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Platinum Priority – Testis Cancer

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International Trends in the Incidence of Testicular Cancer: Lessons from 35 Years and 41 Countries

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Abstract

Background: Incidence rates of testicular cancer (TC) have been increasing in many countries since, at least, the mid-20th century without clear explanation. Examining the varying trends across countries and time provides clues to understanding the causes of TC.
Objective: We have presented incidence data from 41 countries and evaluated incidence trends for the 35-yr period from 1978 to 2012.
Design, setting, and participants: Cancer registry data from Cancer Incidence in Five Continents (CI5) volumes V–XI, CI5plus, and the NORDCAN database were analysed.
Outcome measurements and statistical analysis: Age-standardised rates of TC overall and by histological type were calculated. A joinpoint regression model of the natural log-transformed rates was used to calculate the average annual percent change (AAPC) in incidence. Age-period-cohort modelling was used to examine the effect of birth cohort on rates.
Results and limitations: While the highest incidence of TC remains in Northern Europe, the gap is closing between higher- and lower-incidence regions. Age-period-cohort modelling found flattening of risk among recent cohorts in Denmark and the UK, a steady increase in risk in the USA (particularly for seminomas), and an increase in risk among more recent cohorts in Costa Rica, Croatia, and Slovakia.
Conclusions: The gap between low- and high-incidence countries is closing due to increases in the former and stabilisation in the latter. Understanding the causes of these and other differences in incidence rates between, and within, countries may help further our understanding of the aetiology of this cancer.
Patient summary: We examined the rates of testicular cancer in different countries over time. These rates have been increasing, although the rates in high-incidence countries seem to be slowing down, while rates in low-incidence countries are catching up. These trends might help us understand what is causing testicular cancer in general.

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1. Introduction

Testicular cancer is the most common cancer among young men aged 15–40 yr [1]. While the prognosis is very favourable, with >90% of men surviving beyond 5 yr, survivors are at increased risks of infertility, sexual dysfunction, and other side effects of treatment [2–5]. Around 98% of all testicular cancers are testicular germ cell tumours (TGCTs), which are histologically divided into seminomas (50–60% of tumours), nonseminomas (40–50%), and spermatocytic tumours (<1%) [6,7]. Seminomas are typically diagnosed at around 35 yr of age and nonseminomas at around 25 yr [6], with both forms arising from germ cell neoplasia in situ [6,7].

Incidence rates of testicular cancer have been increasing in many countries since at least the mid-20th century without clear explanation. The incidence tends to be greatest in Northern European countries, while the lowest rates are occurring in Eastern European, Asian, African, and South American countries [8]. However, even within high-incidence regions (including Northern Europe), there are examples of stark divergence in incidence between (and to an extent within) countries. In recent decades, there has been an increase in the rates of testicular cancer in countries that previously had, in relative terms, a low incidence [9], which is predicted to continue in the coming decades [10]. These phenomena are not well explained, and require careful monitoring and consideration, given the public health importance of testicular cancer among young men, and the need for high-quality cancer service delivery to maximise survival prospects and quality of life.

In this manuscript, we have updated and extended our previous assessment of international temporal trends in testicular cancer incidence [9], with the addition of new registries, examination of within-country differences, and an assessment of temporal changes in incidence rate by histological subtype. We have presented incidence data from 41 separate countries and evaluated incidence trends for the 35-yr period from 1978 to 2012. We have also conducted age-period-cohort modelling to distinguish the effects of birth cohort from those of age and period on rates.

2. Patients and methods

2.1. Data sources

Cancer registry data from Cancer Incidence in Five Continents (CI5) volumes V–XI, CI5plus, and the NORDCAN database were analysed to examine temporal trends in testicular cancer incidence over the past 35 yr. The quality of the data sources used in this manuscript has been evaluated elsewhere [11–14]. The International Agency for Research on Cancer has high data quality standards for registries to be included in CI5, based on completeness, comparability, validity/accuracy, and timeliness. The CI5plus database contains annual incidence data reported from regional and national cancer registries, and includes data on cancer site, sex, age, age-specific populations, age-standardised incidence, and histology, where available. Similarly, a new CI5 volume is published every 5 yr with the same variables as CI5plus, but with the data aggregated over the 5-yr interval rather than the 1-yr interval. In the current analysis, the CI5plus data were used where available from 1978 to 2012. Data from countries not included in the latest CI5plus database release were obtained from previous CI5 volumes, including volume V (1978–1982), volume VI (1983–1987), volume VII (1988–1992), volume VIII (1993–1997), volume IX (1998–2002), volume X (2003–2007), and volume XI (2008–2012). Lastly, two countries (Finland and Sweden) that were not able to submit data to CI5 for volume XI were included by appending data from NORDCAN, a database of cancer statistics from the Nordic countries, to the data previously submitted to CI5 (1978–2007) [15–17].

