Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy and childhood malignant central nervous system tumours: the ESCALE study (SFCE).

Matthieu Plichart, Florence Menegaux, Brigitte Lacour, Olivier Hartmann, Didier Frappaz, François Doz, Anne-Isabelle Bertozzi, Anne-Sophie Defaschelles, Alain Pierre-Kahn, Céline Icher, et al.

Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy and childhood malignant central nervous system tumours: the ESCALE study (SFCE*)

Short Title: Smoking, alcohol, coffee, tea and childhood CNS tumours

Matthieu Plichart[1,2], Florence Menegaux[1,2], Brigitte Lacour[1,2,3], Olivier Hartmann[4], Didier Frappaz[5], François Doz[6], Anne-Isabelle Bertozzi[7], Anne-Sophie Defaschelles[8], Alain Pierre-Kahn[9], Céline Icher[10], Pascal Chastagner[11], Dominique Plantaz[12], Xavier Rialland[13], Denis Hémon[1,2], Jacqueline Clavel[1,2,14]

[1]INSERM, U754, Villejuif, France. [2]Univ Paris-Sud, UMR-S754, IFR69, Villejuif, france[3]Registre National des Tumeurs solides de l'Enfant, Nancy, France. [4]Institut Gustave Roussy, Villejuif, France. [5]Centre Léon Bérard, Lyon, France. [6]Institut Curie, Paris, France. [7]Hôpital des Enfants, Toulouse, France. [8]Centre Oscar Lambret, Lille, France. [9]Hôpital des Enfants Malades, Paris, France. [10]Hôpital Pellegrin Tripode, Bordeaux, France. [11]Hôpital d'Enfants, Vandoeuvre les Nancy, France. [12]Service de Pédiatrie, Grenoble, France. [13]CHU D'Angers, France. [13]Registre National des Hémopathies Malignes de l'Enfant

*SFCE: Société Française de lutte contre les Cancers de l'Enfant et de l'Adolescent

This work was supported by grants from INSERM, the Fondation de France, the Association pour la Recherche contre le Cancer (ARC), the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), the Agence Française de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET) and the association 'Cent pour sang la vie'.

Corresponding author:
Dr. Florence Menegaux
INSERM U754
16, av. Paul Vaillant-Couturier
F-94807 VILLEJUIF Cedex
Tel: 33 1 45 59 51 53
Fax: 33 1 45 59 51 91
E-mail: menegaux@vjf.inserm.fr

This is a non-final version of an article published in final form in Eur J Cancer Prev. 2008 Aug;17(4):376-83.

Abstract

Objectives: Parental smoking and maternal alcohol and caffeinated beverage consumption are prevalent exposures which may play a role, either directly or through their influence on metabolism, in the aetiology of childhood malignant Central Nervous System (CNS) tumours. The hypothesis was investigated in the ESCALE study, a national population-based case-control study carried out in France in 2003-2004.

Methods: The study included 209 incident cases of CNS tumours and 1681 population-based controls, frequency matched with the cases by age and gender. The data were collected through a standardized telephone interview of the biological mothers.

Results: No association between maternal smoking during pregnancy and CNS tumours (OR = 1.1 [0.8-1.6]) was observed. Paternal smoking during the year prior to birth was associated with CNS tumours (p for trend = 0.04), particularly astrocytomas (OR = 3.1 [1.3-7.6]). Maternal alcohol consumption during pregnancy was not associated with CNS tumours. Associations between ependymomas and the highest consumption of coffee (OR = 2.7 [0.9-8.1]) and tea (OR = 2.5 [1.1-5.9]) were observed. A strong association between CNS tumours and the highest maternal consumption of both coffee and tea during pregnancy was observed (OR = 4.4 [1.5-13]).

Conclusions: The results constitute additional evidence for a role of paternal smoking and suggest that maternal coffee and tea consumption during pregnancy may also increase the risk of CNS tumours. The study does not suggest an increased risk of CNS tumours related to alcohol consumption during pregnancy.

Keywords: Child, Brain neoplasms, epidemiology, risk factor, smoking, alcohols, coffee, tea

Introduction

Central nervous system (CNS) tumours are the second most common pediatric cancer in developed countries. In France, the annual incidence rate is 29.1 per million children, equivalent to about 350 new cases per year (Desandes et al., 2004). Except for ionizing radiation and a few rare genetic factors, the aetiology of CNS tumours remains largely unknown (Baldwin and Preston-Martin, 2004). The central nervous system is more vulnerable to carcinogens early in life and the relatively young age at onset suggests that prenatal and early post-natal exposures may be considered potential risk factors (Rice and Wilbourn, 2000). Pre-conception exposure of germ cells to carcinogens, especially in the father, is also suspected of being related to an excess of tumours in the offspring (Anderson et al., 2000). The influence of exposure to tobacco smoke on the risk of CNS tumours has been investigated in numerous studies and a recent review has summarized the epidemiologic evidence (Baldwin and Preston-Martin, 2004). While no or a limited association has been found with maternal smoking during pregnancy, there is some evidence for an association between CNS tumours and pre-conception paternal smoking. Maternal alcohol and caffeinated beverage consumption during pregnancy have been shown to be associated with other childhood cancers, especially childhood leukaemia (Severson et al., 1993 ; Van Duijn et al., 1994 ; Shu et al., 1996 ; Ross et al., 1998 ; Menegaux et al., 2005 ; Menegaux et al., 2007). For childhood CNS tumour, those factors have been less investigated. No consistent association with maternal alcohol drinking during pregnancy has been detected for childhood CNS tumours (Little, 1999). However, two studies reported a link with maternal beer drinking during pregnancy (Howe et al., 1989 ; Bunin et al., 1993), supporting the hypothesis that N-nitroso compounds play a role. To the authors' knowledge, only two studies have investigated the role of maternal caffeinated beverage consumption during pregnancy with respect to childhood CNS tumours (Bunin et al., 1993 ; Bunin et al., 1994 ; Cordier et al., 1994). Neither reported a significant association.

