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Clustering of cancer among families of cases with Hodgkin Lymphoma (HL), Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL), Soft Tissue Sarcoma (STS) and control subjects

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Abstract

Background: A positive family history of chronic diseases including cancer can be used as an index of genetic and shared environmental influences. The tumours studied have several putative risk factors in common including occupational exposure to certain pesticides and a positive family history of cancer.

Methods: We conducted population-based studies of Hodgkin lymphoma (HL), Multiple Myeloma (MM), non-Hodgkin's Lymphoma (NHL), and Soft Tissue Sarcoma (STS) among male incident case and control subjects in six Canadian provinces. The postal questionnaire was used to collect personal demographic data, a medical history, a lifetime occupational history, smoking pattern, and the information on family history of cancer. The family history of cancer was restricted to first degree relatives and included relationship to the index subjects and the types of tumours diagnosed among relatives. The information was collected on 1528 cases (HL (n = 316), MM (n = 342), NHL (n = 513), STS (n = 357)) and 1506 age ± 2 years and province of residence matched control subjects. Conditional logistic regression analyses adjusted for the matching variables were conducted.

Results: We found that most families were cancer free, and a minority included two or more affected relatives. HL [(OR_{adj} (95% CI) 1.79 (1.33, 2.42)], MM (1.38(1.07, 1.78)), NHL (1.43 (1.15, 1.77)), and STS cases (1.30(1.00, 1.68)) had higher incidence of cancer if any first degree relative was affected with cancer compared to control families. Constructing mutually exclusive categories combining "family history of cancer" (yes, no) and "pesticide exposure ≥10 hours per year" (yes, no) indicated that a positive family history was important for HL (2.25(1.61, 3.15)), and for the combination of the two exposures increased risk for MM (1.69(1.14, 2.51)). Also, a positive family history of cancer both with (1.72 (1.21, 2.45)) and without pesticide exposure (1.43(1.12, 1.83)) increased risk of NHL.

Conclusion: HL, MM, NHL, and STS cases had higher incidence of cancer if any first degree relative affected with cancer compared to control families. A positive family history of cancer and/or shared environmental exposure to agricultural chemicals play an important role in the development of cancer.

Background

At the cellular level, all cancers are genetic [1]. A positive family history of chronic diseases including cancer can be used as an index of genetic and shared environmental influences [2,3]. The four types of tumours under investigation (Hodgkin Lymphoma, Multiple Myeloma, Non-Hodgkin's Lymphoma and Soft Tissue Sarcoma) have several putative risk factors [4-63] in common, which include occupational exposure to certain chemicals and specific pesticides [4-37], a positive family history of cancer specifically of the hematopoietic system [29,30,37-54], a positive personal history of cancer or other diseases, as well as certain types of medical treatments for cancer and personal habits [38,55-63].

Researchers have stated that more than 80% of human cancers can be attributed to environmental factors [2,3,64,65]. Inherited and shared environmental influences among family members (such as tobacco smoke, viruses, agricultural chemicals and dusts, animal contact) that contribute to cancer's development can sometimes be delineated by (a) deconstructing the familial pattern of tumour occurrences (parent-offspring versus sibling-sibling), and (b) collecting detailed information of historical exposure by utilizing various methods. Simultaneously, in order to compare the family history of cancer, we conducted population-based case-control studies of Hodgkin Lymphoma, Multiple Myeloma, Non-Hodgkin's Lymphoma and Soft Tissue Sarcoma among male incident case and control subjects in six Canadian provinces using postal questionnaires in order to compare details of family history of cancer among them.

