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International Variations and Trends in Testicular Cancer Incidence and Mortality

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Abstract

Context: Testicular cancer (TC) is the most common cancer in men aged 15–44 yr in many countries that score high or very high on the Human Development Index (HDI). Despite the very good prognosis for TC, wide variations in mortality rates have been reported internationally.
Objective: To describe and contrast global variations and recent trends in TC incidence and mortality rates.
Evidence acquisition: To compare TC incidence and mortality rates, we used GLOBOCAN 2008 estimates. We used the *Cancer Incidence in Five Continents* series to analyse recent trends in TC incidence in 41 countries by way of joinpoint analysis. To examine recent trends in mortality, we used the World Health Organisation mortality database.
Evidence synthesis: Northern Europe remains the highest TC incidence area, with the highest rates observed in Norway and Denmark. Incidence rates continue to increase in most countries worldwide, more markedly in Southern Europe and Latin America, while attenuating in Northern Europe, the United States, and Australia. Mortality from TC shows a different pattern, with higher rates in some countries of medium to high HDI. The highest mortality rates were seen in Chile and Latvia, as well as in selected Central European and Eastern European countries. In high-income countries, TC mortality rates are declining or stable at very low levels of magnitude, while no significant decreases were observed in middle-income regions in Latin America and Asia.
Conclusions: The rises in TC incidence appear to be recently attenuating in countries with the highest HDIs, with corresponding mortality rates either continuing to decline or stabilising at very low levels. In a number of countries transiting towards higher levels of development, the TC incidence is increasing while mortality rates are stable or increasing.
Patient summary: In this study we looked at international testicular cancer trends. We found that testicular cancer is becoming more common in low- and middle-income countries, where the optimal treatment might not yet be available.

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1. Introduction

Testicular cancer (TC) is relatively rare, with >52 000 new cases and almost 10 000 deaths estimated worldwide for 2008. The disease makes up approximately 1% of all new male cancer cases globally. However, TC is the most common cancer form in men 15–44 yr in many countries that have attained high or very high scores on the Human Development Index (HDI) [1].

In recent decades, rapid increases in incidence rates have been observed in white Caucasian populations, with some evidence emerging of a stabilisation in trends in some

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of the highest-incidence countries [2,3]. The specific determinants responsible for such a "TC epidemic" remain largely unknown. The main histologic types of TC are seminoma and nonseminoma [4], which, according to current evidence, develop from carcinoma in situ (CIS) that arises during embryogenesis [5]. Therefore, apart from high familial risks, in utero exposures—particularly to oestrogen—as well as perinatal factors have been postulated to play the key role in the progression of CIS [6–8].

The risk factors most consistently associated with TC are cryptorchidism and a previous diagnosis of TC [9,10]. In addition, the perinatal risk factors, confirmed by recent meta-analyses, are inguinal hernia, twinning, maternal bleeding, birth order, and sibship size [11,12]. A positive association with adult height was also confirmed in a recent meta-analysis [13]. Genome-wide association studies identified several loci associated with TC [14–16]. Some researchers have suggested that the increasing incidence of TC worldwide should be interpreted in the context of testicular dysgenesis syndrome, consisting of TC, undescended testis, hypospadias, and infertility problems [17].

In contrast to the lack of present prospects of primary prevention, the treatment of TC represents a milestone in modern oncology. Following the introduction of cisplatin-based therapies in the late 1970s, relative survival proportions reached 95%, driving mortality downwards in the most affluent world regions to rates of 0.2–0.3 per 100 000 [1,2,18–20]. However, the decline in mortality trends still has not been observed in several South Eastern and Eastern European countries [21], and there is only sparse information available on geographic variations and time trends of TC in less developed regions [3,19].

The aim of our study is to present and describe the contemporary global variations in TC incidence and mortality rates, comparing and contrasting recent trends in TC incidence and mortality in >40 countries worldwide.

2. Evidence acquisition

TC (ICD-10 code C62), incidence, and mortality estimated rates for 2008 for 184 countries worldwide and world regions were obtained from the International Agency for Research on Cancer (IARC), compiled in GLOBOCAN 2008 (http://globocan.iarc.fr) [1]. The underlying principle in the estimation process is a reliance on the best available data on cancer incidence and/or mortality within a country to build up the global picture. The results are more or less accurate for different countries, depending on the extent and accuracy of locally available data.

To examine temporal patterns of observed TC incidence, data series from regional or national population-based cancer registries were extracted from *Cancer Incidence in Five Continents* (CI5), volumes 1–9 [4]. The inclusion requirement was ≥10 consecutive years of data and compilation in the last volume of the CI5 series—a criterion indicative of each registry's data quality over time, given that the editorial process involves a detailed assessment of the comparability, completeness, and validity of the

Table 1 – Estimated number of new testicular cancer cases and deaths by world area, 2008, for all ages

Region	Male population size, in millions	Cases		Deaths	
		n	ASR	*n*	ASR
Africa	*492.1*	*1481*	*0.4*	*849*	*0.3*
Northern Africa	103.3	551	0.6	308	0.3
Eastern Africa	154.1	451	0.5	273	0.3
Middle Africa	60.7	66	0.2	37	0.1
Southern Africa	28.0	191	0.7	98	0.4
Western Africa	146.0	222	0.2	133	0.2
Americas	*454.8*	*16 845*	*3.5*	*1836*	*0.4*
Caribbean	20.6	154	0.7	52	0.2
Central America	73.7	2910	3.7	523	0.7
South America	190.3	4764	2.4	848	0.4
North America	170.2	9017	5.1	413	0.2
Asia	*2097.6*	*14 775*	*0.7*	*5525*	*0.3*
Eastern Asia	808.2	4182	0.5	817	0.1
Southeast Asia	286.4	2166	0.8	945	0.3
South-Central Asia	888.2	6661	0.8	3032	0.4
Western Asia	114.8	1766	1.5	731	0.6
Europe	*352.5*	*18 326*	*4.8*	*1627*	*0.4*
Central and Eastern Europe	137.7	4199	2.6	942	0.6
Northern Europe	48.0	3365	6.7	130	0.2
Southern Europe	75.0	3363	4.2	260	0.3
Western Europe	91.9	7399	7.8	295	0.2
Oceania	*17.5*	*895*	*4.9*	*37*	*0.2*
Australia/New Zealand	12.6	868	6.7	27	0.2
Melanesia	4.3	19	0.6	10	0.4
Micronesia/Polynesia	0.6	8	1.2	0	0.0
World	*3414.6*	*52 322*	*1.5*	*9874*	*0.3*

