Time Trends and Sex Patterns in Hodgkin's Disease Incidence in Canada, 1970-1995

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ABSTRACT

Purpose: To examine time trends and sex patterns in Hodgkin's disease incidence in Canada, from 1970 through 1995.

Method: In addition to analyses of the secular trends and sex ratio in incidence rates, age-period-cohort models were fitted to estimate the effects on the trends. Age-specific male/female incidence rate ratios were examined for the disease and for its two major histologic subtypes.

Results: The overall age-adjusted incidence rate of Hodgkin's disease decreased significantly in males (3.5 per 100,000 in 1970-71 to 2.8 in 1994-95) but only slightly in females (2.4 per 100,000 to 2.3). There was a significant increase in the incidence among females aged 10-29 and among males aged 10-24, but a dramatic decrease among older ages. Age-period-cohort modelling showed that birth cohort and period effects were responsible for the observed trends in males and females, respectively.

Conclusion: The risk factors responsible for Hodgkin's disease are different in females and males. Reproductive factors are likely to be associated with the occurrence of the disease in young women.

ABRÉGÉ

But : Examiner les tendances temporelles et les répartitions par sexe de l'incidence de la maladie de Hodgkin au Canada, de 1970 à 1995.

Méthode : En plus des analyses des tendances à long terme et du sex-ratio dans les taux d'incidence, des modèles utilisant des cohortes fondées sur les périodes de la vie ont été intégrés pour estimer les effets sur les tendances. Les ratios d'incidence hommes/femmes pour des groupes d'âge déterminés ont été examinés pour la maladie de Hodgkin et pour deux grands sous-types histologiques.

Résultats : Le taux global d'incidence de la maladie de Hodgkin ajusté en fonction de l'âge a baissé sensiblement chez les hommes (de 3,5 à 2,8 pour 100 000 hommes entre 1970-71 et 1994-95) mais il a peu changé pour les femmes (de 2,4 à 2,3 pour 100 000 femmes). On a observé une augmentation notable de l'incidence parmi les personnes de sexe féminin de 10 à 29 ans et parmi les personnes de sexe masculin de 10 à 24 ans, mais un fléchissement marqué parmi les groupes plus âgés. Les modèles fondés sur les cohortes par périodes de la vie démontraient que les effets des cohortes de naissance et les effets des périodes de la vie étaient responsables des tendances observées chez les personnes d'un sexe comme de l'autre.

Conclusion : Les facteurs de risque responsables de la maladie de Hodgkin sont différents chez les femmes et chez les hommes. Il est probable que des facteurs liés à la reproduction ont un rapport avec l'occurrence de la maladie chez les jeunes de sexe féminin.

Hodgkin's disease is a relatively uncommon malignancy, representing less than 1.0% of all cancer;[1,2] however, it is one of the most common forms of malignancy affecting young adults. An unusual bimodal age-specific incidence curve with peak occurrence at age 20 to 29 years and at age 75 to 84 years supports the "two-disease hypothesis" of Hodgkin's disease causation.[2-5] Epidemiologic studies have identified several factors that increase the risk of developing Hodgkin's disease, including age (young adult), race (Caucasian), family history of Hodgkin's disease, and occupational exposure to wood and some chemicals.[3,5,6] Research has also focussed on specific viruses in the pathogenesis of Hodgkin's disease.[7-9] Molecular genetic studies have found evidence of the Epstein-Barr virus (EBV) genome in malignant cells of approximately half of Hodgkin's disease patients.[3,5,8] Nevertheless, the understanding of the etiology of this lymphoma is incomplete.

A few studies have shown that reproductive factors may play a role in the pathogenesis of Hodgkin's lymphoma, but no association has been established.[4,10,11] In this paper, Canadian cancer registry data were used to examine time trends and gender differences in Hodgkin's disease incidence, with a focus on generating etiologic hypotheses.

