Childhood Determination of Hodgkin Lymphoma among U.S. Servicemen

Thomas M. Mack1, James E. Norman Jr2, Edward Rappaport1, and Wendy Cozen1

Abstract

Background: Hodgkin lymphoma in young adults is inexplicably linked to economic development.

Methods: We conducted a nested case-control study of the 656 servicemen with Hodgkin lymphoma diagnosed between ages 17 to 32 while on active duty in the U.S. military during 1950–68. Controls, chosen randomly from the servicemen on duty at the time, were matched on service, birth year, and induction date. Information came from preinduction records and military records for the period ending at onset or the equivalent date.

Results: Risk was independently increased with small ship size [OR, 2.3; confidence interval (CI), 1.6–3.5], low birth order (OR, 1.9; CI, 1.4–2.6), and an interval of at least 5 years between birth and that of a previous or subsequent sibling (OR, 2.1; CI, 1.5–3.1). Other factors independently and significantly associated with elevated risk of Hodgkin lymphoma were: tallness, high body mass index, more education (but not higher income) in the county of birth, BB or AB blood type, and past infectious mononucleosis (but a deficit of other childhood viral infections). Early fatherhood conveyed high risk (OR, 2.6; CI, 1.4–4.8), especially if with a high-risk sibling configuration. Factors unrelated to risk included personal education, preinduction or military occupation, induction test score, and rank. Findings were similar for nodular sclerosis and mixed cell histologic subtypes.

Conclusions: Protection from the environment in childhood, but not in adulthood, increases the likelihood of young adult Hodgkin lymphoma, which may result from nonspecific isolation from early infections and/or exposure to late infection by a specific but unidentified ubiquitous childhood virus.

Impact: Events in childhood protect against later Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev; 24(11); 1–9. ©2015 AACR.

Introduction

Hodgkin lymphoma is a neoplasm with three modes in agespecific incidence: childhood, old age, and during adolescence and young adulthood. In 1957, MacMahon (1) concentrated on the young adult mode, and recognized an internationally variable trend in incidence (2, 3), with a link between population-specific rates of incidence and economic development that suggests an acquired determination. He further recognized the distinctive immunologic characteristics of the disease (4), and listed factors that distinguished these cases from cases among older persons: a sex ratio nearer unity, presentation above the diaphragm, longer survival, and usually nodular sclerosis histology (5). Pathologists have long distinguished diverse histologic subcategories (6), and the nodular sclerosis subgroup is characterized by very sparsely distributed malignant cells, multinucleated Hodgkin and Reed–Sternberg (HRS) cells, surrounded by diverse hematopoetic cells and wide bands of fibrosis. This condition has now been designated by consensus as adolescent/young adult Hodgkin lymphoma (AYAHL; refs. 7, 8). Although in 1994, AYAHL cases were classified by pathologists on clinical and immunophenotypic grounds in combination with older mixed cellularity cases as “classic” Hodgkin lymphoma (9, 10), Weiss and colleagues (11) subsequently validated the earlier etiologic dichotomy by demonstrating antigens of Epstein–Barr virus (EBV) in the nuclei of HRS cells in the tumors of most older cases but not in those of most AYAHL cases (12–14).

Accumulating evidence now indicates a strong genetic susceptibility to AYAHL: incidence is linked to race and specific HLA haplotypes (15), occurrence is high among the relatives (16), siblings (17, 18), and especially the identical co-twins (19) of cases, and genome-wide association studies suggest specific HLA, cytokine, T-helper type 2 (Th2), and B-cell differentiation pathways, modified in those cases positive for EBV (20). Empirically, immunologic characteristics such as a Th2-skewed immune response are present at diagnosis and have been found to predict risk (4, 21, 22). Interest in heritable determinants has now diverted attention from acquired determinants (23).

However, whether defined by age, nodular sclerosis histology, or the absence of EBV antigens, the incidence of AYAHL continues to increase with changes in economic status, both in developed (24–26) and developing (27–29) countries. Although registry-based descriptions and analytic studies repeatedly show a socioeconomic gradient (24, 30), it has been unclear which particular attributes of social class are responsible, and whether the social status at diagnosis represents the prediagnosis status or that of the childhood environment.