As a measure of each registry's data quality over time, registries that had been included in the most recent CI5 volume (volume XI) or had CI5plus data from 2008 to 2012, and had 15 consecutive years of data within either CI5plus or previous CI5 volumes were eligible for inclusion in the current analysis [15,16]. Forty-one countries from Africa, Asia, Europe, the Americas, and Oceania were included (Supplementary Table 1).

2.2. Statistical analysis

Age-standardised rates of testicular cancer overall and by histological type, where available, were calculated using the World Standard Population [18,19] and plotted by 5-yr intervals from 1978–1982 through 2008–2012. To examine trends in rates over time, a joinpoint regression model of the natural log-transformed rates was used to calculate the estimated annual percent change (APC) and to determine whether a second joinpoint was appropriate to characterise the change in rates within each country [20]. A joinpoint model allows for nonlinear trends in incidence over time, by indicating at which time points the trend changes significantly. If one or more joinpoints were incorporated into the model, an average APC (AAPC) was calculated to describe the changes in rates over the 35-yr period more precisely. If no joinpoints were incorporated into the model, then the AAPC exactly reflected the APC. For volume XI or CI5plus, years 2008–2012 included plotting the age-standardised rates against AAPC on an arithmetic scale, plotting the overall age-standardised rate by country.

Histology was categorised as seminoma, nonseminoma, or other histology. Volumes V–VIII classified spermatocytic seminomas (recently renamed as spermatocytic tumours, ICD-O morphology code 9063) as classic seminomas; thus, these volumes include spermatocytic seminomas in the overall estimate of seminomas (ICD-O morphology codes 9060–9064). In volumes IX–XI and CI5plus, spermatocytic tumours were not included with seminomas; thus, seminomas were identified by ICD-O morphology codes 9060–9062 and 9064. Embryonal carcinomas, malignant teratomas, yolk sac tumours, choriocarcinomas, and mixed germ cell tumours were categorised as nonseminomas and were identified by ICD-O morphology codes 9065–9102 for all included CI5 volumes. Histologies categorised as “other/unspecified” in the current analysis include sex cord-stromal tumours and any tumour with ICD-O morphology codes 8000–8005. Age-standardised rates by histological type were calculated and plotted by calendar time for the period 1978–2012 for selected high-quality registries representing various regions of the world: Chile, Colombia, Croatia, Denmark, France, India, Israel, Italy, Japan, New Zealand, Norway, Philippines, Slovakia, Slovenia, the UK, and the USA.

Age-period-cohort modelling was used to examine the effect of birth cohort on testicular cancer rates. Birth cohort trends were calculated for Costa Rica, Croatia, Denmark, Slovakia, the USA, and the UK by subtracting the midpoints of 5-yr age groups from the corresponding 5-yr calendar periods. Owing to the identification problem inherent in all age-period-cohort analyses, wherein age, period, and cohort are linearly dependent on each other, the linear component of the period effect was assumed to have zero slopes when presenting the cohort effects [9]. The cohort effects were estimated using the full age-period-cohort model with incidence rate ratios presented relative to the reference cohort, with

midpoint at 1965. More detailed methods used to perform these calculations have been reported previously [9].

As a supplementary analysis, the highest and lowest incidence rates were plotted by registry/ethnic group within each country where applicable (Supplementary material, Box 1). We also plotted seminoma rates against nonseminoma rates to visually represent the magnitude of the burden according to major histological subtypes (Supplementary Fig. 1).

SAS statistical software (v9.4; SAS Institute Inc., Cary, NC, USA) was used for data management and rate calculations. The highest and lowest age-standardised rates within each country were obtained from the International Agency for Research on Cancer's online analysis tool [21]. Sigmaplot was used to create figures (v12.5; SY Software Inc., San Jose, CA, USA). The Joinpoint Regression Program was used to calculate joinpoints, APC, and AAPC (v4.6.0.0; IMS, Inc., Calverton, MD, USA). All age-period-cohort modelling was performed using apc.fit [22] in R (v3.5.3) and graphics were performed using Stata (v13; StataCorp, LP, College Station, TX, USA).

3. Results

The highest incidence rates of testicular cancer circa 2008–2012 occurred in Europe, with all the top 12 highest-incidence countries being from Northern, Central, Southern, or Eastern Europe (Fig. 1). The highest incidence was observed in the Northern European countries of Norway (age-standardised rate: 11.5 cases/100 000 person years) and Denmark (10.2/100 000 person years). These very-high-rate countries were followed by Switzerland (8.9/100 000 person years) and Slovenia (8.8/100 000 person years). In contrast, the lowest incidence of TGCTs occurred in Africa (Uganda 0.3/100 000 person years) and Asia (Thailand 0.5/100 000 person years, India 0.6/100 000 person years, the Philippines 0.8/100 000 person years, and China 1.5/100 000 person years).

