Childhood Social Environment and Hodgkin’s Lymphoma: New Findings from a Population-Based Case-Control Study

Ellen T. Chang, Tongzhang Zheng, Edward G. Weir, Michael Borowitz, Risa B. Mann, Donna Spiegelman, and Nancy E. Mueller

Abstract

Background: Risk of Hodgkin’s lymphoma in young adults has previously been associated with higher childhood socioeconomic status (SES) and other markers of delayed infection with common childhood pathogens, especially the Epstein-Barr virus. This study examines the current role of childhood social environment in the development of Hodgkin’s lymphoma. Methods: A population-based case-control study of 565 Hodgkin’s lymphoma cases and 679 controls was conducted in the Boston, MA metropolitan area and the state of Connecticut to investigate the viral etiology of Hodgkin’s lymphoma. Results: A novel association was detected between attendance of nursery school or day care and reduced risk of Hodgkin’s lymphoma among individuals ages 15 to 54 years. The odds ratio (95% confidence interval) for having attended preschool for at least 1 year was 0.64 (0.45-0.92). Risk of young-adult Hodgkin’s lymphoma was also associated with family history of hematopoietic cancer, Jewish ethnicity, and cigarette smoking. Other indicators of childhood SES were not associated with young-adult Hodgkin’s lymphoma. Among older adults ages 55 to 79 years, Hodgkin’s lymphoma was associated with lower childhood SES but not with preschool attendance. Conclusions: Early exposure to other children at nursery school and day care seems to decrease the risk of Hodgkin’s lymphoma in young adults, most likely by facilitating childhood exposure to common infections and promoting maturation of cellular immunity. This finding supports the delayed infection model of Hodgkin’s lymphoma etiology in young adults while introducing a new major determinant of age at infection. Hodgkin’s lymphoma seems to have a separate pathogenesis among older adults.

Introduction

Hodgkin’s lymphoma features an unusual bimodal age-incidence curve, with an initial incidence peak among young adults ages 15 to 39 years and a second peak among older adults age ≥55 years in developed countries. Epidemiologic evidence strongly links the risk of Hodgkin’s lymphoma among young adults to high maternal education, smallishibship size, low housing density, and other correlates of higher standard of living in childhood. These conditions can postpone exposure to common childhood infections, which are often more severe when delayed until adolescence. Age at infection, as a modifier of severity of infection, thus seems to play a pivotal role in Hodgkin’s lymphoma pathogenesis in young adults. However, these factors are not related to the occurrence of Hodgkin’s lymphoma in adults within the second incidence peak, suggesting that the etiology of the disease differs for older adults.

The Epstein-Barr virus (EBV), a lymphotropic herpesvirus that infects >90% of the worldwide population usually during childhood, has long been the leading suspect in Hodgkin’s lymphoma etiology. Primary EBV infection in childhood is typically mild, whereas half of primary infections in adolescence develop into infectious mononucleosis, which predicts a 3-fold increase Hodgkin’s lymphoma risk. Monoclonal EBV viral DNA and gene products are detectable in the malignant Hodgkin’s and Reed-Sternberg cells of 25% to 50% of Hodgkin’s lymphoma cases examined. Furthermore, altered EBV antibody levels have been found in patients years before and after Hodgkin’s lymphoma diagnosis, with antibody patterns suggestive of enhanced viral replication or an abnormal host-virus interaction. At birth, infants are skewed toward type 2 helper T-cell (Th2) immunity, characterized by the B-cell antibody-mediated response to infection by parasites, helminths, or nematodes. In contrast, the phagocyte-dependent, inflammatory type 1 helper T-cell (Th1) immune response matures with age likely due to postnatal exposure to Th1 stimulatory antigens such as intracellular bacteria and viruses, including but not limited to EBV. Children who are sheltered from contact with Th1-type antigens can continue to be biased toward Th2 immunity, which promotes the development of asthma and other atopic, Th2-mediated conditions.
Children attending day care generally experience more infections than those not attending day care (36, 37), where the increased contact with other children lowers the risk of childhood atopy (38-40). Other investigators have reported an inverse relationship between number of siblings and allergic sensitization (40-42). The similarity of childhood social risk factors for atopic conditions and young-adult Hodgkin's lymphoma suggests that their etiologies may share in common a Th1/Th2 imbalance. Host control of EBV infection is primarily mediated by a Th1-promoted cytotoxic T-cell response to viral antigens; thus, for younger persons with a skewed Th1/Th2 response, late infection with EBV may trigger an abnormal host-virus interaction, leading in some cases to Hodgkin's lymphoma. Delayed exposure to other infectious processes, including either specific or nonspecific agents, may also be involved in the development of Hodgkin's lymphoma, especially those cases lacking the EBV genome in tumor cells.

In recent decades, demographic changes in the United States may have modified previously reported associations between Hodgkin's lymphoma and childhood social factors (43). In particular, higher population-wide socioeconomic status (SES) may have reduced disparities in childhood social background between Hodgkin's lymphoma cases and controls, whereas day care and nursery school attendance may have replaced family structure and home environment as key determinants of social interaction among children. Here, we report the findings from a population-based case-control study to reevaluate the relationship between Hodgkin's lymphoma risk and childhood social environment.

