Cigarette Smoking and Alcohol Consumption by Parents of Children with Acute Myeloid Leukemia: An Analysis within Morphological Subgroups—A Report from the Children's Cancer Group

Richard K. Severson, Jonathan D. Buckley, William G. Woods, Denis Benjamin, and Leslie L. Robison

Division of Epidemiology, University of Minnesota, Minneapolis, Minnesota 55454 [R. K. S., L. L. R.]; Division of Pediatric Hematology/Oncology, University of Minnesota, Minneapolis, Minnesota 55455 [R. K. S., W. G. W., L. L. R.]; Department of Preventive Medicine, University of Southern California, Los Angeles, California 90033 [D. B. J.]; and Department of Pediatric Pathology, Children's Hospital and Medical Center, Seattle, Washington 98105 [D. B. J.]

Abstract

Data from a case-control study of childhood acute myeloid leukemia (AML) including 187 matched case-control pairs were examined for evidence of associations between parental cigarette smoking and alcohol consumption and the subsequent development of childhood AML. The cases were stratified by French-American-British morphology in order to evaluate potential differences in risk based on this classification system. There was little evidence of any association between cigarette smoking by parents during the index pregnancy and childhood AML. There was an increased risk of AML among children who were diagnosed at or before 2 years of age and whose mothers reported consuming alcohol during their pregnancies (odds ratio, 3.00; 95% confidence interval, 1.23 to 8.35). This finding appeared to be especially pronounced for AML with a monocytic component (M4/M5) (odds ratio, 9.00; 95% confidence interval, 1.25 to 394.5), but a cautious interpretation of these data are advised because of the small number of cases.

Introduction

AML is a malignancy which is more frequently diagnosed in adults than in children. In children, the vast majority of leukemias are acute lymphoblastic leukemia, with AML comprising only about 15% of these malignancies. The annual incidence rate of AML in the United States is approximately 4 per 1 million in children younger than 15 years of age.

An increased risk of AML in adults has been strongly associated with exposures to ionizing radiation, benzene, and alkylating agents (2-5). Several preliminary reports have recently suggested that smokers may be at increased risk of AML (6-11), but further work in this area is needed. Due in part to the relative rarity of childhood AML, very few epidemiological studies have been undertaken.

It is now generally accepted that there is an increased risk of acute leukemia in children with specific congenital or inherited conditions (12-14) and in children exposed in utero to ionizing radiation (15-16). Some of the other reported, but less well established, risk factors include direct exposure of children to residential electromagnetic fields (17, 18), pesticides (19), and human growth hormone (20), maternal marijuana (21), or cigarette (22, 23) use during pregnancy, and selected paternal occupations prior to conception including those in nuclear power plants (24).

As part of its ongoing epidemiological research program, the CCG conducted a case-control study of childhood AML which was designed to investigate selected in utero and postnatal exposures. Previous reports have considered occupational exposures of the parents (19) and maternal drug use during pregnancy (21). This article examines tobacco and alcohol consumption by the parents during the index pregnancy. The cases were stratified by FAB morphology (25, 26) in order to evaluate potential differences in risk based on this classification system.

Materials and Methods

Cases were identified through the registration files of the CCG, a cooperative clinical trials group which, at the time...
of this study, included approximately 100 primary and affiliate institutions throughout the United States and Canada. Detailed study methods are presented elsewhere (19, 21). Briefly, patients were eligible if they were newly diagnosed with AML from January 1980 through December 1984 and were younger than 18 years old at diagnosis. In addition, there had to be a telephone in the residence of the patient and the biological mother of the patient had to be available for interview and speak English. Table 1 provides basic demographic information on the cases and controls included in the study.

For each case of AML within the CCG, initial diagnostic bone marrow was examined by a pathologist at the institution of diagnosis and categorized according to the FAB classification system. Of the 262 cases of AML identified as eligible through this process, 204 (77.9%) mothers were interviewed. Subsequent to the initial diagnosis of AML, five cases were determined at the institutional level to be leukemias other than AML and 12 cases were not classified because adequate case materials were unavailable. These 17 cases were excluded, leaving a total of 187 cases of AML included in this analysis (Table 1).

