Smoking in Adult Survivors of Childhood Acute Lymphoblastic Leukemia

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Background: Health-related behaviors are of particular concern in survivors of childhood cancer as they are at increased risk for second cancers and long-term organ dysfunction. The purpose of this study was to compare the smoking behavior and associated factors in young-adult survivors of childhood acute lymphoblastic leukemia (ALL) with those in sibling controls.

Methods: A telephone interview that surveyed smoking behavior was conducted with 592 young-adult survivors, treated before age 20 years on Children’s Cancer Group ALL protocols, and 409 sibling controls. Using stratified chi-squared analyses and Cox proportional hazards models, we compared the rates of smoking initiation and smoking cessation between survivors and control subjects. Demographic characteristics (age, sex, race, and education) and psychological factors (mood and self-concept) were examined as predictors interacting with survivorship in logistic regression analyses to try to distinguish a subgroup of survivors who may be at greater risk for smoking.

Results: Survivors were significantly less likely to have ever smoked (23.0% versus 35.7%; P<0.0001) and thus were less likely to ever be regular, daily smokers than sibling controls (19.1% versus 31.3%; P<0.0001). Survivors were less likely to quit smoking than sibling controls (26.6% versus 35.2%), although this result was not statistically significant. There were no interactions between survivor status and either demographic or psychological features on smoking behavior.

Conclusions: Young-adult survivors of childhood ALL are less likely to experiment with smoking but, once having started, are at similar risk for becoming habitual, persistent smokers as sibling controls. [J Natl Cancer Inst 1998;90:219–25]

Survivors of childhood leukemia not only have a sevenfold excess risk for second cancers (1) but also have an increased risk for chronic cardiac and pulmonary damage due to their previous therapy (2, 3). Health-related adverse behaviors, like cigarette smoking, can promote or exacerbate these long-term vulnerabilities.

Although many survivors of childhood cancer have levels of social competence and adjustment similar to those of their peers who have not had cancer, a vulnerable subset not only may have more psychological and behavioral problems (4, 5) but also may have worse decision-making skills and engage in more risk-taking behaviors, such as smoking (6, 7). One study (8) has shown that, despite survivors and parents believing that it was more important for these former patients to remain healthy compared with others, actual health-related behaviors, including tobacco use, did not correlate with this belief.

Three reports (9–11) have indicated that, in previous decades, childhood cancer survivors smoked at rates similar to those noted in control subjects or in the general population. However, one study (11) showed that the smoking rate in more recent years has declined significantly more rapidly in survivors than in control subjects.

Previous reports on cigarette smoking in survivors of childhood cancer have pooled survivors of all cancer types. This methodology may confound results because of variation in adjustment and predisposition to risk-taking behaviors related to heterogeneity of cancer diagnoses, prognoses, and treatments.

The goal of our study was to compare the smoking behavior and associated factors in a large sample of young-adult survivors of childhood acute lymphoblastic leukemia (ALL) with those in sibling controls. We hypothesized that, in the last decade, initiation and habitation of smoking are now less frequent in survivors than in control subjects and that smoking cessation occurs at a higher rate among survivors. Secondly, we expected to identify certain demographic or psychological variables that differentially affect survivors’ rates of smoking compared with sibling controls. Although this report focuses on a comparison between survivors and sibling controls, a subsequent report is planned to examine the relationship of medical treatment variables and smoking behavior among survivors.

Patients and Methods

Study Design and Participants

The study cohort consisted of long-term survivors of childhood ALL who were enrolled in Children’s Cancer Group (CCG) ALL protocols during the period from January 1, 1970, through December 31, 1987 [see Appendix Table 1]. The participants were interviewed by telephone during the period from November 15, 1989, through June 15, 1991. Eligibility criteria for study entry were as follows: 1) diagnosis of ALL in 1970 or later; 2) treatment for ALL before 20 years of age; 3) at least 18 years of age by October 15, 1990; 4) survival for at least 2 years.
years after diagnosis (95% of the sample had survived for at least 5 years after diagnosis); and 5) alive, in remission, and not receiving antileukemia treatment at follow-up.

Sibling controls had to be at least 18 years old within 9 months after their sibling survivor’s interview. One control subject per survivor was selected, if available, by matching as closely as possible on full sibling, sex, and age (in that priority order). All survivors and sibling controls had to speak and understand English.

