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BRIEF REPORT

International testicular cancer incidence trends: generational transitions in 38 countries 1900–1990

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Abstract
Purpose Rapid increases in testicular cancer incidence have marked the second half of the last century. While these secular rises, observed mainly in countries attaining the highest levels of human development, appear to have attenuated in the last decade, rates continue to increase in countries transiting toward high developmental levels. The purpose of our study was to provide a comprehensive analysis and presentation of the cohort-specific trends in testicular cancer incidence rates in 38 countries worldwide.
Methods We used an augmented version of the Cancer Incidence in Five Continents series to analyze testicular cancer incidence in men aged 15–54 in 38 countries, via age–period–cohort analysis.
Results In many European countries, the USA, Canada, Australia, and New Zealand, there is a continuation of the increasing risk among successive generations, yet rates are attenuating in male cohorts born since the 1970s in several Northern European countries, in contrast to the steeply increasing trends in recent cohorts in Southern Europe. Incidence rates have also been increasing in the populations traditionally at rather low risk, such as in the Philippines, Singapore, China, and Costa Rica.
Conclusions The attenuation of testicular cancer risk in younger generations (in the most developed countries) alongside concomitant increases (in countries undergoing developmental change) is indicative of a global transition in the risk of testicular cancer. While identifying the underlying causes remains a major challenge, increasing awareness and adapting national healthcare systems to accommodate a growing burden of testicular cancer may prevent future avoidable deaths in young men.

Keywords Testicular cancer · Age–period–cohort analysis · Incidence · Trends

Abbreviations
CI5 Cancer Incidence in Five Continents
APC Age–period–cohort

Introduction

Testicular cancer has been one of the most rapidly increasing cancers in white Caucasian populations in the last half century [1, 2]. While the global estimate of around 55,000 new cases in 2012 represents <1 % of the total male cancer incidence annually, testicular cancer is the most common cancer among young men (ages 15–44), predominantly in countries having attained a high or very high level of human development. Incidence rates vary at least 20-fold worldwide, with age-standardised (World) rates of above 12 (per 100,000) in high-risk Norway and Switzerland, to considerably <1 in Africa and parts of Asia [3].

Explanatory factors for the distinctive incidence patterns of testicular cancer or the predominance of birth cohort effects in rates over time [1, 4–7] are in short supply. Established or putative risk factors for the disease include cryptorchidism, a previous diagnosis of testicular cancer and genetic factors identified through genome-wide association studies [8–12]; several perinatal risk factors may

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Table 1 Average annual number of new testicular cancer cases, truncated age-standardised rates (TASR) and estimated annual percent of change (EAPC) by country (national unless otherwise stated)

Region	Country	Number of cases[a]	TASR/ 100 000[b]	EAPC (95 % CI)[c]
Central & South America	Colombia (regional)	105	3.8	3.5 (0.2; 6.9)
	Costa Rica	300	4.7	5.5 (3.6; 7.3)
	Ecuador (regional)	130	6.1	0.4 (−2.1; 3.1)
Northern America	Canada (except Quebec)	2,818	8.0	1.6 (1.1; 2.2)
	USA (regional):Black	98	2.0	−0.5 (−3.3; 2.3)
	USA (regional):White	3,359	10.8	1.2 (0.7; 1.7)
Asia	China (regional)	330	1.5	2.6 (0.9; 4.3)
	India (regional)	66	0.9	2.7 (−0.8; 6.4)
	Israel	593	6.8	3.0 (1.8; 4.3)
	Japan (regional)	407	2.2	0.7 (−0.8; 2.1)
	Philippines (regional)	98	1.2	−1.5 (−4.2; 1.3)
	Singapore	76	1.5	5.4 (2.1; 8.7)
Oceania	Australia	2,931	10.2	1.4 (0.9; 2.0)
	New Zealand	655	11.8	1.1 (−0.0; 2.2)
Central & Eastern Europe	Belarus	373	2.6	4.5 (2.8; 6.2)
	Bulgaria	721	6.3	2.0 (1.0; 3.1)
	Czech Republic	1,844	11.9	2.1 (1.4; 2.8)
	Poland (regional)	334	6.4	2.6 (0.9; 4.3)
	Russian Federation	4,938	2.3	2.8 (2.4; 3.2)
	Slovakia	1,002	12.1	2.6 (1.7; 3.5)
Northern Europe	Denmark	1,259	16.4	0.3 (−0.5; 1.0)
	Estonia	87	4.8	2.7 (−0.4; 6.0)
	Finland	442	6.6	4.1 (2.8; 5.5)
	Iceland	42	9.8	0.9 (−3.2; 5.3)
	Ireland	607	10.3	3.3 (2.1; 4.5)
	Latvia	134	4.1	4.3 (1.7; 7.1)
	Lithuania	165	3.3	2.4 (0.1; 4.8)
	Norway	1,134	17.4	2.6 (1.8; 3.5)
	Sweden	1,196	9.9	2.7 (1.9; 3.5)
	UK, England	7,236	10.3	1.8 (1.5; 2.1)
	UK, Scotland	927	13.1	1.7 (0.7; 2.6)
Southern Europe	Croatia	604	10.1	8.5 (7.1; 9.9)
	Italy (regional)	788	9.0	4.5 (3.3; 5.6)
	Slovenia	456	15.1	4.1 (2.6; 5.6)
	Spain (regional)	243	4.2	6.2 (4.0; 8.5)
Western Europe	Austria	1,567	12.9	−0.2 (−0.9; 0.5)
	France (regional)	578	9.5	2.0 (0.8; 3.3)
	Germany (regional)	4,034	13.2	2.8 (1.9; 3.7)
	Switzerland (regional)	211	15.6	−0.2 (−2.1; 1.8)
	The Netherlands	2,590	11.2	4.4 (3.8; 5.0)

