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7Rambam Medical Center and Rappaport Faculty of Medicine, Technion, Haifa, Israel;
8Chaim Sheba Medical Center, Tel Hashomer and Tel Aviv University, Israel;
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Running head: B-NHL exposure persistence clearance hepatitis B

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Although 90-95% of adults recover completely from Hepatitis B (HBV) infection, a minority are unable to clear the virus\textsuperscript{1}. Epidemiological studies have demonstrated an increased risk of B-NHL among those with persistent HBV and B-NHL\textsuperscript{2-5}. Yet the roles of exposure per se, occult infection, antibody response and viral clearance remain unclear.

Occult HBV infection (OBI) signifies persistence of the viral genome in blood and liver tissue, in patients without hepatitis B surface antigen (HBsAg), with or without antibodies to hepatitis B core (anti-HBc) or hepatitis B surface (anti-HBs). Most subjects with OBI are in fact positive for anti-HBc and negative for HBsAg, while some are seronegative for all HBV markers\textsuperscript{6}. The association between OBI and B-NHL is clinically important due to the risk of reactivation of HBV following immunotherapy or chemotherapy; however, few studies have addressed OBI as a risk factor for NHL\textsuperscript{7-9}.

Immune response to HBV (defined as anti-HBs) is elicited either by natural response to viral exposure (anti-HBc+ with anti-HBs+) or by vaccination (anti-HBc- with anti-HBs+). Limited data have suggested a negative association between the presence of anti-HBs and B-NHL\textsuperscript{7,8}.

Hereditry plays a role in NHL etiology, as evidenced by the doubling of risk in first-degree relatives of NHL patients\textsuperscript{10}. It is unknown whether host genetic factors related to viral clearance are also related to NHL susceptibility.

The role of HBV infection in B-NHL has not been previously evaluated in Israel or the West Bank, where HBsAg seroprevalence has been estimated at 0.22 to 1.8% respectively\textsuperscript{11,12}. In a case-control study (Supplemental Methods) we explored associations between exposure, persistence, and immune response to HBV with overall B-NHL as well as with two major subtypes: diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), in these populations. Additionally, we assessed whether a family history of hematopoietic malignancies was associated with HBV persistence.

We recruited 823 (516-Israelis/307-Palestinians) incident cases of B-NHL (median time from diagnosis- three months). DLBCL was the most common histology, comprising 427 (52%) cases while FL was diagnosed in 186 (23%). We recruited 808 healthy controls (414-Israelis/394-Palestinians) from among individuals accompanying patients to hospital or health centers. Cases and controls (Supplemental Table 1) differ in distributions of sex,
age, marital status and family history of hematopoietic malignancies (P<0.01 for all); thus we adjusted for these variables in our models.

HBV serology was performed in 96.8% of participants (see results of individual markers, Table 1a). Most seromarkers (with the exception of eAg), including anti-HBc, HBsAg, anti-HBs and e-antibodies (anti-HBe) were more prevalent among Palestinians than Israelis. In contrast, antibody response to vaccine was more prevalent among Israelis. In addition, the combination of anti-HBc+ without anti-HBs, representing lack of immune response to HBV, was more common in Palestinians (9.0% vs. 3.0% in Israelis, P<0.0001) (Table 1b). Case-control association patterns were similar in the two groups.

Comparing cases and controls we found that persistence of HBV, as evidenced by HBsAg+ was associated with DLBCL (odds ratio (OR)=2.39, 95% confidence-interval (CI):1.13-5.06). Moreover, the prevalence of HBsAg+ among those exposed to HBV (anti-HBc+) was higher in cases than in controls (15% vs.7.8%, P=0.03), indicating lower viral clearance rates among cases. However, no case-control differences were found regarding exposure to HBV (anti-HBc+) (OR=0.94, CI:0.72-1.23) or OBI (OR=0.84, CI:0.64-1.12) (Figures 1-2), anti-HBe or HBeAg prevalence (data not shown).

