No Evidence for Anticipation in Lymphoproliferative Tumors in Population-Based Samples

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Abstract

Genetic anticipation in familial non–Hodgkin’s lymphoma, Hodgkin’s lymphoma, and chronic lymphocytic leukemia (CLL) has been consistently reported in the literature. However, most of these findings were based on data from families ascertained for genetic studies. Fecundity bias, right censoring bias, and secular trends can lead to erroneous conclusions regarding the presence of anticipation. Our report investigates anticipation in four lymphoproliferative cancers, non–Hodgkin’s lymphoma, Hodgkin’s lymphoma, CLL, and multiple myeloma, drawn from Swedish and Danish population-based registries. We used marginal survival methods to test for a relative difference in age at diagnosis between parents and offspring and to account for other risk factors, staggered entries, censored data, and correlations among relatives. Changes in incidence rates of lymphoproliferative tumors were accommodated in the models by using time-varying covariates for different periods of diagnosis. Whereas no anticipation was observed for Hodgkin’s lymphoma, CLL, and multiple myeloma, our initial model, which controlled for gender and country, suggested a significant difference (hazard ratio, 0.5; 95% confidence interval, 0.33-0.75) in age at diagnosis between the parents and offspring in the non–Hodgkin’s lymphoma sample. However, once we accounted for the significant change in non–Hodgkin’s lymphoma incidence over time, the statistical difference between parents and offspring disappeared (hazard ratio, 0.99; 95% confidence interval, 0.56-1.76). Our results emphasize the importance of considering secular trends when evaluating the possibility of anticipation in lymphoproliferative cancers. This is the first study to consider the changes of incidence over time as a source of bias when evaluating anticipation in lymphoproliferative cancers. (Cancer Epidemiol Biomarkers Prev 2005;14(5):1245-50)

Introduction

Genetic anticipation is a term that refers to an earlier age at onset or increasing severity of a disease in successive generations. Trinucleotide repeat expansions are the genetic mechanisms that explain the phenomenon of anticipation in some Mendelian neurodegenerative diseases such as Huntington’s disease, myotonic dystrophy, and spinocerebellar ataxia (1). Epigenetic changes (2) and abnormalities in telomeres (3) have also been suggested as possible mechanisms that may contribute to anticipation in more complex diseases. Anticipation has been widely investigated in complex diseases such as psychiatric disorders, Crohn’s disease, Alzheimer’s disease, and cancer (4).

When investigating anticipation, a distinction between biological and statistical anticipation must be made (5). Multiple biases can lead to erroneous conclusions regarding the presence of anticipation (4, 6). For some diseases, there is a fecundity bias that results from the ascertainment of later age at onset parents to the exclusion of many individuals with early-onset disease that may have had their reproductive capabilities limited by their diagnosis (5). Differences in the length of follow-up time between the generations can also cause bias because the later generations are often not followed through the entire period of risk (4, 5, 7). Secular trends, such as changes in diagnostic techniques or reporting practices (period effects) or increases in the prevalence of environmental risk factors affecting specific birth cohorts, can also bias findings of anticipation (8).

Secular trends are particularly important when investigating anticipation in some lymphoproliferative cancers. The incidence of non–Hodgkin’s lymphoma has been increasing dramatically worldwide (9). For example, in Europe, estimated increases every 5 years for non–Hodgkin’s lymphoma incidence range from 15% to 40% (10). More modest increases in multiple myeloma in many parts of the world have been noted (11). The reported trends for chronic lymphocytic leukemia (CLL) have been less consistent with possible increases in the United Kingdom (12) and decreases in the United States (13). Whereas Hodgkin’s lymphoma has been declining in the elderly in the United States and Europe, the incidence of Hodgkin’s lymphoma among adolescents and young adults has been increasing over the past few decades in the United States (14) and in Nordic countries (15). No studies of anticipation to date have accounted for the secular disease trends in lymphoproliferative cancers.

