

International Trends in the Incidence of Testicular Cancer, 1973-2002

Victoria M. Chia, Sabah M. Quraishi, Susan S. Devesa, Mark P. Purdue, Michael B. Cook, and Katherine A. McGlynn

Abstract

Background: Whereas testicular cancer incidence rates have been widely reported in populations of Northern European ancestry, rates in other populations have been less frequently examined. In a prior report, global testicular cancer incidence rates and trends for the years 1973 to 1997 were summarized. The current report extends these analyses with an additional 5 years of data from *Cancer Incidence in Five Continents*.

Methods: Age-standardized incidence rates over successive 5-year time periods were obtained for populations in the Americas, Asia, Europe, and Oceania.

Results: In general, testicular cancer incidence remained highest in Northern European populations (8.0-9.0 per 100,000) and lowest in Asian and African populations (<1 per 100,000). One notable exception to this pattern, however, was the very high rate reported by the Valdivia, Chile registry (8.8 per 100,000). In many populations, rates rose between 1973 and 2002, although the increases were strongest and most consistent among populations of European ancestry. In certain European populations, such as those of Denmark and of Geneva, Switzerland, some recent plateauing of rates was evident. There was little evidence of increase and possible evidence of a modest decline in rates among east Asian populations. Trends by histology (seminoma and nonseminoma) were generally similar to one another.

Conclusions: Risk of testicular cancer remains relatively high in Northern European populations and low in Asian and African populations. Similar trends by histology suggest common risk factors.

Effect: Reasons for increasing rates among Northern Europeans and stable or declining rates among East Asians are unexplained, supporting the need for future etiologic studies. *Cancer Epidemiol Biomarkers Prev*; 19(5); 1151-9. ©2010 AACR.

Introduction

On a population basis, testicular cancer is relatively rare. In many countries, however, it is the most common cancer among men ages 15 to 40 years. The incidence of testicular cancer has been increasing over the last 30 to 40 years (1, 2), although there are large variations in risk in different countries and among different racial and ethnic groups. Incidence rates among young white men in Nordic countries are as high as 11.5 per 100,000 men, which is in stark contrast to rates of 1 to 2 per 100,000 among black and Asian men (2, 3).

Germ cell tumors account for ~98% of testicular cancers. Histologically, testicular germ cell tumors are grouped into three main types: seminomas, nonseminomas, and spermatocytic seminomas. In the United States,

seminomas account for ~55% of germ cell tumors whereas nonseminomas, composed of embryonal carcinomas, teratomas, choriocarcinomas, yolk-sac tumors, and mixed germ cell tumors, comprise ~44%. The median age at diagnosis of seminoma is 35 to 39 years, whereas for nonseminoma, the median age at diagnosis is 10 years younger, at 25 to 29 years. Although seminomas and nonseminomas have different clinical characteristics, studies have revealed similar trends in incidence in the majority of countries, which may indicate that both types share common etiologic risk factors (4, 5). The third and least common type of testicular germ cell tumor (spermatocytic seminoma) comprises ~1% to 2% of germ cell tumors in males (6). The incidence of spermatocytic seminoma peaks among men ages 50 to 54 years (6), and the tumor is thought to have an etiology distinct from that of either seminomas or nonseminomas.

Testicular cancer rates have been increasing in many populations over time and across successive birth cohorts, including those in the Nordic countries (5), the United Kingdom (5), Germany (7), France (8), the United States (4), and Australia (9). Although trends in testicular cancer incidence have been well described in the United States and Europe, few studies have examined and compared international trends in incidence rates by histology.

Authors' Affiliation: Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland

Corresponding Author: Katherine A. McGlynn, Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, EPS/Suite 550, 6120 Executive Boulevard, Rockville, MD 20892-7234. Phone: 301-435-4918; Fax: 301-402-0916. E-mail: mcglynnk@mail.nih.gov

