

Israeli lifestyle and environment may pose exceptional risks for Hodgkin's lymphoma

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Hodgkin's Lymphoma (HL) is a common malignancy in early adulthood, accounting for approximately 30 percent of all lymphomas (cancers of the lymph system). The incidence of HL in Israel is among the highest in the world: based on GLOBOCAN estimates for 2012, Israeli females have the highest age-standardized incidence rate of HL worldwide, and Israeli males have the second highest worldwide. From 1960 through 2005, Israel experienced a sharp rise in the incidence of HL among Israeli-born Jews of both sexes, with similar rates in the Jewish and non-Jewish populations.

Despite evidence for an environmental etiology, very few risk factors have been identified. Epstein-Barr virus (EBV) infection is causally associated with development of EBV-positive HL, which is common in tropical regions but less common in Israel and other developed countries. Studying immigrant populations provides a means of investigating the relative importance of genetic factors as compared to environmental factors in disease development. Since Israel is a multi-ethnic society to which extensive immigration took place since the establishment of the state in 1948, and in which extensive population data is available over the course of several decades, it provides a unique setting to conduct a large-scale, population-based migrant cohort study.

For this reason, researchers at the Hebrew University-Hadassah Braun School of Public Health and Community Medicine, led by Dr. Hagai Levine and Prof. Jeremy Kark, in collaboration with Dr. Merav Leiba from the Sheba Medical Center, conducted a migrant cohort study to

assess what impact immigration status and origin have on the development of HL in Israelis.

The study, which appears today in the journal *Leukemia and Lymphoma*, included Jewish men and women aged 16 to 19 at examination, with no history of a cancer diagnosis. Nationwide data on 2,285,009 adolescents, collected from 1967-2011, were linked to Israel's Cancer Registry to obtain the incidence of HL until 2012. The study protocol was approved by the Institutional Review Board of the IDF Medical Corps.

During 47 million person-years of follow-up, 2,093 HL cases were detected. Among the cohort of 2.3 million men and women, an association was found between being born in Israel and subsequent occurrence of HL. This association was independent of paternal country of origin, year of birth, sex, socio-demographic characteristics, BMI and height.

Risk of HL was greater for more recent year of birth, higher BMI, taller stature, and apparently for women. These findings suggest that exposure to as yet unidentified elements of the Israeli environment increase the risk of nodular sclerosis HL, and should aid in directing research efforts.

Remarkably, the elevated risk appeared within one generation; the low incidence of HL observed for immigrants from Western Asia was no longer evident among Israeli-born individuals of Asian origin. Among immigrants, there was no difference by age at migration.

The higher risk was driven largely by an elevated risk for the predominant NS subtype of HL (there are four main subtypes as defined by the World Health Organization classification: nodular sclerosis (NS), mixed cellularity (MC), lymphocyte-rich and lymphocyte-depleted).

Thus, the researchers suggest that immigration from a low-risk to a high-

risk location, mostly to locales with a modern lifestyle and environment, is associated with an increase in HL incidence (mainly the NS subtype) within short periods, making genetic drift unlikely as a causal explanation. However, the Israeli life-style and environment, either independently or by gene-environment interaction, may pose exceptional risks for HL, as suggested by the very high and increasing incidence in Israel and the increased risk even among Israeli-born of European origin compared to European-born immigrants.

Dr. Hagai Levine, Head of the Environmental Health Track at the Hebrew University-Hadassah Braun School of Public Health and Community Medicine, explains: "While we still need further studies to identify the specific causes of the high rates of Hodgkin lymphoma among native Israelis, our findings direct us to search for possible environmental causes in Israel and the neighboring countries. These causes could be not only environmental exposures, but also diet, climate, social environment and stress that may be related to chronic regional conflict."

"There is increasing evidence for developmental origins of health and disease, with different possible mechanisms, including epigenetic changes or endocrine disruption. There is also increasing evidence on the role of prenatal stress in offspring development, including cancer development, especially for hematological malignancies. These data suggest that risk of HL (the nodular sclerosis subtype) is possibly increased due to preconception, prenatal or early life exposures to a changing lifestyle and environment and its interaction with susceptibility genes," adds Dr. Levine.

More information: *Leukemia and Lymphoma*, [DOI: 10.1080/10428194.2016.1220552](https://doi.org/10.1080/10428194.2016.1220552)

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