Although some studies have reported anticipation among familial lymphoproliferative cancers (3, 16-20), our preliminary results on CLL from the Swedish Family Cancer Database, a population-based sample, did not support these findings (21). Thus, we have conducted a more detailed study of anticipation in lymphoproliferative tumors including non–Hodgkin’s lymphoma, Hodgkin’s lymphoma, CLL, and multiple myeloma using registry data from Sweden and Denmark. We applied marginal survival models to test for generational effects and account for changes in incidence rates of lymphoproliferative tumors by incorporating a time-varying covariate for period of diagnosis into the models. Our investigation is unique because of the large, population-based...
databases from which we drew our samples, the high-quality registry-based cancer diagnoses identified over the course of 40 years, and a careful account of the potential sources of bias in the analysis.

**Materials and Methods**

**Study Population.** Each of the four lymphoproliferative data sets was created from the Swedish Family Cancer Database, and by linking the Danish Cancer Registry and the Danish Central Population Registry, described below and elsewhere (22, 23). Each data set included parents and offspring of all subjects with a diagnosis of non–Hodgkin’s lymphoma, Hodgkin’s lymphoma, multiple myeloma, or CLL recorded in the respective database. We classified relatives as affected if they had a first, second, or third primary cancer registration involving the tumor of interest. For those families with more than one affected member, the family was duplicated so to include each case as a proband in the data set.

**Swedish Family Cancer Database.** Sweden maintains a multigenerational registry of individuals born since 1932 along with those parents who were linkable to these individuals. This multigenerational registry has been linked to the Swedish Cancer Registry, which was established in 1958, to create the Swedish Family Cancer Database. Approximately 50% of the offspring in the multigenerational database who died before 1991 (and 12% of offspring with malignant disease) do not have links to their parents. All offspring who died before 1960 are missing from the Swedish Family Cancer Database. The version of the Swedish Family Cancer Database from which we drew our samples contains 10.2 million people, which includes 75% of all cancers registered between 1958 and 1998 in the Swedish Cancer Registry, and has been linked with the Swedish national census and death notification databases to obtain information on vital statistics and demographic characteristics. For this study, we selected cases with a first primary diagnosis of any of the four lymphoproliferative tumors listed above.

**Danish Registry.** Similar familial samples were obtained using the Danish Cancer Registry and the Danish Central Population Registry. The Danish Cancer Registry was established nationwide in 1943 but we limited the selection of lymphoproliferative tumor cases to those diagnosed after April 1, 1968 to improve the chances that the cases could be linked to relatives using the Central Population Registry. The Central Population Registry contains links of offspring to parents (and vice versa) starting with all children born in 1968 as well as linkages among family members who were living at the same address in 1968. Approximately 37% of the lymphoproliferative cases that we selected from the Danish Cancer Registry were linkable to relatives.

**Statistical Methods.** To assess anticipation, we used survival methods to evaluate risk for each of the four lymphoproliferative cancers by relative type (parent, offspring). The outcome of interest was age at diagnosis of the respective lymphoproliferative cancer. Censoring events were age of death, emigration, or the end of the data acquisition period (1998 for Sweden and 1997 for Denmark). The person-time for each individual was censored at age 85. We used the Kaplan-Meier method to estimate unadjusted probabilities of all outcomes among parents and offspring. Unadjusted comparisons between parents and offspring were based on the log-rank test for the respective lymphoproliferative cancer. The \( P \) value for the log-rank test does not account for the correlations between family members, and therefore over-estimates significance.

To account for staggered entries and censored data as well as adjust for potential confounding variables in the relationship between age at diagnosis and relative type, we used Cox proportional hazards models (24). We modeled \( t_y \), the age at diagnosis of a disease or the age at censoring for member \( j \) in family \( i \), by marginal proportional hazards model, \( \lambda(t_{y} | X_y, Z_y) = \lambda_0(t_{y}) \exp(\beta X_y + \gamma Z_y) \). The term \( \lambda_0 \) represents the arbitrary baseline hazard function, \( X_y \) denotes the measured covariates for a given individual (in our analysis, gender and country), and \( Z_y \) represents type of relative (0 for offspring, 1 for parent).

