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# Family history of cancer and the risk of childhood brain tumours: A pooled analysis of the ESCALE and ESTELLE studies (SFCE)

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**Abbreviations:**

CBT            Childhood Brain Tumours

CI             Confidence Interval

CMMRD       Constitutional Mismatch Repair Deficiency

ESCALE       Etude Sur les Cancers et les Leucémies de l'Enfant (Study of childhood cancers and  
leukemias)

ESTELLE	Etude Sur les Tumeurs Embryonnaires, Leucémies et Lymphomes de l'Enfant (Study of childhood embryonal tumours, leukaemias and lymphomas)
ICCC-3	International Classification of Childhood Cancer 3 <sup>rd</sup> Edition
NF	Neurofibromatosis
OR	Odds Ratio
RNCE	Registre National des Cancers de l'Enfant (National Registry of Childhood Cancers)
SFCE	Société Française de lutte contre les Cancers et les leucémies de l'Enfant et de l'Adolescent (French Society for the fight against cancers and leukaemia in childhood and adolescence)

## Abstract

**Purpose:** Although some specific genetic syndromes such as neurofibromatosis (NF) have been identified as risk factor of childhood brain tumours (CBT), the potential role of inherited susceptibility in CBT has yet to be elucidated.

**Methods:** To further investigate this, we conducted a pooled analysis of two nationwide case-control studies ESCALE and ESTELLE. The mothers of 509 CBT cases and 3,102 controls aged under 15 years who resided in France at diagnosis/interview, frequency-matched by age and gender, responded to a telephone interview conducted by trained interviewers. Pooled odds ratio (OR) and 95% confidence intervals (95% CI) were estimated using unconditional logistic regression.

**Results:** CBT was significantly associated with the family history of cancer in relatives (OR 1.2, 95% CI 1.0-1.5). The OR was slightly higher for maternal relatives than for paternal relatives, and when at least two relatives had a history of cancer. CBT was significantly associated with a family history of brain tumour (OR 2.1, 95% CI 1.3-3.7). This association seemed stronger for first-degree relatives

(mother, father and siblings), for whom, by contrast, no association was seen for cancers other than CBT. No specificity by CBT subtypes or by age of the children were found for any of these findings.

Conclusion: Our findings support the hypothesis of a familial susceptibility of CBT, not due to being a known NF carrier.

## **Background**

Childhood brain tumours (CBT) constitute a heterogeneous group of tumours, the most common group of solid tumours with about 400 new cases diagnosed each year in France. The aetiology remains still largely unknown in most cases [1]. Except for high ionizing radiation, the only established risk factors are certain familial cancer syndromes such as neurofibromatosis (NF) type 1 and 2, tuberous sclerosis, Li-Fraumeni syndrome, Cowden disease, constitutional mismatch repair deficiency (CMMRD) syndrome, and nevoid basal cell carcinoma syndrome [2–7]. They account for around 8% of the malignant CBT cases [8, 9]. Besides these genetic syndromes, inherited susceptibility in CBT may also be related to a family history of cancers.

The literature regarding family history of cancer and the risk of CBT is inconsistent. Among four studies [10–13] investigated family history of cancer and the risk of CBT only two found an association among selected subsets, namely childhood astrocytoma cases [10] or only in paternal relatives [12]. Among seven studies which focused their analysis on the family history of brain tumours [10, 12, 14–17], only a small US case-control study [14], and two Nordic registry-based studies with some overlap of cases [15, 17] reported a positive association between CBT and family history of brain tumours. More recently, a cohort study [18] reported a 2-fold increased risk with family history of brain tumours, but this association was not specific to CBT because of the inclusion of young adulthood brain tumours in the analysis.

The aim of this study was to investigate whether the family history of cancer in the first- and second-degree relatives of the index children was associated with the risk of CBT, using pooled data from

two nationwide case-control studies ESCALE and ESTELLE that have been conducted by the same investigators with similar methodologies.

## **Materials & Methods**

The ESCALE and ESTELLE studies were two nationwide population-based studies designed to investigate the role of environmental, infectious and genetic factors of childhood cancers.

The ESCALE study included children diagnosed over the period 2003-2004 with leukaemia, lymphoma, malignant CBT and neuroblastoma while the ESTELLE study included cases of leukaemia, lymphoma, malignant or benign CBT, neuroblastoma, Wilms' tumour and hepatoblastoma diagnosed in 2010-2011. Both studies have been previously described elsewhere [19–21]. This article focusses on CBT.

