Original Contribution

Non-Hodgkin's Lymphoma and Family History of Hematologic Malignancy

F. K. Mensah¹², E. V. Willett¹, P. Ansell¹, P. J. Adamson¹, and E. Roman¹

¹ Epidemiology and Genetics Unit, Department of Health Sciences, University of York, York, United Kingdom.
² Department of Social Policy and Social Work, University of York, York, United Kingdom.

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Familial aggregation of non-Hodgkin's lymphoma, and the co-occurrence of non-Hodgkin's lymphoma and other hematologic malignancies within families, provide evidence for genetic or common environmental etiologies for these conditions. The authors analyzed the association between non-Hodgkin's lymphoma risk and family history of hematologic malignancy using a case-control study based in the United Kingdom. The study recruited patients diagnosed with lymphoma during 1998–2001. Results indicated an increased risk of non-Hodgkin’s lymphoma for persons with a positive family history of any hematologic malignancy (odds ratio = 1.70, 95% confidence interval: 1.08, 2.69) and particularly of any lymphoma (odds ratio = 2.43, 95% confidence interval: 1.14, 5.19). The authors compared the number of hematologic malignancies among relatives reported by the cases and controls with that expected from the national rates of hematologic malignancy registered in the United Kingdom. Through these comparisons, the authors raise questions about the validity of self-reported family history of hematologic malignancy, especially regarding identification of specific types of hematologic malignancies. Given these reservations, they consider how future epidemiologic studies may contribute to further understanding the role of familial susceptibility in non-Hodgkin's lymphoma.

epidemiologic methods; family; genetics; hematologic neoplasms; lymphoma, non-Hodgkin; research design

Abbreviations: CI, confidence interval; NHL, non-Hodgkin’s lymphoma; OR, odds ratio; SFCD, Swedish Family Cancer Database.

In this paper, we present the results from an analysis of association between the risk of non-Hodgkin’s lymphoma (NHL) and family history of hematologic malignancy using a case-control study based in the United Kingdom. Hematologic malignancies arise from the neoplastic transformation of cells within the hematopoietic and lymphoid systems, of which NHL is one of the main diagnostic groups, accounting for approximately 40 percent of the total (1). To understand the possible genetic determinants of NHL, frequent investigations have been made of whether the disease aggregates in families and/or co-occurs within families who have been affected by other hematologic malignancies. Much of this evidence has been provided by analyzing family history data reported by participants in case-control studies of NHL (2–7), which together suggest an increased risk of NHL for persons with a specific family history of NHL or a broader family history of any type of lymphoma or hematologic malignancy.

Case-control studies have mostly relied on self-reported data for determining family histories of hematologic malignancy, with a minority including validation of the data. In the recent study by Chang et al. (3), self-reported family history data were validated by linking participants to the Swedish Family Cancer Database (SFCD) to identify cancers registered for their family members. The study demonstrated a 30 percent overestimation of the odds ratio for NHL associated with family history of lymphoma estimated by analyzing self-reported family history data. This exaggeration of the
risk estimate was attributed to differential reporting of family history of lymphoma by NHL cases and controls. In the earlier United Kingdom study (2), investigators attempted to confirm self-reported incidences of hematologic malignancy via routine cancer registrations and death certificates, but less than half of the reports could be confirmed. Their estimates of risk based on self-reported and confirmed histories were comparable.

Validation of self-reported family history of hematologic malignancy is strongly recommended. It is unusual, however, for sources of family cancer data such as the SFCD to be available. Consulting routine cancer registrations or medical records is a potential, if time consuming and expensive method (8). Family history data can cover long time periods, particularly when considering the lifetimes of relatives from earlier generations, which presents difficulties in validation because it becomes unlikely that medical records will be available (9) or that routine cancer registrations will be complete and accurate (10) over the full time period. Here, we describe a method in which, as an alternative to validation of individual family history reports, we compare reported incidences of hematologic malignancy with those expected according to historically registered national rates.

We consider the completeness of registration for the United Kingdom national data, which we use as a reference in our comparisons. The completeness of United Kingdom cancer registration data in one regional cancer registry has been estimated to be 92.1 percent by 5 years after diagnosis for cancers diagnosed in 1987 (11). In the United Kingdom national cancer registration system, 90 percent completeness was estimated for cancers ascertained until 1999 (12). However, variability in the completeness and accuracy of registration by cancer site has been described in each of these studies. In the United Kingdom, comparison of cancer registrations with a specialist database established by hematologists suggested that only 70 percent of the hematologic malignancies diagnosed between 1994 and 1996 were registered (13). In this paper, we present comparisons in which we assume the completeness of registration of hematologic malignancy to be 90 percent and 70 percent.

