

Occupational Risk Factors for Cancer of the Central Nervous System (CNS) Among US Women

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Background: In a recent report, we found an elevated risk of cancer of the central nervous system (CNS) in several occupations and industries, and a modest association with exposure to solvents and to contact with the public.

Methods: To further explore the occupational risk of CNS cancer among women, we extended the analysis of the previous death certificate-based case-control study, including 12,980 female cases (ICD-9 codes 191 and 192) in 24 US states in 1984-1992 and 51,920 female controls who died from diseases other than malignancies and neurological disorders. We applied newly designed job-exposure matrices for 11 occupational hazards, previously reported as brain cancer risk factors, to the occupation and industry codes in the death certificates. We also conducted a separate analysis of 161 meningioma cases (ICD-9 codes 192.1 and 192.3), a tumor more frequent among women, particularly in the postmenopausal age group.

Results: Overall, CNS cancer risk showed a 20-30% increase among women exposed to electromagnetic fields (EMF), methylene chloride, insecticides and fungicides, and contact with the public. Risk for meningioma was elevated among women exposed to lead (OR = 1.9; 95% CI 1.0, 3.9). CNS cancer did not show a clear pattern of risk increase by probability and intensity of exposure to any of the explored risk factors. Cross-classification by probability and intensity of exposure did not reveal any significant trend. Cases were too few to explore trends of meningioma by probability and intensity of exposure to lead.

Conclusions: We did not find evidence of a strong contribution of 11 occupational hazards to the etiology of CNS cancer. However, limitations of the occupational information might have reduced our ability to detect clear patterns of risk. *Am. J. Ind. Med.* 36:70-74, 1999.
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INTRODUCTION

In a recent article, we investigated the risk of mortality from central nervous system (CNS) tumors associated with

occupation and industry in the USA by gender and race [Cocco et al., 1998a]. Our findings revealed an increased CNS cancer risk among education- and health-related occupations and industries, and a modest association with exposure to solvents and to contact with the public. Exposure to these risk factors was assessed using simple job-exposure matrices. To further explore the association between occupation and CNS cancer in U.S. women, we designed more detailed job-exposure matrices for 11 occupational hazards that may be associated with CNS cancer based on our previous study and others [Inskip et al., 1996]. We applied these job-exposure matrices to occupations and industries appearing in the death certificates of women who died from CNS cancer in 24 US states in 1984-1992.

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METHODS

Case and Control Selection

Details on the 24 US states database and the case-control study design are reported elsewhere [Cocco et al., 1998a]. Briefly, we identified 12,980 cases of cancer of the brain and other parts of the CNS (ICD-9 codes 191 and 192) among women who died in 24 states in 1984–1992. They included 161 cases of meningioma (ICD9 codes 192.1 and 192.3), who were the subject of a separate analysis. For each case, we selected four controls among women who died from nonmalignant diseases, excluding neurological disorders, frequency-matched by state, race, and 5-year age-group.

Exposure Assessment

We designed new job-exposure matrices for 11 occupational hazards: electromagnetic fields (EMF), solvents, chlorinated aliphatic hydrocarbons (CAHs), methylene chloride, benzene, lead, nitrosamines, polycyclic aromatic hydrocarbons (PAHs), insecticides and fungicides, herbicides, and contact with the public. An estimate of intensity level of exposure (none = 0, low = 1, medium = 2, high = 3) and probability of exposure (none = 0, low = 1, medium = 2, high = 3) to each hazard was developed by two authors (M.D. and P.C.) for each 3-digit occupation and each 3-digit industry U.S. Census code. A final intensity level score and a final probability score were then developed for each occupation/industry combination appearing in study subjects' death certificates. Intensity level of exposure was estimated based on industrial hygiene and occupational health textbooks [Parmeggiani, 1983; Zenz et al., 1994], computerized exposure databases (OSHA files, NIOSH inspections database), unpublished industrial hygiene reports, and professional experience. The intensity score for contact with the public, a surrogate for exposure to transmissible pathogens, was calculated differently. Five components were identified and scored individually, namely, frequency of contact with the public (episodic or daily), ambient spaciousness in which contact with the public occurs (outdoor, large indoor meeting room or classroom, standard size room), average number of daily contacts (≤ 20 , 21–50, 51–100, ≥ 101), average health status of contacted persons (good, possible contact with sick persons, likely contact with sick persons), and contact mainly with elders or children. The individual scores were then combined to derive the public contact intensity score, which was categorized in four levels (none, low, medium, high). The probability index was estimated based on the proportion of workers within a given job title or industry that are typically exposed to the hazard.

