on the whole, convincingly associated with increased ORs for CBT. Although the increased ORs we observed for CBT related to the use of 'other beauty products' might be construed as evidence of some transplacental effect of chemicals that may be contained in some of these products, the wide variety of substances reported within this category, including soap and toothpaste, makes it more likely to be a chance finding. The positive subanalyses results related to tumor type, birth years, and center-specific data also should be interpreted cautiously given the imprecise measurement of exposure and the small numbers within categories. Nonetheless, further research is warranted given the ubiquitous exposure of women worldwide to a wide variety of beauty products.

Future studies would benefit from basic science information on the plausible mechanisms and effects of fetal exposure to specific beauty-product chemicals. Improved methods to determine frequency and intensity of these exposures would help to elucidate the role of beauty-related agents and potential risk for CBT. In the context of measuring exposure to specific beauty-product chemicals, biomarker-based assays may be used to provide more precise estimates of exposure in conjunction with questionnaires. Investigating the etiology of complex phenomena such as CBT remains a major epidemiologic challenge. The multiple genetic and environmental factors that may be responsible are likely to have only modest effect sizes that will vary across populations and by gene-gene and gene-environment interactions among these variables.

Acknowledgements

This research was supported by grants, contracts or contributions to individual collaborators as follows: USA, National Institutes of Health (CA47082, CA17054, N01-CN-25403, G12RR-003061) and California Department of Health Services 050(C-G)-8709; Israel, National Cancer Institute (USA) CA51117; Milan, National Research Council Applied Project 'Oncology', Associazione Italiana Ricerca Cancro; Valencia, FIS (84/1913, 86/1832, 88/1832) and the Consellaria de Sanitat of Valencia and the SEOP; Sydney, New South Wales Cancer Council; Paris, French National League against Cancer. Data from the Seattle registry were supported by the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center, which is funded by Contract No. N01-CN-05230 from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute with additional support from the Fred Hutchinson Cancer Research Center. This research also was supported in

part by the SEARCH program of the International Agency for Research on Cancer. We thank Alexander Walker, Jackie Hawkin, John Potter, Peter Boyle, Julian Little and other collaborators who gave valuable input during the early work on this study. Dr. Richard Yanagihara, M.D., M.P.H. and Sarah Lopez offered valuable comments during the writing of this manuscript and their knowledge and insight has been greatly appreciated. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of any funding agency.

References

1. Ries L, Eisner M, Kosary C, Hankey B, Miller B, Clegg L, Mariotto A, Fay M, Feuer E, Edwards B (eds): SEER Cancer Statistics Review, 1975–2000 (http://seer.cancer.gov/csr/1975_2000). Bethesda, MD: National Cancer Institute, 2000
2. Gurney J, Smith M, Bunin G: Chapter III: CNS and miscellaneous intracranial and intraspinal neoplasms. In: Ries L, Smith M, Gurney J, Linet M, Tamra T, Young J, Bunin G (eds) Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995, National Cancer Institute, SEER Program. NIH Pub. No. 99-4649. Bethesda, MD, 1999, pp 51–63
