



## **Original article**

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## Gliomas among men employed in the Swedish pulp and paper industry

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**Objectives** This study investigated whether previous findings of an increased risk of gliomas among workers in some pulp and paper mills could be confirmed for all Swedish pulp and paper mill workers and whether the increase could be attributed to certain occupational groups.

**Methods** The study was based on the Swedish Cancer Environment Register, which links the incidence of cancer from 1971 to 1990 and the 1960 and 1970 census data on codes of occupation and industry for the whole population. Standardized incidence ratios (SIR) were used to estimate the risks for men in different occupations in pulp (N=28 142) and paper (N=39 169) mills in 1960, 1970 or both years as compared with those of all gainfully employed men in Sweden.

**Results** Maintenance workers employed in pulp or paper mills in 1960, 1970 or both years, as well as pulp workers, showed an increased incidence of gliomas in 1971–1990 [SIR 1.5, 95% confidence interval (95% CI) 1.1–2.1 and SIR 1.5, 95% CI 1.0–2.2, respectively], whereas the incidence among process workers in paper mills was lower than expected (SIR 0.6, 95% CI 0.3–0.9). Taken together, all employed men in the pulp mill industry had an increased incidence of gliomas (SIR 1.3, 95% CI 1.0–1.7).

**Conclusions** Pulp mill workers, but not paper mill workers, were found to have more gliomas in 1971–1990 than expected. There was an increased risk of gliomas among maintenance workers in both pulp and paper mills. Few risk factors for brain tumors are recognized, and the causes of the increase are not obvious.

**Key terms** brain tumor, epidemiology, register study, sulfate, sulfite, terpenes.

The production of pulp and paper is an important industrial trade in Sweden. This work environment entails a variety of exposures depending on the process. The pulp processes have been the alkaline sulfate process, mechanical processes, the acidic sulfite process, and during the last few decades waste paper pulping as well. The main occupational exposures have been wood dust, terpenes and bleaching chemicals in the pulp mills (1). In the sulfate mills also hydrogen sulfide and other reduced sulfur compounds are used. In the sulfite mills sulfur dioxide is found as well, whereas paper dust and different additives appear in the paper mills. There is a multitude of chemicals in this industry, including some potential carcinogens. Other exposures are noise, heat, microorganisms, and shift work.

In two case-referent studies, one among sulfite mill workers and the other in sulfate mills, we found increased mortality from primary brain tumors (2, 3). Most of the cases were gliomas (9 of 10 cases and 20 of 22 cases, respectively). In addition, an increased risk of tumors in the central nervous system has been identified in a few pulp and paper mill cohort studies (4, 5). Knowledge of the etiology of brain tumors is limited. Brain tumors may have different etiologies with different histological types (6). The most common form of primary brain tumor among adults is glioma, which originates in neuroglial cells (6). Gliomas are more common among men than women, and occupational exposures have been proposed to be more important for gliomas than for other types of brain tumors (6, 7). The

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only established risk factors among adults are genetic predisposition and treatment with ionizing radiation (6). Different occupational risks have been suggested, such as work in the rubber industry and chemical industry or work with metal and exposure to vinyl chloride (7). N-nitroso compounds experimentally cause brain tumors in animals, but epidemiologic studies have not confirmed this finding (8). Exposure to electromagnetic fields has been discussed as a risk factor for brain tumors (9).

The Swedish Cancer Environment Register made it possible to construct a historical cohort of persons that had worked in the pulp and paper industry in 1960, 1970, or both years. The cancer incidence from 1971 to 1990 was investigated. The aim was to study the incidence of glioma in the pulp and paper industries separately and also the incidence for different occupations. We restricted the study to glioma since it is a more-specific diagnosis than brain tumor, and occupational factors have been suggested.

### **Subjects and methods**

The Swedish Cancer Environment Register (CER 6070) links occupational information from the national census in 1960 and 1970 with cancer incidence data registered in the national cancer register in the period 1971–1990 (10). All persons living in Sweden have a unique personal identification number that allows this link. The population base for the studied historical cohort was all Swedish men gainfully employed on a half-time or greater basis at the time of the 1960 or 1970 census or in both years and were still living at the beginning of 1971. Only persons born in 1896–1950 were included, leaving 2 375 340 men in the cohort. Those gainfully employed in both 1960 and 1970 were also studied, and the population was then restricted to men born in 1906–1940.

