Parental alcohol consumption and risk of childhood acute lymphoblastic leukemia and brain tumors

Short title: Parental alcohol and childhood ALL and brain tumors.

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ABSTRACT (250 words)

Purpose

Childhood acute lymphoblastic leukemia (ALL) is the most common childhood malignancy and brain tumours (CBTs) are the leading cause of cancer death in children. In our Australian case-control studies of these cancers, we investigated whether parental alcohol consumption before or during pregnancy was associated with risk.

Methods

Cases were identified through the ten Australian pediatric oncology centers, and controls were recruited through national random-digit dialling. Detailed information on alcohol consumption, including beverage type, amount and timing, was collected from 690 case families (388 ALL and 302 CBT) and 1396 control families. Data were analysed using unconditional logistic regression.

Results

We found no evidence that maternal alcohol use before or during pregnancy was associated with an increased risk of either cancer; rather, there was evidence of inverse associations, particularly with wine. For both cancers, we observed U-shaped associations with paternal alcohol consumption in the year before the pregnancy, possibly driven by reduced risk at moderate levels of beer and wine intake and increased risk associated with high levels of beer intake. Moderate intake of spirits by fathers was associated with an increased risk of CBT but not ALL. These findings would be strengthened by corroboration in other studies. While the inverse associations with wine may be interesting mechanistically, the public health message remains that maternal alcohol use during pregnancy causes serious disorders in the offspring and should be avoided.

Conclusions

Our findings suggest that men, as well as women, should limit their alcohol intake when planning a pregnancy.

Keywords: alcohol, leukemia, brain tumors, childhood, epidemiology, neoplasms, pregnancy

Childhood acute lymphoblastic leukemia (ALL) is the most common childhood malignancy and brain tumours (CBTs) are the leading cause of cancer death in children. The causes of these childhood malignancies are largely unknown and, as they usually occur early in childhood, the focus of recent research has been largely on pre-natal and early post-natal factors. Although various environmental factors have been investigated, results published so far have been largely non-definitive [1,2].

Alcohol is rated as a Class 1 carcinogen by the International Agency for Research on Cancer [3,4]. Through its metabolite acetaldehyde, alcohol can interfere with DNA synthesis and repair and lead to DNA hypomethylation [5]. There is evidence that alcohol consumption increases the risk of cancers of the breast, liver, oropharynx and colon in adults [3,6] and, when consumed during pregnancy, has damaging effects on the fetus [7]. Thus, it is plausible that parental alcohol consumption in specific time windows may influence the risk of cancers in the offspring through mechanisms previously described and, perhaps, others not yet understood [8].

Two recent reviews of the published literature relating to maternal alcohol consumption during pregnancy and risk of ALL have reported significant heterogeneity among the study results [8,9]. The largest studies have tended to produce null results [9]. The review by Latino-Martel *et al*. included a meta-analysis, and the authors concluded that maternal alcohol intake was not associated with risk of ALL; however, they were unable to examine dose-response associations due to lack of published data [9]. In another review, Infante-Rivard and Zein concluded that it was not possible to draw definitive conclusions because of methodological limitations, inconsistent results and a lack of consideration of genotype and disease subtypes [8]. Fewer studies have specifically investigated paternal preconception alcohol consumption and risk of ALL [10-13] and the results among those that have are inconsistent; however, two of these studies provided some evidence of an increased risk at higher levels of intake [10,12].

Most studies of maternal alcohol consumption during pregnancy and risk of CBT have reported null findings [14-19], while one study reported an increased risk of CBT with maternal beer consumption [20]. The only published study of paternal alcohol consumption and CBT [21] reported an increased risk with lifetime paternal consumption of >200 litres of ‘hard liquor’.

We have conducted two national population-based case-control studies of childhood malignancies in Australia: one of ALL between 2003 and 2006 (Aus-ALL) and one of CBT between 2005 and 2010 (Aus-CBT). They had very similar designs, and aimed to investigate nutritional, environmental and genetic risk factors for these malignancies. We ascertained specific disease subtypes among the cases, and collected detailed information about specific types and quantities of alcohol consumed by both parents during key time periods related to the index pregnancy. We set

out to analyse the associations between parental alcohol consumption and risk of ALL and CBT separately, and to report our findings in separate manuscripts. However, early in this process, we observed similarities between the results for the two outcomes and decided to present the results together in this paper.

METHODS

Study design and methods for Aus-ALL and Aus-CBT have been described previously [22-24]. Briefly, incident cases aged 0-14 years were identified through all 10 Australian pediatric oncology centers, where the large majority of cases are treated. In the complete years of recruitment for which registry data were available (to 2008), 100% of ALL and 97% of CBT cases were registered as having been treated at the participating hospitals (Personal communication, Australian Paediatric Cancer Registry November 2012). Controls were recruited by national random digit dialling (RDD), and frequency matched to cases by age (within 1 year), sex and state of residence in a ratio of approximately 3:1. To the extent possible, we frequency matched the controls recruited in 2005 and 2006 to both case series. Both studies were approved by the Human Research Ethics Committees at all participating hospitals, and parents of participating children provided written informed consent.

