Clues to the aetiological heterogeneity of testicular seminomas and non-seminomas: time trends and age-period-cohort effects

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Background
Most previous epidemiological studies have treated testicular cancer as a single entity. However, some investigators suggest that testicular seminomas and non-seminomas may have different risk profiles. We examine the time trends in incidence of the two main histological types separately.

Methods
From 1970 through 1995, 7296 cases of testicular cancer were registered in the Canadian provinces of Ontario, Saskatchewan and British Columbia. In addition to analyses of the secular trends by age group and birth cohort, an age-period-cohort (APC) model with standard Poisson assumptions was fitted to the data to assess the time effects.

Results
The age-adjusted incidence rate for seminomas increased by 53%, from 1.5 per 100 000 males in 1970–1971 to 2.3 per 100 000 males in 1994–1995. Non-seminomas increased by 91%, from 1.1 to 2.1 per 100 000 males over the same period. Non-seminomas were more frequent at young ages whereas seminomas dominated in older ages. In contrast to seminomas, non-seminomas occurred predominantly among adolescent men (15–19 years), with a fourfold increase between 1970–1971 and 1994–1995. Age-period-cohort modelling showed that the increase in the risk of both seminomas and non-seminomas followed a birth cohort pattern, but with differences in birth cohorts in addition to significantly distinct age patterns.

Conclusions
Our findings support the hypothesis postulating aetiological heterogeneity in the development of seminomas and non-seminomas. We suggest that epidemiological studies of testicular cancer treat seminomas and non-seminomas separately.

Keywords
Testicular cancer, cancer incidence, cohort effect, statistical models, Canada

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The incidence of testicular cancer has been increasing considerably in many parts of the world over the past several decades.1–4 The increasing trend in risk of testicular cancer has been shown to follow a birth cohort pattern.3–5 In a previous study, we showed that the age-adjusted incidence of testicular cancer in Canada increased by 50%, from 2.8 per 100 000 males in 1969–1971 to 4.2 in 1991–1993.6 That study also revealed that birth cohort effects were largely responsible for the increase.6

Previous studies have suggested that the two main histological types of testicular cancer, namely seminomas and non-seminomas, may have distinctive aetiological profiles, even though they may share risk factors.7,8 Several epidemiological studies have examined time trends in the incidence of testicular cancer by histological type. Zheng et al. found that seminoma incidence peaks at about age 35 while non-seminomas peak about 10 years earlier among Connecticut (US) males.4 Wanderás et al. and Weir et al. also reported different age patterns in the incidence of the two histological subtypes of testicular cancer in Norway and Ontario, Canada.9,10 However, limited sample sizes in these studies prevented the investigators from extensively examining epidemiological difference between seminomas and non-seminomas. The paucity of clues to the aetiological heterogeneity of seminomas and non-seminomas suggests that further epidemiological studies are needed. This study examines the differences in the incidence patterns of testicular seminomas and non-seminomas using cancer registry data from the Canadian provinces of Ontario, Saskatchewan and British Columbia.
Methods

Information on histological classification of testicular cancer was not consistently recorded by all provincial and territorial cancer registries in Canada until 1983, although Ontario, Saskatchewan and British Columbia collected such data for several previous years. The combined population of these three provinces accounts for about 60% of the Canadian population. Data on testicular cancer incidence in these three provinces were obtained from the National Cancer Incidence Reporting System (NCIRS) of Statistics Canada for 1970–1991 and for 1992–1995 from the Canadian Cancer Registry (CCR) which replaced the NCIRS. Annual population estimates for these provinces were obtained from the Demography Division of Statistics Canada.

The information regarding the CCR and the quality of Canadian cancer incidence data has been well documented. Generally, cancer data from these three provincial registries are comparable and reliable, and the completeness and the quality are rated highly. All three cancer registries used the Systematized Nomenclature of Pathology for histological classification before 1979, but those records were then converted to the International Classification of Disease for Oncology first edition (ICD-O-1) codes. By 1974–1978, 95% of testicular cancer cases had been confirmed by microscopy, and 1% by death certificates only. Testicular cancer was coded as 186 in the ICD-O-1. The cases were sub-divided into three broad histological groups: seminomas (ICD-O-1 morphology code 906), germ-cell non-seminomas or non-seminomas (ICD-O-1 morphology codes 907, 908, 910), and unspecified and other histological types of testicular cancer.

Secular trends in the incidence of seminomas and non-seminomas between 1970 and 1995 were estimated by linear regression models using the logarithms of the yearly rates for specific age groups of interest. The average annual per cent change (AAPC) was derived from the expression $\exp(\beta) - 1 \times 100$, where $\beta$ is the regression coefficient of the model. All age-adjusted incidence rates were calculated using direct standardization with the World Standard Population serving as the standard.