The trends in rates among the 41 countries examined are displayed in Table 1. According to the AAPC, the greatest rise in TGCT incidence rates over the 35-yr study period occurred in Croatia, with an average of 6% growth in incidence per year (95% confidence interval [CI] 2.5–9.5%) and a current rate of 7.6/100 000 (Table 1). Other high-incidence countries including Slovakia (3.9%, 95% CI 3.6–4.2), Slovenia (3.7%, 95% CI 2.3–5.2), and the Netherlands (4.0%, 95% CI 3.5–4.5) also exhibited a strong annual growth in rates. The rates of change in the highest-incidence countries of Norway (2.4%, 95% CI 2.0–2.8) and Denmark (0.8%, 95% CI 0.4–1.3%) were more modest over the follow-up period, with APCs nearing 0% in more recent decades (Supplementary Table 2). The majority of countries from regions with a relatively low testicular cancer incidence experienced 3–5% average annual growth in incidence rates, including all Central/Eastern European (ranging from 2.2% to 4.1%) and Latin American and Caribbean countries (2.1% to 4.1%; Fig. 2 and Table 1).

In most countries where histology data were available, the incidence of seminomas tended to be greater than the

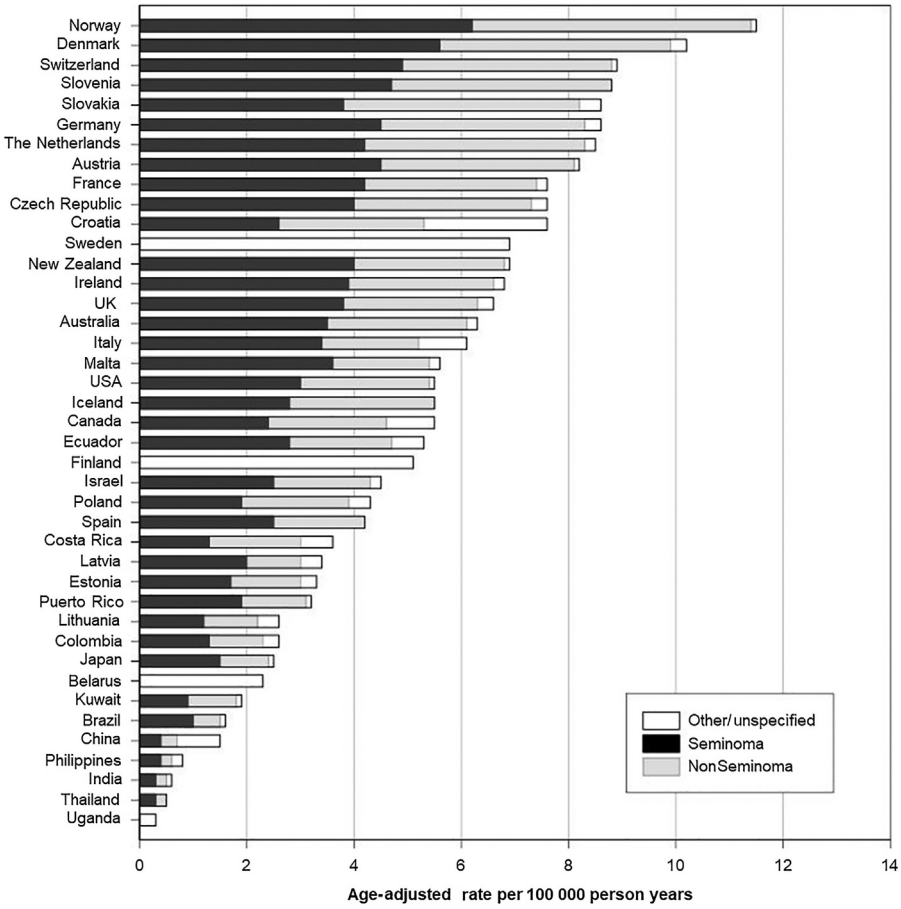

Fig. 1 – Age-standardised (World Standard Population) rates of testicular cancer incidence by histological type, 2008–2012.

Table 1 – Age-standardised (World Standard Population) testicular cancer incidence rates per 100 000 person years (2008–2012)