Questionnaires mailed to parents asked about demographic characteristics, medical and residential histories, engagement in activities involving potential exposure to carcinogens, dietary intake and supplement use. Mothers were asked if they had consumed alcohol in the 12 months before pregnancy and during each trimester of pregnancy, and fathers were asked if they had consumed alcohol in the 12 months before the pregnancy. Parents who answered positively were asked to estimate their weekly intake of light, mid-strength and full-strength beer, wine, pre-mixed soda and spirits during those periods. To aid recall, each type of alcohol was recorded in the volumes commonly served: a 375 ml can or bottle for beer and alcoholic mixers, a 150ml glass of wine, and a 30 ml nip or shot of spirits. The percent of alcohol by volume for each beverage type was obtained from the Australian National Health and Medical Research Council website (http://www.nhmrc.gov.au/your-health/alcohol-guidelines) and the grams of alcohol of each beverage type consumed per week calculated. Grams of alcohol were then converted to standard drinks; a ‘standard drink’ in Australia contains 10g of alcohol [25] .

In addition to parent-reported measures of socio-economic status (SES), each participant’s address was linked to an Australian Bureau of Statistics (ABS) Census Collection District (CD). The ABS assigns each CD a score for its area-based Index of Relative Socio-Economic Disadvantage (IRSD) after each quinquennial census.[26].

Unconditional logistic regression was used to estimate odds ratios (ORs) for the association between parental alcohol consumption and each outcome. The controls recruited contemporaneously with the cases in each study were included in the respective data analyses; controls recruited in 2005-2006 were included in the analysis of both outcomes. We also undertook a sensitivity analysis by randomly assigning the 2005-2006 controls to one study or the other and repeating the analysis to assess the impact on results. As the results were virtually unchanged (data not shown), only the results from our primary analysis are presented below.

Alcohol intake was initially modelled as a categorical variable. For paternal alcohol dose, linear and quadratic terms were estimated by recoding each dose category to its orthogonal polynomial rank, and these were entered into the model as continuous variables; their p-values were used to assess the trend. All analytical models included age, sex and State of residence (the frequency matching variables) and variables meeting the classical definition of confounding; that is, they were associated with case/control status, and with alcohol use among control parents. The variables included on this basis were: ethnicity, child's year of birth, parental age, parental smoking, household income and birth order (for maternal alcohol and ALL). All analyses were undertaken using PASW statistics v18 (SPSS Inc., IBM Corporation, Armonk, New York).

RESULTS

We were notified of 568 incident ALL cases, of whom 49 were ineligible: 30 from non-English speaking backgrounds, 12 overseas visitors, three whose biological mother was unavailable, and four who did not reach remission. Of the 519 eligible cases, 416 (80%) consented to participate in the study. Information on alcohol consumption was available for 388 (93%) case mothers and 328 (79%) case fathers: 4 case families provided only demographic data and 23 provided no data. We were notified of 794 incident CBT cases; 64 were ineligible (36 with no English-speaking parent, 23 non-residents, five with no biological parent available). Of the 730 eligible cases, 374 cases (51.2%) consented to participate. Information on alcohol consumption was provided by 302 (85.1%) consenting case mothers and 247 (66.0%) consenting case fathers; 33 case families provided only demographic data and 39 provided no data. Two clinicians independently assigned each case to a CBT subtype; there was complete agreement. The numbers of cases in each subtype, and their recorded diagnoses, have been previously published [24].

Between 2003 and 2010, 4703 families eligible to be controls were identified by RDD, of whom 3012 (64%) agreed to participate. In accordance with requirements for age and sex frequency-matching, we recruited 2165 of these children to the study. Information on alcohol use was available for 1396 control mothers (64% of recruited) and 1198 control fathers (55% of recruited), while 587 control families provided only demographic data and 170 families provided no data.

Demographic and other characteristics of participating cases and controls were similar, although there were some differences (Table 1). CBT controls were slightly more likely than CBT cases to be female; ALL controls were more likely than ALL cases to have parents with a tertiary education, and less likely than cases to be first born; and both sets of controls were more likely to be of European ethnicity and to have parents aged over 35 years than the cases. More CBT controls than cases were born in the period 1998-2003 because some were frequency matched to ALL cases, as explained previously. Cases and controls lived in similarly socially advantaged CDs, and both groups lived in more highly socially advantaged CDs than the Australian population as a whole. The mean IRSD scores were 1027 and 1025 for ALL case and control CDs (respectively), 1024 for both CBT case and control CDs, and 1006.0 for all Australian CDs. T-test P-values for ALL and CBT cases vs all Australian CDs were both <0.001. These data were consistent with the fact that income and education were comparable among cases and controls (Table 1).

