# The Incidence of Lymphoma in First-Degree Relatives of Patients with Hodgkin Disease and Non-Hodgkin Lymphoma

## *Results and Limitations of a Registry-Linked Study*

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**BACKGROUND.** The precise incidence of familial Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL) in first-degree relatives is unknown. Through record linkage using two population-based sources, the authors estimated the risk of HD and NHL in family members of lymphoma probands.

**METHODS.** The authors identified 8037 first-degree relatives of 2606 lymphoma cases (28.5% HD, 71.5% NHL) treated between 1970 and 1993 in 3 hospitals in Israel via the family file of the Population Registry. The authors linked this file with the Israel Cancer Registry, then calculated the standardized incidence ratio (SIR) by dividing the observed number of cases with the expected, adjusting for age, gender, calendar year, and continent of origin.

**RESULTS.** The family file yielded incomplete ascertainment of relatives (for 771 probands, no relatives were identified). Twenty cases of lymphoma—6 HD and 14 NHL—were identified among relatives of lymphoma patients. The SIR for HD was 1.15 (95% confidence interval [CI]: 0.42–2.51) and for NHL 1.71 (95% CI: 0.93–2.87), considering the entire population of first-degree relatives. SIRs among siblings of lymphoma probands were 3.12 (95% CI: 1.01–7.29) for HD, 2.16 (95% CI: 0.45–6.31) for NHL, and 2.68 (95% CI: 1.15–5.27) for all lymphomas. There were 4 HD/HD, 1 NHL/NHL, and 3 NHL/HD sibling pairs. For HD/HD and NHL/NHL sibling pairs, the interval between lymphoma occurrence in proband and sibling was 1–4 years, whereas for HD/NHL pairs this ranged from 16 to 21 years.

**CONCLUSIONS.** The risk of lymphoma among siblings of lymphoma probands was over 2.5-fold that of the general population and lower among other family members. The temporal proximity of HD/HD and NHL/NHL sibling pairs argues for environmental as well as genetic etiology. This method was hampered by incomplete data. ***Cancer*** **2000;88:2357–66.** *© 2000 American Cancer Society.*

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Many risk factors for the development of lymphoma have been identified, including genetic and environmental factors. The latter include infection with the Epstein–Barr virus (EBV), human T-cell lymphoma virus 1 (HTLV-1), and human immunodeficiency virus 1 (HIV-1).[1–3] Other proposed risk factors are chemotherapy, radiation, and exposure to herbicides and solvents.[4–7]

Patients with congenital immunodeficiency syndromes, such as Chediak–Higashi syndrome, ataxia-telangectasia, B-cell lymphoproliferative syndrome, Bruton agammaglobulinemia, common variable immunodeficiency, and Wiscott–Aldrich syndrome, are known to be

predisposed to lymphoma.[1–4] Apart from these syndromes, familial aggregation of lymphoma has been reported repeatedly,[1–3,8–20] but few population-based studies have been published. Some authors have proposed an autosomal dominant transmission of lymphoma,[2,6] but in most families the pattern of transmission is unclear. Patients with lymphoma are more likely than unaffected controls to have a positive family history of hematopoietic diseases.[1–3,8–10]

Reports of two siblings with Hodgkin disease[5,7,11,15,17] as well as parents and children with malignant lymphoma are common.[1,6,7,9–10,12,15,17] In some studies even second-degree relatives with lymphoma are described.[17,18] As early as 1959 the familial risk of Hodgkin disease was estimated to be approximately 3 times the risk for the general population.[21] Despite the large number of reports, the precise incidence of familial lymphoma is unknown. It is clear, however, that familial cases do not represent the majority of lymphoma cases.

Most of the published studies are based on information provided by patients themselves regarding their family,[4,9,12,15] on questionnaires sent to patients or their families,[8,9,16,17] or on hospital-based case series.[1,5,7,9,15,18] Few authors have used objective data sources or sources independent of patient recall, such as population or cancer registries.[9,14,16,18–20]

Special circumstances in Israel allowed us to perform a linkage study. First, a unique identification number used both by the government and the health care system is assigned to each resident. Secondly, the Population Registry has documentation of dates of birth and death and country of origin and ethnicity (divided along religious lines) of all residents. Residents and their first-degree relatives are linked in the "family" file of the Population Registry, so it is possible to locate the relatives of patients using their identification number. Finally, the Israel Cancer Registry (ICR), part of the Health Ministry, was established in 1960, and since 1982 reporting of all cancer cases in Israel to the ICR has been required by law. Information about cancer rates in Israel, by age, gender, and ethnic group, is published annually by the ICR. The accuracy of the data has been found to be high, and the rate of reporting by hospitals and other institutions (even prior to 1982) is approximately 95%.[22]

## PATIENTS AND METHODS

We performed a population-based study to estimate the risk of familial lymphoma in first-degree relatives of known lymphoma patients. We compared our results with the published literature and with a survey based on clinical records, which was carried out at the same three hospitals that participated in the current study. Data were obtained from hospitals, the Population Registry, and the ICR. We compared the observed number of lymphoma cases with the expected number had these persons been randomly selected from the general population in Israel, and calculated the standardized incidence ratio (SIR) for the development of lymphoma adjusting for gender, ethnicity, and 5-year age categories for the period 1970–1994.