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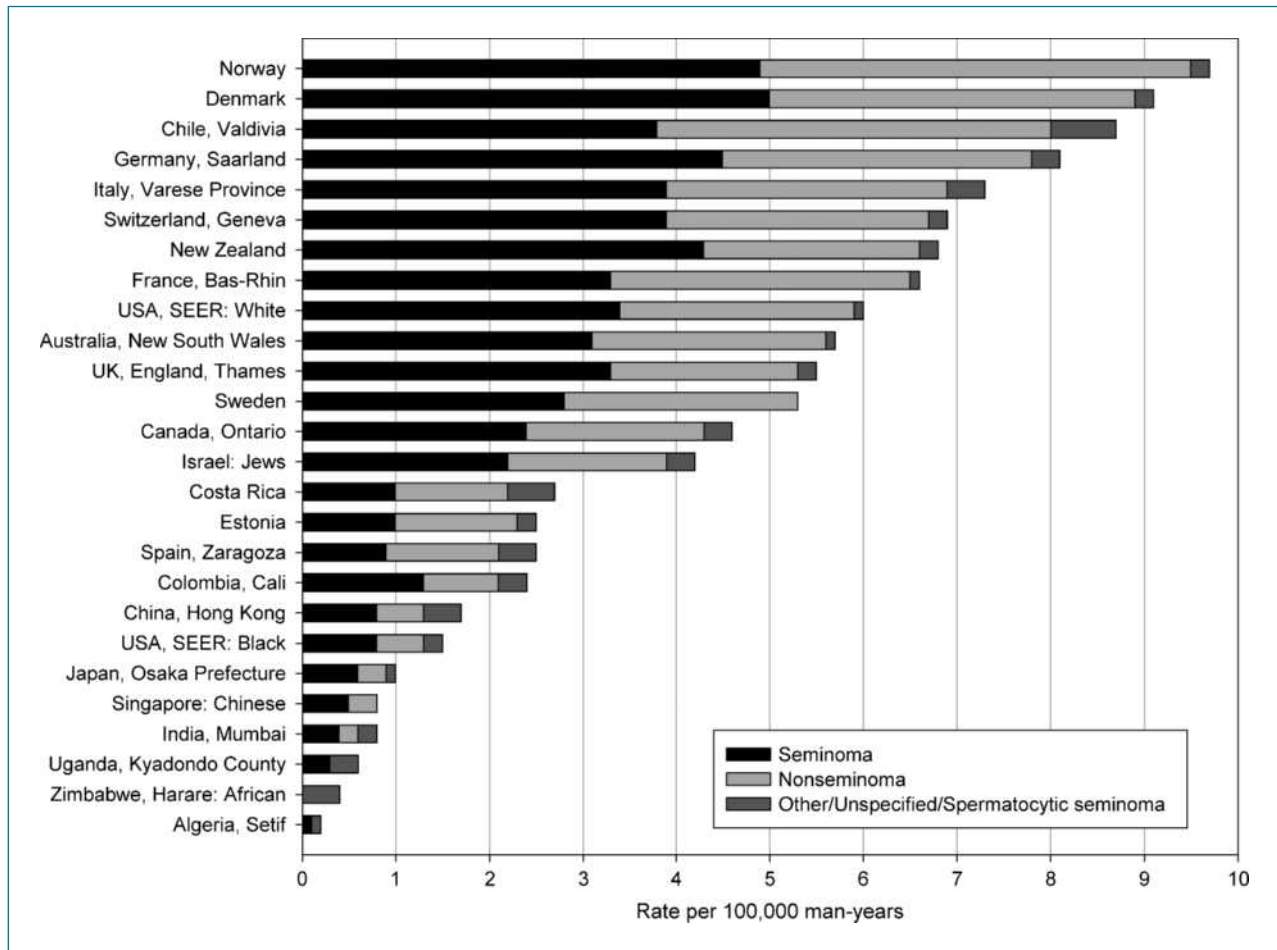


Figure 1. Incidence rates of testicular cancer (per 100,000 man-years) age-standardized to the world population (1998-2002).

As a follow-up to our previous study (2), we examined international trends in testicular cancer incidence overall and by histology for the 30-year period 1973 to 2002.