One control per case was obtained utilizing a previously described procedure for random digit dialing (27). Controls were individually matched to the cases on date of birth (±2 years for cases ≥4 years of age; ±1 year for cases 1–3 years of age, and ±6 months for cases younger than 1 year old), race (white and nonwhite); and telephone area code and exchange. Eligibility criteria and interviewing procedures for the controls were the same as for the cases. A total of 260 eligible controls was identified, of whom 204 (78.5%) were interviewed.

Mothers and fathers of study subjects were interviewed separately by telephone. The mother’s interview lasted approximately 1 h and included questions on demographics, events and exposures during the index pregnancy and birth, occupational history, reproductive history, family medical history, and postnatal exposures to the child. The father’s interview took approximately 30 min and concentrated on occupational factors, medications, and X-ray exposures. Interviewers were informed of neither the case/control status of the index child nor the specific hypotheses under investigation.

As part of the interview, both the mother and the father were asked about cigarette smoking status (current, past, or never) and smoking practices during; (a) the month immediately preceding the index pregnancy; (b) the index pregnancy; and (c) nursing. Detailed information was requested regarding the trimesters in which the parent smoked and the number of cigarettes smoked/day during the pregnancy. Both the mother and father were also asked about current and past alcohol consumption habits. If either parent consumed alcohol during the month immediately prior to conception, during the index pregnancy, or while nursing, detailed information was sought regarding the type (wine or beer or spirits), amount (number of glasses, cans, bottles, or ounces consumed per day, week, or month), and the trimesters during which consumption occurred.

Odds ratios and exact (two-sided) 95% confidence intervals were calculated using a matched pairs analysis (28). Results were considered to be significant if 1.0 was not included within the confidence interval. Conditional logistic regression was used to compare cases and controls while adjusting for potential confounding factors and to assess potential dose-response relationships (29).

Results

Table 2 shows the estimates of the relative risk of AML among children of mothers who: (a) were smoking cigarettes at the time of interview (current smoker); (b) had ever smoked cigarettes; and (c) smoked cigarettes during the pregnancy with the index child. Note that, since this is an individually matched study, the numbers in the discordant pairs columns refer to the number of case and (matched) control pairs in which the control exposure differed from the case exposure. Risks are shown for all cases combined and for separate FAB categories. The small number of patients with FAB classification of M6, acute erythroleukemia (three cases), and M7, acute megakaryocytic leukemia (one case), precluded their analysis as separate entities, and they were included only in the analyses based on all cases combined. No statistically significant associations were found for any measure of maternal cigarette smoking. More specifically, no statistically significant associations were noted when exposures were restricted to the month immediately preceding pregnancy; the first, second, or third trimester of pregnancy; or during the time the mother was nursing the index child (data not shown). Also, there were no significant associations when these data were stratified by age at diagnosis (0–2, 3–10, and 11–17 years of age at diagnosis). Analysis of the paternal smoking data resulted in similar nonsignificant findings (data not shown).

Data on maternal alcohol consumption are shown in Table 3. There were no statistically significant associations for mothers who were either current drinkers or ever drinkers. There was a significantly increased risk of acute monocytic leukemia (M5) among children whose mothers consumed alcohol during the pregnancy. This increased risk was consistently associated with alcohol consumption during each of the three trimesters of pregnancy (first trimester OR, 4.0; second trimester OR, 5.0; third trimester OR, 2.5). Risk
Table 2  Risk of childhood AML by FAB classification and maternal cigarette smoking

<table>
<thead>
<tr>
<th>Smoking exposure</th>
<th>FAB</th>
<th>Positive cases; negative controls</th>
<th>Negative cases; positive controls</th>
<th>OR</th>
<th>95% CI</th>
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<td>40</td>
<td>44</td>
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<td>4</td>
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<tr>
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<td>M4</td>
<td>7</td>
<td>6</td>
<td>1.17</td>
<td>0.34-4.20</td>
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<td>M5</td>
<td>4</td>
<td>5</td>
<td>0.80</td>
<td>0.16-3.72</td>
</tr>
</tbody>
</table>

Current smoker

Ever smoked

Smoked during pregnancy

Table 3  Risk of childhood AML by FAB classification and maternal alcohol consumption

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<th>Alcohol exposure</th>
<th>FAB</th>
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<th>Negative cases; positive controls</th>
<th>OR</th>
<th>95% CI</th>
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<td>8</td>
<td>4</td>
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</table>

Current drinker

Ever drank

Drank during pregnancy

also appeared to be increased for each type of beverage consumed (wine OR, 4.5; beer OR, 2.0; and spirits OR, 4.0).