Analyses integrating age at diagnosis, time period of diagnosis and birth cohort were then performed. Age at diagnosis was grouped into 5-year intervals (15–19 years to 70–74 years). The period of diagnosis is reduced to cover from 1971 to 1995 in order to obtain five equal 5-year intervals. Corresponding to these age groups and time periods, a total of 16 overlapping 10-year birth cohorts (1896–1905 to 1971–1980, identified by the central year of birth from 1901 to 1976) were constructed.

Poisson regression modelling was used to estimate the age, period, and cohort effects with the assumptions that the number of cancer incident cases follows a Poisson distribution and the incidence rates are a multiplicative function of the included model parameters, making the logarithm of the rates an additive function of the parameters. For example, the form of the age-period-cohort (APC) model was given by

$$\log(d_{ij}/p_{ij}) = \mu + \alpha_i + \beta_j + \gamma_k$$

where $d_{ij}$ denotes the number of the incident cases in the $i$th age group and $j$th period; $p_{ij}$ the male population at risk in the $i$th age group and $j$th period; $\alpha_i$ the effect of the $i$th age group; $\beta_j$ the effect of the $j$th period category; and $\gamma_k$ the effect of the $k$th cohort category ($k = I - i + j$ when $i = 1, 2, \ldots, I$). To incorporate the non-identifiability component that is inherent in these models, we express each of the time effects in terms of an overall linear trend, along with a remaining curvature or departure from that trend assuming the linear component of the period effects is zero. To compare the curvatures of the three time trends between seminomas and non-seminomas we included data for seminomas and non-seminomas in the same model using an additional variable to define histological type, then we introduced type-interactions with the three time factors into the above general model. Parameters of the models were estimated by means of the maximum likelihood method with the S-PLUS function GLM (S-Plus 2000 user’s guide, MathSoft, Inc., Seattle, WA, 1999).

Results

A total of 7296 incident cases of testicular cancer were registered by the three provincial cancer registries from 1970 through 1995. The overall age-adjusted incidence rate for testicular cancer increased consistently over the period. By histological type, the rate for seminomas increased from 1.5 per 100,000 males in 1970–1971 to 2.3 in 1994–1995, while the rate for non-seminomas increased from 1.1 to 2.1 per 100,000 males over the same period. The rate for other histological or unspecified types remained stable over time (Figure 1).

Among the testicular cancer cases, 6886 (94%) were classified as seminomas or non-seminomas. Eighty-eight per cent of them occurred in adult men aged 20–59 years. Compared with seminomas, non-seminomas were observed more frequently in younger ages. For example, among 425 cases of the testicular cancer diagnosed in children and teenage boys (age 0–19 years), 366 were non-seminomas and only 15 were seminomas (Table 1—data for unspecified or other histological types were not shown).

Overall, non-seminomas increased more rapidly than seminomas, i.e. 2.3% and 1.7% per year, respectively. In the age group 20–34 years, the incidence rate of seminomas increased more rapidly than the rate of non-seminomas. The reverse was true for those aged 35–59 years. Non-seminomas occurred predominantly in children (0–14 years) and adolescent men (15–19 years) with the incidence in adolescent men increasing fourfold from 1970–1971 to 1994–1995 (Table 1). Patients with seminomas and those with non-seminomas were on average 6.2 years and 6.8 years younger at diagnosis in 1994–1995 compared to the corresponding cases in 1970–1971. Patients with non-seminomas were on average 7.9 and 8.5 years younger than the patients with seminomas in 1970–1971 and 1994–1995, respectively (data not shown).

The age-specific incidence rates for seminomas and non-seminomas by birth cohort were plotted in Figures 2 and 3, respectively. The incidence of seminomas showed a slight decline in men born between 1921 and 1941 and a dramatic increase in those born in later cohorts. The highest rates were observed among those aged 30–39 years in all birth cohorts. Non-seminomas showed a plateau in early birth cohorts but a substantial increase in cohorts since 1941. The incidence rates were the highest among those aged 25–29 years across the observed birth cohorts.
The significance tests derived from fitting the APC model to the data are summarized in Table 2. The model gives a better description of seminomas, compared with non-seminomas, because the goodness-of-fit tests were less than the degrees of freedom. In addition, cohort was a significant factor in describing the trends in incidence rates for both seminomas and non-seminomas, although the latter is marginally significant. Because of the non-identifiability problem, the period and cohort tests only consider curvatures, although period effects are not statistically significant.

Table 3 presents significance tests that compare the curvatures between the two histological types of testicular cancer by considering type-curvature interactions. The interactions with age show a strong significance, and the interactions with birth cohorts suggest a mild effect ($P = 0.0592$). These tests demonstrate that the two types of testicular cancer have different time trends in terms of age and birth cohorts. Furthermore, by contrasting the ‘unique’ trend lines obtained from fitting the APC models for the two histological types, we can see that the patterns for seminomas and non-seminomas are different in age groups and birth cohorts (Figure 4).