The presence of anti-HBs antibodies was inversely associated with B-NHL (OR=0.73, CI:0.57-0.93) and DLBCL (OR=0.68, CI:0.51-0.92). This pattern held for antibody response to vaccine (OR=0.67, CI:0.48-0.93 for overall B-NHL; OR=0.55, CI:0.36-0.85 for DLBCL), but was not statistically significant for natural antibody response, (OR=0.76, CI:0.56-1.04). Conversely, a lack of antibody response was positively associated with DLBCL (OR=1.62, CI:1.01-2.61).

As expected, having a first-degree relative with hematopoietic cancer was associated with overall B-NHL (OR=1.69, CI:1.16-2.48) and DLBCL (OR=1.83, CI:1.17-2.87). Of interest, this variable was also strongly associated with persistent HBV infection among controls (OR=6.80, CI:1.14-23.8).

**In summary**, we confirm that persistent HBsAg carriers had a significantly increased risk of DLBCL and non-significant increased risk for overall B-NHL. The European Epilymph study\(^2\) reported a non-significant increased risk of B-NHL in HBsAg carriers (OR=1.58, CI:0.69-3.64) and DLBCL (OR=1.50, CI:0.47-4.82), while a Turkish study\(^3\) reported
OR=1.26, CI:0.65-2.46 and OR= 2.68, CI:1.19-6.01 for B-cell lymphoid tumors and DLBCL, respectively, and a strong relation for FL (OR=5.48, CI:1.02-29.5). Korean investigators reported a significant positive association between HBsAg and NHL (hazard ratio=1.74, CI:1.45-2.09) and a twofold risk of DLBCL in a cohort study\textsuperscript{4} and adjusted OR (2.09, CI:1.11–3.92) in a case-control study\textsuperscript{5}, respectively. In the latter study, investigators did not detect HBV-DNA in lymphoma tissues, but found HBV S, X, and C genes in DNA extracted from peripheral blood mononuclear cells, suggesting an indirect effect on lymphomagenesis\textsuperscript{5}.

In the current study, the presence of anti-HBc was not associated with B-NHL or its subtypes, implying that exposure to HBV \textit{per se} is not a risk factor for B-NHL. This finding is supported by a single Japanese cohort study of 20,360 subjects\textsuperscript{13}.

Chen \textit{et al}\textsuperscript{9} defining OBI as HBsAg- and HBV-DNA+, reported a non-significant positive association with B-NHL. DNA extracted from tumour samples also failed to detect the HBV genome.

The inverse association between the presence of anti-HBs with B-NHL and DLBCL is consistent with Marcucci et al's report\textsuperscript{7} of an OR=0.61 (CI:0.44-0.85), both in indolent (OR=0.57, CI:0.38-0.88) and aggressive (OR=0.63, CI:0.44-0.93) B-NHL. Similarly, Wang \textit{et al}\textsuperscript{8} reported an OR of 0.60 (CI:0.40-0.70). In contrast, Kim \textit{et al}\textsuperscript{14} found no significant difference in anti-HBs+ prevalence comparing NHL patients with subjects with non-hematological malignancies and non-malignant conditions.

Distinguishing between naturally acquired and vaccine-associated immunity is not clear cut, as HBV DNA was not available to confirm actual exposure status. Nevertheless, we found a significant inverse association of B-NHL and DLBCL with anti-HBs overall. Similarly, Wang \textit{et al}\textsuperscript{8} reported a lower proportion of immune individuals among B-NHL cases. In contrast, the Epilymph study\textsuperscript{2} found no association between vaccine immunity and B-NHL. However the OR for DLBCL (OR=0.56, CI:0.29-1.06) was similar to the current study’s point estimate.

Lack of immune response showed a significant positive association with DLBCL in our study. Likewise, Wang \textit{et al}\textsuperscript{8} concluded that patients with B-NHL may show lower clearance of the virus. Marcucci \textit{et al}\textsuperscript{7} also demonstrated that lack of an antibody response was positively associated with B-NHL (OR=2.05, CI:1.24-3.37). These findings suggest that immune competence may be protective against B-NHL. Alternative explanations include
diminished immune response to HBV in B-NHL patients due to the lymphoma itself or reduction in antibody titres due to treatment, especially rituximab\textsuperscript{15}, or waning immunity with age. Most of the sera (75\%) among cases were collected post-treatment. However, among a subgroup with available paired samples, pre- and post-treatment sera showed agreement (Kappa=1.0 for HBsAg and anti-HBs biomarkers, and Kappa=0.81 (CI:0.55-1.00) for anti-HBc, due to two patients with positive pre-treatment anti-HBc+ becoming seronegative post-treatment. Wang et al's study\textsuperscript{8} in which 85\% of cases were recruited before treatment also demonstrated a significant negative association between anti-HBs+ and B-NHL.