Materials and Methods

Incidence rates of testicular cancer [ICD-8 (10) and ICD-9 (11) code 186, ICD-10 code C62 (12)], age-standardized to the world population, were obtained from volumes 4 to 9 of *Cancer Incidence in Five Continents* (CI5; refs. 13, 14). For volumes 4 to 8, the CI5 electronically updated data were used. Electronic updates are provided only for selected cancer registries that have been included in at least three consecutive volumes published in the CI5 series (15). At the current time, volume 9 data are yet to be electronically updated. The CI5 series includes incidence data from areas within the Americas, Europe, Africa, Asia, and Oceania that are covered by selected population-based registries and for the 5-year time periods 1973 to 1977, 1978 to 1982, 1983 to 1987, 1988 to 1992, 1993 to 1997, and 1998 to 2002. Incidence rates by histology (seminoma, non-

seminoma, and other/unspecified) were obtained from the CI5 ADDS software package (13) for volumes 4 to 8 and directly from the website for volume 9.

The registries selected for the current study were, to the greatest extent possible, identical to the registries included in our previous study (2). Inclusion criteria for the registries have been previously described (2). Briefly, only one registry from each country was chosen for trend analysis. However, if more than one registry within a country met the basic inclusion criteria, the registry that covered the largest population was included.

Data from the Puerto Rico registry were not included in the current report as the registry was absent from volume 9. In place of data from the Puerto Rico registry, the current study included data from the registry in Costa Rica. Two registries changed population coverage or reporting format between volumes 4 through 9. In volumes 4 and 5, the New Zealand registry included incidence data stratified by ethnicity (Maori and non-Maori populations). In volumes 6 to 9, however, stratified data were not reported. Through volume 8, the South Thames, England registry covered a population

of 6.8 million persons. In volume 9, the former South Thames registry expanded to include the entire Thames region, covering >14 million persons. In addition, registries for Saarland, Germany and Mumbai, India were included in the current analysis. Incidence rates for the U.S. Surveillance Epidemiology and End Results registries for whites and blacks, age-standardized to the world population, were obtained from the SEER*Stat package (16, 17), as race-specific rates were not included in CI5 volumes 4 and 5.

To display incidence rates from as wide a geographic range as possible, incidence rates from the latest time period were abstracted from 26 registries. To examine trends in testicular cancer incidence over the 30-year span, rates from 21 of these registries were included, and to examine trends in seminoma and nonseminoma, rates from eight registries were included.

Percentage change in incidence between the intervals 1973 to 1977 and 1998 to 2002 was calculated for each

Table 1. Global testicular cancer incidence rates per 100,000 man-years (1973-1977 and 1998-2002)

| Population | 1973-1977 | | | 1998-2002 | | | |
|--|-----------|-------|-------------------------|-----------|-------|-------------------------|----------------|
| | Cases | Rate* | 95% confidence interval | Cases | Rate* | 95% confidence interval | Percent change |
| Europe, Nordic countries | | | | | | | |
| Norway | 448 | 4.5 | 4-4.9 | 1171 | 9.6 | 9.0-10.2 | 116% |
| Denmark | 936 | 7.0 | 6.6-7.5 | 1361 | 9.2 | 8.7-9.7 | 31% |
| Sweden | 668 | 3.1 | 2.9-3.4 | 1214 | 5.3 | 5.0-5.6 | 70% |
| Finland | 205 | 1.6 | 1.4-1.8 | 469 | 3.7 | 3.3-4.1 | 131% |
| Europe, other countries | | | | | | | |
| Germany, Saarland | 87 | 3.2 | 2.5-3.9 | 247 | 8.1 | 7.0-9.2 | 153% |
| Italy, Varese Province | — | — | — | 95 | 7.3 | 5.7-8.9 | — |
| Switzerland, Geneva | 48 | 5.0 | 3.6-6.5 | 82 | 6.9 | 5.4-8.4 | 37% |
| France, Bas-Rhin | 50 | 3.5 | 2.5-4.5 | 198 | 6.6 | 5.7-7.5 | 89% |
| United Kingdom, England, (South) Thames [†] | 541 | 3.3 | 3-3.6 | 2156 | 5.6 | 5.4-5.8 | 70% |
| Spain, Zaragoza | 33 | 1.7 | 1.1-2.3 | 57 | 2.5 | 1.8-3.2 | 47% |
| Estonia | 48 | 1.3 | 0.9-1.7 | 85 | 2.5 | 2-3 | 92% |
| Oceania | | | | | | | |
| New Zealand | — | — | — | 696 | 6.8 | 6.3-7.3 | — |
| Australia, New South Wales | 386 | 3.0 | 2.7-3.3 | 1044 | 5.8 | 5.4-6.2 | 95% |
| Americas | | | | | | | |
| United States: white population | 1625 | 3.8 | 3.6-4 | 3465 | 6.0 | 5.8-6.2 | 58% |
| Canada, Ontario | — | — | — | 1508 | 4.6 | 4.4-4.8 | — |
| Costa Rica | — | — | — | 276 | 2.6 | 2.3-2.9 | — |
| Colombia, Cali | 26 | 1.5 | 0.9-2.2 | 115 | 2.3 | 1.8-2.8 | 52% |
| United States: black population | 34 | 0.8 | 0.5-1.1 | 121 | 1.4 | 1.1-1.7 | 75% |
| Chile, Valdivia | — | — | — | 86 | 8.8 | 6.9-10.7 | — |
| Asia | | | | | | | |
| Israel: Jewish population | 140 | 1.9 | 1.6-2.2 | 520 | 4.1 | 3.7-4.5 | 114% |
| China, Hong Kong | 114 | 1.3 | 1.1-1.6 | 292 | 1.6 | 1.4-1.8 | 19% |
| Japan, Osaka | 212 | 0.9 | 0.8-1 | 264 | 1.1 | 1.0-1.2 | 22% |
| Singapore: Chinese population | 32 | 0.8 | 0.5-1.1 | 64 | 0.9 | 0.7-1.1 | 8% |
| India, Mumbai | 92 | 0.9 | 0.6-1.2 | 256 | 0.7 | 0.6-0.8 | -24% |
| Africa | | | | | | | |
| Algeria, Setif | — | — | — | 6 | 0.2 | 0-0.4 | — |
| Uganda, Kyandodo County | — | — | — | 7 | 0.6 | 0.1-1.1 | — |
| Zimbabwe, Harare: African population | — | — | — | 16 | 0.6 | 0.2-1.0 | — |