For each study subject, a final intensity level score and a final probability score was calculated for each hazard by

combining the occupation and industry scores in the following ways: 1) If both the occupation and industry involved exposure to the hazard (e.g., driver in a chemical industry), then the final intensity score was equal to the product of the individual intensity scores. The final probability score was that attributed to the industry code alone. 2) If exposure was related only to occupation, regardless of industry (e.g., painter), only the intensity and probability scores related to occupation were used to derive the final scores. Intensity score was squared in these instances to maintain consistency in units. The final intensity and probability scores were then grouped into four levels (unexposed, low, medium, and high). Low, medium, or high probability and intensity of exposure are meant as comparisons within a given exposure and are not comparable across exposures.

This procedure for designing job-exposure matrices has been validated in a study of asbestos exposure and risk of peritoneal cancer [Cocco and Dosemeci, 1999] and has been applied in two other studies [Cocco et al., 1998b; 1999]. The categorization of exposure probability and intensity levels in the newly designed job-exposure matrices resulted in greater sensitivity in identifying exposures, particularly in the low probability / low intensity groups. In fact, for each risk factor considered in our previous analysis, a number of occupations and industries considered as unexposed in the former "yes/no" exposure assessment were now included in the most sensitive exposure category (low probability / low intensity). Therefore, the total number of people exposed to each risk factor is greater in this study compared to the previous one.

Statistical Analysis

Odds ratios (ORs) were calculated with logistic regression for each workplace exposure, adjusting for marital status (never vs. ever married), socioeconomic status (SES) (three levels, based on Green's Standardized Score for Specific Occupations [Green, 1970]), and age at death (continuous). ORs and 95% confidence intervals (95% CI) were calculated with the Wald method using the GMBO program in the Epicure software package [Preston et al., 1990]. The statistical significance of the linear trend by increasing intensity and probability of exposure to the 11 CNS cancer risk factors was tested by dividing the regression coefficients of the variables assumed as noncategorical by their standard error to generate a Z statistic. Under the null hypothesis, this test behaves as a normal standard deviate [Breslow and Day, 1980]. Two-tailed *P* values were considered throughout this study.

RESULTS

Table I shows ORs for CNS cancer and meningioma for each of the 11 workplace risk factors (none vs. any

TABLE I. Risk of Mortality From CNS Cancer and Meningioma Associated With 11 Occupational Hazards: None vs. Any Exposure; Female Deaths in 24 US States 1984–1992

Exposure	CNS cancer exposed			Meningioma exposed		
	cases/controls	OR	95% C.I.	cases/controls	OR	95% C.I.
Electromagnetic fields	2,901/10,567	1.2	1.1–1.2	34/10,567	0.9	0.6–1.4
Solvents	1,047/4,059	1.1	1.1–1.2	14/4,059	1.0	0.6–1.8
Chlorinated aliphatic hydrocarbons	1,585/6,414	1.1	1.1–1.2	25/6,414	1.1	0.7–1.8
Methylene chloride	867/3,239	1.2	1.1–1.3	13/3,239	1.2	0.7–2.2
Benzene	711/2,740	1.1	1.0–1.2	12/2,740	1.3	0.7–2.5
Lead	366/1,459	1.1	1.0–1.2	9/1,459	1.9	1.0–3.9
Nitrosamines	289/11,183	1.1	1.0–1.3	3/1,183	0.7	0.2–2.2
Polycyclic aromatic hydrocarbons	364/1,457	1.1	1.0–1.3	2/1,457	0.4	0.1–1.6
Insecticides and fungicides	210/725	1.3	1.1–1.5	4/725	1.6	0.6–4.3
Herbicides	61/240	1.2	0.9–1.6	0/240	—	—
Contact with the public	2,959/9,724	1.2	1.1–1.2	39/9,724	1.4	0.9–2.1

exposure). As observed in our previous study, there was a modest, but statistically significant, increase in risk of mortality from CNS cancer (10–30%) among women exposed to solvents, insecticides and fungicides, and contact with the public. Unlike the previous study, risk associated with exposure to EMFs was significantly increased, and risk associated with exposure to herbicides was no longer statistically significant. Among the other risk factors, only CAHs and methylene chloride showed a statistically significant increase in CNS cancer risk. Risk of meningioma was elevated among women exposed to lead, insecticides and fungicides, and who had contact with the public, but the findings were not statistically significant.