The occupations in the 1960 national census were classified according to the Nordic Classification of Occupations, and these codes were used in this study. Similar codes were used in the 1970 national census, and translations were done when necessary. All workers employed in 1960, 1970 or both years in pulp mills (N=28 142, industrial codes 260 and 261) and paper mills (N=39 169, industrial codes 262 and 264, including the paper packaging industry), as well as different occupations in pulp and paper mills were compared with all gainfully employed Swedish men. Occupational codes for the workers in pulp and paper mills were combined and analyzed according to worktasks: chemical process workers (occupational codes 830–839); maintenance workers, broadly defined (occupational codes

700–799), “chemistry workers”; mostly chemistry technicians working in process operations (occupational codes 4, 11, 14); and “packers”, paper product workers and packers (occupational codes 857, 881). Single occupational codes with more than three cases were also analyzed and reported. Some workers could be employed in one occupation in a pulp or paper mill in 1960 and in another in 1970 and thus classified both as a pulp and a paper worker.

Gliomas were defined by code 1930 of the 7th revision of the International Classification of Diseases (ICD 7) and histology code (WHO/HS/CANC/24) 475 (astrocytoma grade 1–2 and oligodendroglioma) or 476 (astrocytoma grade 3–4, mostly glioblastoma multiform). The Swedish cancer register has used the Kernohan system for classification, grading astrocytoma from 1–4 according to malignancy (11). In the Swedish cancer register, brain tumors (ICD code 1930) include benign tumors such as meningiomas.

Each subject contributed with person-time from 1971 until the year of event (time of diagnosis of glioma or death) or until the end of the follow-up in 1990. Standardized incidence ratios (SIR) were calculated for different occupational codes and combinations of codes in the pulp and paper mills separately and together. The expected number of cases was calculated using 5-year birth cohorts stratified by calendar period (5 years) and region. The regions were three rural (southern, middle and northern Sweden) and one urban (combining the three largest cities) region. The subjects registered in different regions in 1960 and 1970 were allocated to a fifth “region”. The standardized incidence ratios were determined if three or more cases were observed, and 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution.

### **Results**

A total of 201 brain tumors, of which 123 were gliomas, were recorded among the men employed in the pulp and paper industry during the follow-up period of 1971–1990 (two of them had worked in both pulp and paper mills). The corresponding numbers among all the employed Swedish men were 7620 and 4101, respectively. About 80% of the gliomas were astrocytomas, grade 3–4.

The incidence of gliomas in 1971–1990 was higher among the men employed in pulp mills in 1960 or 1970 or both years as compared with other employed Swedish men (table 1). Both process and maintenance workers in pulp mills appeared to have about 50% more cases than expected. The incidence for maintenance workers was about the same in the paper mills as in the pulp

**Table 1.** Standardized incidence ratios (SIR) for gliomas for different occupational groups employed in 1960, 1970 or both years and in both 1960 and 1970 in Swedish pulp and paper mills in comparison with all employed Swedish men. (95% CI = 95% confidence interval)

Industry	Employed in 1960, 1970 or both years				Employed in both 1960 and 1970			
	Exposed (N)	Cases (N)	SIR	95% CI	Exposed (N)	Cases (N)	SIR	95% CI
<b>Pulp mills</b>								
All employed	28142	61	1.3	1.01–1.7	7542	21	1.5	0.9 –2.3
Process workers	10531	26	1.5	0.98–2.2	1832	7	2.0	0.8 –4.1
Maintenance workers	7617	18	1.5	0.9 –2.4	1186	5	2.3	0.7 –5.3
<b>Paper mills</b>								
All employed	39169	64	0.9	0.7 –1.2	11013	20	0.8	0.5 –1.3
Process workers	15594	15	0.6	0.3 –0.9	3099	3	0.5	0.1 –1.3
Maintenance workers	6885	18	1.5	0.9 –2.4	1147	5	2.0	0.7 –4.7
<b>Pulp and paper mills</b>								
Maintenance workers	14299 <sup>a</sup>	36	1.5	1.1 –2.1	2514 <sup>a</sup>	10	2.0	0.95–3.6
Chemistry workers	4867	10	1.1	0.5 –2.1	893	4	2.1	0.6 –5.3
Packers	5398	9	1.0	0.4 –1.8	538	0	.	0.0 –3.1