[a] Age group 15–54, period 2000–2004

[b] Truncated age-standardised rates (World) for the age group 15–54, period 2000–2004

[c] Estimated annual percent of change based on drift for the most recent 15-year period [except for Germany (1998–2007)], 95 % confidence interval

play a role in the disease, including inguinal hernia, twinning, maternal bleeding, birth order, and sibship size [13, 14].

Testicular cancer is one of the most curable cancers, with mortality declines and survival increments observed from the mid- to early-1970s in more affluent countries following the introduction of cisplatin-based therapies for advanced germ cell tumors. Major disparities in these indicators across Europe and elsewhere have been observed subsequently, linked to the extent of adequate resources and effective management at the national level [1, 15–20].

This study aims to provide a comprehensive analysis and presentation of the cohort-specific trends in testicular cancer incidence rates in 38 countries worldwide. We

speculate that a global transition in testicular cancer is underway, with incidence attenuating among recent generations in countries characterised by markedly high levels of incidence and human development, while increasing markedly in those countries in developmental transition and at low or intermediate risk. We focus on incidence to highlight the need to accommodate the ever-growing number of testicular cancer patients and to adapt cancer care facilities accordingly, most notably in countries undergoing major socioeconomic change.

Materials and methods

To examine temporal patterns of observed testicular cancer incidence, data series from regional or national population-based cancer registries were extracted from Cancer Incidence in Five Continents (CI5) Volumes I–IX [21]. The inclusion requirement was at least fifteen consecutive years of data and compilation in the ninth 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 incidence data. To improve on the timeliness of the information, the dataset was supplemented with data up to 2010 published by the corresponding cancer registries, accessible online or via a special request to the cancer registry (Ireland). Of the 38 countries studied for incidence, we obtained national data for 23 countries. For the remaining countries, regional registry data were aggregated to obtain a proxy of the national incidence (see footnote, Fig. 2). In addition, we obtained data for US Blacks and US Whites. Corresponding population data were obtained from the same sources as the incidence data.

To summarise the magnitude of the burden, we present the number of new cases and calculated truncated age-standardised rates (World) for ages 15–54 [22] (Table 1).We then analysed cancer incidence trends in men aged 15–54 in 38 countries, by age and birth cohort. The latter were obtained on subtracting the midpoints of 5-year age groups (15–19, 20–24,…, 50–54) from the corresponding 5-year periods, and trends in incidence rates versus birth cohort by age are presented using a semilog plot. We restricted presentation to 16 populations on the basis of geographical representation and whether the observed rates could be meaningfully visually interpreted. Assuming incidence rates were constant within the 5-year age classes and 5-year periods of diagnosis p, an age–period–cohort (APC) model was fitted [23, 24]. We assumed the number of new cases followed a Poisson random variable with the logarithm of the person-years at risk specified as an offset:

