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Maternal alcohol and coffee drinking, parental smoking and childhood leukemia: a French population-based case-control study

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Running title

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Summary

The role of maternal alcohol and coffee drinking during pregnancy and that of parental smoking in the etiology of childhood leukemia were investigated.

A French, population-based, case-control study including 472 (407 acute lymphoblastic leukemia, ALL and 62 acute myeloblastic leukemia, AML) incident cases of childhood acute leukemia (AL) and 567 population controls frequency matched with cases on age, gender and region of residence was conducted. The case and control mothers filled in a comprehensive self-administered standardized questionnaire eliciting detailed data on maternal alcohol and coffee consumption during pregnancy and parental smoking before, during and after pregnancy.

Maternal alcohol consumption of more than 1 drink per day was related to ALL (OR=2.8 [1.8,5.9]). While maternal coffee consumption was not significantly related to AL (OR=1.4 [0.9,2.3]), highest intake of coffee (more than 3 cups per day) during pregnancy was associated to AL in children whose mothers were non-smokers (OR=1.9 [1.0,3.5]). No association with parental smoking, either maternal or paternal, was observed in acute leukemia.

The present results suggest a possible role of the highest consumption of alcohol by the mother during pregnancy in the etiology of childhood acute leukemia.

Acute leukemia (AL) is the most common cancer in children aged less than 15 years, with an incidence of 43 cases per million and per year in France .¹ With the exception of exposure to x-rays, specific chemotherapy and some genetic syndromes, relatively little is known about the causes of childhood acute leukemia. Its young age distribution suggests that events or environmental exposures occurring in the pre- or perinatal periods or during pregnancy may affect its pathogenesis. Factors such as maternal alcohol and coffee drinking during pregnancy and parental smoking are relatively prevalent and may play a role in the etiology of childhood leukaemia, either directly or indirectly through their influence on other metabolites. The literature on maternal alcohol and coffee drinking during pregnancy is relatively scarce. An association between acute myeloid leukemia (AML) and maternal alcohol drinking during pregnancy was observed in all 4 studies on AML.²⁻⁵ The results for maternal alcohol and coffee drinking during pregnancy and acute lymphoid leukemia (ALL) are more inconsistent. Studies on maternal smoking before, during or after pregnancy do not appear to suggest an association with AL. The results for paternal smoking are more inconsistent and call for further investigation.

METHODS

A population-based case-control study was conducted in 14 regions of France between 1995 and 1998. The study design has been described in detail elsewhere.⁶ The cases were derived from the National Registry of Childhood Blood Malignancies (NRCL). In order for cases to be eligible, acute leukemia was to have been newly diagnosed in subjects aged less than 15 years and residing in metropolitan France at the time of diagnosis. The eligibility criteria for cases also included the physician's consent to the mother being contacted and the mother's ability to fill in a self-administered questionnaire. During the period 1995-1998, the NRCL registered 786 cases of acute leukemia in the 14 regions, of whom 140 were not eligible: 25 were not known at the time of the study, 2 were known not to have parents, 3 had parents who were unable to fill out the questionnaire and 110 were too sick for their parents to be interviewed. Out of the 646 eligible cases, 472 (72%) were included, consisting of 407 cases of ALL, 62 of AML and 3 of acute leukemia NOS

Controls were randomly selected from the overall population from a sample of 30,000 phone numbers representative of the French population with respect to region of residence and municipality population category. Recruitment was frequency matched on age, gender and region using quotas determined *a priori* on the basis of the expected distribution of cases. Out of the 805 eligible controls, 572 (71%) completed the questionnaire. Five cases were excluded because they turned out to be adopted and finally 567 controls (70%) were included.

The mothers completed a standardized self-administered questionnaire that was distributed by the physician for the cases and sent by mail to the controls. Data on parental socio-demographic characteristics and occupational history, pregnancy history, birth characteristics, the child's illnesses and familial history of cancer were

collected. The data on smoking habits included the number of cigarettes smoked per day by the mother, 3 months before pregnancy, during pregnancy and from birth to diagnosis, and the number of cigarettes smoked per day by the father, 3 months before pregnancy and from birth to diagnosis. The data on maternal alcohol and coffee consumption during pregnancy included the number of alcoholic drinks per day of wine, beer or cider, in the one hand, and of spirits or liquor, on the other hand, and the number of cups of coffee per day (without any distinction between instant/ground or regular/decaffeinated).