NOTE: Before volume 6 (1983-1987), New Zealand rates were split into Maori and non-Maori populations.

*Rate is age-standardized to the world population, per 100,000 man-years.

[†]Through volume 8, the United Kingdom, England (South) Thames data included only the South Thames regions, covering ~6.8 million persons; in volume 9, this registry expanded to include the entire Thames region, expanding to >14 million persons.

population. Trends in age-standardized (world standard population) incidence rates were assessed for the following 5-year periods: 1973 to 1977, 1978 to 1982, 1983 to 1987, 1988 to 1992, 1993 to 1997, and 1998 to 2002. For certain registries, coverage was not complete over the entire earliest time period (1973-1977). Registries with non-continuous coverage were Bas-Rhin, France (1975-1977); Cali, Colombia (1972-1976); and Hong Kong, China (1974-1977). For the 1978 to 1982 time period, Costa Rica only had data for 1977 to 1981, and Cali, Colombia had data for 1980 to 1982. For Zaragoza, Spain, data that correspond to volumes 4 to 9 covered the periods 1973 to 1977, 1978 to 1982, 1983 to 1985, 1986 to 1990, 1991 to 1995, and 1996 to 2000, respectively. Trends in age-standardized incidence rates were plotted on graphs using a semilog scale to facilitate the comparison of temporal trends and magnitude (18). Data were plotted at the midpoint of each 5-year time interval.

Results

In the most recent time period (1998-2002), there was a >10-fold difference in testicular cancer incidence between Norway (9.6 per 100,000 man-years), the registry with the highest rate, and Setif, Algeria (0.2 per 100,000), the registry with the lowest rate (Fig. 1). Overall, the incidence was highest in Nordic registries and lowest in African and Asian registries and among U.S. black men. Among Asian registries, rates were notably lower in the east Asian registries (0.7-1.6 per 100,000) than they were in the sole west Asian registry, Israel (Jewish population; 4.1 per 100,000). Among the Central and South

American registries, Valdivia, Chile reported rates strikingly higher (8.8 per 100,000) than the rates reported by Cali, Colombia (2.3 per 100,000) or Costa Rica (2.6 per 100,000). Among the Nordic registries, the discrepancy between the high-rate registries (Norway and Denmark) and the lower-rate registries (Sweden and Finland) was notable.

