Risks of Brain Tumors in Rubber Workers: A Metaanalysis

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Objective: *To better understand whether rubber industry workers suffer increased risks of brain tumor, a concern that has persisted for over 40 years despite numerous well-conducted studies.* ***Methods:*** *We performed a formal metaanalysis of brain tumor risk estimates reported in cohort studies of rubber and tire workers. Twenty unique cohorts were identified who met a priori inclusion criteria. Metaanalysis was performed using the general variance-based method; the variance of risk estimates was calculated for each study using a chi-squared method. Homogeneity was tested by means of the Q statistic.* ***Results:*** *The metaanalysis determined an overall relative risk of 0.90 (95% CI = 0.79–1.02).* ***Conclusions:*** *The analytical results are consistent with a conclusion that risks of brain tumor are not increased as a result of occupational exposures in the rubber and tire industry.* (J Occup Environ Med. *2005;47:294–298*)

Increased risks of cancer among workers in the rubber and tire industry have been recognized for more than 50 years. Early reports described excess bladder cancer,[1] which were followed by reports of excess lung and stomach cancer.[2–4] Subsequent investigations, conducted mainly in the United Kingdom[5] and the United States,[6–8] confirmed those earlier reports; some also documented elevated rates for other types of cancer. By 1982, an IARC Working Group was able to conclude that evidence was "sufficient" for an excess of bladder cancer, leukemia, stomach cancer, and lung cancer in rubber workers,[9] although evidence of a causal association was sufficient for only bladder cancer and leukemia. Evidence for a variety of other cancers was judged "limited" or "inadequate."

Since then, the carcinogenic risks of rubber industry employment have been the subject of extensive research. A 1998 review,[10] summarizing the evidence from studies published after the 1982 IARC evaluation, identified 12 cohort studies, seven nested case–control studies, 48 community-based case–control studies that considered rubber industry employment, and 23 relevant administrative studies. Since 1998, a number of additional cohort and case–control studies have been published.

While shedding much light on the hazards of rubber industry occupations, this extensive body of research has also yielded a variety of inconsistent or contradictory findings. One important example is brain tumors.

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The possibility that rubber industry workers suffered increased risks of brain tumor was first raised in 1963,[11] and support for that possibility was found in cohort[6,12,13] and case–control studies.[14,15] On the other hand, numerous well-conducted studies failed to detect such an excess of brain tumors. The 1982 IARC Monograph[10] concluded that evidence for brain tumors was "inadequate," whereas the 1998 review[10] identified five cohort studies that found excess brain tumors and four other studies that found no such excess.

To better understand this possible association, we undertook a formal metaanalysis of brain tumor risk estimates reported in cohort studies of workers employed in the rubber and tire industry. The methods used and the analytical findings are described subsequently.

Methods

Cohort studies considered for inclusion in this metaanalysis were identified in three ways. First, we considered the 33 epidemiologic studies listed in the 1982 IARC Monograph on the rubber industry.[9] Among those 33 studies, 12 presented data on brain tumors, of which 10 were cohort studies. We then considered the 90 studies listed in the 1998 review of studies published subsequent to the IARC Monograph[10]; nine cohort studies presented data on brain tumors. Finally, we searched the MEDLINE and CANCERLIT databases to identify studies of rubber and tire industry worker cohorts published subsequent to 1998 and we identified those that specifically considered brain tumors.

Studies were reviewed to ensure that the data presented were adequate and appropriate for metaanalysis. Each study was expected to provide relative risk estimates as measures of association. Such relative risk estimates could have been provided as rate ratios (eg, standardized mortality rate [SMR]), odds ratios ([OR] = [observed] ÷ [expected]), or risk ratios. The most frequently used estimate of relative risk was SMR; for consistency, it was selected over other measures (eg, standardized incidence rate [SIR]) for reports that included more than one measure of relative risk. Studies were excluded if they did not provide enough information to ascertain both a relative risk estimate and its variance.

