Trends in testicular germ cell cancer incidence in Australia

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Abstract

Objective: Although increasing incidence of testicular germ cell cancer has been reported in many developed nations, national estimates for Australia, with histological differentiation, are not currently available.

Methods: Using data from all state and territory population-based cancer registries in Australia, this paper reports on incidence trends for seminomas and non-seminomas in Australia between 1982 and 2004 using Joinpoint and Age-Period-Cohort models.

Results: Of the 10528 testicular germ cell cancers diagnosed during this period, 6086 (58%) were seminomas. Incidence rates have increased (2.6% per year) in Australia since 1982, with the effect stronger among seminomas (3.4% per year) rather than non-seminomas (1.4% per year). There was a strong age effect evident for both subtypes, peaking in the 25-29 year age group for non-seminomas and the 30-34 year age group for seminomas. Non-seminoma rates reflected a significant birth cohort effect, following a U-shaped pattern with the lowest risk among the 1945 birth cohort.

Conclusions: The differential trends observed for Australia for seminomas and nonseminomas are consistent with those reported for the United States, but slightly different to those reported for Europe. The trends may be at least partly due to changes over time in the prevalence of etiologic or protective factors around the time of birth.

Introduction

The majority of testicular cancers are germ cell tumours, and these tumours are classified into three distinct types(1). Type I testicular germ cell cancer (GCC) refers to the teratomas and yolk sac tumours occurring in childhood, Type II GCC to the seminomas and nonseminomas occurring in adolescents and adults, and Type III GCC refers to the very rare spermatocytic seminomas, which likely occur in adult men of all ages (2). These three types of testicular GCC have different clinical features and prognoses, and likely distinctive pathogenesis, risk factors, and incidence trends (3).

Approximately 55-60% of Type II testicular GCC are seminomas, malignant cells with many similarities with primordial germ cells. These have been reported to have a peak incidence in the fourth decade of life. In contrast, because they consist of embryonal stem cells, nonseminomas can differentiate into extra-embryonic tissues or somatic elements, and approximately 20% of this heterogeneous group of tumours contains both seminoma and nonseminoma components. Nonseminomas have been reported to have a peak incidence in the third decade of life (3).

The incidence of Type II testicular GCC has been increasing in developed nations over most of the past century, although rates appear to be levelling in some populations (4). In Canada and the US, the increases in rates appear to be larger for seminomas than nonseminomas (5, 6). The increases in incidence seem to be driven by a strong birth cohort effect, although in some Northern European countries and the US, this trend was interrupted by a decrease in rate for men born during the Second World War (5, 7).

Incidence rates vary widely between different nations and ethnic groups, and, remarkably, rates are also highly variable even within relatively homogeneous populations such as Europe. For example, among the highest rates reported are those for Denmark (9.9/100 000), in contrast to Sweden (5.0/100 000) and Finland (2.7/100 000) (4). Asians and black populations have much lower incidence rates, whereas the rate in New Zealand Maoris is relatively high (7.1/100 000) (4).

Previous estimates of seminoma and nonseminoma incidence trends in Australia have been limited by the use of non-nationwide data, and have not been reported stratified

by histological type (4, 8). In this paper, we report the national population-based incidence trends for Australia between 1982 and 2004, and examine the possible influences of period, birth cohort and age group on these trends.

Materials and Methods

Testicular cancer incidence data were obtained from the National Cancer Statistics Clearing House (NCSCCH). The NCSCCH is maintained by the Australian Institute of Health and Welfare (AIHW), and receives data from individual State and Territory (population-based) cancer registries. Cancer notification and registration in Australia has been a statutory requirement for all public and private hospitals, nursing homes and pathology services since 1982.

Data on testicular GCC (ICD-0-2 code C62, morphology codes M9060-M9102) were extracted, and then Type I testicular GCC were excluded based on the age at diagnosis (cancers diagnosed among boys aged 0-14 were assumed to be Type 1 GCC) and Type III testicular GCC were excluded based on histology (M9063). Type II testicular GCC were then further categorised into seminomas (M9061, M9062, M9064) and non-seminomas.