Here, we propose to further elucidate the age-specific environmental determination of AYAHL. Speculation about the nature of acquired determinant(s) has focused on two possibilities that are not mutually exclusive and may even be additive. Although searches have proved fruitless (31), an infectious
viral determinant was first suggested by the histologic and clinical pattern (32), and by analogy with the carcinogenetic actions of herpes viruses in chickens and primates (33, 34), the age pattern of paralytic polio (34), and the occurrence of EBV-associated lymphomas among the immune-compromised (35). Alternatively, long-term immunologic susceptibility to an infection or other exposure might cluster among those persons who had been isolated in early life from the environmental exposures and microbial infections required for normal immune development.

Well-controlled analytic studies of a disease as uncommon as AYAHL have been limited in number and size. Cohort investigations necessarily enroll few youthful subjects, and case–control power considerations often favor the inclusion of older and etiologically disparate cases (36). Appropriate attention to the environmental exposures or even social class in childhood rarely has been feasible using conventional methods of data collection (37, 38).

This report describes a very large case–control study nested in a defined population and conducted under particularly advantageous conditions. All cases appearing among young men after induction into the U.S. military during a period of universal conscription and diagnosed under uniform clinical conditions were ascertained and compared with individually matched healthy conscripts from the same period on the basis of information recorded prior to diagnosis.

Materials and Methods

This protocol was reviewed and approved for the protection of human subjects by the Department of Defense and the National Research Council. Rosters of the service numbers of all men diagnosed with confirmed Hodgkin lymphoma while on active duty were provided by the offices of the U.S. Military Surgeons General. Cases were ascertained from the Navy during 1950–1967, from the Army during 1951–1964, and from the Air Force during 1958–1968. Eligibility required each case to have at least one year of service before symptom onset and to have been diagnosed before age 32, and each to be verified in records at the National Personnel Records Center (NPRC) in St. Louis. The date of onset was assigned by medical abstractors in consultation with one of us (TMM) using the following criterion: the first appearance of any symptom other than weight loss in the illness episode leading to the diagnosis. Cases with symptom onset before service entry were excluded.

Initially, 1,568 service numbers on separate rosters (Navy, Army, and Air Force) were identified as potential cases. Five hundred and sixty-two exclusions were made on the basis of disease rubric, preservice onset, age at diagnosis, length of service eligibility, or duplicate service number, reducing the total to 1,006. Of these, 14 could not be linked to a service record, and 82 records could not be located at NPRC. Of the remaining 910 cases, 201 ultimately proved ineligible on the basis of age at diagnosis or length of service. Controls were sought for the remaining 709 cases by matching in sequence on branch of service, birth date (±1 calendar year), date of entry into active duty (EAD; ±6 months), and length of service (see below) from a roster assembled to comprise a representative cross-section of those on duty during each year of potential diagnosis, that is, 1950 through 1970. Because no rosters based on year-specific active duty existed, this roster was created by combining a 1% sample of all separations between June 1, 1955 and December 31, 1970; a 1% sample of all service personnel still on active duty at the cutoff date: in the Army on December 31, 1970, or in the Navy or Air Force on June 30, 1971, and a 0.1% sample of all discharges and other separations from service between July 1, 1950 and October 31, 1955 (the two sampling fractions differing because this period witnessed the demobilization of a very large number of troops after the Korean conflict).

Because the military and medical careers of Hodgkin lymphoma cases are inevitably affected by disease, a cutoff reference date was established; the day of hospitalization during which Hodgkin lymphoma was first confirmed for each case, and the day which terminated an equivalent length of active service for each matched control. In the summer of 1973, after service records for three fourths of the controls had been identified and removed for abstraction, a fire at the NPRC in St. Louis destroyed over 80% of all filed records of eligible Army and Air Force personnel, including those of the controls who had been identified but whose records had not been removed. Fortunately, the records filed (by service number) in the bottom drawers of each of the dozens of file cabinets burned in the fire were soaked by fire-hoses before destruction, and could be salvaged by freeze drying. The controls whose records had been destroyed were then replaced (using the original eligibility and matching criteria) by random selection from the sampling frame of the combined contents of the bottom drawers, which provided a representative cluster sample (by service number) of the original complete set of files. In the end, appropriate matched controls were found for all but 53 cases. Thus 656 population-based cases (92.5% of those eligible) and the matched controls form the basis for this report.

The experiences and characteristics of each subject were gathered from four sources: the induction and enlistment records; the physical examination and medical history forms completed at the time of service entry; the medical records (outpatient entries and inpatient clinical records) generated during service before the established reference date; and the non-medical service records covering the period of service before the reference date. Items descriptive of antecedent experience with general biologic significance, validity, and consistency were abstracted and are grouped as follows.