ASR = age-standardized rate (world standard population) per 100 000 individuals.
Numbers are rounded to the nearest 10 or 100 and may not sum up to total.
Source: GLOBOCAN 2008 [1].

incidence data. To improve on the timeliness of the information, the data set was supplemented with data up to 2010 published by the corresponding cancer registries, accessible online or by special request to the cancer registry (Ireland). Of the 41 countries studied for incidence, we obtained national data for 25 countries. For the remaining countries, regional registry data were aggregated to obtain a proxy of the national incidence (65 regional registries in total). The varying start-up and overall years available for each registry within a given country led to a pragmatic selection of registries to maximise the population coverage of the country by selecting as many registries as possible that had a common registration period and met the inclusion criteria. In addition, we obtained data for US blacks and US whites. Corresponding population data were obtained from the same sources as the incidence data.

National mortality data series were extracted for 40 countries directly from the World Health Organisation mortality databank, with the inclusion criteria again set as ≥10 yr of consecutive data [22]. The quality of mortality data in terms of coverage and completeness, as well as accuracy, varies from country to country.

Cases and deaths were stratified by 5-yr age group. Rates were age standardised to the world standard population [23]. To graphically summarise the direction of the trends, locally weighted regression (Lowess) curves were fitted to provide smoothed lines through the scatterplot of age-standardised rates (ASRs) by calendar period. A bandwidth of 0.3 was used; that is, 30% of the data were used in smoothing each point. To analyse incidence and mortality trends, we used the joinpoint regression analysis [24], which includes fitting a series of joined straight lines to the trends in the ASRs. A logarithmic transformation of the rates, the standard error calculated using the binomial approximation, and a maximum number of three joinpoints were specified as options in the analysis. To estimate the magnitude and

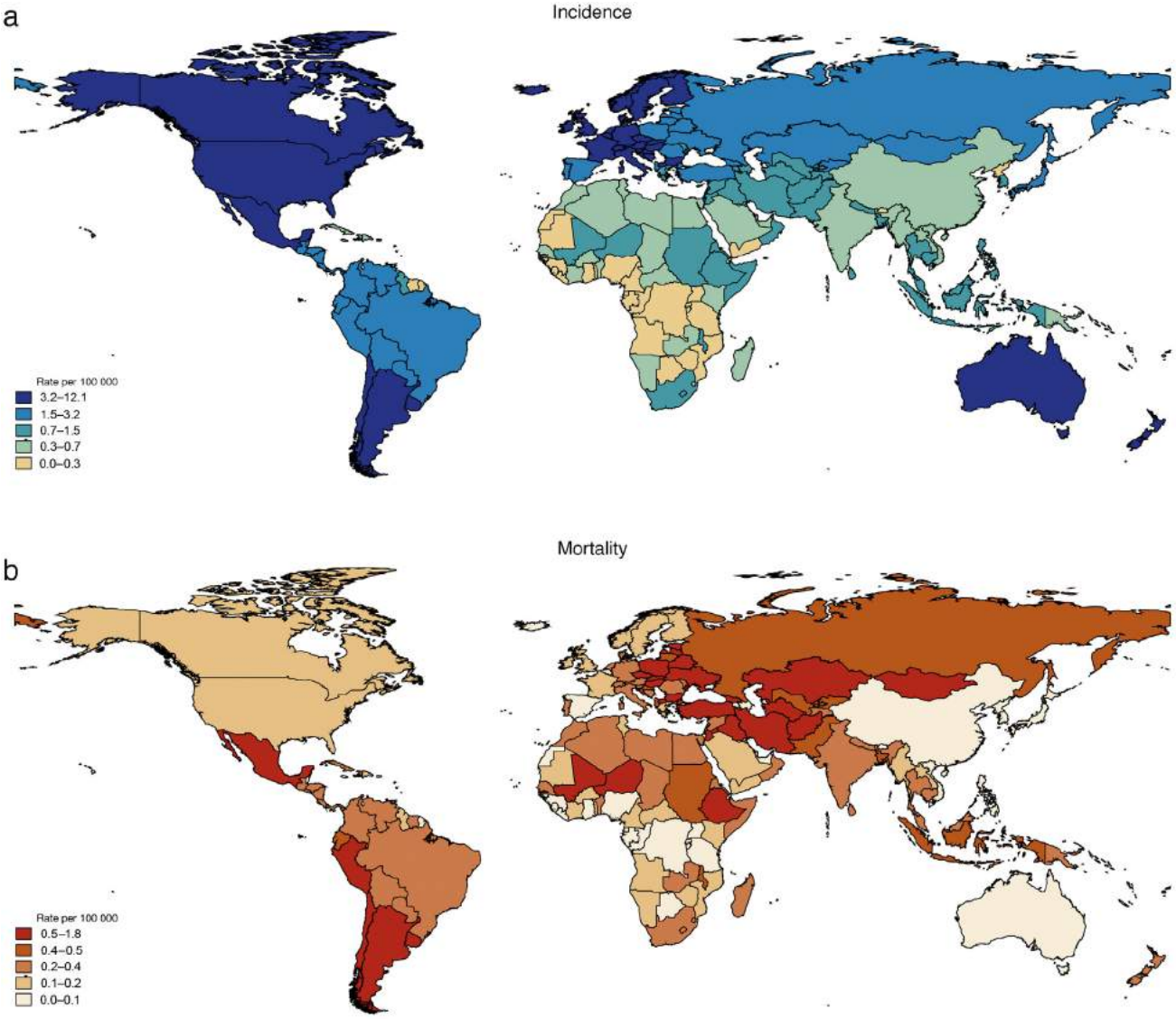

Fig. 1 – International variation in estimates of national age-standardised testicular cancer (a) incidence rates and (b) mortality rates, all ages. Source: GLOBOCAN 2008 [1].

direction of recent trends, we calculated the average annual percentage change (AAPC) and the corresponding 95% confidence intervals for the last available 10 yr of incidence and mortality data for each country. The AAPC is a geometrically weighted average of the different annual percentage changes from the joinpoint trend analysis, with the weights equal to the length of each segment during the specified time interval [25].

The data management and statistical computations were performed using Stata statistical software v.11.2. (StataCorp, College Station, TX, USA), as well as the figures, maps, and additional help of MiKTeX (http://www.miktex.org) for the tables.