### **Study population**

The cases in both studies were directly identified by the French National Registry of Childhood Cancer (RNCE) in the departments of paediatric oncology and paediatric neurosurgery. The definition of a case was any child diagnosed with a tumour in diagnostic group III according to the International Classification of Childhood Cancer Third edition (ICCC-3)[22]. To classify CBT by histological subtypes, the RNCE uses wherever possible microscopic reports (~85%), imaging or clinical diagnosis. Eligible cases were children aged less than 15 years who lived in France at the time of cancer diagnosis. The children who were adopted or whose biological mother had died, did not speak French or had serious psycho-social problems were ineligible. For ethical reasons, case children who had died or were in palliative care were also ineligible. During the study time periods, a total of 697 children aged less than 15 years were diagnosed with a CBT. Of these, 79 (11.3%) were ineligible as the children had either died or were receiving palliative care, nine (1.3%) because the biological mother was unavailable (mother deceased or child adopted) and 28 (4.0%) as the mother either did not speak French or could not be interviewed for serious psychosocial reasons.

The population controls were children aged less than 15 years, free from cancer, randomly selected by telephone using quota-sampling methods. Quotas ensured that controls had similar age and sex distribution to that of all cancer cases and, conditionally to age, the same distribution of number of children under the age of 15 living in the household as the overall population, based on population censuses. The control children were ineligible if they were adopted or if their biological mother had died, did not speak French, or had a serious psychosocial problem. There were 45 controls ineligible because their biological mother was unavailable (mother deceased or child adopted).

### **Data collection and standardization**

In both studies, trained interviewers conducted standardized computer-assisted telephone interviews with the biological mothers under identical conditions for cases and controls, with an average duration of the interview around 50 minutes. The mean time elapsed between CBT diagnosis and interview in the ESCALE and ESTELLE studies was six months and four months, respectively. The questionnaire elicited information on socio-demographic information, environmental exposures, family and personal medical histories.

In regards to family history, the mothers were first asked about their family composition, including their number and the first names of biological offspring, brothers and sisters so the family tree was well defined before any questions about cancer histories to increase reliability. For each first-degree (parents, siblings) and second-degree (grandparents, uncles, aunts, half-siblings) relative, mothers were then asked "Have you or any of member of your family had any of the following diseases: (leukaemia, Hodgkin's disease, lymphoma, myeloma) or another cancer?" In the latter case, they were asked to choose in a list of solid tumour sites read by the interviewer "oral cavity, ear, nose or throat), lung, digestive system (oesophagus or stomach, liver, colon, rectum or anus), breast, thyroid, skin (specifically melanoma), bone, genitourinary (kidney, bladder, uterus or ovary, prostate) or brain) or another site" (with the details collected). Mothers were then asked the same questions about the father and his family. For each declaration of cancer within a branch of the family, they

were also asked to verify the person's name and give the date of or the age at diagnosis. When a relative was said to have more than one cancer, we retained only the first one in the analyses to avoid the inclusion of metastatic cancers.

### **Statistical analyses**

Study-specific and pooled odds ratio (ORs) and 95% confidence intervals (95% CI) were estimated by unconditional logistic regression (SAS 9.4, SAS Institute Inc., Cary, NC, USA), while polytomous logistic regression was used for CBT subtypes. All models included the study matching factors, age and sex, and for pooled analyses, the indicator of study origin.

The following variables were considered as potential confounders: number of siblings, number of aunts/uncles, number of half-siblings, maternal age at child's birth, maternal education degree and mean of grandparents' age at diagnosis/interview, parental smoking during pregnancy and parental country of birth (both European/at least one African/ at least one Asian/Others). These potential confounders were tested to determine whether they were independently associated with both the exposure and outcome. Only number of siblings, number of half-siblings, number of aunts/uncles, and maternal age at child's birth were retained in the final models.

We tested between-study heterogeneity using an interaction term between the specific study and the exposure of interest. Stratification analyses and fitting interaction terms were used to explore a potential effect modification by age class (0-4 years / 5-14 years) at the reference date, that is, at diagnosis for cases and at interview for controls.

We conducted sensitivity analyses by excluding children with known NF or by excluding the cancers given as responses to the question about sites not otherwise listed. In additional analysis, the data from grandparents, who were the oldest second-degree relatives, were excluded. To evaluate a possible bias induced by the ineligibility of children whose biological mother had died, we estimated the association under the extreme hypotheses that the unavailable mothers had cancer and therefore accounted as first-degree relatives with cancer for both cases and controls, cases only, or



controls only. Finally, as controls were recruited from a sample of landline phone numbers we also excluded case mothers with no landline (information available in ESTELLE only).