We used Joinpoint regression (9, 10) to assess trends in age-standardised incidence rates. This is a standard method used in descriptive cancer epidemiology to detect changes in the direction and or magnitude of linear trends. These models describe trend data in the form of a number of contiguous line segments connected by “join points”, at which the linear trends change. The final model is the simplest model that the data support. Trends were expressed as percent change per year.

To assess the independent effects of age, period, and birth cohort on the incidence rates, we calculated overlapping 10-year birth cohorts (with mid-years from 1895 to 1975). These were based on period of diagnosis (5 year periods from 1985) and age group (5 years). Due to small numbers, birth cohorts prior to 1925 and later than 1970, and men aged 70 years and over, were not included in the regression models.

Poisson regression was initially used to model the incidence counts on age, period and birth cohort, with the log of the specific population used as the offset variable, and the

parameter estimates expressed as incidence rate ratios. Since there was evidence of significant overdispersion, we assumed a negative binomial distribution to the data. A series of separate models were fitted sequentially, using the method proposed by Clayton and Schiffrers (11). The first model consists of age alone (A), with no temporal variation. The second model consists of age and a “drift” term (A+drift), representing a linear trend in incidence that could be attributed to either period or cohort. Comparison of the first and second model provides a test for the “drift” term. Following this, age-period (AP) and age-cohort (AC) models are constructed separately. Comparison of each of these models with the second model above provides tests for period effects and cohort effect separately (using likelihood ratio tests). It is not possible to assess whether the age-period model provides a significantly better fit to the data than the age-cohort model.

Finally, the full age-period-cohort model (APC) was fitted, and compared to the age-period and age-cohort models. Since these parameter estimates from the APC models are not unique, no specific interpretation can be placed on them. However the relevant statistical significance tests remain valid when assessing the relative importance of age, period and birth cohort on incidence trends.

We also fitted a combined model containing data for seminomas and non-seminomas, and then tested the differences between the period effects between the two histology groups by assessing the interaction between period and histology group, and then separately testing for differences in birth cohort effects by assessing the interaction between birth cohort and histology group.

Results

Overall summary of testicular incidence data

There were 11052 malignant, primary tumours of the testis registered between 1982 and 2004 in Australia, of which 10690 (96.7%) were known germ cell testicular cancers. Of the germ cell cancers, 96 (0.9%) were Type I and 66 (0.6%) were Type III. Excluding these cases, left 10528 Type II GCCs, an average of 458 per year (ranging from 297 to 646). Of these, 6086 (57.8%) were seminomas and 4442 (42.2%) were non-seminomas. Combining the Type II cases across 1982-2004, the Australian age standardized incidence rate for Type II cancers was 6.40 cases/100,000

men (95% CI=6.3-6.5), 3.79 (3.7-3.9) for seminomas and 2.61 (2.5-2.7) for nonseminomas.

State-based comparisons

Average incidence rates of Type II GCC collated over 1982-2004 were very similar in the five most populous states of Australia (New South Wales, Victoria, Queensland, Western Australia and South Australia), with age standardised rates per 100,000 population ranging from 6.19 to 6.46 (Table 1). Tasmania, the most southern state, had the highest incidence rate, while the Northern Territory, which has a high proportion of Indigenous people, had the lowest incidence rate. Fairly similar rankings held for seminomas and nonseminomas separately (Table 1).

Age patterns

The median age for all Type II testicular GCC was 33 years (inter-quartile range (IQR)=27-40 years), with around 1% of cases occurring in men aged 70 years and over at diagnosis. The peak in incidence for seminomas was in the 30-34 year age group (median age of 36 years; IQR=30-43), suggesting a slightly older age distribution compared to non-seminomas that had an incidence peak in the 25-29 year age group (median age of 29 years; IQR=24-35) and a more pronounced reduction in age (Figure 1)..