METHODS

Data on the incidence of Hodgkin's disease were obtained from the National Cancer Incidence Reporting System (NCIRS) of Statistics Canada, which began collecting data from provincial and territorial cancer registries in 1969. Data for 1992 to 1995 were obtained from the Canadian Cancer Registry (CCR) which replaced the NCIRS in 1992. Data for the province of Quebec were excluded from this analysis because improved reporting procedures were not implemented in Quebec until 1981. In general, cancer registry data included in this study are comparable and reliable. The information regarding the CCR and the quality of Canadian cancer incidence data has been well documented.[12,13] Annual population estimates were obtained from the Demography Division of Statistics Canada.

Information on histologic classification of Hodgkin's disease was not consistently recorded by all provinces and territories in Canada until 1983, although Ontario, Saskatchewan and British Colombia collected such data for previous decades. The combined population of these three provinces accounts for about 60% of the Canadian population. Although several systems of classification and coding for primary site have been used by the registries during the decades of cancer registration, all the records were recoded according to the International Classification of Disease for Oncology (ICD-O). Hodgkin's disease is coded as ICD-O codes 9650-9667.

We contrasted average 3-year age-specific rates by sex for the period 1970-72 with rates for 1993-95. The secular trends in age-adjusted incidence rates as well as male/female rate ratios were modelled using linear regression based on the logarithm of the annual rates.[14] The average annual percent change (AAPC) in Hodgkin's disease incidence was derived

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from the expression [exp (ß)-1]x100, where ß is the regression coefficient. The age-adjusted rates were calculated using direct standardization with the World Standard Population serving as the standard.[15] Male/female incidence rate ratios by age group for all cases of Hodgkin's disease and for the two main histologic subtypes – nodular sclerosis and mixed cellularity – were calculated using the most recent 5 years of data, i.e., from 1991 to 1995. Nodular sclerosis (ICD-O 9663-9667) and mixed cellularity (ICD-O 9652) encompass more than 75% of all Hodgkin's disease cases in those five years.

Based on our preliminary analysis, we focussed our analysis on two particular age groups: one showing increasing incidence (ages 10-24 years among males and 10-29 years among females), and the other decreasing incidence over the study period (ages 25-84 years among males and 30-84 years among females). Analysis integrating age at diagnosis, time period of diagnosis and birth cohort were then performed for the two age groups by sex. Age at diagnosis was grouped into 5-year intervals. The entire period of diagnosis was divided into four 5-year intervals from 1970 through 1989 and two 3-year intervals from 1990 through 1995. Corresponding to these age intervals and time periods, the appropriate number of birth cohorts were derived. The effects of age, time period and birth cohort on Hodgkin's disease incidence were then estimated separately for each sex and the particular age group.

Age-period-cohort models were fitted with the standard Poisson assumption.[16,17] To test the effect of period and cohort individually after controlling for the effect of age, respective two-factor models were compared to the full model. Parameters of the models were estimated by means of the maximum likelihood method with SAS procedure GENMOD (release 6.12, SAS Institute Inc., Cary, NC 1996). The goodness of fit of models was evaluated using the deviance (defined to be twice the difference between the maximum achievable log likelihood and the log likelihood at the maximum likelihood estimates of the regression parameters) and specific effects (such as cohort and period effects) were tested by comparing the difference in deviance between the respective models.

Figure 1. Age-specific incidence rates of Hodgkin's disease per 100,000 males in Canada excluding Quebec, 1970-1972 and 1993-1995