For the ESTELLE participants only, some fathers also completed a self-administered questionnaire about family history of cancer in paternal relatives, and we used this data to calculate the observed kappa score with maternal reports.

## **Results**

The pooled analyses included 509 CBT cases (87.6% of eligible; 209 from ESCALE and 300 from ESTELLE) and 3,102 controls (77.1% of eligible; 1,681 from ESCALE and 1,421 from ESTELLE). Using the ICCC-3 classification, there were 64 ependymomas (12.6% of CBT cases), 119 astrocytomas (23.4%), 206 embryonal tumours (40.5%), 109 other gliomas (21.4%) and 11 other specified or unspecified neoplasms (2.1%). Among the CBT cases, there were 436 malignant tumours (85.7%) and 73 non-malignant tumours (eligible only in ESTELLE).

### **Comparability of cases and controls**

The distribution of cases and controls by age and sex differed as controls were selected to have the same age and sex distribution as all childhood cancer cases, but there were at least four controls for every case in each age and sex class. Controls tended to have a higher birth order than cases and accordingly case siblings were younger than control siblings (Table 1).

### **Between-study heterogeneity**

Mothers tended to be older at child's birth and had a higher level of education in the ESTELLE study than in the ESCALE study which was conducted seven years earlier. There were also more half-siblings and fewer uncles and aunts in the ESTELLE study than in the ESCALE study (Table 1).

### **Comparability of Maternal and paternal response**

For a subsample of the ESTELLE study consisting of 138 cases of any type of childhood cancer, (including seven cases of CBT) and 177 controls, whose father had filled a self-administered -

questionnaire, we compared the history of cancer in paternal relatives as reported by the father and by the mother. There was a high level of agreement which was similar for cases and controls (kappa 0.88 and 0.89, respectively). Altogether, 79.4% of the paternal relatives reported with a cancer by the father were also reported with the same cancer by the mothers (75.7% for cases and 80.9% for controls). Conversely, 75.3% of the paternal relatives reported with a cancer by the mother were consistently reported by the mothers (77.1% for cases and 73.9% for controls).

### **Family history of cancer**

A history of cancer in at least one first- or second-degree relative was reported slightly more often in the CBT cases (46.6%) than in controls (42.0%) with an OR of 1.2 (95% CI 1.0-1.5) (Table 2). The proportions were very similar in the ESCALE study (46.9% of the cases and 42.4% the controls) and in the ESTELLE study (46.3% of the cases and 41.5% of the controls) (Results not tabulated). The association was more pronounced when at least two relatives were reported with a cancer (OR 1.5, 95% CI 1.1-2.0) and appeared more evident for maternal than for paternal relatives. Very few of the cancers were in first-degree relatives (3.5% of the cases and 2.6% of the controls) (Table 2). The OR for the association between CBT and family history of cancer was of the same order of magnitude in the second-degree (OR 1.2, 95%CI 1.0-2.1) and first-degree relatives (OR 1.4, 95%CI 0.8-2.4) (Table 2). No between-study heterogeneity was found.

Table 3 shows the associations between CBT and family history of cancer by specific types. A family history of brain tumours was significantly associated with CBT (OR 2.4, 95% CI 1.4-4.0). The association was also visible in first-degree relatives although based on small numbers. The association seemed similar across the main CBT subtypes (Table 4). Among the 21 cases and 58 controls with a family history of a brain tumour, only one case had more than one family member (results not shown).

We also found associations with a family history of cancers of other specified sites (OR 1.2, 95% CI 1.0-1.4), particularly genitourinary cancers (uterus or ovary cancers (OR 1.4, 95% CI 0.9-2.1), prostate

cancer (OR 1.4, 95% CI 1.0-2.2)), and non-Hodgkin's lymphomas (OR 2.2, 95% CI 1.0-4.5) (Table 3).

This association disappeared when we restricted the analysis to first-degree relatives (OR 1.0, 95% CI 0.6-1.9).

### **Additional analyses**

Neither the exclusion of children with known NF (10 cases, 2 controls) nor the exclusion of cases without a landline telephone in the ESTELLE study changed our findings. Similarly, there was no change when we excluded the data from grandparents, who were the oldest second-degree relatives (OR 1.5, 95% CI 1.1-2.1) although the prevalence of any cancer in the family was much less frequent (9.8% and 7.4% for case and control children, respectively) (results not otherwise shown). The exclusion of cancers in sites not otherwise listed (testis, pancreas, and other or non-specified solid tumours) did not change our findings (OR 1.2, 95% CI 1.0-1.5) (results not otherwise shown).