Period patterns

The age-standardised incidence rate for Type II testicular GCC increased from 4.91/100,000 in 1982 to 8.19 cases/100,000 in 2004. This represents an increase of 2.6% per year (95% CI=2.2-2.9). Most of that increase was among seminomas, increasing from 2.74/100,000 in 1982 to 5.14 in 2004 (3.4% per year [2.8-3.9]), while the incidence rate for nonseminomas increased from 2.17 to 3.05 (1.4% per year [0.9-1.9]). There was no evidence of any departure from a linear trend for Type II GCC or its two histological subgroups.

For both seminomas and all Type II combined, the increase in incidence rates from 1985-1989 to 2000-2004 was fairly consistent across the age groups (Figure 1). The pattern amongst the non-seminomas was less clear.

Cohort patterns

When we graphically examined the trends in birth cohort by age group (Figure 2) we found that, within a specific age group, incidence rates for seminomas were generally increasing for subsequent birth cohorts. A birth cohort effect for non-seminomas was not as obvious (Figure 2).

Regression models

The results in Table 2 show the incidence rate ratios (IRR) for the AP (period adjusted for age) and AC (birth cohort adjusted for age) models separately for all Type II testicular GCC, non-seminomas and seminomas. Compared to the incidence rates in 1985-1989, rates of Type II testicular GCC in 2000-2004 had increased by 30% for nonseminomas, 66% for seminomas, and 50% when combining seminomas and nonseminomas. The difference in period effects between seminomas and non-seminomas was not statistically significant (interaction_{period and histology}=0: chi-sq=7.27, df=3, p=0.064)

The birth cohort patterns were significantly different for seminomas compared to non-seminomas (interaction_{birth cohort and histology}=0: chi-sq=103.68, df=9, p=<0.001). Incidence risks for seminomas increase fairly consistently for subsequent birth cohorts (Table 2) while for nonseminomas the birth cohort effect appears quadratic in nature, with the lowest risks among the 1945 birth cohort, and highest risks in the earliest and latest cohorts. Compared to the 1945 birth cohort and after adjusting for age, incidence rates among the 1965 birth cohort were 34% higher for non-seminomas, 93% higher for the seminomas, and 69% higher for both types combined.

The 'drift' parameter, which represents a linear trend in incidence due to either a period or cohort effect, was significant (p<0.05) for all three groups. For non-seminomas there was a 9% increase in incidence risk per 5-year period or birth cohort, while for seminomas this increase was 17% per 5-year period or birth cohort. These linear trends were significantly different between seminomas and non-seminomas (interaction_{drift and histology}=0: chi-sq=6.67, df=1, p=0.010). For all Type II GCC combined combined there was a 14% increase in incidence risk per 5-year period or birth cohort (Table 2).

Due to these significant differences in birth cohort and drift effects between seminomas and non-seminomas, the full age-period-cohort analysis was completed only for seminomas and non-seminomas separately. The birth cohort effect, after adjustment for age and drift, was significant for non-seminomas ($\chi^2=18.48$, $df=8$, $p=0.018$), however was not significant for seminomas ($\chi^2=13.28$, $df=8$, $p=0.103$). In contrast, the period effect, after adjustment for age and drift, was significant for seminomas ($\chi^2=11.69$, $df=2$, $p=0.003$) but not for non-seminomas ($\chi^2=0.91$, $df=1$, $p=0.339$). For seminomas, there was no evidence of an additional cohort effect after adjusting for age and period (comparison of age-period-cohort model with the age-period model: $\chi^2=12.21$, $df=8$, $p=0.142$). For non-seminomas there was no evidence of an additional period effect after adjusting for age and cohort (comparison of age-period-cohort model with the age-cohort model: $\chi^2=0.95$, $df=2$, $p=0.621$). Therefore the age-cohort model was preferred for non-seminomas and the age-period model was preferred for seminomas.