Methods

The detailed methodology has been previously published [38]. Briefly, we contacted male incident cases aged 19 years or older with a first diagnosis of Hodgkin Lymphoma (ICD-9 201), Multiple Myeloma (ICD-9 203), Non-Hodgkin's Lymphoma (ICD-9 200 or 202), Soft Tissue Sarcoma (ICD-9 code 171 and any other ICD-9 category with certain specified morphology codes), who were diagnosed on or after September 1st, 1991 until at the latest on or before December 31st, 1994, and who were residents of six Canadian provinces (Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia). The Cases were ascertained from provincial cancer registries except in Quebec where hospital registries were used. The control subjects were males aged 19 years and older selected from provincial Health Insurance records (Alberta, Saskatchewan, Manitoba, and Quebec), telephone listings (Ontario) or Voter's lists (British Columbia). The random control subject selection was stratified by age \pm 2 years to be comparable to the age distribution of the entire case group within each province.

The family history section of the postal questionnaire used in this study was developed and validated by McDuffie *et al* [66]. The family history section was designed to collect information on the number and sex of siblings and children of the index subjects. Additional queries ascertained information on the index subject's children who were either stillborn, born with a genetic disease and/or a birth defect. The definition of family was restricted to first degree relatives; parents, siblings and children. Within each family there were three generations: parents, sibling and children. Half-siblings, adopted siblings or children and stepchildren were excluded. Both living and deceased first degree relatives were included. The information on family history of cancer included the affected individual's relationship of to the index subject, the site of the cancer, and the year and province of diagnosis. Reported cancer in family members was not verified.

The questionnaire instrument was also used to collect personal demographic data, health history, smoking pattern and lifetime occupational history. Exposure to broad classes of pesticides (herbicides, insecticides, fumigants, fungicides, and algacides) was included as these were potential confounders of the putative association between a positive family history of cancer and each of the tumours of interest. Pesticide exposure was a calculated variable that required affirmative responses to questions concerning exposure to any combination of the pesticides listed. Cumulative exposure of ten hours per year or more to pesticides was considered a positive response.

Data Management and Statistical Analysis

The questionnaires were reviewed for completeness and consistency of the responses by the coordinators in each province. The data were computer coded in the province of origin using SPSS-DE [67]; they were also checked and transported on disks to the coordinating centre where the data were reviewed for completeness and internal consistency. The analytic approach was that suggested by Breslow *et al* [68]. We used SAS [69] computer software to conduct the analyses.

We conducted descriptive statistical analyses and compared family history of cancer among each case group to the control group's family history data. In addition four mutually exclusive categories combining the variables family history of cancer (yes, no) and pesticide exposure \geq 10 hours/year (yes, no) were constructed. Similar mutually exclusive categories were formed for family history of cancer and smoking status (non-smokers, ex-smoker or current smoker). We conducted conditional logistic regression analyses adjusted for the matching variables

age and province of residence. We report adjusted odds ratios (OR_{adj}) and 95% confidence intervals (95% CI).

Ethical Approval

The letters of informed consent, the questionnaires and other written material provided to potential subjects were submitted to and approved by each of the relevant agencies in each province. For Saskatchewan, the University of Saskatchewan Biomedical Research Ethics Board (#89-12); for British Columbia, the University of British Columbia Behavioural Research Ethics Board (#B91-185); for Quebec, the University of McGill Human Ethics Board; for Alberta, the University of Alberta Health Research Ethics Board (Biomedical Panel); for Manitoba, the University of Manitoba Biomedical Research Ethics Board; and for Ontario, the University of Toronto Health Sciences Research Board approved the study protocol. All information that could be used to identify the individuals remained within the province of origin under the control of each province's principal investigator. After receiving permission to contact a potential case by the attending physician, a letter of informed consent and a questionnaire was mailed. Relatives of cases known to be deceased at ascertainment were not contacted because of the need to obtain detailed information concerning occupation and occupational exposures including a variety of types of pesticides. Control subjects were contacted directly by mail. Living control subjects were eligible. Additional methodological details have been previously published [38].