Population	Number of registries included	1978–1982		2008–2012		AAPC	AAPC 95% CI
		Rate	95% CI	Rate	95% CI	(%)	
Africa							
Uganda	1			0.3	(0.1, 0.4)	−3.9	(−10.5, 3.3)
Asia							
China	2	1.5	(1.3, 1.6)	1.5	(1.3, 1.6)	0.6	(−1.3, 2.5)
India	2			0.6	(0.5, 0.6)	−1.1*	(−1.7, −0.4)
Japan	3	1.3	(1.2, 1.5)	2.5	(2.3, 2.7)	2.1*	(1.5, 2.6)
Philippines	1			0.8	(0.6, 0.9)	−0.3	(−2.4, 1.8)
Thailand	1			0.5	(0.3, 0.7)	−0.2	(−2.9, 2.6)
Middle East							
Israel	1	2.1	(1.8, 2.5)	4.5	(4.1, 4.8)	2.7*	(1.6, 3.9)
Kuwait	1	1.1	(0.2, 1.9)	1.9	(1.4, 2.5)	3.0*	(1.2, 4.8)
Central/Eastern Europe							
Belarus	1[a]			2.3	(2.2, 2.5)	3.4*	(2.5, 4.4)
Czech Republic	1[a]			7.6	(7.3, 7.9)	2.2*	(1.3, 3.1)
Poland	1			4.3	(3.6, 5.0)	4.1*	(3.3, 4.9)
Slovakia	1[a]	2.6	(2.4, 2.9)	8.6	(8.0, 9.2)	3.9*	(3.6, 4.2)
Northern Europe							
Denmark	1[a]	7.8	(7.3, 8.3)	10.2	(9.7, 10.8)	0.8*	(0.4, 1.3)
Iceland	1[a]	3.0	(1.6, 4.3)	5.5	(3.9, 7.0)	1.9	(−0.5, 4.3)
Finland[b]	1[a]	1.5	(1.3, 1.7)	5.1	(4.7, 5.5)	4.2*	(3.6, 4.8)
Norway	1[a]	5.8	(5.4, 6.3)	11.5	(10.9, 12.1)	2.4*	(2.0, 2.8)
Sweden[b]	1[a]	3.3	(3.1, 3.6)	6.9	(6.5, 7.2)	2.2*	(1.8, 2.7)
Estonia	1[a]			3.3	(2.7, 3.9)	3.1*	(2.1, 4.1)
Latvia	1[a]			3.4	(2.8, 4.0)	4.5*	(3.8, 5.3)
Lithuania	1[a]			2.6	(2.2, 2.9)	3.6*	(1.0, 6.2)
Western Europe							
France	4	3.5	(3.0, 3.9)	7.6	(7.0, 8.2)	2.5*	(2.1, 2.9)
Ireland	1[a]			6.8	(6.4, 7.3)	2.6	(−0.6, 6.0)
The Netherlands	1[a]			8.5	(8.2, 8.8)	4.0*	(3.5, 4.5)
UK	11			6.6	(6.5, 6.8)	1.0	(−0.3, 2.3)
Southern Europe							
Croatia	1[a]			7.6	(7.1, 8.2)	6.0*	(2.5, 9.5)
Italy	2	2.7	(1.8, 3.6)	6.1	(4.9, 7.3)	3.2*	(2.1, 4.4)
Malta	1[a]			5.6	(4.2, 6.9)	3.6	(−1.5, 9.1)
Slovenia	1[a]			8.8	(8.0, 9.6)	3.7*	(2.3, 5.2)
Spain	2	1.3	(0.7, 1.8)	4.2	(3.4, 5.1)	4.3*	(2.9, 5.8)
Austria	1[a]			8.2	(7.0, 9.5)	1.2*	(0.1, 2.3)
Germany	1	5.3	(4.4, 6.2)	8.6	(7.4, 9.8)	1.5*	(0.9, 2.0)
Switzerland	3	6.8	(5.8, 7.8)	8.9	(7.9, 9.9)	0.5	(−0.3, 1.3)
North America							
Canada	8	3.3	(3.2, 3.5)	5.5	(5.3, 5.7)	1.5*	(1.1, 1.9)
Costa Rica	1[a]	1.6	(0.8, 2.4)	3.6	(3.2, 4.0)	3.4*	(2.4, 4.5)
Puerto Rico	1[a]	1.0	(0.8, 1.2)	3.2	(2.9, 3.6)	4.1*	(3.5, 4.8)
USA[c]	1	3.8	(3.7, 4.0)	5.5	(5.3, 5.7)	1.1*	(0.9, 1.4)
Latin America and Caribbean							
Brazil	1			1.6	(1.1, 2.0)	4.0*	(0.2, 7.9)
Colombia	1			2.6	(2.1, 3.0)	2.1*	(0.6, 3.5)
Ecuador	1			5.3	(4.6, 6.0)	2.5*	(1.3, 3.8)
Oceania							
Australia	5			6.3	(6.1, 6.5)	1.9*	(1.2, 2.6)
New Zealand	1[a]			6.9	(6.4, 7.4)	1.0*	(0.5, 1.6)

AAPC = average annual percent change; CI = confidence interval; SEER = Surveillance, Epidemiology, and End Results.
[a] Registry contributed national-level data
[b] Data provided by the NORDCAN database for years 2008–2012.
[c] Includes SEER 9 registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah).
* Statistically significant at the 0.05 level.

incidence of nonseminomas, with both histological types increasing over time (Fig. 3). In terms of temporal trends, rates of seminomas and nonseminomas tended to move in parallel with each other over time; however, there was some evidence of divergence over the last decade, wherein incidence of seminomas appears to be increasing at a somewhat greater rate than that of nonseminomas in some higher-incidence countries, including Denmark, the USA, Italy, and the UK. A sensitivity analysis was conducted to examine the difference between rates including, and excluding, spermatocytic seminomas among selected CI5plus countries, and negligible changes in rates were found (Supplementary Table 3).