3. Bunin G, Buckley J, Boesel C, Rorke L, Meadows A: Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: a report from the children's cancer group. Cancer Epidemiol Biomarker Prev 3: 197–204, 1994
4. Kuijten R, Bunin G, Nass C, Meadows A: Gestational and familial risk factors for childhood astrocytoma: results of a case–control study. Cancer Res 50: 2608–2612, 1990
5. Preston-Martin S, Yu M, Benton B, Henderson B: *N*-nitroso compounds and childhood brain tumors: a case–control study. Cancer Res 42: 5240–5245, 1982
6. McCredie M, Maisonneuve P, Boyle P: Antenatal risk factors for malignant brain tumours in New South Wales children. Int J Cancer 56: 6–10, 1994
7. Holly E, Bracci P, Hong M, Mueller B, Preston-Martin S: West Coast study of childhood brain tumours and maternal use of hair-colouring products. Paediatr Perinat Epidemiol 16: 226–235, 2002
8. Cordier S, Mandereau L, Preston-Martin S, Little J, Lubin F, Mueller B, Holly E, Filippini G, Peris-Bonet R, McCredie M, Choi N, Arsla A: Parental occupations and childhood brain tumors: results of an international case–control study. Cancer Causes Control 12: 865–874, 2001
9. Kuijten R, Bunin G, Nass C, Meadows A: Parental occupation and childhood astrocytoma: results of a case–control study. Cancer Res 52: 782–786, 1992
10. McKean-Cowdin R, Preston-Martin S, Pogoda J, Holly E, Mueller B, Davis R: Parental occupation and childhood brain tumors: astroglial and primitive neuroectodermal tumors. J Occup Environ Med 40: 332–340, 1998
11. de Groot A, Weyland J, Nater J: Unwanted Effects of Cosmetics and Drugs Used in Dermatology, 3rd edn. Elsevier, Amsterdam, 1994
12. International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Vol. 35. Polnuclear Aromatic Compounds, Part 4: Bitumens, Coal-Tars and Derived Products, Shale-Oils and Soots. Lyon, 1985
13. International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Vol. 57. Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants; Some Hair Dyes, Cosmetic Colourants, Industrial Dyestuffs and Aromatic Amines. Lyon, 1993
14. International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Vol. 16. Some Aromatic Amines and Related Nitro Compounds – Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals. Lyon, 1978
15. International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Vol. 1. Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, *N*-Nitroso Compounds, and Natural Products. Lyon, 1972
16. International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Vol. 4. Some Aromic Amines, Hydrazine and Related Substances, *N*-Nitroso Compounds and Miscellaneous Alkylating Agents. Lyon, 1974
17. International Agency for Research on Cancer (IARC): Overall Evaluation of Carcinogenicity: An Updating of IARC Monographs, Volumes 1–42 [Suppl. 7, p. 248: *N*-Methyl-*N*'-Nitro-*N*-Nitroguanide (MNNG)]. Lyon, 1987
18. Ames B, Kammen H, Yamasaki E: Hair dyes are mutagenic: identification of a variety of mutagenic ingredients. Proc Natl Acad Sci USA 72: 2423–2427, 1975
19. Van Duuren B: Carcinogenicity of hair dye components. J Environ Pathol Toxicol 3(4 Spec No): 237–251, 1980
20. Flamm W: Hair dyes: laboratory evidence. IARC Sci Publ 65: 53–56, 1985
21. Vecchia C, Tavani A: Epidemiologic evidence on hair dyes and the risk of cancer in humans. Eur J Can Prev 4: 31–43, 1995
22. Sontag J: Carcinogenicity of substituted-benzenediamines (phenylenediamines) in rats and mice. J Natl Cancer Inst 66: 591–602, 1981
23. Searle C, Jones E: Effects of repeated applications of two semi-permanent hair dyes to the skin of A and DBAf mice. Br J Cancer 36: 467–468, 1977
24. Thun M, Altekruse S, Namboodiri M, Calle E, Myers D, Heath C: Hair dye use and risk of fatal cancers in US women. J Natl Cancer Inst 86: 210–215, 1994