Approximately 63% of ALL case mothers, 76% of ALL control mothers, 70% of CBT case mothers and 77% of CBT control mothers reported drinking alcohol in the 12 months before the index pregnancy (Table 2). The proportions of mothers who drank during pregnancy were much lower; the respective percentages were 30%, 41%, 30% and 38%. The kappa statistics for agreement between alcohol use before and during pregnancy were 0.35 for ALL study mothers and 0.30 for CBT study mothers (both *P*-values <0.001). Wine was the most commonly consumed beverage – and beer the least – by mothers in both time periods (Table 2).

The ORs for maternal alcohol use and risk of ALL and CBT were consistently below the null in both time periods, with evidence of an inverse trend for ALL and, to a lesser extent, CBT (Table 3). The results for any alcohol intake before pregnancy were unchanged when the analysis was restricted to women who did not drink during pregnancy (results not shown). Similarly, the ORs for maternal consumption of beer, wine and spirits were consistently below the null for ALL and CBT, with the exception of maternal use of spirits, where the OR for CBT was close to the null. The results did not change materially when associations with one beverage type were adjusted for all other types, or when the models were adjusted for paternal alcohol use (not shown). When these associations were analysed by trimester of pregnancy, the results were the same as for the whole pregnancy (not shown). The observed associations with maternal alcohol intake were similar among women who used folic acid supplements before or during pregnancy and those who did not (not shown).

Approximately 86% of ALL case fathers, 90% of CBT case fathers and 90% of all control fathers reported drinking alcohol in the 12 months before the index pregnancy (Table 2), and the amounts consumed were generally higher than consumed by mothers. Among fathers, beer was the most

commonly consumed beverage and wine the least. On average, the weekly volume of pure alcohol consumed by fathers from beer was approximately double that from either wine or spirits.

There was some evidence of a U-shaped relationship between the amount of alcohol fathers consumed in the 12 months before the pregnancy and risk of both cancers. The ORs with increasing consumption fell to a minimum at >14 to 21 standard drinks a week and rose to a maximum at >28 drinks a week. The *P*-values for the quadratic terms in the ALL and CBT models were 0.005 and 0.02 respectively (Table 4). Evidence of a U-shaped relationship with intake was also observed in (and possibly driven by) consumption of beer; the *P*-values for the quadratic terms in the ALL and CBT models for beer were 0.03 and 0.18 respectively (Table 4). Relatively few fathers drank ≥ 7 drinks of wine or spirits per week, so it was not possible to investigate associations with higher intake of these beverages. As among mothers, there was evidence of an inverse association at moderate levels of wine intake, while the ORs for spirits were elevated even at moderate intake levels for CBT but not for ALL (Table 4). The ORs for any beer, wine or spirits did not change when mutually adjusted or adjusted for maternal intake (not shown).

The associations observed with parental alcohol consumption in immunophenotypic and cytogenetic subtypes of ALL were similar to the overall results, although the numbers of cases in some subtypes precluded the estimation of stable or precise estimates (Supplementary Table 1). There were insufficient cases in most subgroups to investigate dose-response associations or associations with individual beverage types.

The pattern of results for maternal alcohol use was consistent among the two largest CBT subtypes, low grade gliomas and embryonal tumours, with ORs below unity for any intake before or during pregnancy (Supplementary Table 2). Similar patterns of results were seen for maternal wine consumption. There were insufficient data to examine dose-response associations or associations with other beverage types. The results for paternal alcohol intake in the two subtypes were also consistent with the overall results, with some indication of U-shaped associations, although data were relatively sparse (Supplementary Table 2). Similar to the overall results, the ORs for spirit consumption were elevated for both subtypes, while the ORs for wine and beer consumption were somewhat inconsistent between them. There were insufficient cases to investigate dose-response associations with individual beverages, and there were too few cases in other subgroups to analyse separately.

To assess the possible impact on our findings of non-completion of exposure questionnaires, which was higher among control than case parents, we carried out a multiple imputation analysis. Among questionnaire completers, alcohol drinking patterns were associated with income group (i.e. higher beer intake with lower income, and higher wine intake with higher income). No income data were

available for non-completers, but their IRSD (which was strongly correlated with income group) was similar to that of completers in the $40-$70,000 pa income group for mothers, and to the <$70,000 pa income group for fathers. Therefore, we imputed alcohol consumption in non-completers by randomly assigning to them overall alcohol use and beverage-specific patterns of intake seen in these lower income groups, and repeated the logistic regression analysis (adjusting for matching variables, birth year and IRSD – the only variables available for parents with missing data). The process was repeated 50 times and the results averaged. The resulting adjusted ORs for mothers and fathers for specific alcohol exposures were not materially different from the main reported results (Supplementary Table 3).

An additional analysis was undertaken to explore the potential for bias in recall relative to the child's age and, therefore, the recall interval, by restricting the analysis to children aged 0-2 years. The patterns of results for maternal intake were similar, although the ORs were somewhat closer to the null for ALL and further from the null for CBT, and the confidence intervals were wider (Supplementary table 4). The biggest difference was an elevated OR for CBT seen with maternal spirit intake. The patterns for paternal intake were also relatively unchanged, with the lowest ORs still seen for 14-21 drinks per week, although the statistical evidence for a U-shaped association was weaker, as expected with the smaller numbers. The beverage specific results also showed trends similar to, but weaker than, those in the original analysis (Supplementary table 5).