If multiple reports described the same worker cohort studied at different times or analyzed in different ways, only the report with the longest follow-up time or the largest number of subjects was included in the analysis.

None of the studies reported the variance or standard deviation of the risk estimate, none reported calculated chi-squared values, and none reported calculated *P* values. Only four reported confidence intervals around the risk estimate. Accordingly, for purposes of metaanalysis, the variance of the risk estimates for each study was calculated using a two-step process: First, χ^2 was calculated by means of the formula: $\chi^2 = ([O - E]^2 \div E)$, where O = observed number of brain tumors and E = expected number of brain tumors. Then, the variance was calculated using the formula: variance $= ([\ln(OR)]^2 \div \chi^2)$. Because brain tumors are rare events, an OR was estimated as the relative risk divided by 100.

Metaanalysis was performed using the general variance-based method,[17,18] a fixed-effects model that calculates a weighted average of the individual measures of effect where the weights are the inverse of the variance of the individual measures. Homogeneity of effects was tested by means of the Q statistic, which is calculated by reference to a chi-square distribution.[17,19] The hypothesis of homogeneity was rejected if the *P* value of the test was <0.05. In that case, metaanalysis was repeated after efforts to identify and address sources of heterogeneity.

Results

We identified 21 reports that described risks of brain tumor in cohorts of rubber and tire industry workers.[2,3,5–8,12,13,20–32] Three of those reports, by Monson and colleagues,[25,6,22] considered the same worker cohort. For purposes of metaanalysis, we included only the most recent one,[22] which had the longest period of observation (1940–1978) and included the largest number of workers (15,643). The report by Fox and Collier presented data for 40,867 male rubber industry workers and also for a subset of 16,035 male tire-sector workers. We included the tire-sector cohort, rather than the overall cohort, because of historical concerns that brain tumor risks are elevated in tire assembly workers[6] and because relative risks for brain tumor were higher in the tire-sector workers than in the overall cohort.

Four reports each described two subcohorts that could not be readily combined. Three[13,29,32] presented findings separately for males and females, whereas the fourth, Fox and Collier[3] presented mortality data for two distinct follow-up periods (1968–1971 and 1972–1974). For each of those four reports, both subcohorts were individually included in the metaanalysis. Three small cohorts (Delzell et al.,[23] female workers in Solinova,[13] and female workers in Straughan[29]) were excluded because they did not provide enough information to ascertain both a relative risk estimate and its variance. Each of those cohorts had no reported brain tumors.

The remaining 20 cohorts, described in Table 1, were included in the metaanalysis. Seventeen of the cohorts included only males, one included only females, and two did not describe gender distributions. Relative risk was reported as SMR for 18 cohorts and as SIR in the other two.[13,27] Three studies[7,8,20] included all workers employed on a particular historical starting date, but imposed no minimum duration of employ-