Intriguingly, among controls, we found a higher proportion of individuals with a positive family history among HBsAg carriers. This association has not been reported previously and suggests the possibility of a joint inherited susceptibility to both diminished viral clearance and hematologic malignancy. Alternatively it could reflect increased NHL risk in families where vertical transmission has occurred.

Limitations of this study include the inclusion of spouses as controls for 12\% of enrolled cases. Use of spouse controls could theoretically alter case-control comparisons and bias the study towards the null. However no couples were concordant for HBsAg+; in one couple both members were anti-HBc+. Sensitivity analysis excluding spouse controls did not alter any of the reported associations (not shown). Other drawbacks are the lack information on specific HBV genotypes, which may influence type and degree of immune responses.

The study's strengths include its unique population and the examination of several hepatitis biomarkers, enabling assessment of combinations and their association with B-NHL. Although a number of studies have examined associations between HBV seromarkers and B-NHL, few have clearly distinguished the roles of exposure, persistence and viral clearance in disease etiology.

Higher seroprevalence observed among Palestinians imply that this population is at increased risk for HBV complications, including hepatocellular carcinoma and potentially B-NHL. It is particularly important to screen this population and all groups with high levels of exposure before immunosuppressive treatments in order to prevent potentially fatal flare-ups of pre-existing hepatitis infection.

In conclusion, our findings support an association between persistent HBV infection with B-NHL. We raise the possibility that hereditary factors may be related both to susceptibility to
lymphoma and viral persistence, and that exposure *per se* does not explain the observed association between HBV and B-NHL. Prospective studies may clarify both the role of HBV vaccination in the prevention of B-NHL in endemic populations, and long-term B-NHL risk in individuals with poor antibody response to vaccine. The results of this study prompt a rethinking of the mechanism of virus-associated B-NHL beyond effects of chronic antigenic stimulation or viral integration, to include host response to infection as a marker of disease susceptibility.
Authorship Contributions

GK - Performed and coordinated the Israeli population study, responsible for data collection, data analysis, statistical modeling, data interpretation, literature search, figures, and writing of the manuscript.

RAS - Performed and coordinated the Palestinian population study, responsible for data collection, lab work, data interpretation, writing of the manuscript.

RP – participated in training of study personnel, study design, obtaining funding, data collection and interpretation.

ZA - Designed and supervised the Palestinian side of the project, facilitated access to patients and controls, data collection, data interpretation, writing of the manuscript.

AK – Served as PI at one study site (AVH), supervised viral serology performance, participated in data interpretation, writing of the manuscript.

HE – Was responsible for data collection at Beit Jalla Hospital, data interpretation.

ED - Providing patients and manuscript revision.

MK - Providing patients and manuscript revision.

ME - Providing patients and manuscript revision.

AN - Was the PI in one site (Sheba Tel Hashomer), responsible for data collection at the site, writing of the manuscript.

GA - Provided pathology expertise, data interpretation, writing of the manuscript.

DBY – Involved in study design, facilitated patient recruitment, aided in obtaining IRB approval and funding, data interpretation, writing of the manuscript.

RS – Provided hepatology expertise, interpretation of serologic data, writing of the manuscript.

OP - Was responsible for the study design, obtaining IRB approval and funding, data collection, review of clinical data, interpretation of data and writing of the manuscript.

All authors reviewed and approved the final manuscript.