The present paper analyzes the role of parental tobacco smoking and maternal alcohol and caffeinated beverage consumption during pregnancy with respect to childhood CNS tumours using data generated by the ESCALE study. The latter investigated the role of environmental and genetic factors with regard to the 4 most frequent types of childhood cancers: leukaemias, lymphomas, CNS tumours and neuroblastomas.

Patients and methods

Study population

Cases

Details of the study have been published elsewhere (Rudant et al., 2007). For the present analysis, the eligible cases comprised all children aged less than 15 years, residing in mainland France at the time of diagnosis of a primary malignant CNS tumour in 2003-2004. The tumours were defined as per the International Classification of Diseases for Oncology, third version (ICD-O-3). Investigators, assigned to each French pediatric oncology hospital department, directly recruited CNS tumour cases with the support of the French National Registry of Childhood Haematopoietic Malignancies (NRCH) (Clavel et al., 2004) and the French National Registry of Childhood Solid Tumours (NRCST) (NRCST website). Adopted children (5 cases) and children whose mother did not speak French (14 cases) or had a serious psychiatric disorder (5 cases) were not eligible. For ethical reasons, children who had died or were receiving palliative care before the inclusion date (58 cases) were not eligible either. Out of the 343 cases identified, 261 were eligible, 19 of them refused to participate and 33 could not be contacted by the interviewers. Thus, 209 (80%) incident cases classified as malignant CNS tumours (/3 behaviour) according to ICD-O-3 were included and grouped using the International Classification of Childhood Cancer (Steliarova-Foucher et al., 2005). The cases consisted of 100 cases (48%) of embryonal tumour (ICD-O-3 codes 9470/3, 9471/3, 9473/3, 9474/3, 9480/3, 9508/3), 33 cases (16%) of ependymoma (9390/3-9393/3), 26 cases (12%) of astrocytoma (9380/3, 9400/3, 9420/3, 9424/3, 9440/3) and 45 cases (21%) of other glioma (9380/3, 9382/3, 9430/3, 9450/3, 9451/3). The remaining cases were distributed as follows: 3 (2%) not otherwise specified tumours and 2 (1%) otherwise specified tumours.

Controls

A random sample of French children (up to age 14 years) was obtained from a representative list of 60,000 addresses provided by the French national telephone company, enriched by random generation of unlisted phone numbers. Quotas were designed a priori to make the control group representative of, first, all cases of childhood cancer (leukaemia, lymphoma, neuroblastoma and central nervous system tumour) in terms of age and gender, and, secondly, the French population with regard to the number of children under 15 years of age living in the household. Out of the 50,217 phone numbers dialed, 46,994 were non-eligible numbers (22,584 businesses or inactive numbers, 18,456 households without children, 5,277 outside of the quotas, 677 unreliable interviews). The eligibility of 862 phone numbers could not be determined. Finally, out of the 2361 children who were eligible as controls, 1681 (71%) were included in the study (679 parents refused and 1 child had a prior history of neuroblastoma).

Data collection

Trained interviewers conducted telephone interviews with the biological mothers of the cases and controls. The mean interview duration was 40 minutes. The standardized questionnaire sought information on demographic and socioeconomic characteristics, parental occupational history, parental lifestyle, family and personal medical history, history of pregnancy and childhood environment. The present study particularly focused on parental tobacco smoking and maternal alcohol and caffeinated beverage consumption. Mothers were asked whether they had ever smoked or drunk alcohol, coffee, tea, chocolate or cola during pregnancy. If so, further questions were asked to elicit the daily or weekly amount consumed, for each of the items. The period of interest for paternal smoking was the year prior to the index child's birth.

Statistical analyses

The SAS® software package (version 9.1, Cary, North Carolina) was used for all the analyses. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by non-conditional logistic regression for all CNS tumours, with systematic adjustment for the stratification variables, age and gender. Adjustment for potential confounding factors, such as the place of residence at the time of diagnosis, maternal and paternal educational level and socioeconomic category, was also conducted. The countries of birth of the 4 grand-parents were used as surrogates of ethnic origin (Europe, Africa / the Caribbean, Asia, North

Africa, mixed). Analyses of tumour histologic subgroups were conducted using polytomous regression models.

Results

Sample description

The cases and controls did not differ with respect to gender (Table 1). Since the age quotas for control selection had been defined so as to be representative of all types of cancer and not only of CNS cases, there was a small age discrepancy between the CNS cases and controls. However, the mean ages of the cases and controls were very similar (6.3 vs 6.0 years). There were at least 5 controls for each case in each age group. No significant difference between the cases and controls was observed with respect to parental educational level or socioeconomic category.

Parental smoking

No association between maternal smoking during pregnancy and CNS tumours in the children was detected (OR = 1.1 [0.8-1.6]). No association or trend with the number of cigarettes smoked per day was observed (Table 2).

Paternal smoking was associated with CNS tumours, and the ORs increased with the number of cigarettes smoked (< 20 cig/day: OR = 1.1 [0.8-1.6]; ≥ 20 cig/day: OR = 1.4 [1.0-2.1] ; $p_{\text{for trend}}$ = 0.04). When both the mother's and the father's smoking was considered, the OR was 1.3 [1.0-1.9] for only the father smoking, 1.6 [0.9-3.0] for only the mother smoking, and 1.2 [0.7-1.8] for both parents smoking.