The age-period-cohort models (Fig. 4) demonstrated that the peak age at diagnosis remains approximately 10 yr later

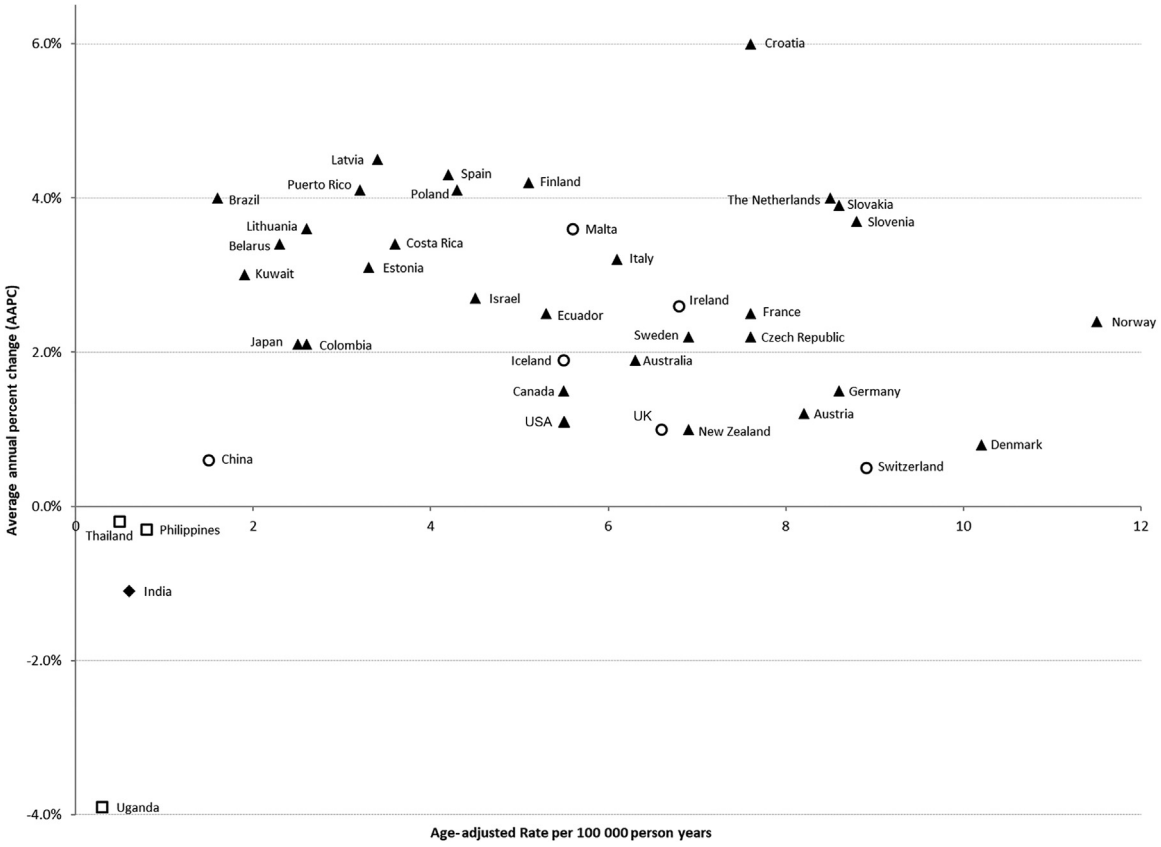

Fig. 2 – Average annual percent change (1978–2012) and age-standardised rates of testicular cancer incidence by country (2008–2012). Triangle icons refer to a significant increase over time ($p < 0.05$), circles refer to a nonsignificant increase, squares refer to a nonsignificant decrease, and diamonds refer to a significant decrease.

for seminomas (~35 yr) than for nonseminomas (~25 yr). This was true across all investigated regions, with the unusual exception of Croatia in which the peak age of seminoma diagnosis occurred between the ages of 40 and 45 yr. Regarding a birth cohort effect, we observed flattening of risk among recent cohorts in Denmark and the UK, a steady increase in risk in the USA (particularly for seminomas), and an increase in risk among more recent cohorts in Costa Rica, Croatia, and Slovakia. There was heterogeneity between regions in terms of birth cohort trends by histological subtype, with some regions experiencing uniformly greater generational increases in the risk of seminomas (Croatia, Denmark, and the USA), while this pattern was unclear for other regions.