The association with first-degree relatives disappeared in the extreme scenario considering all the unavailable control mothers but none of the unavailable case mothers as having cancer, and remained in the other extreme scenarios.

### **Discussion**

In this pooled analysis of the ESCALE and ESTELLE studies, we observed a 2-fold increased risk of CBT with a family history of brain tumour in first- and second-degree relatives, not explained by known NF status of the index child, and independent of the CBT subtype. The association was stronger for first-degree relatives and uncles/aunts. We also found an increased risk of CBT with the family history of cancer in relatives with no specificity by CBT subtypes or by age of the children detected. This association appeared more evident in second-degree than in first-degree relatives because of a low prevalence of cancer in the latter. The OR was slightly higher for maternal relatives than paternal relatives, or when at least two relatives had a history of cancer.

The previous literature is heterogeneous in terms of definition of the cases (any childhood cancer, any CBT, specific CBT subtypes), definition of relatives (first- or second-degree or both) or the choice of the main variable (family history of “cancer” or family history of “brain tumours”). Three case-control studies [10, 12, 13] and one cohort study [11] have investigated the family history of any cancer and the risk of CBT. A study [10] who focused on childhood astrocytoma cases reported an OR of 1.7 (95% CI 1.0-2.7) with a family history of cancer in second-degree relatives. A US study [12] only observed a positive association between the history of cancer, which was obtained from each parent, in paternal male relatives and CBT (OR 1.34, 95% CI 0.98-1.84). Due to small number of CBT (57 CBT cases among 593 cases of childhood cancer), the Russian case-control study [13] lacked sufficient power to find any association. Unlike us, another study [11] did not find an association between the history of cancer in any first- or second-degree relatives and CBT in their cohort study which included 230 CBT cases. However, they investigated the history of cancer in second-degree relatives (aunts, uncles and grandparents of the offspring) only if a parent or a sibling of the CBT case was found to have an invasive cancer, which was a different definition. To our knowledge, our study is the first showing a stronger association for children with more than one relative with a history of cancer.

Our findings on brain tumours in relatives are consistent with that of five previous studies [10, 12, 14–16]. Regarding subtypes of CBT in the index child, associations with CBT in families was specifically reported in astrocytomas by a study in the USA and Canada [10] but not in a US SEER study [12]. The SEARCH study [16], which pooled data from seven countries, reported no association, except for a history of brain tumours in male relatives among what was called at this time ‘primitive neuroectodermal tumour’ cases. Other studies focused their analyses on first-degree relatives. A case-control study in the USA [14] reported 5-fold and 8-fold increased risks of CBT respectively when a parent or a sibling had previously a brain tumour, based on small numbers. There have been four reports from the Nordic countries with overlapping data [15, 17, 18, 23]. Firstly, a Swedish registry-based study [15] on CBT linked Cancer Registry data with a family database of cases diagnosed between 1958 and 1996 and the Standardized Incidence Ratios (SIR) for brain tumours in

offspring of affected parent compared with offspring of non-affected relatives was 1.88 (95% CI 1.23-2.67). They replicated this study with data of CBT cases aged under 19 years diagnosed between 1958 and 2004 from five Nordic countries which increased the number of cases from 2,060 to 7,590 and found similar results [17]. Similarly, using the cohort of births in Sweden between 1973-2008, a study [18] reported a significant 2-fold increased risk with family history of brain tumours, but as this analysis included cases diagnosed up until 38 years of age, their findings are not comparable to ours. A Norwegian study [23] found an increasing risk for the first-degree relatives with any solid tumours (except lymphoma) diagnosed before 30 years (Hazard Ratio 2.28, 95% CI 1.57-3.32). We replicated this analysis in our dataset (6 cases and 19 controls with family history of any solid tumours diagnosed before 30 years in the first-degree relatives) with similar but not significant association (OR 2.1, 95% CI 0.8-5.4). Due to having few cases, we were unable to focus this analysis on children with family history of specifically brain tumours diagnosed before 30 years in the first-degree relatives.

To our knowledge, our findings on genitourinary cancers and non-Hodgkin's lymphomas in relatives have never been reported in the literature before. However, the European consortium 'Care for CMMRD (Constitutional Mismatch Repair Deficiency)' showed that individuals with CMMRD syndrome (biallelic germline mutations in one of the four MMR genes, *MLH1*, *MSH2*, *MSH6* or *PMS2*) have a higher risk of developing non-Hodgkin's lymphomas, and genitourinary cancers [7]. Thus, our findings may reflect undiagnosed CMMRD.