None of the histological subgroups was significantly associated with maternal smoking during pregnancy, whereas paternal smoking of more than 20 cigarettes per day during the year prior to pregnancy was associated with astrocytoma (OR = 3.2 [1.2-9.1]) and ependymoma (OR = 2.6 [1.2-5.9]) (Table 3). In contrast, neither embryonal tumors nor other gliomas appeared to be linked to paternal smoking.

Maternal consumption of coffee and tea

There was no association between CNS tumours taken as a whole and consumption of caffeinated beverages by the mother during pregnancy (table 4). Slightly, but not significantly, increased ORs were associated with the highest consumptions of coffee (OR = 1.4 [0.8-2.4]) and tea (OR = 1.4 [0.9-2.1]). Higher ORs were observed for ependymoma, but the number of cases was small. The associations were more marked for the highest maternal consumptions of both coffee (>3 cups per day) and tea (>1 cup per day). Adjustment for maternal and paternal smoking did not change the results.

Maternal alcohol consumption during pregnancy

No association between CNS tumors and maternal consumption of any kind of alcohol during pregnancy was detected (OR = 0.9 [0.7-1.3]) (Table 5).

The results remained unchanged after adjusting for parental educational level and socioeconomic category.

Discussion

In this study, paternal smoking during the year prior to pregnancy was associated with CNS tumours, and the association was more pronounced for astrocytoma. On the whole, there was no significant association with maternal smoking during pregnancy, although a borderline association with maternal smoking in the absence of paternal smoking was found. Maternal alcohol consumption during pregnancy was not associated with childhood CNS tumours, while maternal coffee and tea consumption during pregnancy were significantly associated with CNS tumours and particularly with ependymomas.

The size of the present study enabled detection of minimum odds ratios of 1.5 and 1.6 for exposure prevalence in controls of 30 and 20%, respectively, i.e. of the same order of magnitude as those of maternal alcohol drinking during pregnancy or parental smoking.

The cases were identified through the data collection system of the French National Registries of Childhood Cancer (NRCH, NRCST), making selection of cases at the identification step unlikely. Cases who had died or were receiving palliative care were not eligible, which might have lead to survival bias. Nevertheless, we were able to compare the prevalence of parental smoking of 19 cases that died after their mothers' interviews with the prevalence of parental smoking of the survivors. The prevalence of parental smoking, either for maternal and paternal smoking, did not differ between the non-surviving and surviving children making a survival bias unlikely in the present study.

Eighteen percent of the eligible cases did not answer the questionnaire. However, the age and gender distributions were similar for the respondent and non-respondent cases.

The controls were randomly selected from the general population, based on the national telephone directory. Unlisted numbers were randomly generated in order to avoid the selection of controls with listed numbers.

There were no differences between the cases and controls with regard to gender or age (considering all the types of cancer covered by the ESCALE study), or between the controls and overall population, particularly with regard to birth order, number of children living in the household and socio-demographic characteristics, indicating that quota sampling was successful. The socioeconomic status and educational level of the control parents were very similar to those of the cases and the French population (Blondel et al., 1997 ; Blondel et al., 2006). Adjustments for those variables did not change the results. Additional adjusment for ethnic origin (countries of birth of the 4 grand-parents) of the index child did not change the results as well.

All the information was based on the child's mother's interview. The mothers could have misreported their smoking habits and those of the father. However, the number of cigarettes smoked by the control mothers was comparable to that of the French population (Blondel et al., 1997 ; Blondel et al., 2006), as was the number smoked by the control fathers (Guilbert P et al., 2005). The results are therefore unlikely to be explained by under-reporting of smoking by the controls. In addition, the case mothers may have under-reported their own smoking, leading to under-estimation of the association with maternal smoking. However, the results reported herein are consistent with 2 meta-analyses that found no association between CNS tumours and maternal smoking during pregnancy (Boffetta et al., 2000 ; Huncharek et al., 2002). One recent cohort study (Brooks et al., 2004) reported a significantly increased risk related to maternal smoking, but this association was found to be significant for low grade astrocytomas, which were not eligible in the present study, and not for malignant brain tumours. However, an association with maternal smoking during pregnancy cannot be completely ruled out, given the slightly increased OR with maternal smoking in the absence of paternal smoking observed herein.

Case mothers may have over-reported smoking by the father, which would explain the relationship with paternal smoking. However, the paternal smoking habits of the controls were very similar to those of the French population (Guilbert P et al., 2005). Moreover, several previous studies, that investigated paternal smoking by interviewing the father himself also found positive associations (McCredie et al., 1994 ; Ji et al., 1997 ; Fillipini et al., 2002 ; Cordier et al., 2004). Two meta-analyses estimated ORs of 1.22 [1.05-1.40] and 1.29 [1.07-1.53] for paternal smoking during pregnancy (Boffetta et al., 2000 ; Huncharek et al., 2001 ; respectively). Cordier et al. reported an increased risk of malignant astrocytoma among children whose father was exposed to PAH from smoking, before the conception (Cordier et al., 2004). In the study by McCredie et al., malignant brain tumours were associated with pre-conception paternal smoking and maternal exposure to side-stream smoke from the father during pregnancy (McCredie et al., 1994). Two biologically-plausible mechanisms have been proposed to explain those findings. A direct hypothesis, supported by both animal and human data (Baldwin and Preston-Martin, 2004), suggests an impact of pre-conception paternal germ-cell exposure. Spermatogenesis is a continuous process, with intense replication of DNA, making germ cells more vulnerable to mutagenic changes (Anderson et al., 2000). The second hypothesis suggests that paternal smoking may act through the mother's passive exposure to side-stream smoke during pregnancy. Biochemical studies showed that some constituents of environmental tobacco smoke may cross the placenta and interact with fetal DNA (Tredaniel et al., 1994 ; Anderson et al., 2000 ; Rice, 2004). However, the epidemiological data on this question are contradictory. Among the studies that explicitly addressed the role of passive exposure to tobacco smoke, some evidenced an association between CNS tumor and maternal exposure to side-stream smoke (Preston-Martin et al., 1982 ; McCredie et al., 1994 ; Filippini et al., 2002) while as many others did not (Kuijten et al., 1990 ; Cordier et al., 1994 ; Hu et al., 2000) . It is noteworthy that paternal smoking remains difficult to differentiate from maternal smoking. Similarly, there are strong correlations between pre-conception, gestational and post-natal maternal and paternal smoking that make it difficult to elucidate the actual exposure with certainty in the context of paternal pre-conception smoking. However, the literature has not reported any evidence of an association with passive smoking during childhood (Ji et al., 1997 ; Little, 1999 ; Filippini et al., 2002).