DISCUSSION

We found no evidence that maternal alcohol use in the 12 months before or during pregnancy increased the risk of ALL or CBT; rather, there was some evidence of inverse associations, particularly with wine. As wine was the beverage most commonly consumed by mothers, the pattern of results we observed for any alcohol intake may be attributable to the association with wine. For both ALL and CBT, there was a suggestion of a U-shaped association with paternal alcohol consumption in the 12 months before the pregnancy that may have been driven by decreasing ORs at moderate levels of beer and wine intake and increased risk associated with high levels of beer intake. Paternal consumption of moderate levels of spirits was associated with an increased risk of CBT but not ALL. We were not able to determine the strength or direction of any associations with high levels of maternal wine intake or heavy paternal intake of beverages other than beer, as few parents reported high intake levels for those beverages.

Most previous studies of maternal alcohol use and risk of ALL or CBT have focussed on intake during pregnancy rather than before pregnancy. The weak inverse associations we observed between maternal consumption of alcohol during pregnancy and risk of ALL were consistent with those seen in some previous studies [27-29,12], but not others. Some studies reported evidence of

an increased risk for total alcohol [10,13], for wine, beer and spirits [30], for 'wine/beer/cider' [31], or for beer and liquor but not wine [32]. Among the three studies that reported associations with maternal pre-pregnancy alcohol use, one reported a positive association [13], while two reported no association [10,12]. All but one previous study of maternal alcohol use during pregnancy and risk of CBT reported null findings, both for any alcohol intake [15,17,28,18,19] and for consumption of specific beverages [14,17,16,19]. An exploratory study [20] reported an increased risk of CBT with maternal beer consumption during pregnancy: OR 3.53 (95% CI 1.16, 10.8), but only 10/74 case mothers and 10/138 control mothers reported drinking beer in that study.

Relatively few previous studies of ALL or CBT have investigated associations with paternal alcohol intake. The authors of a study of infant ALL [10] concluded that 'neither the type nor the amount of alcohol consumed by fathers was related to the risk of infant leukemia' (p27). However, the findings were suggestive of a weak U-shaped association for overall paternal alcohol intake in the month before pregnancy, with the lowest OR being 0.52 (95% CI 0.24, 1.14) for 31-45 drinks/month and the highest OR being 1.60 (95% CI 0.90, 2.85) for ≥46 drinks/month. The patterns of intake of different beverages may have accounted for the apparent U-shape, but the relative frequency of consumption of each beverage was not reported in the paper. In addition, the results for wine and liquor were consistent with weak inverse associations, with the ORs for ≥16 drinks per month being 0.60 (95% CI 0.23, 1.56) and 0.70 (95% CI 0.34, 1.43) respectively, while the ORs for beer were indicative of an increased risk: 1.58 (95% CI 0.88, 2.83) and 1.53 (95% CI 0.91, 2.55) for 16-30 and ≥31 cans of beer per month respectively. On the other hand, a Canadian study (Quebec) observed a 50% increased risk with paternal intake of spirits (OR: 1.5, 95% CI: 1.1, 1.9) and beer (OR: 1.5, 95% CI: 1.1, 2.0), but not wine (OR: 1.2, 95% CI 0.8, 1.5) in the month before the pregnancy [12]. The ORs were similarly elevated for total alcohol intake.

The only previous study of paternal alcohol use and CBT [21] reported an increased risk (OR 4.43, 95% CI 1.94, 10.14) among children of fathers who had consumed more than 200 litres of 'hard liquor' during their lifetime. In China, where this study was conducted, hard liquor is consumed mainly as white distilled alcohol with an alcohol content of up to 60% by volume, which is higher than spirits sold in Australia (around 40%, 80 proof). Nonetheless, these results are consistent with our observation of an increased OR for paternal spirit consumption.

Some alcoholic beverages – including beer and wine – contain anti-oxidant compounds, such as polyphenols, that are known to mitigate the DNA damaging effects of ethanol and acetaldehyde, at least at low to moderate levels of intake [33,34]. Such mechanisms would be consistent with the U-shaped association with beer and inverse association with wine at moderate levels of intake suggested by our results. However, the bioavailability of polyphenols from wine, particularly at the

doses seen during pregnancy in this study, are not known with certainty [35,36], and their potential anti-carcinogenic effect in the current context is speculative.

Paternal pre-conception intake of a moderate level of spirits, which do not contain polyphenols, was associated with an increased risk of CBT, possibly due to the unameliorated harmful effects of ethanol and acetaldehyde. This is consistent with the fact that ethanol disrupts the normal antioxidant systems within the testes and causes oxidative stress that can result in a variety of DNA lesions in sperm [37]. That we did not observe an association between the paternal spirits consumption and risk of ALL indicates different pathways for effects of alcohol on risk of ALL and CBT. For example, in ALL, chromosomal translocations are stable and tend to occur in the absence of other types of DNA aberration, while in CBT (an epithelial malignancy) the presence of multiple deletions and unbalanced translocations occurring in clonally derived tumor cell populations is a common feature indicative of chromosomal instability [38].