Our study has several strengths. Firstly, cases were selected from the RNCE, which has a high degree of completeness, limiting case selection at the identification stage. The overall participation rate among eligible cases and controls minimized the selection bias. However, we cannot exclude a potential for selection bias because of the exclusion of the most serious cases of CBT for ethical reasons. The relatively short time between the date diagnosis and the mother's interview limited the likelihood of survival selection bias. Furthermore, with a sample of 509 cases and 3,102 controls, our

study is currently one of the largest case-control investigations of CBT although the estimates by CBT subtypes lacked power. However, our findings did not seem to differ by CBT subtype. While predisposing syndromes have been previously noted for some of the subtypes, this is not the case for ependymomas, which makes our finding particularly interesting for this subtype. Another strength of our study was that we could take into account the family size and constitution.

In our study, only families with a landline telephone could be contacted for control recruitment, while case recruitment was accessible to cases with only a mobile telephone. Thus, there was a potential for selection bias if owning a landline telephone was associated with size or constitution of family or maternal reliability of family history. However, there was no difference in our findings for ESTELLE when these cases have been excluded. We do not have this information for ESCALE, but this study was conducted seven years before the ESTELLE study when mobile telephone was less common, and thus there is high likelihood that there were less cases who did not have a landline than in the ESTELLE study.

This study has also some limitations. Non-differential errors cannot be excluded. Information about family history of cancer in relatives was reported by the mothers, which was a potential for recall bias. We attempted to limit misclassifications by using specific closed questions for each relative of the child, only after the family tree had been defined, which were asked by trained investigators blinded to case-control status. A previous study [24] which investigated the accuracy of family history of cancer data reported by mothers of children with cancer, found positive predictive values (PPV) of 88% and 71% for first- and second-degree relatives, respectively. However, misclassification could be higher by types of cancer. In adult cancers, a recent literature review [25] investigated validity of self-reported family history of cancer and showed high variations between PPV of different types of cancer with, for instance, a minimum observed PPV of 88% for leukaemia while the maximum PPV for liver cancer was of 40%. For brain tumours, among the four studies [26–29] there were two studies with at least five reported cancer diagnoses with available reference standard and the PPV

was 67% [29] and 87% [26], respectively. Differential misclassifications is a major concern as mothers of cases may have remembered in more detail the family history of cancer than control mothers because of their rumination which could have led them to wonder about this association and investigate the family history of cancer in depth before the interview. This hypothesis could be more particularly true about the family history of specifically brain tumours. However, a study [30] showed that reliability of reporting family history by parents of children with leukaemia was not associated with case-control status. Mothers were asked about family history of cancer diagnosed before the index child's diagnosis for the cases and before interview for the controls. We have double-checked that there had been no cancer declared in case families between diagnosis and interview. There is a chance that mothers may have confused brain metastases with primary brain cancers so we only included the first cancer diagnosis of the family member. In our study, nine cases and 45 controls were ineligible because their biological mother was unavailable (mother had died or child was adopted), which could have led to underestimate cancer among deceased mothers. Given the sensitivity analyses, a substantial impact is very unlikely.

Maternal responses for second-degree relatives may be less reliable for paternal family history of cancer than maternal history of cancer because the mothers may not have known the full details of the fathers' families. However, in the small subset of ESTELLE fathers who answered a self-administered questionnaire, there was a similar level of agreement for cases and controls between mother's and father's report of family history of cancer in paternal relatives. The mothers are expected to report more accurately a history of cancer in first-degree relatives (herself, the father and her children). First-degree relatives were young and had limited opportunity to develop a cancer. Conversely, some cancers in relatives is likely to be due to ageing, and thus not part of the hypothesis of genetic susceptibility which could have modified our findings. However, after excluding grandparents of our analysis, there was no difference in the association with family history of cancer.

Finally, despite our sensitivity analysis with exclusion of known NF cases (10 CBT cases and 2 controls), which is the most common genetic syndrome currently associated with CBT [5], we were not able to take in consideration some other genetic syndromes which could impact our findings such as tuberous sclerosis, Cowden disease, CMMRD syndrome, and nevoid basal cell carcinoma syndrome [3], because none of these diagnoses were declared in our sample. As the registry collects the data at least one year after the diagnosis, it was able to include some NF and other genetic syndromes genotyped after time of the CBT diagnosis. However, the prevalence of these familial cancer syndromes are very low [3] and suggests that it is highly unlikely that these would modify our findings.