During the most recent time period, seminomas comprised 50% to 60% of all testicular cancers in the majority of registries (Fig. 1). The proportion of tumors that were seminomas, however, ranged from 36% in Zaragoza, Spain to 63% in New Zealand and Singapore (Chinese population). There was no relationship between the proportion of tumors that were seminomas (or nonseminomas) and the overall rate of testicular cancer.

The incidence rates during the earliest (1973-1977) and latest (1998-2002) time periods are shown in Table 1. Between the two time periods, the registries with the largest proportional increases in incidence were those of Saarland, Germany (153%) and Finland (131%). Other registries that experienced increases of >100% were Norway (116%) and Israel (Jewish population; 114%). In contrast, increases in incidence were modest in Hong Kong, China (19%) and Singapore (Chinese population; 8%). A drop in incidence (-24%) was seen in one registry, that of Mumbai, India.

Trends in testicular cancer incidence between 1973 to 2002 and 1998 to 2002 are presented in Fig. 2. Among the Nordic countries, the incidence in Norway surpassed that in Denmark (9.6 versus 9.2 per 100,000) in the most recent time period. Whereas the rates in Denmark and

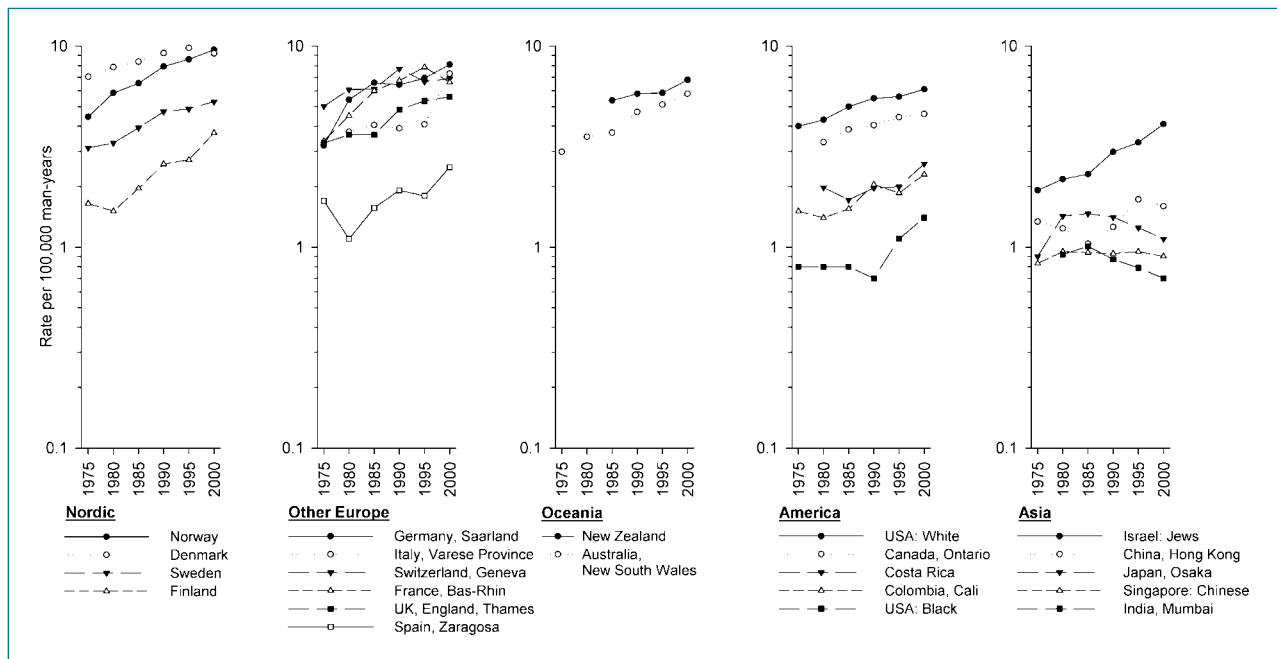


Figure 2. Trends in age-standardized testicular cancer incidence rates (per 100,000 man-years) by continent and area (1973-1977 to 1998-2002).