Eligible index patients were Israeli residents of any age who were diagnosed with Hodgkin disease (HD) or non-Hodgkin lymphoma (NHL) between 1970 and 1993 and treated in one of three major hospitals (Hadassah Medical Center, Jerusalem; Rambam Medical Center, Haifa; or Rabin Medical Center, Petach-Tikva), and reported to the Israel Cancer Registry. These three hospitals treat patients from the northern, coastal, and central areas of Israel. The investigators provided data (name, identity number, gender, and, if known, date of birth) on consecutive lymphoma patients who were diagnosed or treated in these hospitals; thus, a mixture of incident and prevalent cases was included and the completeness of these lists was not verified.

We used the identification number (ID) to identify each index. This is a unique number assigned by the government to all residents of Israel, and it is used for administrative purposes and by the health care system. The list of patients was transferred to the Population Registry, where demographic information and vital status were confirmed and added. Patients who were not identified by the Population Registry were excluded from the study.

First-degree relatives of the patients were identified using the family file of the Population Registry. This computerized file was established in the 1970s, and since 1976 all those who were born in Israel are listed there. Both immigrants and residents who were born in Israel are listed in this file, together with their first-degree relatives. Information about residents born prior to 1976 and immigrants who arrived prior to that year is partial. Even new immigrants arriving today are not always listed with their family members if they arrived in Israel alone. The name, identity number, gender, birth date, year of death, and country of origin of each patient and family member were added to the original file.

The expanded file, containing index patients and identified family members, was then linked to the ICR, and all pathologic diagnoses that were found there were added to the file. The names and identification numbers of the family members were then erased, and they were coded according to their lymphoma proband and their relation to him or her (sibling, parent, and offspring). The linkage was approved by the Min-

**TABLE 1**
**Frequency Distribution within the Study Group**

| | HD | | | NHL | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | All | Male | Female | All | Male | Female | All |
| Index cases | 393 | 351 | 744 | 1009 | 857 | 1866 | 1400 | 1206 | 2606[a] |
| Offspring | 628 | 594 | 1222 | 1629 | 1346 | 2975 | 2257 | 1940 | 4198[b] |
| Parents | 371 | 344 | 715 | 283 | 255 | 538 | 654 | 599 | 1253 |
| Siblings | 681 | 715 | 1396 | 601 | 589 | 1190 | 1304 | 1282 | 2586 |
| Total | 2073 | 2004 | 4077 | 3522 | 3047 | 6569 | 5617 | 5029 | 10643 |

HD: Hodgkin disease; NHL: non-Hodgkin lymphoma.
[a] Four patients had both HD and NHL.
[b] Gender was unknown in one case.

istry of Justice and Ministry of Health and took place under strict guidelines for confidentiality.

### Statistical Analysis

Comparison of mean ages and mean number of identified relatives, was tested using the Student *t* test for independent means. A two-sided *P* value of 0.05 was considered statistically significant. For the calculation of the SIR we first calculated the number of all cancers and the number of all lymphomas (HD and NHL, including chronic lymphocytic leukemia [CLL]) and other hematopoietic malignancies that would be expected in the Israeli population for the study period. Person-years for each individual were calculated from the date of birth to the date of death or 1994 (whichever came first). A matrix of person-time by calendar year and 5-year age group was calculated separately for men and women and for continent of origin (i.e., ethnicity). Cancer rates specific to age, gender, and ethnicity, obtained from the ICR reports between 1970 and 1994, were applied to each cell of the matrix and summed over all calendar years, age, gender, and origin to derive the "expected" number of cases.

To estimate the relative risk for family members compared with the general population, we calculated the SIR for HD, NHL, all hematopoetic malignancies, and all cancers by dividing the observed number of cases by the expected number, and calculated the confidence intervals of these SIR estimates. The analysis was performed using SPSS for Windows [SPSS, Chicago, IL] and a FORTRAN program designed specifically for calculating the person-years matrix. We calculated SIRs for all first-degree relatives and for siblings separately. *P* values for SIRs are one-sided, corresponding to an alternative hypothesis of increased risk among family members compared with the general population. Confidence intervals for the SIRs were calculated using the Poisson distribution.[23] In order to increase comparability with other studies in the literature that assessed the risk of familial lymphoma, we show 95% confidence intervals.

### Clinical Study

We compared the results of our statistical analysis with the results from a clinical chart–based study, which was undertaken by one of us (R.C.). Available medical files of lymphoma patients were reviewed. All patients were identified using hospital archives, with retrieval done according to the International Classification of Disease (ICD-9) code. The family history as reported in the medical files was reviewed. This study was performed to determine the prevalence of a positive family history of lymphoma among first-degree relatives of lymphoma patients, as reported by the patients themselves, and to provide a comparison with the registry-derived information.

## RESULTS

The original list of patients provided by the hospitals included 3564 lymphoma probands. Of these, 333 patients were not identified in the Population Registry (either because of wrong ID number or because they were not Israeli residents) and were excluded. Patients who were treated in more than one hospital (n = 6), and therefore were listed more than once, were identified and included only once. Cases that were not registered in the ICR as lymphoma probands or whose lymphoma diagnosis was prior to 1970 (n = 619), as well as their relatives, were excluded.