Given the potential for different beverage-specific biological effects, the patterns and types of alcoholic drinks consumed in different study populations may explain some of the between-study variation in findings. While wine was the alcoholic beverage most commonly consumed by mothers in our study and in the three other studies that provided this information [12,30,32], in our study and in the Quebec study the percentages of mothers who drank any wine during pregnancy (Australia: 30%, Quebec: 38%) was greater than the percentage who drank any beer or spirits (Australia: 15%, Quebec: up to 29% (exact figure not provided in text)). Inverse associations were observed with overall alcohol use in these two studies. In studies where the percentages of mothers who drank any wine were less than the percentages who drank any beer or spirits, however, no associations were seen with ALL [30,32] or CBT [19] (same study population as Rudant et al., 2008 [32]). Thus, given the possible protective effect of polyphenols in wine, it is plausible that the inverse associations with maternal alcohol intake seen in some studies were attributable to the relative preponderance of wine consumption in those populations. Alternatively, it may be that some as yet unknown lifestyle factor or other confounder could explain the apparent inverse associations we and others have observed for maternal wine consumption. Although residual confounding is possible, no strong contenders for such an effect are obvious from current evidence, and income as a measure of socio-economic status was included in our analyses.

The proportion of fathers who consumed alcohol was substantially higher than the proportion of mothers who did so in our study and the other three that provided this information [10,13,12]. The proportion of fathers who drank alcohol in our study (90%) was higher than in any other, and our highest intake category was 28 drinks/week, compared with 11 (converted from 46 drinks/month) [10], 14 [13], and 21 [12] drinks/week, suggesting higher intake in fathers in our study population.

Thus, it is possible that U-shaped associations for alcohol intake were not reported in these other studies because there were insufficient fathers in the highest categories of intake. Moreover, there is no indication that non-linear relationships were explored. However, while our ORs for ≥7 - <21 drinks/week were below the null, the corresponding ORs in the study by Infante-Rivard et al.[12] were around 1.5, not consistent with a U-shaped association. No previous study reported an inverse association with paternal wine consumption or a U-shaped association with beer intake, although only one previous study investigated dose-response associations for individual beverages [10]. In our study and a Canadian study [13], the proportions of fathers who drank beer in the year before the index pregnancy were similar to the combined proportions of wine and spirit drinkers. However, unlike our study, the Canadian study reported null findings for total paternal alcohol intake and for beer, wine and liquor individually.

The most plausible mechanism by which paternal pre-conception alcohol consumption could contribute to the development of cancer in the offspring is through DNA damage in developing sperm. Human studies have shown that alcohol use can increase sperm DNA aneuploidy [39] or demethylation.[40] Importantly, sperm are limited in their ability to repair DNA damage during the final weeks of spermatogenesis [41,42] and sperm containing DNA lesions can reach and fertilize an ovum, which may cause disease in the offspring [43,41]. Studies in rats have demonstrated that increased paternal alcohol intake can affect sperm cytosine methyltransferase mRNA levels [44], probably as a result of perturbed folate metabolism, which could alter the fidelity of establishment of normal epigenetic marks after fertilization [45].

Maternal alcohol consumption during pregnancy affects the cells of the developing fetus via the placental circulation; that is, more directly than the putative mechanism for the effect of paternal exposure (via the germ cell). And the weak inverse associations suggested by our results for maternal wine consumption during pregnancy are consistent with a mitigating effect of polyphenols contained in wine (the beverage preferred by mothers in our study) against the harmful effects of other carcinogens, including acetaldehyde produced from ethanol. Mechanisms potentially underlying an inverse association with maternal preconception alcohol use are less well understood.

Our studies had strengths and limitations. Participation fractions among eligible case families were 80% for ALL and 51% for CBT. As information about those who were eligible but did not participate was not available (other than age and sex, where the distributions were similar to participating cases), it was not possible to determine whether participating cases were representative of all eligible cases with respect to potential risk factors. Control families were recruited by national RDD using state-of-the-art methods and, according to the most recent data available [46,47], approximately 90% of Australian households had a landline telephone connection during

the recruitment period. Therefore, residences contacted are likely to be representative of the wider population. Overall, participation among eligible control families was 64% and, although no individual information was available for those who declined, area-based SES scores were higher among participating controls than among the general Australian population. However, importantly, participating cases and controls had similar distributions of socio-economic variables indicating that they were drawn from similar population bases.

The representativeness of our control mothers with respect to alcohol consumption during pregnancy is difficult to determine in the absence of a standardized national survey instrument [48] and by the fact that published estimates vary widely, possibly due to differences in methodology. The range of reported estimates of maternal alcohol use during pregnancy – 34% [49] to 80% [50] – include the value of 39% among control mothers in our study. Among our control parents, 89% of fathers and 76% of mothers reported any alcohol consumption in the 12 months prior to the index pregnancy. These figures are similar to those published in the 2004 National Drug Strategy Survey Report; 91% of men and 87% of women aged 20-40 years reported any alcohol consumption in the previous 12 months [51].