The analyses were performed using the SAS[®] software package (version 9.1, Cary, North Carolina). Unconditional logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI). All analyses were adjusted for the stratification variables. Socio-demographic factors such as the mother's educational level, place of residence at diagnosis and other factors that had been previously been shown to be related to childhood leukemia in the present study were also included as potential confounders.⁶

RESULTS

There were no major differences between the cases and controls with respect to gender, age, region of residence at diagnosis, parental socio-professional category, parental educational level or population of the place of residence (Table 1).

An association between childhood leukemia and maternal alcohol consumption of more than 1 drink per day (OR=2.3 [1.1,4.9]) (Table 2) was observed. The relationship was restricted to consumption of wine, beer or cider, since very few mothers reported having drunk spirits, and even none more than a glass per day. The results were similar for ALL. No AML case had a mother who drank more than 1 drink per day.

Maternal coffee consumption of more than 3 cups per day during pregnancy was slightly, although not significantly, associated to acute leukemia (OR=1.4 [0.9,2.3]) (Table 3). The estimates were similar for ALL and AML.

No association between AL and parental smoking whether maternal or paternal was observed (Table 3). However, maternal smoking during pregnancy was associated to ALL (OR=1.4 [1.0,1.9]). All results related to parental smoking and AML showed ORs lower than 1.0 but they were all based on very small numbers (less than 10 cases).

Interestingly, the association with maternal coffee consumption of at least 3 cups/day during pregnancy was different for smokers (0.9 [0.3,2.4]) and non-smokers (1.9 [1.0,3.5]). However, the interaction between maternal coffee drinking and maternal smoking during pregnancy was not significant.

The estimates for AL were unchanged when maternal alcohol, coffee drinking and parental smoking were included in the same model (Table 4). The observed association between ALL and maternal smoking during pregnancy did not remain

significant after adjustment for maternal coffee and alcohol consumption during pregnancy (OR=1.3 [0.9,1.9]).

The results remained unchanged after adjustment for socio-demographic factors (parental socio-professional categories, parental educational levels, place of residence) and for factors that had previously been shown to be related to childhood leukemia in the present study, such as birth order, repeated early common infections, day-care attendance and familial history of cancer.⁶

DISCUSSION

The role of maternal alcohol and coffee drinking during pregnancy, and parental smoking in childhood acute leukemia was investigated in a French, population-based, case-control study including 472 incident cases and 567 controls. An association with maternal alcohol consumption of more than 1 drink per day during pregnancy was observed. The highest consumption (more than 3 cups per day) of maternal coffee during pregnancy was related to AL in children whose mothers were non-smokers. Finally, no association with parental smoking was observed.

The exhaustiveness of the NRCL was estimated to be 99%, making selection in the case-identification process unlikely.¹ The attending physician's consent was required for inclusion of each case. This may have tended to select cases in better medical condition and underestimate those whose health was more seriously compromised such as children with AML or infants aged less than 2 years. However, the distributions of parental smoking and maternal alcohol and coffee drinking during pregnancy were very similar for the surviving cases and those who died after inclusion in the study.

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

The controls were randomly selected from the overall population. There was no difference between the cases and controls for the stratification variables (age, gender and region at the time of diagnosis) or for the socio-demographic characteristics

(parental educational level, socio-professional category), indicating that the recruitment process for the control group was successful.

The control group in the study was compared with the overall population from two French population-based surveys conducted on representative samples of 5508 and 13459 deliveries in 1981 and 1995, respectively.⁷ The controls' mothers had smoking habits and alcohol consumptions, especially for consumptions of more than 2 drinks per day, which were similar to those of the mothers interviewed in the surveys.

