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The utility of t(14;18) in understanding risk factors for non-Hodgkin lymphoma

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Abstract

Characteristic chromosomal abnormalities are associated with specific histologic subtypes of non-Hodgkin lymphoma (NHL). The chromosomal translocation t(14;18)(q32;q21) is one of the most common chromosomal abnormalities in NHL, occurring in 70–90% of cases of follicular lymphoma, 20–30% of diffuse large B-cell lymphoma, and 5–10% of other less common subtypes. The t(14;18)-positive NHL may represent a homogenous group and, consequently, increase etiologic specificity in epidemiologic studies. Although the t(14;18) has important clinical ramifications, its etiologic significance remains to be determined. Two population-based, case-control studies addressed this issue by evaluating potential risk factors for t(14;18)-positive and t(14;18)-negative subgroups of NHL. Both studies found that the association between pesticide exposures and risk of NHL was largely limited to t(14;18)-positive NHL cases. However, the findings regarding cigarette smoking, family history of hematopoietic cancer, and hair dye use were not entirely consistent. These results indicate that defining subgroups of NHL according to t(14;18) status may be useful for etiologic research, particularly for exposures that are genotoxic or may contribute to the development of NHL through pathways involving the t(14;18). Studies to further evaluate these associations and delineate the effects of various exposures in other genetically-defined subgroups of NHL are warranted.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) includes many different subtypes with a variety of different molecular characteristics (1). The patterns of change in the incidence of NHL over the past 30 years vary across the different subtypes (2), suggesting differences in etiologic factors (3). Non-Hodgkin lymphoma is presently classified according to the new World Health Organization (WHO) classification, which reflects the postulated cell lineage and stage of differentiation (1). However, many of the WHO-defined subtypes remain heterogeneous at the molecular level (4–6). Whether or not molecularly-defined subgroups of NHL have etiologic significance is largely unknown. Two epidemiologic studies (7–10) have addressed this issue

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by evaluating potential risk factors for t(14;18)-positive and t(14;18)-negative subgroups of NHL. This paper describes the rationale for integrating molecular characteristics with epidemiologic data, summarizes the findings from these two epidemiologic studies, and suggests some lessons to be learned from the use of this novel approach.

Chromosomal Abnormalities

Non-Hodgkin lymphoma arises when reciprocal rearrangements of B-cell immunoglobulin or T-cell receptor genes occur with oncogenes within immature lymphoid cells in the bone marrow or more mature cells in the peripheral lymphoid organs (11,12). These chromosomal translocations often result in the overexpression of oncogenes and cause the cells to become malignant and proliferate in an uncontrolled manner (12). Characteristic chromosomal abnormalities are often associated with specific histologic subtypes of NHL (13–15). These include the t(14;18)(q32;q21), t(2;18)(p11;q21), and t(18;22)(q21;q11) involving the *BCL2* proto-oncogene in follicular lymphoma and diffuse large B-cell lymphoma; t(3;14)(q27;q32) and other translocations of 3q27 involving the *BCL6* proto-oncogene in follicular lymphoma and diffuse large B-cell lymphoma; t(8;14)(q24;q32), t(2;8)(p11;q24), t(8;22)(q24;q11) involving the *C-MYC* proto-oncogene in Burkitt lymphoma and diffuse large B- cell lymphoma; and the t(11;14)(q13;q32) involving the *BCL1* proto-oncogene in mantle cell lymphoma (13,16). There is convincing evidence suggesting that NHL can be subdivided on the basis of these non-random chromosomal translocations (17). However, the etiology of these translocations remains unknown.

One of the most common chromosomal abnormalities in NHL is the t(14;18)(q32;q21), which occurs in 70–90% of cases of follicular lymphoma, 20–30% of diffuse large B-cell lymphoma, and 5–10% of other less common subtypes (1,13,15). The t(14;18) joins the *BCL-2* gene on chromosome 18 to the immunoglobulin heavy chain gene on chromosome 14, leading to an inhibition of programmed cell death through *BCL2* overexpression and, consequently, prolonged survival of the affected B cells (17). The t(14;18) has important clinical ramifications. Patients with germinal center B cell-like diffuse large B-cell lymphoma, which is typically associated with the t(14;18)(q32;q21) and *BCL2* over-expression, have better survival than patients of activated B cell-like diffuse large B-cell lymphoma, which lack the t (14;18)(q32;q21) (18,19). Recently, two epidemiologic studies have explored whether defining subgroups of NHL according to presence or absence of the t(14;18) also has etiologic significance (7–10).