25. Jacobs M, Burnett C, Penicnak A, Herrera J, Morris W, Shubik P, Apaja M, Granroth G: Evaluation of the toxicity and carcinogencity of hair dyes in Swiss mice. Drug Chem Toxicol 7: 573–586, 1984
26. OEHHA: Evidence on the Carcinogenicity of 4-Amino-2-Nitrophenol. Draft report to the Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency – September, 1998 (http://www.oehha.org/prop65/pdf/4am2ntro.pdf)
27. Hecht S: *N*-nitrosamines. In: Rom W (ed.) Environmental and Occupational Medicine. Philadelphia: Lippincott-Raven Publishers, Philadelphia, 1998, pp 1227–1238
28. International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Vol. 17. Some *N*-Nitroso Compounds. Lyon, 1978
29. Jones E, Searle C, Smith W: Medulloblastomas and other tumours in mice treated neonatally with *N*-ethyl-*N*-nitrosourea. Acta Neuropathol 36: 57–70, 1976
30. Koestner A, Denlinger R: Induction of neurogenic and lymphoid neoplasms by the feeding of threshold levels of methyl- and ethylnitrosourea precursors to adult rats. Food Cosmet Toxicol 13: 605–609, 1975
31. U.S. NTP: Toxicology and Carcinogenesis Studies of Diethanolamine (CAS no. 111-42-2) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies). NTP technical report 478, NIH publication no. 97-3968. National Toxicology Program, Research Triangle Park, NC, 1997
32. U.S. NTP: Toxicology and Carcinogenesis Studies of Lauric Acid Diethanolamine Condensate (CAS no. 120-40-1) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies). NTP technical report 480, NIH publication no. 97-3970. National Toxicology Program, Research Triangle Park, NC, 1999

33. U.S. NTP: Toxicology and Carcinogenesis Studies of Coconut Oil Acid Diethanolamine Condensate (CAS no. 68603-42-9) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies). NTP technical report 479, NIH publication no. 01-3969. National Toxicology Program, Research Triangle Park, NC, 2001
34. U.S. NTP: Toxicology and Carcinogenesis Studies of Triethanolamine (CAS no. 102-71-6) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies). NTP technical report 449, NIH publication no. 98-3365. National Toxicology Program, Research Triangle Park, NC, 1998
35. Council on Scientific Affairs: Formaldehyde. JAMA 261: 1183–1187, 1989
36. Flamm W, Frankos V: Formaldehyde: laboratory evidence. IARC Sci Publ 65: 85–90, 1985
37. Shaham J, Gurvich R, Kaufman A: Sister chromatid exchange in pathology staff occupationally exposed to formaldehyde. Mutation Research 514: 115–123, 2002
38. International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Vol. 62. Wood Dust and Formaldehyde. Lyon, 1995
39. U.S. NTP: Carcinogenesis Bioassay of Di(2-Ethylhexyl)Phthalate (CAS no. 117-81-7) in F344 rats and B6C3F1 mice (Feed Study). NTP technical report 217, NIH publication no. 82-1773. National Toxicology Program, Research Triangle Park, NC, 1982
40. Kozumbo W, Kroll R, Rubin R: Assessment of the mutagenicity of phthalate esters. Environ Health Perspect 45: 103–109, 1982
41. Seed J: Mutagenic activity of phthalate esters in bacterial liquid suspension assays. Environ Health Perspect 45: 111–114, 1982
42. Ward J, Diwan B, Ohshima M, Hu H, Schuller H, Rice J: Tumor-initiating and promoting activities of di(2-ethylhexyl) phthalate in vivo and in vitro. Environ Health Perspect 65: 279–291, 1986
43. David R, Moore M, Cifone M, Finney D, Guest D: Chronic peroxisome proliferation and hepatomegaly associated with the hepatocellular tumorigenesis of di(2-ethylhexyl)phthalate and the effects of recovery. Toxicol Sci 50: 195–205, 1999
44. International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Vol. 52. Chlorinated Drinking-water; Chlorination By-products; Some Other Halogenated Compounds; Cobalt and Cobalt Compounds. Lyon, 1991