Results

Information about the family history of cancer in first degree relatives of 1528 cases: (HL ($n = 316$), MM ($n = 342$), NHL ($n = 513$), STS ($n = 357$)) and 1506 control subjects was obtained. Descriptive characteristics of the families studied are shown in Tables 1 through 4 [See additional file 1: Table 1; additional file 2: Table 2; additional file 3: Table 3; additional file 4: Table 4]. The age distribution, the mean age and standard deviation, the number of first degree relatives, the mean number of siblings and offspring, and the mean number of first degree family members including parents among controls and within each case group are shown in Table 1 [See additional file 1: Table 1]. HL cases were much younger compared to MM, NHL, and STS cases. HL families were the smallest with smaller mean number of siblings, sons and daughters compared to families of other case groups and controls. The four categories: small, medium, large and largest categories were used to define the family size (for definition see footnote under Table 2 [See additional file 2: Table 2]). There were distinctive differences in the family size patterns (chi square = 61.5, $df = 12$, $p < .0001$) across the case groups and controls, however the family

size patterns were not significantly different between STS cases and controls (Table 2 [See additional file 2: Table 2], chi square = 1.80, $df = 3$, $p > 0.05$). HL families were the smallest. Families of HL, MM and STS were significantly more likely to have had one affected generation than controls, while a higher proportion of NHL families reported two or more affected generations (Table 3 [See additional file 3: Table 3]). A small minority of families reported affected members in two or more generations. The distribution of affected family members (chi-square = 59.8, $df = 8$, $p < .0001$, the categories were zero, one, ≥ 2 affected per family) and the percentage of families with two or more affected individuals are presented in Table 4 [See additional file 4: Table 4]. The majority of families were cancer free, excluding the index subjects. A minority of families included two or more affected first degree relatives of the index subjects.

Table 5 [See additional file 5: Table 5] compares distribution of positive history of cancer in (i) at least one parent; (ii) at least one sibling; and (iii) at least one child of each case group with controls stratified by age distribution of the index subject. Patterns of cancer prevalence are similar among the index subjects diagnosed with four types of cancer (HL, MM, NHL, and STS). The index subjects in the age groups $> 40, \leq 49$, and $> 49, \leq 59$ had higher proportion of at least one parent affected with cancer compared to controls. The proportion of at least one sibling affected with cancer increases with age of the index subject. The siblings of older index subjects may be comparatively older compared to the siblings of younger index subjects and it is well known that risk of cancer increases with age. In most of the age groups, index subjects have higher proportion of at least one sibling affected with cancer compared to controls. For the younger age groups (≤ 40 , and $> 40, \leq 49$), there was hardly any child affected with cancer, because children of the index subjects in these age groups may be younger and had very low risk of developing cancer. The proportions of at least one child affected with cancer are small in the older age groups and among all cases and controls.

Families ascertained through HL, MM, NHL, and STS cases were compared to control families in Table 6 [See additional file 6: Table 6]. Cases of HL [OR_{adj} (95% CI 1.79 (1.33, 2.42)], MM [OR_{adj} (95% CI 1.38 (1.07, 1.78)], NHL [OR_{adj} (95% CI 1.43 (1.15, 1.77)] and STS [1.30 (1.00, 1.68)] were more likely to have at least one first degree relative diagnosed with cancer compared to controls. Although the crude odds ratios (data not shown) for several variables related to history of cancer among families ascertained through HL cases were statistically non-significant, adjustment for age and province of residence produced statistically significant results due to the

strength of the associations within certain strata. Index subjects with at least one affected parent with a diagnosis of cancer had increased risk of being diagnosed with HL [1.57 (1.15, 2.14)]. This pattern did not appear in any of the other case/control comparisons. HL [1.94 (1.12, 3.34)], MM [1.71 (1.22, 2.40)] and NHL [1.68 (1.23, 2.31)] cases were significantly more likely to have at least one affected sibling than controls after adjustment for total number of siblings. The excess of siblings was due to more affected sisters among HL families [1.89 (1.05, 3.38)], MM families [1.66 (1.14, 2.40)] and NHL families [1.52 (1.07, 2.17)]. Few children of index subjects (range 0.6% of HL families to 3.7% of MM families) had been diagnosed with cancer.