Integrating t(14;18) Status with Epidemiologic Data

The first study was conducted by Schroeder and colleagues (9,10) using a population- based, case-control study conducted in Iowa and Minnesota between 1981–83 as the data source. The parent study included 622 cases and 1,245 controls and was limited to men. Tumor blocks were retrieved for 248 of the 622 cases (40%) in the parent case-control study. The presence of the t(14;18) was determined by a polymerase chain reaction (PCR) method that detected translocations involving the major breakpoint region in chromosome 18, and 182 of the 248 blocks (73%) were successfully assayed. In total, 37% (68) of these cases were t(14;18)-positive and 114 were t(14;18)-negative.

The second study was conducted by Chiu and colleagues (7,8) using a population-based, case-control study conducted in Nebraska between 1983–86 as the epidemiologic data source. The parent case-control study included 385 cases and 1,432 controls and included both men and women. Tumor blocks were obtained for 175 of the 385 cases (45.5%) in the parent study. Fluorescence *in situ* hybridization (FISH) analysis was used to determine the t(14;18). FISH analysis was successfully conducted on 172 of the 175 cases (98.3%). In total, 37% (64) of the

cases were t(14;18)-positive, and 62% (108) were t(14;18)-negative. The prevalence of t (14;18)-positive NHL was comparable in these two studies (7–10).

Risk factors evaluated in these two epidemiologic studies include agricultural activities and exposures, cigarette smoking, hair dye use, and a family history of hematopoietic cancer. These risk factors have been associated with a higher risk of NHL (3,20–30). In some studies, these risk factors were not associated, or only weakly associated with risk of NHL overall, but were specifically associated with risk of either follicular lymphoma, diffuse large B-cell lymphoma, or chronic lymphocytic leukemia/small lymphocytic lymphoma (21–23,25,28–31). There is also evidence that these risk factors may be associated with development of t(14;18). Farmers who are exposed to pesticides have an increased prevalence of the t(14;18) during the high pesticide use period (32) and the use of pesticides was more common among t(14;18)-positive individuals (33–35). One study found that the frequency of *BCL2* translocations was 3.6-fold higher in heavy smokers than in nonsmokers (36). In that study, greater smoking was associated with a higher frequency of the t(14;18). Thus, Schroeder and colleagues (9,10) and Chiu and associates (7,8) proposed that defining subtypes of NHL according to t(14;18) status may increase the etiologic specificity relative to all NHL combined, and allow risk factors to be better identified because cases with t(14;18) may be more closely related etiologically than NHL cases as a whole.

Risk Factors for t(14;18)-defined Subgroups of NHL

Agricultural activities

Studies in Iowa/Minnesota and Nebraska both found a consistent pattern of greater risk for t (14;18)-positive NHL than t(14;18)-negative associated with agricultural exposures (8,9). In the Iowa/Minnesota study (9), t(14;18)-positive NHL was associated with farming (odds ratio (OR)=1.4; 95% confidence interval (CI)=0.9–2.3) and exposures to fungicides (OR=1.8; 95% CI=0.9–3.6) as well as a few specific pesticides, including dieldrin (OR=3.7; 95% CI=1.9–7.0), lindane (OR=2.3; 95% CI=1.3–3.9), toxaphene (OR=3.0; 95% CI=1.5–6.1), and atrazine (OR=1.7, 95%CI=1.0–2.8), whereas there were no such associations with t(14;18)-negative NHL. In the Nebraska study (8), the risk of t(14;18)-positive NHL was significantly elevated among farmers who used animal insecticides (OR=2.6; 95% CI=1.0–6.9), crop insecticides (OR=3.0; 95% CI=1.1–8.2), herbicides (OR=2.9; 95% CI=1.1–7.9), and fumigants (OR=5.0; 95% CI=1.7–14.5), compared with farmers who never used pesticides. None of these categories of pesticides were associated with t(14;18)-negative NHL. Consistent with the findings of Schroeder and colleagues (9), Chiu et al. (8) also found that the risk of t(14;18)-positive NHL was elevated among farmers using dieldrin (OR=2.4; 95% CI=0.8–7.9), toxaphene (OR=3.2; 95% CI=0.8–12.5), and lindane (OR=3.5; 95% CI=1.4–8.4), compared with non-farmers. In addition, the risk of t(14;18)-positive NHL associated with insecticides and herbicides increased with longer duration of use. The Iowa/Minnesota study (9) used non–farmers and farmers without exposures as the referent group, whereas the Nebraska study (8) used farmers who never used pesticides as the referent group. When the same definition for the referent group was applied to the Nebraska data, the researchers found that the ORs for t(14;18)-positive NHL became smaller but remained statistically significant, whereas the ORs for t(14;18)-negative NHL were essentially unchanged.