$$\log(\lambda(a, p)) = \alpha_a + \beta_p + \gamma_c \quad (1)$$

where λ refers to the rate; α_a, β_p, and γ_c are functions of, respectively, the age variable a, the period p, and the birth cohort c. The non-identifiability inherent in APC analyses—knowledge of the values of any two of age, period, and cohort implies knowledge of the third, making one of the factors redundant—was managed by constraining the linear component of the period effect to have zero slope and therefore assuming that the linear changes in testicular cancer incidence were a result of cohort-related factors. The substantial contribution of cohort influences in explaining testicular cancer incidence trends has been consistently demonstrated in previous reports [1, 4–7]. By default, the reference points are placed at the median value (with respect to the number of cases) of the cohort variable. As the solution presented is entirely dependent on our choice of allocation of the overall time trend (drift) [23], caution should be applied when interpreting the results. The cohort effects are estimated and presented as incidence rate ratios using the full APC model for all 38 populations by region. For these populations, we also quantify recent trends, the estimated annual percent of change (EAPC) in the last 15 years based on drift (Table 1). We used the default number of four internal knots for the spline bases for the cohort variable, and hence, the knots were placed at each quintile. The model analysis and presentation was performed using *APCfit* [25] in Stata [26].

Results

The quasi-parallel appearance of the observed testicular cancer incidence rates versus birth cohort across age groups is indicative of the importance of generational effects, most clearly observed in North America and in Europe (Fig. 1). In European countries with long-established registries, such as Denmark, Sweden, and Norway, a transient stabilisation in risk of cohorts born around 1940 was observed, followed by uniform increases. The cohort-specific risks have levelled off in Austria, in generations born after the mid-1960s, as well as in the most recent generations in Denmark. Steep increases in cohort-specific risks were observed in most Southern European countries (Fig. 2).

In the USA, Canada, Australia, and New Zealand, the increasing risk in successive generations was also apparent. In addition to the Nordic populations outlined above, attenuation of risk of cohorts born around 1940 was also observed in US Whites and in Canada (Fig. 2).

Of the three Latin American countries analysed, incidence was significantly increasing in Costa Rica for the cohorts born since late 1970s. In Asia, cohort-specific risks were increasing for generations born since the 1960s in the Philippines,