## **Conclusion**

Our findings support the hypothesis of a familial susceptibility of CBT, not due to known NF carriers. They underline the need for international consortium for large-scale pooled studies, able to deepen the analyses by subtypes and kind of relatives, and to allow whole-genome genotyping for a better understanding of genetic risk factors.

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## Conflict of interest

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Table 1. Distribution of the cases and controls by sociodemographic and familial characteristics and by study – Pooled analyses of ESCALE and ESTELLE studies – France, 2003-2004 and 2010-2011.

	ESCALE (2003-2004)		ESTELLE (2010-2011)		ESCALE/ESTELLE		Control/case ratio <sup>1</sup>							
	Cases (n=209)	Controls (n=1,681)	Cases (n=300)	Controls (n=1,421)	Cases (n=509)	Controls (n=3,102)								
	n	%	n	%	n	%	%							
Sex														
Female	84	40.2	749	44.6	95	41.7	683	48.1	209	41.1	1,432	46.2	6.8	
Male	125	59.8	932	55.4	133	58.3	738	51.9	300	58.9	1,670	53.8	5.6	
Age (years)														
< 2	34	16.3	369	22.0	55	18.3	317	22.3	89	17.5	686	22.1	7.7	
2-4	57	27.3	464	27.6	84	28.0	417	29.3	141	27.7	881	28.4	6.2	
5-9	77	36.8	466	27.7	107	35.7	322	22.7	184	36.1	788	25.4	4.3	
10-14	41	19.6	382	22.7	54	18.0	365	25.7	95	18.7	747	24.1	7.8	
Mean (SD)	6.3	(3.9)	6.0	(4.3)	6.0	(4.0)	6.1	(4.6)	6.2	(4.0)	(6.1)	(4.5)		
Maternal education														
Did not complete secondary education	80	38.3	659	39.2	99	33.0	399	28.1	179	35.2	1,058	34.1		
Secondary education	45	21.5	320	19.0	59	19.7	308	21.7	104	20.4	628	20.3		
Tertiary education	84	40.2	701	41.7	142	47.3	714	50.2	226	44.4	1,415	45.6		
Missing	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	1	0.0		
Maternal age at child's birth (years)														
< 25	17	8.1	163	9.7	39	13.0	147	10.4	56	11.0	310	10.0		
25-29	81	38.8	664	39.5	117	39.0	455	32.0	198	38.9	1,119	36.1		
30-34	77	36.8	571	34.0	90	30.0	506	35.6	167	32.8	1,077	34.7		
≥ 35	34	16.3	283	16.8	54	18.0	313	22.0	88	17.3	596	19.2		
Birth order														
1	80	38.3	708	42.1	134	44.7	594	41.8	214	42.0	1,302	42.0		
2	94	45.0	608	36.2	105	35.0	496	34.9	199	39.1	1,104	35.6		
3 or more	35	16.7	365	21.7	61	20.3	331	23.3	96	18.9	696	22.4		
Number of siblings														
0	40	19.2	474	28.2	82	27.3	440	31.0	122	24.0	914	29.5		
1	105	50.2	706	42.0	140	46.7	588	41.4	245	48.1	1,294	41.7		
2 or more	64	30.6	501	29.8	78	26.0	393	27.6	142	27.9	894	28.8		
Number of half-siblings														
0	172	82.3	1,451	86.3	228	76.0	1,142	80.4	400	78.6	2,593	83.6		

1	17	8.1	105	6.3	37	12.3	132	9.3	54	10.6	237	7.6
2 or more	20	9.6	125	7.4	35	11.7	147	10.3	55	10.8	272	8.8
Number of uncles/aunts												
0-2	47	22.5	374	22.2	76	25.3	417	29.4	123	24.2	791	25.5
3-4	57	27.3	585	34.8	109	36.3	475	33.4	166	32.6	1,060	34.2
5-6	49	23.4	326	19.4	56	18.7	256	18.0	105	20.6	582	18.7
7 or more	56	26.8	396	23.6	59	19.7	273	19.2	115	22.6	669	21.6
Mean age at diagnosis/interview in years (SD)												
Mother	37.2	(5.8)	36.2	(5.8)	36.8	(6.2)	37.2	(6.4)	37.0	(6.1)	36.7	(6.1)
Father	39.5	(6.7)	38.6	(6.7)	39.0	(9.5)	39.5	(8.1)	39.2	(8.5)	39.0	(7.3)
Siblings	9.3	(6.0)	9.2	(5.4)	8.0	(5.1)	9.3	(5.1)	8.6	(5.6)	9.2	(5.3)
Grandparents	65.0	(7.4)	63.4	(7.3)	63.9	(7.4)	64.2	(7.5)	64.0	(7.2)	63.8	(7.4)
Uncles/aunts	38.4	(7.2)	37.2	(7.6)	38.6	(8.9)	38.6	(8.6)	38.5	(8.2)	37.8	(8.1)
SD Standard Deviation												