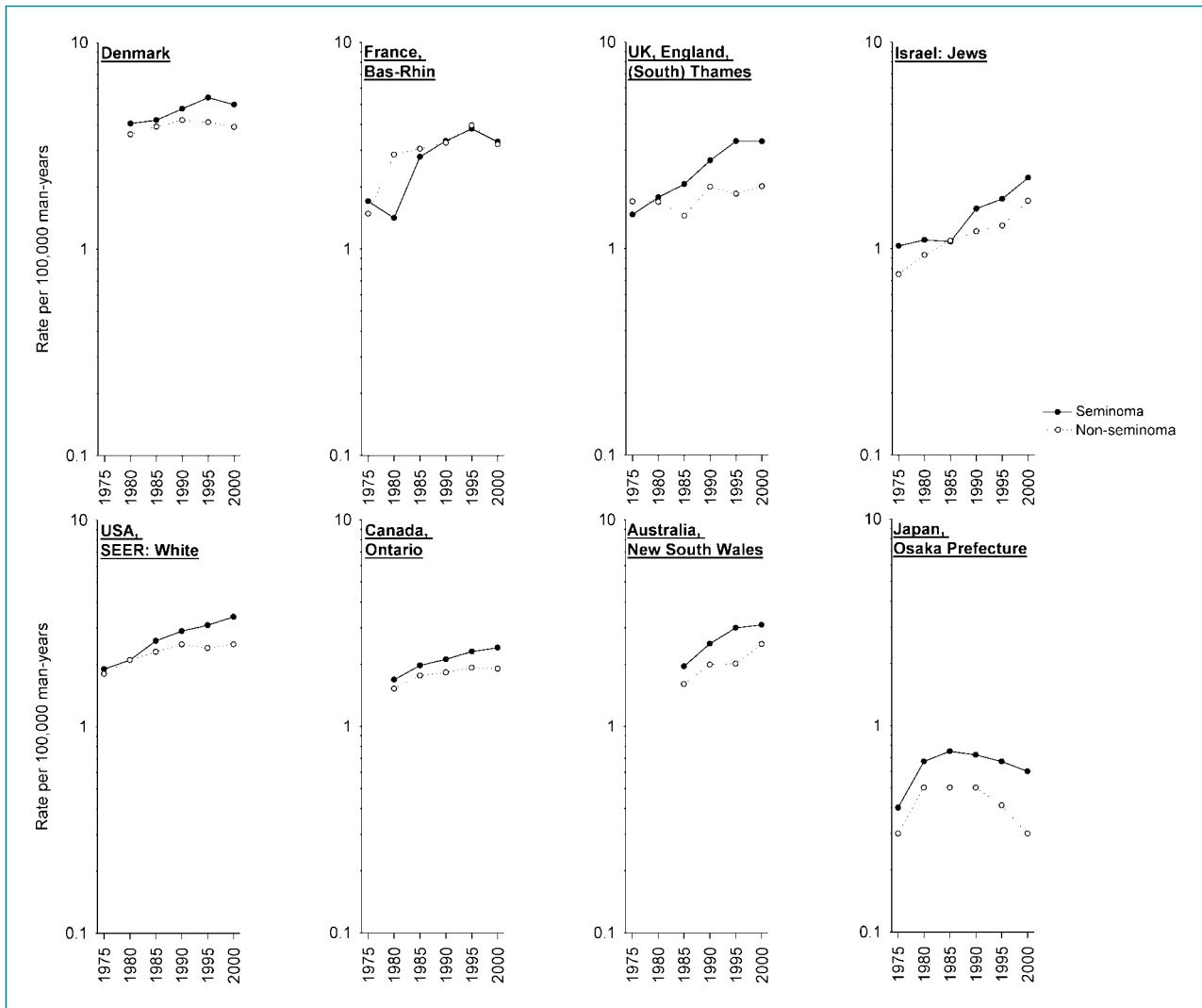


Figure 3. Trends in age-standardized testicular cancer incidence rates (per 100,000 man-years) by histology (seminoma and nonseminoma; 1973-1977 to 1998-2002).

Sweden seemed to be leveling, rates in Norway and Finland continued to increase. In other European registries, testicular cancer incidence increased in Saarland, Germany, whereas the incidence in the Thames, England and Geneva, Switzerland registries seemed to be plateauing. In contrast, the rate in Bas-Rhin, France declined in the final time period. The incidence in the Zaragoza, Spain registry was lower than that of other European registries but was continuing to increase during the most recent time interval. Rates in the Varese Province, Italy registry remained relatively stable until the 1993 to 1997 time period but then increased from 4.1 per 100,000 to 7.3 per 100,000 between the final two time periods. Rates in New Zealand, New South Wales, Australia, and the Americas all continued to increase. In Asian registries, other than that of Israel (Jewish population), incidence rates were low and either stable or modestly declining. By contrast, rates in the Israel (Jewish

population) registry were in the moderate range (4.1) and increased >100% between the earliest and latest time periods.