3. Evidence synthesis

3.1. Geographic variation

According to the global estimates in GLOBOCAN for 2008, there were >52 000 estimated new cases of TC and close to 10 000 TC deaths worldwide (Table 1). ASRs of TC incidence varied from <1 per 100 000 in large parts of Africa and Asia to >9 per 100 000 in the highest-incidence areas of Northern Europe and Western Europe (Table 1 and Fig. 1a).

Based on the cancer registry data, the highest incidence rates were observed in Norway (9.9 per 100 000), Denmark (9.4 per 100 000), and Switzerland (9.2 per 100 000), but also

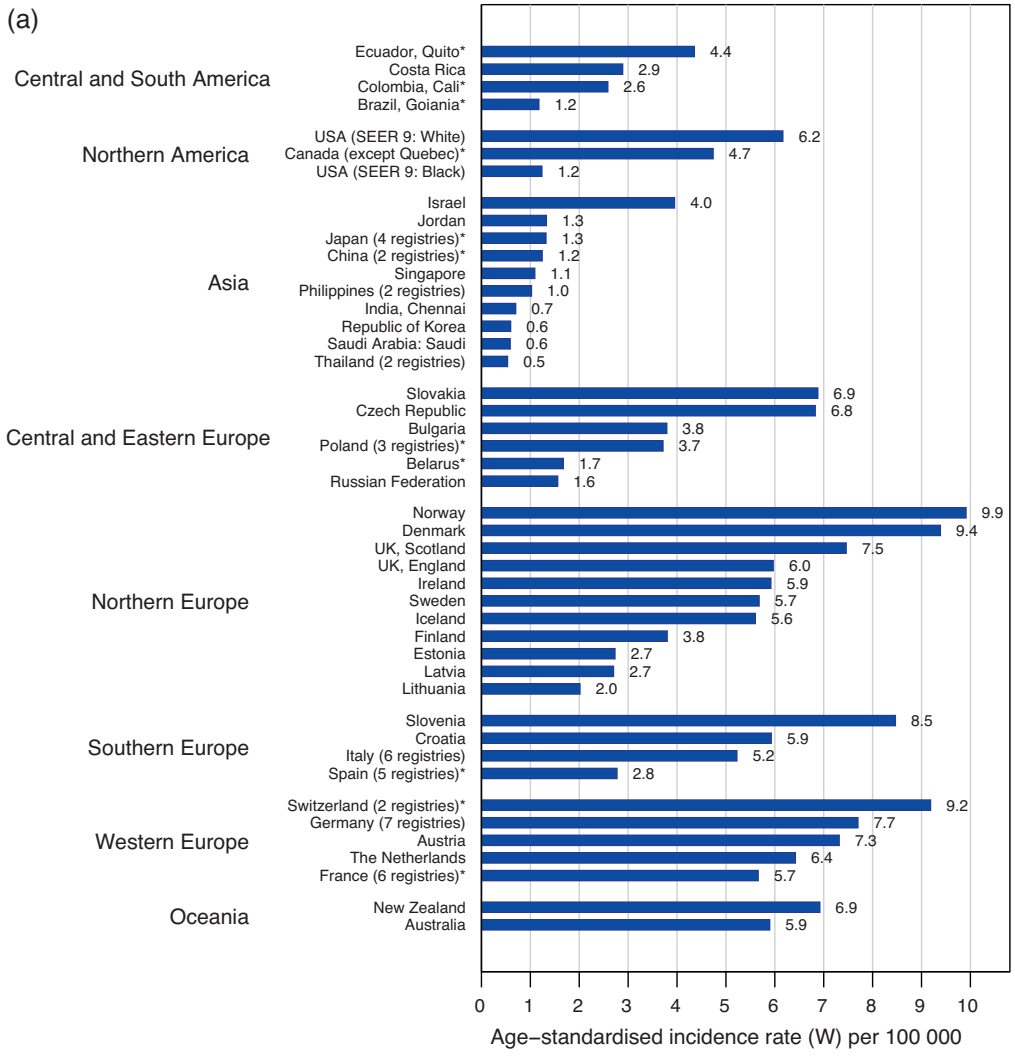

Fig. 2 – (a) Testicular cancer incidence in selected cancer registries, 2000–2004; average of rates for 5 yr in the time period, all ages; countries with <5 yr are indicated with an asterisk. Source: Cancer Incidence in Five Continents [4]. (b) Testicular cancer mortality rates in selected countries, 2000–2006, sorted in descending order of magnitude of age-standardised rates; average of rates for 7 yr in the time period, all ages; countries with <7 yr are indicated with an asterisk. Source: WHO mortality database [22]. The following is a list of regional registries (in parentheses) that provided incidence data and represent their countries: Brazil (Goiania), Canada (Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland, Nova Scotia, Northwest Territories, Ontario, Prince Edward Island, Saskatchewan), China (Hong-Kong and Shanghai), Colombia (Cali), Ecuador (Quito), France (Bas-Rhin, Calvados, Doubs, Isere, Somme and Tarn), Germany (Berlin, Brandenburg, Mecklenburg, Saxony, Saxony-Anhalt, Schleswig-Holstein and Thuringia), India (Chennai), Italy (Florence, Romagna, Veneto and Ferrara, Latina, Modena and Parma provinces), Japan (Miyagi, Nagasaki, Osaka and Yamagata), Philippines (Manila and Rizal), Poland (Cracow city, Kielce and Warsaw city), Spain (Granada, Murcia, Navarra, Tarragona and Zaragoza), Switzerland (Geneva and St-Gall-Appenzell), Thailand (Chiang Mai and Khon Kaen), United Kingdom (England and Scotland), United States blacks and whites (SEER: states of Connecticut, Hawaii, Iowa, New Mexico, and Utah; metropolitan areas of San Francisco-Oakland [California], Detroit [Michigan], Seattle-Puget Sound [Washington], and Atlanta [Georgia]).
SEER = Surveillance Epidemiology and End Results; W = world.