<sup>1</sup>These are only given for study matching factors

Table 2. Family history of cancer and childhood brain tumours – Pooled analyses of the ESCALE and ESTELLE studies – Metropolitan France, 2003-2004 and 2010-2011.

	Cases (n=509)		Controls (n=3,102)		OR <sup>1</sup>	95% CI
	n	%	n	%		
Family history of cancer						
First-degree relatives <sup>2</sup>						
No	491	96.5	3,020	97.4	1.0	Ref.
Yes	18	3.5	82	2.6	1.4	[0.8-2.4]
Second-degree relatives <sup>3</sup>						
No	281	55.2	1,851	59.7	1.0	Ref.
Yes	228	44.8	1,251	40.3	1.2	[1.0-1.5]
First- and second-degree relatives						
No cancer in family	272	53.4	1,799	58.0	1.0	Ref.
Any cancer in family	237	46.6	1,303	42.0	1.2	[1.0-1.5]
Number of relatives with cancer						
1	168	33.0	978	31.5	1.2	[0.9-1.4]
2 or more	67	13.2	325	10.5	1.5	[1.1-2.0]
Maternal/Paternal relatives with cancer						
Only maternal relatives	105	20.6	538	17.3	1.3	[1.0-1.7]
Only paternal relatives	89	17.5	543	17.5	1.1	[0.8-1.4]
Both	43	8.5	222	7.2	1.4	[1.0-2.0]
Earliest cancer onset age in family						
≤ 45 years	76	14.9	385	12.4	1.3	[1.0-1.7]
> 45 years	154	30.3	860	27.7	1.2	[1.0-1.5]
Missing	7	1.4	58	1.9		
CI Confidence interval						
OR Odds Ratio						

<sup>1</sup> OR and 95% CI estimated by unconditional logistic regression models adjusted for the matching variables (age, sex), number of siblings (except for the only second-degree analysis), number of aunts/uncles (except for the only first-degree analysis), number of half-sisters/half-brothers (except for the only first-degree analysis), and maternal age at child's birth.



<sup>2</sup> First-degree relatives were mother, father, and brothers/sisters

<sup>3</sup> Second-degree relatives were grandparents, half-sisters/half-brothers and biological aunts/uncles

Table 3. Family history of specific types of cancer and childhood brain tumours – Pooled analyses of the ESCALE and ESTELLE studies– Metropolitan France, 2003-2004 and 2010-2011.

	Cases (n=509)		Any relatives (n=3,102)				First-degree <sup>1</sup> relatives (n=509)					
	n	%	n	%	OR <sup>2</sup>	95% CI	n	%	n	%	OR <sup>3</sup>	95% CI
Brain tumours	21	4.1	58	1.9	2.4	[1.4-4.0]	5	1.0	3	0.1	10.7	[2.4-46.9]
Other cancers than brain tumours	226	44.4	1,272	41.0	1.2	[1.0-1.4]	13	2.6	79	2.6	1.0	[0.6-1.9]
Leukaemia	18	3.5	107	3.4	1.0	[0.6-1.7]	0	-	10	-	-	-
Hodgkin's Lymphoma	6	1.2	24	0.8	1.5	[0.6-3.7]	2	0.4	3	0.1	-	-
Non-Hodgkin's Lymphoma	10	2.0	30	1.0	2.2	[1.0-4.5]	2	0.4	2	0.1	-	-
Myeloma	2	0.4	11	0.4	0.4	-	0	-	1	0.0	-	-
Oral cavity, ENT	17	3.3	123	4.0	0.8	[0.5-1.4]	0	-	0	-	-	-
Lung	42	8.3	232	7.5	1.1	[0.8-1.6]	1	0.2	3	0.1	-	-
Oesophagus, stomach	11	2.2	67	2.2	1.0	[0.5-2.0]	0	-	0	-	-	-
Liver	11	2.2	78	2.5	0.9	[0.5-1.7]	0	-	2	0.1	-	-
Colon, rectum, anus	22	4.3	119	3.8	1.2	[0.7-1.9]	0	-	4	0.1	-	-
Breast	57	11.2	322	10.4	1.1	[0.8-1.5]	1	0.2	20	0.6	-	-
Thyroid	5	1.0	15	0.5	1.9	[0.7-5.4]	0	-	2	0.1	-	-
Melanoma	2	0.4	13	0.4	0.4	-	0	-	5	0.2	-	-
Bone	5	1.0	33	1.1	1.0	[0.4-2.6]	0	-	1	0.0	-	-
Kidney	4	0.8	41	1.3	1.3	-	1	0.2	1	0.0	-	-
Bladder	1	0.2	29	0.9	0.9	-	0	-	1	0.0	-	-
Uterus, ovary	25	4.9	111	3.6	1.4	[0.9-2.1]	1	0.2	9	0.3	-	-
Prostate	33	6.5	141	4.5	1.4	[1.0-2.2]	1	0.2	1	0.0	-	-
Unspecified cancers <sup>4</sup>												
Pancreas	3	0.6	29	0.9	0.9	-	0	-	0	-	-	-
Testis	5	1.0	15	0.5	1.9	[0.7-5.4]	1	0.2	4	0.1	-	-
Other or non-specified solid cancer	16	3.1	90	2.9	1.1	[0.7-2.0]	4	0.8	6	0.2	-	-