4. Discussion

The peak incidence of testicular cancer remains centred in Europe, with the highest rates of disease remaining in Norway and Denmark. This observation is in keeping with previous evidence [8,9]. However, given that the increasing AAPC in testicular cancer incidence rates is showing signs of stabilisation or decline in most of the highest-incidence countries, there is a suggestion that countries are nearing (or may have already hit) an incidence "ceiling". The stabilisation of testicular cancer incidence among high-incidence countries was noted more than a decade ago as possibly representing "a mature phase in the epidemic" [23]. Just as the reasons for the abrupt increases in incidence in these countries in the latter half of the 20th century remain largely unexplained, so too does the stabilisation in the early part of the 21st Century.

By contrast, the rising incidence rates in previously lower-incidence countries (such as Croatia and Slovakia) appears to have accelerated in recent decades, leading to narrowing of the incidence gap among European countries. As previously noted by Znaor et al. [8], the steepest increases in incidence appear to be occurring in Southern European states. Our age-period-cohort models suggest that recent birth cohorts (from the 1960s onwards) have experienced an increase in the relative risk of testicular cancer (Fig. 4). However, what exposure(s) could be driving the risk in the more recent birth cohorts is unclear, as risk factors for TGCTs remain poorly understood in all countries.

Quickening of the rise in incidence among previously low-incidence regions has not been limited to Europe. In Latin America and the Caribbean, both Costa Rica and Puerto Rico continue to experience average annual increases of 3–4%, while the Middle East (2–4%) is also experiencing notable increases in incidence. The acceleration of rates in these regions, and in Europe, could be related to the following: (1) an actual increase in the prevalence of

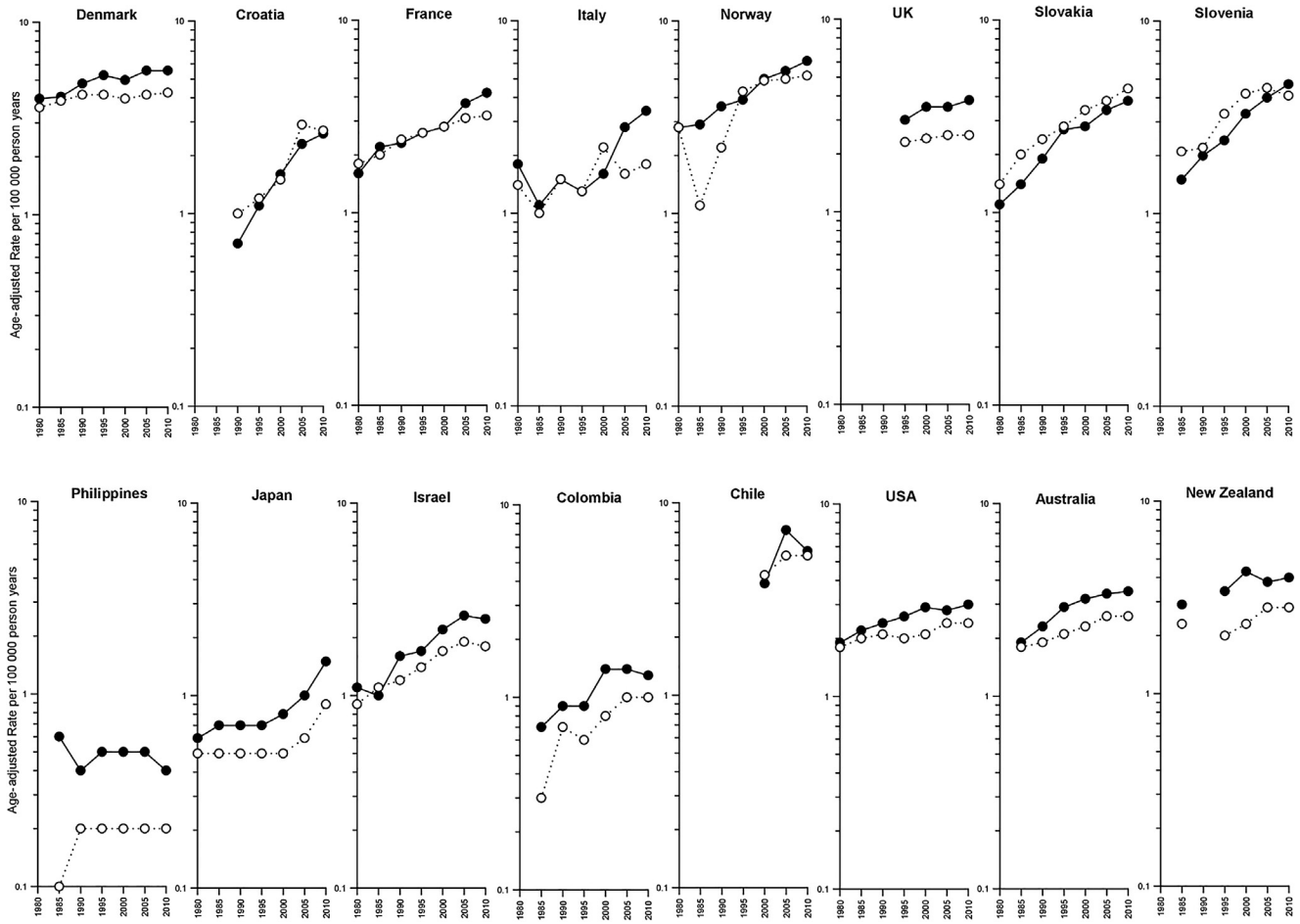

Fig. 3 – Trends in testicular cancer incidence rates for seminomas and nonseminomas for selected countries, 1978–2012.