There was no increase in CNS cancer risk with increasing probability of exposure to any of the occupational hazards (Table II). The greatest excess risk (40–50%) was associated with high probability of exposure to insecticides and fungicides (but the same excess was also observed for low probability of exposure) and to herbicides. Exploring trends in CNS cancer risk by intensity of exposure also did not show clear patterns of risk increase (Table III). The trend was inverse with intensity of exposure to methylene chloride. The cross-tabulation of risk by categories of probability and intensity of exposure did not provide further information for any of the explored risk factors, as most exposed women were in the low probability and low intensity cells. Risk in the high probability / high intensity cell was highest for exposure to insecticides and fungicides (OR = 1.5; 95% CI 1.1, 2.1) and herbicides (OR = 1.7; 95% CI 1.2, 2.3). After excluding subjects with any probability of exposure to herbicides, risk associated with insecticides and fungicides was still elevated (all probability categories combined: OR = 1.4; 95% CI 1.1, 1.6; high probability / high intensity: OR = 1.4; 95% CI 0.5, 3.7).

For most exposures, cases of meningioma were very few or absent, particularly in the high exposure probability and intensity cells. Therefore, we were unable to explore trends in risk. Contact with the public showed a significant 60% excess risk associated with high probability of exposure (test for trend: $P = 0.05$).

DISCUSSION

In this large case-control study of CNS cancer among women based on death certificates from 24 US states, we found equivocal associations with potential exposure to 11 workplace risk factors identified with the aid of job-exposure matrices. Risk showed a 20–30% increase among women exposed to EMF, methylene chloride, agricultural chemicals, and contact with the public. However, risk did not show a clear increase by probability or intensity of exposure to any of the occupational risk factors. Risk of meningioma was elevated among women exposed to lead, contact with the public, and insecticides and fungicides, but numbers of deaths were small.

In our previous article [Cocco et al., 1998a], CNS cancer risk was elevated in a few industries and occupations related to EMF exposure, such as manufacture, use, maintenance, and sale of electrical devices and telephones, as well as for air transportation. Risks were generally consistent between genders, while these occupations were seldom represented among African-American cases to evaluate race consistency in CNS cancer risk. Our new analysis of the same data with a more detailed job-exposure matrix for EMF showed a 20% increase in CNS cancer risk among women, but no increasing trend with exposure probability and intensity. The 24 states death certificate database does not provide enough information to discriminate type and

TABLE II. Risk of Mortality From CNS Cancer for 11 Occupational Hazards: by Probability of Exposure; Female Deaths in 24 U.S. States 1984–1992

Exposure	Probability of exposure										
	None		Low			Medium			High		
	Cases/ controls	OR	Cases/ controls	OR	95% CI	Cases/ controls	OR	95% CI	Cases/ controls	OR	95% CI
Electromagnetic fields	10,079/41,393	1.0	2,312/8,115	1.2	1.1–1.2	255/1,045	1.2	1.0–1.4	334/1,367	1.2	1.0–1.3
Solvents	11,933/47,871	1.0	475/2,028	1.1	1.0–1.2	163/483	1.2	1.0–1.4	409/1,548	1.2	1.0–1.3
Chlorinated aliphatic hydrocarbons	11,395/45,506	1.0	791/3,258	1.1	1.0–1.2	545/1,976	1.2	1.1–1.3	249/910	1.2	1.0–1.4
Methylene chloride	12,113/48,681	1.0	756/2,839	1.2	1.1–1.3	83/311	1.2	1.0–1.6	28/89	1.3	0.9–2.0
Benzene	12,269/49,180	1.0	170/711	1.0	0.9–1.2	422/1,602	1.1	1.0–1.2	119/427	1.2	1.0–1.5
Lead	12,614/50,461	1.0	214/865	1.1	0.9–1.3	94/381	1.0	0.8–1.3	58/213	1.2	0.9–1.6
Nitrosamines	12,691/50,737	1.0	174/695	1.1	1.0–1.3	88/371	1.1	0.9–1.4	27/117	1.0	0.7–1.6
Polycyclic aromatic hydrocarbons	12,616/50,463	1.0	197/772	1.1	1.0–1.3	52/224	1.0	0.7–1.4	115/461	1.1	0.9–1.4
Insecticides and fungicides	12,770/51,195	1.0	125/417	1.4	1.1–1.7	19/89	0.9	0.6–1.6	66/219	1.4	1.1–1.9
Herbicides	12,919/51,680	1.0	7/33	1.0	0.4–2.3	7/61	0.5	0.2–1.2	47/146	1.5	1.1–2.1
Contact with the public	10,021/42,196	1.0	260/1,031	1.1	1.0–1.3	99/363	1.2	0.9–1.5	2,600/8,330	1.2	1.1–1.2