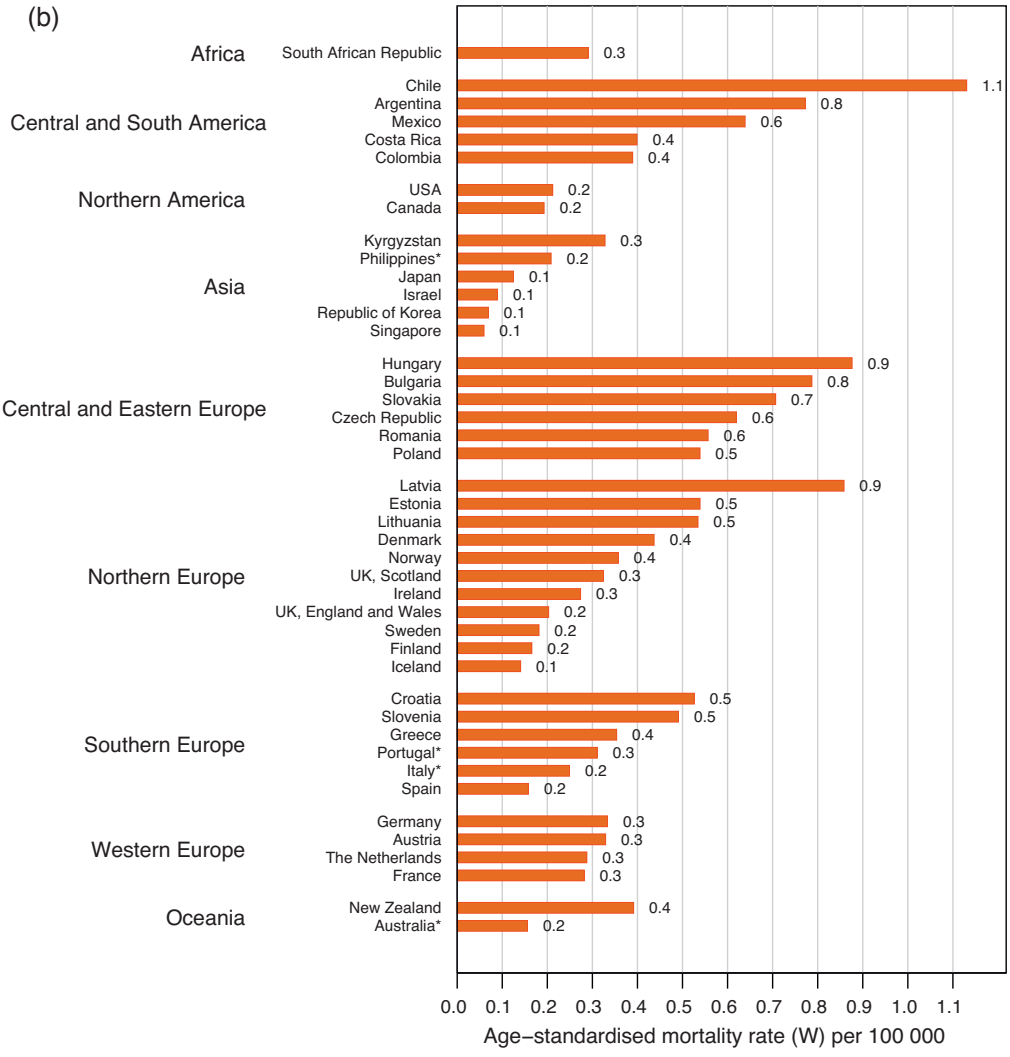

Fig. 2. (*Continued*).

in Slovenia (8.5 per 100,000) in Southern Europe. In the United States, a greater than fivefold difference was observed between whites (6.2 per 100 000) and blacks (1.2 per 100 000). Threefold variations were observed among the populations of Central America and South America (1.2–4.4 per 100 000), while the incidence rates across Asia were more homogeneous (0.5–1.3 per 100 000). The exception was Israel, with substantially higher incidence rates (4.0 per 100 000) than its geographic counterparts (Fig. 2a).

TC mortality shows a different global pattern, with higher rates estimated in low- and middle-income countries (≥0.5 per 100 000) than in high-income countries (Fig. 1b). The highest mortality rates were observed in Chile (1.1 per 100 000), Latvia (0.9 per 100 000), and Central European and Eastern European countries (0.5–0.9 per 100,000). The lowest mortality rates were observed in Asia. Mortality rates were also very low (≤0.2 per 100 000) in some higher-incidence areas, such as Australia, the United States, and some Northern European countries (United Kingdom, England and Wales; Sweden; Finland; and Iceland) (Fig. 2b).

Although half of all estimated incident cases in 2008 were in Europe, Northern America, and Australia/New Zealand, these areas contributed to only one-fifth of TC mortality worldwide. The incidence-to-mortality ratios ranged from 26 to 1 in Northern Europe to approximately 2 to 1 in South-Eastern Asia, South-Central Asia, and Africa.

3.2. *Age-standardised incidence trends*

The recent observed trends indicated persistent increases in incidence in most countries worldwide (Fig. 3, Fig. 4a). Where observed data were available, the AAPCs were lowest or nonsignificant in Asian populations, except for annual increases in incidence in Israel of 3.2%, in China of 2.1%, and in Singapore of 0.9% (Fig. 4a, Supplemental Table 1). Significant, but modest, increases were observed in most countries in Oceania and Northern America. Of the three Latin American registries contributing data, a significant increase in incidence was observed in Costa Rica (AAPC of 3.8%) (Fig. 4a, Supplemental Table 1). Most of the European countries showed significant increases in incidence, most

prominently Southern Europe, with average rises in TC incidence rates exceeding 6% per annum in Croatia and Spain. Incidence was increasing at 4% annually in Finland and 1.7% in Switzerland, the latter remaining one of the countries with the highest incidence globally, with 9.2 per 100 000 (Fig. 3). A stabilisation of the rising incidence rates could be noted within the last decade in the United Kingdom (AAPC of 0.9% in England and –0.1% in Scotland), Denmark (AAPC 0.2%), and Austria (AAPC −0.4%). While not yet reflected in the AAPC estimates, there is some visual evidence of an attenuation (or levelling off) of the incidence trends, for example, in Australia and New Zealand and, very recently, in Germany and Ireland (Figs. 3 and 4a).