45. International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Vol. 23. Some Metals and Metallic Compounds. Lyon, 1980
46. International Agency for Research on Cancer (IARC): Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Vols. 1–42 [Suppl. 7, p 248: Lead and Lead Compunds]. Lyon: International Agency for Research on Cancer, 1987(Suppl. 7, p 230)
47. International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Vol. 49. Chromium, Nickel and Welding. Lyon, 1990
48. U.S. Food and Drug Administration (FDA)/Center for Food Safety and Applied Nutrition (CFSAN): Cosmetics – Prohibited Ingredients and Related Safety Issues: contaminants raise concerns (http://www.cfsan.fda.gov/~dms/cos-210.html. Hypertext updated by dms 2001-JUN-14)
49. Routledge E, Parker J, Odum J, Ashby J, Sumpter J: Some alkyl hydroxy benzoate preservatives (parabens) are estrogenic. Toxical Appl Pharmacol 153: 12–19, 1998
50. Okubo T, Yokoyama Y, Kano K, Kano I: ER-dependent estrogenic activity of parabens assessed by proliferation of human breast cancer MCF-7 cells and expression of ERα and PR. Food Chem Toxicol 39: 1225–1232, 2001
51. Zacharewski T, Meek M, Clemons J, Wu Z, Fielden M, Matthews J: Examination of the in vitro and in vivo estrogenic activities of eight commercial phthalate esters. Toxicol Sci 46: 282–293, 1998
52. Matthews J, Celius T, Halgren R, Zacharewski T: Differential estrogen receptor binding of estrogenic substances: a species comparison. J Steroid Biochem Mol Biol 74: 223–234, 2000
53. Depue R, Pike M, Henderson B: Estrogen exposure during gestation and risk of testicular cancer. J Natl Cancer Inst 71: 1151–1155, 1983
54. Walker A, Ross R, Haile R, Henderson B: Hormonal factors and risk of ovarian germ cell cancer in young women. Br J Cancer 57: 418–422, 1998
55. Hsieh C, Tzonou A, Trichopoulos D: Birth order and breast cancer risk. Cancer Causes Control 2: 95–98, 1991
56. Troisi R, Potischman N, Roberts J, Harger G, Markovic N, Cole B: Correlation of serum hormone concentrations in maternal and umbilical cord samples. Cancer Epidemiol Biomarker Prev 12: 452–456, 2003
57. Robison A, Sirbasku D, Stancel G: DDT supports the growth of an estrogen-responsive tumor. Toxicol Lett 27: 109–113, 1985
58. Scribner J, Mottet N: DDT acceleration of mammary gland tumors induced in the male Sprague–Dawley rat by 2-acetamidophenanthrene. Carcinogenesis 2: 1235–1239, 1981
59. Reuber M: Carcinomas, sarcomas and other lesions in Osborne–Mendel rats ingesting endrin. Exp Cell Biol 46: 129–145, 1978
60. Bradlow H, Davis D, Sepkovic D, Tiwari R, Osborne M: Role of the estrogen receptor in the action of organochlorine pesticides on estrogen metabolism in human breast cancer cell lines. Sci Total Environ 208: 9–14, 1997
61. Dewailly E, Dodin S, Verreault R, Ayotte P, Sauve L, Morin J, Brisson J: High organochlorine body burden in women with estrogen receptor-positive breast cancer. J Natl Cancer Inst 86: 232–234, 1994
62. Wolff M, Toniolo P, Lee E, Rivera M, Dubin N: Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 85: 648–652, 1993
63. Guillette L, Gross T, Masson G, Matter J, Percival H, Woodward A: Developmental abnormalities of the gonad and abnormal sex hormone concentrations in juvenile alligators from contaminated and control lakes in Florida. Environ Health Perspect 102: 680–688, 1994
64. Facemire C, Gross T, Guillette L: Reproductive impairment in the Florida panther: nature or nurture? Environ Health Perspect 103(Suppl 4): 79–86, 1995
65. Berger P, Sanders E, Gardner P, Negus N: Phenolic plant compounds functioning as reproductive inhibitors in *Microtus montanus*. Science 195: 575–577, 1977