The final study population comprised 10,643 people, including 2606 index cases (the lymphoma probands) and 8037 family members. Of the index cases, 744 (28.5%) had HD and 1866 (71.6%) had NHL (4 patients had both HD and NHL) (Table 1). The ethnicity and origin (place of birth) of probands are represented in Figure 1 and are compared with the dis-

**TABLE 2**
**Distribution by Ethnicity and Continent of Origin of Study Group**

| Ethnicity | Continent of origin | Index cases | Relatives |
|---|---|---|---|
| Jews | All Jews | 2201[a] (84.5%) | 5622 (70%) |
| | Asia and Middle East | 152 (5.8%) | 209 (2.6%) |
| | Africa | 252 (9.7%) | 418 (5.2%) |
| | Europe and Americas | 1081 (41.5%) | 577 (7.2%) |
| | Israel | 715 (27.4%) | 4418 (55%) |
| Non-Jews | | 405 (15.5%) | 2415 (30%) |
| All | | 2606 (100%) | 8037 (100%) |

[a] In one case the continent of origin was unknown.

tribution of all Israeli lymphoma cases reported to the ICR in 1990 for all of Israel.[24] This year was chosen for comparison because it represented the modal year diagnosis for probands in our study.

The median number of relatives was 3 and the maximum 21. The average number of relatives per index was 3.08; thus, the average family size was 4.08 persons. There were 771 index cases for which no relatives were found. Probands for whom no first-degree relatives were ascertained in the family file differed in many aspects from those for whom family

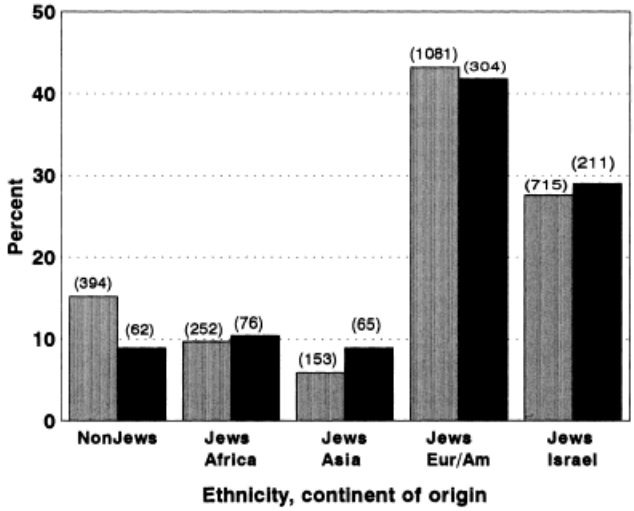


**FIGURE 1.** The distribution of the study population (gray bars) by ethnicity and continent of origin is compared with the distribution of all Israeli lymphoma cases reported to the Israel Cancer Registry (black bars) in 1990.[24] Numbers above the gray bars correspond to the number of probands enrolled in the study, and numbers above the black bars correspond to all incident lymphoma cases (NHL and HD) reported to the cancer registry in 1990.

**TABLE 3**
**Lymphoma Families**

| Proband | | | | | Affected first-degree relative | | | |
|---|---|---|---|---|---|---|---|---|
| No. | Gender | Yr of diagnosis (19-) | Diagnosis | Age (yrs) at diagnosis | Relation | Yr of diagnosis (19-) | Diagnosis | Age (yrs) at diagnosis |
| 1 | Male | 90 | NHL | 40 | Sister | 94 | NHL | 42 |
| 2 | Male | 93 | NHL | 50 | Son | 83 | NHL | 11 |
| 3 | Female | 78 | HD | 14 | Sister | 79 | HD | 16 |
| 4 | Male | 82 | HD | 16 | Mother | 54 | HD | 19 |
| 5 | Female | 90 | HD | 36 | Father | 89 | NHL | 69 |
| 6[a] | Male | 89 | HD | 55 | Daughter | 90 | NHL | 31 |
| 7 | Male | 70 | HD | 3 | Sister | 74 | HD | 9 |
| 8 | Male | 91 | NHL | 41 | Father | 84 | NHL | 64 |
| 9 | Male | 94 | NHL | 42 | Mother | 64 | NHL | 42 |
| 10 | Male | 89 | NHL | 31 | Son | 90 | NHL | 6 |
| 11 | Male | 75 | NHL | 15 | Father | 72 | NHL | 44 |
| | | | | | Sister | 91 | HD | 33 |
| 12 | Female | 87 | HD | 27 | Father | 70 | NHL | 50 |
| 13 | Male | 87 | HD | 26 | Brother | 66 | NHL | 9 |
| 14 | Male | 80 | HD | 19 | Brother | 96 | NHL | 35 |
| 15[a] | Female | 89 | HD | 22 | Sister | 92 | HD | 37 |
| 16[a] | Male | 91 | NHL | 35 | Father | 88 | NHL | 63 |
| 17 | Male | 80 | NHL | 61 | Son | 84 | NHL | 24 |
| | | | | | Son | 89 | NHL | 33 |
| 18[a] | Female | 86 | HD | 24 | Sister | 82 | HD | 22 |

NHL: non-Hodgkin lymphoma; HD: Hodgkin disease.
[a] Familial cases who were also detected in the chart-based study.