Among each case/control family group, tumours of the trachea, bronchus, lung (ICD-9 162) and of the female breast (ICD-9 174) were first or second in frequency (data not shown). The female to male ratio for tumours of the trachea, bronchus, and lung was unexpectedly high; 1.45:1 for NHL relatives. There was also one male breast cancer among NHL relatives. Among families of HL cases, lymphoid leukaemia (ICD-9 204) and Hodgkin lymphoma (ICD-9 201) were third and fourth. Among families of MM cases, colon (ICD-9 153) and prostate (ICD-9 185) tumours were third and fourth while stomach (ICD-9 151) and lymphoid leukaemia occupied these ranks among families of NHL cases. Lymphoid leukaemia and liver cancer (ICD-9 155) tied for third place and rectum, sigmoid junction and anus (ICD-9 154) was fourth in frequency among STS families.

In this study, 54.4% of HL cases; 87.7% of MM cases; 79.7% of NHL cases; and 73.7% of STS cases reported to have at least one child compared to 21.4% controls who reported to have at least one child. The HL families reported a higher frequency of birth defects than the control families although there did not appear to be a clustering of specific types (data is not shown). Cleft palate ($n = 2$) and pyloric stenosis ($n = 2$) were the only conditions to occur in more than one family while Turner's syndrome, hypospadias and atrophic testis each occurred in one HL family.

Table 7 [See additional file 7: Table 7] displays certain characteristics of the index subjects stratified by family history of cancer. The variables include pesticide exposure ≥ 10 hours per year as a surrogate for occupational and environmental pesticide exposure, cigarette smoking history (non-smokers, ex-smoker or current smoker) and age at diagnosis. Comparisons of each case group with the controls using mutually exclusive categories combining family history status (positive, negative) with either pesticide exposure ≥ 10 hours/year or lesser exposure indicated that a positive family history (but not pesticide exposure)

was important for HL [(2.25 (1.61, 3.15))], that the combination of pesticide exposure and a positive family history of cancer increased risk for MM [1.69 (1.14, 2.51)] and that a positive family history of cancer both with [1.72 (1.21, 2.45)] and without [1.43 (1.12, 1.83)] pesticide exposure increased risk of NHL. A family history of cancer both with [2.34 (1.57, 3.48)] and without [1.68 (1.01, 2.78)] a history of cigarette smoking increased risk of HL. Cigarette smoking [1.46 (1.01, 2.12)] and family history [1.73 (1.07, 2.80)] independently and in combination [1.79 (1.22, 2.63)] increased risk of MM while only the combination of cigarette smoking and a positive family history [1.45 (1.07, 1.96)] influenced risk of NHL. There were no statistically significant results of comparisons of STS cases and controls.

Contrary to the expectation that those with a positive family history of cancer will have experienced genetic and/or environmental factors which might lower the age at diagnosis, HL, MM, and STS cases and the age at recruitment of control subjects with a positive family history were significantly older than those with a negative family history.

Discussion

Data from postal questionnaires based on responses from 513 NHL cases (67.1% of those contacted); 316 HL cases (68.4% of those contacted); 342 MM cases (58.0% of those contacted); 357 STS cases (60.8% of those contacted); and 1506 controls (48.0% of those contacted) were analyzed. Due to budget constraints, this study was restricted to males. Previous studies [66,70-75] have demonstrated that first degree family members are capable of accuracy in reporting chronic illnesses such as cancer among their immediate family members while accuracy declines when the definition of family is expanded [71,75]. Therefore, the study definition of family was restricted to first degree relatives. We collected information on (a) the number and the sex of siblings and children, (b) the children of index subjects who had a genetic disease, a birth defect or who were stillborn; and (c) relatives, specifically on: the type of cancer, the relationship to the index subjects, and the year and province of diagnosis was collected. This comprehensive documentation permitted us to consider family cancer history as stratified by sex, by generation (parental, sibling, children) and by multiple generations and to incorporate the total number of siblings into the analyses.