TABLE 1
Characteristics of the Cohort Studies Included in the Metaanalysis

Author	Year	Gender	No.	Observed	Expected	Odds Ratio	Risk Type	Work Period	Follow-up Period	Minimum Employment
Andjelkovich[8]	1976	M	8418	8	8.7	0.9	SMR	pre-1964	1964–1973	?
Baxter and Werner[2]	1980	M	40,867	21	34.8	0.6	SMR	pre-1967	1967–1977	1 yr
Barnadinelli[12]	1987	M	4917	2	0.95	2.1	SMR	1962–1972	1962–1983	1 yr
Bovet and Lob[20]	1980	M	931	2	0.91	2.2	SMR	pre-1955	1955–1975	?
Carlo[21]	1993	M	2306	1	1.4	0.7	SMR	1962–1989		1 yr
Delzell and Monson[22]	1981	M	15,643	31	34.0	0.91	SMR	1925–1969	1940–1978	2 yrs
Fox and Collier[3]	1976	M	16,035	6	5.1	1.18	SMR	1967–1971	1968–1971	1 yr
Fox and Collier[3]	1976	M	16,035	4	4.2	0.95	SMR	1967–1974	1972–1974	1 yr
Holmberg[24]	1983	?	16,611	8	5.7	1.4	SMR	1931–1975	1961–1978	1 yr
McMichael[7]	1974	M	6678	4	5.9	0.68	SMR	pre-1964	1964–1973	
Negri[26]	1989	M	6629	9	10.2	0.88	SMR	1946–1981	1946–1981	1 yr
Norseth[27]	1983	M	2448	5	4.23	1.18	SIR	1940+	1953–1978	1.5 yr
Parkes[5]	1982	M	33,815	35	41.1	0.85	SMR	1946–	1956–1975	1 yr
Solinova[13]	1993	M	1178	3	0.6	5.0	SIR	1969–1983	1979–1988	10 yrs
Sorahan[28]	1989	M	36,691	67	76.3	0.88	SMR	1946–1960	1946–1985	1 yr
Straughan[29]	2000	M	7561	4	2.92	1.37	SMR	1982–1991	1983–1998	1 yr
Szesenia[30]	1991	M	6078	7	5.5	1.27	SMR	1945–1973	1945–1985	3 mos
Weiland[31]	1996	M	11,663	9	10.8	0.83	SMR	pre-1981	1981–1991	1 yr
Wilczynska[32]	2001	M	10918	8	12.0	0.67	SMR	1950–1995	1950–1995	3 mos
Wilczynska[32]	2001	F	6087	1	3.2	0.31	SMR	1950–1995	1950–1995	3 mos

SMR, standardized mortality rate.

ment for inclusion; the other cohorts had a minimum employment duration criteria that ranged from 3 months to 10 years. Eight of 20 cohorts had an OR greater than 1.0 and 12 had an OR less than 1.0.

Results of the metaanalysis indicated a pooled relative risk of 0.90 with a 95% confidence interval of 0.79–1.02. The Q statistic test of homogeneity found no evidence of a lack of homogeneity among the various studies ($Q = 24.14$, $df = 19$, $P = 0.191$).

Discussion

The results of this metaanalysis are consistent with the conclusion that risks of brain tumor are not increased as a result of occupational exposures in the rubber and tire industry. The overall relative risk of 0.90 (95% confidence interval = 0.79–1.02) even suggests the possibility of a small deficit of risk. However, we do not think that there is any basis to suggest that working in this industry imparts protective effects with respect to brain tumors.

In light of this finding, it is interesting to reexamine the literature that has been cited as documenting increased brain cancer risks. The first two positive reports by Mancuso evaluated rubber workers in Summit County, Ohio, "principal center for the manufacture of automobile rubber tires in the US."[11] (Workers in Akron, the county seat of Summit County, have been the subjects of numerous rubber industry studies, including 3 studies listed in Table 1.) Mancuso reported that brain tumor deaths in Summit County were consistently greater than expected; he also described six brain tumor deaths among those who had worked at a former rubber plant.[11] Mancuso did not discuss expected rates, and he cautioned that his study had "marked limitations" because of its small size.

The second Mancuso report considered age-adjusted mortality rates resulting from central nervous system tumors in Ohio during 1944–1952.[33] Categorized by industry, rates were highest in electrical equipment and rubber tire manufacture. Six brain tumor deaths were noted in one plant, but no data were provided for the other three plants described elsewhere in the report. The statistical significance of that finding was not discussed. These two reports were cited in the "Historical Overview" chapter of the IARC Monograph,[9] but neither was included among epidemiologic studies relied on by the Working Group.