The present study did not generate any evidence of an association between alcohol consumption during pregnancy and malignant CNS tumours. Alcohol consumption is difficult to quantify by questionnaires, and an information bias may have occurred, even though its extent would have been reduced by the use of a detailed standardized questionnaire. Guilt feelings may have led the cases' mothers to minimize their alcohol consumption during pregnancy and the resulting recall bias may have masked an association. However, the bias is more likely to affect the dose-response relationship than the ever/never relationship. The literature on maternal alcohol drinking during pregnancy and CNS tumours is very limited and shows no consistent association. However, two studies evidenced that beer drinking during pregnancy was associated with CNS tumours (Howe et al., 1989) or with primitive neuroectodermal tumours (PNET) (Bunin et al., 1993). Beer is a known source of N-nitroso compounds (NOC), which are suspected to play a role in childhood brain tumours. In the present study, beer consumption was slightly, but not significantly, related to CNS tumours and particularly to PNET and other gliomas.

The results for maternal coffee and tea consumption raise some questions. A recall bias is unlikely given that there is no particular public concern with those habits. Wilkins et al. reported no differences between cases and controls for mothers recalling their own diet in a case-control study on childhood brain tumours (Wilkins and Bunn, 1997). Furthermore, associations with maternal consumption of coffee and tea during pregnancy were limited to ependymomas, which makes bias less likely. Cordier et al. found an increased OR associated with coffee (1.9 [0.9-3.9]), but nor with tea (0.7 [0.3-1.4]) (Cordier et al., 1994).

In conclusion, the findings reported herein constitute additional evidence for a role of paternal smoking during the year prior to birth in childhood CNS tumours. The results also suggest that maternal coffee and tea consumption may increase the risk of CNS tumours, directly or through an influence on the metabolism of unknown risk factors. Further investigations are needed in order to elucidate the role of those factors further and account for their possible synergy.

Acknowledgements: We are grateful to Marie-Hélène Da Silva and Christophe Steffen (INSERM, U754), who coordinated the recruitment of the cases; Sandra Guissou, Emmanuel Désandes and the staff of the French National Registry of Childhood Solid Tumours, who contributed to case detection and verification; Sabine Mélèze and Marie-Anne Noël (Institut CSA), who coordinated the selection of the controls and the interviews; Catherine Tricoche (Callson) and the team of interviewers, who interviewed the cases and the controls; and Andrew Mullarky for his skilful revision of the manuscript.

REFERENCES

Anderson LM, Diwan BA, Fear NT and Roman E (2000). "Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models." *Environ Health Perspect* **108 Suppl 3**: 573-594.

Baldwin RT and Preston-Martin S (2004). "Epidemiology of brain tumors in childhood--a review." *Toxicol Appl Pharmacol* **199**(2): 118-131.

Blondel B, Breart G, du Mazaubrun C, Badeyan G, Wcislo M, Lordier A, et al. (1997). "[The perinatal situation in France. Trends between 1981 and 1995]." *J Gynecol Obstet Biol Reprod (Paris)* **26**(8): 770-780.

Blondel B, Supernant K, Du Mazaubrun C and Breart G (2006). "[Trends in perinatal health in metropolitan France between 1995 and 2003: results from the National Perinatal Surveys]." *J Gynecol Obstet Biol Reprod (Paris)* **35**(4): 373-387.

Boffetta P, Tredaniel J and Greco A (2000). "Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: A meta-analysis." *Environ Health Perspect* **108**(1): 73-82.

Brooks DR, Mucci LA, Hatch EE and Cnattingius S (2004). "Maternal smoking during pregnancy and risk of brain tumors in the offspring. A prospective study of 1.4 million Swedish births." *Cancer Causes Control* **15**(10): 997-1005.

Bunin GR, Kuijten RR, Buckley JD, Rorke LB and Meadows AT (1993). "Relation between maternal diet and subsequent primitive neuroectodermal brain tumors in young children." *N Engl J Med* **329**(8): 536-541.

Bunin GR, Kuijten RR, Boesel CP, Buckley JD and Meadows AT (1994). "Maternal diet and risk of astrocytic glioma in children: a report from the Childrens Cancer Group (United States and Canada)." *Cancer Causes Control* **5**(2): 177-187.

Clavel J, Goubin A, Auclerc MF, Auvrignon A, Waterkeyn C, Patte C, et al. (2004). "Incidence of childhood leukaemia and non-Hodgkin's lymphoma in France: National Registry of Childhood Leukaemia and Lymphoma, 1990-1999." *Eur J Cancer Prev* **13**(2): 97-103.

Cordier S, Iglesias MJ, Le Goaster C, Guyot MM, Mandereau L and Hemon D (1994). "Incidence and risk factors for childhood brain tumors in the Ile de France." *Int J Cancer* **59**(6): 776-782.