Preservice demography and geography

Date and county of birth, date and residential address and county at induction (urban or rural), length of preinduction education in years, civilian occupation, religion, race, Hispanic or other ethnicity (deduced from surname; ref. 39), number and ages of siblings, parental age, and marital/parental status at service entry, meteorological and geographical characteristics of U.S. counties in 1959 (40). Counties were divided into quartiles on the basis of 1950 Hodgkin lymphoma mortality rates (41) to examine the effects of preinduction migration between counties at disparate levels of risk.

Physical examination and prior medical history at induction

Family history of (unspecified) cancer or asthma, height and weight, ABO blood type, color vision status, eye color, handedness, history, hay-fever, asthma, childhood infections, infectious mononucleosis, sexually transmitted diseases, tuberculosis, appendectomy, tonsillectomy.
Service experience

Service aptitude test score, rank at reference date, assignment to a medical unit, to duty entailing X-ray or radar exposure, to duty entailing food preparation or handling, or to combat duty.

History of AYAHL

Clinical date of onset and pathologic confirmation were obtained from records linked to those on file at the Armed Forces Institute of Pathology. Each diagnostic specimen was categorized using the modified Lukes system (42) into nodular sclerosis (ND), lymphocyte predominant (LP), lymphocyte depleted (LD), and mixed cellularity (MC).

The abstraction of all records, data entry, and data quality control were completed by September of 1974.

Statistical analyses

The variables were screened using matched pair comparisons after reducing variables measured on a continuous or expanded ordinal scale into succinct ordinal categories. Conventional univariate matched pair estimates of the relative risk for each individual variable were then calculated. All factors found or expected to significantly influence the risk of AYAHL were then reanalyzed using multivariate logistic regression using Epilog (Epicenter Software) producing a risk estimate with 95% confidence interval (CI) for each variable after adjustment for all other variables.

Results

Sibling configuration

Several characteristics of the sib-ship were independent predictors of diagnosis (Table 1). Risk was linked to lower sib-ship size, diminishing stepwise with each additional sibling (Fig. 1). Risk was also predicted by earlier birth order and by the interval between birth and that of the next youngest or oldest sibling. Table 2 combines sib-ship size, birth order and these intervals, indicating that no single characteristic is wholly responsible. Maternal age was not significantly associated with AYAHL (not shown).

Preservice geographic factors

Crude measures of higher risk for those born in a high 1950 Hodgkin lymphoma-mortality, urban, or affluent county, or in a...

Table 1. Overall impact of sibling configuration: sib-ship size, birth order, interval in age from nearest sibs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>CA/CO</th>
<th>Referent</th>
<th>CA/CO</th>
<th>OR UNIV</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sib-ship size</td>
<td>1 (only child)</td>
<td>103/60</td>
<td>&gt;3 (OR, 1.0)</td>
<td>121/121</td>
<td>2.3</td>
<td>1.6–1.5</td>
</tr>
<tr>
<td>Sib-ship size</td>
<td>2–3</td>
<td>265/245</td>
<td>&gt;3 (OR, 1.0)</td>
<td>121/121</td>
<td>1.4</td>
<td>1.1–1.9</td>
</tr>
<tr>
<td>Birth order</td>
<td>First-borne</td>
<td>304/219</td>
<td>Middle-borne (OR, 1.0)</td>
<td>132/178</td>
<td>1.9</td>
<td>1.4–2.6</td>
</tr>
<tr>
<td>Birth order</td>
<td>Last-borne</td>
<td>123/127</td>
<td>Middle-borne (OR, 1.0)</td>
<td>132/178</td>
<td>1.3</td>
<td>0.93–1.8</td>
</tr>
<tr>
<td>Interval between case and sibling births</td>
<td>Number of sibs born within 5 y of case</td>
<td>225/154</td>
<td>Younger and older sibs born within 5 y of case (OR, 1.0)</td>
<td>92/136</td>
<td>2.1</td>
<td>1.5–3.0</td>
</tr>
<tr>
<td>Interval between case and sibling births</td>
<td>Younger sibs, none born within 5 y of case</td>
<td>150/142</td>
<td>Younger and older sibs born within 5 y of case (OR, 1.0)</td>
<td>92/136</td>
<td>1.6</td>
<td>1.1–2.2</td>
</tr>
<tr>
<td>Interval between case and sibling births</td>
<td>Older sibs, none born within 5 y of case</td>
<td>110/111</td>
<td>Younger and older sibs born within 5 y of case (OR, 1.0)</td>
<td>92/136</td>
<td>1.5</td>
<td>1.0–2.2</td>
</tr>
</tbody>
</table>