A brain tumor excess was also described in a subcohort (but not the overall cohort) of Akron rubber workers studied on three occasions by Monson and colleagues. Monson and Nakano[6] reported a deficit of brain tumors (O/E = 20/25) in the overall cohort of 13,751 male workers employed for at least 5 years; a nonsignificant excess (O/E = 7/3.7) was noted in a subcohort of 1905 tire assembly workers. In a follow-up study, Monson and Fine found that no additional cases had occurred in that subcohort during 2 more years of follow up.[25] They also reported that brain tumors were found mainly in men who had worked less than 15 years in tire assembly. A third study (Delzell and Monson[22]) added another 2 years of follow up and considered 15,643 white male union workers employed at least 2 years; the tire assembly subcohort was not considered separately. This study, which is included in the current metaanalysis and in Table 1, found an overall relative risk of 0.91 (O/E = 31/34).

We identified another eight cohorts, listed in Table 1, for which relative risks of brain tumors were greater than 1.0. Most contained small numbers of subjects and most reported only small excess risks: five of the eight had relative risks ≤1.4 and none described statistically significant findings. These eight cohorts accounted for only 37 (15.7%) of the 235 tumor cases reported in the 20 study cohorts.

Other findings that might be regarded as suggesting a brain tumor excess come from the study of another Akron cohort by Andjellkovic et al.[8] That study, listed in Table 1, found a deficit of brain tumors in the overall cohort of 8418 white men, but a significant excess (SMR = 323, $P < 0.05$) was noted among retired workers aged 40–64 years. Interpretation of that finding is difficult because only three cases were reported in that group and because a deficit was noted among older retirees.

In a follow-up report, Andjelkovic and colleagues[34] clarified that finding. First, they noted that the 40–64-year-old retirees comprised a group with serious, chronic disease: "the SMR for brain cancers... should be considered relative to an all cause SMR of 202." They also reviewed findings of numerous unpublished studies of rubber worker cohorts by the Occupational Health Studies Group at University of North Carolina and found little support for the hypothesis of an excess risk of brain tumor deaths. They concluded that their data "do not agree with the reports of Mancuso and Monson."

Accordingly, it seems likely that concerns about increased brain tumor risks in rubber and tire workers derive from a handful of studies that documented excesses in selected subgroups, findings that have not been generally corroborated. We cannot exclude the possibility that some job categories or specific tasks are associated with increased risks, but that possibility remains hypothetical. Nevertheless, such concerns are not biologically implausible. Although the etiology of most nervous system tumors is unknown,[35] increased risks of brain tumor have been associated with exposures to vinyl chloride, acrylonitrile, and N-nitroso compounds,[35–37] chemicals that may be encountered in the synthetic rubber and plastics industries.

This metaanalysis supports the view that rubber industry workers are not at increased risk of brain tumor. A strength of the current study is that it focused solely on cohort studies, of which all but two used the same measure of relative risk. Because the studies selected for metaanalysis were mainly those identified earlier by IARC and by an international group of IARC-associated epidemiologists, selection bias seems unlikely. The analytic results are also unlikely to reflect publication bias, an effect most often associated with the tendency to underreport negative findings.[17] Such underreporting would not have affected our analytic results. Moreover, because most of these were large-scale cohort studies with numerous health effects end points, it is unlikely that publication would have hinged on their findings with respect to brain tumors. The fact that the studies provided no evidence of heterogeneity is also reassuring. Despite that finding, the analysis was also performed including only the 17 all-male cohorts; the results were nearly identical (data not shown), indicating no apparent gender-related effects.

It should also be noted that "brain tumor" names a heterogeneous group of benign and malignant disorders[35] and that most of the studies did not distinguish between them. If rubber industry exposures contributed to only a specific subset of "brain tumor," then failure to find causal associations in the various studies might be the result of their failure to identify and count the appropriate end point tumors. That possibility, which would reduce the statistical power of individual studies, is at least partially addressed by metaanalysis that applies quantitative methods to pooling of results.[18]

In conclusion, the results of this metaanalysis indicate no significant increased risk of brain tumors overall in rubber and tire industry workers.

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