Over- and under-declaration by the case and control mothers were minimized in the present study, due to the fact that the use of standardized questionnaires reduced potential differential misclassifications. The general feeling of guilt associated with smoking and alcohol drinking may be stronger in mothers of children with AL than in mothers of healthy children. Such a bias seems unable to explain the absence of a relationship with smoking. Moreover, if the same guilt feeling had existed for alcohol drinking during pregnancy, it would have tended to underestimate the association. However, an association was clearly demonstrated. Conversely, non-differential misclassifications with respect to the number of cigarettes smoked or to the quantities of coffee or alcohol consumed during pregnancy are rather more likely. Besides, as expected, low birth weights were more frequent in children whose mother smoked during pregnancy. No particular birth outcome was associated with alcohol drinking, but the intake may be too low on average to produce an observable relationship.

Most of the literature concurs with respect to the absence of a relationship between parental smoking and childhood leukemia.^{2,4-5,8-14} Few studies have found maternal smoking to be significantly associated with the risk of ALL.¹⁵⁻¹⁶ Interestingly, two

studies have reported an association with maternal smoking that was restricted to children presenting with the CYP1A1*1 mutant genotype.^{11,17} The role of paternal smoking during childhood has been much less investigated, but most of the studies did not observe an association.^{4-5,10,14}

With regard to maternal alcohol consumption during pregnancy, the proportion of mothers consuming more than 1 drink per day was the same for the control group of this study and the population-based surveys.⁷ No association with ALL was reported by Van Steensel-Moll *et al.* 1985, Petridou *et al.* 1997, or Schuz *et al.* 1999.^{8-9,12} Infante-Rivard *et al.* even observed an inverse association with ALL, but those authors also reported a positive association with maternal alcohol drinking during the second or third trimester of pregnancy for children with a null GSTM1 genotype or a CYP2E1*5 mutation.¹⁸ Although very few studies of AML are available, they all evidenced a positive association with alcohol consumption.²⁻⁵ The influence of maternal alcohol intake may differ according to the kind of alcohol. In France, wine and beer to a lesser extent are the most popular drinks, while in other countries spirits and liquor might be preferred. The observed OR of 1.9 associated with high maternal coffee drinking during pregnancy in non-smoking mothers may be observed by chance in subgroup analyses, but it may also reflect a direct or indirect effect of caffeine. Interestingly, it has been shown that, for a given caffeine intake, blood caffeine concentrations were lower in smokers than in non-smoking women.¹⁹ Moreover, Ross *et al.* have suggested that coffee may act as an inhibitor of DNA topoisomerase II and induce abnormalities of chromosome 11q23 that resemble those induced by epipodophyllotoxins.²⁰ To the best of the authors' knowledge, only 4 studies have investigated the association between maternal coffee drinking and

childhood leukemia.^{5,9,20-21} An association was reported in two of those studies with OR values close to 2.5.^{5,20}

In conclusion, the present results suggest a possible role of the highest consumption of maternal alcohol during pregnancy in the etiology of childhood acute leukemia.

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Table 1: Sample description for the cases and controls

	Cases (%) n = 472	Controls (%) n = 567	p
Gender*			ns
Male	260 (55)	326 (58)	
Age at diagnosis (year)*			ns
< 2	44 (9)	78 (14)	
2-3	115 (24)	148 (26)	
4-5	110 (23)	109 (19)	
6-9	113 (24)	130 (23)	
≥ 10	90 (19)	102 (18)	
Region of residence at diagnosis			ns
Aquitaine	59 (13)	42 (7)	
Bretagne	45 (10)	70 (12)	
Centre	51 (11)	62 (11)	
Franche-Comté / Alsace	56 (12)	60 (11)	
Languedoc-Roussillon	31 (7)	48 (8)	
Midi-Pyrénées	32 (7)	42 (7)	
Haute / Basse Normandie	58 (12)	55 (10)	
Pays de Loire	48 (10)	75 (13)	
Picardie / Champagne Ardennes	53 (11)	69 (12)	
Poitou-Charentes / Limousin	39 (8)	44 (8)	
Parental socio-professional category			ns
Professional, technical workers, administrators, managers	196 (42)	228 (41)	
Clerical, sales and services workers	86 (18)	134 (24)	
Factory and agricultural workers	186 (40)	200 (36)	
Maternal education			ns
≤ High school	336 (74)	415 (74)	
> High school	120 (26)	144 (26)	
Paternal education			ns
≤ High school	336 (77)	424 (79)	
> High school	102 (23)	113 (21)	
Place of residence at diagnosis (population)			ns
< 2,000	165 (37)	223 (39)	
2,000 – 9,999	75 (17)	100 (18)	
10,000 – 49,999	58 (13)	62 (11)	
50,000 - 19,999	64 (14)	82 (15)	
≥ 200,000	86 (19)	98 (17)	