Abbreviations: CA/CO, #cases/#controls; OR UNIV, univariate OR.
county subject to high annual days below freezing, days over 90°, or hours of insolation, were not significant after adjustment for family configuration and other individual predictors, but a link with the mean birth county educational level remained conventionally significant after adjustment, as did an association with a single meteorological variable: the annual days of birth county humidity (Table 3). When conscripts had moved between counties at different 1950 Hodgkin lymphoma mortality rates before induction, the direction of movement was mostly toward counties at higher apparent risk and the level of risk tracked significantly with birthplace rather than residence at induction. Neither season of birth nor season of diagnosis was related to risk (data not shown).

Demographic factors

The mean age of cases was 19.8 years with an SD of 2.2 and a median age of 19.3 years. Inductees with Hispanic surnames, but not African Americans, tended to be at lower risk of subsequent AYAHL (Table 4). The few Jewish servicemen were at (nonsignificantly) higher risk, but no meaningful difference in risk was found between Catholics and Protestants, or between other ethnic subgroups (not shown). Greater height and weight [body mass index (BMI)] at induction were independently found at higher risk, in each case with a significant ordinal trend. The higher crude risk of those with higher rank, with more education, with a higher score from the “aptitude” test given at induction, or with a professional preinduction occupation (not shown) was reduced to near unity after adjustment for other variables. Although marital status was not related to risk, those who had become parents before induction were found to be at significantly higher risk, especially after adjustment.

Medical and service-related factors

Carriers of blood group B, with or without A, were at significantly increased risk. A history of childhood transmissible infection (exanthemata, mumps) was significantly linked

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>CA/CO</th>
<th>Referent</th>
<th>CA/CO</th>
<th>UNIV</th>
<th>OR</th>
<th>ADJ*</th>
<th>ADJ CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth county median family income in 1959</td>
<td>&gt; $5787</td>
<td>315/259</td>
<td>$4185 (OR, 1.0)</td>
<td>179/229</td>
<td>1.6</td>
<td>1.1</td>
<td>0.78-1.7</td>
<td></td>
</tr>
<tr>
<td>Birth county median years education in 1959</td>
<td>&gt;10 y</td>
<td>324/256</td>
<td>0-10 y (OR, 1.0)</td>
<td>330/392</td>
<td>1.5</td>
<td>1.4</td>
<td>1.1-1.8</td>
<td></td>
</tr>
<tr>
<td>Birth county mean annual humidity (pan evaporation)</td>
<td>&gt;37.8° North</td>
<td>462/405</td>
<td>&lt;37.9° N (OR, 1.0)</td>
<td>193/243</td>
<td>1.5</td>
<td>1.1</td>
<td>0.70-1.6</td>
<td></td>
</tr>
<tr>
<td>Birth county mean annual humidity (pan evaporation)</td>
<td>0-48 inches</td>
<td>416/360</td>
<td>&gt;48 inches (OR, 1.0)</td>
<td>234/277</td>
<td>1.4</td>
<td>1.4</td>
<td>1.1-1.8</td>
<td></td>
</tr>
<tr>
<td>Preinduction migration to another county</td>
<td>To next higher county risk quartile*</td>
<td>27/25</td>
<td>None (OR, 1.0)</td>
<td>554/537</td>
<td>0.8</td>
<td>0.7</td>
<td>0.38-1.2</td>
<td></td>
</tr>
<tr>
<td>Preinduction migration to another county</td>
<td>To two quartiles of county risk higher*</td>
<td>9/26</td>
<td>None (OR, 1.0)</td>
<td>554/537</td>
<td>0.4</td>
<td>0.5</td>
<td>0.20-1.0</td>
<td></td>
</tr>
<tr>
<td>Residence at induction</td>
<td>Urban</td>
<td>497/465</td>
<td>Rural (OR, 1.0)</td>
<td>159/190</td>
<td>1.3</td>
<td>1.2</td>
<td>0.83-1.6</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CA/CO, #cases/#controls; OR UNIV, univariate OR; OR ADJ, adjusted OR; ADJ CI, adjusted confidence interval.