Methods

Study Population. In 1997, we initiated a population-based case-control study to investigate the viral etiology of Hodgkin's lymphoma in the greater Boston, MA metropolitan area and the state of Connecticut. Cases were Hodgkin's lymphoma patients between ages 15 and 79 years at diagnosis, living within the defined geographic area, and without evidence of HIV infection. Between August 1, 1997 and December 31, 2000, 743 eligible cases of Hodgkin's lymphoma were diagnosed. Permission for contacting subjects was granted by the treating physicians for 685 (92%) of 743 patients. Each case was sent an explanatory letter inviting him or her to participate in the study. Of those contacted, 335 (84%) of 398 Massachusetts cases and 240 (86%) of 280 Connecticut cases participated. Ten patients were excluded by study pathologists as not Hodgkin's lymphoma, leaving 565 Hodgkin's lymphoma cases.

A total of 679 population controls were frequency matched to the distribution of the cases by age (within 5 years), sex, and state of residency. Controls were living residents of the study area without prior history of Hodgkin's lymphoma. From the Boston region, population controls were randomly identified from the current “Town Books” for the 132 cities and towns within the study area. The Town Books are annually compiled records including the name, sex, street address, and year of birth of all town or city residents ages ≥17 years; these records are ≥90% complete (44). When a selected control refused to participate or could not be reached, the next eligible person listed was selected as a replacement control. Like the cases, all controls were sent an initial letter of invitation to participate in the study. Of the 835 Massachusetts residents who were selected as potential controls, 115 (14%) could not be contacted. Of the 720 who were contacted, 238 (33%) did not respond to multiple telephone calls, 31 (4%) did not respond to mailed requests, 4 cited a language barrier, 2 were incapacitated, and 1 was deceased. Seventy-seven (11%) persons refused to participate and 367 (51%) consented. Among the enrolled Massachusetts controls, 178 (49%) were initial selections from the Town Books, whereas the other 189 were replacements for refusing or noncontacted selections.

In Connecticut, where 98.9% of residents have home telephone service (45), controls between ages 18 and 65 years were identified by random digit dialing (46). Controls between ages 66 and 79 years were randomly selected from files provided by the Health Care Financing Administration. Only one participant was recruited per household to avoid overlap of subject responses and clustering by social class; to prevent geographic clustering, the maximum number of households screened by random digit dialing within a block of 100 telephone numbers was limited to 8. Among 5,632 phone numbers attempted by random digit dialing, 4,747 were successfully screened; of these, 450 (9%) corresponded to eligible Connecticut residents of the targeted age range and sex. Twelve persons could not later be reached by telephone. Of the remaining 438 individuals, 21 (5%) did not respond to multiple telephone calls, 4 (1%) were incapacitated, 128 (29%) refused, and 276 (63%) completed the survey. Among the 65 contacted individuals of 69 eligible Health Care Financing Administration members, 8 (12%) did not respond to telephone calls, 2 (3%) were incapacitated, 19 (29%) refused, and 36 (55%) consented.

All study participants or, if minors, their guardians gave written informed consent at the time of enrollment in the study. This research protocol was approved by the institutional review boards of the Harvard School of Public Health, Yale University School of Medicine, and Johns Hopkins Medical School as well as all participating hospitals, the Massachusetts Cancer Registry, and the Connecticut Tumor Registry in the Connecticut Department of Public Health.

Data Collection. The introductory letter was followed by a telephone request for scheduling a structured telephone interview. Next-of-kin interviews were done for two cases and two controls. Thirty-one subjects who could not be reached by telephone completed an abbreviated mailed questionnaire.

The interviews gathered information on several exposures related to childhood social environment, including housing density, homeownership status, level of parental education, nursery school or day care attendance, number of regular neighborhood playmates, number of siblings, and birth order. Except for nursery school or day care enrollment, all questions about childhood referred to the time when the subject was 8 years old, or approximately in the third grade of elementary school, to address the average age at exposure to common childhood infections.
Childhood housing density was recoded as single-family house, two-family house, three-family house, apartment building of at least four units, or ‘other’ (a write-in category that was later coded to the closest approximation among the four specified categories). Homeownership status distinguished between owners and renters. Education levels were grouped into four levels for analyses: below high school, high school, college, and beyond college. Nursery school or day care attendance before kindergarten was recorded as yes or no, with an additional yes/no question for enrollment for ≥1 year. The subject’s reported number of regular playmates was assessed categorically, with cutoffs at 0, 1 to 5, 6 to 10, 11 to 14, and 16 to 20. Sibship size and birth order were both recorded as continuous variables that were later categorized into quartiles. Data on median household income in census tract and percentage of census tract below poverty level, which were categorized into quartiles, were obtained for each subject based on his or her residential street address (47).

**Histopathology.** The study pathologists (M.B., R.B.M., and E.G.W.) reviewed all available pathology material to verify the diagnosis of Hodgkin’s lymphoma. Archived tissue blocks were retrieved and examined for 411 (71%) of 575 cases. For those cases without adequate, available, or consented diagnostic specimens, the original pathology reports were reviewed. Pathology report-based diagnoses were made for 156 cases (27%); pathology material was unavailable for 8 (1%) cases.