To test the null hypothesis \( H_0: \gamma = 0 \) (i.e., hazards ratio = 1) evaluates a difference in relative hazard between parents and offspring. The parameter \( \beta \) and \( \gamma \) were estimated under the working independence assumption (PROC PHREG, SAS Version 8.02, SAS, Inc., Cary, NC). An individual entered the risk period at the start of the registry or birth, accommodated in the model by the “entry” statement. A robust sandwich estimate for the covariance matrix that sums the cross product of the scored residuals for each family cluster was used to account for the correlations between family members in this analysis. Further details can be found in Pfeiffer et al. (25).

To address secular trends, we assumed that individuals diagnosed before 1985 had a different hazard than individuals diagnosed after 1985. This difference in risk was accommodated in the survival model by a time-varying covariate that was set to 0 before 1985 and changed to 1 after 1985. The risk thus changed for individuals born before 1985 but diagnosed after that year, whereas for subjects born and diagnosed before 1985 and for those born after 1985, the hazard was constant. We used 1985 as a cut point to capture periods of high and low risk based on reported trends of non–Hodgkin’s lymphoma rates (the lymphoproliferative cancer with the greatest change in incidence over time) in Surveillance, Epidemiology, and End Results. Alternative cut points and a nonlinear period variable were considered to assess sensitivity of the model. As SAS 8.0 does not allow one to compute robust variance estimates when time-varying covariates are included in the model, we used a bootstrap procedure that resampled families to obtain variance estimates (25). Quantiles of the bootstrap empirical distribution function were used to obtain 95% confidence intervals (95% CI).

We also tested for anticipation following a nonparametric approach developed by Rabinowitz and Yang (26) based on parent-offspring pairs rather than parents and offspring of the proband. We only applied this method to the non–Hodgkin’s lymphoma data (no truncation) due to limited numbers of pairs for the other lymphoproliferative cancers. To briefly summarize, let \( C_p \) and \( C_c \) denote the ages at enrollment for the parent and offspring, respectively, and \( T_p \) and \( T_c \) the ages at diagnosis for the parent-offspring pair. Rabinowitz and Yang (26) defined two test statistics to assess exchangeability of the ages of diagnosis for parents and offspring as:

\[
T_1 = \sum \{ I(T_{ci} < T_{pi}) - 0.5 \} \max(T_{ci}, T_{pi}) \leq \min(C_{ci}, C_{pi})
\]

\[
T_2 = \sum \{ I(T_{cj} < T_{pj}) - 0.5 \} \max(T_{cj}, T_{pj}) \leq \min(C_{cj}, C_{pj})
\]

Under the null hypothesis, both test statistics have mean 0. The 95% CIs were computed using the empirical bootstrap distribution function of the respective test statistic. For other details of the distributional properties of the two statistics, see Rabinowitz and Yang (26).
Table 1 identifies the number of lymphoproliferative cases diagnosed in Denmark and Sweden and the number of parents and offspring for each sample. As expected from population rates, the largest samples of relatives were parents and offspring of subjects with non–Hodgkin’s lymphoma. From Sweden, 87 non–Hodgkin’s lymphoma probands had either a parent or an offspring that was affected with non–Hodgkin’s lymphoma. Relatives of non–Hodgkin’s lymphoma and Hodgkin’s lymphoma subjects were pooled from both Swedish and Danish registries. For CLL and multiple myeloma, we did not have a sufficient number of informative relatives in the Danish sample. Therefore, only those relatives from Sweden were included in the analysis for these two lymphoproliferative cancers.