* Stratification variables

ns: p>0.05

Table 2: Maternal alcohol consumption and childhood leukemia

	Controls n=567 (%)	AL^a n=472 (%)	OR^b	95% CI^c	ALL^d n=407 (%)	OR^b	95% CI^c	AML^e n=62 (%)	OR^b	95% CI^c
<i>DURING PREGNANCY</i>										
All alcohol										
No	494 (90)	404 (89)	1.0	reference	344 (88)	1.0	reference	58 (95)	1.0	reference
Yes	54 (10)	51 (11)	1.1	[0.8-1.7]	47 (12)	1.3	[0.8-2.0]	3 (5)	0.4	[0.1-1.3]
≤ 1 glass / day	43 (8)	28 (6)	0.8	[0.5-1.3]	24 (6)	0.8	[0.5-1.5]	3 (5)	0.4	[0.1-1.6]
> 1 glass / day	11 (2)	23 (5)	2.4	[1.1-5.0]	23 (6)	2.8	[1.3-5.9]	0 (0)	-	-
Wine, beer, cider										
Yes vs. no	45 (8)	49 (10)	1.3	[0.9-2.1]	45 (11)	1.5	[0.9-2.3]	3 (5)	0.4	[0.1-1.5]
≤ 1 glass / day	37 (7)	29 (6)	1.0	[0.6-1.6]	25 (6)	1.0	[0.6-1.7]	3 (5)	0.5	[0.1-1.7]
> 1 glass / day	8 (1)	20 (4)	2.8	[1.2-5.6]	20 (5)	3.3	[1.4-7.6]	0 (0)	-	-
Spirits										
Yes vs. no	11 (2)	5 (1)	0.6	[0.2-1.8]	5 (1)	0.7	[0.2-2.2]	0 (0)	-	-
≤ 1 glass / day	10 (1.8)	5 (1)	0.7	[0.2-2.0]	5 (1)	0.8	[0.3-2.4]	0 (0)	-	-
> 1 glass / day	1 (0.2)	0 (0)	-	-	0 (0)	-	-	0 (0)	-	-
<i>AT TIME OF INTERVIEW</i>										
All alcohol										
No	451 (81)	377 (82)	1.0	reference	327 (82)	1.0	reference	48 (79)	1.0	reference
Yes	108 (19)	85 (18)	0.9	[0.7-1.3]	71 (18)	0.9	[0.7-1.3]	13 (21)	0.9	[0.4-1.8]
≤ 1 glass / day	68 (12)	40 (9)	0.7	[0.5-1.1]	32 (8)	0.7	[0.4-1.1]	8 (13)	0.8	[0.3-1.9]
> 1 glass / day	40 (7)	45 (10)	1.3	[0.8-2.1]	39 (10)	1.3	[0.8-2.2]	5 (8)	1.0	[0.3-2.7]
Wine, beer, cider										
Yes vs. no	91 (16)	78 (17)	1.0	[0.7-1.4]	67 (17)	1.0	[0.7-1.5]	10 (16)	0.7	[0.3-1.5]
≤ 1 glass / day	59 (11)	43 (9)	0.9	[0.6-1.3]	35 (9)	0.8	[0.5-1.3]	7 (11)	0.7	[0.3-1.8]
> 1 glass / day	32 (6)	35 (6)	1.3	[0.8-2.1]	32 (8)	1.4	[0.8-2.4]	3 (5)	0.6	[0.2-2.3]
Spirits										
Yes vs. no	34 (6)	21 (5)	0.8	[0.4-1.4]	16 (4)	0.7	[0.4-1.2]	4 (7)	1.3	[0.4-4.1]
≤ 1 glass / day	32 (5.7)	16 (4)	0.6	[0.3-1.1]	12 (3)	0.5	[0.3-1.0]	3 (5)	1.0	[0.3-3.4]
> 1 glass / day	2 (0.3)	5 (1)	3.4	[0.1- 18]	4 (1)	3.1	[0.5- 18]	1 (2)	10.9	[0.7-166]