Histopathologic classification of tumors was based on the 1994 REAL Classification of Lymphoid Neoplasms and the 2001 WHO Classification of Hematopoietic and Lymphoid Tumors (48, 49). These pathologic classification schemes distinguish among several subtypes that are considered broadly as “classic” Hodgkin’s lymphoma: nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich classic Hodgkin’s lymphoma. Nodular lymphocyte predominance Hodgkin’s lymphoma is considered a distinct entity and is grouped separately from the classic subtypes. Study pathologists also confirmed Hodgkin’s lymphoma cases that could not be further subclassified, including cases for whom there was an insufficient amount of diagnostic tissue for subtyping as well as those in which nodular sclerosis and mixed cellularity Hodgkin’s lymphoma could not be differentiated due to early involvement of a lymph node in an interfollicular variant pattern.

The presence of EBV in Hodgkin’s lymphoma biopsy material was determined by in situ hybridization for EBV-encoded RNA transcripts and/or by immunohistochemical assay for the viral latency membrane protein-1 in the malignant Hodgkin’s and Reed-Sternberg cells (50, 51). A Hodgkin’s lymphoma tumor was considered EBV genome positive if results were positive for either assay; a tumor was considered EBV genome negative if both assays were negative or only a single assay was done and its result was negative (52). Interpretation of EBV assays was done by consensus of all three study pathologists.

**Statistical Analysis.** All exposures with more than two levels were analyzed first as categorical variables and then as ordinal variables. Likelihood ratio tests were done to determine whether these exposures should be entered in statistical models as single ordinal terms. Based on these tests, monotonic trends for association with the log odds of Hodgkin’s lymphoma were observed for education level (subject, maternal, and paternal), sibship size, childhood housing density, number of regular childhood playmates, census tract median household income, and percentage of census tract population below poverty level. All of these exposures were coded as ordinal variables in statistical models.

Odds ratios (OR), 95% confidence intervals (CI), and corresponding two-sided P for χ² tests of association were estimated using multiple logistic regression to control for sex and state of residence. All analyses were stratified by age between younger/middle-aged subjects (15 to 54 years) and older subjects (55 to 79 years) based on previous findings that associations with Hodgkin’s lymphoma risk vary between the two age groups. Potential confounders were considered based on prior knowledge as well as change-in-estimate criteria (53) and likelihood ratio tests comparing models with and without additional variables.

To detect heterogeneity, the data were stratified by additional factors, and likelihood ratio tests were done to assess the significance of interaction terms. Distributions of demographic characteristics and main exposures among pathologically unconfirmed cases were compared with those among confirmed cases, whereas distributions for Massachusetts cases not found in the Town Books were compared with those for cases who were listed. After ensuring that there were no significant differences between the compared groups, all eligible cases were combined in the analyses. All statistical analyses were done with the SAS System software, release 8.01 (SAS Institute, Inc., Cary, NC).

**Results**

The initial study population consisted of 565 cases and 679 controls frequency matched to the cases by age, sex, and state of residence. The distribution of demographic characteristics according to case status is shown in Table 1. Table 2 summarizes the associations between univariate risk factors and Hodgkin’s lymphoma adjusted for sex and state. Age-specific analyses were conducted within groups of subjects ages 15 to 54 years (young and middle-aged adults) and 55 to 79 years (older adults). In the younger age group, cases were more likely than controls to be Jewish rather than Catholic (OR 2.29, 95% CI 1.26-4.19) or Protestant (OR 1.77, 95% CI 1.01-3.13), to be less well educated (OR 0.82, 95% CI 0.70-0.96), to have smoked at least 10 lifetime packs of cigarettes (OR 1.31, 95% CI 1.03-1.69), and to have a family history of cancer, especially hematopoietic cancer (OR 2.06, 95% CI 1.10-3.87). Adjustment for additional variables, including further markers of SES, did not significantly alter these results. In contrast to findings from previous studies, parental education, sibship size, housing density, and history of infectious mononucleosis were not significantly associated with Hodgkin’s lymphoma risk among young adults. Other determinants of childhood social environment, including number of regular playmates and homeownership status during childhood, were also unassociated with Hodgkin’s lymphoma risk.