Consistent with other studies of similar design [39-41,53,66] with a range of 50% to 65% of cancer free families, we found that the majority of families were cancer-free (excluding the index subjects). Previous studies [37-54,66,70-73,75] have shown that the proportion of cancer free families varies with the type of index cancer, with the manner in which the index subject is ascertained, with

the age of the index subject and with the size of the family. We found that HL families had the lowest (5.4%) and MM families the highest (17.6%) percent of families with two or more affected individuals per family compared to 8.3% controls families with two or more affected per family.

An exploration of the generational pattern [2,3,30,49,66] of cancer in affected relatives was useful in discussions related to discriminating between inherited and environmental factors contributing to a positive family history of cancer. In our data and that of others as well, the generational patterns of cancer that emerged are parental only, sibling only and multi-generational. A concentration of tumours in one generation, whether parental or sibling, might relate etiologically to time-dependent environmental exposures. In contrast, sibling clustering could also relate to recessively inherited susceptibility. Additional information on exposure to putative carcinogens, such as tobacco smoke or specific pesticides, during the relevant time periods aids in the assessment of the inherited/environmental/interaction triad. In this study, statistically significant increases in risk of at least one affected sibling of the index subject were demonstrated for HL, MM and NHL compared to control families. Among HL families, there were also statistically significant increases in risk in the parental generation (mother was affected, father was unaffected and vice-versa, with; at least one affected parent). This pattern of parental generation involvement was not apparent for MM, NHL or STS families.

Ottman [76] summarized a variety of models illustrating the potential modes of interaction among genetic and environmental factors. By constructing mutually exclusive categories that utilize the variables family history of cancer in combination with either exposure to pesticides > 10 hours per year or cigarette smoking, an examination of the independent and combined effect of a personal characteristic and environmental exposures to known or suspected carcinogenic risk factors for these four types of tumours was examined. Among HL index subjects, those with a positive family history of cancer were at higher risk when unexposed to pesticides while smoking status did not substantially influence the increased risk of HL conferred by a positive family history. These patterns were consistent with the genetic susceptibility etiological hypothesis [1,2] related to HL. In the stratified analysis, the combination of a positive family history and exposure to pesticides increased risk of MM while neither variable did so independently. In a cohort study [77], ex-smokers experienced a three-fold risk of MM compared to life-time non-smokers, with a dose-response effect. Positive histories of cigarette smoking and family history independently and in combination increased risk of MM without an apparent dose effect in this study. This pattern suggests a lack of synergism between the lifestyle factor, cigarette smoking

and the inherent factor, positive family history of cancer. A positive family history of cancer both with and without pesticide exposure increased risk of NHL suggesting that a positive family history was more important than pesticide exposure as defined in these analyses. Zahm *et al* [30] reported that refining the definitions of family histories from "any affected family member" to "affected first degree relative with hemopoietic cancer", and pesticide exposure (i.e. from residence on a farm to personal application of a specific chemical class of insecticide) resulted in a dose response pattern among women. The relationship of cigarette smoking to risk of NHL is controversial and smoking risk may only be related to specific subtypes of NHL. In this study, only the combination of cigarette smoking and positive family history significantly influenced risk of NHL, although the odds ratios and 95% confidence intervals for the combinations of positive family history with non smokers and ever smokers were similar. Linet *et al* [78] reported that only the combination of positive family history and cigarette smoking increased risk of NHL.

The major limitation of this study is the fact that the family history of cancer was obtained by report from the index subjects and these reports were not validated by reference to the appropriate provincial cancer registries. There are difficulties involved in validation of self-reported family history of cancer by index subjects as reported by other authors [66,79].

Our study has the advantages of recruiting incident cases and controls from population-based sources covering a large geographical area of Canada. There were three to five controls for each case which increased the statistical power of the study. The use of a common control group and identical methodology permitted comparisons of the importance of a family history of cancer among the four types of cancer studied.