Figures 1-4 display the Kaplan-Meier curves comparing ages at diagnosis for parents and offspring for each lymphoproliferative cancer. No significant differences in the age at diagnosis by relative type were identified by the log-rank test for Hodgkin’s lymphoma, CLL, and multiple myeloma. However, a significant difference was found in the survival curves between parents and offspring for non–Hodgkin’s lymphoma ($P < 0.0001$), suggesting that the offspring have earlier ages at diagnosis for non–Hodgkin’s lymphoma than parents.

Table 2 displays the results of our initial models assessing the difference in hazard for each lymphoproliferative cancer between parents and offspring (Model 1). Before fitting the Cox proportional hazards model, we checked the proportionality assumption of the hazards for parents and offspring. Although the proportional hazards assumption was appropriate for the Hodgkin’s lymphoma, CLL, and multiple myeloma data sets, we censored both parent and offspring ages at diagnosis at 66 years to meet the proportional hazards assumption for the non–Hodgkin’s lymphoma data set.

As was indicated by the Kaplan-Meier curves, a difference in hazard by type of relative was evident in the time-to-event analysis for the non–Hodgkin’s lymphoma sample. The hazard ratio for parents was 0.5 times (95% CI, 0.33-0.75) the hazard for offspring after adjusting for gender and country. No significant difference in age at diagnosis for Hodgkin’s lymphoma, CLL, and multiple myeloma among parents and offspring was noted after adjusting for gender and country. Because the non–Hodgkin’s lymphoma data set was sizable, we were able to explore birth cohort effects. We divided the parents and offspring into two birth cohorts—those born before 1941 and those born during or after 1941. No significant birth cohort effect was observed (hazard ratio, 1.26; 95% CI, 0.80-1.98). Moreover, adjusting for the effect of birth cohort did not change the significant relative effect (hazard ratio, 0.54; 95% CI, 0.34-0.85) seen in Model 1. That is, the difference in risk for non–Hodgkin’s lymphoma by age at diagnosis between parents and offspring was not explained by the offspring generation being exposed to a risk factor at an earlier age than the parental generation.

Table 1. Number of cases among parents and offspring of subjects with respective cancer registered in the Swedish and Danish family cancer databases

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Proband Sweden</th>
<th>Proband Denmark</th>
<th>Parents Sweden</th>
<th>Parents Denmark</th>
<th>Offspring Sweden</th>
<th>Offspring Denmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non–Hodgkin’s lymphoma</td>
<td>19,651</td>
<td>6,290</td>
<td>87</td>
<td>11</td>
<td>87</td>
<td>11</td>
</tr>
<tr>
<td>No non–Hodgkin’s lymphoma</td>
<td>8,335</td>
<td>2,152</td>
<td>9</td>
<td>4</td>
<td>38,646</td>
<td>11,348</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>5,047</td>
<td>2,429</td>
<td>4,309</td>
<td>2,122</td>
<td>7,749</td>
<td>3,590</td>
</tr>
<tr>
<td>No Hodgkin’s lymphoma</td>
<td>9,221</td>
<td>2,130</td>
<td>15</td>
<td>15</td>
<td>1,562</td>
<td>19,496</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>5,918</td>
<td>1,837</td>
<td>15</td>
<td>15</td>
<td>20</td>
<td>2,067</td>
</tr>
<tr>
<td>No multiple myeloma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>12,314</td>
</tr>
<tr>
<td>CLL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>2,067</td>
</tr>
<tr>
<td>No CLL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>12,314</td>
</tr>
</tbody>
</table>

Figure 1. Kaplan-Meier curves comparing age at diagnosis for non–Hodgkin’s lymphoma among parents and offspring registered in the Swedish and Danish Family Cancer Databases.
Table 2 also presents the results of the survival models that accounted for changes in incidence over time for all lymphoproliferative cancers (Model 2). For non–Hodgkin’s lymphoma, a significant period effect was observed. Risk of non–Hodgkin’s lymphoma was 2.69 times (95% CI, 1.65-4.39) higher after 1985 than before 1985. Moreover, after adjusting for gender, country, and period of diagnosis, there was no difference in risk for non–Hodgkin’s lymphoma between parents and offspring. Indeed, anticipation was no longer evident once the trend in non–Hodgkin’s lymphoma incidence had been accounted for in the model. These results were not sensitive to specific period cut points or to the nonlinear period variables (results not shown). The nonparametric approach based on parent-offspring pairs developed by Rabinowitz and Yang (26) corroborated this null finding with $T_1 = 0.5$ (95% CI, 1.5 to 1.5) and $T_2 = 0.5$ (95% CI, 7.5 to 5.0).