*Excluding factor of interest, adjusted for birth county humidity and median education, family configuration, height, parental status, blood type, infectious mononucleosis, sexually transmitted infections, lymphadenitis, and childhood exanthemata/mumps.

Test for trend.

*Migration to a higher-risk county; crude P = 0.02; adjusted P = 0.04.
to lower risk, as was a past sexually transmitted infection (STD; Table 5). Preinduction infectious mononucleosis was positively and significantly associated with future AYAHL. Past asthma was nonsignificantly predictive of diagnosis, although neither hay fever, unspecified allergy, nor a family history of asthma (or of unspecified cancer) was associated with disease. Nonsignificant positive associations were found for prior appendectomy and especially tonsillectomy/tonsillitis. No service history factor (combat, medical, radar, food service) was associated with risk (not shown).

Risk modification by family configuration
Each adult characteristic was examined according to three empirically defined strata of risk based on the sib-ship (childhood) configuration (Table 6). Associations between Hodgkin lymphoma and infectious mononucleosis, blood group, BMI, tonsillectomy, height, parental status and childhood infection all became more extreme after this adjustment.

Risk modification by histologic type
Of the 501 tumor specimens examined, 50.0% were of nodular sclerosis, 33.5% of mixed cellularity, and 16.5% of the less frequent histotypes (Table 7). No meaningful differences distinguished risk factors for nodular sclerosis from those for mixed cellularity.

### Discussion
Abstraction of records for this study began in 1972 and was completed within 2 years; no previous publications have appeared. Many of the individual findings have been previously reported by smaller and/or less well controlled investigations. Belated publication is warranted not only because of a few provocative novel findings, but also because the sample is large, the findings are detailed and extraordinarily free from bias, and the results can be applied with virtually no restriction to previously healthy U.S. males ages 17 to 32 years.

More frequent diagnoses of AYAHL have repeatedly been found among those of higher social class, as measured by education, income, or occupation, and that fact is consistent on a population basis with an increase in risk accompanying economic development. One important question to address is whether that link represents a causal event in the post-pubertal or adult years just before diagnosis, or, because adult social class is largely determined by parental education and affluence, whether the causal roots go back to early life. Some determinants do not distinguish between the alternatives. Adult increases in height and BMI, common factors cited in previous studies (43–51), can be tracked back to the nutritional and clinical benefits of childhood affluence (52). Information

### Table 4. Impact of demographic and personal characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>CA/CO</th>
<th>Referent (OR, 1.0)</th>
<th>CA/CO</th>
<th>Univariate OR</th>
<th>Adjusted OR</th>
<th>ADJ CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity (from surname)</td>
<td>Hispanic</td>
<td>6/24</td>
<td>English (OR, 1.0)</td>
<td>259/227</td>
<td>0.3</td>
<td>0.3</td>
<td>0.10–1.0</td>
</tr>
<tr>
<td>Religion</td>
<td>Jewish</td>
<td>14/7</td>
<td>Protestant (OR, 1.0)</td>
<td>415/349</td>
<td>2.0</td>
<td>1.7</td>
<td>0.56–5.1</td>
</tr>
<tr>
<td>Race</td>
<td>African American</td>
<td>53/49</td>
<td>White (OR, 1.0)</td>
<td>603/596</td>
<td>0.9</td>
<td>1.5</td>
<td>0.93–2.5</td>
</tr>
<tr>
<td>Height&lt;sup&gt;b&lt;/sup&gt;</td>
<td>67–69 inches</td>
<td>202/188</td>
<td>&lt;67 inches (OR, 1.0)</td>
<td>192/238</td>
<td>1.4</td>
<td>1.2</td>
<td>0.90–1.7</td>
</tr>
<tr>
<td>Height&lt;sup&gt;b&lt;/sup&gt;</td>
<td>70+ inches</td>
<td>257/218</td>
<td>&lt;67 inches (OR, 1.0)</td>
<td>107/153</td>
<td>1.5</td>
<td>1.5</td>
<td>1.1–2.1</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20–24.9</td>
<td>243/261</td>
<td>&lt;20 (OR, 1.0)</td>
<td>119/144</td>
<td>1.1</td>
<td>1.1</td>
<td>0.78–16</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25+</td>
<td>289/238</td>
<td>&lt;20 (OR, 1.0)</td>
<td>119/144</td>
<td>1.5</td>
<td>1.5</td>
<td>1.0–2.1</td>
</tr>
<tr>
<td>Years of education</td>
<td>&gt;11</td>
<td>398/340</td>
<td>0–10 (OR, 1.0)</td>
<td>267/307</td>
<td>1.4</td>
<td>1.0</td>
<td>0.67–1.4</td>
</tr>
<tr>
<td>Induction test score&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Quintile 2–3</td>
<td>447/404</td>
<td>Quintile 1 (OR, 1.0)</td>
<td>59/49</td>
<td>0.9</td>
<td>1.2</td>
<td>0.77–2.0</td>
</tr>
<tr>
<td>Induction test score&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Quintile 4–5</td>
<td>98/134</td>
<td>Quintile 1 (OR, 1.0)</td>
<td>59/49</td>
<td>0.9</td>
<td>0.8</td>
<td>0.45–1.4</td>
</tr>
<tr>
<td>Rank</td>
<td>Officer</td>
<td>48/40</td>
<td>Enlisted man (OR, 1.0)</td>
<td>608/614</td>
<td>1.3</td>
<td>1.0</td>
<td>0.54–1.8</td>
</tr>
<tr>
<td>Preinduction marital status</td>
<td>Yes</td>
<td>59/61</td>
<td>Single (OR, 1.0)</td>
<td>590/588</td>
<td>1.0</td>
<td>0.9</td>
<td>0.52–15</td>
</tr>
<tr>
<td>Preinduction parental status</td>
<td>Yes</td>
<td>62/37</td>
<td>No (OR, 1.0)</td>
<td>594/619</td>
<td>1.9</td>
<td>2.6</td>
<td>1.4–4.8</td>
</tr>
</tbody>
</table>