MATERIALS AND METHODS

Study data

Data on 699 Caucasian NHL cases and 742 Caucasian controls from a case-control study of lymphoma based in the United Kingdom were included in the analysis. Full details of the study have been provided by Willett et al. (14). The study recruited patients aged 18–64 years diagnosed with lymphoma during 1998–2001 and who normally resided in regions of the north and southwest of England. For each case, a person matched on age and sex who had no history of lymphoma or leukemia was selected as a control from the local residential population, identified through primary care registers. The study was conducted with the ethical approval of the United Kingdom Multi-Regional Ethical Committee, and informed consent was given by all participants. The overall study participation rates were 75 percent for identified lymphoma cases and 71 percent for successfully contacted controls. Socioeconomic status was assigned to each case and control by using the Townsend deprivation indicator of the address at which they resided on the date of diagnosis for cases or, for controls, the date on which the control was the same age as his or her matched case at the time of lymphoma diagnosis (14, 15).

All participants took part in a face-to-face interview and provided information about their first-degree relatives in a questionnaire completed before the interview. For each relative, the study participant was asked to report date of birth, any serious medical conditions, and whether the relative was still alive or, if the relative had died, the date and cause of death. Consistency checking was implemented for birth and death dates within each family and for reported medical data. Medical conditions and causes of death were specified as open-ended text responses and were coded by using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (16). Reported hematologic malignancies were classified as any type of hematologic malignancy (codes C81–C96); any type of lymphoma (codes C81–C85 and C96); any type of leukemia (codes C91–C95); and any other hematologic malignancy, comprising multiple myeloma and other malignant immunoproliferative disease (codes C88–C90). The censoring age and follow-up period for each relative were determined by using his or her date of birth; the censoring date was taken as the date of death or, if alive, the date of the interview. For 2 percent of relatives for whom the date of birth was not reported or the end of follow-up was indeterminable, a start date and/or follow-up time were imputed such that the period between the relative’s date of birth and the case’s or control’s date of birth, and their follow-up time, corresponded to the mean values for relatives of the same type, that is, other fathers, mothers, siblings, or offspring.

Expected hematologic malignancies

Population age- and sex-specific rates of hematologic malignancy for England and Wales were extracted from the Eurocim cancer database (17) for the totality of the period 1971–1987 and in 5-year periods from 1988 to 1997. To take into account the potential that these rates were based on incomplete hematologic malignancy registration, multiplying factors were applied in the analysis to correct the registration rates for assumed 70 percent and 90 percent registration completeness across all time periods. Age-, sex-, and period-specific national rates were applied across the follow-up period for each of the relatives to determine the expected total number of incidences of hematologic malignancy for each of the cohorts of relatives of cases and of relatives of controls. To account for selectivity of survival to reproductive age and successful reproduction, it was assumed that, prior to the birth of the case or control, no hematologic malignancy was diagnosed among the parents, so the follow-up period was restricted to begin at the date of birth of the case or control. National rates for the period 1971–1987 were applied for follow-up time prior to 1971 and rates for the period 1993–1997 for follow-up time after 1997. Ratios and corresponding 95 percent confidence intervals comparing the reported with the expected hematologic malignancy for
each cohort were estimated (18). All statistical analyses were carried out using Stata software (19).

Analysis of association

Association between NHL and family history of each of lymphoma, leukemia, other hematologic malignancies, as well as all hematologic malignancies, was estimated by comparing the frequency of self-reported positive family history for cases with that for controls. Any case or control reporting one or more relatives who had been affected by or had died from the hematologic malignancy was considered to have a positive family history. Odds ratios and 95 percent confidence intervals were estimated by using unconditional logistic regression. The estimates were adjusted for age at diagnosis for cases or, for controls, the age equivalent to the age of the matched case at diagnosis, and for sex, study region, deprivation score, and total number of relatives. Exact methods were used when fewer than five positive family histories were reported by either the case or the control group. Data for all cases and controls who had completed the family history questionnaire and had provided health information for at least one relative were included in the analysis. The population attributable fraction of disease was estimated for family history of hematologic malignancy by using the methodology of Greenland and Drescher (20, 21).