3.3. *Age-standardised mortality trends*

Most of the high-income countries display quite divergent trends in incidence and mortality (Figs. 3 and 4). The

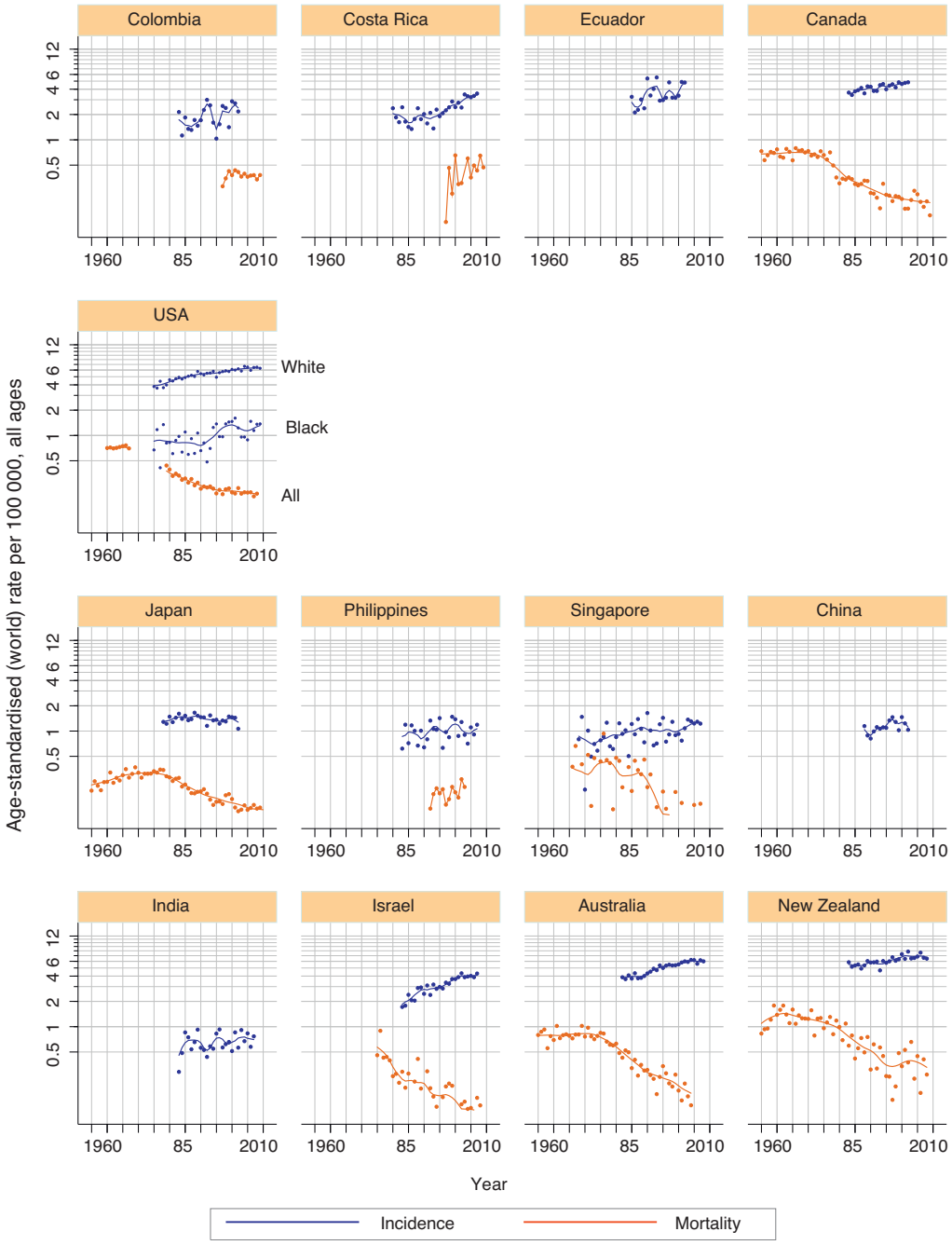

Fig. 3 – Trends in testicular cancer; age-standardised (world) incidence (regional or national) and mortality (national) rates, all ages. Rates ≤0.1 per 100 000 are not plotted. In the United States, there were no available mortality data for the 1968–1978 period. In Iceland, the mortality rate was 0.0 for 26 nonconsecutive years, including the 1986–2000 period. Mortality data are for England and Wales. Dots are observed values; solid lines are locally weighted regression curves (30% of the data were used in smoothing each point). Sources: incidence, *Cancer Incidence in Five Continents* [4] and cancer registry Web sites; mortality, World Health Organization Mortality Database [22].

