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SHORT REPORT

Parental smoking and risk of childhood brain tumours

Short title: Parental smoking and CBT

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Abbreviations: CBT: childhood brain tumors, OR: odds ratio, CI: confidence interval, CD: collection district, IRSD: Index of relative socioeconomic disadvantage, RDD: random digit dialling, PNET: primitive neuroectodermal tumor.

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Novelty and impact of paper:

In our national study of childhood brain tumors, we used a novel method to measure parental smoking. Parents were asked about annual smoking quantity, with recall anchored to occupational and residential history to reduce bias. Overall, parents' smoking was not related to brain tumour risk, but the OR for maternal smoking during pregnancy was consistent with a four-fold increase in risk among children aged under 2 years, suggesting a possible association with early childhood tumours.

Abstract = 245

Childhood brain tumors (CBT) are the leading cause of cancer death in children, yet their etiology remains largely unknown. Tobacco smoke contains 61 known carcinogens and increases the risk of several adult cancers. This study investigated associations between parental smoking and risk of CBT in a population-based case-control study conducted between 2005 and 2010. Cases were identified through all 10 Australian paediatric oncology centres, controls via nationwide random-digit dialling, frequency matched to cases on age, sex and state of residence. Parental smoking information was obtained for 302 cases and 941 controls through mailed questionnaires that requested average daily cigarette use in each calendar year from age 15 to the child's birth, linked to residential and occupational histories. Data were analysed using unconditional logistic regression, adjusting for frequency matching variables and potential confounders. Overall, parental smoking before or during pregnancy showed no association with CBT risk. The odds ratios for maternal smoking before and during pregnancy were 0.99 (95% CI: 0.70, 1.40) and 0.89 (95% CI: 0.61, 1.21) respectively, and those for paternal smoking before and during pregnancy were 0.99 (95% CI: 0.71, 1.38) and 1.04 (95% CI: 0.74, 1.46) respectively. In children under 24 months of age, the odds ratios for maternal smoking preconception and during pregnancy were 5.06 (95% CI 1.35-19.00) and 4.61 (95% CI: 1.08, 19.63), although these results were based on modest numbers. Future studies should investigate the associations between maternal smoking and risk of CBT by the child's age of diagnosis.

Introduction

Childhood brain tumors (CBT) are the leading cause of cancer death in children, and apart from a few genetic syndromes and ionising radiation, their etiology is largely unknown. A range of environmental factors have been investigated as potential risk factors, but most of the findings have been inconclusive.[1]

Tobacco smoke contains 61 known carcinogens and is considered to increase the risk of adult cancers including lung, oro-pharyngeal, pancreatic and renal cancers.[2] The results of previous studies of maternal smoking and CBT risk have been inconsistent. While most early studies, including a 1996 review[3] and a 2002 meta-analysis,[4] concluded there was no evidence of associations with maternal smoking before pregnancy and during pregnancy, moderately increased risks with smoking before[5] pregnancy and during pregnancy[6] have recently been reported.. In addition, Schuz and co-workers reported positive associations between maternal smoking during pregnancy and risk of ependymoma and medulloblastoma, but not astrocytoma[7] but other relatively recent studies have reported null results.[8-10] Previous studies of paternal smoking and risk of CBT have also produced inconsistent results; two studies published after the review by Norman and colleagues[3] reported positive associations,[8, 11] while six reported no association.[5, 7, 12-15]

These inconsistent findings could be partly due to differences in study design and the way parental smoking histories were obtained and quantified; and, perhaps to lack of investigation of disease subtypes in some studies.[4] Here we present results from our Australian case-control study, in which detailed smoking histories were obtained from both parents, and associations within CBT subtypes were examined.

Methods

The Australian Study of Childhood Brain Tumours (Aus-CBT) was a national population-based case-control study conducted between 2005 and 2010. The study design has been described previously.[16] Briefly, incident cases were identified through all 10 Australian pediatric oncology centers where most CBTs are treated. Cases were eligible for inclusion if they were resident in Australia and had a biological parent available with adequate English skills to complete the questionnaires. Cases diagnosed in 2005 were recruited retrospectively, while 2006-2010 cases were recruited as soon as possible after diagnosis. Controls were recruited by national random digit dialing (RDD) between 2005 and 2010, and frequency matched to cases by age (within 1 year), sex and state of residence in a ratio of approximately

3:1. The RDD method has been described in detail elsewhere.[17] Aus-CBT was approved by the Human Research Ethics Committees at all participating hospitals.