Of the 53 CCG institutions that enrolled children on ALL protocols, 23 agreed to study participation and obtained Human Subjects Protection Committee approval at their respective institutions. Of the non-participating institutions, seven were no longer active CCG members, one had a competing study, one declined participation, and one was unable to obtain institutional review board approval. Of the total 731 eligible survivors enrolled, 68 (9.3%) could not be traced, 46 (6.3%) declined participation, 13 (1.8%) were unable to be interviewed (nine with Down’s syndrome, two drug dependent, one non-English speaking, and one with brain damage), and 11 (1.5%) were deceased. One subject (0.14%) did not provide information on smoking behavior. This resulted in a total of 592 survivors who completed the smoking portion of the interview. Of the 488 siblings chosen as control subjects, 43 (8.8%) could not be located, 33 (6.8%) refused, two (0.4%) were unable to be interviewed (one with schizophrenia and one deaf since birth), and one (0.2%) did not complete the interview, resulting in 409 control subjects who provided smoking information. Of the 592 survivors who completed the smoking portion of the interview, 183 did not have an eligible or available sibling control.

Each participant was mailed a consent form that was approved by their institution’s human subject’s approval committee. The consent form informed survivors that their siblings, if available, would also be contacted. Once the participant signed the form and the principal investigator received it, telephone interviews were arranged and conducted by trained interviewers. The interview process was similar for all survivors and their sibling controls. Participants had to be available for interview, and no proxies were accepted. With respect to smoking, data were collected regarding (a) ever having smoked, (b) ever having smoked regularly, (c) intensity of regular smoking, (d) age began smoking regularly, and (e) cessation history. Questions on education, employment history, marriage and family plans, fertility, offspring, health status, self-esteem, mood disturbance, and other risk-taking behaviors such as alcohol and drug use, and demographic characteristics were also included. Other reports on this cohort (12–14) have addressed different portions of the larger interview, e.g., psychological well-being, birth defects of offspring, and educational achievement. This study focuses only on smoking as an outcome measure.

The reliability and validity of telephone survey, recall, and self-report of smoking behavior have been tested by comparing telephone survey to in-person survey (15,16), subject recall to longitudinal documentation (17), and self-report to serum cotinine measurements (a biochemical marker of tobacco use) (18). Acceptable correlations between compared methods were demonstrated in all of these studies.

Definition of Key Variables

Smoking behavior was categorized as never smoker, ever smoker, and ever regular smoker (which was divided into current and former smoker). Never smoker was defined as never having smoked greater than or equal to 100 cigarettes (in total) in one’s lifetime. Ever smoker was defined as ever having smoked at least one cigarette per day for 6 months (henceforth denoted as regular smoker). Regular smoker has been variably defined in the literature. Some studies use qualitative measures, such as “getting used to smoking”; others use quantitative measures, such as smoking a certain number of cigarettes or smoking at a certain frequency. Our definition is relatively conservative, but it clearly distinguishes those smokers who have had a pattern of persistently regular use at some time and conveys the notion that smoking has progressed beyond experimentation or occasional use. Current smokers and former smokers were both classified under ever regular smokers but differentiated by answering “yes” or “no” to the question, “Do you still smoke?”

Age at smoking initiation was considered the age at which the respondent first began smoking regularly (as similarly defined in the NHS). Intensity of regular smoking was measured by the number of cigarettes smoked per day for those who smoked regularly. To obtain the prevalence of cessation, we divided the number of former smokers by the number of regular smokers and then multiplied that fraction by 100%.

Demographic variables were age at interview, which reflected participants’ birth year, sex, race/ethnicity (Caucasian versus minorities, primarily Hispanics and African-American), and amount of education (no college education versus any college education). Our sample consisted of survivors who were primarily treated in large referral centers, and the categorization of education reflects the background of such patients.

Psychological well-being was measured by use of the Profile of Mood States (POMS) for mood disturbance and the Harter Self-Perception Profile (Harter) for self-esteem. Previous studies have defined the validity and reliability of these scales (14). McNair et al. (22) suggest the use of the total POMS score as a single measure of affective state. A total summary self-concept score is also provided by the Harter measure.

These demographic and psychological variables have all been shown to significantly affect cigarette smoking both in adults and in adolescents (23–29).

