A Sharp Rise in the Incidence of Hodgkin's Lymphoma in Young Adults in Israel

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ABSTRACT: **Background:** Hodgkin's lymphoma is a distinct primary solid tumor of the immune system that shows wide variation in incidence among different geographic regions and among various races. It was previously suggested that susceptible people living in certain parts of Israel had a higher risk of HL because of exposure to unidentified environmental factors in these regions. Compared with other parts of Israel, these regions were characterized by a higher proportion of Israeli-born Jews.

Objectives: To study time trends in the incidence rate of HL in Israeli-born Jews of all age groups during the years 1960–2005.

Results: A total of 4812 Jewish cases of HL were reported to the Israel Cancer Registry during the study period 1960–2005. There has been a persistent increase in the age-standardized incidence rate of HL, all subtypes pooled, in Israeli-born Jews in both men and women. The age distribution pattern in both genders was bimodal in all periods. The highest incidence was observed in the 20–24 year age group: for women (9.13 per 100,000 per year) during the period 1988–1996, and for men (6.60 per 100,000 per year) during the period 1997–2005.

Conclusions: The reported incidence level of HL in Israeli-born young adult Jews in Israel has increased in recent years to high levels compared with other western countries. Our findings suggest a cohort effect to unidentified factors affecting Israeli-born young adult Jews in Israel.

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KEY WORDS: Hodgkin's lymphoma, incidence, time trend, young adults, measles

Hodgkin's lymphoma is a distinct primary solid tumor of the immune system that shows wide variation in incidence among different geographic regions and among various races [1,2]. A unique age-specific incidence of HL, associated with particular clinicopathologial features, characterizes regions of differing socioeconomic levels of development. A bimodal age distribution of HL has been described in many countries, including Israel [3,4]. In these areas of higher socioeconomic standards, the first peak usually occurs in adolescents or young adults, predominantly women, who tend to present with nodular sclerosis HL, often with limited stage of disease and confined to the cervical and mediastinal lymph nodes. The second peak occurs in the sixth and seventh decades and is seen primarily in men.

In 1980, Abramson et al. [5] reported that susceptible people living in certain parts of Israel had a higher risk of HL, suggesting exposure to unidentified environmental factors in these regions Most important, compared with other parts of Israel, these regions were characterized by a higher proportion of Israeli-born Jews. This finding was in contrast to the lower incidence of HL found in other populations in Israel, including new immigrants. The aim of the present population-based study was to study the behavior of HL in Israeli-born Jews in Israel over a longer period. In the present study we report an increase in the incidence rates of HL in this particular group to levels unparalleled in other countries.

HL = Hodgkin's lymphoma

PATIENTS AND METHODS

Cases with histologically confirmed HL were retrieved from the Israel Cancer Registry file, and included all subjects notified and recorded as HL [International Classification of Diseases of Oncology (ICD-9), 201 (World Health Organization, 1979)] during the years 1960–2005. The Israel Cancer Registry utilizes a passive notification system based on routine record linkage with files of the Population Registry, the National Death File and hospital files. The cancer registry data include details of the histological diagnosis and stage of the tumor. No attempt was made to retrieve additional clinical data on HL cases from treating institutions, or to review histological sections. The study population comprised the total Jewish population living in Israel. Demographic data were obtained from the Population Registry, using the national population censuses and annual estimates stratified by ethnic group, gender, and 5 year age group. Incidence rates of HL in Israeli-born Jews were separately calculated for nine age

groups over the following five year-periods: 1960–1969, 1970–1978, 1979–1987, 1988–1996, and 1997–2005. Calculations were based on the direct method of comparison [6].

RESULTS

A total of 4812 Jewish cases of HL were reported to the Israel Cancer Registry during the study period 1960–2005. Age-standardized incidence rates of HL for both Jewish males and females in Israel for the five consecutive periods are presented in Table 1. The incidence rates for men were higher than for women in all five periods. Incidence rates showed a persistent rise in both genders along all five periods. The annual incidence rates and time trends of HL in Israeli-born Jews during the period 1960–2005 are presented in Figure 1. Age-specific incidence rates of HL in Israeli-born Jews during the five periods are separately presented for men and women in Figure 2. The age distribution pattern in both genders is bimodal in all periods. The highest incidence was observed in young adults, the 20–24 year age group: 6.6 per 100,000 per year for men during the years 1997–2005, and 9.13 per 100,000 per year for women during the period 1988–1996. The incidence rate for the age group 25–29 years during the period 1997–2005 was 8.46 per 100,000 per year among women and 6.15 per 100,000 per year among men. The majority of cases belonging to the 15–34 age group in all periods were of the nodular sclerosis histological subtype (data not shown).

Table 1. Number of cases and age-standardized incidence rate (ASR/100,000) of Hodgkin's lymphoma per year in Jews in Israel, by gender and period, 1960–2005

	Male		Female	
Year period	No. of cases	ASR	No. of cases	ASR
1960–1969	246	2.27	215	2.01
1970–1978	335	2.58	295	2.24
1979–1987	440	2.85	401	2.51
1988–1996	613	3.27	613	3.14
1997–2005	841	3.61	813	3.36

ASR = age-standardized rate

Figure 1. Age-standardized incidence rates per 100,000/year of Hodgkin's lymphoma in Israeli-born Jews, by gender 1960–2005 (time-trends by moving average)