Questionnaires mailed to parents asked about demographic characteristics, medical histories, engagement in activities involving potential exposure to carcinogens and diet. Parents were asked to indicate the average number of cigarettes smoked per day (CPD) in each calendar year from age 15 until the year after the index child's birth along with their residential address and occupation in each year. Smoking data were referenced to the child's birth year so that smoking during critical periods relating to the pregnancy could be determined. Smoking during pregnancy was defined as smoking during the birth year (if the child was born in or after May) or during the year before the birth year (if the child was born before May). Preconception smoking was defined as smoking in the year before the birth (for births in or after May) or in the year two years before the birth (for births before May). We also investigated whether parental ever smoking, former smoking or pack-years of smoking were associated with CBT risk. In addition to parent-reported measures of socio-economic status (SES), each participant's address was linked to an Australian Bureau of Statistics (ABS) Census Collection District (CD). The ABS assigns each CD a score for its area-based Index of Relative Socio-Economic Disadvantage (IRSD) after each quinquennial census [http://www.ausstats.abs.gov.au/Ausstats/subscriber.nsf/0/D729075E079F9FDECA2574170011B088/$File/20390_2006.pdf].

Statistical analysis

Unconditional logistic regression was used to estimate odds ratios (ORs) for the association between parental smoking in specific time periods and risk of CBT. All analyses included the frequency matching variables age, sex and State of residence, and variables that met the classical definition of confounding; that is, they were associated with case/control status, and with smoking among control parents. The variables included on this basis were ethnicity, parental age, child's year of birth, household income and maternal alcohol consumption (for maternal smoking models). Interactions with child's age and parental alcohol consumption were tested by fitting interaction terms in the models. Subgroup analyses were undertaken by CBT subtype where there were sufficient cases.

Results

We were notified of 794 CBT cases, of whom 64 were ineligible (36 with no English-speaking parent, 23 non-residents, five with no biological parent available). Of the 730

eligible cases, 568 (77.8%) were invited to take part by a physician, while a physician chose not to invite the other 162 for medical or psychosocial reasons. Parents of 374 cases consented (65.8% of invited, 51.2% of eligible). Information on smoking was available for 302 (85.1%) case mothers and 247 (68.5%) case fathers, while 29 families provided only demographic information and 39 provided no data. Between 2005 and 2010, 3,624 families eligible to be controls were identified by RDD, of whom 2,255 (62.2%) agreed to participate. In accordance with our age and sex frequency-matching quotas, we recruited 1,467 of these children to the study. Information on smoking was available for 941 control mothers (69.0% of recruited) and 801 control fathers (58.8% of recruited), while 413 families provided only demographic data and 104 families provided no data.

Demographic and other characteristics of cases and controls who provided at least some data were similar, with some exceptions (Table 1). Controls were slightly more likely than cases to be female, have a mother aged over 35 years and have European ethnicity. A higher proportion of controls than cases were recruited in 2005-2006, as controls from our national leukemia study were frequency matched to CBT cases diagnosed in those years. The use of the 2005 and 2006 leukemia study controls also resulted in a higher percentage of controls than cases born between 1998 and 2003. Thus, the child's age and year of recruitment were related.

Both cases and controls lived in more socially advantaged CDs than the Australian population as a whole. The mean IRSD scores were 1025.3 for case CDs, 1030.5 for control CDs, and 1006.0 for all Australian CDs (t-test P-values: 0.33 for case vs control CDs and <0.001 for both case and control CDs vs all Australian CDs) (data not shown in tables). These findings are consistent with the observation that income and education were comparable among cases and controls (Table 1).

Overall, 22% of mothers smoked preconception, 16.8% of mothers smoked during pregnancy, 29% of fathers smoked in the preconception year and 26% of fathers smoked during the pregnancy. Paternal smoking in both periods was moderately correlated with maternal smoking during pregnancy: Spearman's $\rho = 0.36$, $P < 0.001$. Overall, there was little evidence that maternal or paternal smoking was associated with risk of CBT (Table 2). Although the ORs for paternal smoking 1-14 CPD in both periods were around 1.3, the estimates lacked precision due to a relatively small number of smokers, and the ORs for higher levels of smoking were below the null. The results were similar when parental smoking was mutually adjusted, when the analysis was restricted to children whose other parent did not smoke (data

not shown), and when the reference level was changed to 'no smoking from 2 years before the birth year' for mothers, and 'no smoking ever before the birth' for the fathers (data not shown). The OR for maternal smoking during pregnancy and paternal smoking in the preconception year was 0.87 (95% CI: 0.50, 1.50). No evidence was seen for associations with ever smoking, ex-smoking, or increasing pack-years for either parent (results not shown).