Abbreviations: CA/CO, #cases/#controls; ADJ CI, adjusted CI.

<sup>a</sup>Excluding factor of interest, adjusted for birth county humidity and median education, family configuration, height, parental status, blood type, infectious mononucleosis, sexually transmitted infections, lymphadenitis, and childhood exanthema/mumps.

<sup>b</sup>Tests for trend:

<sup>c</sup>Height: crude P = 0.02; adjusted P = 0.05.

<sup>d</sup>BMI: crude P = 0.01; adjusted P = 0.03.

<sup>e</sup>Induction test score: crude P = 0.04; adjusted P = 0.07.

### Table 5. Impact of medical and service history

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>CA/CO</th>
<th>Referent (OR, 1.0)</th>
<th>CA/CO</th>
<th>OR UNIV</th>
<th>OR ADJ&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ADJ CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood type</td>
<td>B/AB</td>
<td>95/60</td>
<td>O/A (OR, 1.0)</td>
<td>505/535</td>
<td>1.8</td>
<td>1.7</td>
<td>1.3–2.5</td>
</tr>
<tr>
<td>Asthma</td>
<td>Yes</td>
<td>13/5</td>
<td>No (OR, 1.0)</td>
<td>600/584</td>
<td>2.4</td>
<td>2.0</td>
<td>0.64–6.5</td>
</tr>
<tr>
<td>Hay fever</td>
<td>Yes</td>
<td>34/27</td>
<td>No (OR, 1.0)</td>
<td>572/263</td>
<td>1.2</td>
<td>1.1</td>
<td>0.62–2.1</td>
</tr>
<tr>
<td>Allergy</td>
<td>Yes</td>
<td>42/39</td>
<td>No (OR, 1.0)</td>
<td>650/648</td>
<td>1.1</td>
<td>1.0</td>
<td>0.59–18</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>Yes</td>
<td>470/498</td>
<td>No (OR, 1.0)</td>
<td>470/498</td>
<td>1.6</td>
<td>1.3</td>
<td>0.88–1.8</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>Yes</td>
<td>78/70</td>
<td>No (OR, 1.0)</td>
<td>53/521</td>
<td>1.1</td>
<td>1.2</td>
<td>0.76–1.8</td>
</tr>
<tr>
<td>Sexually transmitted infection</td>
<td>Yes</td>
<td>53/72</td>
<td>No (OR, 1.0)</td>
<td>603/584</td>
<td>0.7</td>
<td>0.6</td>
<td>0.39–0.97</td>
</tr>
<tr>
<td>Childhood exanthema/mumps</td>
<td>Yes</td>
<td>8/26</td>
<td>No (OR, 1.0)</td>
<td>652/640</td>
<td>0.3</td>
<td>0.2</td>
<td>0.08–0.48</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>Yes</td>
<td>16/4</td>
<td>No (OR, 1.0)</td>
<td>640/652</td>
<td>4.0</td>
<td>5.6</td>
<td>1.7–19</td>
</tr>
</tbody>
</table>

Abbreviations: CA/CO, #cases/#controls; OR UNIV, univariate odds ratio; OR ADJ, adjusted odds ratio; ADJ CI, adjusted confidence interval.