Discussion

In summary, we found incidence rates of Type II testicular germ cell cancers have increased in Australia since 1982, with the effect most pronounced among seminomas rather than non-seminomas. There was a strong age effect evident for both subtypes, peaking in the 25-29 year age group for non-seminomas and the 30-34 year age group for seminomas. Non-seminoma rates reflected a significant birth cohort effect for non-seminomas, following a U-shaped pattern with the lowest risk among the 1945 birth cohort. While the birth cohort patterns for seminomas suggest that the incidence rates for men born in the same birth cohort have increased over time, this cohort effect was not statistically significant after adjusting for age and period.

As Type II testicular GCC tumours do not spontaneously regress (3), and clinical presentation is almost always symptomatic, it is unlikely that improvements in diagnostic capabilities are responsible for these rate increases. Germ cell cancers are histologically well-characterized, so that changes in rates over time are unlikely to be due to errors in classification with other cancers.

Although the aetiology of Type II testicular GCC and other testicular cancers remains unknown, the most widely accepted paradigm is that testicular GCC is initiated during embryogenesis in the form of precursor lesions (intratubular neoplasia), and that both pre- and post-natal factors are subsequently involved in the progression of these tumours (12). Given the rarity of disease, the early age distribution, and the birth cohort effect for Type II testicular GCC, plausible aetiologic exposures would have to be present *in utero* or during very early in life in boys who have different susceptibilities to develop testicular GCC, and these factors and/or vulnerability would have to have increased strongly over time. Thus, it is likely that increasing trends are at least partly due to changes over time in the prevalence of etiologic or protective factors (13) at around the time of birth. This hypothesis is consistent with a birth cohort effect driving the increase in rates as found in our study, as well in several others (5, 7, 14-16).

To date, apart from age, there are only four risk factors that have been demonstrated with a high level of evidence: cryptorchidism, contralateral testicular GCC, genetic abnormalities and familial trends, and gonadal dysgenesis (12). Cryptorchidism, the most common of these risk factors, is present in only about 10% of testicular germ cell cancers (13), but its incidence may also have been increasing in the past few decades (17).

Exposure to a relative excess of estrogens or other endocrine disrupters during the first trimester of pregnancy may be an important risk factor, and this hypothesis is compatible with established histogenetic pathways of the development of foetal germ cells into intratubular neoplastic cells (18, 19). Possible sources of oestrogen excess may include endogenous hormonal imbalances, and there is some evidence that conditions which increase maternal estrogen levels during pregnancy, such as twin pregnancies, primigravid state and obesity, are associated with increased risk of testicular cancer (20, 21).

Fat-soluble chemicals with anti-androgenic and oestrogenic properties, such as polychlorinated biphenyls, hexachlorobenzene, and chlordanes, can accumulate and persist in the body for many years; these chemicals have been found to be in higher concentrations in mothers of sons with testicular cancer (22, 23). Furthermore, the

concentrations of these chemicals increased in breast milk until the 1970s in Northern Europe, and subsequently decreased, possibly associated with the levelling in Type II testicular GCC rates recently in some countries (8).

As reported in the United States, (5) rates for seminomas are increasing in Australia, while the increase is less pronounced among non-seminoma. However differences in trends by histologic subtype have not been found consistently in Europe (24). The possibility that most cryptorchid testes develop seminomas (3) might be offer a partial explanation. If there has been a temporal increase in the incidence of maldescended testes in Australia, as reported in other countries (17), a common risk factor to the development of cryptorchidism and Type II testicular GCC may be involved, such as prenatal exposure to a relative excess of oestrogens (13). Moreover, in their etiologic development, seminomas require a different number of stages than nonseminomas (3), so that these two tumour subtypes may have different vulnerabilities to develop under the influence of the same exposures (25).

In some northern European countries (Norway, Denmark, Sweden) and the US there was a marked decrease in rates among men born during World War II (5, 7, 26). There are however inconsistencies in this pattern: France and Switzerland experienced a similar temporary decreases in rates, but in the late 1930s rather than early 1940s; the decrease in Norway was limited to seminomas; and there was no decrease in the United Kingdom or several other European countries. In our data, there appeared to be slightly lower rates of increase of nonseminoma in the Australian cohort born around 1940, but it is not as marked as that reported in some northern European countries. Malnutrition and access to goods such as tobacco have been posited to be associated with this temporary decreasing trend, however the inconsistencies in the findings across countries suggest that there is no simple explanation.