Data Analysis

We examined the likelihood of ever smoking versus never smoking; ever regularly smoking versus not regularly smoking; and, once designated as a regular smoker, quitting smoking versus not quitting smoking. The association between survivor versus control status and smoking status was examined by comparing analyses with 2 × 2 tables, stratifying by demographic variables. The Cox proportional hazards model was used to evaluate the end points: rate of smoking initiation and smoking cessation over time. This methodology accounts for the differential time at risk for smoking between survivors and control subjects, inasmuch as control subjects were older and had more time to start or stop smoking. Race was not included in the Cox model for quitting smoking because of the relatively small proportion of minorities, who comprised a heterogeneous group and therefore violated assumptions of the Cox model. Multivariate logistic regression analyses were performed to adjust for the influence of age at interview, sex, race, and level of education on the probability of smoking or quitting in survivors compared with control subjects. Our analyses follow the same approach as that of Haupt et al. (14) and Zeltzer et al. (12); both groups of investigators also used this dataset and treated the survivors and control subjects as independent samples.

The age distribution differed substantially between the survivor and the control groups. Because smoking rates have declined in the general population over the years, the differences in smoking behavior between survivors and control subjects may have been influenced by the birth cohort effect, i.e., secular trend. To examine the potential confounding effects of age/birth year on our conclusions, we reconstructed the dataset to make the age distributions between the two groups more similar. We created a subsample that matched survivors and control subjects on the basis of birth year. This approach resulted in two comparison groups that were balanced on birth year, with a reduced sample size of 316 subjects in each group.

In addition, those participants who were older had more time to start or stop smoking. To adjust for this difference in time at risk for a smoking event, we first determined the younger age of each matched survivor and sibling control pair. Then, we ignored any smoking events (i.e., starting or quitting smoking) that occurred after this age in the pair. For example, if a survivor was 20 years old at the time of interview and his or her sibling control was 23 years old at the time of the interview, any changes in survivor smoking status that occurred after 20 years of age were ignored. Similarly, following the same strategy as the above approach, we used 18 years of age as the cutoff for both groups and ignored any changes in smoking status that occurred beyond that age. Analyses were repeated for each reconstructed dataset. The results with the use of these three separate reconstructed datasets were essentially the same as those in which the entire uncensored dataset was used. The significance level was consistent with the reduction in sample size.

When those survivors who smoked prior to their diagnoses and control subjects who smoked prior to the diagnosis of their matched sibling were excluded from the analyses, the results did not change. We also repeated the analyses after excluding survivors without sibling controls, and the results were similar. In an additional paired analysis, the McNemar test was used to compare the percentages of regular smokers between paired survivors and sibling controls (excluding survivors without sibling controls). The results again were consistent with those in which the groups were treated as independent samples. We therefore report the results using all survivors and control subjects and treat the two groups as independent samples.

Among current smokers, we used the two-sided t
Results

Demographics

Comparison of the demographic variables between survivors and the sibling controls has been described in detail in two previous reports (12,14). Of note, the survivors were younger at interview (median = 21.8 years; range = 18.0–33.2 years) than control subjects (median = 24.5 years; range = 18.1–41.6 years) (P < .01). Correspondingly, the relative distribution of survivors who were born after 1965 was much greater than that of control subjects (79% versus 53%). There were no significant differences between survivors and control subjects with regard to sex (male, 50.8% versus 46.2%), race (Caucasian, 87.8% versus 89.7%), and amount of education (any college, 48.6% versus 52.8%).

Smoking Initiation

Survivors were significantly less likely to have ever smoked than sibling controls (23.0% versus 35.7%; \( \chi^2 = 19.4; P < .0001 \)) and thus were also less likely to ever become regular daily smokers (19.1% versus 31.3%; \( \chi^2 = 19.7; P < .001 \)) (Table 1). Once having smoked 100 cigarettes or more, survivors were as likely as control subjects to become regular smokers (83.1% versus 87.7%; \( \chi^2 = 1.2; P = .3 \)). Multivariate logistic regression analyses showed that, for both survivors and control subjects, older subjects, females, and those who had some college education were more likely than others to have ever smoked and thus were more likely to ever become regular smokers. If we controlled for these demographic characteristics, the differences in percentage of ever smokers and of regular smokers between survivors and control subjects remained statistically significant (P = .002 and P = .005, respectively).

The Cox proportional hazards model demonstrated that, for both survivors and control subjects, smoking initiation increased rapidly with successive years after 12 years of age, peaked at 16–19 years of age, and then declined substantially after 19 years of age (Fig. 1). Relatively few subjects became smokers after the age of 20 years. When we controlled for age, sex, race, and education, smokers were significantly less likely to ever become regular smokers over time than control subjects (P = .007), which corroborated the above regression analysis.