To further characterize this association, data were stratified by age of the child at the time of diagnosis (0–2, 3–10, and 11–17 years of age). Because of the small number of cases, the myelomonocytic (M4) and monocytic (M5) subtypes were combined in these analyses. As shown in Table 4, there was a significantly increased risk of all AML combined among children less than 3 years of age whose mothers consumed alcohol during the pregnancy. Although the data are based on small numbers, this increased risk appears to be accounted for primarily within the myelomonocytic (M4) and monocytic (M5) subtypes. Ideally, it would be of interest to evaluate this association by trimester of pregnancy, but the limited number of subjects precluded a meaningful analysis of these data. Paternal drinking during the month prior to conception had no significant effect on the risk of leukemia in their offspring (data not shown).

Multivariate analyses were performed to evaluate potential dose-response relationships and to assess findings within the context of interaction and possible confounding factors. In general, the multivariate findings confirmed the results from the classical analyses. There was no statistically significant interaction between maternal consumption of alcohol during the index pregnancy and any of the following: (a) age of the mother at the time of birth of the index child; (b) education of the mother; (c) use by the mother of mind altering drugs during or in the year prior to the index preg-
Parental Smoking and Drinking and Childhood AML

Discussion

Previous studies have established that in utero exposures may result in the development of cancer in children and young adults (30–33). Thus, a major focus of this study, which is the first large epidemiological case-control study of AML in children, was on exposures during the time of the index pregnancy. Previous reports from this study have suggested that maternal exposure to pesticides or maternal marijuana use during pregnancy may result in the subsequent development of AML in the child (19, 21).

Two studies have suggested that maternal smoking during pregnancy may be related to the development of lymphoma (34) and Wilms tumor (35) in the child, but other studies have found no association with brain tumors (36, 37), rhabdomyosarcoma (38), germ cell tumors (39), Wilms tumor (40), neuroblastoma (41), hepatoblastoma (42), and all cancers combined (43–45). In six previous studies of childhood leukemia, three studies have reported a positive association with maternal smoking during pregnancy (23, 34, 35) while the other three found no association (45–47). The present study is the first study to find no association for AML and to investigate morphology-specific subtypes of AML. There have been fewer studies of paternal smoking, with associations noted for neuroblastoma (41), rhabdomyosarcoma (38), and brain tumors, lymphoma, leukemia, and all cancers combined (34). Other studies, however, have reported no association (37, 39, 42, 47, 48), and a follow-up report (49) on rhabdomyosarcoma from the investigators on the original study of rhabdomyosarcoma (38) was negative. Based on all the studies to date, we suggest that there is very little convincing evidence that parental smoking is causally related to the occurrence of cancer in their children.

The potential relationship between maternal alcohol consumption during pregnancy and childhood cancer has been less well studied, with positive associations noted for brain tumors (37) and neuroblastoma (41). However, most studies have been negative (36,38–40,42,46,48). The two studies of childhood leukemia which considered maternal alcohol consumption found no association, although one of these studies was restricted to acute lymphoblastic leukemia (46) and the other was based on all leukemias combined (which presumably includes only a small number of patients with AML) (48). Thus, this study is the first to evaluate the association between maternal alcohol consumption and childhood AML. An increased risk of AML was found among children under 3 years of age whose mothers consumed alcohol during pregnancy. Risk appeared to be increased consistently across each trimester of pregnancy and there did not appear to be any important differences by type of beverage consumed (wine, beer, or spirits). Although the numbers were small, much of the increased risk appeared to be accounted for within the myelomonocytic and monocytic subtypes of AML, which are characteristic of a younger age at diagnosis.

There was no significant evidence of a dose-response based on the total number of drinks consumed during the pregnancy; (d) sex of the index child; and (e) race of the index child. There was also little evidence for confounding of the relationship between maternal alcohol consumption during pregnancy and the risk of AML in the index child for any of these variables.