To take into account the individual characteristics of the relatives, a further analysis of association was made by using the method of reconstructed cohort analysis (22, 23). The analysis considered the relatives of the cases and controls as if each were a cohort of individuals who had been followed up throughout their lifetime until the point at which they were censored by their death or at the time of the interview. We compared the frequency with which relatives of cases and controls were reported to have been affected by a hematologic malignancy. Odds ratios and 95 percent confidence intervals were estimated following the marginal model for binary disease status methodology described by Pfeiffer et al. (24). Estimates were adjusted for both the characteristics of each relative—sex and censoring age—and the characteristics of the case or control to whom the relative was related: age at diagnosis for cases or, for controls, age equivalent to the age of the matched case at diagnosis; sex; study region; and deprivation score. The dependence between relatives within each family was accounted for by using generalized estimating equations. Ideally, survival analysis techniques would have been used in the analysis of the reconstructed cohort data (22, 25). However, the date of disease onset had not been collected for the majority of the reported hematologic malignancies so we were unable to perform such analyses; thus, we used the methodology of Pfeiffer et al. as an alternative.

RESULTS

Of 699 cases and 742 controls participating in the case-control study, 698 cases (99.9 percent) and 738 controls (99.5 percent) completed a family history questionnaire with information for at least one relative. Cases and controls each reported a mean of 6.3 first-degree relatives and comparable numbers of both siblings and offspring (table 1). Health information was reported for 95.0 percent and 95.2 percent of the relatives of cases and controls, totaling 4,194 and 4,471 relatives, respectively.

Expected hematologic malignancies

The distribution of expected hematologic malignancies in the case and control populations over time was as follows: pre–1971, 23.9 percent; 1971–1987, 34.5 percent; 1988–1992, 15.5 percent; 1993–1997, 17.7 percent; and post–1997, 8.4 percent, assuming that the age- and sex-specific
incidence rates for 1971–1987 were applicable to the pre–1971 period and that the age- and sex-specific incidence rates for 1993–1997 were applicable to the post–1997 period. Comparisons between the reported incidences of hematologic malignancies in the relatives of the cases and the controls, and the incidences that would be expected from national cancer registration rates, are presented in table 2. When we assumed the completeness of national registration to be 90 percent, significantly increased numbers of hematologic malignancies were reported for the relatives of the cases compared with the expected number (ratio $= 1.42$, 95 percent confidence interval (CI): 1.07, 1.87). For the relatives of the controls, a slightly decreased number, compared with that expected, was observed (ratio $= 0.88$, 95 percent CI: 0.63, 1.23). An excess of lymphoma in the relatives of the cases and a deficit of lymphoma in the relatives of the controls were estimated, although neither was significant statistically. In contrast, excesses of leukemia were estimated for relatives of both the cases and the controls. When we assumed the completeness of national registration to be 70 percent, no evidence was provided for any excess hematologic malignancy in the relatives of the cases compared with that expected (ratio $= 1.10$, 95 percent CI: 0.83, 1.45); however, a significant deficit of hematologic malignancies in the relatives of controls (ratio $= 0.68$, 95 percent CI: 0.49, 0.96) was estimated.

### Association between NHL and family history

We present the association analyses of the self-reported data in table 3. However, given the discrepancies that we have noted between the rates reported and those that would have been expected given national registration rates, we advocate caution in interpreting these results.

An increased risk of NHL in association with a positive family history of any hematologic malignancy was observed (odds ratio (OR) $= 1.70$, 95 percent CI: 1.08, 2.69). The association was particularly apparent for a positive family history of lymphoma (OR $= 2.43$, 95 percent CI: 1.14, 5.19). These estimates correspond to population attributable fractions of 3.0 percent (95 percent CI: 0.5, 5.4 percent) for all hematologic malignancies and 1.9 percent (95 percent CI: 0.4, 3.4 percent) for lymphoma, representing the proportion of NHL in the population that may be attributed to the excess risk experienced by persons with a family history of these conditions. Some increased risk was described in association with a positive family history of leukemia and “other hematologic malignancies,” comprising multiple myeloma and other malignant immunoproliferative diseases; however, these estimates were not significant statistically.

When we considered the relatives of cases and controls as reconstructed cohorts and compared the lifetime history of hematologic malignancy between these cohorts, the risk of any hematologic malignancy for the relatives of the cases was found to be elevated compared with that for the relatives of the controls (OR $= 1.58$, 95 percent CI: 1.02, 2.45). The risk of lymphoma for the relatives of the cases was elevated compared with the relatives of the controls (OR $= 2.14$, 95 percent CI: 1.04, 4.43). Increased risks of leukemia and of “other hematologic malignancies” were also estimated for the relatives of the cases. However, these estimates were not significant statistically.