**Discussion**

This study shows that seminomas increased by 53% while non-seminomas increased by 91% in three provinces of Canada over the last 26 years. Age-period-cohort modelling showed that the increased risk of both seminomas and non-seminomas followed
Aetiologial heterogeneity of testicular cancer

This study represents the largest descriptive study of testicular cancer by histological type to date with time trends and APC analysis. These findings imply that there are major differences in epidemiological characteristics between seminomas and non-seminomas, and support the hypothesis that aetiological heterogeneity may exist in the development of seminomas and non-seminomas.

Figure 2 Age-specific incidence rates of seminomas by birth cohort in Canada, 1971–1995

Figure 3 Age-specific incidence rates of non-seminomas by birth cohort in Canada, 1971–1995
It is generally accepted that the frequent occurrence of testicular cancer in young men and the rarity of the disease in old men suggest that exposures to risk factors early in life, possibly in utero, are likely to be more important than exposures in adulthood.22,23 Also, the rapid increase in testicular cancer in young males is most likely the result of multiple risk factors acting in combination. However, the only well-established association is that between cryptorchism and testicular cancer.23,24

Many aetiological hypotheses have been proposed to explain the observed increase in testicular cancer. These include increases in exposure to oestrogen in utero, early life exposure to viruses, trauma to the testis, parental occupational exposures, effects from male sex hormones and genetic factors.25–27

In most earlier analytical and descriptive epidemiological studies, testicular cancer has been treated as a single entity. Little attention was given to the differences in the epidemiological features of the two major histological types because of the unavailability of reliable histological data and the relatively small number of subjects with this disease. A few descriptive studies have examined the age-specific incidence patterns, although no distinct conclusive clues to aetiological differences were derived, in part because of the limited size of the population studied.4,28 On the other hand, analytical studies have suggested that aetiological heterogeneity between the two main histological types of testicular cancer may exist.8,29,30 One study further suggests that seminomas and non-seminomas may have different factors at the initiating or promoting stage of carcinogenesis.7 Another study has proposed that one causative factor might be responsible for the observed earlier increase in seminomas between 1935 and 1965 and another for the later increase in non-seminomas beginning in the 1970s.1

A study which focused on the analysis of testicular cancer in young boys and adolescent men using combined data from three European countries lends support to the hypothesis that testicular cancer in young boys is aetiologically distinct from testicular cancer in adults.31 This study also proposed that the particularly high increase (average annual increase of 6%) in the incidence rates of testicular cancer in adolescent men is likely the result of a secular trend towards earlier age at puberty. However, that study did not examine testicular cancer by histological type in either age group. Our study shows that non-seminomas predominated in both groups of males (boys and adolescents). This suggests that adolescent men, unlike older adults, are exposed to factors which predispose them to developing non-seminomas. This implies that non-seminomas which occurred mostly in children and younger men have one or more unique aetiological factors as opposed to seminomas.

<table>
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<th>Source</th>
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<td>Cohort curvature</td>
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<th>Source</th>
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<tr>
<td>Age curvature</td>
<td>10 d.f. 141.19 &lt;0.0001</td>
</tr>
<tr>
<td>Period curvature</td>
<td>3 d.f. 2.93 0.4033</td>
</tr>
<tr>
<td>Cohort curvature</td>
<td>14 d.f. 23.06 0.0592</td>
</tr>
</tbody>
</table>

8 Each interaction with a curvature effect is considered in the presence of the other two.

Figure 4 Age, period and cohort effects for testicular seminomas (solid line) and non-seminomas (dashed line) constrained so that the sum is zero.
Nevertheless, some risk factors in perinatal and environmental exposures may be shared between the two types of testicular cancer.

Age-period-cohort modelling has considerable advantages over the simple analysis of temporal trends in cancer rates, though some limitations, such as the non-identifiability problem, are inherent. The coefficients obtained depend on the particular constraint imposed. In this analysis, however, the relative patterns for two histological types were based on constraints to obtain linear effects and departures from linearity as described by Holford. We observed substantial differences in the time trend effects in the incidence of testicular seminomas and non-seminomas. In most previous studies, in which testicular cancer was modelled as a single entity, birth cohort was identified as the determinant responsible for the observed increase. Testicular cancer is an anatomically and clinically distinct entity and diagnostic practice in this disease has not changed since at least the late 1970s. However, errors in cancer registration and coding may play a minor role in period effects over time. Therefore, we examined the time trends and compared the differences of incidence patterns between seminomas and non-seminomas in the presence of all the three time factors.

In summary, substantial epidemiological variations may provide clues for the development of specific testable aetiological hypotheses. It appears that no other cancer shows such distinctive incidence patterns between histological types as testicular cancer. Thus, in-depth analytical investigations are warranted to examine aetiological differences between the two main histological types of testicular cancer. We suggest that such studies treat testicular seminomas and non-seminomas separately.

Acknowledgements

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References