Cigarette smoking

The results on tobacco product use from the Iowa/Minnesota (10) and Nebraska (7) studies are not entirely consistent. In the Iowa/Minnesota study in men (10), cigarette smoking was not associated with either t(14;18)-positive NHL (OR=1.3; 95% CI=0.8– 2.2) or t(14;18)-negative NHL (OR=1.0; 95% CI=0.7–1.4). The Nebraska study (7) also found no association between cigarette smoking and risk of either t(14;18)-positive or t(14;18)-negative NHL among men.

However, among women, there was a positive association between cigarette smoking and risk of t(14;18)-negative NHL (OR=1.7; 95% CI=0.9–3.4 for ex-smokers and OR=2.1; 95% CI=1.1–4.4) for current smokers compared with never smokers) (7). The risk increased with longer duration of use (OR=2.1 for having smoked >30 years; 95% CI=1.1–4.1) and early initiation (OR=2.2 for starting smoking at <20 years-of-age; 95% CI=1.1–4.4).

Family history of hematopoietic cancer

In the Iowa/Minnesota study (10), a family history of hematopoietic cancer among first-degree relatives was associated with t(14;18)-negative NHL (OR=2.4; 95% CI=1.4–3.9), but not t (14;18)-positive NHL (OR=1.3; 95% CI=0.5–3.3). In the Nebraska study (7), in both men and women, a positive family history of hematopoietic cancer among first-degree relatives was non-significantly associated with an approximately two-fold higher risk of both t(14;18)-positive NHL and t(14;18)-negative NHL compared to those with no family history of hematopoietic cancer. The point estimates changed little when analyses combined men and women (OR=2.1 for t(14;18)-positive NHL, 95% CI=0.8– 5.2; and OR=1.9 for t(14;18)-negative NHL, 95% CI=1.0–3.8).

Hair dye use

In the Iowa/Minnesota study (10), hair dye use was associated with both t(14;18)-positive NHL (OR=1.8; 95% CI=0.9–3.7) and t(14;18)-negative NHL (OR=2.1; 95% CI=1.3–3.4) among men. In contrast, in the Nebraska study (7) hair dye use was not associated with either t(14;18)-positive NHL or t(14;18)-negative NHL among men or women. However, the use of permanent dyes was associated with a nonsignificant increased risk of t(14;18)-negative NHL among Nebraska women (OR=1.4; 95% CI=0.7–2.7).

Lessons Learned and Future Directions

In a recent editorial, Potter (37) suggested that "*it is essential to work toward a better* molecular classification of disease, particularly of cancer, rather than continue to rely *extensively on histopathology*." The recent studies by Schroeder et al. (9,10) and Chiu et al. (7,8) represent the first epidemiologic studies of NHL that have defined subgroups of NHL molecularly to investigate risk factors for NHL. Both studies found that the association between pesticide exposure and risk of NHL was limited to t(14;18)-positive NHL cases. In addition, both studies reported no association between smoking and risk of either t(14;18)-defined subtypes of NHL among men. However, there is discrepancy for familial cancer and hair dye use. Because the sample sizes are not large in these two studies, these differences could be just chance variation. The Iowa/Minnesota study (9,10) was limited to men, while the Nebraska study (7,8) included both men and women. It is possible that the distributions of risk factors vary between the two study populations. Furthermore, while the prevalence of t(14;18)-positive NHL is similar between the two studies (i.e., 37% in both studies) (7–10), misclassification of t(14;18) status may be possible in the Iowa/Minnesota study in which PCR was used, a process that might miss t(14;18) breakpoints (38). Nevertheless, the consistent findings for pesticides argue against a significant role that these explanations may play in the discrepancy. Alternatively, findings from these two studies (7–10) suggest that defining subgroups of NHL according to t(14;18) status may be a useful approach for etiologic research only if an exposure involves the development of NHL through a t(14;18) pathway. Specific chromosomal translocations have not been convincingly linked to hair dye use (39) or reported as a feature of familial lymphoma (40). In contrast, a high frequency of the t(14;18) in healthy subjects has been associated with pesticides (32,34), smoking (36,41), organic pollutants such as polychlorinated byphenyls or dioxins (41), hepatitis-C virus infection (42), and ultraviolet levels (41,43). Analytic epidemiologic studies evaluating the association of these exposures with NHL risk might benefit particularly from defining subgroups of NHL according to t(14;18) status.