**TABLE 4a**
**Standardized Incidence Ratios for All First-Degree Family Members of Lymphoma Probands**

| Cancer | Observed | Expected | SIR | *P* value[a] | 95% CI |
|---|---|---|---|---|---|
| All sites | 152 | 146.99 | 1.03 | 0.351 | 0.88–1.21 |
| Hodgkin disease | 6 | 5.20 | 1.15 | 0.419 | 0.42–2.51 |
| Non-Hodgkin lymphoma | 14 | 8.18 | 1.71 | 0.04 | 0.94–2.87 |
| All lymphomas | 20 | 13.38 | 1.49 | 0.054 | 0.91–2.31 |
| Multiple myeloma | 2 | 1.13 | 1.77 | 0.312 | 0.21–6.4 |
| Leukemias | 7 | 6.42 | 1.09 | 0.461 | 0.44–2.25 |
| Leukemia + lymphoma | 27 | 19.81 | 1.36 | 0.071 | 0.9–1.98 |
| All hematopoetic | 29 | 20.94 | 1.39 | 0.055 | 0.93–1.99 |
| All nonhematopoetic | 123 | 126.05 | 0.98 | 0.416 | 0.81–1.16 |

SIR: standard incidence ratio; CI: confidence interval.
[a] One-sided.

**TABLE 4b**
**Standardized Incidence Ratios for Siblings**

| Cancer | Observed | Expected | SIR | *P* value[a] | 95% CI |
|---|---|---|---|---|---|
| All sites | 22 | 17.33 | 1.27 | 0.157 | 0.80–1.92 |
| Hodgkin disease | 5 | 1.60 | 3.12 | 0.024 | 1.01–7.29 |
| Non-Hodgkin lymphoma | 3 | 1.39 | 2.16 | 0.164 | 0.45–6.31 |
| All lymphomas | 8 | 2.99 | 2.68 | 0.012 | 1.15–5.27 |
| Multiple myeloma | 0 | 0.04 | 0 | 0.961 | 0–92.25 |
| Leukemias | 3 | 1.44 | 2.08 | 0.177 | 0.43–6.07 |
| Leukemia + lymphoma | 11 | 4.44 | 2.48 | 0.006 | 1.24–4.44 |
| All hematopoetic | 11 | 4.48 | 2.46 | 0.006 | 1.23–4.4 |
| All nonhematopoetic | 11 | 12.85 | 0.86 | 0.364 | 0.43–1.53 |

SIR: standard incidence ratio; CI: confidence interval.
[a] One-sided.

members were found. The mean age at diagnosis of probands with relatives was 40.7, versus 65.8 for probands without relatives ($P < 0.001$). In the group with relatives the ratio of men to women was 1.39:1, whereas in the without relatives the ratio was reversed at 0.76:1. The ratio of NHL to HD cases among probands with relatives was 1.85:1, whereas among those without relatives this ratio climbed to 6.63:1. Non-Jews represented 18.6% of probands with relatives detected and only 6.2% of those without. There was no difference among the three participating hospitals in terms of ascertainment of relatives.

We use the term "family" to describe the lymphoma proband and all his/her first-degree relatives. For families with at least 1 relative, the average number of relatives detected was 4.8 persons. Among non-Jews, 5.96 relatives were detected per proband, compared with Jewish families, among whom 2.55 relatives per proband were detected. Whereas non-Jewish probands comprised 405 (15.5%) of the original lymphoma cases, non-Jewish family members comprised 30% of the total population of first-degree relatives ascertained in the family file of the Population Registry (Table 2). The average number of offspring per proband for HD patients in our study was 1.64 and for NHL 1.59. The mean age at diagnosis for all HD patients was 33 years (range 2–92 years, SD = 17) and for NHL 54 years (range 0–94 years, SD = 20). In comparison, the mean age at diagnosis for HD probands in which a familial lymphoma case was found was 24.2 years (range 3–55 years, SD = 13.9), whereas for NHL the mean age was 38 years (range 15–61 years, SD = 13.75) for those with familial lymphoma.

There were 18 probands (0.7%) with at least 1 relative who also had lymphoma. The "lymphoma families" are shown in Table 3. We found 16 families with 2 lymphoma cases and 2 families with 3 cases. In 1 family the proband (No. 17) and 2 sons had NHL, and in another the proband (No. 11) had NHL, whereas his father was diagnosed with NHL and his sister with HD. There were 9 NHL-NHL pairs, 5 HD-HD pairs, and 6 mixed pairs of HD-NHL/NHL-

**TABLE 5a**
**Cancer Cases (All First-Degree Relatives)**

| Ethnicity | Gender | Origin | All sites | HD | NHL | Leukemias | Lymphatic leukemia | Myeloid leukemia | Other leukemias | MM |
|---|---|---|---|---|---|---|---|---|---|---|
| Non-Jews | Men | Israel | 11 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Women | | 7 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |
| Jews | Men | Israel | 23 | 0 | 4 | 2 | 1 | 1 | 0 | 0 |
| | Men | EU+Am | 26 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| | Men | AS+AF | 19 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| | Women | Israel | 27 | 5 | 0 | 3 | 0 | 2 | 1 | 0 |
| | Women | EU+Am | 15 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Women | AS+AF | 24 | 1 | 1 | 1 | 0 | 0 | 1 | 1 |
| All | | | 152 | 6 | 14 | 7 | 2 | 3 | 2 | 1 |

HD: Hodgkin disease; NHL: non-Hodgkin lymphoma; MM: multiple myeloma; EU: Europe; AF: Africa; AS: Asia; Am: Americas.