Disclosure of Conflicts of Interest

There is no conflict of interest with any of the authors of this manuscript.
References


Table 1. Seropositivity for HBV and HCV biomarkers in Israelis versus Palestinians for Overall B-NHL, DLBCL, FL patients and controls

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Controls</th>
<th>Overall B-NHL</th>
<th>DLBCL</th>
<th>FL</th>
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<td></td>
<td>Isr</td>
<td>Pal</td>
<td>p'</td>
<td>Isr</td>
</tr>
<tr>
<td>HBsAg+</td>
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<td>3.1</td>
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<td>&lt;0.0001</td>
<td>14.9</td>
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<td>Anti-HBs+</td>
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<td>38.1</td>
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<td>21.3</td>
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<tr>
<td>Anti-HBe+</td>
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<td>21.7</td>
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<td>10.0</td>
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<td>HBeAg+</td>
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<td>0.50</td>
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</table>

b

Biomarker combinations

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<th>p'</th>
<th>Isr</th>
<th>Pal</th>
<th>p'</th>
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<th>Isr</th>
<th>Pal</th>
<th>p'</th>
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<tbody>
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<td>OBI</td>
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<td>12.5</td>
<td>27.9</td>
<td>&lt;0.0001</td>
<td>12.7</td>
<td>28.1</td>
<td>&lt;0.0001</td>
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<td>OBI with Anti-HBe+</td>
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<td>11.4</td>
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<td>6.4</td>
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<td>0.18</td>
<td>9.0</td>
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<td>HBsAg+ with Anti-HBe+</td>
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<td>0.06</td>
<td>1.5</td>
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<tr>
<td>Naturally immune</td>
<td>11.6</td>
<td>24.8</td>
<td>&lt;0.0001</td>
<td>9.4</td>
<td>20.8</td>
<td>0.02</td>
<td>8.9</td>
<td>21.0</td>
<td>0.01</td>
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<tr>
<td>Immune via vaccine</td>
<td>16.9</td>
<td>13.6</td>
<td>&lt;0.0001</td>
<td>11.2</td>
<td>8.1</td>
<td>0.001</td>
<td>8.9</td>
<td>9.5</td>
<td>0.001</td>
<td>13.4</td>
<td>4.8</td>
<td>0.04</td>
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<tr>
<td>Lack of immune response</td>
<td>3.0</td>
<td>9.0</td>
<td>&lt;0.0001</td>
<td>5.5</td>
<td>12.8</td>
<td>&lt;0.0001</td>
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<td>14.8</td>
<td>0.02</td>
<td>4.5</td>
<td>7.1</td>
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Total No. | 414 | 394 | 516 | 307 | 210 | 217 | 143 | 43 |

B-NHL=B-cell non-Hodgkin lymphoma; DLBCL= diffuse large B-cell lymphoma; FL=follicular lymphoma; Isr=Israelis; Pal=Palestinians; HBsAg=hepatitis B surface antigen; Anti-HBc=hepatitis B core antibodies; Anti-HBs=hepatitis B surface antibodies; Anti-HBe=hepatitis B e antibodies; HBeAg=hepatitis B e antigen; Combinations: OBI (anti-HBc+, HBsAg-); Naturally immune (anti-HBe+, anti-HBs+); Immune via vaccine (anti-HBc-, anti-HBs+); Lack of immune response (anti-HBc+, anti-HBs-); *Fisher’s exact and χ² tests comparing positive biomarker or combination versus negative.
**Figure Legends**

**Figure 1.** Forest plots showing the odds ratio (OR) and 95% confidence interval (CI) for individual hepatitis biomarkers and their associations with overall B-cell non-Hodgkin lymphoma (B-NHL), diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) for the pooled populations (Israelis and Palestinians). ORs were stratified by population (Israelis, Palestinians), sex and age categories (four year grouping); adjusted for marital status, education (yrs), family history of hematopoietic malignancies in first-degree relatives. Hepatitis biomarkers: hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (anti-HBc) and hepatitis B surface antibodies (anti-HBs). **Bold font** indicates P<0.05.