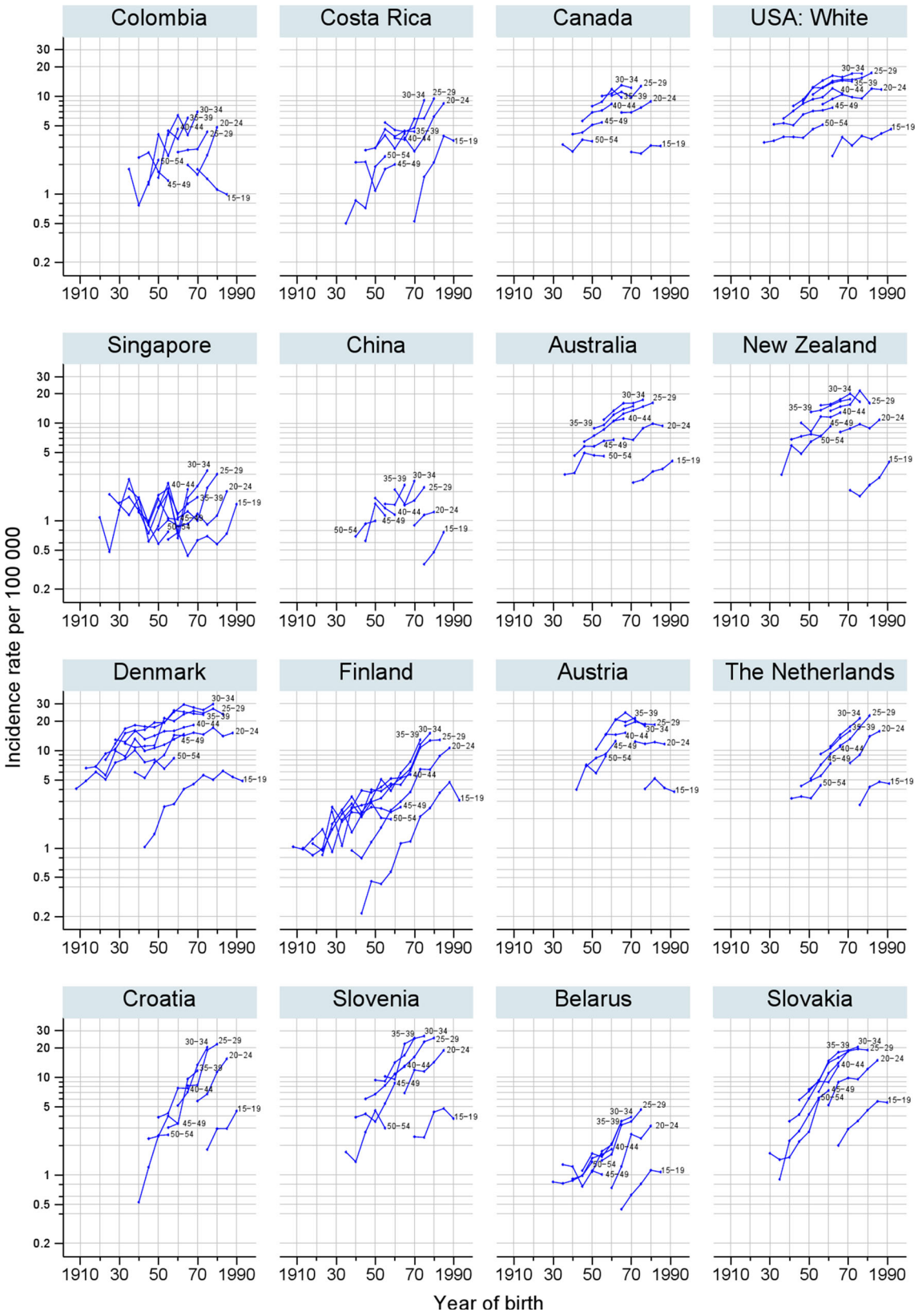

Fig. 1 Testicular cancer incidence rates versus 5-year birth cohorts by 5-year age groups (ages 15–54) for selected countries. Rates are displayed on a log scale