Among older adults, there was a suggestion that Hodgkin’s lymphoma risk was associated with lower childhood SES. Parents of cases were less well educated...
Table 1. Distribution of demographic characteristics among Hodgkin’s lymphoma cases and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 565)</th>
<th>Controls (n = 679)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>25-34</td>
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<td>35-44</td>
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<td>45-54</td>
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<td>12</td>
</tr>
<tr>
<td>55-64</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>≥65</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>35.7</td>
<td>36.7</td>
</tr>
<tr>
<td>Sex, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>Female</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>State, %</td>
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<tr>
<td>Massachusetts</td>
<td>57</td>
<td>54</td>
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<tr>
<td>Connecticut</td>
<td>43</td>
<td>46</td>
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<tr>
<td>Race, %</td>
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<tr>
<td>White</td>
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<td>86</td>
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<tr>
<td>Other</td>
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<td>4</td>
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<tr>
<td>Religion, %</td>
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<td>Catholic</td>
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<td>Protestant</td>
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<tr>
<td>Jewish</td>
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<td>4</td>
</tr>
<tr>
<td>Other/none</td>
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<td>14</td>
</tr>
<tr>
<td>Subject education, %</td>
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<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>10</td>
<td>7</td>
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<tr>
<td>High school</td>
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<td>25</td>
</tr>
<tr>
<td>College</td>
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<td>51</td>
</tr>
<tr>
<td>Advanced degree</td>
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<td>17</td>
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<tr>
<td>Maternal education, %</td>
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<td></td>
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<td>Less than high school</td>
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<td>18</td>
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<tr>
<td>High school</td>
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<tr>
<td>College</td>
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<td>30</td>
</tr>
<tr>
<td>Advanced degree</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Median household income strata ($)</td>
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<tr>
<td>&lt;59,171</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>59,171-70,984</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>70,985-85,763</td>
<td>29</td>
<td>25</td>
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<tr>
<td>≥85,764</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Median household income ($)</td>
<td>72,779</td>
<td>70,985</td>
</tr>
<tr>
<td>Below poverty level strata (%)</td>
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<td>&lt;5</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>5-9</td>
<td>24</td>
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<td>10-19</td>
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<tr>
<td>≥20</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Median below poverty level (%)</td>
<td>4.11</td>
<td>4.06</td>
</tr>
</tbody>
</table>

*U.S. Census data based on participants’ census tract of residence.

Table 1. Distribution of demographic characteristics among Hodgkin’s lymphoma cases and controls

than those of controls (OR 0.52, 95% CI 0.32-0.83 for increasing maternal education; OR 0.64, 95% CI 0.44-0.95 for increasing paternal education), and cases also seemed to have had more siblings than controls (OR 1.21, 95% CI 0.96-1.53 for increasing sibship size). Other indicators of childhood SES were nonsignificantly associated with Hodgkin’s lymphoma risk, and history of infectious mononucleosis similarly showed no association with risk in this age group. Having had a job involving wood or wood products was somewhat associated with Hodgkin’s lymphoma risk overall. The OR (95% CI) for having been employed in a wood-related job was 1.39 (0.98-1.97) for younger adults and 2.30 (0.87-6.07) for older adults.

In the younger age group, 37% of cases and 41% of controls attended nursery school or day care prior to kindergarten; 17% of nursery and 24% of controls were enrolled for ≥1 year. Among older adults, 4% of cases and 7% of controls attended nursery school or day care, with 3% of both groups reporting at least 1 year of enrollment. Table 2 shows the associations between Hodgkin’s lymphoma risk and preschool attendance. Among younger subjects, the adjusted OR (95% CI) for having attended preschool was 0.87 (0.68-1.13), and the adjusted OR for having attended at least 1 year of preschool, compared with not having attended at all, was 0.64 (0.45-0.92). Among older subjects, the adjusted OR (95% CI) for ever attending nursery school was 0.63 (0.19-2.15) and that for attending at least 1 year of preschool was 1.20 (0.25-6.4). Additional adjustment for other characteristics of childhood social environment, including subject’s education, parental education, sibship size, housing density, and number of playmates, did not significantly alter the ORs in either age group (data not shown). The associations of nursery school attendance for at least 1 year and low subject education with Hodgkin’s lymphoma risk in young adults remained statistically significant after mutual adjustment.

There was no heterogeneity in the effect of preschool attendance on young-adult Hodgkin’s lymphoma risk, except by number of childhood playmates. The inverse association with nursery school or day care attendance seemed to be stronger among those who had more regular playmates during childhood (P test for heterogeneity = 0.01).

To examine whether the association between Hodgkin’s lymphoma and preschool attendance varied by the presence of the EBV genome in tumor cells, case-control comparisons were stratified by EBV genome positivity among the cases. Among 15- to 54-year-olds, 70 (20%) of 345 cases with known EBV status were positive for the EBV genome. Tumor EBV genome status did not modify the OR for nursery school or day care attendance for at least 1 year (P = 0.27), suggesting no difference in preschool attendance between EBV genome-positive and genome-negative cases. Among cases age ≥55 years, 26 (42%) of 62 cases were EBV genome positive. The proportion of preschool attendance among older adults was too low to allow for meaningful stratified analyses by EBV genome status.

We did a series of analyses to evaluate whether there was any evidence of selection bias in our method of control selection. Of a random sample of half of the Massachusetts residents originally selected as potential controls, those who lived in census tracts with higher median household income were more likely to participate: the OR (95% CI) for consent versus refusal, comparing persons from higher-income versus lower-income areas, was 1.26 (1.03-1.54), controlling for age and sex. However, because nonenrolled individuals were replaced with controls from the same residential area, the income distribution of the final Massachusetts control population was representative of that of the source population (OR 1.03, 95% CI 0.91-1.18 for higher income). A sensitivity analysis (see Appendix) revealed that selection bias by SES among the controls would have resulted in minimal (−4%) bias of the OR for preschool...
attendance for ≥1 year, assuming no selection bias among the cases and no other sources of bias or confounding (54). The minimal bias was due to the close correlation between median household income and nursery school or day care attendance for ≥1 year (U = 0.20, P = 0.0005 among Massachusetts controls) and the lack of difference in income between the source and study populations in Massachusetts.