When stratified by the child's age at diagnosis or recruitment, the ORs for maternal smoking, both preconception and during pregnancy, were high for CBT diagnosed under 24 months of age, although this was based on small numbers (Table 3). There was no evidence of a similar age-interaction for paternal smoking (Table 3). There was no evidence of an interaction between parental smoking and alcohol consumption (data not shown).

For low grade gliomas, the ORs for maternal smoking during pregnancy and paternal smoking preconception were 1.02 (95% CI 0.62, 1.67) and 1.02 (95% CI 0.66, 1.60) respectively (results not shown in tables). For PNET/medulloblastoma, the ORs were 0.82 (95% CI 0.39, 1.70) and 0.90 (95% CI 0.47, 1.70) for mother and father respectively. Other subtypes had insufficient numbers to analyse separately. There were insufficient numbers to investigate any interaction between smoking and child's age within CBT subtypes.

Discussion

Overall, neither maternal nor paternal smoking before or during pregnancy was associated with an increased risk of CBT; these findings are consistent with most previous reports, as summarised in the introduction. There was an indication that maternal smoking before or during pregnancy was associated with an increased risk of CBT in infants (less than 24 months old), but this was based on a small number of cases and could be due to chance.

Two previous studies also reported some variation in the association between maternal smoking during pregnancy and CBT risk by the child's age. A Swedish cohort study[6] reported an increased risk of CBT among children aged between 2 and 4 years (OR 1.64, 95% CI: 1.15, 2.33), but found little or no evidence of an association at other ages; and a Californian study[18] reported ORs of 0.68 (95% CI: 0 43, 1.1) for CBT among children younger than 6 years, and 1.1 (95% CI: 0.73, 1.6) among older children. No formal assessment of the age by smoking interactions was reported in these papers. Three additional studies reported no differences in associations by age.[7, 15, 19] Only one previous study investigated possible effect modification by alcohol use;[20] no modification of the overall null association with smoking was observed. The reasons for the inconsistencies among previous studies of parental

smoking are not clear, but may be due to a combination of factors: different windows of exposure, dose categories and distributions of CBT subtypes; use of proxy respondents, measurement error, recall bias and lack of investigation of age-specific associations.

An increased risk of CBT among infants associated with maternal smoking during pregnancy is biologically plausible. Chemicals found in tobacco smoke – including neurocarcinogens – can cross the placenta[21] and cause chromosomal damage in the fetus.[22] Animal studies have shown that the developing brain is much more likely to develop tumors as a result of exposure to neurocarcinogens *in utero* than later in life,[23] and this may also be the case for humans. Hence, it is plausible that tumors initiated through tobacco-induced damage to the fetal brain would manifest themselves relatively early in life. This is consistent with our finding that maternal smoking appeared to be associated with CBT risk only among very young children.

Almost 78% of eligible cases were invited to participate by the treating clinician and 66% of invited parents consented, resulting in an overall participation fraction of 51%. Except for age and sex, where the distributions were similar to participating cases, information about eligible cases who did not participate was unavailable, so we could not determine whether our cases were representative of all eligible cases with respect to potential risk factors. Control families were recruited by national RDD using state-of-the-art methods and, according to the most recent data available, approximately 90% of Australian households had a landline telephone connection during the recruitment period [http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1367.5Sep%202008]. Therefore, residences contacted are likely to be representative of the wider population. Telephone-based methods have been evaluated and shown to perform well in Australia for control subject recruitment, compared with other methods,[24] and RDD is likely to be the best and most cost-effective method available.

Participation among eligible control families was 62% and, although no individual information was available for those who declined, area-based SES scores were higher among participating controls than among the wider Australian population. However, importantly, participating cases and controls had very similar SES distributions.

Information about smoking was provided by approximately 81% case and 64% control mothers, and 66% case and 55% control fathers. Selection bias is possible since control parents who provided smoking data lived in areas with (on average) higher IRSD scores than those who did not; thus, they may have a lower prevalence of smoking. However, the

prevalence of smoking during pregnancy among our control mothers (16.8%) was similar to New South Wales Midwives data (population-based surveillance system) for birth years 1995-2007 (17.2%)[25], suggesting that they are representative of the general population with respect to smoking. Further, the most likely consequence of selection bias due to the over-representation of higher SES controls would be inflated ORs for smoking; if this has occurred, then the true ORs for smoking would be even further below the null, which seems unlikely. All analyses were adjusted for household income and further adjustment for IRSD or education did not alter the effect estimates.