66. Leopold A, Erwin M, Oh J, Browning B: Phytoestrogens: adverse effects on reproduction in California quail. Science 191: 98–100, 1976
67. Whitten P, Lewis C, Naftolin F: A pytoestrogen diet induces the premature anovulatory syndrome in lactationally exposed female rats. Biol Repro 49: 1117–1121, 1993
68. Whitten P, Lewis C, Naftolin F: Phytoestrogen influences on the development of behavior and gonadotropin function. Proc Soc Exp Biol Med 208: 82–86, 1995
69. Whitten P, Lewis C, Russell E, Naftolin F: Potential adverse effects of phytoestrogens. J Nutr 125: 771S–776S, 1995
70. Kapur R, Timiras P: Estrogen-brain relationship during development and aging: effects on glial cells. Neuroendrocrinol Lett 18: 215–220, 1997
71. Shughrue P, Stumpf W, MacLusky N, Zielinski J, Hochberg R: Developmental changes in estrogen receptors in mouse cerebral cortex between birth and postweaning: studies by autoradiography with 11 beta-methoxy-16 alpha-[125I] iodoestradiol. Endrocrinology 126: 1112–1124, 1990
72. Keefer D, Holderegger C: The ontogeny of estrogen receptors: brain and pituitary. Brain Res 351: 183–194, 1985
73. McEwen B, Alves S, Bulloch K, Weiland N: Ovarian steroids and the brain: implications for cognition and aging. Neurology 48(5 Suppl 7): S8–S15, 1997
74. McEwen B, Alves S, Bulloch K, Weiland N: Clinically relevant basic studies of gender differences and sex hormone effects. Psychopharmacol Bull 34: 251–259, 1998
75. Pilgrim C, Hutchison J: Developmental regulation of sex differences in the brain: can the role of gonadal steroids be redefined? Neuroscience 60: 843–855, 1994

76. Murphy D, Cole N, Segal M: Brain-derived neurotrophic factor mediates estradiol-induced dendritic spine formation in hippocampal neurons. Proc Natl Acad Sci USA 95: 11412–11417, 1998
77. Agrati P, Ma Z, Patrone C, Picotti G, Pellicciari C, Bondiolotti G, Bottone M, Maggi A: Dopaminergic phenotype induced by oestrogens in a human neuroblastoma cell line. Eur J Neurosci 9: 1008–1016, 1997
78. Murphy D, Cole N, Greenberger V, Segal M: Estradiol increases dendritic spine density by reducing GABA neurotransmission in hippocampal neurons. J Neurosci 18: 2550–2559, 1998
79. Gould E, Woolley C, Frankfurt M, McEwen B: Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood**.** J Neurosci 10: 1286–1291, 1990
80. McEwen B, Coirini H, Westlind-Danielsson A, Frankfurt M, Gould E, Schumacher M, Woolley C: Steroid hormones as mediators of neural plasticity. J Steroid Biochem Mol Biol 39: 223–232, 1991
81. Murphy D, Segal M: Regulation of dendritic spine density in cultured rat hippocampal neurols by steroid hormones. J Neurosci 16 :4059–4068, 1996
82. Sherwin B: Estrogen and cognitive functioning in women. Endro Rev 24: 133–151, 2004
83. Packard M: Posttraing estrogen and memory modulation. Horm Behav 34: 126–139, 1998
84. Tanriverdi F, Silveira L, MacColl G, Bouloux P: The hypothalamic-pituitary-gonadal axis: immune function and autoimmunity. J Endocrinol 176: 293–304, 2003
85. Blount B, Silva M, Caudill S, Needham L, Pirkle J, Sampson E, Lucier G, Jackson R, Brock J: Levels of seven urinary phthalate metabolites in a human reference population. Environ Health Perspect 10: 979–982, 2000
86. Hsu D, Efird J, Hedley-Whyte E: Progesterone and estrogen receptors in meningiomas: prognostic considerations. J Neurosurg 86: 113–120, 1997
87. Carroll R, Zhang J, Black P: Expression of estrogen receptors alpha and beta in human meningiomas. J Neurooncol 42: 109–116, 1999
88. Von Schoultz E, Bixo M, Backstrom T. Silfvenius H, Wilking N, Henriksson R: Sex steroids in human brain tumors and breast cancer. Cancer 65: 949–952, 1990