<sup>a</sup> Some had worked both in a pulp and a paper mill.

**Table 2.** Standardized incidence ratios (SIR) for gliomas for different occupations in 1960, 1970 or both years in Swedish pulp and paper mills in comparison with all employed Swedish men. Only occupations with three or more exposed cases have been included. (95% CI = 95% confidence interval)

Occupation <sup>a</sup>	Exposed (N)	Cases (N)	SIR	95% CI
Mechanical engineers, technicians (3)	1121	3	1.4	0.3 –4.2
Chemical engineers, technicians (4)	3976	8	1.1	0.5 –2.1
Engineers, technicians non-specified (6)	710	3	2.2	0.5 –6.4
Motor-vehicle drivers (633)	1249	3	1.3	0.3 –3.8
Toolmakers, machine-tool setters and operators (750) - mechanics	1555	7	2.8	1.1 –5.7
Machinery repairmen (752)	4135	15	2.2	1.2 –3.7
Construction carpenters, joiners (771)	968	3	1.7	0.4 –5.0
Frame/circular sawyers, planers (774)	1050	5	2.8	0.9 –6.5
Concrete, construction workers (793)	567	3	3.4	0.7 –10
Typographers, lithographers (801)	1351	3	1.3	0.3 –3.8
Chemical process workers (831)	1296	4	1.7	0.5 –4.5
Paper pulp workers (834)	11040	28	1.5	1.00–2.2
Paper, paperboard workers (836)	14292	12	0.5	0.3 –0.8
Unskilled manual workers (861)	2469	7	1.7	0.7 –3.5
Stationary engine and related equipment operators (871)	1502	4	1.5	0.4 –3.8
Truck, conveyor operators (875)	2920	3	0.6	0.1 –1.8
Store, warehouse workers (883)	1345	3	1.3	0.3 –3.8

<sup>a</sup> Code of the Nordic Classification of Occupations in parentheses.

mills, but the process workers in the paper mills had a lower incidence of gliomas than expected.

The incidences of gliomas among workers in categories representing different occupational codes in the pulp and paper industry are shown in table 2. Pulp workers showed an increased incidence. The standardized incidence ratio was based on a few cases in most of the occupations. Several of the occupations in the group of maintenance workers had a standardized incidence ratio that was higher than unity, but only the mechanics and machinery repairmen had a significantly increased risk.

For the men employed in pulp and paper mills in both 1960 and 1970, the standardized incidence ratios were similar or further from unity when compared with those employed in 1960, 1970 or both years (table 1).

## Discussion

This study, based on data from the Swedish Cancer Environment Register, showed an increased incidence of

gliomas in 1971–1990 among maintenance workers in the pulp and paper industry and among pulp workers as compared with all gainfully employed Swedish men. Process workers in paper mills showed a lower incidence than expected.

Brain tumors are an ambiguous entity not quite appropriate for comparison in epidemiologic studies. Some countries include nonmalignant brain tumors in their cancer registers and others do not (6). Some studies also include all tumors of the central nervous system. In cohort studies it is not always obvious which tumors were included. Brain tumor mortality is thus more representative for glioma than brain tumor incidence is.