Information about beverage-specific intake was requested from both parents, including the timing of consumption with respect to the index pregnancy. This information was provided by approximately 93% ALL case mothers, 79% ALL case fathers, 81% CBT case mothers, 66% case fathers, 70% control mothers overall and 60% control fathers overall. Parents who did not provide data on alcohol consumption lived in areas with lower IRSD scores (on average) than those who completed questionnaires. However, the results from our analysis of imputed intake data were similar to those from our main analysis. We adjusted for household income in all analyses, and further adjustment for IRSD or education did not alter the effect estimates.

Inherent in case-control studies is the possibility that case parents' rumination about the causes of their child's cancer might lead them to recall exposure more completely than control parents, thus causing recall bias. If maternal alcohol consumption were protective against CBT and/or ALL, recall bias due to rumination could obscure such a result. Furthermore, the results of our analysis of parental alcohol use among children aged 0-2 (where recall intervals are shorter) were similar to, although less precise than, our overall findings, suggesting that recall bias is unlikely to account for our findings.

Australian women are aware of the undesirability of alcohol consumption during pregnancy [52], although this knowledge does not necessarily alter their behaviour [49]. Thus, it is plausible that guilt about having possibly harmed their child may have led case mothers to under-report their alcohol use; this could, perhaps, explain why the ORs in our and some previous studies have tended

to be below unity. This type of response bias is less likely to account for our findings for paternal alcohol intake in the year prior to conception, however, as relatively little is known about potential paternal effects during this period. Moreover, the observed patterns of results for paternal use – that is, an inverse association with wine and an elevated OR for spirits (CBT only) – are not consistent with responses having been influenced in this way. Error in exposure measurement is nonetheless likely, particularly as the data on alcohol use were self-reported and the index pregnancy was 15 years earlier for some parents; however, the recall period for about half the families was less than five years: 55.2% for ALL cases, 43% for CBT cases and 47.3% for all controls (Table 1).

Although we collected detailed information about average weekly intake of specific beverage types, we were unable to investigate potential effects of episodic heavy ('binge') drinking, or the effects of drinking alcohol with or without food. As these behaviours may also be associated with beverage type [36], we recommend that future studies collect information about them.

In conclusion, our findings suggest that higher levels of paternal pre-conception alcohol consumption, or any intake of spirits, may increase the risk of CBT. Recent Australian data indicate that approximately 8% of men aged 30-39 yrs (the average age group of fathers in our study) drink at least four standard drinks every day or on most days [53], so a large number of men may be putting their future offspring at risk. We also found some evidence of inverse associations between parental wine consumption before or during pregnancy and risk of both CBT and ALL. While this may be of interest mechanistically, it does not change the public health message that maternal alcohol use during pregnancy should be avoided as it is associated with serious cognitive deficits and fetal alcohol spectrum disorders [7]. Our findings suggest that men, as well as women, should be advised to limit their alcohol intake when planning a pregnancy.

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Table 1: Distribution of demographic characteristics of cases and controls in the Australian Study of Acute Lymphoblastic Leukemia Australian Study of Childhood Brain Tumors.

	Category	ALL case n (%)	ALL Control n (%)	CBT case n (%)	CBT Control n (%)
Any data available		393	1249	335	1363
Maternal alcohol data available		388 (98.7)	870 (69.7)	302 (90.1)	941 (69.0)
Paternal alcohol data available		328 (83.5)	750 (60.0)	247 (73.7)	801 (58.8)
Child sex	Female	177 (45.0)	588 (47.1)	138 (41.2)	643 (47.3)
	Male	216 (55.0)	661 (52.9)	197 (58.8)	720 (52.8)
Child age group	0-1	35 (8.9)	100 (8.0)	35 (10.4)	144 (10.6)
	2-4	179 (45.5)	539 (43.2)	95 (28.4)	422 (31.0)
	5-9	111 (28.2)	430 (34.4)	101 (30.1)	444 (32.6)
	10-14	68 (17.3)	180 (14.4)	104 (31.0)	353 (25.9)
Birth year	1988-1997	121 (30.8)	368 (28.5)	91 (27.2)	332 (24.4)
	1998-2003	254 (64.6)	825 (66.1)	139 (41.5)	679 (49.8)
	2004-2010	18 (4.6)	56 (4.5)	105 (31.3)	352 (25.8)
Child state of residence[a]	NSW/ACT	123 (31.3)	403 (32.3)	114 (34.0)	404 (29.6)
	Victoria/Tasmania	118 (30.0)	365 (29.2)	97 (29.0)	378 (27.7)
	SA/NT	43 (10.9)	109 (8.7)	20 (6.0)	111 (8.1)
	Western Australia	40 (10.2)	119 (9.5)	44 (13.1)	148 (10.9)
	Queensland	69 (17.6)	253 (20.3)	60 (17.9)	322 (23.6)
Year of diagnosis/ Recruitment	2003-2004	188 (47.8)	632 (50.6)	-	-
	2005-2006	205 (52.2)	617 (49.4)	115 (34.4)	617 (45.2)
	2007-2008	-	-	116 (34.6)	392 (28.8)
	2009-2010	-	-	104 (31.0)	354 (26.0)
Maternal age group	<25	60 (15.3)	154 (12.4)	55 (16.5)	134 (9.9)
	25-34	266 (67.7)	806 (64.7)	205 (61.4)	843 (62.3)
	35+	67 (17.0)	286 (23.0)	74 (22.2)	376 (27.8)
Paternal age group	<25	23 (6.4)	32 (4.3)	18 (6.2)	26 (3.2)
	25-34	222 (61.7)	448 (59.6)	167 (57.2)	442 (54.1)
	35+	115 (31.9)	272 (36.2)	107 (36.6)	349 (42.7)
Highest parent education	No university /college	224 (57.0)	678 (54.3)	166 (49.6)	677 (49.7)
	University/college	169 (43.0)	570 (45.7)	169 (50.4)	685 (50.3)