89. Martinez R, Marcos M, Figueras A, Vaquero J: Estrogen and progesterone receptors in intracranial tumors. Clin Neuropharmacol 7: 338–342, 1984
90. Arush M, Postovsky S, Goldsher D, El Hasid R, Constantini S: Clinical and radiographic response in three children with recurrent malignant cerebral tumors with high-dose tamoxifen. Pediatr Hematol Oncol 16: 245–250, 1999
91. Pollack I, DaRosso R, Robertson P, Jakacki R, Mirro J, Blatt J, Nicholson S, Packer R, Allen J, Cisneros A, Jordan V: A phase I study of high-dose tamoxifen for the treatment of refractory malignant gliomas of childhood. Clin Cancer Res 3: 1109–1115, 1997
92. Madden J, Fenton L, Weil M, Winston K, Partington M, Foreman N: Experience with tamoxifen/etoposide in the treatment of a child with myxopapillary ependymoma. Med Pediatr Oncol 37: 67–69, 2001
93. Mastronardi L, Puzzilli F, Couldwell W, Farah J, Lunardi P: Tamoxifen and carboplatin combinational treatment of high-grade gliomas. J Neurooncol 38: 59–68, 1998
94. Furth J, Clifton K. Experimental pituitary tumours: In: Harris G, Donovan B (eds) The Pituitary Gland. University of California Press, Berkeley and Los Angeles, 1966, pp 460–497
95. Brunnemann K, Hecht S, Hoffmann D: *N*-nitrosamines: environmental occurrence, *in vivo* formation and metabolism. J Toxicol-Clin Toxicol 19: 661–688, 1982
96. Kiese M, Rauscher E: The absorption of *p*-toluenediamine through human skin in hair dyeing. Toxicol Appl Pharmacol 13: 325–331, 1968
97. Maibach H, Leaffer M, Skinner W: Percutaneous penetration following use of hair dyes. Arch Dermatol 111: 1444–1445, 1975
98. Marzulli F, Anjo D, Maibach H: *In vivo* skin penetration studies of 2,4-toluenediamine, 2,4-diaminoanisole, 2-nitro-*p*-phenylenediamine, *p*-dioxane and *N*-nitrosodiethanolamine in cosmetics. Food Cosmet Toxicol 19: 743–747, 1981
99. Hofer H, Hruby E: Skin penetration by 2,3-diaminoanisole in the rat. Food Chem Toxicol 21: 331–334, 1983
100. Tsomi V, Kalopissis G: Cutaneous penetration of some hairdyes in the hairless rat. Toxicol Eur Res 4: 119–127, 1982
101. Wolfram L, Maibach H: Percutaneous penetration of hair dyes. Arch Dermatol Res 227: 235–241, 1985
102. Steiling W, Kreutz J, Hofer H: Percutaneous penetration/dermal absorption of hair dyes in vitro. Toxicol in Vitro 15: 565–570, 2001
103. Bronaugh R, Congdon E, Scheuplein R: The effect of cosmetic vehicles on the penetration of *N*-nitrosodiethanolamine through excised human skin. J Invest Dermatol 76: 94–96, 1981
104. Dal Pozzo A, Pastori N: Percutaneous absorption of parabens from cosmetic formulations. Int J Cosmetic Sci 18: 57–66, 1996
105. Komatsu H, Okamoto H, Miyagawa K, Hashida M, Sezaki H: Percutaneous absorption of butylparaben from liposomes in vitro. Chem Pharm Bull 34: 3423–3430, 1986
106. Komatsu H, Suzuki M: Percutaneous absorption of butylparaben through guinea pig skin in vitro. J Pharm Sci 68: 596–598, 1979
107. Elsisi A, Carter D, Sipes I: Dermal absorption of phthalate diesters in rats. Fundam Appl Toxicol 12: 70–77, 1989
108. Lansdown A: Lead in hair dyes, short-term appeal vs. long-term risk. Int J Cosmetic Sci 22: 167–168, 2000
109. Sykes C, Claeys-Thoreau F: Blood lead levels and cosmetics. Int J Cosmetic Sci 22: 395–396, 2000
110. Marzulli F, Watlington P, Maibach H: Exploratory skin pentration findings relating to the use of lead acetate hair dyes. Hair as a test for monitoring uptake of systemic lead. Curr Probl Dermatol 7: 196–204, 1978
111. Bearer C: Environmental health hazards: how children are different from adults. The Future of Children – Critical Issues for Children and Youths 5: 11–26, 1995
112. Goyer R: Transplacental transport of lead. Environ Health Perspect 89: 101–105, 1990