^a AL: Acute Leukemia ^b Odds ratios adjusted for age, gender, region, socio-professional category and birth order ^c 95% CI: 95% Confidence Interval ^d ALL: Acute Lymphoblastic Leukemia ^e AML: Acute Myeloblastic Leukemia

Table 3: Maternal coffee consumption and childhood leukemia

	Controls n=567 (%)	AL^a n=472 (%)	OR^b	95% CI^c	ALL^d n=407 (%)	OR^b	95% CI^c	AML^e n=62 (%)	OR^b	95% CI^c
<i>DURING PREGNANCY</i>										
No	203 (37)	154 (34)	1.0	reference	134 (34)	1.0	reference	20 (33)	1.0	reference
Yes	341 (63)	298 (66)	1.1	[0.9,1.5]	255 (66)	1.1	[0.8,1.4]	40 (67)	1.6	[0.8,2.9]
≤ 3 cups / day	296 (55)	245 (54)	1.1	[0.8,1.4]	208 (54)	1.1	[0.8,1.4]	35 (59)	1.6	[0.8,3.0]
> 3 cups / day	45 (8)	53 (12)	1.5	[0.9,2.4]	47 (12)	1.4	[0.9,2.4]	5 (8)	1.4	[0.5,4.4]
<i>AT TIME OF INTERVIEW</i>										
No	108 (19)	81 (18)	1.0	reference	71 (18)	1.0	reference	10 (16)	1.0	reference
Yes	451 (81)	381 (82)	1.1	[0.8,1.5]	327 (82)	1.0	[0.7,1.5]	51 (84)	1.4	[0.6,3.0]
≤ 3 cups / day	364 (65)	295 (64)	1.1	[0.8,1.5]	254 (64)	1.0	[0.7,1.4]	39 (64)	1.3	[0.6,2.8]
> 3 cups / day	87 (16)	86 (19)	1.2	[0.8,1.9]	47 (18)	1.2	[0.7,1.8]	12 (20)	1.8	[0.7,4.7]

^a AL: Acute Leukemia ^b Odds ratios adjusted for age, gender, region, socio-professional category and birth order ^c 95% CI: 95% Confidence Interval ^d ALL: Acute Lymphoblastic Leukemia ^e AML: Acute Myeloblastic Leukemia