Cordier S, Monfort C, Filippini G, Preston-Martin S, Lubin F, Mueller BA, et al. (2004). "Parental exposure to polycyclic aromatic hydrocarbons and the risk of childhood brain tumors: The SEARCH International Childhood Brain Tumor Study." *Am J Epidemiol* **159**(12): 1109-1116.

Desandes E, Clavel J, Berger C, Bernard JL, Blouin P, de Lumley L, et al. (2004). "Cancer incidence among children in France, 1990-1999." *Pediatr Blood Cancer* **43**(7): 749-757.

Filippini G, Maisonneuve P, McCredie M, Peris-Bonet R, Modan B, Preston-Martin S, et al. (2002). "Relation of childhood brain tumors to exposure of parents and children to tobacco smoke: the SEARCH international case-control study. Surveillance of Environmental Aspects Related to Cancer in Humans." *Int J Cancer* **100**(2): 206-213.

Guilbert P, Gautier A, Beck F, Perreti-Wattel P, Wilquin J, Léon C, et al. (2005). "[Tabagisme: estimation de la prévalence déclarée, baromètre santé, France 2004-2005]." *BEH* **21-22**: 97-98.

Howe GR, Burch JD, Chiarelli AM, Risch HA and Choi BC (1989). "An exploratory case-control study of brain tumors in children." *Cancer Res* **49**(15): 4349-4352.

http://www.chu-nancy.fr/rntse/.

Hu J, Mao Y and Ugnat AM (2000). "Parental cigarette smoking, hard liquor consumption and the risk of childhood brain tumors--a case-control study in northeast China." *Acta Oncol* **39**(8): 979-984.

Huncharek M, Kupelnick B and Klassen H (2001). "Paternal smoking during pregnancy and the risk of childhood brain tumors: results of a meta-analysis." *In Vivo* **15**(6): 535-541.

Huncharek M, Kupelnick B and Klassen H (2002). "Maternal smoking during pregnancy and the risk of childhood brain tumors: a meta-analysis of 6566 subjects from twelve epidemiological studies." *J Neurooncol* **57**(1): 51-57.

Ji BT, Shu XO, Linet MS, Zheng W, Wacholder S, Gao YT, et al. (1997). "Paternal cigarette smoking and the risk of childhood cancer among offspring of nonsmoking mothers." *J Natl Cancer Inst* **89**(3): 238-244.

Kuijten RR, Bunin GR, Nass CC and Meadows AT (1990). "Gestational and familial risk factors for childhood astrocytoma: results of a case-control study." *Cancer Res* **50**(9): 2608-2612.

Little J (1999). "Epidemiology of Childhood Cancer." *IARC Scientific Publications n°149*.

McCredie M, Maisonneuve P and Boyle P (1994). "Antenatal risk factors for malignant brain tumours in New South Wales children." *Int J Cancer* **56**(1): 6-10.

Menegaux F, Steffen C, Bellec S, Baruchel A, Lescoeur B, Leverger G, et al. (2005). "Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia." *Cancer Detect Prev* **29**(6): 487-493.

Menegaux F, Ripert M, Hémon D and Clavel J (2007). "Maternal alcohol and coffee drinking, parental smoking and childhood leukemia: a French population-based case-control study." *Paediatr Perinat Epidemiol* (In press).

Preston-Martin S, Yu MC, Benton B and Henderson BE (1982). "N-Nitroso compounds and childhood brain tumors: a case-control study." *Cancer Res* **42**(12): 5240-5245.

Rice JM and Wilbourn JD (2000). "Tumors of the nervous system in carcinogenic hazard identification." *Toxicol Pathol* **28**(1): 202-214.

Rice JM (2004). "Causation of nervous system tumors in children: insights from traditional and genetically engineered animal models." *Toxicol Appl Pharmacol* **199**(2): 175-191.

Ross JA (1998). "Maternal diet and infant leukemia: a role for DNA topoisomerase II inhibitors?" *Int J Cancer Suppl* **11**: 26-28.

Rudant J, Menegaux F, Leverger G, Baruchel A, Nelken B, Bertrand Y, et al. (2007). "Family history of cancer in children with acute leukemia, Hodgkin's lymphoma or non-Hodgkin's lymphoma: The ESCALE study (SFCE)." *Int J Cancer*. Feb 28; [Epub ahead of print]

Severson RK, Buckley JD, Woods WG, Benjamin D and Robison LL (1993). "Cigarette smoking and alcohol consumption by parents of children with acute myeloid leukemia: an analysis within morphological subgroups--a report from the Childrens Cancer Group." *Cancer Epidemiol Biomarkers Prev* **2**(5): 433-439.

Shu XO, Ross JA, Pendergrass TW, Reaman GH, Lampkin B and Robison LL (1996). "Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a Childrens Cancer Group study." *J Natl Cancer Inst* **88**(1): 24-31.

Steliarova-Foucher E, Stiller C, Lacour B and Kaatsch P (2005). "International Classification of Childhood Cancer, third edition." *Cancer* **103**(7): 1457-1467.

Tredaniel J, Boffetta P, Little J, Saracci R and Hirsch A (1994). "Exposure to passive smoking during pregnancy and childhood, and cancer risk: the epidemiological evidence." *Paediatr Perinat Epidemiol* **8**(3): 233-255.

van Duijn CM, van Steensel-Moll HA, Coebergh JW and van Zanen GE (1994). "Risk factors for childhood acute non-lymphocytic leukemia: an association with maternal alcohol consumption during pregnancy?" *Cancer Epidemiol Biomarkers Prev* **3**(6): 457-460.

Wilkins JR, 3rd and Bunn JY (1997). "Comparing dietary recall data for mothers and children obtained on two occasions in a case-control study of environmental factors and childhood brain tumours." *Int J Epidemiol* **26**(5): 953-963.