There was a statistically significant interaction between maternal consumption of alcohol during the index pregnancy and age of the child at the time of diagnosis. This interaction was noted for all AML combined (P = 0.043) and for the monocytic (M4/M5) subtypes (P = 0.039). The age-specific risk estimates were similar to those reported in Table 4, with most of the increased risk accounted for within the youngest age group. For children less than 3 years of age at diagnosis, the risk for AML associated with maternal drinking during the pregnancy was 3.50 (95% CI, 1.47–8.67) and the risk for the monocytic (M4/M5) subtype was 9.00 (95% CI, 1.14–71.04). There was some suggestion of an increasing risk of all AML combined in children younger than 3 years old with increasing total number of drinks consumed by the mother during the pregnancy (compared to children of nondrinkers, OR = 2.1 for children whose mothers consumed 1–20 drinks, OR = 2.8 for children whose mothers consumed 21 or more drinks), but the test for trend was not significant (P = 0.63). There was also a significantly increased risk of the myelomonocytic and monocytic subtypes among children diagnosed at less than 3 years of age whose mothers consumed 21 or more drinks during the pregnancy (OR, 9.9; 95% CI, 1.1–92.7), but the test for trend was not significant (P = 0.79). Of the seven mothers who consumed 21 or more drinks during pregnancy and whose children developed myelomonocytic or monocytic leukemia prior to 3 years of age, the median numbers of drinks consumed during pregnancy was 80 (approximately 2 drinks/week) and the mean was 100.7 (approximately 2.5 drinks/week).

Discussion

Previous studies have established that in utero exposures may result in the development of cancer in children and young adults (30–33). Thus, a major focus of this study, which is the first large epidemiological case-control study of AML in children, was on exposures during the time of the index pregnancy. Previous reports from this study have suggested that maternal exposure to pesticides or maternal marijuana use during pregnancy may result in the subsequent development of AML in the child (19, 21).
pregnancy. On the other hand, there was a 10-fold increased risk of myelomonocytic and monocytic leukemia among children younger than 3 years old whose mothers consumed 21 or more drinks during pregnancy, suggesting that children of mothers who consume relatively large amounts of alcohol during pregnancy may be at increased risk of myelomonocytic and monocytic leukemia immediately or soon after birth.

It may be important to note that many of the increased risks found in this analysis pertained to the M4/M5 subtypes of AML in infants. Previous reports on AML have noted increased risks in the infant M4/M5 subtypes associated with maternal marijuana use during pregnancy (21) and with pesticide exposure both directly to the child and through occupational exposures of the parents (19). Taken as a whole, these findings suggest that the infant M4/M5 subgroup may be one of the more fruitful areas in which to conduct further extensive and detailed studies of potential etiological relationships. For example, it may be helpful to consider focusing attention on infant leukemia cases with chromosome band 11q23 abnormalities which are quite common in the M4/M5 subtypes of AML (50), as well as in infants with acute lymphoblastic leukemia (51) or mixed lineage leukemia (52).

We view this study as primarily hypothesis generating in nature. We urge caution in interpretation of these results since multiple tests were preformed and some findings may be due to chance. Although to our knowledge it is the first large case-control study of childhood AML, many of the morphology-specific analyses were based on relatively small numbers. In addition, we excluded subjects whose families either did not speak English or did not have a telephone. Another concern is that case parents may recall exposures more readily than control parents. In order for this to explain our findings, however, one would have to hypothesize that the mothers of children diagnosed with myelomonocytic and monocytic subtypes of AML were selectively better at recalling (or overreporting) their exposures compared to the mothers of children diagnosed with another subtype of AML.

Referral bias is an obvious concern in this study since cases were identified through major pediatric medical centers. As part of the control selection process, controls were individually matched to the cases on geographic area (in addition to age and race). Our research suggests that over 93% of the expected number of pediatric cancers among children younger than 15 years old in the United States are seen within the two main pediatric oncology groups (the Childrens Cancer Group and the Pediatric Oncology Group) (53). Each of these groups covers relatively well defined geographic regions of the country. For example, a child living in the state of Minnesota who is diagnosed with leukemia is overwhelmingly likely to be seen at a CCG institution. Thus, it seems unlikely that referral bias would be a major problem in this study.