Smoking Cessation

Although there was no statistically significant difference in the smoking cessation rates between survivors and control subjects who were regular smokers (26.6% versus 35.2%; \( \chi^2 = 2.1; P = .20 \)), the sample size for this analysis was considerably smaller than that for ever smokers or current smokers. There is, however, an 8.6 percentage point difference in estimates of quitting between the two groups, which would be clinically important. Multivariate logistic regression analysis showed that, for both survivors and control subjects, older subjects, females, and those who had some college education were more likely to quit. If we controlled for demographic factors, the difference in cessation rates between survivors and control subjects remained statistically not significant.

Table 1. Smoking outcomes for survivors and control subjects by demographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivors</th>
<th>Control subjects</th>
<th>( \chi^2 ) *</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>592</td>
<td>409</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>456</td>
<td>263</td>
<td>64.3</td>
<td>19.4</td>
</tr>
<tr>
<td>Ever smokers</td>
<td>136</td>
<td>146</td>
<td>35.7</td>
<td>19.4</td>
</tr>
<tr>
<td>Current smokers</td>
<td>113</td>
<td>128</td>
<td>31.3</td>
<td>19.7</td>
</tr>
<tr>
<td>Current smokers</td>
<td>83</td>
<td>83</td>
<td>20.3</td>
<td>6.9</td>
</tr>
</tbody>
</table>

*Survivors with education (any college): 286, 98.7% vs. 198, 92.2% (P = .001).

†Among the four survivors and two control subjects with education: 207, 81.1% vs. 156, 83.8% (P = .001).

\( \chi^2 \) = Chi-square statistic from two by two table.
In the Cox proportional hazards model, again no statistically significant difference was found between survivors and control subjects (Fig. 2). Smokers in both the survivor and the sibling control groups continued to quit smoking at a consistent, similar rate for at least 10 years after initiation. However, more than 60% of all participants who were regular smokers continued to smoke at 10 years.

**Current Smokers**

Survivors were significantly less likely to be current smokers (14.0% versus 20.3%; $\chi^2_1 = 6.9; P = .009$). (Table 1)

Multivariate logistic regression analysis showed that, for both survivors and control subjects, older subjects, males, and those with no college education were more likely to be current smokers. After we adjusted for demographic factors, the association between survivorship and current smoking status remained unal-

![Fig. 1. Actuarial rate of smoking initiation for survivors (dashed line) and control subjects (solid line). The cumulative percentage of nonsmokers is plotted against age in years. Median follow-up is 21 years. Covariate information is unavailable in four survivors and two control subjects.](image1)

![Fig. 2. Actuarial rate of quitting smoking for those survivors (dashed line) and control subjects (solid line) who were regular smokers. The cumulative percentage of regular smokers who continued to smoke is plotted against time in years. Median follow-up is 6 years.](image2)
tered. Among current smokers, survivors smoked an average of 14.1 cigarettes per day, and control subjects smoked an average of 17.1 cigarettes per day (95% confidence interval of difference of means = 0.28–5.8). In addition, 10.8% of survivors and 12.1% of sibling controls who were current smokers smoked 25 cigarettes or more per day (distinguished as heavy smoking in the NHIS).

There were no interactions between survivor status and any of the measured demographic variables (age/birth year, sex, race/ethnicity, and level of education) on smoking behavior. Separate reports on psychological outcomes from this same dataset have found that survivors have significantly increased negative mood as measured by the POMS (12) and lower self-concept as measured by the Harter self-concept scale when compared with sibling controls (Zeltzer LK, Chen E, Weiss R, Guo MD, Meadows AT, Mills JL, et al.: unpublished data). There were no significant interactions between survivorship and mood (POMS total score) or between survivorship and self-concept (Harter total score and subscale of global self-worth) with regard to smoking behavior.

The smoking pattern (never, former, or current) of sibling controls was similar to cohort-specific NHIS data (survey year 1990 and 18–24 year olds). In contrast, survivors’ smoking patterns were significantly different from the NHIS data, which is consistent with the above findings. However, for survivors who were smokers, the percentage of heavy smokers (≥25 cigarettes per day) was comparable to both sibling control data and cohort-specific normative NHIS data.