TABLE III. Risk of Mortality From CNS Cancer Associated With 11 Occupational Hazards: by Intensity of Exposure; Female Deaths in 24 U.S. States 1984–1992

Exposure	Probability of exposure										
	None		Low			Medium			High		
	Cases/ controls	OR	Cases/ controls	OR	95% CI	Cases/ controls	OR	95% CI	Cases/ controls	OR	95% CI
Electromagnetic fields	10,079/41,393	1.0	2,200/7,721	1.2	1.1–1.2	616/2,507	1.1	1.0–1.3	85/299	1.3	1.0–1.6
Solvents	11,933/47,871	1.0	474/1,935	1.1	1.0–1.2	422/1,456	1.2	1.1–1.4	151/668	1.0	0.8–1.2
Chlorinated aliphatic hydrocarbons	11,395/45,506	1.0	802/3,549	1.0	1.0–1.1	643/2,272	1.3	1.1–1.4	140/593	1.0	0.9–1.2
Methylene chloride	12,113/48,681	1.0	370/1,316	1.3	1.1–1.5	345/1,255	1.2	1.1–1.4	152/668	1.0	0.8–1.2
Benzene	12,269/49,180	1.0	266/976	1.1	1.0–1.3	245/959	1.1	1.0–1.3	200/805	1.1	0.9–1.3
Lead	12,614/50,461	1.0	187/676	1.2	1.0–1.4	138/623	1.0	0.8–1.2	41/160	1.1	0.8–1.6
Nitrosamines	12,691/50,737	1.0	19/79	1.0	0.6–1.7	212/878	1.1	0.9–1.3	58/226	1.1	0.9–1.5
Polycyclic aromatic hydrocarbons	12,616/50,463	1.0	157/608	1.2	1.0–1.4	141/501	1.2	1.0–1.5	66/348	0.9	0.7–1.1
Insecticides and fungicides	12,770/51,195	1.0	125/380	1.5	1.2–1.8	27/123	1.0	0.7–1.5	58/222	1.2	0.9–1.7
Herbicides	12,919/51,680	1.0	3/15	0.8	0.2–2.8	7/38	0.9	0.4–1.9	51/187	1.3	0.9–1.8
Contact with the public	10,021/42,196	1.0	980/3,309	1.2	1.1–1.3	1,177/3,385	1.2	1.1–1.3	802/3,030	0.9	0.8–1.0

characteristics of EMF exposure in our job-exposure matrix. Therefore, we conclude that such a study design is not powerful enough to exclude an association between CNS cancer and occupational exposure to EMF.

Poor occupational information in the death certificates was a major limitation in this study. Occupation and industry listed on the death certificate represent only a fraction of the work history for each subject, either the "usual" or the last occupation. The 3-digit US Census code may have not been specific enough to accurately identify exposures. Also, women might have different job duties or exposure levels than men in the same occupation. The resulting misclassification of exposure may have impaired the specificity of our job-exposure matrix and weakened positive associations. These disadvantages are particularly important in studies involving women, as the reliability of the occupational information in the death certificate is poorer for women than men [Schade and Swanson, 1988].

Diagnostic bias is also likely to occur in death certificate-based case-control studies, as mortality from all causes combined is generally greater and reliability of death certificate diagnosis is poorer among low SES groups. Therefore, low SES occupations could be underrepresented among cases (subjects with a well-defined diagnosis) and overrepresented among controls (including other and more generic causes of death), which could obscure true associations with occupational risk factors more frequent in low SES groups. To address the possibility of diagnostic bias, we controlled for SES in our analysis and evaluated exposures resulting from a variety of occupations and industries, instead of individual occupations and industries.

Finally, the use of death certificates provides only limited possibility to control for confounding or effect modification by lifestyle factors or other occupational exposures. We adjusted for marital status and residence in the analysis to reduce the effect of lifestyle factors on our results.

In conclusion, we did not find evidence of a strong increase in CNS cancer risk among women potentially exposed to several occupational hazards suspected to increase risk. However, numbers were not sufficient to rule out

a more modest association. Interpreting inconsistent findings by gender may be difficult as women and men, although sharing the same occupational title, may perform different duties and have different exposures. Specially designed job-exposure matrices, based on the exposure experience of the female workforce, could be an asset. Further research is warranted to understand whether different duties at work or different gender-linked susceptibility to workplace carcinogens may play a role in gender-related variations of CNS cancer risk.

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