Household Income	Up to $40,000	96 (24.6)	313 (25.4)	57 (17.3)	183 (15.0)
	$40,001-$70,000	115 (29.5)	391 (31.7)	91 (27.7)	339 (27.7)
	$70,001-$100,000	93 (23.8)	270 (21.9)	83 (25.2)	328 (26.8)
	>$100, 000	86 (22.1)	258 (20.9)	98 (29.8)	373 (30.5)
Birth order	1	187 (47.6)	495 (39.7)	150 (45.1)	557 (40.9)
	2	120 (30.5)	439 (35.2)	109 (32.7)	483 (35.5)
	3+	86 (21.9)	314 (25.2)	74 (22.2)	321 (23.6)
Ethnic group	European	282 (71.8)	957 (76.6)	210 (62.7)	1023 (75.1)
	At least 50% European	80 (20.4)	193 (15.5)	76 (22.7)	203 (14.9)
	At least 50% non-European	14 (3.6)	48 (3.8)	15 (4.5)	59 (4.3)
	Indeterminate	17 (4.3)	51 (4.1)	34 (10.1)	78 (5.7)
Case sub-groups					
ALL	Pre-B ALL	341			
	T-Cell ALL	37			
	Hyperdiploidy	111			
	ETV6-RUNX1 (t12, 21)	59			
	Other transformations	46			
	Trisomy 21	65			
	Any genetic feature	246			
CBT	Low-grade glioma			143	
	Embryonal Tumor			71	

[a] ACT: Australian Capital Territory; NSW, New South Wales; NT, Northern Territory; SA, South Australia.

Table 2: Distribution of maternal and paternal prenatal alcohol intake

	12 months before pregnancy				During pregnancy			
Maternal	ALL cases	ALL controls	CBT cases	CBT controls	ALL cases	ALL controls	CBT cases	CBT controls
Any alcohol	244 (63.4)	653 (76.3)	209 (69.7)	710 (76.6)	117 (30.4)	352 (40.6)	91 (30.3)	361 (38.5)
Any wine	156 (41.2)	443 (52.3)	139 (46.3)	494 (52.7)	84 (21.8)	258 (29.8)	61 (20.3)	263 (28.1)
Any beer	48 (12.6)	129 (15.1)	38 (12.7)	132 (14.1)	21 (5.5)	67 (7.7)	17 (5.7)	72 (7.7)
Any spirits	104 (27.1)	243 (28.5)	91 (30.3)	243 (25.9)	29 (7.5)	77 (8.9)	27 (9.0)	77 (8.2)
Paternal								
Any alcohol	281 (85.9)	672 (90.0)	221 (89.8)	717 (90.0)				
Any wine	99 (30.6)	292 (39.1)	71 (28.9)	287 (36.0)				
Any beer	245 (75.2)	585 (78.3)	192 (78.0)	616 (77.3)				
Any spirits	119 (36.7)	250 (33.5)	103 (41.9)	264 (33.1)				

Table 3: Maternal alcohol consumption before and during pregnancy and risk of acute lymphoblastic leukemia and childhood brain tumors