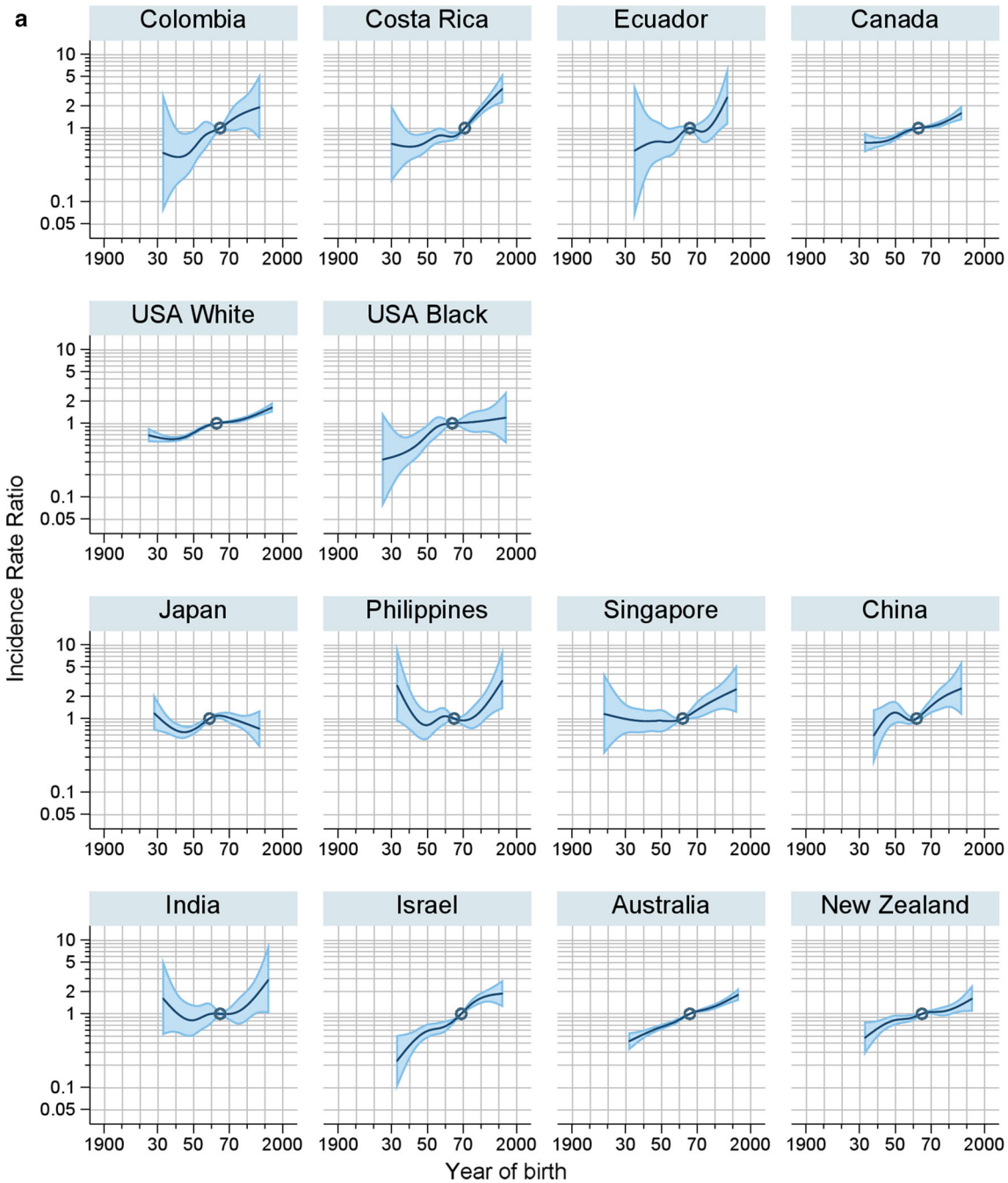

Fig. 2 Testicular cancer incidence rate ratios in successive birth cohorts with corresponding 95 % confidence intervals, men aged 15–54: **a** Americas, Asia, and Australia; **b** Northern and Western Europe; **c** Southern and Eastern Europe. List of regional registries (in brackets) which provided incidence data and represent their country: Brazil (Goiania), Canada (Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland, Nova Scotia, Northwest territories, Ontario, Prince Edward Island, and 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), UK (England and Scotland), US Blacks and US 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)]