For the eight registries with histology data and sufficient numbers of cases, trends by histology are presented in Fig. 3. In all but one registry, rates of seminoma consistently exceeded rates of nonseminoma, although the trends by histology were fairly similar within each population. Only in Bas-Rhin, France did the rates of seminoma and nonseminoma converge around 1985 and then begin to decline around 1995. In Denmark, declines in rates of both seminoma and nonseminoma occurred, although the decline in nonseminoma rates began earlier (1990) than the decline in seminoma rates (1995). In the Thames, England registry, nonseminoma rates were fairly stable over time, whereas seminoma rates increased until the final two time periods, at which point they seemed to plateau. In the

registries of Israel (Jewish population) and New South Wales, Australia, increases in both histologic types were evident. In the U.S. white population and in Ontario, Canada, nonseminoma rates seemed to plateau around 1990, whereas increases in seminoma rates continued to the most recent time period. In Osaka, Japan, rates of both seminomas and nonseminomas began to decline in the mid-1980s.

Because the trends in east Asian registries differed from those in other areas, several other registries from each country were also inspected. Only registries with longitudinal data could be examined. In China, registries other than Hong Kong with longitudinal data included those in Shanghai, Qidong City, and Tianjin. As with the Hong Kong registry, rates were stable or modestly declining in all three (data not shown). In Japan, registries other than Osaka with longitudinal data included those in Hiroshima City, Nagasaki City, Miyagi Prefecture, and Yamagata Prefecture. In contrast to the rates in Osaka, rates in the other registries tended to be increasing than decreasing (data not shown). In India, two other registries could be examined, those of Bangalore and Chennai. As with the rates in Mumbai, rates in both Bangalore trended downward (data not shown).

Discussion

This analysis confirms the wide global discrepancy in testicular cancer incidence rates. Testicular cancer remains a disease predominantly of men descended from European populations, in particular, Northern European populations. Even among Northern European men, however, variability in incidence exists. Norway and Denmark have rates notably higher than those of Sweden and Finland. In general, developed countries have higher rates than developing countries, but the association is linked to the preponderance of European-descended populations in developed countries. In developed countries without European-descended populations, such as Japan, testicular cancer incidence tends to be low. Due to the poor understanding of testicular cancer etiopathogenesis, it is difficult to theorize concerning the possible causes of geographic variation in incidence. Propositions of causative factors have noted that seminomas and nonseminomas arise from carcinoma *in situ* cells. As testicular carcinoma *in situ* cells express markers in common with those expressed by embryonic stem cells and gonocytes, strong support for a very early life oncogenesis has been deduced (19, 20). Epidemiologic observation of a strong birth cohort effect when analyzed using age period cohort models has suggested that environmental factors are instrumental in determining risk (21-23). Proposed risk factors that may account for a birth cohort effect include maternal smoking during pregnancy (24, 25), lower age at puberty (26-28), marijuana use (29), increasing body mass index (30), exposure to endocrine disrupting chemicals (31-35), viral exposure (36-38), and occupational exposures (39-42).

However, epidemiologic evidence in support of any of these exposures has been inconsistent (43-51). The inconsistencies may be explained, in part, by the relative rarity of testicular cancer, and the time lag between perinatal exposures and diagnosis of cancer, which, in turn, result in reduced statistical power, reduced capacity for replication and potentially increased misclassification of epidemiologic and molecular data. Thus, the causes of geographic variability remain to be elucidated.