Our questionnaires were designed to reduce measurement error by 'anchoring' parents' recall of smoking to their residence and occupation in each year. Nonetheless, it is plausible that smoking was recalled less accurately by parents of older children (where the index pregnancy was further in the past). However, why the ORs among older children tended to be below unity is not clear, as parental smoking is unlikely to be protective against CBT among children of any age, and there is little reason to believe that recall of smoking among parents of older controls would be more complete than among parents of older cases. Given these results, it is reasonable to infer that the increased ORs observed for infants are not solely due to bias resulting from over-reporting of smoking among the parents of infant cases.

In summary, this study provides little evidence that parental smoking in the preconception or pregnancy period is associated with an increased risk of CBT, except possibly among infant children of smoking mothers. We recommend that future studies investigate the associations between maternal smoking and risk of CBT by the child's age of diagnosis.

Consortium statement

The Aus-CBT consortium conducted the study and the Telethon Institute for Child Health Research (TICHR), University of Western Australia, was the coordinating centre. Bruce Armstrong (Sydney School of Public Health, University of Sydney), Elizabeth Milne, Nicholas de Klerk, Caroline Bower, Peter Dallas (TICHR), Frank van Bockxmeer (Royal Perth Hospital, University of WA), Rodney Scott and John Attia (University of Newcastle), Lin Fritschi (WA Institute for Medical Research), Lesley Ashton, Michelle Haber and Murray Norris (Children's Cancer Institute Australia for Medical Research, Lowy Cancer Research Centre, UNSW), Margaret Miller (Edith Cowan University) and Judith Thompson (WA Cancer Registry) were the research investigators.

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Table 1: Distribution of demographic and birth characteristics in the Australian Study of Childhood Brain Tumors, 2005-2010.

Variable	Category	Case n	Case %[a]	Control n	Control %[a]
Provided demographic data		335		1363	
Mother returned exposure questionnaire		302		941	
Father returned exposure questionnaire		247		801	
Child gender	Female	122	40.4	445	47.3
	Male	180	59.6	496	52.7
Child age group	0-1	30	9.9	110	11.7
	2-4	85	28.1	303	32.2
	5-9	89	29.5	293	31.1
	10-14	98	32.5	235	25.0
Child state residence[b]	NSW/ACT	102	33.8	283	30.1
	Victoria/Tasmania	85	28.1	251	26.7
	SA/NT	19	6.3	77	8.2
	Western Australia	42	13.9	112	11.9
	Queensland	54	17.9	218	23.2
Birth year	1990-1997	84	27.1	223	23.7
	1998-2003	125	41.4	469	49.8
	2004-2010	93	30.8	249	26.5
Year of diagnosis/ Recruitment	2005-2006	107	35.4	415	44.1
	2007-2008	99	32.8	268	28.5
	2009-2010	96	31.8	258	27.4
Maternal age group	≤24	45	14.9	87	9.2
	25-34	187	61.9	593	63.0
	35+	70	23.2	261	27.7
Paternal age group	<24	15	5.6	26	3.3
	25-34	151	56.8	434	54.6
	35+	100	37.6	335	42.1
Best parental education	Didn't complete secondary school	42	13.9	91	9.7
	Complete secondary school and/or trade certificate	99	32.8	301	32.0
	University/College	161	53.3	549	58.3
Household income	Up to $40, 000	49	16.3	127	13.6
	$40, 001-$70,000	78	26.0	262	28.0
	$70,001-$100,000	80	26.7	249	26.6
	>$100, 000	93	31.0	299	31.9
Birth order	1	138	45.7	399	42.4
	2	98	32.5	326	34.6
	3+	66	21.9	216	23.0
Ethnic group[c]	European	185	61.3	679	72.2
	At least 50%	73	24.2	170	18.1

	European				
	At least 50% non-European	12	4.0	30	3.2
	Indeterminate	32	10.6	62	6.6
Tumor diagnosis	Low grade gliomas	144	47.7		
	High grade gliomas	26	8.6		
	Embryonal tumors[d]	71	23.5		
	Germ cell tumors	20	6.6		
	Ependymomas	22	7.3		
	Others[e]	19	6.3		

[a] Percentages are of participants whose mother returned the exposure questionnaire.
[b] ACT: Australian Capital Territory; NSW, New South Wales; NT, Northern Territory; SA, South Australia.
[c] European, at least 3 European grandparents; 50% European, 2 European grandparents; at least 50% non-European, 2 non-European grandparents and ethnicity of 2 other grandparents non-European or unknown; indeterminate, no 2 grandparents of same ethnicity (i.e European or non-European) and 2+ grandparents of unknown ethnicity.
[d] Includes 46 medulloblastomas, 22 primitive neuroectodermal tumors, 3 atypical teratoid rhabdoid tumors.
[e] Includes 6 meningiomas, 9 choroid plexus tumors, 4 unclassified.