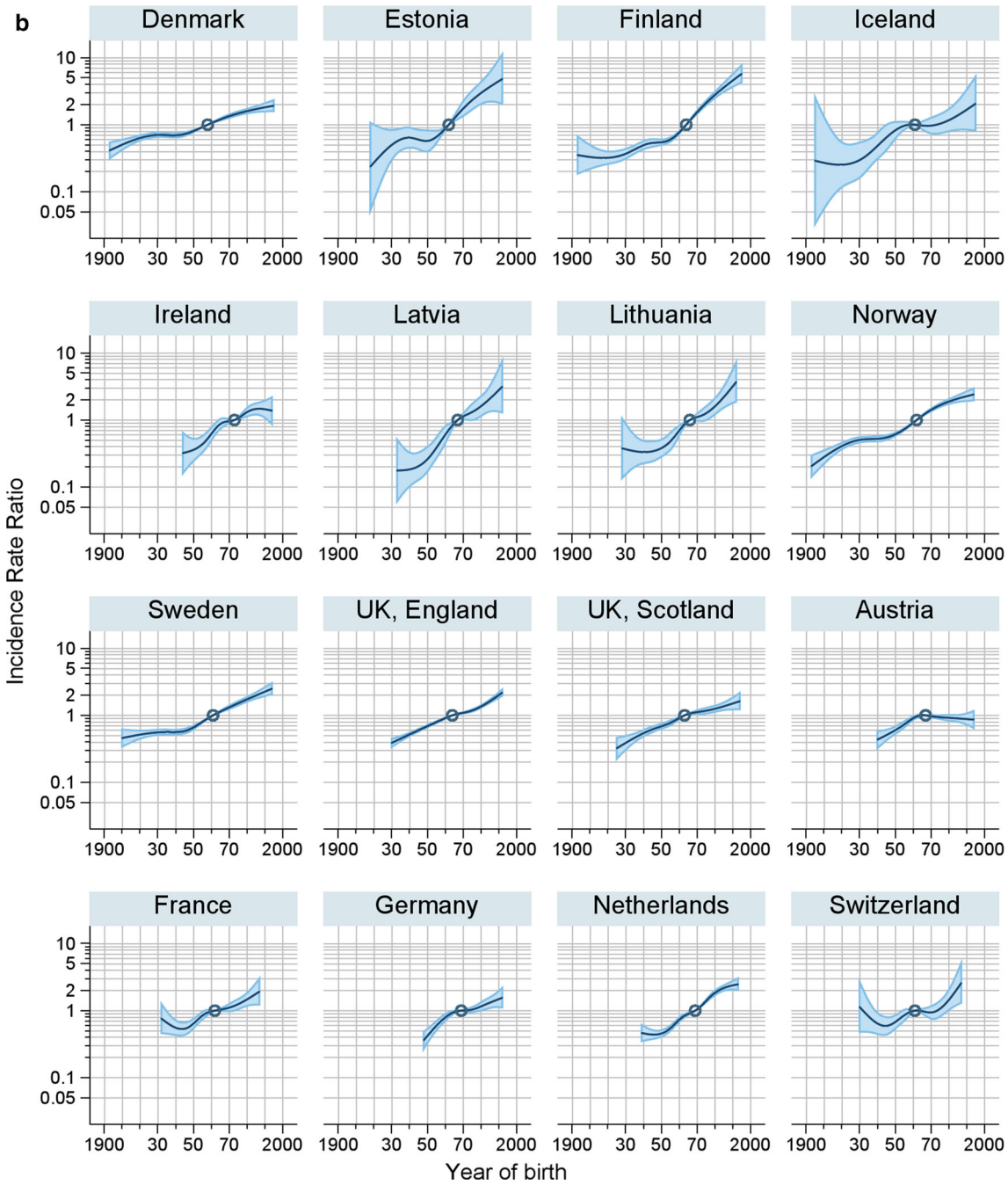

Fig. 2 continued

China, and Singapore, while in Japan, the increase in risk appears to have stabilised among recent generations. Israel had higher incidence rates and a more rapid increase in cohort-specific risks than the other Asian countries.

Discussion

The evidence published thus far from age–period–cohort models has suggested dominant cohort effects in the incidence of testicular cancer, in accordance with the etiological hypotheses of testicular germ cell tumors arising from cancer in situ [27, 28] and the postulated determining factors acting early in life. The results from APC modeling in our global study indicate that cohort effects predominate in the 38 countries, according to descriptions from the visual examination of the observed rate curves as well as the significance of nonlinear cohort effects in the APC analysis of deviance (data not shown).