The highest incidences of testicular cancer are found within Northern Europe and have long been of interest due to large differences in rates between countries within this geographic area: very high rates in Denmark and much lower rates in Finland. It is evident, however, that changes are occurring in this region (52). As shown in Fig. 1, Norway has now surpassed Denmark in having the highest incidence in the world. This change in position occurred due to the simultaneous plateauing of Denmark's rates and continuing increase in Norway's rates. Another notable trend is that Finland, noted for lower rates than any other Nordic country, had an increase in incidence of >100% between 1973 to 1977 and 1998 to 2002. According to predictions calculated by the NORDPRED package (53) using data from the NORDCAN project (54), rates in Finland will continue to increase until they eventually surpass rates in Sweden some time during the years 2023 to 2027. The causes of this predicted Finnish increase, however, are unclear, as are the reasons behind the current differences in rates among the Nordic countries. Although some differences in genetic backgrounds exist, particularly between Finnish and Scandinavian populations (55), migrant studies indicate that testicular cancer incidence rates move toward those of the adopted country within one generation of migrating (56-58). These findings imply that environmental exposures are playing a large role in determining risk, although genetic susceptibility to the effects of the exposure is almost certainly required to result in an increased incidence.

The current analysis provides evidence that testicular cancer rates may be reaching a plateau in the United Kingdom and Switzerland and possibly starting a decline in France. In far eastern Asia, incidence rates also seem to be declining in Mumbai, India; Osaka, Japan; and recently in Hong Kong, China and among the Chinese population of Singapore. Japanese registries other than that of Osaka, however, seem to have increasing rather than decreasing rates, suggesting that the Osaka registry may not reflect trends in other areas of the country. The Osaka registry, however, is notably larger than the other Japanese registries examined, so it may provide a better approximation of testicular cancer rates in the national population. Whatever is happening in Japan as a whole, these declines seen in Osaka, Mumbai, and Hong Kong are notable as they argue against Westernization being a risk factor. Lack of genetic susceptibility to a putative risk factor may be affecting rates in eastern Asian populations, but

declining rates over a 30-year period argue that environmental influences are also at play.

In contrast to the low rates in eastern Asia is the high rate reported by the Valdivia, Chile registry. Explanation of this high rate, however, is unclear, as other South American registries reported rates that were one quarter of the rate in Chile.

It has been perceived that seminoma and nonseminoma have a similar etiopathogenesis insofar that they arise from a common precursor lesion (59), have overlapping risk factors (60-66), and, for many countries, have fairly comparable incidence trends as shown by this and prior studies (3, 67-70). However, whereas secular trends for each subtype are fairly comparable within each country, differences still exist in both the trend and magnitude of incidence. Based on specific registries, this analysis suggests that the discrepancy between the incidence of nonseminoma and seminoma is widening in all countries analyzed, except, perhaps, France, Israel (Jewish population), and Australia. Moreover, previous analyses have noted disparate trends by histology in East Anglia, United Kingdom (71), Vaud, Switzerland (72), USA (21), Sweden (70), Italy (5), and Germany (73). Age period cohort models also lend credence to the idea that there are dissimilarities between testicular histologic tumor types, specifically in analyses of data from Finland (70), United States, (3), Canada (3, 74), Denmark (3), and Australia (3, 9). The magnitude of these differences may be smaller relative to other cancers that have been analyzed by histologic subtype, but this may be related to the relatively low incidence rate of testicular cancer. Differences between seminoma and nonseminoma remain evident and suggest that some of the unknown causative factors of testicular cancer may partially or exclusively affect risk of a single histologic group.

The current examination of testicular cancer rates had a number of strengths in that the data were abstracted from large, well-established registries throughout the

world. In addition, for the first time, rates of particular histologic types of testicular cancer could be examined separately. The conclusions of the study, however, were limited by the lack of nationwide cancer registries in many countries. Whereas every effort was made to select large, representative registries from each country, it remains possible that the registries included in the study do not accurately reflect patterns in their nations. Finally, as testicular cancer is a rare neoplasm even in countries that experience the highest rates, the trends reported in low-rate countries must be interpreted cautiously as they are based on small numbers, which are prone to random variation.

In summary, this analysis of published testicular cancer incidence data suggests that incidence continued to increase in many populations worldwide between 1973 to 1977 and 1998 to 2002. The increase, however, was most notable among some European-descended populations. Eastern Asian populations, in contrast, continued to have low rates that remained stable or declined. The increases in testicular cancer rates over a 30-year period argue that environmental risk factors are likely to be involved, although the great discrepancy in rates among persons of different racial and ethnic groups suggests that genetic susceptibility may also be an important determinant.

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No potential conflicts of interest were disclosed.

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