Table 2: Association between parental smoking before and during the pregnancy and risk of childhood brain tumors

	Case n	%	Control n	%	OR	95% CI
Maternal smoking preconception[a]						
None	228	76.0	731	78.0	1.00	Referent
1-14 CPD	41	13.7	101	10.8	1.16	0.76, 1.78
15+ CPD	31	10.3	105	11.2	0.82	0.52, 1.31
Any	72	24.0	206	22.0	0.99	0.70, 1.40
P-value for dose trend						0.61
Maternal smoking during pregnancy[a]						
None	249	83.0	780	83.2	1.00	Referent
1-14 CPD	28	9.3	85	9.1	0.91	0.56, 1.47
15+ CPD	23	7.7	72	7.7	0.88	0.52, 1.49
Any	51	17.0	157	16.8	0.89	0.61, 1.31
P-value for dose trend						0.57
Paternal smoking preconception[b]						
None	168	69.4	568	71.9	1.00	Referent
1-14 CPD	32	13.2	71	9.0	1.31	0.82, 2.11
15+ CPD	42	17.4	151	19.1	0.83	0.55, 1.24
Any	74	30.6	222	28.1	0.99	0.71, 1.38
P-value for dose trend						0.54
Paternal smoking during pregnancy[b]						
None	171	70.7	588	74.4	1.00	Referent
1-14 CPD	29	12.0	65	8.2	1.30	0.79, 2.13
15+ CPD	42	17.3	137	17.4	0.92	0.61, 1.38
Any	71	29.3	202	25.6	1.04	0.74, 1.46
P-value for dose trend						0.85

[a] Adjusted for matching variables, child's ethnicity, year of birth group, mother's age group, alcohol consumption during pregnancy, household income.
[b] Adjusted for matching variables, child's ethnicity, year of birth group, father's age group, household income.

Table 3: Parental smoking stratified by child's age at diagnosis or recruitment

Age	Smoking	n Case/Controls	OR	95% CI	P-value of Interaction
Maternal smoking preconception [a]					
0-1	None	20/93	1.00	Referent	0.09
	Any	10/17	5.06	1.35, 19.00	
2-4	None	65/241	1.00	Referent	
	Any	20/60	1.34	0.69, 2.60	
5-9	None	71/226	1.00	Referent	
	Any	18/67	0.78	0.39, 1.54	
10-14	None	72/171	1.00	Referent	
	Any	24/62	0.61	0.32, 1.16	
Maternal smoking during pregnancy [a]					
0-1	None	23/98	1.00	Referent	0.10
	Any	7/12	4.61	1.08, 19.63	
2-4	None	71/251	1.00	Referent	
	Any	14/50	1.00	0.48, 2.07	
5-9	None	79/244	1.00	Referent	
	Any	10/49	0.60	0.26, 1.35	
10-14	None	76/187	1.00	Referent	
	Any	20/46	0.73	0.36, 1.47	
Paternal smoking preconception [b]					
0-1	None	20/80	1.00	Referent	0.25
	Any	6/24	1.11	0.29, 4.20	
2-4	None	47/190	1.00	Referent	
	Any	28/68	1.45	0.79, 2.68	
5-9	None	54/176	1.00	Referent	
	Any	19/69	0.74	0.38, 1.44	
10-14	None	47/122	1.00	Referent	
	Any	21/61	0.75	0.39, 1.44	
Paternal smoking during pregnancy [b]					
0-1	None	20/82	1.00	Referent	0.26
	Any	6/22	1.48	0.39, 5.65	
2-4	None	49/198	1.00	Referent	
	Any	26/60	1.61	0.86, 3.01	
5-9	None	55/182	1.00	Referent	
	Any	18/63	0.75	0.38, 1.49	
10-14	None	47/126	1.00	Referent	
	Any	21/57	0.82	0.43, 1.60	

[a] Adjusted for matching variables, child's ethnicity, year of birth group, mother's age group, alcohol consumption during pregnancy, household income.

[b] Adjusted for matching variables, child's ethnicity, year of birth group, father's age group, household income.