**TABLE 5b**
**Cancer Cases (Siblings)**

| Ethnicity | Gender | Origin | All sites | HD | NHL | Leukemias | Lymphatic leukemia | Myeloid leukemia | Other leukemias | MM |
|---|---|---|---|---|---|---|---|---|---|---|
| Non Jews | Men | | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Women | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Jews | Men | Israel | 6 | 0 | 2 | 1 | 0 | 1 | 0 | 0 |
| | Men | EU+Am | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Men | AS+AF | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Women | Israel | 11 | 4 | 0 | 2 | 0 | 1 | 1 | 0 |
| | Women | EU+Am | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Women | AS+AF | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| All | | | 22 | 5 | 3 | 3 | 0 | 2 | 1 | 0 |

HD: Hodgkin disease; NHL: non-Hodgkin lymphoma; MM: multiple myeloma; EU: Europe; AF: Africa; AS: Asia; Am: Americas.

HD. There were 12 parent-child pairs and 8 sibling pairs. Sixteen of the families were Jewish and two were Arab. The average number of members of these families was 7.78 (range 4–12), which was significantly larger than the number of members of families without affected first-degree relatives (mean 4.06, range 1–21) ($P = 0.0034$).

The standardized incidence ratios (SIRs) for all cancers and different types of hematopoetic cancers for the entire study population are listed in Tables 4a–b. There was a statistically significant increased risk of NHL among first-degree family members of lymphoma patients (SIR 1.71, 95% CI: 0.93–2.87, $P = 0.04$). Findings for all lymphomas and all hematopoetic malignancies were of borderline significance ($P = 0.054$ and 0.055, respectively). The specific SIR for HD family members of HD probands was 2.59 (95% CI: 0.84–6.05, $P = 0.047$) and for NHL in families of NHL probands was 2.03 (95% CI: 0.93–3.85, $P = 0.038$) (data not shown in tables). There was no excess risk of nonhematopoietic cancer (SIR 0.98, 95% CI: 0.81–1.16), nor for cancer at all sites (SIR 1.03, 95% CI: 0.88–1.21).

Twenty-two cancer cases were ascertained among siblings of lymphoma probands, with an SIR of 3.12 (95% CI: 1.01–7.29, $P = 0.024$) for HD among siblings and elevated SIRs for all lymphomas, leukemia and lymphoma, and all hematopoetic malignancies (Table 4b). Once again, there was no excess risk for nonhematopoietic cancer (SIR 0.86, 95% CI: 0.43–1.53) or cancer at all sites (SIR 1.27, 95% CI: 0.80–1.92). For HD/HD and NHL/NHL sibling pairs, the interval between disease occurrence in proband and sibling ranged from 1 to 4 years, whereas for the HD/NHL pairs this interval ranged from 16 to 21 years. Combining both types of lymphoma in probands, we found that the median time between diagnosis in probands and their relatives was 4 years (mean 8.3) among the 8 sibling pairs and 6.5 years (mean 8.8) among the 12 parent/offspring pairs.

A detailed list of cancer cases among relatives

stratified by gender and ethnicity is shown in Tables 5a–b.

### Clinical Chart Review

In the clinical study based on a review of hospital charts, 1984 patients with lymphoma were ascertained by the hospital computers, but only 1036 medical files (54%) were retrieved, all patients belonging to patients diagnosed during the period 1980–1993. Among these, 24 cases of familial lymphoma (2.3%) were identified: 5 families with a lymphoma proband and "unspecified lymphoma" in a first-degree relative, and 19 families with familial HD or NHL. Of these 24 lymphoma probands with familial lymphoma, 3 were not identified in the Population Registry and thus could not have been part of the linkage study. One familial case of lymphoma-unspecified was diagnosed and died abroad, and hence would also not have been detectable in our registry-based study. Of the remaining 20 cases, there were 18 for whom first-degree relatives were identified in the family file of the Population Registry. However, only in five instances the *specific* relative identified in the chart as an affected lymphoma case was identified in the family file as a relative of the proband. Four of these cases were confirmed in the ICR as lymphoma cases, and one was not listed at all as a cancer case in the ICR. Thus, the overlap between the chart-based and registry-based study was only four cases.