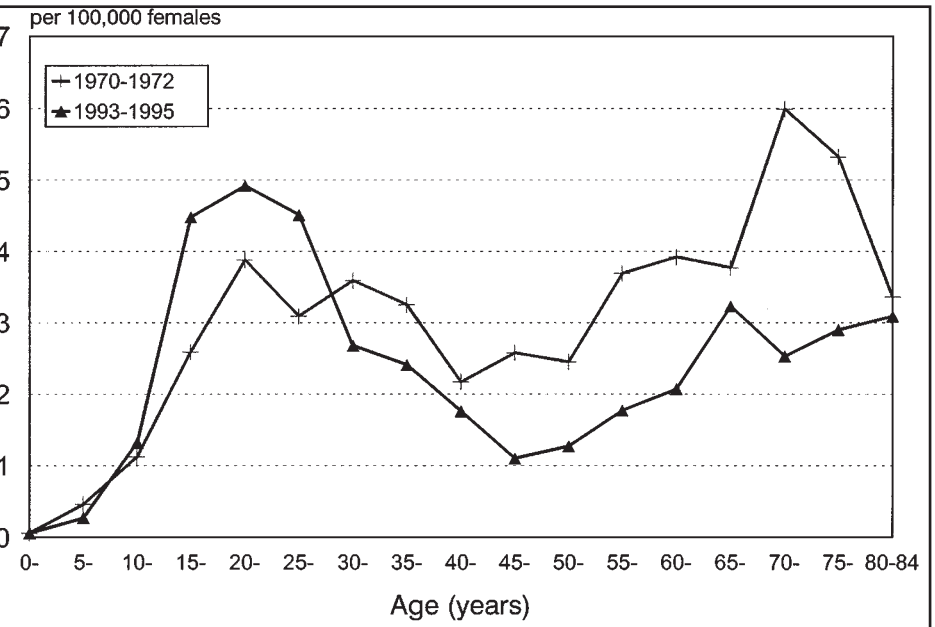

Figure 2. Age-specific incidence rates of Hodgkin's disease per 100,000 females in Canada excluding Quebec, 1970-1972 and 1993-1995

RESULTS

A substantial change in age-specific rates of Hodgkin's disease was seen over the two periods 1970-72 and 1993-95. Two incidence peaks were seen across the age range among both males and females: the first in young adults, and another in older persons. An apparent increase in the rates was observed in age 10-14 years through age 20-24 years, and age 10-14 years through age 25-29 years, respectively, in males and females. A substantial decrease over time was seen among those aged 25 years and older (Figures 1 and 2). The overall age-adjusted incidence rate decreased significantly in males (AAPC = -0.83%, $p < 0.01$), from 3.50 per 100,000 in 1970-71

TABLE I
Overall Age-adjusted Incidence Rate (AAIR) and Number of Cases of Hodgkin's Disease by Sex and Time Period, 1970-1995, in Canada*

	Males		Females		
Year	No. of Cases	AAIR†	No. of Cases	AAIR‡	Rate Ratio (M/F)¶
1970-71	562	3.50	382	2.37	1.48
1972-73	542	3.18	398	2.32	1.37
1974-75	576	3.25	360	1.99	1.63
1976-77	542	2.92	408	2.13	1.37
1978-79	576	3.00	374	1.86	1.61
1980-81	634	3.16	382	1.78	1.78
1982-83	630	3.04	435	2.02	1.50
1984-85	665	3.13	455	2.10	1.49
1986-87	603	2.76	484	2.20	1.25
1988-89	618	2.79	481	2.17	1.29
1990-91	644	2.80	529	2.32	1.21
1992-93	649	2.75	488	2.13	1.29
1994-95	668	2.80	551	2.31	1.21
Total	7079		5727		

* World Standard Population used as the standard
† AAPC = -0.83%, p-value for trend < 0.01
‡ AAPC = 0.15%, p-value for trend > 0.05
¶ AAPC = -1.00 %, p-value for trend < 0.01

TABLE II
Male/female Incidence Rate Ratios for All Types of Hodgkin's Disease and for the Two Major Histologic Subtypes, by Age Group, Canada, 1991 to 1995

		Histologic Subtypes	
Age Group (Years)	Hodgkin's Disease	Nodular Sclerosis	Mixed Cellularity
5-9	1.37	0.55	N/A
10-14	1.30	0.95	N/A
15-19	0.82	0.69	4.56
20-24	0.99	0.78	2.73
25-29	1.12	0.98	2.31
30-34	1.53	1.19	3.60
35-39	1.24	0.91	5.22
40-44	1.52	1.03	2.30
45-49	2.13	2.77	1.86
50-54	1.60	1.60	1.36
55-59	2.20	1.81	2.02
60-64	1.71	1.82	1.27
65-69	1.64	1.91	0.85
70-74	1.44	2.21	1.08
75-79	1.15	1.27	1.17
80-84	1.23	2.46	2.74
≥ 85	2.35	4.58	3.45
Total*	1.24	0.98	2.12