For Hodgkin’s lymphoma, we found no effect of relative type when secular trends were ignored (see Table 2). However, when period of Hodgkin’s lymphoma diagnosis was entered into the model, we found that parents had a higher risk than offspring (although nonsignificant), which is opposite to what would be expected if there was anticipation. In addition, a significant period effect was observed for relatives diagnosed with Hodgkin’s lymphoma after 1985 compared with those diagnosed before 1985. We plotted the distribution for Hodgkin’s lymphoma age at diagnosis among offspring and parents separately. We observed the bimodal distribution expected for Hodgkin’s lymphoma among the parents but only observed a unimodal distribution for the offspring (the oldest offspring was 52.5 years). Thus, the elevated risk for Hodgkin’s lymphoma among parents compared with offspring may be due to the right censoring of offspring.

For CLL and multiple myeloma, there were no effects of relative type whether or not the period effect was included in the model (Table 2). Thus, there is no evidence for anticipation for these two tumor types.

**Discussion**

This study did not find evidence of anticipation in non–Hodgkin’s lymphoma, Hodgkin’s lymphoma, CLL, or multiple myeloma.
myeloma in population-based samples. Our findings contradict several published articles that reported anticipation in familial non–Hodgkin’s lymphoma (18), CLL (3, 17, 19, 20), and Hodgkin’s lymphoma (16). However, most of these findings relied on data from multiplex families that had been ascertained for genetic studies. Such families are informative for genetic studies only when multiple affected individuals are alive. Thus, this selection process may lead to preferential inclusion of families with later-onset parents and early-onset offspring and thus cause bias in the observed ages at diagnosis. In contrast, our data stem from two large population-based studies with long periods of follow-up.

Shugart et al. (16) reported anticipation in Hodgkin’s lymphoma and non–Hodgkin’s lymphoma using an earlier version of the Swedish Cancer Family Database by comparing the mean age-at-onset of parents and offspring. Although Shugart et al. (16) did stratify by parent birth cohort, they did not incorporate changes in non–Hodgkin’s lymphoma incidence and right censoring. The results from our report highlight the importance of accounting for non–Hodgkin’s lymphoma incidence trends when evaluating anticipation in non–Hodgkin’s lymphoma families. Our initial results from the Kaplan-Meier and Cox proportional hazards model for non–Hodgkin’s lymphoma were consistent with the anticipation hypothesis. Birth cohort, as defined in our study, did not explain the differences in hazard between parents and offspring in this population. However, once we accounted for the changes in non–Hodgkin’s lymphoma incidence over time, the difference between ages at diagnosis of parents and offspring disappeared. This is the first study to consider the changes of non–Hodgkin’s lymphoma incidence over time as a source of bias when evaluating anticipation in lymphoproliferative cancers.

No differences in age at diagnosis of CLL and multiple myeloma among parents and children were observed. Accounting for incidence trends did not alter the initial null results, which is consistent with the lack of significant secular trends in CLL and multiple myeloma incidence. We observed a nonsignificant increase in Hodgkin’s lymphoma hazard for parents compared with offspring as well as a significant period effect for Hodgkin’s lymphoma diagnosis. The nonsignificant increase in Hodgkin’s lymphoma hazard for parents may be due to premature censoring of the follow-up time among offspring. Instead of the typical bimodal distribution for Hodgkin’s lymphoma, we observed a unimodal distribution among the offspring, which suggests the follow-up time for some offspring was truncated before the period of Hodgkin’s lymphoma risk was complete. The increase in Hodgkin’s lymphoma hazard in later periods in our study may reflect the reported increase in Hodgkin’s lymphoma incidence among younger individuals and a decrease in Hodgkin’s lymphoma incidence among older individuals, between 1978 and 1997, in Nordic countries (15).