**Figure 2.** Forest plots showing the odds ratio (OR) and 95% confidence interval (CI) for combinations of hepatitis B (HBV) biomarkers and their associations with overall B-cell non-Hodgkin lymphoma (B-NHL), diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) for the pooled populations (Israelis and Palestinians). ORs were stratified by population (Israelis, Palestinians), sex and age categories (four year grouping); adjusted for marital status, education (yrs), family history of hematopoietic malignancies in first-degree relatives. HBV biomarkers: hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (anti-HBc) and hepatitis B surface antibodies (anti-HBs). Combinations: Occult hepatitis B infection (OBI: anti-HBc+, HBsAg-); Naturally immune (anti-HBc+, anti-HBs+); Immune via vaccine (anti-HBc-, anti-HBs+); Lack of immune response (anti-HBc+, anti-HBs-); **Bold font** indicates P<0.05.
Supplemental Methods

Study design

This is a hospital and community-based case-control study in Israel and the West Bank including Palestinians and Israelis (Supplemental Methods). For purposes of analysis Israeli citizens of Muslim origin were grouped together with Palestinians.

Study population

Inclusion criteria

We enrolled incident cases (target: within 18 months of diagnosis), aged ≥18 years, with pathologically confirmed CD20+ (or other B-cell marker+) B-NHL, and healthy controls aged ≥18 years accompanying or visiting out- and inpatients in participating centers.

Exclusion criteria were inability to provide written informed consent; HIV positivity; being a blood relative of a case; and being a spouse of an enrolled case for Palestinian controls (given frequent cousin marriages).

Recruitment:

Cases were recruited in: a) Hadassah–Hebrew University Medical Center (HMC), a tertiary center on two campuses between October 2010 - March 2014 (N=507); b) Chaim Sheba, Meir, Rambam and HMC Medical Centers, university hospitals in the center and north of Israel, which participated in an uncompleted case-control study conducted in 2003 (Epilymph-Israel) (N=86); c) Augusta Victoria Hospital (AVH) in East Jerusalem, National Hospital of Nablus (NHN) and Al-Husein Hospital (AHH) in Beit Jalla in the West Bank (N=170), 2009-2013 and, d) using the West Bank Cancer Registry files, 2009-2013 (N=60).

Controls were recruited in: a) HMC for the Israeli cases (N=414); b) AVH, NHN, AHH, and 16 ambulatory health centers in the West Bank for the Palestinian cases (N=394).

Study variables

Participants were interviewed in Hebrew, Arabic, Russian or English utilizing a questionnaire adapted from that used in the European Epilymph study. Questionnaire items included demographic characteristics as well as family and medical history (reported separately).

Hepatitis B Biomarkers
Serum samples were obtained and tested for the presence of HBsAg, anti-HBc, anti-HBs, hepatitis B e antibodies (anti-HBe) and hepatitis B e antigen (HBeAg), by ELISA (Roche Elecsys®, Basel, Switzerland) at AVH.

Anti-HBc+ individuals were considered "exposed" to HBV. Among these, individuals who were HBsAg+ were considered to have persistent infection while those HBsAg- were considered to have occult infection (OBI). Individuals who demonstrated anti-HBs+ with anti-HBc- were considered immune via vaccine, while anti-HBs+ with anti-HBc+ were considered naturally immune via exposure, although some of the individuals designated "vaccinated" might actually be naturally immune. Individuals who were anti-HBc+ and anti-HBs- were considered to lack immune response following viral exposure.

**Statistical analysis**

Distribution of baseline variables in cases and controls were assessed using two-sided Fisher’s exact and χ² tests. Conditional logistic regression models were built to test the association [reported as ORs and 95% confidence intervals (CIs)] between B-NHL status (and subtypes DLBCL and FL) and hepatitis biomarkers- stratified by population (Israelis/Palestinians), sex and age categories (four year groupings); and adjusted for factors associated with the outcome (B-NHL) or exposure (hepatitis serology) including marital status, education (yrs), family history of hematopoietic malignancies in first-degree relatives. Individuals with missing data for the exposure variable of interest were excluded. Heterogeneity was assessed between population groups and serologic markers by adding an interaction term into the conditional logistic model.

Agreement of pretreatment serology results performed for clinical purposes and post-treatment within the study among a subgroup of cases was assessed using Kappa scores with 95% CIs.