113. Takahashi O, Oishi S: Disposition of orally administered 2,2-bis(4-hydroxyphenyl)propane (Bisphenol A) in pregnant rats and the placental transfer to fetuses. Environ Health Perspect 108: 931–935, 2000
114. Newman C: The thalidomide syndrome: risks of exposure and spectrum of malformations. Clin Perinatol 13: 555–573, 1986
115. Colborn T, vom Saal F, Soto A: Developmental effects of endrocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 101: 378–384, 1993
116. Newsom W, Davies D, Doucet J: PCB and organochlorine pesticides in Canadian human milk – 1992. Chemosphere 30: 2143–2153, 1995
117. Tomatis L, Turusov V, Cardis E, Cabral J: Tumour incidence in the progeny of male rats exposed to ethylnitrosourea before mating. Mutat Res 229: 231–237, 1990
118. Finette B, O'Neill J, Vacek P, Albertini R: Gene mutations with characteristic deletions in cord blood T lymphocytes associated with passive maternal exposure to tobacco smoke. Nature Med 4: 1144–1151, 1998
119. Holly E, Lele C, Bracci P: Hair-color products and risk for non-Hodgkin's lymphoma: a population-based study in the San Francisco Bay Area. Am J Public Health 88: 1767–1773, 1998
120. McCredie M, Little J, Cotton S, Mueller B, Peris-Bonet R, Choi N, Cordier S, Filippini G, Holly E, Modan B, Arslan A, Preston-Martin S: SEARCH International Case–Control study of childhood brain tumours: role of index pregnancy and birth, and mother's reproduction history. Paediatr Perinat Epidemiol 13: 325–341, 1999
121. Preston-Martin S, Pogoda J, Mueller B, Lubin F, Modan B, Holly E, Filippini G, Cordier S, Peris-Bonet R, Choi W, Little J, Arslan A: Results from an international case–control study of childhood brain tumors: the role of prenatal vitamin supplementation. Environ Health Perspect 106: 887–892, 1998

122. Preston-Martin S, Pogoda J, Mueller B, Lubin F, Modan B, Holly E, Filippini G, Cordier S, Peris-Bonet R, Choi W, Little J, Arslan A: Prenatal vitamin supplementation and pediatric brain tumors: huge international variation in use and possible reduction in risk. Child's Nerv Syst 14: 551–557, 1998
123. Filippini G, Maisonneuve P, McCredie M, Peris-Bonet R, Modan B, Preston-Martin S, Mueller B, Holly E, Cordier S, Choi N, Little J, Arslan A, Boyle P: Relation of childhood brain tumors to exposure of parents and children to tobacco smoke: the SEARCH International Case–Control Study. Int J Cancer 100: 206–213, 2002
124. McKean-Cowdin R, Pogoda J, Lijinsky W, Holly E, Mueller B, Preston-Martin S: Maternal prenatal exposure to nitrosatable drugs and childhood brain tumours. Int J Epidemiol 32: 211–217, 2003
125. Norman M, Holly E, Ahn D, Preston-Martin S, Mueller B, Bracci P: Prenatal exposure to tobacco smoke and childhood brain tumors: results from the U.S. West Coast Childhood Brain Tumor Study. Cancer Epidemiol Biomarker Prev 5: 127–133, 1996
126. Holly E, Bracci P, Mueller B, Preston-Martin S: Farm and animal exposures and pediatric brain tumors: results from the United States West Coast childhood brain tumor study. Cancer Epidemiol Biomarker Prev 7: 797–802, 1998
127. Cordier S, Iglesias M, Le Goaster C, Guyot M, Mandereau L, Hemon D: Incidence and risk factors for childhood brain tumors in the Ile de France. Int J Cancer 59: 776–782, 1994
128. Cordier S, Lefeuvre B, Filippini G, Peris-Bonet R, Farinotti M, Lovicu G, Mandereau L: Parental occupation, occupational exposure to solvents and polycyclic aromatic hydrocarbons and risk of childhood brain tumors (Italy, France, Spain). Cancer Causes Control 8: 688–697, 1997
129. Mueller B, Newton K, Holly E, Preston-Martin S: Residential water source and the risk of childhood brain tumors. Environ Health Perspect 109: 551–556, 2001