Table 1: Characteristics of the cases and controls

	Cases (ca) n = 209 (%)		Controls (co) n = 1681 (%)		Co/Ca) ratio	p
Histological subtypes						
Embryonal tumors (including PNET)	100	*(48)*				
Ependymomas	33	*(16)*				
Astrocytomas	26	*(12)*				
Other gliomas	45	*(21)*				
Other specified tumors	5	*(3)*				
Gender						**ns**[b]
Male	125	*(60)*	932	*(55)*		
Age at the reference date (years)						0.03[b]
< 2	34	*(16)*	369	*(22)*	10.5	
2	15	*(7)*	153	*(9)*	10.2	
3	17	*(8)*	166	*(10)*	9.8	
4	25	*(12)*	145	*(9)*	5.6	
5-6	34	*(16)*	228	*(14)*	6.5	
7-8	33	*(16)*	163	*(10)*	4.8	
9-11	27	*(13)*	225	*(13)*	8.3	
12-14	24	*(11)*	232	*(14)*	9.7	
Countries of birth of the 4 grand-parents						ns[c]
Europe	149	*(71)*	1209	*(72)*		
Africa / the Caribbean	5	*(2)*	34	*(2)*		
Asia	0	*(0)*	5	*(0.3)*		
North Africa	7	*(3)*	59	*(4)*		
Mixed	34	*(16)*	216	*(13)*		
missing data (at least one grand-parent)	14	*(7)*	158	*(9)*		
Paternal educational level						ns[c]
≤ High school	126	*(61)*	1063	*(63)*		
> High school	79	*(39)*	601	*(36)*		
missing data	4	*(1)*	17	*(1)*		
Maternal educational level						ns[c]
≤ High school	125	*(60)*	979	*(58)*		
> High school	84	*(40)*	701	*(42)*		
Socioeconomic categories						ns[c]
Intellectual and scientific jobs, intermediate profession	92	*(44)*	713	*(42)*		
Administrative employees and sales workers	51	*(24)*	477	*(28)*		
Service workers	29	*(13)*	215	*(13)*		
Farmers, agricultural, craftsmen and factory workers	37	*(18)*	274	*(16)*		

[b] *Chi square test*
[c] *Non-conditional logistic regression adjusted on age and gender*

Table 2: Parental smoking and childhood central nervous system tumours

	Cases n = 209 (%)		Controls n = 1681 (%)		OR[a]	95% CI[b]
Maternal smoking (pregnancy)						
No	165	(79)	1356	(81)	**1.0**	reference
Yes	44	(21)	325	(19)	**1.1**	[0.8-1.6]
< 10 cig/day	29	(9)	220	(13)	**1.1**	[0.7-1.6]
≥ 10 cig/day	13	(6)	99	(6)	**1.1**	[0.6-2.0]
p for trend						*ns*
Paternal smoking (year prior to birth)						
No	101	(50)	897	(55)	**1.0**	reference
Yes	103	(50)	746	(45)	**1.2**	[0.9-1.6]
< 20 cig/day	52	(25)	426	(26)	**1.1**	[0.8-1.6]
≥ 20 cig/day	51	(25)	310	(19)	**1.4**	[1.0-2.1]
p for trend						*0.04*
Parental smoking						
None	87	(43)	815	(50)	**1.0**	reference
Mother only	14	(7)	82	(5)	**1.6**	[0.9-3.0]
Father only	74	(36)	516	(31)	**1.3**	[1.0-1.9]
Both parents	29	(14)	230	(14)	**1.2**	[0.7-1.8]

[a] OR: Odds Ratios adjusted for age and gender, [b] 95% CI: 95% Confidence Interval

Table 3: Parental smoking by histological subgroup of central nervous system tumour

	Controls n = 1681	PNET n = 100			Ependymomas n = 33			Astrocytomas n = 26			Other gliomas n = 45		
		n	**OR**	**95% CI**	**n**	**OR**	**95% CI**	**n**	**OR**	**95% CI**	**n**	**OR**	**95% CI**
Maternal smoking (pregnancy)													
No	1356	79	**1.0**	reference	27	**1.0**	reference	20	**1.0**	reference	35	**1.0**	reference
Yes	325	21	**1.1**	[0.7-1.8]	6	**1.0**	[0.4-2.4]	6	**1.3**	[0.5-3.2]	10	**1.2**	[0.6-2.4]
< 10 cig/day	220	16	**1.2**	[0.7-2.1]	4	**0.9**	[0.3-2.7]	4	**1.3**	[0.4-3.8]	5	**0.9**	[0.3-2.3]
≥ 10 cig/day	99	5	**0.9**	[0.3-2.2]	1	**0.6**	[0.1-4.3]	2	**1.4**	[0.3-5.9]	4	**1.6**	[0.5-4.5]
p for trend				*ns*			*ns*			*ns*			*ns*
Paternal smoking (year prior to birth)													
No	897	50	**1.0**	reference	14	**1.0**	reference	7	**1.0**	reference	26	**1.0**	reference
Yes	746	49	**1.2**	[0.8-1.8]	18	**1.6**	[0.8-3.3]	18	**3.1**	[1.3-7.6]	17	**0.8**	[0.4-1.4]
< 20 cig/day	426	27	**1.2**	[0.7-1.9]	7	**1.0**	[0.4-2.6]	10	**3.1**	[1.2-8.4]	8	**0.7**	[0.3-1.5]
≥ 20 cig/day	310	22	**1.2**	[0.7-2.1]	11	**2.6**	[1.2-5.9]	8	**3.2**	[1.2-9.1]	9	**0.9**	[0.4-2.0]
p for trend				*ns*			*0.02*			*0.02*			*ns*