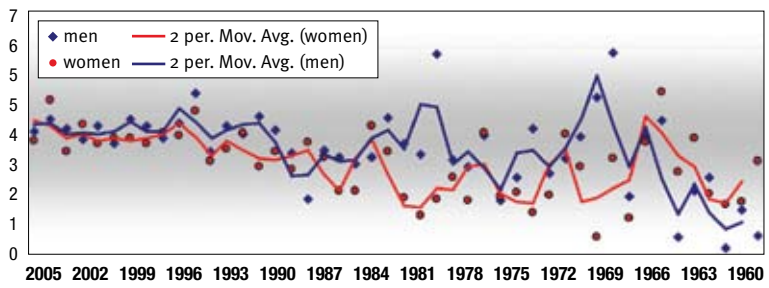
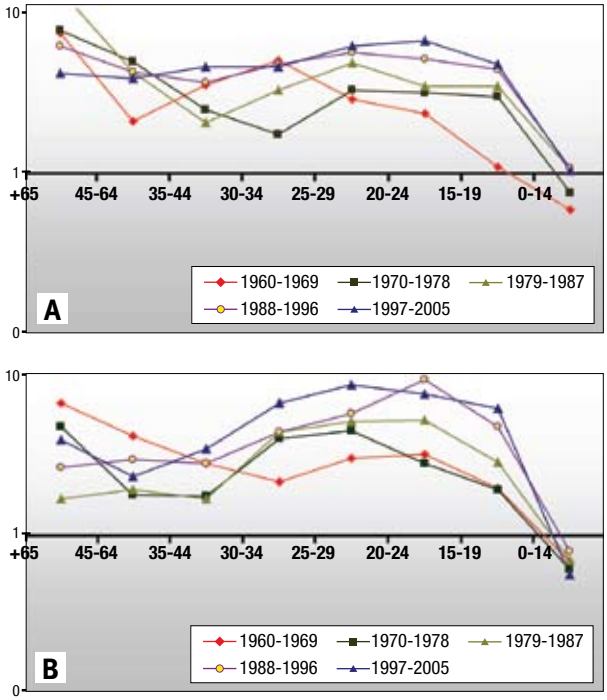


Figure 2. Age-specific incidence rate of Hodgkin's lymphoma in Israeli-born Jews in Israel (rate/100,000) by period), 1960–2005: **[A]** men, **[B]** women



DISCUSSION

Our study shows a persistent increase in the age-standardized incidence rate of HL, all subtypes pooled, in Israeli-born Jews – both men and women – over recent decades. Fewer cases were recorded in older adults, with a parallel decrease in rates, perhaps due to improvement in the diagnosis of HL. In the young adult group, incidence rates climbed to the highest levels in the world [6]. While the rates of HL in women peaked for age 20–24 during the period 1988–1996, during the recent period 1997–2005 rates peaked for the 25–29 age group, suggesting some cohort effect.

Similar trends of increase in the incidence of HL have been observed in many other western countries. A rising trend in the incidence of HL among young adults aged 20–44 was noted in Connecticut during the period 1935–1992 [7]. The incidence increased dramatically among females after 1970 but less significantly among males, and was primarily associated with nodular sclerosis histological subtype. Age-period-cohort analyses indicated that the observed increases in young adults were cohort phenomena to unidentified risk factors. Experience in Canada during the years 1970–1995 showed a more significant increase in the incidence of HL among females aged 10–29 and among males aged 10–24, but a dramatic decrease among older

ages [8]. Age-period-cohort modeling showed that birth cohort and period effects were responsible for the observed trends. In Nordic countries, the incidence of HL increased continuously among adolescents and young adults but decreased among those aged 40 years or more during the years 1978–1997 [9]. In contrast, different patterns of change were reported in the UK for the period 1984–1993, with a fall in incidence in both males and females in all age groups except for males aged 1–24 years [10]. A recent report from Singapore showed a persistent increase among adolescents and young adults during the years 1968–2004 [11]. However, the incidence peak remained considerably lower than among young adults in the western world.

We confirmed the seminal observation of Sacks et al. [3] of a bimodal age distribution pattern in the incidence of HL in the Jewish population in Israel, with the first peak observed in young adults and the second peak above the age of 50. Levels of incidence in the young adult group were higher for females than for males in all periods. These findings indicate that the behavior of HL in the Jewish population in Israel over all periods is similar to that in other industrialized countries [1]. Although HL is among the most common cancers in the young, its causes remain largely unknown. A variety of parameters indicative of higher socioeconomic class has been associated with the first modal peak [12,13]. It has been suggested that HL in young adults may be caused, in some part, by late exposure to a common childhood virus with low oncogenic potential (the "late host response model"). Studies in the UK and California showed that early exposure to infection, including chickenpox, measles, mumps, pertusis and rubella, protects against HL [14,15]. An association between infectious mononucleosis and Epstein-Barr virus-positive subgroup of HL in young adults was suggested [15-17], but the conclusions were inconsistent. Immunohistochemical and molecular studies showed that EBV is related to HL in young adults in only a minority of cases and is unlikely to play a major etiologic role in this age group [18,19]. In a cohort of HL patients from southern Israel, measles virus antigens and EBV-related latent membrane protein-1 were detected in 54% and 31% of biopsies, respectively, suggesting a possible association of measles with HL in this particular population [20,21]. However, the possible contribution of measles or measles outbreaks in Israel to the rise in the incidence of HL observed in our study remains to be clarified.

In conclusion, we report a sharp rise in the incidence of HL in young adult Jews in Israel in recent years, reaching the highest levels in the world. The age distribution pattern remained bimodal in all periods. A cohort effect to unidentified factors is suggested.

EBV = Epstein-Barr virus

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