<table>
<thead>
<tr>
<th>TABLE 2. Comparison of the number of reports of hematologic malignancies with that expected from national cancer registration data, United Kingdom, 1998–2001</th>
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<tbody>
<tr>
<td>Reported (no.)</td>
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<td>---------------------------------------------------------------</td>
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<td>---------------------------------------------------------------</td>
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<tr>
<td>Relatives of cases</td>
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<tr>
<td>($n = 4,194$)</td>
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<tr>
<td>Hematologic malignancy of any type</td>
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<tr>
<td>Lymphoma</td>
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<td>Leukemia</td>
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<tr>
<td>Other hematologic malignancy</td>
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<tr>
<td>Relatives of controls</td>
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<tr>
<td>($n = 4,471$)</td>
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<tr>
<td>Hematologic malignancy of any type</td>
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<td>Lymphoma</td>
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<tr>
<td>Leukemia</td>
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<td>Other hematologic malignancy</td>
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* Ratio comparing the reported to the expected numbers of hematologic malignancies. † CI, confidence interval.
Evidence for an association between NHL and family history of lymphoma, or specifically NHL, has been demonstrated in both European and US populations. In a Swedish case-control study, Chang et al. (3) estimated an odds ratio of 2.5 (95 percent CI: 1.2, 5.1) associated with lymphoma in first-degree relatives based on self-reported data, which reduced to an odds ratio of 1.9 (95 percent CI: 1.2, 3.2) when the analysis used family histories determined from the SFCD. An association between NHL and family history of lymphoma has been demonstrated in case-control studies of US males (OR = 3.0, 95 percent CI: 1.7, 5.2) for history of lymphoma in first-degree relatives (Zhu et al. (7)); and odds ratio = 1.5, 95 percent CI: 0.5, 4.2 for history of lymphoma in a parent, odds ratio = 3.8, 95 percent CI: 1.3, 11.5 for history of lymphoma in a sibling (Pottern et al. (6)). In a further US case-control study, Chatterjee et al. (4) reported a nonsignificant association between NHL and family history of NHL (OR = 2.06, 95 percent CI: 0.73, 5.76) and family history of NHL or lymphoma not otherwise specified (OR = 1.56, 95 percent CI: 0.75, 3.22). In a full population study by Hemminki et al. (26) using the SFCD, the standardized incidence rates for NHL were estimated to be 1.82 (95 percent CI: 1.43, 2.28) for having a parent affected by NHL and 2.25 (95 percent CI: 1.44, 3.35) for having an affected sibling; and, in a full population study based on the Utah Population Database by Goldgar et al. (27), the familial relative risk of NHL was estimated as 1.68 (95 percent CI: 1.04, 2.48).

The estimates of association between NHL and family history of other hematologic malignancies have shown less consistency. An association between NHL and family history of hematologic malignancy was demonstrated by Chang et al. (3), with odds ratios of 2.1 (95 percent CI: 1.3, 3.2) using self-reported data and 1.7 (95 percent CI: 1.1, 2.4) using data from the SFCD. Chiu et al. (5) demonstrated an association (OR = 2.7, 95 percent CI: 1.9, 3.7) in a combined analysis of three US case-control studies, two of which included only male, while one included both male and female, participants. Zhu et al. (7) demonstrated an association for US males (OR = 2.0, 95 percent CI: 1.2, 3.4). Chatterjee et al. (4) did not find evidence for an association between NHL and family history of hematologic malignancy (OR = 1.17, 95 percent CI: 0.76, 1.81) nor between NHL and family history of Hodgkin’s lymphoma, leukemia, or multiple myeloma. Cartwright et al. (2) demonstrated an association between NHL and lymphoma or leukemia in first-degree relatives (OR = 4.4, 95 percent CI: 2.0, 10.0) using self-reported family history data, finding comparable estimates when the analysis was restricted to reports confirmed by routine cancer registrations or death certificates. In a full population study using the SFCD, Dong and Hemminki (28) demonstrated an association between lymphoma and parental myeloma (OR = 1.51, 95 percent CI: 1.05, 2.11); however, they found no other evidence for concordance between lymphoma and either leukemia or myeloma within families. In an analysis of the Utah Population Database, Thomas et al. (29) demonstrated significant excesses of leukemia and myeloma in the relatives of those who had been affected by lymphoma, but Goldgar et al. (27) found no excesses of any other hematologic malignancy in the relatives of those affected by NHL.

In the study by Chang et al. (3), comparisons between the family histories that were self-reported and those derived from the SFCD indicated a sensitivity of reporting...
hematologic malignancy of 60 percent for lymphoma cases compared with 38 percent for controls. Specificity was extremely high for both lymphoma cases and controls—98 and 99 percent, respectively—but it is important to note that identification of the type of hematologic malignancy within the broader classification of all hematologic malignancies was not considered in these estimates. This study provided new insight into the reporting of hematologic malignancy, demonstrating a larger case-control differential than has been previously observed for neoplasms such as colorectal and breast cancer (30–32). If differential sensitivity of reporting hematologic malignancy holds true for other case and control populations, it would imply that the results described by previous case-control studies may be overestimated for the association between NHL and family history of NHL and/or other hematologic malignancies. However, the effects do not appear to be strong enough to fully undermine the associations that have been previously described.

