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Papers

Amalgam Fillings, Diagnostic Dental X-rays and Tumours of the Brain and Meninges

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A population-based case-control study of incident brain tumours in adults in Adelaide, South Australia considered possible associations of exposures to amalgam fillings and diagnostic dental X-rays with subsequent development of glioma and meningioma. The study, conducted in 1987–1990, recorded data from 110 subjects with glioma, 60 with meningioma and 417 controls. Principal findings were unexplained decreased risks for glioma associated with both exposure to amalgam fillings (age- and sex adjusted relative risk = 0.47, 95% confidence interval: 0.25–0.91; $P = 0.02$) and to diagnostic dental X-rays (adjusted relative risk = 0.42; 95% confidence interval: 0.24–0.76; $P = 0.004$), and a possible increased risk for meningioma in males exposed to dental X-rays. The choice of the unexposed comparison group is important in determining if an increased risk is associated with panoramic or full-mouth X-rays in glioma.
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INTRODUCTION

LITTLE IS known for certain of environmental exposures which may predispose to cerebral tumours. In the field of dental care, one study on the occupational morbidity of dentists and dental assistants [1] has shown increased standardised morbidity ratios for glioblastoma and glioma. The proximity of teeth to the cranium has led to speculation that exposure to dental X-rays may be associated with development of cerebral tumours, and evidence from several, but not all, population-based case-control studies supports this [2–5]. Mercury-containing amalgam is the substance used most commonly for dental fillings, but information on its possible carcinogenicity in general and its effects on the central nervous system in particular is sparse. Mercury has been found in higher concentrations in the pituitary glands of dentists at necropsy [6], and in the occipital lobe of patients with amalgam fillings [7], but there is as yet no evidence of any role in cerebral malignancy [8].

The Adelaide (South Australia) Adult Brain Tumour Study is one of 10 case-control studies of brain tumours in adults being coordinated by the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) Programme of the International Agency for Research on Cancer (IARC) in Lyon, France.

This paper reports the results of our investigations of prior exposure to dental X-rays and to mercury-containing amalgam fillings and development of brain tumours. As only one dentist and two dental assistants (all controls) were in the study, occupational exposure amongst dental workers is not considered further.

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MATERIALS AND METHODS

Study design

Between February 1987 and March 1990 data were collected from 190 incident cases of brain tumour (ICD-9 classifications 191–192) and from 419 controls by an experienced nurse-interviewer using the SEARCH Programme questionnaire. A further 20 incident cases had refused interview. Cases were defined by the protocol as adults aged between 25 and 74 years with primary tumours of the brain or meninges newly diagnosed within, and resident within, the study period in the study area (metropolitan Adelaide). Cases were identified by notification to the study centre by all neurosurgeons in Adelaide, supplemented by weekly contact with surgeons' rooms and all relevant hospitals. There were two mechanisms for checking for missed cases: lists of patients with malignant tumours were provided quarterly by the South Australian State Cancer Registry, to which notification of cancers is a statutory requirement, and new diagnoses of malignancy or menigioma sent by hospitals to the Australian Brain Tumour Registry in Melbourne were also reviewed. Apart from 5 cases (not used in this part of the study) all cases had their diagnoses confirmed histologically.

Controls were selected from the Australian electoral roll (on which 95% of adults are registered) using a systematic process to achieve a pseudo-random sample, frequency matched by age (±2 years), sex and postcode to the anticipated distribution of incident cases of brain tumour. The distribution was inferred from the age- and sex-specific data on brain cancers published by the South Australian State Cancer Registry for the years 1984–1985.

No effort was made to match cases with controls on an individual basis. If a selected control refused interview, or could not be traced within the study area, a replacement from the same age, sex and postcode stratum was substituted. 419 controls were interviewed from a total of 662 selected.