We compared the distribution of several demographic characteristics within our Connecticut control group to the distribution across the entire state of Connecticut according to current U.S. Census data (45). Study controls were generally more educated (OR 1.18, 95% CI 1.07-1.32) and more likely to live in single-family housing units (OR 1.40, 95% CI 1.10-1.80) but were similar to Connecticut residents overall in the proportion who owned homes (OR 1.13, 95% CI 0.88-1.46) and the prevalence of nursery school attendance before age 5 years (OR 1.16, 95% CI 0.91-1.47).

**Discussion**

In this population-based case-control study, younger adults who attended nursery school or day care before kindergarten had a 13% lower risk of Hodgkin’s lymphoma compared with those who did not. This apparent protective effect was enhanced among those who were enrolled for ≥1 year, leading to a 36% decrease in Hodgkin’s lymphoma risk among 15- to 54-year-olds.

### Table 2. Adjusted OR and 95% CI for association with Hodgkin’s lymphoma risk by age group

<table>
<thead>
<tr>
<th>Risk factor (comparison groups)</th>
<th>Ages 15-54 y (470 cases, 557 controls), OR* (95% CI)</th>
<th>Ages 55-79 y (95 cases, 122 controls), OR* (95% CI)</th>
<th>P for test of heterogeneity by age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (Black/White)</td>
<td>0.91 (0.51-1.62)</td>
<td>0.75 (0.49-1.15)</td>
<td>0.03</td>
</tr>
<tr>
<td>Race (other/White)</td>
<td>0.64 (0.12-3.48)</td>
<td>7.38 (0.86-63.15)</td>
<td>0.03</td>
</tr>
<tr>
<td>Religion (Protestant/Catholic)</td>
<td>0.77 (0.57-1.05)</td>
<td>0.73 (0.39-1.37)</td>
<td>0.34</td>
</tr>
<tr>
<td>Religion (Jewish/Catholic)</td>
<td>1.77 (1.01-3.13)</td>
<td>0.60 (0.17-2.13)</td>
<td>0.34</td>
</tr>
<tr>
<td>Subject education (less than high school/high school/college/advanced degree)</td>
<td>0.82 (0.70-0.96)</td>
<td>0.80 (0.59-1.09)</td>
<td>0.92</td>
</tr>
<tr>
<td>Median household income (quartiles 1-4)</td>
<td>1.02 (0.91-1.14)</td>
<td>0.92 (0.72-1.18)</td>
<td>0.44</td>
</tr>
<tr>
<td>Percentage below poverty level (quartiles 1-4)</td>
<td>0.99 (0.89-1.11)</td>
<td>1.05 (0.81-1.35)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Childhood social factors</strong></td>
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<tr>
<td>Maternal education (less than high school/high school/college/advanced degree)</td>
<td>0.95 (0.82-1.10)</td>
<td>0.52 (0.32-0.83)</td>
<td>0.01</td>
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<td>Paternal education (less than high school/high school/college/advanced degree)</td>
<td>1.02 (0.89-1.17)</td>
<td>0.64 (0.44-0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Number of siblings (0-1/2/3-4/≥5)</td>
<td>0.93 (0.82-1.05)</td>
<td>1.21 (0.96-1.53)</td>
<td>0.05</td>
</tr>
<tr>
<td>Number of regular childhood playmates (0-5/6-10/≥11)</td>
<td>1.02 (0.87-1.20)</td>
<td>0.81 (0.56-1.17)</td>
<td>0.14</td>
</tr>
<tr>
<td>Housing density in childhood (1-family/2-family/3-family/4-family)</td>
<td>1.10 (0.97-1.25)</td>
<td>0.89 (0.70-1.12)</td>
<td>0.10</td>
</tr>
<tr>
<td>Housing ownership in childhood (own/rent)</td>
<td>0.92 (0.68-1.25)</td>
<td>1.20 (0.69-2.08)</td>
<td>0.44</td>
</tr>
<tr>
<td>Nursery school or day care attendance (yes/no)</td>
<td>0.87 (0.68-1.13)</td>
<td>0.63 (0.19-2.15)</td>
<td>0.50</td>
</tr>
<tr>
<td>Nursery school or day care attendance for &lt;1 year (yes/no)</td>
<td>1.02 (0.79-1.40)</td>
<td>0.26 (0.03-2.29)</td>
<td>0.16</td>
</tr>
<tr>
<td>Nursery school or day care attendance for ≥1 year (yes/no)</td>
<td>0.64 (0.45-0.92)</td>
<td>1.20 (0.25-5.64)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of mononucleosis (yes/no)</td>
<td>0.92 (0.65-1.31)</td>
<td>0.78 (0.24-2.48)</td>
<td>0.82</td>
</tr>
<tr>
<td>History of allergy (yes/no)</td>
<td>0.93 (0.71-1.21)</td>
<td>0.64 (0.36-1.15)</td>
<td>0.31</td>
</tr>
<tr>
<td>History of asthma (yes/no)</td>
<td>0.90 (0.64-1.27)</td>
<td>0.54 (0.22-1.32)</td>
<td>0.32</td>
</tr>
<tr>
<td>History of autoimmune disease (yes/no)</td>
<td>1.57 (0.76-3.28)</td>
<td>0.90 (0.28-2.85)</td>
<td>0.57</td>
</tr>
<tr>
<td>Family history of any cancer (yes/no)</td>
<td>1.43 (1.10-1.87)</td>
<td>0.68 (0.36-1.29)</td>
<td>0.05</td>
</tr>
<tr>
<td>Family history of hematopoietic cancer (yes/no)</td>
<td>2.06 (1.10-3.87)</td>
<td>1.76 (0.58-5.35)</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Other factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking (≥10 packs in lifetime; yes/no)</td>
<td>1.31 (1.03-1.69)</td>
<td>1.12 (0.61-2.06)</td>
<td>0.56</td>
</tr>
<tr>
<td>Any tobacco product (e.g., cigarettes, cigars, and tobacco; yes/no)</td>
<td>1.30 (1.01-1.67)</td>
<td>1.31 (0.65-2.63)</td>
<td>0.77</td>
</tr>
<tr>
<td>Job with wood or wood products (yes/no)</td>
<td>1.39 (0.98-1.97)</td>
<td>2.30 (0.87-6.07)</td>
<td>0.63</td>
</tr>
<tr>
<td>Hobby with wood or wood products (yes/no)</td>
<td>0.91 (0.67-1.24)</td>
<td>0.80 (0.40-1.59)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Adjusted for sex and state. ORs for binary risk factors compare the first category to the second category (e.g., yes versus no); ORs for ordinal risk factors compare increasing levels.