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Figure 1

Type II GC Testicular cancer incidence (Men aged 15-69 years) Age group by Period of Diagnosis

Data source: National Cancer Statistics Clearing House, AIHW
Y axis on log scale

Figure 2

Type II GC Testicular cancer incidence (Men aged 15-69 years)
Birth cohort by age group

Data source: National Cancer Statistics Clearing House, AIHW
Y axis on log scale

Table 1: Age-standardised incidence rates (/100,000 population), and 95% confidence intervals, for Type II testicular GCC by Australian state and territory between 1982 and 2004.

State / Territory	Type II GCC	Seminomas	Non seminomas
New South Wales	6.46 [6.3-6.7]	3.91 [3.8-4.1]	2.55 [2.4-2.7]
Victoria	6.44 [6.2-6.7]	3.84 [3.7-4.0]	2.60 [2.5-2.8]
Queensland	6.20 [5.9-6.5]	3.51 [3.3-3.7]	2.69 [2.5-2.9]
South Australia	6.19 [5.8-6.6]	2.98 [2.7-3.3]	3.20 [2.9-3.5]
Western Australia	6.35 [6.0-6.8]	4.03 [3.7-4.4]	2.32 [2.1-2.6]
Tasmania	7.55 [6.7-8.4]	5.03 [4.4-5.8]	2.52 [2.1-3.1]
Northern Territory	4.82 [3.9-5.9]	2.93 [2.2-3.9]	1.89 [1.4-2.6]
Australian Capital Territory	7.32 [6.4-8.4]	4.78 [4.0-5.7]	2.54 [2.0-3.2]
Australia	6.40 [6.3-6.5]	3.79 [3.7-3.9]	2.61 [2.5-2.7]

Table 2: Incidence rate ratios (IRR) and 95% confidence intervals (CI) for the period and cohort effects adjusted for age group in Australia, 1985-2004

	Non seminomas	Seminomas	Type II GCC combined
Period			
1985-1989	<u>1.00</u>	<u>1.00</u>	<u>1.00</u>
1990-1994	1.11 [1.01, 1.22]	1.30 [1.19, 1.42]	1.21 [1.13, 1.29]
1995-1999	1.15 [1.05, 1.27]	1.54 [1.42, 1.68]	1.36 [1.28, 1.45]
2000-2004	1.30 [1.18, 1.44]	1.66 [1.53, 1.80]	1.50 [1.41, 1.59]
Birth cohort (central birth year)			
1925	1.00 (0.53, 1.88)	0.73 (0.53, 0.99)	0.77 (0.58, 1.01)
1930	1.62 (1.05, 2.51)	0.53 (0.41, 0.68)	0.67 (0.54, 0.84)
1935	1.08 (0.78, 1.51)	0.76 (0.64, 0.9)	0.81 (0.7, 0.95)
1940	1.02 (0.80, 1.29)	0.89 (0.78, 1.01)	0.92 (0.82, 1.03)
1945	<u>1.00</u>	<u>1.00</u>	<u>1.00</u>
1950	1.08 (0.90, 1.28)	1.21 (1.09, 1.35)	1.17 (1.07, 1.29)
1955	1.22 (1.02, 1.46)	1.51 (1.35, 1.68)	1.42 (1.29, 1.56)
1960	1.35 (1.12, 1.62)	1.72 (1.52, 1.94)	1.6 (1.45, 1.77)
1965	1.34 (1.10, 1.63)	1.93 (1.68, 2.22)	1.69 (1.51, 1.89)
1970	1.69 (1.38, 2.08)	2.32 (1.95, 2.75)	2.08 (1.84, 2.35)
“Drift”, IRR per 5 years	1.09 [1.05, 1.12]	1.17 [1.14, 1.20]	1.14 [1.12, 1.16]