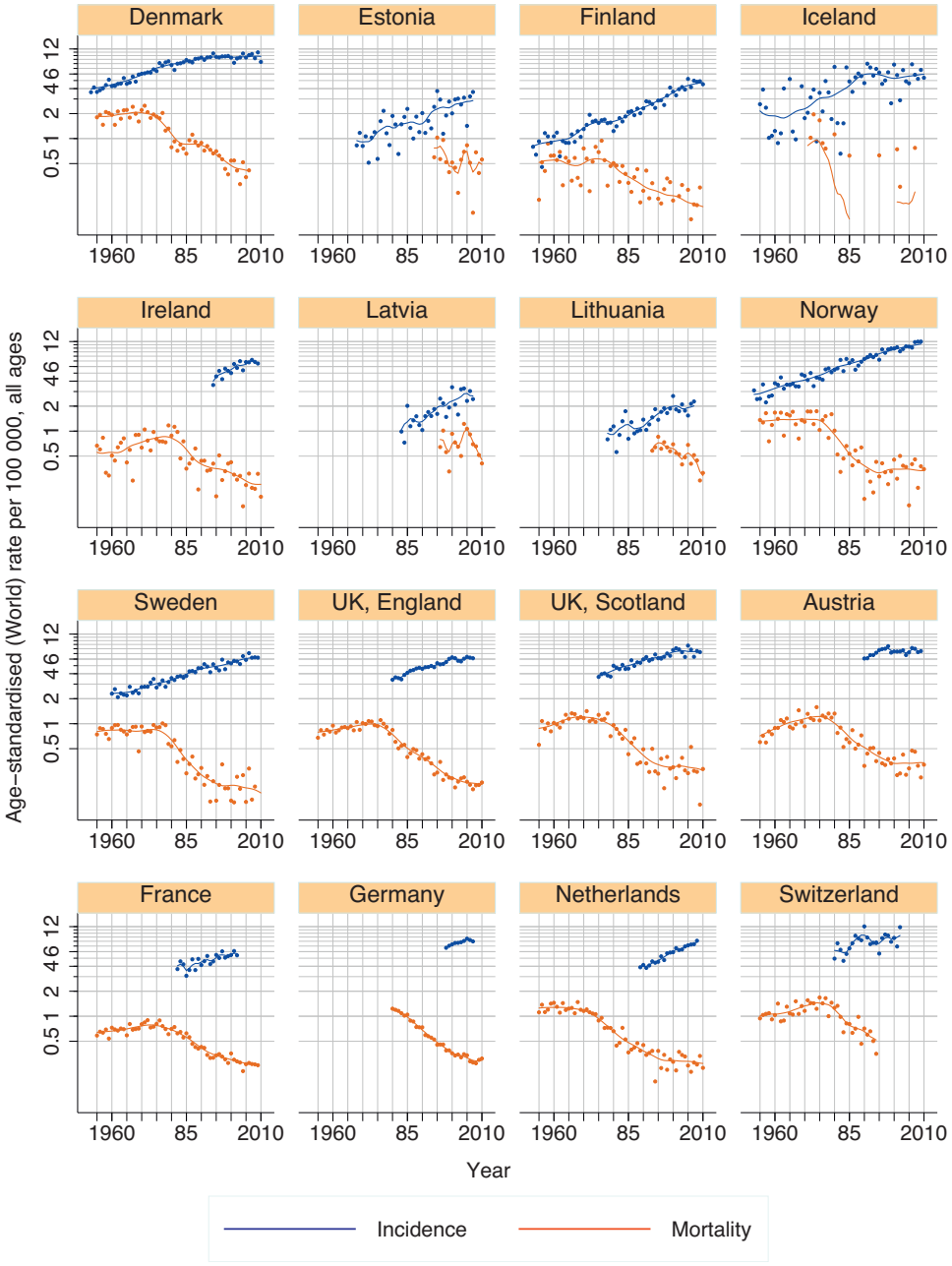

Fig. 3. (*Continued*)

declines in TC mortality started between 1970 and 1980 in the United States, Canada, Australia, New Zealand, and most countries in Northern and Western Europe but also in other high-income countries including Italy, Spain, Japan, Singapore, and Israel.

In Central European and Eastern European countries, the declines mostly started in the late 1980s. No clear declines were observed for Southern European countries (except for Spain, with an AAPC of −2.0%). In Austria, the Netherlands, and Scotland, the declining mortality trends have stabilised in the recent period (Fig. 4b, Supplemental Table 2) to mortality rates ≤0.3 per 100 000 (Fig. 3).

In Latin American countries and in the South African Republic, there were no significant changes in mortality rates in the recent period. Among Asian populations, significant decreases of mortality were observed in Japan and Israel (AAPC −1.7% and −5.2%, respectively), while the trend was stable in Kyrgyzstan and was significantly increasing in the Philippines (AAPC 4.0%) (Fig. 4b, Supplemental Table 2).

3.4. *Discussion*

Rapid increases of TC incidence rates in populations of European ancestry have marked the second half of the last century [2,3,26–28], with the increase at the beginning of the current (21st) century still evident in 38 of the 43 populations worldwide included in this study. In Europe,

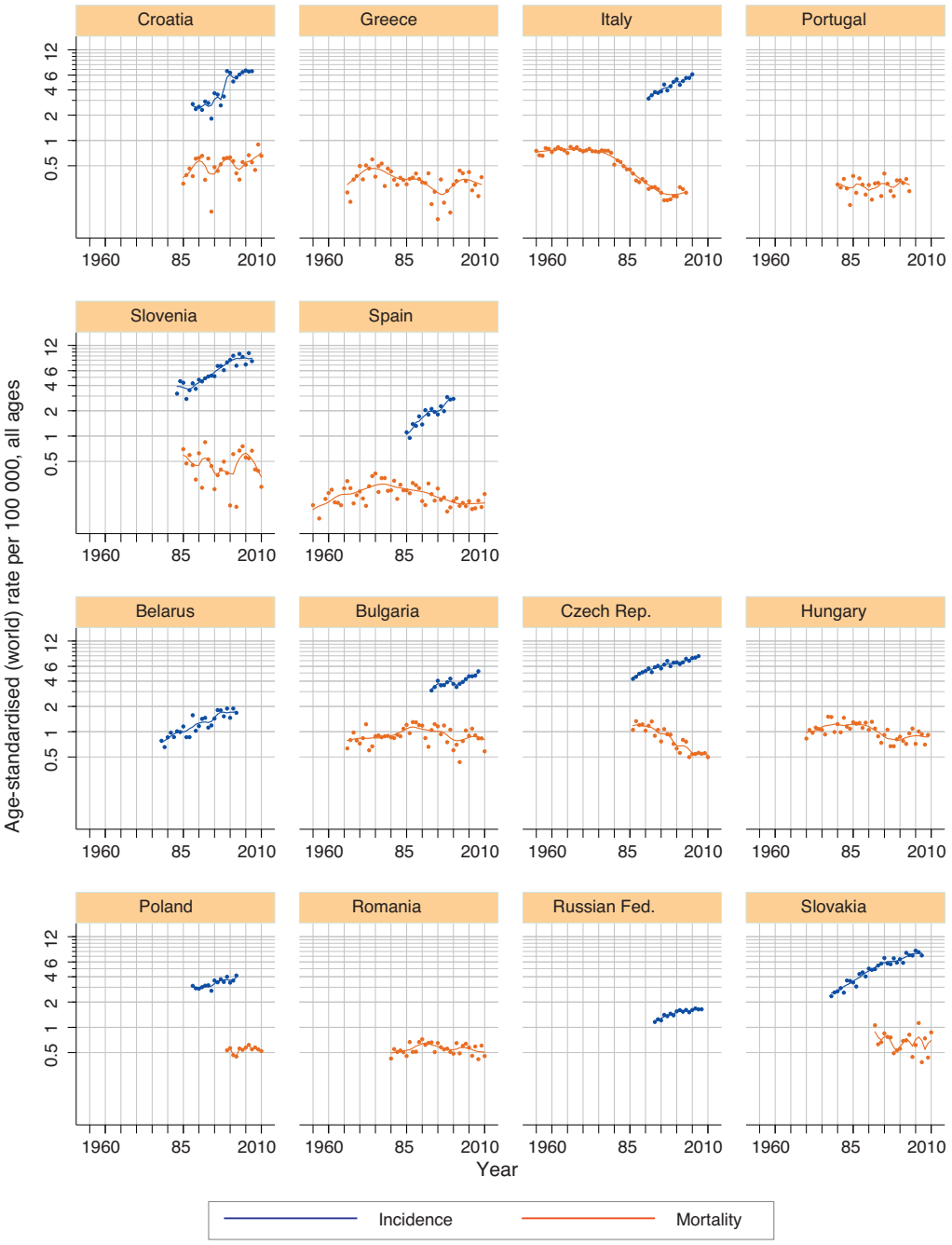

Fig. 3. (*Continued*).

the north remains the highest incidence area, with the highest age-standardised incidence rates globally observed in Norway and Denmark (9.9 per 100 000 and 9.4 per 100 000, respectively). However, in addition to reported stabilisation of trends in Denmark [2,28], the levelling off of incidence is also now evident in the United Kingdom and Ireland. The steepest increases of incidence are observed in Southern Europe, formerly an area of low incidence [2].