If a familial aggregation of cancer is a surrogate for an inherited, genetic etiology, certain predictions apply [2,66] and we have evaluated our data with respect to several of these. The predictions include: 1. a younger age at diagnosis among those with a positive family history of cancer compared to the general population or those with a negative family history. Our data demonstrated a significantly older age at diagnosis among those with a positive family history for each cancer group and the controls compared to those with a negative family history. Previously, Schneider *et al* [80] demonstrated familial clustering of cancer among relatives of randomly selected cancer cases without regard to age of the index subject. 2. A multigenerational pattern of tumours occurring in both sexes is of interest because the inherited, genetic hypothesis predicts that at least one of the precancerous steps occurred prena-

tally and each cell within the body therefore has a heightened susceptibility. The predicted pattern was strongest for HL families followed by NHL and MM families. The predicted pattern was not found among STS families. 3. The potential role of environmental factors is complex as specific exposures may act as tumour initiators, or as agents influencing progression or promotion of tumour growth. In the stratified analyses exploring the contributions of pesticide exposure or cigarette smoking independently and in combination with a positive family history of cancer, we did not find strong evidence of synergism in those with combined exposure.

Conclusion

HL, MM, NHL, and STS cases had higher incidence of cancer if any first degree relative affected with cancer compared to control families. A positive family history of cancer and/or shared environmental exposure to agricultural chemicals play an important role in the development of cancer.

Abbreviations

(NHL): Non-Hodgkin's Lymphoma; (ICD): International Classification of Diseases; (STS): Soft Tissue Sarcoma; (HL): Hodgkin lymphoma; (MM): Multiple Myeloma; (EBV): Epstein-Barr Virus; (SD): Standard deviation; (SE): Standard Error; (OR_{adj}): Adjusted Odds Ratio; (95% CI): 95% confidence Interval; (IARC): International Agency for Research on Cancer.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HHM's main contribution was grant writing, study design, questionnaires development, and study coordination. The concept of including family history variables in this study was HHM's idea and she prepared the manuscript. PP was involved at the grant writing stage; she participated in the design of the study, and in the development of the questionnaires. PP was the national coordinator and biostatistician for this study. PP trained data managers from the six provinces about the data entry process, and supervised every stage of data cleaning. PP conducted the entire statistical analysis required for the manuscript and contributed to the preparation of the manuscript in sections relevant to statistical analysis. CPK made contributions to the statistical analysis and manuscript preparation. JJS was the co-investigator and British Columbia representative who participated in the design of the study and who supervised any data collection for the province of British Columbia. JAD and HHM were co-principal investigators of the study. JAD's main contribution was grant writing

and questionnaires development. All authors read and approved the final manuscript.

Additional material

Additional file 1

Table 1. Age distribution of cases and controls and descriptive Characteristics of the Families Studied: Numbers of first degree relatives* stratified by relationship to the index subjects**. This is a table of age distribution of cases and controls and descriptive characteristics of first degree relatives.

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Additional file 2

Table 2. Descriptive characteristics of the families studied: family size*** categorized as small, medium, large and largest excluding the index subjects. This is a table of descriptive characteristics of family size of the families studied.

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Additional file 3

Table 3. Descriptive characteristics of the families studied: distribution of number of reported generations with at least one family member affected with cancer excluding the index subjects. This is a table of the distribution of number of reported generations with at least one family member affected with cancer excluding the index subjects.

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Additional file 4

Table 4. Descriptive characteristics of the families studied: distribution of reported numbers**** of family members affected with cancer excluding the index subjects. This is a table of the distribution of reported number of family members affected with cancer excluding the index subjects.

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Additional file 5

Table 5: Cancer in family relatives stratified by age distribution. This is a table of the distribution of age of family relatives who are with cancer.

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Additional file 6

Table 6. Comparisons of families of cases of HL, MM, NHL, STS to families of controls: relationship of relatives with cancer to index subjects. This is a table of comparisons of families of cases of HL, MM, NHL, STS to families of controls.

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Additional file 7

Table 7. Characteristics of index subjects among those with and without a family history of cancer. This is a table of characteristics of index subjects among those with and without a family history of cancer.

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[<http://www.biomedcentral.com/content/supplementary/1471-2407-9-70-S7.pdf>]

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