Discussion

Compared with our study, previous reports from surveys conducted at least 10 years before our study (9–11) showed higher rates of smoking with greater intensity in long-term survivors of childhood cancer, which overall was not significantly different from those of their control subjects. In one of these studies (11), survivors of childhood cancer diagnosed during the period from 1945 to 1964 had relatively high rates of current smoking (39.0%), which were similar to those of matched sibling controls (36.8%). In contrast, the youngest cohort of survivors of childhood cancer, diagnosed during the period from 1965 to 1974, not only had lower rates of smoking compared to earlier years but also were significantly less likely to become smokers than their sibling controls (21.8% versus 26.2%; P<.05). In our study, survivors were diagnosed during the period from 1970 through 1987. Older age at interview, which corresponded to earlier birth year, was predictive of increased likelihood to smoke regularly for both survivors and control subjects. After we adjusted for the birth cohort effect, survivors continued to have consistently lower rates of smoking than their sibling controls.

Longer time since diagnosis may also be a determinant in lowering smoking rates, as was suggested by Haupt et al. (11). This association is difficult to determine in our study, given confounding by the birth cohort effect, as longer time period since diagnosis correlated with earlier birth year.

In our study, almost all survivors and sibling controls who were regular smokers began before 20 years of age, which is consistent with the findings for the general population (30). Experimentation with cigarettes has been described as part of adolescents’ developmentally based exploration, in search for individuation (31–34). Our results showed that survivors are less likely to experiment with occasional cigarette smoking than their siblings and thereby have reduced their overall cigarette use. This encouraging reduction in tobacco exposure may reflect more intensive and more effective anti-smoking counseling by those caring for cancer survivors, as the general attention to the dangers of smoking has increased with more prominent public health campaigns.

In our study, those subjects born in more recent decades were more likely to quit smoking, as is consistent with this national trend (24,25). However, after adjustment for the cohort effect, survivors who were regular smokers had the same if not higher risk for continued habitual use as sibling controls. In addition, among current smokers, both survivors and control subjects had similar habits, averaging between 10 and 20 cigarettes a day. Both groups also had a similar proportion of hard-core smokers of 25 cigarettes or more per day. These findings underscore the point that, once survivors become smokers, they behave very similarly to their sibling controls and are just as susceptible to nicotine addiction.

Survivors of childhood cancer are especially vulnerable to tobacco-related health problems because they may have reduced pulmonary function (3), possibly related to methotrexate, and are at risk for congestive heart failure if treated with doxorubicin (2). Cigarette smoking, which slows lung growth in normal adolescents (35) and is an independent risk factor for heart disease in adulthood, would further compound these predispositions. There is a sevenfold excess of all cancers after ALL in childhood, with an estimated cumulative incidence of 2.53% at 15 years after diagnosis (1). In adults, cigarette smoking has been associated with the development of second cancers for a variety of cancer diagnoses, such as head and neck cancers, Hodgkin’s disease, and bladder cancer (36–38). Although the actual contribution of tobacco use to the development of second cancers in childhood leukemia survivors is unknown, the effects are minimally additive to their baseline predisposition.

Recently published recommendations on designing smoking intervention programs for pediatric cancer patients and survivors (39) emphasize the need to routinely assess for tobacco use as well as to focus on the increased health risks that cancer patients face relative to healthy peers. Personalizing risk information and identifying immediate adverse social and physical consequences of smoking may raise survivors’ perceived vulnerability and prevent smoking or increase cessation rates (39).

Limitations to our study include the possibility that survivors were less likely to admit to cigarette use than their sibling controls because survivors may be aware of their increased vulnerabilities to the ill effects of smoking. However, regular smokers in both groups reported similar intensity of smoking. Also, studies on siblings of survivors of childhood cancer suggest that the experience of a family member with cancer affects this group (40–42). However, siblings’ smoking behaviors were similar to cohort-specific NHIS data. Finally, survivors were substantially younger than control subjects.
The use of age as a covariate may not entirely correct for the influence of the cohort effect on smoking rates. Alternative approaches used to reduce or eliminate the age difference between the groups yielded similar results; however, these approaches, in turn, reduced the sample size. Again, comparisons to cohort-specific normative data from NHIS, showing that sibling controls had smoking behaviors very similar to those of the general population and that survivors had significantly different smoking behaviors, may further substantiate our conclusions.

This study suggests that survivors of childhood ALL have a reduced rate of smoking initiation compared with the rate in sibling controls. However, not only must physicians continue to provide anticipatory guidance and education as part of their routine follow-up care but also they must actively promote cessation programs for those long-term survivors who have already acquired a cigarette habit.

References


Notes


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