† U.S. Census data based on subjects’ census tract of residence.
The inverse association with Hodgkin’s lymphoma risk remained consistent across strata of other determinants of childhood social environment. Among older adults, there was a significant association between preschool attendance and risk of Hodgkin’s lymphoma.

Whereas we detected this new association in younger adults, we found that previously reported childhood SES predictors of Hodgkin’s lymphoma risk were not associated with Hodgkin’s lymphoma. These factors included maternal and paternal education, sibship size, number of regular playmates, housing density, and homeownership status (2-9). Surprisingly, in contrast to several previous studies (3, 14-23), history of infectious mononucleosis was not associated with Hodgkin’s lymphoma risk in our population, even when the analysis was limited to young adults under age 35 years (data not shown). The lack of an association in our study may have been due in part to misclassification of infectious mononucleosis history, because exposure was assessed by self-report rather than medical records or serologic evidence. If misclassification was nondifferential between cases and controls, this would have biased the OR toward the null. Overenrollment of high SES controls may also have elevated the prevalence of a history of infectious mononucleosis in the control population, because delayed EBV infection and resultant infectious mononucleosis are associated with higher SES. Control selection bias may also explain our unexpected observation that young-adult Hodgkin’s lymphoma cases were less well educated than controls.

Our findings of increased risk of Hodgkin’s lymphoma among Jewish persons, individuals with a family history of hematopoietic cancer, and those previously employed in a woodworking industry correspond with results from previous studies (1, 3, 7, 55-58). The higher relative risk for wood exposure in the older age group of our population could reflect longer duration of wood dust exposure. It could also be related to the poor air quality, and consequent chronic airway irritation, in wood and paper processing facilities prior to the implementation of effective air filters and fans in more recent decades.

The positive association between Hodgkin’s lymphoma and cigarette smoking could be explained by the deleterious impact of smoking on the immune system (59) or by selection bias. Although smoking history was not associated with SES among our controls, smokers in the general population may have been less likely than nonsmokers to participate as controls in our study. However, our findings corroborate those of another recent case-control study that found an increased risk of Hodgkin’s lymphoma among cigarette smokers (60).

Consistent with previous studies (4, 61, 62), there was evidence of lower childhood SES among older Hodgkin’s lymphoma cases who had more siblings and less well educated mothers and fathers than controls. Lower childhood SES could suggest very early infection with common childhood pathogens and/or poorer immune status in older Hodgkin’s lymphoma cases.

The lack of association between childhood social factors and young-adult Hodgkin’s lymphoma in this population, and the new association with preschool attendance, likely reflect secular changes in the social environment of children in the United States. The enrollment of young children in nursery school has risen substantially in recent decades from 5% in 1964 to 50% between 1995 and 1999 (63). This trend can be attributed in part to advances in women’s education, the rise of single-parent and two-working parent households, reductions in average family size, and changes in child-rearing practices. As a result of these demographic changes, the relative importance of nursery school or day care enrollment in influencing childhood social environment and Hodgkin’s lymphoma risk may have increased. These societal developments may account for some of the discrepancies in our findings from those of earlier studies. In support of this theory, Glaser et al. (43) failed to detect significant associations between markers of childhood SES and Hodgkin’s lymphoma in a recent case-control study among young adult women in San Francisco. They, too, postulated that this lack of association might be due to the rising enrollment of children in nursery school. These changes might also be expected to cause a drop in the incidence of young-adult Hodgkin’s lymphoma—a trend that may have been reflected in the lower than anticipated number of cases identified by our study between 1997 and 2000.