## DISCUSSION

Non-Hodgkin lymphoma represents the sixth most frequently occurring neoplasm in Israel,[24] and its incidence is increasing, as it is elsewhere in the world.[25] HD incidence is stable. In order to estimate the degree of familial predisposition to lymphoma, we studied first-degree relatives of 2606 index patients. We found 18 families (0.7%) with more than 1 affected family member, a total of 20 familial cases. The risk for a first-degree relative of a lymphoma patient to have lymphoma was 1.49 ($P = 0.054$) compared with the risk for the general population. The relative risk for siblings is even higher, at 2.68 ($P = 0.012$). A $>$ 3-fold risk of HD among siblings of lymphoma patients was noted. Probands with another lymphoma case in the family were younger on average than the entire group of HD and NHL cases. Younger age for familial cases of NHL compared with the general population with NHL has been reported previously by Goldgar et al.[19] The SIR values were calculated for the population of Israel, taking into account the different ethnic groups comprising this population. One cannot assume that these values can be generalized to other populations.

Most investigators of familial lymphoma have used different methods in order to estimate the familial risk of hematologic malignancies. Cuttner, in an uncontrolled study,[12] used patient files to assess the prevalence of familial hematologic malignancy among her patients with CLL. She found a positive family history in 34% of 29 CLL patients. Her study, interestingly, involved mainly Jewish patients in New York. This method resembles our clinical chart-based study and has some major disadvantages. Not all physicians ask their patients about family history, the diagnoses of the relatives are not confirmed, and many patients do not know the medical history of their relatives. In order to calculate risk, it is necessary to know how many relatives the patient has. This kind of information is rarely available in the medical file.

Haim et al.[15] estimated a nine-fold increased risk of developing Hodgkin disease for first-degree relatives of HD patients. On the other hand, they did not find an increased risk for NHL among relatives of NHL patients. In order to circumvent the problem of lack of information about the number of healthy relatives, they calculated the expected number of cases by estimating the number of relatives and their ages, using information about average family size in Israel. This assumption did not take into account the possibility that cancer survivors may have smaller-than-average families; that different ethnic groups in Israel have different rates of lymphoma, some of which persist across generations;[26] or that average family size differs among ethnic groups.

In another Israeli study, Shpilberg et al.[8] calculated the odds ratio for hematologic neoplasms among relatives of patients with hematologic neoplasms compared with two control groups (one consisting of diabetic patients and their families and the other consisting of patients with nonmalignant hematologic disease and their families) to be 3.62 (95% CI: 1.4–9.07, $P < 0.01$). The specific odd ratios for relatives of lymphoma cases were not calculated. The authors used self-administered questionnaires in which the overall response rate was 75%, with no mention of specific rates response among the 3 groups. Diagnoses among the relatives were not confirmed. A person-time analysis was not carried out. Finally, there was the potential for recall bias, whereby lymphoma patients may have been more likely to be aware of other patients with hematologic neoplasms in their families than would diabetic patients.

Both of these studies[8,15] yielded higher estimates of relative risk among family members than our current study. Sackett[27] originally reported the biased tendency of affected family members to recall a positive family of disease compared with their unaffected siblings. Two studies that specifically addressed self-

reported versus data base–linked family history of cancer, but not lymphoma per se, found generally high agreement comparing the two methods,[28,29] although there was considerable variation in recall of particular cancer sites. A further methodologic issue was raised by Khoury and Flanders,[30] who determined that odds ratios derived from case–control studies of familial aggregation overestimated the degree of familial risk compared with approaches such as ours, which report a cumulative risk ratio based on lifetime risk.

Le Bihan et al.[17] undertook a family study of children treated for NHL at Institute Gustave-Roussy. Families of 284 patients were asked about the number of first-, second-, and third-degree relatives and filled out a questionnaire regarding vital status, causes of death, and occurrence of cancer. The calculated SIR for all hematologic malignancies among first-degree relatives was 1.3 (95% CI: 0.7–2.3). There were no affected first-degree relatives with NHL, and for HD the SIR was 5.0 (95% CI: 0.6–18.4). The study was limited by small numbers, a low participation rate (259 of 570 eligible families), and medical confirmation of only 76% of reported diagnoses.

The method used by Goldgar et al.[19] is probably closest to the ideal. Data concerning relatives were obtained from the Genealogical Society of Utah and supplemented by death certificates and demographic information. Cancer diagnoses were obtained from the Utah Cancer Registry. Controls were family members of individuals who had died in Utah. The main drawbacks of this study were that the information regarding deaths and state of residence were incomplete and that the study population was unique, both genetically and in terms of life-style characteristics (which may have influenced the cancer rates). The total number of HD cases was 365 and of NHL cases 1362. Their results were as follows: The relative risk for relatives of HD patients to develop HD was 1.27 times that for the general population (95% CI: 0.12–3.65), and the relative risk for relatives of NHL patients to develop NHL was 1.68 times that for the general population (95% CI: 1.04–2.48). These results were comparable to ours, in which SIR estimates were 2.59 and 2.03, respectively.

Goldgar et al. did not differentiate between siblings and other first-degree relatives. We found that the risk of hematopoetic malignancies was approximately 2.5 for siblings of patients with lymphoma. The SIR was 3.12 for HD. Mack et al.[11] studied 179 pairs of monozygotic twins and 187 pairs of dizygotic twins. Among the monozygotic twins were 10 pairs of HD (SIR 99), whereas no HD pairs were found in dizygotic twins. We had no twins in our study, but we were able to detect an increased risk of lymphoma among siblings who genetically were equivalent to dizygotic twins. Pottern et al.,[9] in a study of males age 30 years and older, found odds ratios for NHL of 3.8 (95% CI: 1.3–11.5) among siblings with lymphoma. Family history was obtained by interview without medical record validation.