8 interviewed cases and 2 interviewed controls were subsequently excluded from the study because they did not satisfy the eligibility criteria. In addition, 12 cases are excluded from the present analysis, which will concentrate on the glioma and meningioma series. These 12 comprise 5 unclassified malignancies (no tissue diagnosis was available), 3 microglioma (this tumour type is now thought to be a primary B-lymphoid tumour, rather than arising from the microglial cells[9]), 1 benign Schwann cell tumour, 1 plasma cell leukaemia, 1 non-Hodgkin lymphoma and 1 unclassified lymphoma.

Ethical approval for the study was granted by the research ethics review committees of each of the participating hospitals.

Questionnaire

The dental record was one of 26 records of the study questionnaire. Subjects were asked about the number of present teeth which had ever had an amalgam filling, even if a tooth subsequently had been filled. The age at first amalgam filling and last amalgam filling were recorded. Subjects were asked whether they had ever had diagnostic dental X-rays, and, if so, the age at first and last X-ray and the usual frequency of X-rays before and after the age of 25. There were separate questions inquiring about exposure to full-mouth or panoramic ("Panorex") radiological examinations. In all analyses, exposures which could only have affected the subject within 2 years of date of diagnosis (cases) or date of interview (controls) were ignored.

Tumour coding

Tumour histology was coded according to the International Classification of Diseases for Oncology [10]. ICD-O codes for glioma are 938–948 and for miningioma, 953.

Data management

Data were double-entered into a data entry package and merged into the main Scientific Information Retrieval (SIR) [11] study database. Appropriate system files for the SYSTAT [12] statistical program were generated from the SIR database. Each step involved data validation and consistency checking.

Statistical methods

Standard statistical methods for the analysis of case-control studies were used throughout [13]. Odds ratios were calculated as estimates of relative risk (RR) for levels of categorical risk factors; adjustment for confounding factors was achieved by unconditional multiple logistic regression. All tests were 2-tailed and the conventional 95% confidence interval (95% C.I.) and 5% significance level were used. When expected numbers in cells were small, probabilities (P) and confidence intervals based on exact methods are reported. Data analysis used the SYSTAT and EGRET [14] statistical packages.

RESULTS

After the exclusions detailed above, the data set comprised 110 glioma subjects, 60 meningioma subjects and 417 controls. The frequency of missing values on some variables is due to the relatively high proportion of proxy interviews for gliomas (38%), the adverse effects on memory of the diseases being studied, and the retrospective nature of the questionnaire. In general, inferential results are presented for the entire (non-missing) data set; where possible, separate analyses of data from directly-interviewed subjects, whose responses were judged by the interviewer at time of interview as being "generally reliable" or of "high quality", are also reported.

Tables 1–4 show the distributions of the exposures studied, and Table 5 summarises the relative risks associated with them.

Table 1. Distribution of exposure to amalgam (mercury-containing) dental fillings in subjects in the Adelaide Adult Brain Tumour Study 1987–1990

	Controls ($n=417$)	Glioma ($n=110$)	Meningioma ($n=60$)
At least 1	291 (70)	51 (46)	43 (72)
1–5*	66 (16)	13 (12)	11 (18)
6–9	64 (15)	7 (6)	5 (8)
10–13	62 (15)	10 (9)	10(17)
14+	76 (18)	17 (15)	10 (17)
Number unknown	23 (6)	4 (4)	7 (12)
No fillings	54 (13)	18 (16)	8 (13)
Within†	6 (1)	0 (0)	0 (0)
Missing	66 (16)	41 (37)	9(15)

Entries show number of subjects (percentage of total number in diagnostic category) percentages may not sum to 100 due to rounding to nearest per cent.
*Categories formed from approximate quartiles of control distribution after exclusion of nil (reference category), within and missing categories.
†Only exposure was within 2 years of date of diagnosis or interview.