Based on an assumed average prevalence (Israelis and Palestinians) in controls of 2% for HBV, two sided test with α=0.05; a study with 800 cases and 800 controls provided at least 85% power to detect an OR of 2.5.

Sensitivity analyses were performed for the OR estimations, a) using different stratification strategies to assess the stability of the results, b) for overall B-NHL and DLBCL associations excluding spouse controls, c) excluding those with borderline anti-HBc results, and d) interpreting borderline results as negative or positive.
Ethics

The study was approved by the Research Ethics Committee (IRB) of the Hadassah University Hospital and other participating institutes in Israel and the Institutional Review Board of the Palestinian Ministry of Health. All participants provided written informed consent.

Role of the funding source

The funding sources played no role in the design, execution or analysis of the study.

Supplemental Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DLBCL</th>
<th>FL</th>
<th>Overall B-NHL</th>
<th>Controls</th>
<th>P*</th>
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<tr>
<td></td>
<td>N</td>
<td>(%)</td>
<td>N</td>
<td>(%)</td>
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<td>186 (27.7)</td>
<td>823 (100)</td>
<td>808 (100)</td>
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<td>Population</td>
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<td>210 (48.1)</td>
<td>143 (76.9)</td>
<td>516 (62.7)</td>
<td>414 (51.2)</td>
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<td>282 (34.8)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>200 (46.8)</td>
<td>97 (52.2)</td>
<td>413 (50.2)</td>
<td>352 (43.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female</td>
<td>227 (53.2)</td>
<td>89 (47.8)</td>
<td>410 (49.8)</td>
<td>456 (56.4)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;34</td>
<td>74 (17.3)</td>
<td>12 (6.5)</td>
<td>97 (11.8)</td>
<td>99 (12.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>35-54</td>
<td>132 (30.9)</td>
<td>59 (31.7)</td>
<td>253 (30.7)</td>
<td>285 (35.3)</td>
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</tr>
<tr>
<td>55-64</td>
<td>83 (19.5)</td>
<td>59 (31.7)</td>
<td>199 (24.2)</td>
<td>196 (24.2)</td>
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</tr>
<tr>
<td>65-74</td>
<td>82 (19.2)</td>
<td>30 (16.1)</td>
<td>158 (19.2)</td>
<td>163 (20.2)</td>
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</tr>
<tr>
<td>≥75</td>
<td>56 (13.1)</td>
<td>26 (14.0)</td>
<td>116 (14.1)</td>
<td>65 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>46 (10.9)</td>
<td>10 (5.4)</td>
<td>70 (8.5)</td>
<td>53 (6.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Married</td>
<td>305 (71.9)</td>
<td>148 (79.6)</td>
<td>606 (73.9)</td>
<td>715 (88.5)</td>
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</tr>
<tr>
<td>Other</td>
<td>73 (17.2)</td>
<td>28 (15.0)</td>
<td>144 (17.6)</td>
<td>40 (4.9)</td>
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</tr>
<tr>
<td>Education¹ (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0-8</td>
<td>141 (33.6)</td>
<td>32 (17.3)</td>
<td>206 (25.3)</td>
<td>178 (22.2)</td>
<td>0.14*</td>
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<tr>
<td>9-12</td>
<td>115 (27.4)</td>
<td>56 (30.3)</td>
<td>235 (28.9)</td>
<td>218 (27.3)</td>
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<tr>
<td>&gt;12</td>
<td>164 (39.0)</td>
<td>97 (52.4)</td>
<td>372 (45.8)</td>
<td>404 (50.5)</td>
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</tr>
<tr>
<td>First-degree relatives with hematopoietic malignancy Yes</td>
<td>42 (10.2)</td>
<td>15 (8.6)</td>
<td>83 (10.7)</td>
<td>55 (6.8)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

B-NHL=B-cell non-Hodgkin lymphoma; DLBCL= diffuse large B-cell lymphoma; FL=follicular lymphoma; P* calculated for overall B-NHL versus controls; Values were missing for < 5% for exposure variable; ¹Education was not significantly associated with case control status but highly associated with HBV exposure, hence it was included in multivariable models.
References