Alternatively, differences in SES between cases and controls may have been underestimated due to selection bias among the control group. Selection bias occurred in particular in our study due to its low control participation rate, which may have led to the underrepresentation of certain segments of the source population among our study controls. Our sensitivity analysis using census-based income data determined that selection bias did not seem to account for the association between preschool attendance and Hodgkin’s lymphoma. However, although median household income was significantly correlated with all SES measures in our study, it could only be assessed broadly based on geographic residence; selection bias may still have occurred within census tracts. In addition, because population-level data cannot capture characteristics such as health consciousness and other socioeconomic influences, it is still possible that higher social class among controls diminished case-control differences and resulted in null associations between SES and Hodgkin’s lymphoma risk.

The inverse association between young-adult Hodgkin’s lymphoma and preschool attendance reinforces the notion that Hodgkin’s lymphoma is not associated with childhood SES per se but rather with factors that influence age at exposure to infections during childhood. With growing enrollment of young children in nursery school, early exposure to other children now seems to be mediated more regularly through classmates at day care and nursery school rather than siblings at home. Early contact with other young children favors transmission of common viral and bacterial infections, which prime the host immune system toward a more mature type 1 immune response. The preventive effect of preschool against Hodgkin’s lymphoma could be enhanced through childhood infection with EBV, thereby averting adolescent mononucleosis, which increases Hodgkin’s lymphoma risk later in life. Because preschool attendance is associated with lower risk of both EBV genome-positive and genome-negative Hodgkin’s lymphoma in young adults, however, the apparent protective effect may be the result of childhood exposure to viruses and bacteria in general, and the resulting enhancement of Th1-type immunity, or to other specific but yet unidentified infectious agent(s).

Our finding of an inverse association between childhood nursery school or day care attendance and...
Hodgkin’s lymphoma risk supports the delayed infection model of Hodgkin’s lymphoma among young adults (2). Our data suggest a different etiologic model for older-adult Hodgkin’s lymphoma, perhaps involving an age-related immune decline and/or viral reactivation from latency. The large proportion of EBV genome-positive cases among older adults suggests that EBV is involved in the etiology of many of these cases, whereas the development of genome-negative cases may be attributed to another infectious agent or a noninfectious origin.

Appendix

Sensitivity analysis for selection bias (For more information, see ref. 54, pp. 194-219)

Let Sel = selection for study, E = exposure, D = disease; α = probability of selecting an exposed case = Pr(Sel = 1|E = 1, D = 1), β = probability of selecting an unexposed case = Pr(Sel = 1|E = 0, D = 1), γ = probability of selecting an exposed control = Pr(Sel = 1|E = 1, D = 0), and δ = probability of selecting an unexposed control = Pr(Sel = 1|E = 0, D = 0)

\[
\text{BIAS(OR*, OR)} = \frac{\text{OR}^* - \text{OR}}{\text{OR}} = \left(\frac{r_0 - r_0^*}{r_0} \right) = \left(\frac{r_E - r_E^*}{r_E} \right) = \left(\frac{\alpha \delta - \beta \gamma}{\beta \gamma - \alpha \delta} \right) - 1
\]

where OR* is observed OR, OR is true OR, \(r_D = \frac{\alpha}{\beta} = \frac{\gamma}{\delta}\) = selection odds for disease, \(r_D = \frac{\gamma}{\delta}\) = selection odds for nondisease, \(r_F = \frac{\alpha}{\gamma} = \frac{\beta}{\delta}\) = selection odds for exposed, \(r_F = \frac{\gamma}{\delta}\) = selection odds for nonexposed, \(\alpha \delta / \beta \gamma = \text{selection OR}.

In a population-based case-control study, assume unbiased case enrollment (i.e., \(\alpha = \beta \) or \(\alpha / \beta = 1\)), so simplify selection OR to \(\frac{\beta}{\gamma}\).

Among controls (\(D = 0\)),

\[
\delta / \gamma = \frac{\text{Pr}(\text{Sel} = 1|E = 0)}{\text{Pr}(\text{Sel} = 1|E = 1)} \Rightarrow \frac{\text{Pr}(\text{Sel} = 1|E = 1)}{\text{Pr}(\text{E} = 1)}
\]

Using Bayes’ theorem,

\[
\text{Pr}(\text{Sel} = 1|E = 0) = \frac{\text{Pr}(E = 0|\text{Sel} = 1)}{\text{Pr}(\text{Sel} = 1)} \quad \text{and} \quad \text{Pr}(\text{Sel} = 1|E = 1) = \frac{\text{Pr}(E = 1|\text{Sel} = 1)}{\text{Pr}(\text{Sel} = 1)}
\]

so

\[
\delta / \gamma = \left(\frac{\text{Pr}(E = 0, \text{Sel} = 1)}{\text{Pr}(\text{Sel} = 1)} \right) / \left(\frac{\text{Pr}(E = 1, \text{Sel} = 1)}{\text{Pr}(\text{Sel} = 1)} \right)
\]

To estimate the bias in the observed OR for an exposure variable measured in enrolled subjects but not in the source population, consider a related variable measured in the entire source population to be a misclassified version of the exposure of interest.