<sup>a</sup>Excluding factor of interest, adjusted for birth county humidity and median education, family configuration, height, parental status, blood type, infectious mononucleosis, sexually transmitted infections, lymphadenitis, and childhood exanthema/mumps.
obtained at diagnosis may be colored by the moment and analytic studies often have insufficient power to distinguish between the two periods, even if specific childhood circumstances are known. Here, the availability of information is unrelated to either education or retrospective perception, and is free of selection or information bias.

Adjustment for the childhood environment and medical history eliminated the commonly reported risk indicators of higher adult social class, including occupation, service rank, "aptitude" induction test score, marriage, or service assignment. Although previous investigators (53, 54) found a higher risk not only among Jewish servicemen, but also among officers and those with higher induction test scores or professional preservice occupations, no adjustments for childhood characteristics were made. Adult smoking, a surrogate for lower levels of adulthood education, has been linked to all Hodgkin lymphoma, but not consistently to AYAHL (55-59).

In contrast, after adjustment for other determinants, the number, order, and proximity of sibs still differed dramatically between cases and controls (60-63), and those differences are unlikely to have more than negligible bearing on the adult life experience. The next task is to identify the nature of the pertinent childhood exposure, and the first consideration is the particular age at which that occurs. The sib-ship differences are unlikely to be a consequence of gestational events, which have been hypothesized to play a causal role (64), but it could reflect exposures at either preschool ages or later. As infants and toddlers, children explore the world. Affluent parents are likely to be more protective of only children, or children without siblings near in age, and less protective of individual children in large sib-ships. In a study of twins discordant for AYAHL, we found that the twin who reported, and was reported to have, more early oral exposures was five times more likely to be the affected twin (65).

Sib-ship patterns are sure to influence childhood exposures in other ways. Person-to-person infections pass between siblings, and between classmates, and the greater the number of closely spaced siblings, the more infectious agents are passed on. The prevalence of infection with Helicobacter pylori in adulthood, for example, is strongly correlated with sib-ship size (66, 67). Moreover, even after adjustment for their sib-ship configuration, these cases reported fewer childhood viral infections (and fewer sexually transmitted infections) than did controls (68-70). They also had experienced more frequently reported past infectious

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Low-risk sibling configuration</th>
<th>Medium-risk sibling configuration</th>
<th>High-risk sibling configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CA/CO OR CI</td>
<td>CA/CO OR CI</td>
<td>CA/CO OR CI</td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>69+ vs. &lt;67 in (OR, 1.0)</td>
<td>69/82 1.1 0.51-2.2</td>
<td>64/70 0.8 0.34-1.7</td>
<td>124/66 1.7 0.73-3.8</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
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<tr>
<td>25+ vs. &lt;20 (OR, 1.0)</td>
<td>80/87 2.0 0.89-4.4</td>
<td>79/71 2.0 0.76-5.4</td>
<td>130/80 1.1 0.44-2.8</td>
</tr>
<tr>
<td>Parenthood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no (OR, 1.0)</td>
<td>36/29 2.4 1.0-5.9</td>
<td>12/3 4.2 1.2-15</td>
<td>14/5 2.0 0.3-11</td>
</tr>
<tr>
<td>Blood type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-AB vs. O/A (OR, 1.0)</td>
<td>30/28 3.0 1.1-8.3</td>
<td>30/14 1.5 0.42-5.3</td>
<td>33/18 1.8 0.51-6.0</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no (OR, 1.0)</td>
<td>29/27 1.5 0.53-4.2</td>
<td>42/27 1.2 0.51-3.0</td>
<td>71/44 1.2 0.53-2.6</td>
</tr>
<tr>
<td>Childhood exanthema/mumps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no (OR, 1.0)</td>
<td>4/9 0.4 0.08-2.1</td>
<td>1/10 0.1 0.03-0.56</td>
<td>3/7 1.0 0.06-16</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no (OR, 1.0)</td>
<td>2/2 1.5 0.20-11.0</td>
<td>7/0 ~</td>
<td>7/2 3.0 0.31-29</td>
</tr>
<tr>
<td>Abbreviation: CA/CO, #cases/#controls.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Estimated after breaking the pairwise matching.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
mononucleosis (71–78), a separate indication of comparatively infrequent interpersonal childhood exposure. [Hjalgrim and colleagues (12) observed fewer serologic reports of IM among EBV-negative Hodgkin lymphoma cases than expected, a finding seemingly inconsistent with the fourfold increase in risk found here, but his cases of comparable age were still much more likely than expected to have had recent IM within an interval that would have included the preinduction teenage years of these servicemen.]