Amalgam fillings

Table 1 shows the distribution of amalgam fillings amongst the diagnostic groups. If the "missing" and "within 2 years" categories are omitted, recalculation of Table 1 yields 74% of glioma subjects and 84% of meningioma subjects vs. 84% of controls ever having at least one amalgam filling. The estimated relative risk for glioma, adjusted for age and sex, was 0.47 (95% C.I.: 0.25–0.91, $P=0.02$). This diminished risk persisted when analysis was restricted to those subjects having direct (non-proxy) and good quality interviews, although the smaller number involved led to widening of the confidence interval: $RR=0.50$ (95% C.I.: 0.18–1.41; $P=0.19$). Sex-specific analyses (adjusted for age) showed no substantial

Table 2. Distribution of exposure to diagnostic dental X-rays in subjects in the Adelaide Adult Brain Tumour Study 1987–1990

	Controls ($n=417$)	Glioma ($n=110$)	Meningioma ($n=60$)
Ever exposed	222 (53)	32 (29)	36 (60)
age < 25 years*	102 (24)	17 (15)	11 (18)
No X-rays	139 (33)	38 (35)	17 (28)
Within†	20 (5)	2 (2)	3 (5)
Missing	36 (9)	38 (35)	4 (7)

Entries show number of subjects (percentage of total number in diagnostic category) percentages may not sum to 100 due to rounding to nearest per cent.
*Subjects exposed to at least one X-ray before the age of 25.
†Only exposure was within 2 years of date of diagnosis or interview.

Table 3. Distribution of self-reported usual frequencies of exposure to diagnostic dental X-rays before and after age 25 in subjects in the Adelaide Adult Brain Tumour Study 1987–1990

	Age < 25			Age ≥ 25		
	Control	Glioma	Meningioma	Control	Glioma	Meningioma
≥ 1 per year	2 (0)	1 (1)	0 (0)	5 (1)	4 (4)	2 (3)
≥ 1 per 3 years	9 (2)	0 (0)	0 (0)	25 (6)	6 (5)	3 (5)
≥ 1 per 5 years	1 (0)	0 (0)	0 (0)	28 (7)	1 (1)	0 (0)
< 1 per 5 years	209 (50)	31 (28)	36 (60)	163 (39)	21 (19)	31 (52)
No X-rays*	139 (33)	38 (35)	17 (28)	139 (33)	38 (35)	17 (28)
Within†/Missing	57(14)	40 (36)	7 (12)	57 (14)	40 (36)	7 (12)

Entries show the number of subjects (percentage of total number in diagnostic category) percentages may not sum to 100 due to rounding to nearest per cent.
*Baseline group: never exposed to any dental X-rays at any age.
†Only exposure was within 2 years of date of diagnosis or interview.

Table 4. Distribution of exposure to Panorex or full-mouth dental X-rays in subjects in the Adelaide Adult Brain Tumour Study 1987–1990

	Controls ($n=417$)	Glioma ($n=110$)	Meningioma ($n=60$)
At least 1*	16 (4)	6 (5)	3 (5)
age < 25 years†	8 (2)	3 (3)	0 (0)
None‡	388 (93)	79 (72)	55 (92)
Within§	5 (1)	1 (1)	0 (0)
Missing	8 (2)	24 (22)	2 (3)

Entries show number of subjects (percentage of total number in diagnostic category) percentages may not sum to 100 due to rounding to nearest per cent.
*Not exclusive of exposure to other types of dental X-rays.
† Subjects exposed to at least 1 Panorex or full mouth x-ray before the age of 25.
‡ Baseline group: never exposed to Panorex or full-mouth dental X-rays at any age, but may have been exposed to ordinary dental X-rays; see text.
§Only exposure was within 2 years of date of diagnosis or interview.

heterogeneity of effect, although the decreased risk was statistically significant in males only. Each of four categories of lifetime number of fillings was associated with diminished risk, though no linear trend was detected.

No significant effect of any kind was seen for meningioma.

Dental X-rays

Table 2 shows the distribution of diagnostic dental X-rays and Table 3 the comparative frequencies of exposure amongst the three study groups. If the "missing" and "within 2 years" categories are omitted, recalculation of Table 2 yields 46% of glioma subjects and 68% of meningioma subjects vs. 61% of controls every having at least one dental X-ray. The estimated relative risk for glioma, adjusted for age and sex, was 0.42 (95% C.I: 0.24–0.76, $P=0.004$). Again, the result was similar when analysis was restricted to those subjects having direct (non-proxy) and good quality interviews: $RR=0.38$ (95% C.I.: 0.16–0.87; $P=0.02$). Sex-specific analyses (adjusted for age) showed no heterogeneity of effect.