	ALL case/ control n	OR[a]	95% CI	CBT case/ control n	OR[b]	95% CI
In the 12 months before pregnancy						
No alcohol[c]	141/203	1.00	Referent	91/217	1.00	Referent
Any alcohol	244/653	0.50	0.38, 0.66	209/710	0.75	0.55, 1.02
>0-2 d/w	75/198	0.51	0.36, 0.72	54/206	0.66	0.44, 0.98
>2-4 d/w	58/119	0.66	0.44, 0.97	46/140	0.81	0.53, 1.24
>4-7 d/w	47/120	0.51	0.34, 0.78	42/114	0.97	0.62, 1.52
>7 d/w	64/214	0.38	0.26, 0.55	67/250	0.69	0.47, 1.03
Linear trend *P*-value			<0.001			0.29
No beer[d]	332/725	1.00	Referent	257/792	1.00	Referent
Any beer	48/129	0.83	0.58, 1.19	38/132	0.93	0.62, 1.40
No wine[d]	223/404	1.00	Referent	156/424	1.00	Referent
Any wine	156/443	0.64	0.49, 0.84	139/494	0.86	0.64, 1.15
No spirits/mixers[d]	280/610	1.00	Referent	208/686	1.00	Referent
Any spirits/mixers	104/243	0.82	0.61, 1.10	91/243	1.19	0.86, 1.63
During pregnancy						
None[e]	268/514	1.00	Referent	209/576	1.00	Referent
Any	117/352	0.62	0.48, 0.81	91/361	0.75	0.56, 1.00
>0-2 d/w	84/239	0.66	0.49, 0.88	58/246	0.68	0.49, 0.96
>2 d/w	33/112	0.56	0.37, 0.86	33/115	0.90	0.58, 1.40
Linear trend *P*-value			0.001			0.18
No beer[f]	364/798	1.00	Referent	283/865	1.00	Referent
Any beer	21/67	0.71	0.43, 1.19	17/72	0.73	0.41, 1.28
No wine[f]	301/607	1.00	Referent	239/674	1.00	Referent
Any wine	84/258	0.66	0.49, 0.89	61/263	0.74	0.53, 1.03
No spirits/mixer[f]	356/788	1.00	Referent	273/860	1.00	Referent
Any spirits/mixer	29/77	0.74	0.47, 1.17	27/77	1.03	0.63, 1.68

[a] ORs adjusted for matching variables, year of birth group, maternal age group, ethnicity, household income, birth order, maternal smoking.
[b] ORs adjusted for matching variables, year of birth group, maternal age group, ethnicity, household income, maternal smoking.
[c] Reference group is no alcohol before or during pregnancy
[d] Reference group is no alcohol of that type before or during pregnancy.
[e] Reference group is no alcohol during pregnancy.
[f] Reference group is no alcohol of that type during pregnancy.

Table 4: Paternal alcohol consumption in the 12 months before pregnancy and risk of acute lymphoblastic leukemia and childhood brain tumors

	ALL case/ control n	OR[a]	95% CI	CBT case/ control n	OR[a]	95% CI
No Alcohol	46/75	1.00	Referent	25/80	1	Referent
Any Alcohol	281/672	0.72	0.48, 1.08	221/717	1.02	0.62, 1.69
0 to <7 d/w	157/332	1.00	Referent	110/346	1	Referent
≥7 to <14 d/w	68/168	0.86	0.61, 1.22	52/185	0.97	0.66, 1.43
≥14 to <21 d/w	29/120	0.51	0.32, 0.81	24/131	0.58	0.35, 0.96
≥21 to <28 d/w	20/46	0.91	0.51, 1.61	20/57	1.24	0.70, 2.23
≥28 d/w	50/81	1.20	0.79, 1.83	40/78	1.53	0.95, 2.44
Quadratic term *P*-value			0.005			0.02
Beer						
No beer	81/162	1.00	Referent	54/181	1	Referent
Any beer	245/585	0.87	0.63, 1.19	192/616	1.08	0.75, 1.55
>0 to <7 beer/wk	116/294	0.84	0.59, 1.20	98/301	1.14	0.77, 1.69
≥7 to <14 beer/wk	56/133	0.87	0.57, 1.33	27/138	0.69	0.40, 1.17
≥14 to <21 beer/wk	21/86	0.50	0.29, 0.88	32/108	1.11	0.66, 1.88
≥21 to <28 beer/wk	16/16	2.07	0.96, 4.45	8/22	1.26	0.51, 3.10
≥28 beer/wk	36/56	1.23	0.73, 2.05	24/53	1.57	0.87, 2.84
Quadratic term *P*-value			0.03			0.18
Wine						
No wine	225/455	1.00	Referent	175/510	1	Referent
Any wine	99/292	0.69	0.52, 0.94	71/287	0.81	0.58, 1.14
>0 to <7 wine/week	73/202	0.74	0.53, 1.02	53/194	0.89	0.62, 1.30
≥7 wine/week	26/90	0.60	0.37, 0.97	18/93	0.64	0.36, 1.11
Linear trend *P*-value			0.01			0.12
Spirits/mixer						
No spirits	205/497	1.00	Referent	143/533	1	Referent
Any spirits	119/250	1.11	0.84, 1.48	103/264	1.46	1.07, 2.00
>0 to <7 spirits/week	91/193	1.12	0.83, 1.52	85/220	1.46	1.05, 2.03
≥7 spirits/week	28/57	1.07	0.64, 1.78	18/44	1.43	0.78, 2.64
Linear trend *P*-value			0.56			0.03

[a] ORs adjusted for child's age, sex, state of residence, year of birth group, ethnicity, paternal age group, paternal smoking, household income.

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