Despite the similarity of our findings with those of the above-mentioned studies, our study was marred by a number of potential biases:

The patients who served as probands for this study were selected from three hospitals, which presumably represent the general population of Israel, given that they are large hospitals distributed in distinct geographic areas; but this assumption may have been wrong. In our study, as shown in Figure 1, non-Jewish (mainly Arab) lymphoma probands were overrepresented compared with the distribution of cases in Israel,[24] but only 2 (11%) of the familial cases were among this population subgroup.

The linkage of family members in the Population Registry is incomplete; information concerning immigrants is particularly lacking. In several cases we had dates and ID numbers of first-degree relatives and found that although all family members were identifiable in the Population Registry, their ID numbers were not linked, so they could not be identified as a family. This was the main reason for the poor overlap between the chart-based study and the registry-linked approach. We found significant differences in demographic characteristics and lymphoma types between probands with and without identified relatives. However, we had no way to evaluate whether incompleteness occurred in lymphoma families differentially with respect to other residents. Furthermore, because estimates of SIR were performed only for the population of relatives actually ascertained, it is not clear how much this incompleteness may have biased the results. Even in the important study by Goldgar et al. from Utah, cancer incidence was only completely ascertained for cases diagnosed in Utah after 1966. We found, as they did, that the total observed cancer incidence (SIR at all sites) was almost identical to the expected rate in the general population (SIR 1.03, 95% CI 0.88–1.21, with no increase in nonhematopoietic cancers), suggesting that there was no systematic under- or overascertainment of overall cancer incidence in our population of first-degree relatives.

We had no information about relatives who were not living in Israel. Neither demographic nor medical data were available. Because the population of Israel is comprised of many immigrants, this may have been significant to the calculation of risk. Although immigrants tend to be healthier than the populations in

their country of origin, this may not be so if the country to which they are immigrating has better health care facilities than the country of origin, thus serving as an incentive to immigration.[31] For the recent wave of immigrants to Israel from the USSR who came after 1990, there is evidence that cancer mortality of the newcomers is higher than in the veteran population,[32] but information on lymphoma specifically and on previous waves of immigrants is lacking, as are comparisons with cancer rates for the family members who stayed in their country of origin.

The therapy for lymphoma may cause infertility. Most of the patients are young, and their fertility may be reduced compared with that of the general population. The true risk for their children to develop lymphoma may therefore be higher or lower than our estimate. It is noteworthy that we found no difference in the average number of offspring for HD and NHL probands. Finally, there may be a bias related to family size. We found that the average family size was greater for families with two or more affected family members compared with families with only one affected member. This suggests that there may be ascertainment bias in favor of large families and underascertainment for small families.

In our clinical chart–based study, we reviewed patient files and assessed the prevalence of lymphoma among first-degree relatives of lymphoma patients. Many files were not available for review, including those of patients diagnosed before 1980 (3 of the familial cases in the registry-linked study). We found 24 families (2.3%) with more than 1 lymphoma case. There was an overlap of only four cases of lymphoma between the chart-based and registry-based approaches. Possible reasons for these differences include, as noted, incomplete family linkage in the Population Registry, inaccurate information written in the patient file based on the patient's memory, and incomplete recording of the family history in the patient file. Finally, the ID numbers as recorded in the hospitals' computers are often inaccurate, and therefore not all patients can be identified in the Population Registry.

Our current method provides a powerful tool for epidemiologic research on the risk of familial cancers. This method is feasible where registries exist and linkage is possible and legally acceptable; it is based on objective data, is not dependent on the ability to retrieve charts, and is not subject to nonparticipation or recall bias. There is no need to contact the patients, and the data are easy to access and work with because they are computerized. Of course, valid and precise estimates of risk are dependent on the completeness of the data bases. Because no data base is complete, the estimates derived from this method must be weighed against estimates obtained from studies that depend on patient recall and that are limited by other biases noted above. Ideally, research on familial lymphoma would use registry-based data supplemented by data from other sources, including environmental information and tissue samples for molecular diagnosis among affected family members (subject to informed consent).

The higher risks of lymphoma for relatives of lymphoma patients compared with the general population, which we found and which were consistent with the findings of earlier studies, may be due to genetic and/or environmental factors. This study cannot differentiate between these factors. The close temporal proximity of HD/HD and NHL/NHL sibling pairs argues for an environmental as well as a genetic component. Information about the risk among relatives is important for families and their doctors as well as for investigators. Patients are concerned about the risk of cancer in their families and seek counseling. Our results can contribute to the information provided by physicians about the risk for relatives of lymphoma patients and provide further impetus for research on genetic and environmental determinants of increased risk within families.