Through analysis of our self-reported family history data, we demonstrated an association between the risk of NHL and a family history of hematologic malignancy (OR = 1.70, 95 percent CI: 1.08, 2.69) and particularly of lymphoma (OR = 2.43, 95 percent CI: 1.14, 5.19). These associations persisted when we considered the relatives and cases as reconstructed cohorts, providing assurance that the family history associations were not attributable to biases that can be introduced by using traditional methods of analyzing family history data (33, 34). In interpreting our results, however, consideration of the accuracy and completeness of the family history data reported by the study participants is fundamentally important. Through detailed collection of the dates of birth and death of the relatives, we were able to determine the follow-up periods over which each relative may have been affected by hematologic malignancy and thus were able to compare the numbers and types of hematologic malignancies reported with those expected according to historic national registration rates for the United Kingdom.

We may have expected the relatives of the control population to be comparable to the general population regarding their history of hematologic malignancy, but significant deviations were observed between the reported and expected numbers of hematologic malignancies. Increased numbers of leukemias, and decreased numbers of other hematologic malignancies, were reported compared with the numbers that would have been expected assuming either 70 percent or 90 percent completeness of registration. Some of this deviation may have been explained by differential reporting of hematologic malignancy; it is possible that study participants were more likely to have reported that a relative had leukemia rather than lymphoma because leukemia is the better known condition. Completeness of registration may also have varied by type of hematologic malignancy, with those usually indolent, such as chronic lymphocytic leukemia, being less likely to have been registered than more aggressive hematologic malignancies. Thus, what appeared to be overreporting of leukemia by participants may have been due to such a deficit in registration of leukemia.

We recognize that the assumptions that we have made regarding completeness of registration are unlikely to represent the true complexities of variation over time and by type of hematologic malignancy. We note the study by Pinsky et al. (35), in which similar discrepancies in reporting lymphoma and leukemia were observed. Family history data from a US cancer screening trial, comprising cancers reported for siblings, were compared with expected data from the Surveillance, Epidemiology, and End Results Program. The ratio of lymphomas reported compared with those expected were 0.27 and 0.40 for male and female participants, respectively, compared with those for leukemia, which were 0.74 and 0.87 for male and female participants, respectively. The potential for differential reporting of family history by male and female study participants is an issue that we did not address in our study, but it may be of substantial importance if comparisons were made by gender.

In summary, our analysis of self-reported family history data indicates an association between NHL and family history of hematologic malignancy, particularly lymphoma, which contributes to a growing body of literature describing such associations. Comparison of reported hematologic malignancies with expected data indicated that different types of hematologic malignancies may have been differentially reported; however, it was difficult to draw a firm conclusion given uncertainties in the reliability of historic cancer registration rates.

Family history studies have provided evidence for a familial etiology in NHL, suggesting that there may be value in conducting further detailed studies of multiple-case families (36). An immediate question arising for specifying the design of such studies is whether to include only those families affected by NHL or to extend the criteria to include families affected by NHL and any other unusual incidence of hematologic malignancy. Whether self-reported data have provided relative’s histories with sufficient diagnostic accuracy to address this issue is questionable. Studies based on linkage between familial records and routine cancer registrations have provided greater diagnostic accuracy, particularly the recent analysis by Altieri et al. (37), in which detailed histopathologic classification was included. However, such studies have been limited by the time periods over which data were available (26), and historic changes in the diagnostic classification of the hematologic malignancy (38) will be apparent in routinely registered data as well as self-reported data. Decisions regarding which hematologic malignancies may most usefully be assessed together within family studies may best be made by carefully considering the evidence provided by epidemiologic studies as well as the pathogenetic commonalities between the hematologic malignancies (38).

Establishing an international registry of multiple-case families has long been proposed (36), and the networks required for such an undertaking are becoming established through the InterLymph collaboration (39). Detailed studies of these families may provide the opportunity to investigate their medical and environmental histories, as well as perform detailed genetic investigations of the mode of inheritance for NHL and searches for candidate genes. A continued and important role of epidemiologic studies involving NHL cases may be in bringing together a rich resource of systematically documented family histories, through which
multiple-case families may be ascertained to participate in such detailed studies.

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REFERENCES