130. Preston-Martin S, Gurney J, Pogoda J, Holly E, Mueller B: Brain tumor risk in children in relation to electric blankets and water bed heaters: results from the United States West Coast Childhood Brain Tumor Study. Am J Epidemiol 143: 1116–1122, 1996
131. Preston-Martin S, Pogoda J, Mueller B, Holly E, Lijinsky W, Davis R: Maternal consumption of cured meats and vitamins in relation to pediatric brain tumors. Cancer Epidemiol Biomarker Prev 5: 599–605, 1996
132. Gurney J, Mueller B, Preston-Martin S, McDaniel A, Holly E, Pogoda J, Davis R: A study of pediatric brain tumors and their association with epilepsy and anticonvulsant use. Neuroepidemiology 16: 248–255, 1997
133. Gurney J, Preston-Martin S, McDaniel A, Mueller B, Holly E: Head injury as a risk factor for brain tumors in children: results from a multicenter case–control study. Epidemiology 7: 485–489, 1996
134. Preston-Martin S, Pogoda J, Mueller B, Lubin F, Holly E, Filippini G: Prenatal vitamin supplementation and risk of childhood brain tumors. Int J Cancer Suppl 11: 17–22, 1998
135. World Health Organization: International Classification of Disease-Oncology. Geneva: WHO, 1976
136. International Labor Office: International Standard Classification of Occupations (ISCO). Revised Edition, Geneva: International Labour Organisation, 1968
137. Pregibon D: Logistic regression diagnostics. Ann Statistics 9: 705–724, 1981
138. Breslow N, Day N: Statistical Methods in Cancer Research, Vol. 1. The Analysis of Case–Control Studies, IARC Scientific Publ. No. 32. IARC, Lyon, France, 1980
139. Little R, Friend R, Spector P: SAS System for Linear Models. 3rd edn. SAS Institute Inc., Cary, NC, 1991
140. Rice J, Ward J: Age dependence of susceptibilitiy to carcinogenesis in the nervous system. Ann NY Acad Sci 381: 274–289, 1982
141. Isaacs H: I. Perinatal brain tumors: a review of 250 cases. Pediatr Neurol 27: 249–261, 2002
142. Isaacs H: II. Perinatal brain tumors: a review of 250 cases. Pediatr Neurol 27: 333–342, 2002
143. Gago-Dominguez M, Bell D, Watson M, Yuan J, Castelao J, Hein D, Chan K, Coetzee G, Ross R, Yu M: Permanent hair dyes and bladder cancer: risk modification by cytochrome P4501A2 and *N*-actyltransferases 1 and 2. Carcinogenesis 24: 483–489, 2003
144. Zahm S, Weisenburger D, Babbitt P, Saal R, Vaught J, Blair A: Use of hair coloring products and the risk of lymphoma, multiple myeloma, and chronic lymphocytic leukemia. Am J Public Health 82: 990–998, 1992
145. Prival M, Mitchell V, Gomez Y: Mutagenicity of a new hair dye ingredient: 4-Ethoxy-*m*-phenylenediamine. Science 207: 907–908, 1980
146. Kleihues P, Lantos P, Magee P: Chemical carcinogenesis in the nervous system. Int Rev Exp Pathol 15: 153–232, 1976
147. Hartge P, Cahill J, West D, Hauck M, Austin D, Silverman D, Hoover R: Design and methods in a multicenter case–control interview study. Am J Publ Health 74: 52–56, 1984
148. Sorahan T, Hamilton L, Gardiner K, Hodgson J, Harrington J: Maternal occupational exposure to electromagnetic fields before, during, and after pregnancy in relation to risks of childhood cancers: findings from the Oxford Survey of Childhood Cancers, 1953–1981 deaths. Am J Ind Med 35: 348–357, 1999
149. Feychting M, Floderus B, Ahlbom A: Parental occupational exposure to magnetic fields and childhood cancer (Sweden). Cancer Causes Control 11: 151–156, 2000
150. United Nations. International Standard Industrial Classification of All Economic Activities (ISIC). United Nations, New York, 1971

Address for offprints: Jimmy Thomas Efird, Ph.D., M.Sc., John A. Burns School of Medicine, University of Hawaii at Manoa, 1960 East-West Road, Room T-201B, Honolulu, Hawaii 96822-2319, USA; Tel.: +1-650-248-8282; E-mail: Jimmy.efird@ stanfordalumni.org