## REFERENCES


1. Tibebu M, Polliack A. Familial lymphomas: a review of the literature with report of cases in Jerusalem. *Leuk Lymphoma* 1990;1:195–201.
2. Horwitz M. The genetics of familial leukemia. *Leukemia* 1997;11:1347–59.
3. Egler RM, de Kraker J, Slater R, Purtilo DT. Documentation of Burkitt lymphoma with t (8;14) (q24;q32) in X-linked lymphoproliferative disease. *Cancer* 1992;70:683–7.
4. Linet MS, Pottern LM. Familial aggregation of hemapoietic malignancies and risk of non-Hodgkin's lymphoma. *Cancer Res* 1992;52(Suppl):5468s–73s.
5. Armata J, Balwierz W, Tacik J. Hodgkin's disease in siblings [letter]. *Lancet* 1991;337:502.
6. Lynch HT, Marcus JN, Lynch JF. Genetics of Hodgkin's and non-Hodgkin's lymphoma: a review. *Cancer Invest* 1992;10: 247–56.
7. Schlaifer D, Rigal-Huguet F, Robert A, Attal M, Abbal M, Fonck Y, et al. Epstein–Barr virus in familial Hodgkin's disease. *Br J Haematol* 1994;88:636–38.
8. Shpilberg O, Modan M, Modan B, Chetrit A, Fuchs Z, Ramot B. Familial aggregation of haematological neoplasms: a controlled study. *Br J Haematol* 1994;87:75–80.
9. Pottern LM, Linet M, Blair A, Dick F, Burmeister LF, Gibson R, et al. Familial cancers associated with subtypes of leukemia and Non Hodgkin's lymphoma. *Leuk Res* 1991;15:305–14.
10. Hayoz D, Extermann M, Odermatt BF, Pugin P, Regamey C, Knecht H. Familial primary gastric lymphoma. *Gut* 1993;34: 136–40.

11. Mack TM, Cozen W, Shibata DK, Weiss LM, Nathwani BN, Hernandez AM, et al. Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. *N Engl J Med* 1995;332:413–8.
12. Cuttner J. Increased incidence of hematologic malignancies in first-degree relatives of patients with chronic lymphocytic leukemia. *Cancer Invest* 1992;10(2):103–9.
13. Loth TS, Perotta AL, Lima J, Whiteaker RS, Robinson A. Genetic aspects of familial multiple myeloma. *Mil Med* 1991;156:430–3.
14. Knox EG, Gilman EA. Spatial clustering of childhood cancers in Great Britain. *J Epidemiol Commun Health* 1996;50:313–9.
15. Haim N, Cohen Y, Robinson E. Malignant lymphoma in first-degree blood relatives. *Cancer* 1982;49:2197–2200.
16. Hawkins MM, Draper GJ, Winter DL. Cancer in offspring of survivors of childhood leukemia and non-Hodgkin lymphomas. *Br J Cancer* 1995;71:1335–9.
17. Le Bihan C, Moutou C, Chompret A, Abel A, Poisson N, Brugieres L, et al. Cancers in relatives of children with Non-Hodgkin's lymphoma. *Leuk Res* 1996;20:181–6.
18. Winnett A, Thomas SJ, Brabin BJ, Bain C, Alpers MA, Moss DJ. Familial Burkitt's lymphoma in Papua New Guinea. *Br J Cancer* 1996;75:757–61.
19. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 1994;86:1600–8.
20. Eriksson M, Halberg B. Familial occurrence of hematologic malignancies and other diseases in multiple myeloma: a case–control study. *Cancer Causes Control* 1992;3:63–7.
21. Razis DV, Diamona HD, Craver LF. Familial Hodgkin's disease: its significance and implications. *Ann Intern Med* 1959; 51:933–71.
22. Parkin DM, Muir CS, Whelan SL, Gao Y-T, Ferlay J, Powell J, editors. Cancer incidence in five continents. Vol. VI. IARC Scientific Publication No. 120. Lyon: International Agency for Research on Cancer, 1992.
23. Abramson JH, Gahlinger PM. Computer programs for epidemiologic analysis. PEPI. USD. Stone Mountain, Ga, 1995; 203–205.
24. State of Israel. Ministry of Health. Israel Cancer Registry. Cancer in Israel, Jerusalem, 1990.
25. Devesa SS, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. *Cancer Res* 1992; 52(Suppl):5432s–40s.
26. Iscovich J, Parkin DM. Risk of cancer in migrants and their descendants in Israel. 1. Leukemia and lymphomas. *Int J Cancer* 1997;70:649–53.
27. Sackett DS. Bias in analytic research. *J Chron Dis* 1979;32: 51–63.
28. Theis B, Boyd N, Lockwood G, Tritchker D. Accuracy of family cancer history in breast cancer patients. *Eur J Cancer Prev* 1994;3:321–7.
29. Kerber RA, Slattery ML. Comparison of self-reported and database-linked family history of cancer date in a case–control study. *Am J Epidemiol* 1997;146:244–8.
30. Khoury MJ, Flanders WD. Bias in using family history as a risk factor in case-control studies of disease. *Epidemiology* 1995;6:511–9.
31. Marmot M. Changing places changing risks: the study of migrants. *Public Health Rev* 1993/94;21:185–95.
32. State of Israel. Central Bureau of Statistics. Mortality among immigrants from former USSR, 1990–1994. Current briefings in statistics. No 8. 1998:XVI–XII, XXVII–XXIX.