aetiological risk factors within those populations; (2) changes in population screening for testicular cancer; (3) an increase in the diagnosis of testicular cancer (ascertainment bias), in which the detection of disease has increased (as opposed to an actual increase in disease development); (4) changes in competing morbidity risks; and (5) migration of peoples from high-incidence populations towards previously low-incidence populations. Among these possibilities, (1) is the most likely, but it is not clear which factors could be driving the increased risk, as very few risk factors have been identified for testicular cancer. Changes in population screening practices cannot explain changes in incidence, because there are no testicular cancer screening programmes in any country. Increased detection of disease due to better access to medical care is also an unlikely explanation, as men with undiagnosed testicular cancer are still likely to die from it (and thus have the cancer detected at a later stage). In terms of competing morbidity, this is an unlikely explanation as there are few competing risks among young men and the presentation of testicular cancer is fairly specific. In terms of migration, this is also unlikely as most migration is from low- to high-incidence areas, rather than from high- to low-incidence areas. In summary, there is little evidence to suggest that the increases in incidence rates are due to anything other than actual increases in incidence.

While in many regions, the gap between high- and low-incidence countries appears to be closing (eg, Northern Europe and Central/Eastern Europe), surprising differences in incidence between apparently similar countries remain. Key examples are found between border-sharing countries with similar demography—for example, the difference observed between Finland and Norway, or between Poland and Slovakia. In addition, as discussed in the Supplementary material (Box 1), incidence rates for different ethnic groups can differ markedly within the same country, even when these ethnic groups share many demographic and environmental characteristics (eg, Māori and Pacific men in New Zealand). The reasons for these disparities remain obscure, but likely include a combination of genetic and environmental drivers. Furthering our understanding of the root causes of these disparities could lead to new clues in understanding the aetiology of testicular cancer in general.

Rates of seminomas and nonseminomas tended to move in parallel over time, although as previously noted by Speaks et al. [24], there is evidence that the incidence of seminomas appears to be increasing at a greater rate than