CI Confidence interval

OR Odds Ratio

<sup>x</sup>Relatives were defined as biological mother, father, brothers/sisters, aunts, uncles and grandparents

1. First-degree relatives were mother, father, and brothers/sisters

2 OR and 95% CI estimated by unconditional logistic regression models adjusted for the matching variables (age, sex), number of siblings, number of aunts/uncles, number of half-sisters/half-brothers, and maternal age at child's birth.

3 OR and 95% CI estimated by unconditional logistic regression models adjusted for the matching variables (age, sex), number of siblings, and maternal age at child's birth

4 Responses to the question about sites not otherwise listed

Table 4. Family history of cancer and ICC-3 subtypes of childhood brain tumours – Pooled analyses of the ESCALE and ESTELLE studies – Metropolitan France, 2003-2004 and 2010-2011.

	Controls (n=3,102)		Ependyomas (n=64)		Astrocyomas (n=119)		Embryonal tumours (n=206)		Other glioma (n=109)	
	n	%	n	%	OR <sup>1</sup>	95% CI	n	%	OR <sup>1</sup>	95% CI
Family history of cancer										
First-degree relatives										
No	3,020	96.1	62	96.9	1.0	Ref.	115	96.6	1.0	Ref.
Yes	82	2.6	2	3.1	1.4	[0.3-6.0]	4	3.4	1.4	[0.5-4.2]
Second-degree relatives										
No	1,851	59.7	36	56.3	1.0	Ref.	61	51.3	1.0	Ref.
Yes	1,251	40.3	28	43.8	1.2	[0.7-2.1]	58	48.7	1.6	[1.1-2.4]
First- and second-degree relatives										
No cancer in family	1,799	58.0	34	53.1	1.0	Ref.	59	49.6	1.0	Ref.
Any cancer in family	1,303	42.0	30	46.9	1.3	[0.8-2.2]	60	50.4	1.6	[1.1-2.4]
Number of relatives with cancer										
1	978	31.5	23	35.9	1.3	[0.8-2.3]	48	40.3	1.7	[1.2-2.6]
2 or more	325	10.5	7	10.9	1.3	[0.6-3.1]	12	10.1	1.3	[0.7-2.5]
Maternal/Paternal relatives with cancer										
Only maternal relatives	538	17.3	14	21.9	1.5	[0.8-2.8]	22	18.5	1.4	[0.8-2.4]
Only paternal relatives	543	17.5	12	18.8	1.2	[0.6-2.4]	28	23.5	1.7	[1.1-2.7]
Both	222	7.2	4	6.3	1.1	[0.4-3.3]	10	8.4	1.8	[0.9-3.7]
History of brain tumours										
No	3,044	98.1	61	95.3	1.0	Ref.	112	94.1	1.0	Ref.
Yes	58	1.9	3	4.7	3.0	[0.9-10.0]	7	5.9	3.4	[1.5-8.0]
CI Confidence interval										
OR Odds Ratio										

<sup>1</sup> OR and 95% CI estimated by polytomous logistic regression models adjusted for the matching variables (age, sex), number of siblings (except for the only second-degree analysis), number of aunts/uncles (except for the only first-degree analysis), number of half-sisters/half-brothers (except for the only first-degree analysis), and maternal age at child's birth.