* M/F ratio of age-adjusted incidence rates

to 2.80 per 100,000 in 1994-95, but changed very slightly in females (AAPC = 0.15%, p > 0.05), from 2.37 per 100,000 to 2.31 per 100,000 over the same period. The male/female age-adjusted incidence rate ratio decreased from 1.48 in 1970-71 to 1.21 in 1994-95 (AAPC = -1.00%, p < 0.01, Table I).

Based on data for 1991-95, the rate ratio varied substantially by age group for all cases of Hodgkin's disease and for its two main histologic subtypes: nodular sclerosis and mixed cellularity. For all cases, two age groups of young females (15-19 and 20-24 years) experienced higher incidence rates than males of the same age. There was almost no difference in the overall rate ratio for nodular sclerosis, i.e., 0.98, but the overall incidence of the mixed cellularity type of Hodgkin's disease was 2.1 times higher among males than females (Table II). Age-specific rates of the two subtypes of Hodgkin's disease ratio varied significantly by sex. In their reproductive years (15-19 through 40-44 years), women experienced higher or similar incidence rates of nodular sclerosis, although incidence rates for Hodgkin's disease of the mixed cellularity type was much higher in men than women in almost all age groups. In older age groups, the difference in incidence rates by gender were almost comparable for the two subtypes of Hodgkin's disease.

Table III shows the effects of age at diagnosis, time period of diagnosis and birth cohort on the incidence of Hodgkin's disease by sex and particular age group. Among males for both age groups, the age-cohort model significantly improved the explanatory power of the age-period model, indicating that birth cohort was a more important determinant of Hodgkin's disease incidence than time period. Among females, the age-period model was better than the age-cohort model, suggesting that the trends in Hodgkin's disease incidence in females (either age 10-29 years or age 30-84 years) were more likely to have been associated with specific events in calender time.

DISCUSSION

Our analysis shows that the incidence of Hodgkin's disease has increased among adolescents and young adults, but decreased sharply among older persons between 1970 and 1995. The trends differed substantially between males and females in terms of age-specific rates and age-period-cohort effects. Substantial sex differences in age-specific incidence of Hodgkin's disease and its two main subtypes, nodular sclerosis and mixed cellularity, were also observed in recent data (1991-1995). Our data suggest that significant changes in time trends and gender patterns of incidence of Hodgkin's disease have occurred over the last three decades. The observed age-specific incidence patterns among females support the hypothesis that reproductive factors play a role in the development of Hodgkin's disease.

Currently identified risk factors, such as EBV infection, human immunodeficiency virus (HIV) infection, and improved standard of living or economic status are not likely explanations for the observed trends and major sex difference in the incidence of Hodgkin's disease and its two main subtypes in Canada. Over the last decade, the relationship between EBV and Hodgkin's disease has been examined extensively.[3,7-9] Molecular evidence has suggested that EBV plays a role in the development of

Hodgkin's disease, but with a limited direct correlation, because EBV is detectable in only 18-49% of cases. More importantly, the presence of the EBV genome is primarily associated with the mixed cellularity histologic type.[3,8] Our results show that a significant increase is mainly from the nodular sclerosis subtype of Hodgkin's disease, which is more frequently observed in young women than in men (Table II). This finding contradicts the hypothesis of EBV infection. On the other hand, although a few occupations have been reported to be associated with Hodgkin's disease, attributable risks are too low to explain a major sex difference.[3,4,10] Hodgkin's disease also has not been associated with smoking or other high-risk behaviours more prevalent in men. Thus, to date, identified exogenous exposure does not explain the age-dependent gender variations in the incidence of this cancer.