In contrast with the inverse association between childhood infection and AYAHL, another marker of childhood infection, tonsillectomy, which usually occurs at a later age, has repeatedly been found to be associated with risk (37, 60, 79–85), although often without appropriate adjustment for other determinants. While it actually may act as a measure of better access to care (a surrogate for high social class), it has also been found associated with AYAHL in a study of disease-discordant twins (65), uniquely matched on genome, childhood environment, and presumably access to care. Here, we also found a positive (albeit nonsignificant) association with that operation as well as with appendectomy.

For better or worse, advantaged children are deprived at all ages of much of the lifetime protection that follows early infection with specific immunogenic agents, and are also deprived of the early infections and exposures that produce lifetime immune competence. Thus an advantaged childhood as a risk indicator does not serve to exclude either of the hypotheses that could explain the link to economic development/higher socioeconomic status. Although we could not add to the evidence suggesting that diagnosis follows a deficiency of early acquired immunity (7, 65), the major finding of a protected family environment certainly supports that hypothesis.

In contrast with Hodgkin lymphoma at older ages, EBV is unlikely to play a causal role in most cases of AYAHL (86). We found no seasonal mal-distribution of either date of birth or of diagnosis as have some previous investigators (87–90), and although medical workers have (inconsistently) been found at higher risk of Hodgkin lymphoma (91, 92), we found no such suggestion. Causation by a ubiquitous immunogenic virus is not ruled out by such negative findings, and despite the failure to date to identify a promising candidate agent (93), several of our findings do indirectly suggest that possibility. Continued incremental reduction in risk in the presence of higher sib-ship size and a reduction in association with wider spacing of siblings are two observations consistent with personal protection by virtue of early exposure to infected siblings. More suggestive is the higher risk among those who had become parents but not after marriage alone, possibly because the latter does not greatly alter the microbial environment. Others have found prediagnosis infections (other than infectious mononucleosis) to be more prominent among cases (94), and it is tempting to interpret parentage as a measure of exposure to an ubiquitous but unrecognized virus of childhood.

One other observation is weakly suggestive of an infectious agent. A significant increase in risk was attendant upon those who carry the B or AB genotypes of the ABO system. ABO antigens are present on a wide variety of cells, especially those of the gastrointestinal mucosa, and provide receptors for gastrointestinal infections (rotavirus, norovirus; ref. 95), they also have been linked to bacterial throat carriage (96), and B group antigen specifically is known to modulate the composition of the intestinal microbiota (97).

Within this very restricted age group, no etiologic differences between nodular sclerosis and mixed cell Hodgkin lymphoma were found, and other histologic subtypes were infrequent. While the cases were diagnosed before recognition of intra-HRS cell EBV, the proportion of EBV-positive cases among those diagnosed in the United States around age 20 is likely to have been no more than about 25% (98).

In summary, we have provided strong evidence that the genesis of AYAHL occurs in childhood, some additional evidence supporting causation of a ubiquitous childhood virus, and findings compatible with causation by virtue of an insufficiently developed acquired immunity. The strengths of this study are the large sample size, the demographic and clinical uniformity of cases, the wealth of information, the population-based source and the nested case–control design, which together have largely eliminated both selection and information bias. The liabilities include restriction to male cases, the absence of EBV antigen characterization, and the reliance on behavioral descriptors of a past era that may no longer have the same significance. Little girls behave differently than little boys, restricting the interpretation, and the dynamics of social contact have certainly changed, restricting the feasibility of replication, but not the interpretation.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: T.M. Mack
Development of methodology: T.M. Mack
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.E. Norman
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T.M. Mack, J.E. Norman, E. Rappaport, W. Cozen
Writing, review, and/or revision of the manuscript: T.M. Mack, J.E. Norman, W. Cozen
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T.M. Mack, J.E. Norman
Study supervision: T.M. Mack

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References


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