Whereas a previous report on international trends up to 2002 [3] showed stable or decreasing incidence trends, we observe a significant increase of incidence by 2.1% annually in China and a nonsignificant increase in India in the more recent period. In contrast, the increase of incidence observed in the US white population and Australia appears to have slowed down compared with previous studies [26,27].

While stabilisation of the trends is observed in the historically highest-incidence areas, one may speculate that TC is beginning to emerge as an important cause of morbidity and mortality in young men in lower-incidence areas of Latin America and some parts of Asia. Although these findings are in accordance with the global cancer transitions [29], it remains difficult to interpret the observed geographic and temporal variations seen at the

population level in the absence of clear risk determinants and postulated underlying mechanisms.

Since the introduction of cisplatin-based therapies in 1970s, global TC mortality trends have been driven down by the resource-dependent organisation of urologic oncology care in a given country rather than by the concomitant trends in incidence. The declines started in Northern Europe and Western Europe, the United States, and Canada in 1970s and have continued; however, they showed signs of a plateau in the last decade, when very low levels of mortality were reached (approximately 0.2 per 100,000), as has been discussed elsewhere [18,30]. The declines of mortality in the last decade were still statistically significant in the United States, Canada, and most Northern European and Western European countries, in accordance with the results of a recently published comparative study of survival trends in Europe and the United States, showing further scope for increments in survival among nonseminoma and older patients [31].

The decreases of TC mortality in Central Europe and Eastern Europe have been delayed by at least a decade compared with the north and west parts of the region, leading to large disparities in mortality [18,32]. However, in the first decade of the 2000s, we observed significant declines in Bulgaria, the Czech Republic, Hungary, and Romania. In contrast to these favourable trends, mortality is stable or increasing in a number of Southern European countries, as has already been reported from Croatia, Italy, Portugal, and Slovenia [2,18,32,33].

In a previously published analysis of TC mortality in the Americas [19], a parallel was drawn between the observed discrepancies between the European East and West and the American North and South. According to our results, Central Europe, Eastern Europe, Western Asia, and Latin America remain the regions with the highest TC mortality rates worldwide. However, while Eastern Europe seems to be catching up with Western Europe in terms of providing optimal care, possibly triggered by harmonisation of practices and access to care after the European Union expansion, no clear declines of mortality have as yet been observed in Latin America. This finding may partly relate to the present status of the health care systems in the region,

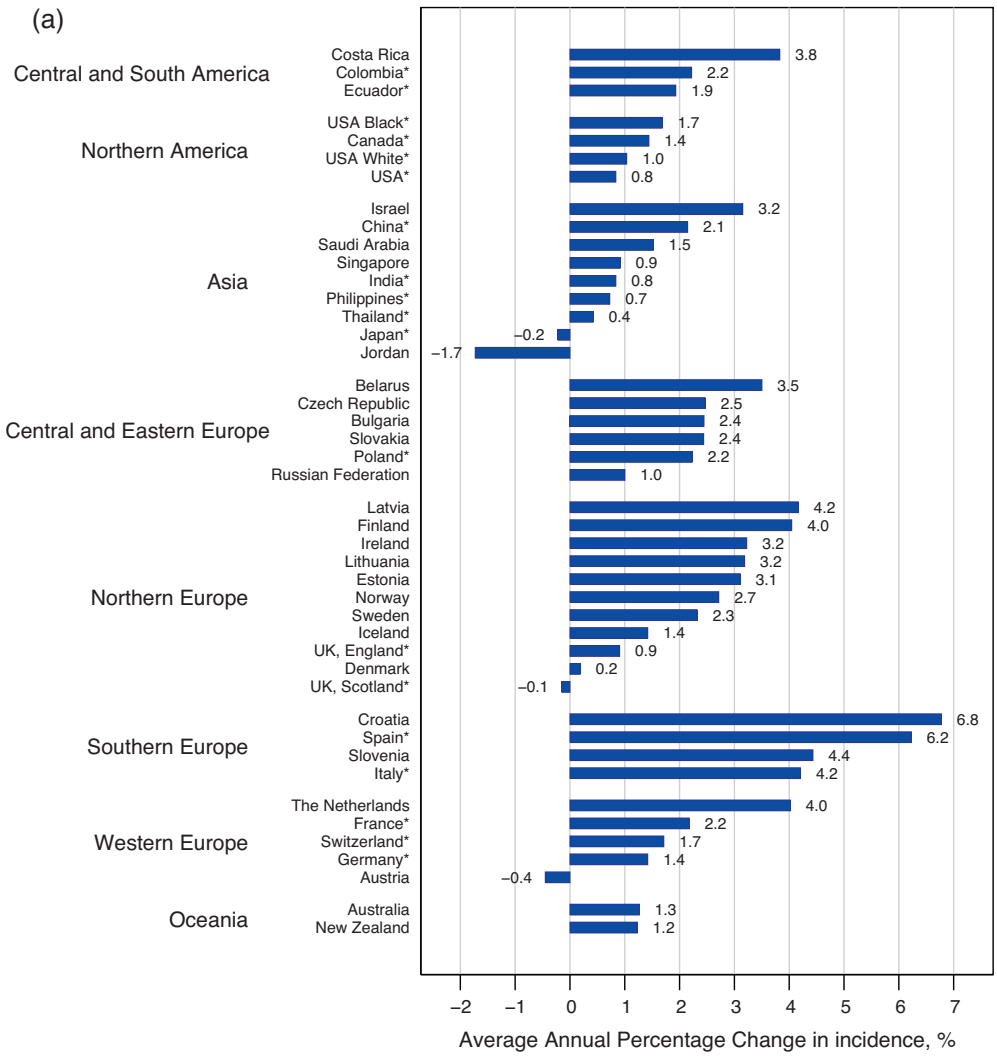

Fig. 4 – Average annual percentage change in testicular cancer (a) incidence and (b) mortality rates for the last 10 yr of available data by region, all ages.
*** Regional registries.**