Table 4: Parental smoking and childhood leukemia

	Controls n=567 (%)	AL^a n=472 (%)	OR^b	95% CI^c	ALL^d n=407 (%)	OR^b	95% CI^c	AML^e n=62 (%)	OR^b	95% CI^c
MATERNAL SMOKING										
<i>Before pregnancy[‡]</i>										
No	357 (66)	302 (67)	1.0	reference	256 (66)	1.0	reference	43 (74)	1.0	reference
≤ 10 cig. / day	105 (19)	81 (18)	0.9	[0.6,1.3]	72 (18)	1.0	[0.7,1.4]	9 (16)	0.6	[0.3,1.3]
> 10 cig. / day	79 (15)	69 (15)	1.0	[0.7,1.4]	63 (16)	1.1	[0.7,1.6]	6 (10)	0.6	[0.2,1.4]
<i>During pregnancy</i>										
No	463 (83)	372 (79)	1.0	reference	315 (78)	1.0	reference	54 (87)	1.0	reference
Yes	97 (17)	98 (21)	1.3	[0.9,1.7]	90 (22)	1.4	[1.0,1.9]	8 (13)	0.6	[0.3,1.5]
≤ 5 cig. / day	58 (10)	50 (11)	1.1	[0.7,1.7]	48 (12)	1.3	[0.9,2.0]	2 (3)	0.2	[0.04,1.0]
> 5 cig. / day	37 (7)	44 (10)	1.4	[0.9,2.2]	41 (10)	1.5	[0.9,2.5]	3 (5)	0.7	[0.2,2.6]
<i>During childhood[§]</i>										
No	377 (69)	315 (70)	1.0	reference	267 (68)	1.0	reference	45 (78)	1.0	reference
≤ 10 cig. / day	97 (18)	74 (16)	0.9	[0.6,1.3]	67 (17)	1.0	[0.7,1.4]	7 (12)	0.5	[0.2,1.2]
> 10 cig. / day	68 (13)	63 (14)	1.1	[0.7,1.5]	57 (15)	1.1	[0.8,1.7]	6 (10)	0.6	[0.2,1.6]
PATERNAL SMOKING										
<i>Before pregnancy[‡]</i>										
No	278 (53)	207 (50)	1.0	reference	176 (49)	1.0	reference	29 (55)	1.0	reference
≤ 20 cig. / day	214 (41)	180 (43)	1.2	[0.9,1.6]	156 (43)	1.2	[0.9,1.6]	23 (43)	0.9	[0.5,1.7]
> 20 cig. / day	33 (6)	28 (7)	1.0	[0.6,1.7]	27 (8)	1.2	[0.7,2.0]	1 (2)	0.2	[0.02,1.7]
<i>During childhood[§]</i>										
No	238 (46)	173 (42)	1.0	reference	146 (41)	1.0	reference	25 (47)	1.0	reference
≤ 20 cig. / day	244 (47)	204 (50)	1.2	[0.9,1.5]	176 (50)	1.2	[0.9,1.6]	27 (51)	1.1	[0.5,1.8]
> 20 cig. / day	33 (7)	31 (8)	1.1	[0.6,1.9]	30 (9)	1.3	[0.8,2.3]	1 (2)	0.2	[0.03,1.7]

^a AL: Acute Leukemia ^b Odds ratios adjusted for age, gender, region, socio-professional category and birth order ^c 95% CI: 95% Confidence Interval ^d ALL: Acute Lymphoblastic Leukemia ^e AML: Acute Myeloblastic Leukemia

Table 5: Maternal smoking, coffee and alcohol during pregnancy in childhood acute leukemia (multivariate model)

	AL^a		ALL^b		AML^c	
	OR^d	95% CI^e	OR^d	95% CI^e	OR^d	95% CI^e
Maternal smoking during pregnancy (Yes vs. no)	1.2	[0.8,1.6]	1.3	[0.9,1.9]	0.3	[0.1,1.0]
≤ 5 cig. / day	1.0	[0.7,1.6]	1.3	[0.8,2.0]	0.2	[0.1,1.0]
> 5 cig. / day	1.3	[0.8,2.1]	1.4	[0.8,2.3]	0.6	[0.2,2.5]
Maternal coffee during pregnancy (Yes vs. no)	1.1	[0.8,1.4]	1.0	[0.7,1.4]	1.7	[0.9,3.4]
≤ 3 cups / day	1.0	[0.8,1.4]	1.0	[0.7,1.3]	1.7	[0.8,3.2]
> 3 cups / day	1.5	[0.9,2.4]	1.4	[0.8,2.3]	2.6	[0.8,8.6]
Maternal alcohol during pregnancy (Yes vs. no)	1.1	[0.7,1.7]	1.2	[0.8,1.9]	0.2	[0.1,1.1]
≤ 1 glass / day	0.8	[0.4,1.3]	0.8	[0.5,1.5]	-	
> 1 glass / day	2.3	[1.1,4.9]	2.7	[1.2,5.7]	-	

^a AL: Acute Leukemia ^b ALL: Acute Lymphoblastic Leukemia ^c AML: Acute Myeloblastic Leukemia ^d Odds ratios adjusted for age, gender, region, socio-professional category and birth order ^e 95% CI: 95% Confidence Interval