[a] OR: Odds Ratios adjusted for age and gender, [b] 95% CI: 95% Confidence Interval

Table 4: Maternal coffee and tea consumption during pregnancy and central nervous system tumours

	Controls n = 1681	All CNS Tumours n = 209			PNET n = 100			Ependymomas n = 33			Astrocytomas n = 26			Other gliomas n = 45		
		n	**OR**	**95% CI**	**n**	**OR**	**95% CI**	**n**	**OR**	**95% CI**	**n**	**OR**	**95% CI**	**n**	**OR**	**95% CI**
Coffee																
No	639	76	**1.0**	reference	37	**1.0**	reference	11	**1.0**	reference	11	**1.0**	reference	15	**1.0**	reference
Yes	1042	133	**1.0**	[0.8-1.4]	63	**1.0**	[0.6-1.5]	22	**1.3**	[0.6-2.8]	15	**0.8**	[0.4-1.7]	30	**1.1**	[0.6-2.1]
≤ 3 cups/day	923	113	**1.0**	[0.7-1.3]	57	**1.0**	[0.6-1.5]	17	**1.2**	[0.5-2.5]	13	**0.8**	[0.3-1.8]	23	**1.0**	[0.5-1.9]
> 3 cups/day	119	20	**1.4**	[0.8-2.4]	6	**0.9**	[0.4-2.2]	5	**2.7**	[0.9-8.1]	2	**0.9**	[0.4-2.2]	7	**2.3**	[0.9-5.9]
Tea																
No	962	108	**1.0**	reference	54	**1.0**	reference	15	**1.0**	reference	14	**1.0**	reference	24	**1.0**	reference
Yes	719	101	**1.3**	[0.9-1.7]	46	**1.1**	[0.8-1.7]	18	**1.6**	[0.8-3.1]	12	**1.2**	[0.5-2.5]	21	**1.2**	[0.6-2.1]
≤ 1 cup/day	491	66	**1.2**	[0.9-1.7]	28	**1.0**	[0.6-1.7]	9	**1.1**	[0.5-2.6]	8	**1.1**	[0.5-2.7]	17	**1.4**	[0.7-2.9]
> 1 cup/day	228	35	**1.4**	[0.9-2.1]	18	**1.4**	[0.8-2.4]	9	**2.5**	[1.1-5.9]	4	**1.2**	[0.4-3.8]	4	**0.7**	[0.2-2.0]
Coffee and tea (cups/day)																
None	353	37	**1.0**	reference	19	**1.0**	reference	4	**1.0**	reference	4	**1.0**	reference	10	**1.0**	reference
Coffee ≤ 3 and tea ≤ 1	919	112	**1.2**	[0.8-1.7]	51	**1.0**	[0.6-1.7]	18	**1.8**	[0.6-5.4]	17	**1.7**	[0.6-5.0]	22	**0.8**	[0.4-1.7]
Coffee > 3 and tea ≤ 1	104	15	**1.4**	[0.7-2.6]	5	**0.9**	[0.3-2.6]	2	**1.9**	[0.3- 10]	1	**0.8**	[0.1-7.1]	7	**2.2**	[0.8-6.0]
Coffee ≤ 3 and tea > 1	210	28	**1.3**	[0.7-2.1]	15	**1.3**	[0.6-2.6]	6	**2.6**	[0.7-9.5]	3	**1.3**	[0.3-5.8]	4	**0.6**	[0.2-2.0]
Coffee > 3 and tea > 1	12	5	**4.4**	[1.5- 13]	1	**1.8**	[0.2- 14]	3	**23.1**	[4.4-120]	1	**8.5**	[0.9- 84]	0	**-**	-

[a] OR: Odds Ratios adjusted for age and gender, [b] 95% CI: 95% Confidence Interval

Table 5: Maternal alcohol consumption during pregnancy and central nervous system tumours