Almost all earlier studies in the pulp and paper industry have investigated all brain or central nervous system tumors as one category and have not reported separate results for glioma. If we had analyzed all brain tumors (ICD7=1930) in this study, the risk for all workers employed in pulp mills would have been a standardized incidence ratio of 1.1 (95% CI 0.8–1.3) as compared with 1.3 (95% CI 1.0–1.7) for glioma. There have nevertheless been some previous indications of an increased risk of brain tumors in the pulp and paper industry, although such an increase was not found in most studies (tables 3 and 4). Tables 3 and 4 include all cohort studies published in English (searched in Medline) with estimates for the incidence (table 3) or mortality (table 4) of brain tumors or tumors of the central nervous system. A pulp and paper mill cohort in Canada showed increased mortality for brain tumors among

sulfite mill workers (table 4) (4). When the incidence in the same cohort was studied, but with a shorter follow-up time, the increase was no longer significant (table 3) (12). In an internal comparison in a large cohort mortality study in the United States, an increased risk was observed among workers in semi-chemical and soda pulp processing (relative risk 2.3, 95% CI 1.4–3.9) as compared with other pulp and paper mill workers (5). A Polish cohort study found increased mortality from brain tumors among women in paper production (standardized mortality ratio 355, 95% CI 143–731) (16). A Danish paper mill cohort showed a higher incidence of brain tumors (not significant) among workers in the maintenance and repair department (13).

In our previously published case-referent studies, where mortality from 1960 to 1989 was analyzed in parishes surrounding three sulfite mills and four sulfate mills, we found increased odds ratios (OR) for brain tumors (OR 3.3, 90% CI 1.2–8.9, and OR 2.6, 90% CI 1.2–5.3, respectively) (2, 3). In the sulfate mill study (3) we analyzed different occupations and found a significantly increased risk among wood-room workers, maintenance workers, and sawmill workers. A case-referent study of death certificates in 24 states in the United States in 1984–1992 demonstrated an increased risk of tumors of the central nervous system among white men in pulp, paper and paperboard mills (OR 1.3 95% CI 1.1–1.6) (21). A study based on the Swedish Cancer Environment Register for 1961–1979 showed an increased risk of intracranial gliomas among male

**Table 3.** Cohort studies reporting the incidence of brain tumors or central nervous system tumors in the pulp and paper industry. (SIR = standardized incidence ratio, CI = confidence interval)

Study	Process	Years	Men (N)	Exposed cases (N)	Risk		Country, follow-up
					SIR	CI	
Band et al, 2001 (12)	Pulp or paper	1950–1992	28278	43	1.14	90% 0.9–1.5	Canada, follow-up 1969–1992 (Mortality in the same cohort, Band et al, 1997)
	Sulfate		20041	23	0.99	90% 0.7–1.4	
	Sulfite		3756	10	1.53	90% 0.8–2.6	
	Both		4481	10	1.24	90% 0.7–2.1	
Rix et al, 1998 (13)	Paper mills	1943–1990	11130	31	0.99	95% 0.7–1.4	Denmark, follow-up to 1993
	Stock preparation		..	5	1.05	..	
	Paper machine		..	5	1.16	..	
	Calendering or winding or cutting or packing		..	11	0.82	..	
	Maintenance or repair		..	9	1.40	..	
	Storage or transport		..	5	1.24	..	
	Power station		..	3	2.83	..	
Rix et al, 1997 (14)	Sulfite mills	1955–1990	2136	2	0.37	95% 0.0–1.3	Denmark, follow-up to 1993
	Process		..	1	0.37	95% 0.0–2.1	
Rix et al, 1997 (15)	Recycling	1965–1990	4450	8	0.88	95% 0.4–1.7	Denmark, follow-up to 1993
	Pulp or paper		..	8	1.10	95% 0.5–2.2	
	Maintenance or storage		..	1	0.70	95% 0.0–3.9	

**Table 4.** Cohort studies reporting mortality from brain tumors or central nervous system tumors in the pulp and paper industry. (SMR = standardized mortality ratio, CI = confidence interval)