For correct misclassification of the exposure variable,

\[
\text{Sensitivity} = \theta = \frac{\text{# observed exposed}}{\text{# truly exposed}} = \frac{\text{# with } \hat{E} = 1}{\text{# with } E = 1}
\]

\[
\text{False unexposed proportion} = 1 - \theta
\]

\[
\text{False exposed proportion} = 1 - \phi
\]

where \(\hat{E}\) is true, correctly classified exposure; \(E\) is observed, misclassified exposure; \(A\) is # true exposed + $\hat{E}$

\[
\begin{array}{c|c|c}
\text{True data} & \text{Misclassified data} \\
\hline
\text{E = 1} & \text{E = 0} & \hat{E} = 1 & \hat{E} = 0 \\
\text{Population} & \text{Population} & \text{Source} & \text{Source} \\
\text{A} & \text{B} & m_1 & \text{m}_A & \text{B} & \text{m}_B \\
\text{D} & \text{D} & m_0 & \text{C} & \text{C} & \text{m}_C \\
\hline
\end{array}
\]

\# false exposed in study population = \(\theta \times A + (1 - \theta) \times B\)

\(\hat{B}\) is # false exposed + # true unexposed in study population = \((1 - \theta) \times A + \phi \times B\)

\(\hat{C}\) is # true exposed + # false unexposed in source population = \(\theta \times C + (1 - \phi) \times D\)

\(\hat{D}\) is # false unexposed + # true unexposed in source population = \((1 - \theta) \times C + \phi \times D\)

\(\hat{m}_1\) is # of controls in study population; and \(m_0\) is # of controls in source population.

\[
A = \frac{\phi m_1 - \hat{B}}{\theta + \phi - 1}, \quad B = \frac{\theta m_1 - \hat{A}}{\theta + \phi - 1}, \quad C = \frac{\phi m_0 - \hat{D}}{\theta + \phi - 1}
\]

From Kleinbaum et al.,

\[
\text{BIAS(OR*, OR)} = \left(\frac{\delta}{\gamma} - 1\right) = \left(\frac{B/m_1 + C/m_0}{\hat{A}/m_1 + \hat{D}/m_0} - 1\right)
\]

Therefore,

\[
\left(\frac{\delta}{\gamma} - 1\right) = \left(\frac{\hat{m}_1 - \hat{A}}{\hat{A}/m_1 + \hat{D}/m_0} - 1\right)
\]
Example 1: Correctly classified data for enrolled and nonenrolled subjects

Define exposure: High median household income of ≥$70,000 versus low median household income of <$70,000

\( \frac{\text{Pr}(\text{high income among enrolled MA controls} = 187/367 = 51.0\%)}{\text{Pr}(\text{low income among enrolled MA controls} = 180/384 = 47.7\%)} \)

\( \frac{\text{Pr}(\text{high income in MA source population} = 195/384 = 50.8\%)}{\text{Pr}(\text{low income in MA source population} = 189/384 = 49.2\%)} \)

MA, Massachusetts.

\[
\text{BIAS(OR)} = \frac{\text{Pr}(E|\text{Sel} = 1)}{\text{Pr}(E|\text{Sel} = 0)} - 1
\]

\[
= \frac{0.490}{0.510} - 1
\]

\[
= -0.008 \quad \text{(If no bias, then BIAS = 0)}
\]

\[
\rightarrow \text{If observed OR}^o = 0.64, \text{then true OR} = 0.64 \quad (1 - 0.008) = 0.65.
\]

Example 2: Correctly classified data for enrolled subjects; misclassified data for enrolled and nonenrolled subjects

Define true exposure: History of nursery school or day care attendance for ≥1 year versus none

Define misclassified exposure: High median household income of ≥$70,000 versus low median household income of <$70,000

\( \theta \) is \( \frac{\text{Pr}(\text{high income } | \text{ nursery school attendance for } \geq 1 \text{ year})}{\text{Pr}(\text{low income } | \text{ no nursery school attendance})} \) among enrolled MA controls = 128/228 = 0.561; \( \phi \) is \( \frac{\text{Pr}(\text{low income } | \text{ nursery school attendance})}{\text{Pr}(\text{low income})} \) among enrolled MA controls = 180/384 = 0.465; \( m_1 \) is # of enrolled MA controls = 384; \( \widetilde{A} \) is # with high income among enrolled MA controls = 180; \( \widetilde{A} \) is # with high income among MA source population = 195; \( D \) is # with low income among low income in MA source population = 189.

\[
\text{BIAS(OR)} = \left( \frac{\theta m_1 - A}{\theta m_1 - B} \right) - 1
\]

\[
= \left( \frac{0.561 * 367 - 180}{0.561 * 367 - 180} \right) - 1 \quad (0.623 * 367 - 187) \quad 0.561 \quad 367 \quad 180 \quad 0.623 \quad 384 \quad 195 \quad 1
\]

\[
= \frac{41.64}{25.89} \quad 26.42 \quad 44.23 \quad -1
\]

\[
= -0.04 \rightarrow \text{If observed OR}^o = 0.64.
\]

Hence, the influence of control selection bias by SES on the OR for the association between Hodgkin’s lymphoma risk and nursery school or day care attendance for ≥1 year is only 4%, causing the true OR of 0.67 to be biased downward to the observed OR of 0.64, assuming no other sources of bias or confounding.

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