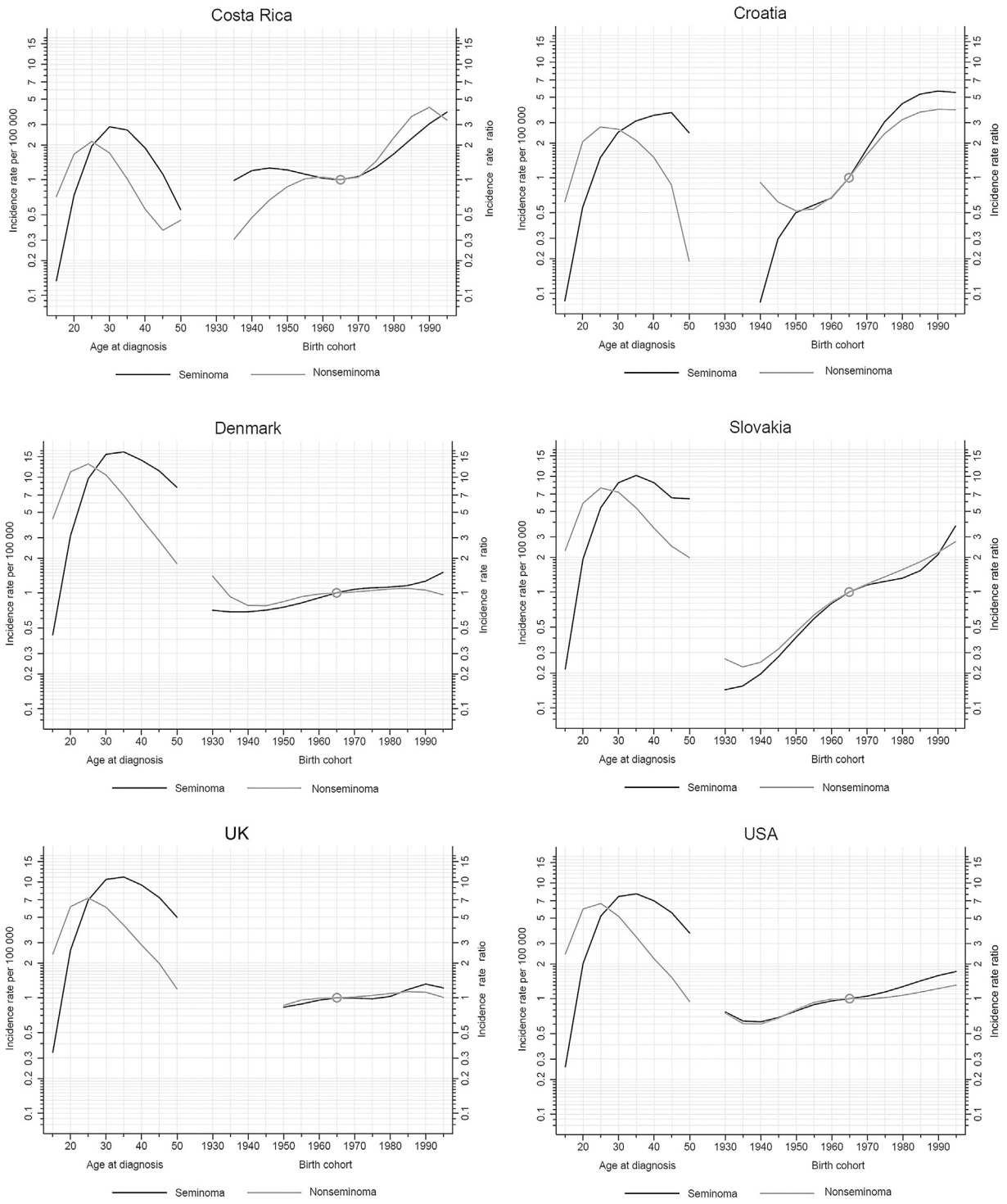

Fig. 4 – Age-period-cohort models of testicular cancer incidence: age-specific rates per 100 000 man years (left) and incidence rate ratios by birth cohort (right) for Costa Rica, Croatia, Denmark, Slovakia, the UK, and the USA.

that of nonseminomas in some higher-incidence countries including Denmark and the USA. However, these observations were somewhat heterogeneous across regions. Seminomas are diagnosed, on average, 10 yr later than nonseminomas, and nonseminomas tend to be more aggressive [9,25,26]. Owing to these differences in tumour presentation, it has been suggested that the most important exposures that lead to seminomas may differ from those that are most important in the development of nonseminomas [27]. However, as previously noted by Bray et al. [28], the lack of consistent and substantial differences over time suggests that the exposures causing the general increase in

rates of testicular cancer are relevant to the aetiology of both histological types [28].

4.1. Key new information

While the current manuscript provides a comprehensive update on previous descriptions of global trends in testicular cancer incidence, it has also revealed and/or confirmed several key pieces of information about the incidence of this disease. Firstly, our broadened perspective using data from 41 countries has allowed us to clearly convey evidence of "gap closing" between high-incidence and previously low-incidence countries. We have updated the evidence showing that this gap is closing due to a combination of increasing rates among low-incidence countries, along with recent stabilisation of rates among high-incidence countries. Secondly, these combined registries have shown the extent to which rates of testicular cancer can vary within countries (Supplementary material, Box 1), which may offer clues regarding the aetiology of this complex disease.

4.2. Strengths and limitations

A strength of this study is the inclusion of data from the CI5 and NORDCAN datasets [15–17], both of which have strict quality control rules for data collection and management. A limitation of this study is that not all countries included in this study have national cancer registries, which required us to combine regional registry data from those countries to infer national incidence rates. Another limitation is the lack of data from several regions, particularly Africa, Asia, and the Pacific Islands—regions that are less likely to have cancer registries. As noted previously [8], the International Agency for Research on Cancer is currently developing Regional Hubs for Cancer Registration, and so future studies may be able to incorporate more data from these regions [29].

5. Conclusions

While the majority of the testicular cancer burden remains in European countries, the gap is closing between higher- and lower-incidence regions, driven by a combination of increasing rates in lower-incidence countries and rate stabilisation in higher-incidence countries. While this stabilisation follows decades of an epidemic rise in incidence, and thus offers some reassurance that we are observing an incidence "ceiling", the absence of clear evidence for the cause(s) underlying these trends is notable and is thus an emerging priority. Unusual disparities within geographically similar regions, and between ethnic groups living within a country, persist and may offer clues to the currently obscure aetiology of this disease.

Author contributions: Jason K. Gurney had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gurney, McGlynn, Znaor, Bray.
Acquisition of data: Gurney, McGlynn, Bray.
Analysis and interpretation of data: Gurney, McGlynn, Florio, Znaor, Ferlay, Laversanne, Sarfati, Bray.
Drafting of the manuscript: Gurney, McGlynn.
Critical revision of the manuscript for important intellectual content: Gurney, McGlynn, Florio, Znaor, Ferlay, Laversanne, Sarfati, Bray.
Statistical analysis: Florio, Ferlay, Laversanne.
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Supervision: None.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.07.002.

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