We also used a method by Rabinowitz and Yang (26) to test for anticipation among parent-offspring pairs in the non–Hodgkin’s lymphoma sample. The ages at diagnosis of parents

Table 2. Hazard ratio for parents compared with offspring of subjects with respective cancers registered in the Swedish and Danish family cancer databases

<table>
<thead>
<tr>
<th></th>
<th>Non–Hodgkin’s lymphoma*</th>
<th>Hodgkin’s lymphoma</th>
<th>Multiple myeloma</th>
<th>CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offspring</td>
<td>1.0 (baseline)</td>
<td>1.0 (baseline)</td>
<td>1.0 (baseline)</td>
<td>1.0 (baseline)</td>
</tr>
<tr>
<td>Parent</td>
<td>0.50 (.33-.75)</td>
<td>1.55 (.73-3.29)</td>
<td>0.67 (0.19-2.30)</td>
<td>0.92 (0.28-3.00)</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offspring</td>
<td>1.0 (baseline)</td>
<td>1.0 (baseline)</td>
<td>1.0 (baseline)</td>
<td>1.0 (baseline)</td>
</tr>
<tr>
<td>Parent</td>
<td>0.99 (0.52-1.69)</td>
<td>2.69 (0.81-7.25)</td>
<td>0.64 (0.00-2.73)</td>
<td>1.16 (0.23-2.93)</td>
</tr>
<tr>
<td>Pre-1985</td>
<td>1.0 (baseline)</td>
<td>1.0 (baseline)</td>
<td>1.0 (baseline)</td>
<td>1.0 (baseline)</td>
</tr>
<tr>
<td>Post-1985</td>
<td>2.69 (1.53-4.70)</td>
<td>3.50 (1.20-9.50)</td>
<td>0.96 (0.44-2.24)</td>
<td>1.29 (0.33-3.47)</td>
</tr>
</tbody>
</table>

NOTE: Both models were adjusted for gender and country.
*Person time truncated at age 66.
1 Sandwich variance.
2 Bootstrap variance.
and offspring for non–Hodgkin’s lymphoma were exchangeable. The results from this analysis provide further support for our null findings. We were not able to apply the Rabinowitz and Yang method to CLL, multiple myeloma, and Hodgkin’s lymphoma due to small numbers of informative parent-offspring pairs.

One potential limitation of our study is the lack of histologic information that would allow us to subtype the lymphoproliferative cancers. Both registries began including histology codes only in more recent years and do not include information on immunophenotype, morphology, cytogenetics, cytochemistry, or other important aspects incorporated into the recent WHO classification of hematopoietic neoplasms and related disorders (27). Thus, we cannot eliminate the possibility that anticipation may exist among the various subtypes of the lymphoproliferative cancers.

Our use of the proportional hazards model to test for anticipation was appropriate for this study because the survival curves (once the non–Hodgkin’s lymphoma data was truncated) met the proportional hazards assumption in each of our four data sets. However, this modeling approach to test anticipation may not be ideal for all data sets. Anticipation may result in no cumulative difference in lifetime hazard but a shift in the age at onset distributions causing a violation of the proportional hazards assumption. In this case, a more flexible model, such as the accelerated failure time model, should be considered.

In summary, we have found no evidence for anticipation in non–Hodgkin’s lymphoma, Hodgkin’s lymphoma, CLL, and multiple myeloma. Our data stem from two large population-based registries, and therefore are less susceptible to ascertainment bias. By using marginal survival methods, we were able to evaluate anticipation and account for other risk factors, staggered entries, censored data, and correlations among relatives. This analysis shows the importance of accounting for changes in incidence trends when evaluating anticipation.

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References

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