The findings on cigarette smoking from the Iowa/Minnesota and Nebraska studies (7,10) are not entirely consistent. While both studies found no association between smoking and either t(14;18)-positive or t(14;18)-negative NHL among men, the Nebraska study reported a positive association between cigarette smoking and risk of t(14;18)-negative NHL among women. Because cigarette smoking has been linked to a higher risk of follicular lymphoma (23–25, 44) and diffuse large B-cell lymphoma (26), the two major subtypes that exhibit t(14;18), one might expect a positive association between cigarette smoking and t(14;18)-positive NHL. Again, these may be chance findings due to small sample size. Alternatively, it is possible that smoking-associated risk varies according to chromosomal abnormalities. A study of acute myeloid leukemia found that smoking was positively associated with the t(8;21)(q22;q22) subgroup, but inversely associated with the t(15;17)(q22;q12) subgroup (45). In NHL, it could be that smoking is associated with chromosomal abnormalities other than the t(14;18). Future studies with larger sample size to assess this possibility are warranted.

It remains to be determined whether or not defining NHL subgroups by t(14;18) status is more specific than classifying NHL by histologic subtypes for etiologic research. In the Nebraska study (7,8), the researchers also compared ORs for t(14;18)-positive NHL versus t(14;18)-negative NHL using multivariate polytomous logistic regression where the dependent variable was treated as a three-level variable (i.e., t(14;18)-positive NHL, t(14;18)-negative NHL, and controls), and the logit estimator always compared t(14;18)-defined NHL subtypes with controls. The researchers found that the associations of pesticides and cigarette smoking (women only) differed significantly between t(14;18)-positive NHL and t(14;18)-negative NHL (p-difference <0.05) (7,8). In contrast, the associations with a family history of hematopoietic cancer and hair dye use were similar between t(14;18)-positive and t(14;18)-negative NHL (7). The researchers also classified the 175 cases in the Nebraska study from whom tumor blocks were available according to the new WHO classification (1). They found that neither agricultural pesticide use, smoking, or hair dye use were associated with follicular NHL or diffuse large B-cell NHL, and a positive family history of hematopoietic cancer was associated with follicular NHL but not diffuse large B-cell NHL. These findings are not entirely consistent with those observed using the molecular cytogenetic approach in that pesticide use was associated with t(14;18)-positive NHL but not t(14;18)-negative NHL, smoking was associated with t(14;18)-negative NHL but not t(14;18)-positive NHL among women, and a family history of hematopoietic cancer was associated with t(14;18)-positive and t(14;18)-negative NHL in both men and women. Together, these findings suggest that defining subsets of NHL by t(14;18) status may add additional information to etiologic research. Unfortunately, the sample size in the Nebraska study is not large enough for additional comparisons (i.e., ORs between t(14;18)-defined subgroups within follicular lymphoma as well as ORs between t(14;18)-defined subgroups within diffuse large B-cell lymphoma), which might be the most appropriate way of evaluating whether defining NHL according to t(14;18) status is more specific than classifying NHL by histologic subtypes.

The presence of the t(14;18) is not sufficient for the development of NHL because it occurs in healthy individuals at a frequency of 10–50%, a range that may be partially dependent on the PCR technology used (15). The causes of the t(14;18) remain largely unknown, although random events and environmental genotoxins such as chemicals or ionizing radiation have been reported (12). Findings from these two epidemiologic studies (7–10) suggest that pesticides contribute to the development of NHL through pathways involving the t(14;18). However, it remains unclear whether pesticides caused the t(14;18) or provide a second or later hit in lymphoid cells with the t(14;18), that ultimately leads to the occurrence of NHL. Nevertheless, observations from these two epidemiologic studies provide clues for additional research regarding potential exposures that may be important in the long-term evolution of t(14;18)-positive cells.

The two studies reviewed in this paper represent the first epidemiologic studies of NHL that have defined subgroups of NHL molecularly to investigate risk factors for NHL. The findings from these studies are intriguing and suggest that molecular classification of NHL according to t(14;18) status is useful for etiologic research, particularly for exposures that involve the development of NHL through a t(14;18) pathway. Future epidemiologic studies that investigate other chromosomal abnormalities, in addition to the t(14;18), are also warranted since t(14;18)-negative NHL remains a molecularly heterogeneous group. Integrating genetic and epidemiologic data may provide additional new insights concerning the pathogenesis of NHL. In addition, studies with repeated measures of exposures and chromosomal abnormalities are needed to delineate the effects of various exposures in molecularly-defined subgroups of NHL.

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