Study	Process	Years	Men (N)	Exposed cases (N)	Risk		Country, follow-up
					SMR	CI	
Matanoski et al, 1998 (5)	Pulp or paper	1970–1991	56000	66	0.96	95% 0.7–1.2	United States follow up to 1991 Employment >10 years
	Sulfate		44372		1.01	95% 0.8–1.3	
	Sulfite		10205		0.34	95% 0.1–0.8	
	Other chemicals		15408		1.39	95% 0.96–2.0	
	Other pulp		16077		0.94	95% 0.6–1.5	
Szadkowska-Stanczuk et al, 1998, (16)	Pulp or paper	1968–1990	6993	8	119	95% 51–234	Poland follow up to 1995
Band et al, 1997 (4)	Pulp or paper	1950–1992	28200	44	1.11	90% 0.9–1.4	Canada follow up 1950–92
	Pulp or paper, employed ≥15 years		..	22	1.51	90% 1.03–2.2	
	Sulfate		19674	17	0.80	90% 0.5–1.2	
	Sulfite		4216	16	1.72	90% 1.08–2.6	
	Sulfite, employed ≥15 years		..	5	2.21	90% 0.9–4.7	
	Both sulfate and sulfite		4310	11	1.21	90% 0.7–2.0	
Coggon et al, 1997 (17)	Paper mills	1955–1992	3094	8	1.33	95% 0.6–2.6	Scotland follow up to 1995
Wong et al, 1996 (18)	Pulp or paper	1975–1992	9358	6	68	95% 25–149	United States follow up to 1992
	Paper machines		..	0	.	.	
	Finishing		..	4	191	..	
	Maintenance		..	1	46	..	
Henneberger et al, 1989 (19)	Pulp or paper	1961–1985	883	2	115	95% 13–417	United States follow up to 1985
Robinson et al, 1986 (20)	Pulp or paper	1945–1955	3572	4	63	95% 21–145	United States follow up to 1977

cellulose pulp mill workers (SIR 1.6,  $P < 0.01$ ) (22). A link between the Finnish Population Census of 1970 and the Finnish Cancer Register in 1971–1985 disclosed an increased incidence of cancer of the brain and nervous system among male chemical process or paper making workers (SIR 1.5, 95% 1.0–2.2) (23). In that study, paper and board mill workers showed an increased incidence (SIR 2.3, 95% 1.3–3.7) in contrast to our findings with a lower incidence for paper workers.

### Validity

The quality of the two registers used in our study is high. When the registers were linked, only 0.9% of the subjects with cancer could not be identified in the census (10). All physicians in Sweden are required to report all new cases of cancer to the national Swedish cancer register, and about 95% of all cases are reported. The cases missed are mainly prostate cancer, hematological malignancies, and stomach cancer. More than 90% of all cancer diagnoses in the cancer register are based on reports of both clinicians and pathologists (10).

Among all the gainfully employed men in our study, 54% of the brain tumors were gliomas, 21% were men-

ingiomas, 8% were malignant unspecified, 6% were benign unspecified, 6% were other specified tumors, and 5% were neurinomas. These percentages are in accordance with the results of other reports when benign tumors are included (24). Of the glioma diagnoses, 99.6% were histologically verified. There could have been gliomas among the malignant unspecified tumors since most of them are radiologically diagnosed.

A limitation of our study is that the exposure assessment was based only on the occupation held at the time of the 1960 and 1970 censuses. The length of employment in the pulp and paper mills was not known. Of those who worked in pulp and paper mills in 1970, 52% did so also in 1960. Another limitation was the follow-up time of 1971–1990; we have no information about cancer for those employed in 1960 for the years 1961–1970. An advantage of CER 6070 is that it was also possible to study those who were employed in both 1960 and 1970. The incidence ratios then tended to be more distant from unity. This is usually an indication of a causal association. Another advantage is that we made comparisons with gainfully employed men and not with the entire population.

The occupational codes in the CER have different degrees of specification according to worktasks. A pulp

worker could work in the wood room, the bleachery or recovery department, or the finishing area, whereas a truck driver in a paper mill is more specific. This lack of specification makes it difficult to apply a job exposure matrix to the material. A further problem with the exposure assessment was that there was no information in the Swedish Cancer Environment Registry on which pulping processes were used.

For part of the time, 1971–1979, and some of the pulp mills, cellulose pulp mills, there was an overlap with the study of McLaughlin et al (22) for those employed in 1960. They found about the same risk for the period 1961–1979 as we found for pulp mills in 1971–1990.