Because of the preliminary nature of these findings, proposing a mechanism by which alcohol consumption during pregnancy may be causally related to AML would be highly speculative at this point. However, there is strong evidence that heavy alcohol consumption by the mother during pregnancy affects the fetus (54) and alcohol and its metabolites have been suggested to be teratogenic and carcinogenic (55). Several case reports have suggested an association between fetal alcohol syndrome and hepatoblastoma (56), neuroblastoma (57), Hodgkin’s Disease (58), rhabdomyosarcoma (59), and acute lymphoblastic leukemia (59) in children. An alternative explanation is that there is some uncontrolled confounding factor which would account for these findings. Further studies of this observation need to be completed before any firm conclusions may be made. The CCG is currently conducting a follow-up case-control study of childhood AML to test hypotheses related to pesticides and marijuana exposure. It will be possible in this larger group of cases to determine if alcohol consumption is associated with AML in general and with those AMLs with a monocytic component (M4/M5) in particular.

We suggest that investigators who are planning to conduct future studies of childhood leukemia seriously consider including a comprehensive maternal alcohol consumption history especially during the index pregnancy. A high priority for future studies of childhood AML should be the subdivision of cases by FAB morphological type. Studies fortunate enough to include this feature should make every effort to include a sufficient number of cases in the less common classifications (such as the myelomonocytic and monocytic morphologies) to achieve sufficient power within each subtype.

Acknowledgments

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Appendix

See p. 439 of this article for Appendix table.

References


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<th>Grant</th>
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<td>Group Operations Office, University of Southern California, Comprehensive Cancer Center, Los Angeles, CA</td>
<td>Denman Hammond, M.D., Harland Sather, Ph.D., Mark Kralio, Ph.D., Jonathan Buckley, M.B.B.S., Ph.D., Madeline Bauer, Ph.D., Daniel Stram, Ph.D., and Jae Won Lee, Ph.D.</td>
<td>CA 11539</td>
</tr>
<tr>
<td>University of Michigan Medical Center, Ann Arbor, MI</td>
<td>Raymond Hutchinson, M.D.</td>
<td>CA 02971</td>
</tr>
<tr>
<td>University of California Medical Center, San Francisco, CA</td>
<td>Katherine Matthay, M.D.</td>
<td>CA 17829</td>
</tr>
<tr>
<td>University of Wisconsin Hospital, Madison, WI</td>
<td>Paul Gaynon, M.D.</td>
<td>CA 05436</td>
</tr>
<tr>
<td>Children's Hospital and Medical Center, Seattle, WA</td>
<td>Ronald Chard, M.D.</td>
<td>CA 10382</td>
</tr>
<tr>
<td>Rainbow Babies and Children's Hospital, Cleveland, OH</td>
<td>Susan Shurin, M.D.</td>
<td>CA 20320</td>
</tr>
<tr>
<td>Children's Hospital National Medical Center, Washington, D.C.</td>
<td>Gregory Reaman, M.D.</td>
<td>CA 03888</td>
</tr>
<tr>
<td>Children's Hospital of Los Angeles, Los Angeles, CA</td>
<td>Jorge Ortega, M.D.</td>
<td>CA 02649</td>
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<td>Children's Hospital of Columbus, Columbus, OH</td>
<td>Frederick Ruymann, M.D.</td>
<td>CA 03750</td>
</tr>
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<td>Columbia Presbyterian College of Physicians and Surgeons, New York, NY</td>
<td>Sergio Piomelli, M.D.</td>
<td>CA 03526</td>
</tr>
<tr>
<td>Children's Hospital of Pittsburgh, Pittsburgh, PA</td>
<td>Joseph Mirro, M.D.</td>
<td>CA 36015</td>
</tr>
<tr>
<td>Vanderbilt University School of Medicine, Nashville, TN</td>
<td>John Lukens, M.D.</td>
<td>CA 26270</td>
</tr>
<tr>
<td>Doernbecher Memorial Hospital for Children, Portland, OR</td>
<td>Robert Neerhout, M.D.</td>
<td>CA 26044</td>
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<td>University of Minnesota Health Sciences Center, Minneapolis, MN</td>
<td>Williams Woods, M.D.</td>
<td>CA 07306</td>
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<td>Children's Hospital of Philadelphia, Philadelphia, PA</td>
<td>Anna Meadows, M.D.</td>
<td>CA 11796</td>
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<td>Peter Steinherz, M.D.</td>
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<td>CA 13809</td>
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