Our analysis by age, period and birth cohort shows different effects in males and females: temporal changes in Hodgkin's disease among males followed a birth cohort pattern while period effects were underlying the trends observed among females. Birth cohort effects imply a change in disease incidence for individuals born at a particular time secondary to particular levels of exposure to a specific risk factor.[18,19] Period effects occur when disease risk is altered for all individuals alive at a particular point in time, regardless of age. For instance, pollution of the air or water supply at a particular time will produce a similar change in disease risk for everyone in the population. Generally speaking, diagnostic and registration practices are major contributors to period effects.[18,19] Our analysis shows that period effects underlie the incidence trends in Hodgkin's disease among females. The absence of period effects among males suggests that changes in diagnosis and registration did not play a major role in the trends observed in Hodgkin's disease incidence. Further, previous studies have shown relatively little diagnostic error and misclassification of Hodgkin's disease.[20] We believe that the period effects observed in Hodgkin's disease incidence among young women represent a true change and this finding provides a clue to etiology.

TABLE III
Analysis of Age, Period and Birth Cohort Models for Incidence of Hodgkin's Disease by Sex and Age Group, in Canada, 1970-1995

Terms in Model	DF	Deviance*	χ^2	p-value
Males, age 10-24 years				
Age	15	28.76		
Age-period	10	21.09	15.63	0.0159
Age-cohort	8	12.19	6.64	0.1565
Age-period-cohort	4	5.56		
Males, age 25-84 years				
Age	60	158.76		
Age-period	55	88.76	49.56	0.0001
Age-cohort	44	44.48	5.28	0.2579
Age-period-cohort	40	39.20		
Females, age 10-29 years				
Age	20	79.78		
Age-period	15	18.90	6.24	0.5122
Age-cohort	12	24.17	11.51	0.0214
Age-period-cohort	8	12.66		
Females, age 30-84 years				
Age	55	114.61		
Age-period	50	55.55	22.88	0.0622
Age-cohort	40	53.40	20.73	0.0004
Age-period-cohort	36	32.67		

* Deviances are from models with standard Poisson assumptions. χ^2 value of a model refers to a comparison of the submodel with a full model, and its degree of freedom is the difference between this submodel and the full model. For example, for males age 10-24 years, χ^2=15.63 refers to a test of whether cohort effects improve an age-period model, while χ^2=6.64 refers to a test of whether period effects improve an age-cohort model, and their degrees of freedom are 6 and 4, respectively.

Some indirect evidence has suggested that reproductive factors, or sex hormones, may play a role in the etiology of Hodgkin's disease.[4,10,11] If true, reproductive factors may underlie the change in Hodgkin's disease incidence which is partially responsible for the observed sex ratio in nodular sclerosis of Hodgkin's disease. Some epidemiologic studies have shown a reduced risk of Hodgkin's disease associated with marriage, higher parity, and young age at first full-term pregnancy less than 30 years. We thus speculate that the increasing frequency of young women with low fertility rate, low parity, later marriage and later age at first pregnancy may also have contributed to the observed increase in Hodgkin's disease incidence (i.e., nodular sclerosis) in young adult women in Canada.[21] For instance, live births to women aged 20-24 years and aged 25-29 years declined substantially in Canada, from 108.8 per 1,000 and 128.3 per 1,000 in 1974 to 72.2 per 1,000 and 114.0 per 1,000 in 1994, respectively.[21]

Glaser[11] suggested that hormonal factors play a role in the pathogenesis of Hodgkin's disease, which may operate through an effect on the immune system. Other studies have also suggested that the role of sex hormones and other hormone-related factors such as oral contraceptives needs further investigation.[4,22,23]

In summary, the understanding of the cause of Hodgkin's disease remains elusive. The main etiologic candidate, EBV, has been detected in only a proportion of cases, and there is lack of evidence of other co-factors. Our data show that Hodgkin's disease incidence increased in young women while decreasing significantly in older persons. A major sex difference was observed in the age-specific incidence rates of Hodgkin's disease and its main subtypes. Prior viral infection seems an unlikely explanation for observed temporal patterns of the disease. Our data suggest that elevated incidence rates of Hodgkin's disease in young women may be associated with childbearing-related reproductive factors.

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