Malignant Lymphomas

Non-Hodgkin's lymphoma and residential proximity to toxic industrial waste in southern Israel

Environmental exposure has been linked to non-Hodgkin's lymphoma (NHL).[1-7] Toxic volatile compounds were found in groundwater downstream of an industrial site in southern Israel.[8-9] The risk of NHL and clinical characteristics of NHL patients were analyzed in relation to their proximity to the site.

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Pesticides (mainly phenoxyacetic herbicides) are suspected to be major contributors to the etiology of non-Hodgkin's lymphoma (NHL).[1-7] We evaluated the association between residential exposure to toxic industrial waste and the risk of NHL. We studied a site which produces potentially toxic waste and is located near Beer-Sheva, the largest town in southern Israel, with a population of 180,000. The effect of residential exposure was analyzed using a geographic information system (GIS). We hypothesized that the risk of NHL would be higher in the area in close proximity to the site.

Eligible patients were over 18 years of age, with a biopsy-proven NHL, diagnosed during 1985-1999 and who had lived in southern Israel for at least 5 years. The exposed group included patients living within 14 kilometers of the site or along desert-washes. These are creeks with seasonal water flow suspected to contain pollutants that originated in the industrial site and to deliver them to distant areas.[8-9] The main town within the exposure area is Beer-Sheva, located 9 to 14 kilometers from the industrial site. A gradient of exposure within the town was not expected. The unexposed group included all other patients in southern Israel. The data collected included demographic characteristics, addresses at diagnosis and during the previous 10 years, occupation, disease stage and specific histology, International Prognostic Index, risk factors for malignancy (see below), treatment, response rate, disease-free survival and overall survival.

Age-standardized rates were calculated using national data on population composition in selected settlements. GIS analysis was performed using Mapinfo software. Survival was analyzed using the Kaplan-Meier method as well as Cox proportional hazards regression.

Out of 370 eligible patients with NHL, 146 (39.4%) were included in the exposed group and 224 (60.6%) in the unexposed group. There were more cases of NHL observed in the town of Beer-Sheva (141 cases) than expected (105 cases, based on the age-adjusted incidence of NHL in other towns in southern Israel). This gives an age-adjusted odds ratio (OR) of 1.34, 95% CI: 1.12 – 1.56. These findings were significant both for patients living in the exposed area for less than 10 years, (OR=1.29, 95% CI: 1.02-1.55) and for those living in it for more than 10 years (OR=1.51, 95% CI: 1.09-1.94). Figure 1 shows the distribution of patients with NHL according to the GIS analysis.

The groups were similar in terms of age, gender, ethnicity, and occupational exposure. There were no differences regarding lymphoma stage, histology, B symptoms, extranodal disease, International Prognostic Index or cell-type. Evaluated risk factors for malignancy included alcohol abuse, autoimmune diseases, immunosuppressive therapy, previous malignancy, prior chemotherapy or radiation therapy, family history of malignancy, hematologic diseases and immune deficiency. Rates of smoking (44.2% vs. 33.6%, p=0.04) and of blood transfusions (10.9% vs. 2.7%, p=0.001) were significantly higher among exposed patients. Complete response rate, disease-free survival and overall survival did not differ between the two groups. When a multivariate analysis for overall survival was performed, residing within the exposed area did not influence survival (Table 1). We found a possible association

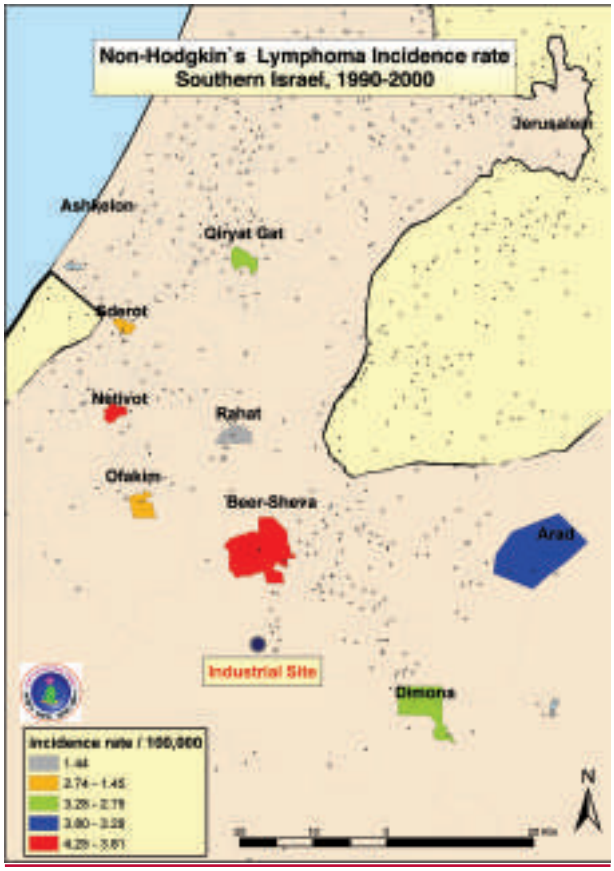

Figure 1. NHL incidence (age-standardized rates) in southern Israel, by settlements, 1990-2000. Major towns with more than 10,000 residents are colored and labeled. Smaller settlements (less than 10,000 residents) are shown as unlabeled black dots.

between the incidence of NHL and groundwater contamination with volatile toxic chemicals. Studies reporting occupational exposure to pesticides found a relative risk of 1.5-2.5 for NHL.[2-7] Therefore, the risk found in the present study, 1.29-1.50, is comparable.

A major limitation of the study is its inherent inability to prove a direct causal association, as no field surveys were performed and no dose-response association could be inferred. Differences between the populations studied, i.e. socioeconomic status, health hazards or exposure to other environmental hazards might exist and were not evaluated. A higher prevalence of smoking and a history of blood transfusions were found in the exposed group, and might partially explain the differences found between the two groups. An association between occupational exposure to pesticides and cytogenetics was previously reported.[10]

Since molecular or cytogenetic studies were not performed in most cases, we could not identify a differential effect of exposure to chemicals on cytogenetic abnormalities. A multivariate Poisson regression model for incidence could not be performed, as data on risk factors for NHL were not available for the population as a whole.

To conclude, this study showed a higher risk of NHL among residents of an area potentially exposed to toxic industrial waste. Causality cannot be deduced from the present study; establishing such an association requires additional studies. The use of GIS for identifying local environmental risk factors for malignancy is likely to increase.

Table 1. Multivariate analysis of overall survival.

(Cox proportional hazards regression)

Variable	*p*	*Hazard ratio*	*95% confidence interval*
Exposure (exposed vs. unexposed)	0.264	0.853	0.645-1.127
Age (increment per year added)	<0.001	1.038	1.028-1.048
Stage (increment per stage)	<0.001	1.324	1.179-1.487
Histology (aggressive vs. indolent)	0.003	1.540	1.164-2.039
Performance status (poor vs. good)	<0.001	2.360	1.730-3.240
Ethnicity (Sephardic Jews vs. other)	0.032	0.739	0.560-0.975

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