The estimated relative risk for meningioma, adjusted for age and sex, was 1.37 (95% C.I.: 0.68–2.73, $P=0.38$). Amongst females (80% of meningioma subjects in our study), the age adjusted relative risk for meningioma was 0.86 (95% C.I.: 0.40–1.85, $P=0.69$). All males with meningioma had been exposed to dental X-rays, preventing estimation of the adjusted relative risk for this group. 10 of 10 male meningioma subjects compared with 106 of 176 (60%) male controls had been exposed (Fisher's exact $P=0.01$; lower limit of exact 95% C.I. = 1.42).

Analysis comparing those who had been exposed at least once before the age of 25 with those never exposed showed a similar pattern in glioma: age- and sex-adjusted $RR=0.42$ (95% C.I.: 0.19–0.93; $P=0.03$). For meningioma, age- and sex-adjusted $RR=0.49$ (95% C.I.: 0.16–1.56; $P=0.17$).

Numbers were too few to assess any trend associated with frequency of exposure to X-rays before the age of 25. After age 25, no trend was evident for glioma.

Panoramic (Panorex) or full-mouth dental X-rays

Table 4 shows the distribution of panoramic or full-mouth X-rays amongst the diagnostic groups. After exclusion of subjects with missing values for exposure and of those whose only exposure was within 2 years of diagnosis or interview, recalculation of Table 4 yields 7% of glioma subjects and 5% of meningioma subjects vs. 4% of controls ever having these types of dental X-ray. The estimated relative risk for glioma, adjusted for age and sex, was 1.98 (95% C.I.: 0.72–5.39, $P=0.18$). Again no difference in effect between sexes was noted. Analysis restricted to good quality, direct interviews gave adjusted $RR=2.72$ (95% C.I.: 0.86–8.72; $P=0.09$).

These analyses reflect comparison against a baseline group who were unexposed to panoramic or full-mouth X-rays, but may have been exposed to ordinary dental X-rays. (No subject exposed to panoramic X-rays was unexposed to ordinary X-rays). However, as we have seen, those subjects exposed to ordinary X-rays in this relatively large baseline group enjoy a diminished risk of glioma, thus explaining the elevated risk for panoramic exposure. Construction of a comparison group consisting of subjects who were unexposed to panoramic but who were exposed to ordinary dental X-rays might be expected to increase this apparent effect, and this is seen to be the case (see Table 5). Conversely, construction of a comparison group consisting of subjects unexposed to any form of dental X-rays might be expected to eliminate this effect, if the true risk in the population was not elevated. The adjusted risk, relative to this new unexposed group, is 1.07 (95% C.I.: 0.33–3.43; $P=0.91$).

No important effect was seen for meningioma. As reflected in the width of confidence intervals, all these estimated risks for panoramic X-rays are based on small numbers.

Table 5. Estimated risks of glioma, adjusted for age and sex, for (i) categories of number of amalgam fillings, relative to subjects with no history of fillings; (ii) exposure to ordinary dental X-rays, relative to subjects never exposed; and (iii) exposure to panoramic dental X-rays, relative to three different comparison groups; Adelaide Adult Brain Tumour Study 1987–1990. Entries show adjusted relative risks (RR), asymptotic 95% confidence intervals and P values from unconditional logistic regression models