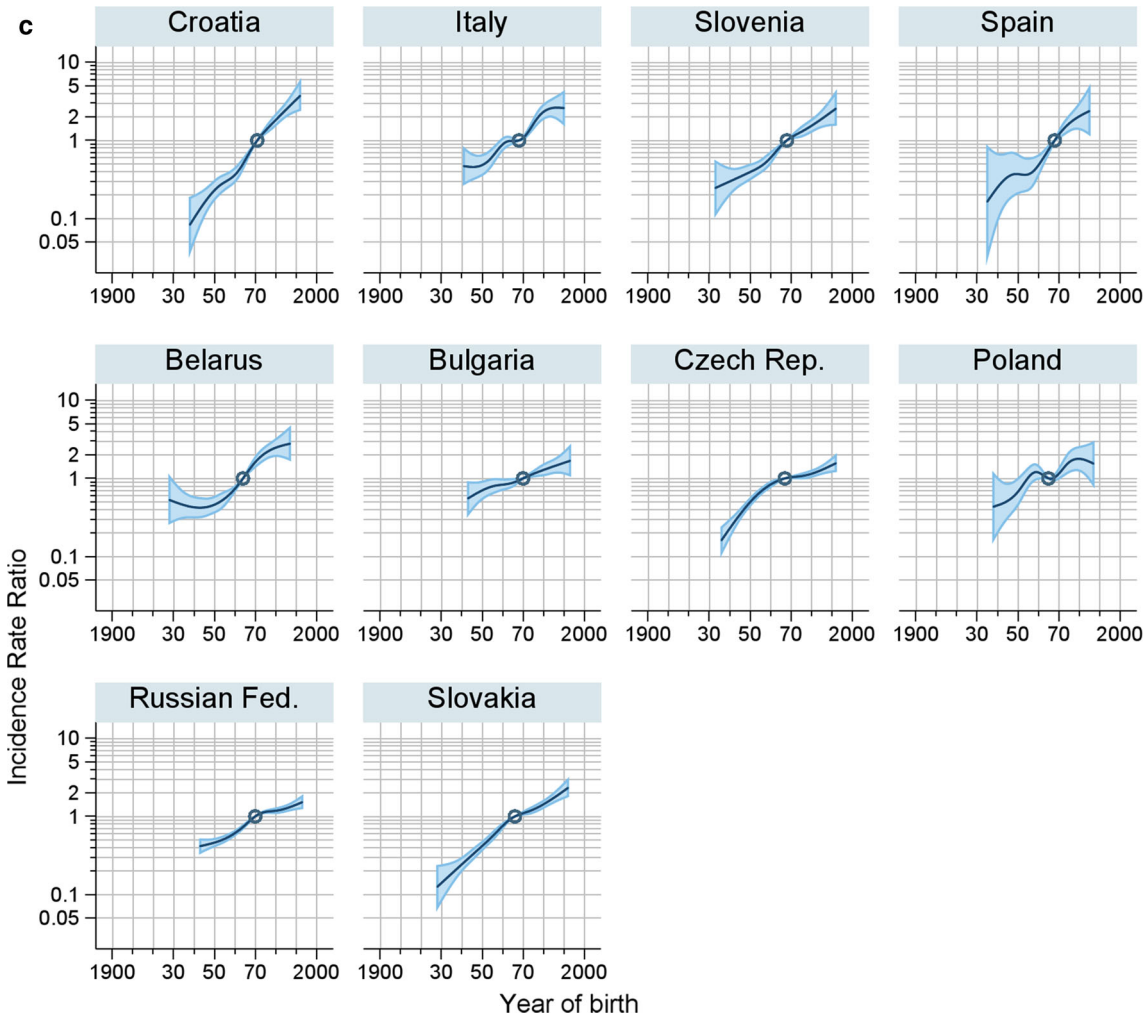

Fig. 2 continued

Our results confirm several previously published reports from Northern Europe documenting an attenuation of risks in younger cohorts of high incidence [1, 5, 6]. The stabilisation of incidence is a rather recent observation and appears restricted to selected European populations where males, in relative terms, have been at very high risk of disease [1, 5, 6]. In contrast, Southern Europe was identified as the area with most rapidly increasing cohort-specific risks globally, while incidence in Latin American countries, although generally lower than observed in Europe, has also been increasing among successive generations, as recently reported [2, 3, 17]. Asia remains the region with very low incidence rates and rather stable or only modestly increasing cohort-specific risks. Israel, however, is the exception in the region, with a high incidence, comparable to other highly developed countries.

A decrease in risk in men born during the World War II has been reported in several European populations and in the US Whites and hypothesised to be due to abrupt modifications in lifestyle factors linked to wartime and factors acting early in life and subsequent changes in prevalence of different perinatal factors [7, 11, 29, 30]. Our study confirmed decreases in risk in cohorts born around World War II in North America, in both Canada, and among US Whites. A second major deceleration in risk appears to have occurred in younger generations born in the 1960s and 1970s, in selected populations characterised by being highly developed and a male population at relatively high risk of the disease. In contrast, rates are markedly increasing in countries in social and economic transition.

Applying age–period–cohort models to 40 countries, it has been predicted that the number of new cancer cases in Europe would rise by 24 % between 2005 and 2025 [31]. In contrast, based on the predicted demographic changes and a conservative estimate of 1 % annual increase in incidence, the annual number of new testicular cancer cases in countries characterised as having medium or high levels of the human development index, comprising Latin American and most of the Asian and eastern European

countries, will increase by more than 50 % between 2012 and 2030 (from 20,826 cases estimated in 2012 to 31,636 in 2030) [3].

Incidence trends and the effects of age, period, and cohort should be monitored systematically to assess the evolution of this cancer transition. While identifying the underlying causes of testicular cancer remains a major challenge, increasing global awareness and adapting national healthcare systems to accommodate a growing disease burden may prevent avoidable deaths among young men in the near future.

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