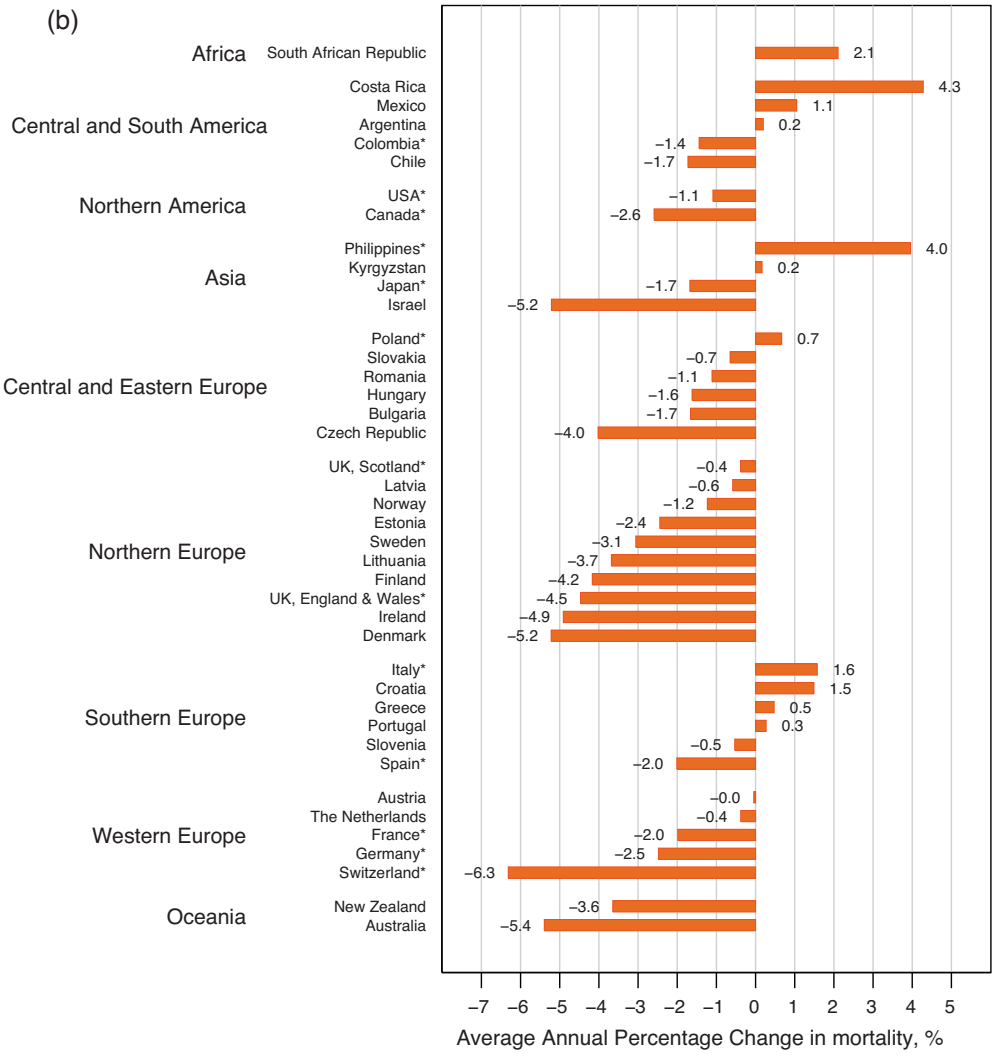

Fig. 4. (*Continued*).

with an inequitable distribution of cancer centres and specialists, as well as variations in access to cancer service, particularly for rural and remote populations [34].

Another example of geographic disparities that has not raised much attention thus far is the twofold higher rates of TC mortality in New Zealand compared with Australia. This could possibly reflect a higher TC incidence and poorer survival in the Maori population [35].

From a perspective of data availability, the proportion of coverage by cancer registration is rather low in some countries, and for those countries it may be considered questionable whether the observed magnitude of the burden and trends is representative of the national profile. A particular difficulty in estimating TC incidence, even in the case of available mortality data, is that the incidence-to-mortality ratio is highly dependent on country-specific circumstances in treatment availability. In general, a major problem in monitoring global cancer trends is the paucity of reliable incidence and mortality data, particularly in Asia and Africa. According to the GLOBOCAN 2008 estimates [1], in some African countries, such as Mali, Niger, Ethiopia, and Malawi, rates of TC mortality are relatively high; however, without an expansion of the coverage and quality of population-based cancer registration and death certification, it is difficult to assess the scale of the burden at the national level. Efforts to address this problem through the development of IARC Regional Hubs for Cancer Registration are under way.

4. Conclusions

In global terms, in countries with elevated TC incidence rates and very high HDI, we observed a stabilisation of the increasing incidence trends, as well as a convergence in cancer mortality rates to a low order of magnitude. The TC epidemic appears to be shifting to those countries that have attained medium and high HDIs, whereas in some countries the health care systems are not yet adequate to provide the optimal multidisciplinary treatment to TC patients [34,36]. A particular problem is posed by remote and rural areas, in which individuals might not have equal access to specialised treatment and, for cultural reasons or lack of

awareness, are less likely to seek immediate diagnosis and treatment, thereby diminishing their prospects of survival.

The latest estimates indicate that TC survival is >95% in the most affluent populations; corresponding mortality rates are <0.2 per 100 000, suggesting that TC deaths are almost completely avoidable [1,31]. However, of the close to 10 000 TC deaths estimated in 2008 worldwide, about three-quarters occurred in Asia, Latin America, and Africa. Urgent action is therefore needed to improve the survival of TC patients in those regions. By establishing the global network of regional cancer registration hubs, IARC is taking steps to expand high-quality population-based cancer registration in these areas, which will be vital to quantify treatment needs and monitor progress in reducing inequalities in TC care worldwide.

Author contributions: Ariana Znaor 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: Jemal, Bray.
Acquisition of data: Lortet-Tieulent.
Analysis and interpretation of data: Znaor, Lortet-Tieulent, Jemal, Bray.
Drafting of the manuscript: Znaor, Bray.
Critical revision of the manuscript for important intellectual content: Znaor, Lortet-Tieulent, Jemal, Bray.
Statistical analysis: Lortet-Tieulent.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: None.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2013.11.004.

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