	Glioma			Meningioma		
	OR	95% C.I.	*P* value	OR	95% C.I.	*P* value
(i) Amalgam						
No fillings	1.00			1.00		
At least 1	0.47	0.25–0.91	0.02	1.04	0.43–2.47	0.94
1–5*	0.53	0.23–1.23	0.14	1.36	0.49–3.79	0.56
6–9	0.25	0.09–0.68	0.01	0.52	0.15–1.82	0.31
10–13	0.38	0.15–0.96	0.04	0.98	0.34–2.88	0.97
14+	0.55	0.25–1.23	0.15	0.78	0.27–2.28	0.65
(ii) X-rays†						
No X-rays	1.00			1.00		
At least 1	0.42	0.24–0.76	<0.01	1.37	0.68–2.73	0.38
age < 25 years‡	0.42	0.19–0.93	0.03	0.49	0.16–1.54	0.21
(iii) Panoramic X-rays						
Comparison group: panoramic(−); ordinary dental X-rays (±)§						
At least 1	1.98	0.72–5.39	0.18	1.13	0.30–4.20	0.86
age < 25 years‡	2.18	0.53–9.08	0.28		Not estimable	
Comparison group: panoramic(−); ordinary dental X-rays(+)						
At least 1	2.73	0.94–7.90	0.07	1.18	0.32–4.43	0.80
age < 25 years‡	2.31	0.51–10.4	0.28		Not estimable	
Comparison group: panoramic(−); ordinary dental X-rays(−)						
At least 1	1.07	0.33–3.43	0.91	0.65	0.12–3.50	0.61‖
age < 25 years‡	1.00	0.19–5.27	1.00		Not estimable	

*Categories formed from approximate quartiles of control distribution after exclusion of nil (reference category), within and missing categories.
†See text for discussion of sex-specific results.
‡Subject exposed to at least one X-ray before the age of 25.
§(−) = unexposed to this type (+) = exposed at least once (±) = may or may not have been exposed.
‖Adjusted by age for females only; covariate pattern prevented convergence for model with both sexes.

DISCUSSION

We found a diminished risk for glioma associated with mercury-containing amalgam fillings. Further adjustment for social class and other factors, in addition to age and sex, did not eliminate this effect. It may be that certain important and unknown cofounders were unmeasured, or that a recall bias was operating such that glioma subjects underestimated the presence and number of fillings. As it was not possible in the case of proxy interviews, the study interviewer did not physically check on the presence or absence of amalgam fillings at the time of interview but adhered to the protocol and asked the prescribed questions only. Old dental records were not sought.

Our results show no excess risk for glioma associated with exposure to diagnostic dental X-rays; again, if anything, there is a diminished risk, which persists on adjustment for other factors. Our results may be due to chance, a recall or other bias (although this process, if it does exist, must be operating differently in meningioma subjects), or due to some confounding factor(s) unadjusted for in our analysis. However, we have repeated analyses with a wide variety of potential confounders, including an index of socio-economic status, smoking, alcohol and lifestyle habits, aspects of medical history, and exposure to other forms of radiation, without materially altering the results. It seems unlikely that a biological mechanism exists for such a "protective" effect associated with dental X-rays: an unexplained bias would seem most likely.

Although numbers are small, a statistically significant increased risk associated with dental X-rays is seen for meningioma in males, though not in females.

Preston–Martin *et al.* [4] found that risk increased for both glioma and meningioma with frequency of any dental X-rays prior to age 25. Frequency of dental irradiation in the United States may well differ from practice in Australia; in our study, data from the more frequent exposure categories were insufficient to draw conclusions. Burch *et al.* [5] reported a non-significant minor elevation in risk for glioma in those ever exposed to dental X-rays ($RR = 1.25$; $P = 1.0$).

For panoramic or full-mouth X-rays, no effect is seen for meningioma, but a statistically non-significant doubling of risk is seen for glioma. This increased risk persists on adjusting for age and sex and when analysis is restricted to the most reliable interviewees. However, the risk is eliminated by the choice of a comparison group completely unexposed to any type of dental X-ray.

As pointed out earlier, this comparison-group-dependent effect is probably a reflection of the unexplained "protective" effect seen for dental X-rays in general. Preston–Martin *et al.* have reported increases in risk, especially for subtentorial meningioma, in both women [2] and men [3], associated with young age at first exposure to multiple full-mouth X-rays prior to 1945, when X-ray doses were relatively high.

In summary, with the exception of an increased risk for meningioma in males due to dental X-rays, we have found no evidence for concern relating exposures to mercury amalgam

fillings, ordinary dental X-rays and panoramic or full-mouth X-rays to subsequent development of cerebral tumours.

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