	Controls	**All CNS Tumours**			**PNET**			**Ependymomas**			**Astrocytomas**			**Other Gliomas**		
	n = 1681	n = 209			n = 100			n = 33			n = 26			n = 45		
		n	**OR**	**95% CI**	**n**	**OR**	**95% CI**	**n**	**OR**	**95% CI**	**n**	**OR**	**95% CI**	**n**	**OR**	**95% CI**
Any alcohol																
No	1065	134	**1.0**	reference	60	**1.0**	reference	22	**1.0**	reference	18	**1.0**	reference	30	**1.0**	reference
Yes	616	75	**0.9**	[0.7-1.3]	40	**1.1**	[0.7-1.7]	11	**0.9**	[0.4-2.0]	8	**0.8**	[0.3-1.8]	15	**0.8**	[0.4-1.5]
< 1 glass/week	285	39	**1.1**	[0.7-1.6]	25	**1.5**	[0.9-2.4]	5	**0.9**	[0.3-2.3]	3	**0.6**	[0.2-2.2]	6	**0.7**	[0.3-1.7]
1 glass/week	136	14	**0.8**	[0.4-1.4]	8	**1.0**	[0.4-2.1]	2	**0.8**	[0.2-3.6]	1	**0.4**	[0.1-3.2]	2	**0.5**	[0.1-2.0]
2 glasses/week	70	9	**1.0**	[0.5-2.1]	2	**0.5**	[0.1-2.2]	1	**0.8**	[0.1-5.8]	2	**1.7**	[0.4-7.5]	4	**2.0**	[0.7-5.8]
≥ 3 glasses/week	125	13	**0.8**	[0.7-1.6]	5	**0.7**	[0.3-1.7]	3	**1.3**	[0.4-4.5]	2	**1.0**	[0.2-4.3]	3	**0.8**	[0.2-2.6]
Wine																
No	1241	159	**1.0**	reference	74	**1.0**	reference	27	**1.0**	reference	20	**1.0**	reference	34	**1.0**	reference
Yes	440	50	**0.9**	[0.6-1.2]	26	**0.9**	[0.6-1.5]	6	**0.7**	[0.3-1.6]	6	**0.9**	[0.3-2.2]	11	**0.9**	[0.4-1.7]
Beer / cider																
No	1474	177	**1.0**	reference	83	**1.0**	reference	31	**1.0**	reference	23	**1.0**	reference	36	**1.0**	reference
Yes	207	32	**1.3**	[0.8-1.9]	17	**1.4**	[0.8-2.5]	2	**0.5**	[0.1-2.0]	3	**1.0**	[0.3-3.2]	9	**1.7**	[0.8-3.6]
Spirits																
No	1411	181	**1.0**	reference	82	**1.0**	reference	27	**1.0**	reference	26	**1.0**	reference	42	**1.0**	reference
Yes	270	28	**0.8**	[0.5-1.2]	18	**1.1**	[0.6-1.9]	6	**1.3**	[0.5-3.2]	0	**-**	-	3	**0.3**	[0.1-1.1]
No alcohol	1065	134	**1.0**	reference	60	**1.0**	reference	22	**1.0**	reference	18	**1.0**	reference	30	**1.0**	reference
Wine only	201	24	**0.9**	[0.6-1.5]	10	**0.8**	[0.4-1.7]	3	**0.8**	0.4-2.6]	5	**1.5**	[0.5-4.2]	6	**1.0**	[0.4-2.5]
Beer/cider only	65	10	**1.3**	[0.6-2.5]	3	**0.8**	[0.3-2.8]	2	**1.5**	[0.4-6.8]	2	**2.0**	[0.4-6.8]	3	**1.7**	[0.5-5.7]
Spirits only	95	11	**0.9**	[0.5-1.7]	8	**1.4**	[0.6-3.0]	3	**1.6**	[0.5-5.7]	0	**-**	-	0	**-**	-
Wine and beer/cider	80	13	**1.2**	[0.7-2.3]	9	**1.8**	[0.9-3.9]	0	**-**	-	1	**0.8**	[0.1-5.9]	3	**1.2**	[0.4-4.1]
Wine and spirits	113	8	**0.6**	[0.3-1.2]	5	**0.8**	[0.3-1.9]	3	**1.5**	[0.4-5.0]	0	**-**	-	0	**-**	-
Beer/cider and spirits	16	4	**2.0**	[0.7-6.2]	3	**3.4**	[0.9- 12]	0	**-**	-	0	**-**	-	1	**2.0**	[0.3- 16]
Wine, beer/cider and spirits	46	5	**0.8**	[0.3-2.1]	2	**0.7**	[0.2-3.0]	0	**-**	-	0	**-**	-	2	**1.3**	[0.3-5.7]

[a] OR: Odds Ratios adjusted for age and gender, [b] 95% CI: 95% Confidence Interval

Appendix

SFCE Investigators	Hospital	City (France)
Olivier Hartmann	Institut Gustave Roussy	Villejuif
Jacques Grill	Institut Gustave Roussy	Villejuif
Christophe Bergeron	Centre Léon Bérard	Lyon
Didier Frappaz	Centre Léon Bérard	Lyon
Jean Michon	Institut Curie	Paris
François Doz	Institut Curie	Paris
Hervé Rubie	Hôpital des Enfants	Toulouse
Anne-Isabelle Bertozzi	Hôpital des Enfants	Toulouse
Alain Pierre-Kahn	Enfants Malades	Paris
Anne-Sophie Defachelles	Centre Oscar Lambret	Lille
Dominique Plantaz	CHU – La Tronche	Grenoble
Anne Pagnier	CHU – La Tronche	Grenoble
Jean-Pierre Vannier	Charles Nicolle	Rouen
Xavier Rialland	CHU	Angers
Pierre Bordigoni	CHU	Nancy
Danièle Sommelet	CHU	Nancy
Jean-Pierre Lamagnere	Centre Gatien de Clocheville	Tours
Claire Berger	CHU	Saint-Etienne
Yves Perel	Pellegrin Tripode	Bordeaux
Céline Icher	Pellegrin Tripode	Bordeaux
Patrick Lutz	Hôpital de Hautepierre	Strasbourg
Virginie Gandemer	CHU – Hôpital Sud	Rennes
Christian Berthou	CHU	Brest
Jean-Louis Bernard	La Timone	Marseille
Jean-Claude Gentet	La Timone	Marseille
François Demeocq	Hôtel-Dieu	Clermont-Ferrand
Françoise Mechinaud	Hôpital Mère et Enfants	Nantes
Geneviève Margueritte	Arnaud de Villeneuve	Montpellier
Lionel De Lumley	CHRU	Limoges
Brigitte Pautard	CHU	Amiens
Nicolas Sirvent	L'Archet	Nice
Patrick Boutard	CHRU	Caen
Frédéric Millot	CHU Jean Bernard	Poitiers
Françoise Lapierre	CHU Jean Bernard	Poitiers-neuro
Emmanuel Plouvier	CHR	Besançon
Catherine Behar	American Memorial Hospital	Reims
André Baruchel	Saint-Louis / Robert debré	Paris
Yves Bertrand	Debrousse	Lyon
Gérard Couillault	Hôpital d'Enfants	Dijon
Alain Fischer	Hôpital des Enfants Malades	Paris
Guy Leverger	Trousseau	Paris
Brigitte Nelken	Jeanne de Flandre	Lille
Alain Robert	Hôpital des Enfants	Toulouse
Christine Soler	Fondation Lenval	Nice