The matter of confounding is problematic when so few risk factors for glioma are known. We standardized for age, calendar year, and geographic area, all of which are possible confounders. Brain tumors are often reported to be more common in white-collar and professional occupations (7) possibly due to better access to the health care system. However, this situation is probably not so important in Sweden. Diet, tobacco, and alcohol are not linked to brain tumors in adults (6, 9, 24).

### *Risk factors*

The discrepancy in our study between process workers in pulp and paper mills is interesting. One exposure that is more frequent among pulp mill workers is that to fresh wood. Working with wood means possible exposures to wood dust, terpenes, formaldehyde, mold, and endotoxins, as well as chloroorganic compounds. The cancer prevention study (25) of the American Cancer Society found an increased mortality of brain tumors for work in wood-related occupations, but not among workers claiming wood dust exposure. The cancer risk of terpenes has not been studied extensively. A French case-referent study of brain tumors found that exposure to chloroorganic compounds and organic solvents was more common among wood-working cases than wood-working referents (26). Bleaching the pulp with chlorine dioxide introduces chloroorganic compounds (27, 28), but cohorts exposed to chloroorganic compounds and sawmill workers exposed to chlorophenate wood preservatives had no increased mortality because of brain tumors (29, 30). Formaldehyde was proposed to cause the increased risk of brain tumors among pathologists, but later cohort studies of workers exposed to formaldehyde have not found any increased risk of brain tumors (31, 32).

Occupations included in maintenance work in our study are mechanics and machinery repairmen, as well as carpenters and sawyers. All these occupations seemed to contribute to the increased risk. Some are exposed to fresh wood, but there may be a variety of different

exposures in these occupations (33), and a few more will be discussed.

While maintenance workers and other occupational groups in the pulp and paper mills can occasionally be exposed to organic solvents, the cumulative exposure is probably low. Study results concerning organic solvents and brain tumors are conflicting. Rodvall et al (34) demonstrated an increased risk of glioma among persons reporting exposure to organic solvents. An American case-referent study found an increased risk of astrocytic brain cancer with increased cumulative exposure to organic solvents (35). However, a meta-analysis of mortality among workers exposed to organic solvents reported no heightened risk of brain tumors (36).

Some maintenance workers are also exposed to lubricating oils and cutting fluids, and some studies have proposed that these substances are risk factors (7, 37). A cohort study among workers exposed to cutting oil mist did not find increased mortality from brain tumors (38).

For our study population we determined the glioma incidence for all Swedish maintenance workers (defined as in this study) and all machinery repairmen, and these groups did not show any increased risk when compared with all gainfully employed Swedish men (SIR 1.00, 95% CI 0.95–1.05 and SIR 1.08, 95% CI 0.93–1.25, respectively). This finding indicates that it could have been something in the work conditions in the pulp and paper mills rather than maintenance work as such that gave slightly more gliomas than expected.

Exposure to high levels of electromagnetic fields can occur in some areas of pulp and paper mills, such as close to steam generators and some powerful engines, but it has been reported that such exposure is generally on a level with the normal background exposure (39) and major differences between pulp and paper mills are not expected. Furthermore, it is claimed that, if there is an increased risk of brain tumors among persons with occupational exposure to electromagnetic fields, it is so small that is almost impossible to measure (40). Meta-analyses have found a possible increase of about 10–20% (9).

### *Concluding remarks*

The finding of an increased incidence of glioma among some occupational groups in pulp and paper mills in our study is supported by the results of some mortality studies in which the risk of brain tumor was reported. The underlying causes are not obvious. Study results of different proposed risk factors for glioma and brain tumor are conflicting. The work environment in pulp and paper mills has changed a great deal in recent decades,

and nowadays the process is mostly surveyed in enclosed rooms with less chemical exposure. It would be of interest to study whether there is any change in glioma risk over time in the pulp and paper industry and with the use of methods that permit more etiologic considerations. Furthermore, studies of brain tumors should report and analyze different diagnostic entities, as they may have different etiologies.

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