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International Variations and Trends in Renal Cell Carcinoma Incidence and Mortality

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Abstract

Context: Renal cell carcinoma (RCC) incidence rates are higher in developed countries, where up to half of the cases are discovered incidentally. Declining mortality trends have been reported in highly developed countries since the 1990s.
Objective: To compare and interpret geographic variations and trends in the incidence and mortality of RCC worldwide in the context of controlling the future disease burden.
Evidence acquisition: We used data from GLOBOCAN, the *Cancer Incidence in Five Continents* series, and the World Health Organisation mortality database to compare incidence and mortality rates in more than 40 countries worldwide. We analysed incidence and mortality trends in the last 10 yr using joinpoint analyses of the age-standardised rates (ASRs).
Evidence synthesis: RCC incidence in men varied in ASRs (World standard population) from approximately 1/100 000 in African countries to >15/100 000 in several Northern and Eastern European countries and among US blacks. Similar patterns were observed for women, although incidence rates were commonly half of those for men. Incidence rates are increasing in most countries, most prominently in Latin America. Although recent mortality trends are stable in many countries, significant declines were observed in Western and Northern Europe, the USA, and Australia. Southern European men appear to have the least favourable RCC mortality trends.
Conclusions: Although RCC incidence is still increasing in most countries, stabilisation of mortality trends has been achieved in many highly developed countries. There are marked absolute differences and opposing RCC mortality trends in countries categorised as areas of higher versus lower human development, and these gaps appear to be widening.
Patient summary: Renal cell cancer is becoming more commonly diagnosed worldwide in both men and women. Mortality is decreasing in the most developed settings, but not in low- and middle-income countries, where access to and the availability of optimal therapies are likely to be limited.

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1. Introduction

In 2012 there were an estimated 338 000 new cases of kidney cancer worldwide [1]. Renal cell carcinoma (RCC) comprises more than 90% of such malignancies, with clear cell (70%), papillary (10–15%), and chromophobe (5%) carcinoma the main histologic types [2]. Kidney cancer is currently the ninth most common cancer in men (214 000

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cases) and the 14th most common in women (124 000 cases) worldwide. There were an estimated 143 000 deaths from kidney cancer in 2012 (91 000 in men, 52 000 in women), with the disease ranking as the 16th most common cause of death from cancer worldwide.

Rates vary 15-fold worldwide. The highest incidence rates are found in the Czech Republic, and rates are elevated in Northern and Eastern Europe, North America, and Australia. Relatively low rates are estimated in much of Africa and South-East Asia [1]. Increasing incidence trends have been reported worldwide, with some evidence of stabilisation in most developed countries [3].

Established lifestyle risk factors for RCC include smoking and obesity [4,5]: smoking increases the risk of RCC by 50% in male and 20% in female smokers [6], and 5-kg/m^2 increments in body mass index (BMI) increase the risk of RCC by 24% in men and 34% in women [5]. In terms of occupational exposure, only trichloroethylene has been evaluated as a human carcinogen [7]. It has been reported that hypertension is an independent risk factor for RCC [8], and patients on maintenance dialysis also appear to have an increased risk of kidney cancer [9]. Fruit and vegetable consumption (in particular cruciferous vegetables) has been associated with a reduction in the risk of RCC [10,11]. Approximately 2–3% of RCC cases are familial, with a twofold higher risk among first-degree relatives of RCC patients. RCC can develop within certain syndromes, of which von Hippel Lindau is the most common [2]. A recent survey by the Cancer Genome Atlas Research Network identified 19 mutated genes of statistical significance including *VHL*, *PBRM1*, *SETD2*, *KDM5C*, *PTEN*, *BAP1*, *MTOR*, and *TP53* [12]. Gene-environment interactions have also been reported [13,14].

RCC incidence rates tend to be elevated at older ages and in more developed countries, where 70% of new cases occur (34% in Europe and 19% in North America) [1], and more than half of cases may be discovered incidentally [15–17]. The profound increases in incidence are largely attributable to the increase in localised tumours [18,19]. Declining mortality trends have been reported for some highly developed European countries since the 1990s [20,21].

The aim of this study was to comprehensively describe and compare variations and trends in RCC incidence and mortality worldwide, and interpret these epidemiological observations in the context of disease control by reviewing relevant changes in diagnostic practices, risk factors, and treatment regimens.

2. Evidence acquisition

RCC has been defined as malignant neoplasms of the kidney, except the renal pelvis (ICD-10 C64). Geographic and temporal patterns of observed RCC incidence were examined using data series from regional or national population-based cancer registries extracted from *Cancer Incidence in Five Continents* (CI5) Volumes I–X [22]. The requirement for inclusion was at least 15 consecutive years of data and compilation in the last volume of the CI5 series, a criterion indicative of the data quality of each registry over time, given that the editorial process involves a detailed assessment of the comparability, completeness, and validity of the incidence data. Of the 42 countries studied, we obtained national incidence 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; Supplementary Table 1). The varying start date and overall years available for each registry for a given country led to a pragmatic selection aimed at maximising population coverage while ensuring all registries met the inclusion criteria and had a sufficient and equal span of registration years available. Corresponding population data were obtained from the same sources as the incidence data.

National mortality data series were extracted for 34 countries from the World Health Organisation (WHO) mortality database, with the inclusion criteria again set as at least 15 yr of consecutive data available [23]. The quality of mortality data in terms of coverage and completeness, as well as accuracy, varies from country to country [23].

Cases and deaths were stratified by 5-yr age groups. Rates were age-standardised (ASR) to the world standard population [24]. To graphically summarise the direction of the trends, locally weighted regression (LOWESS) curves were fitted to provide smoothed lines through a scatter plot of ASRs by calendar period. A bandwidth of 0.3 was used; in other words, 30% of the data were used in smoothing each point. To analyse incidence and mortality trends, we used joinpoint regression [25], which involves fitting a series of joined straight lines to ASR trends. Logarithmic transformation of the rates, calculation of standard errors using the binomial approximation, and a maximum number of three joinpoints were specified as options in the analysis. To estimate the magnitude and direction of recent trends, we calculated the average annual percentage change (AAPC) and the corresponding 95% confidence interval for the last available 10 yr of incidence and mortality data for each country. AAPC is a geometrically weighted average of the different annual percentage changes from the joinpoint trend analysis, for which weights are equal to the length of each segment during the specified time interval [26].

3. Evidence synthesis

3.1. *Geographic variation of incidence and mortality rates*

Among men, RCC incidence rates in 2012 (cases per 100 000 population) vary from approximately 1 in African countries to >15 in the Baltic countries, Belarus, Czech Republic, and Slovakia, and in US blacks. The highest incidence rates worldwide are observed in the Czech Republic (22.0/100 000 in men and 9.9/100 000 in women), with intermediate rates among US whites and in Canada, Australia, and New Zealand. The lowest rates are seen in most African and Asian populations, with the exception of Israel. Similar geographic patterns are observed between the sexes, although rates in women tend to be half those observed in men (Figs. 1 and 2).

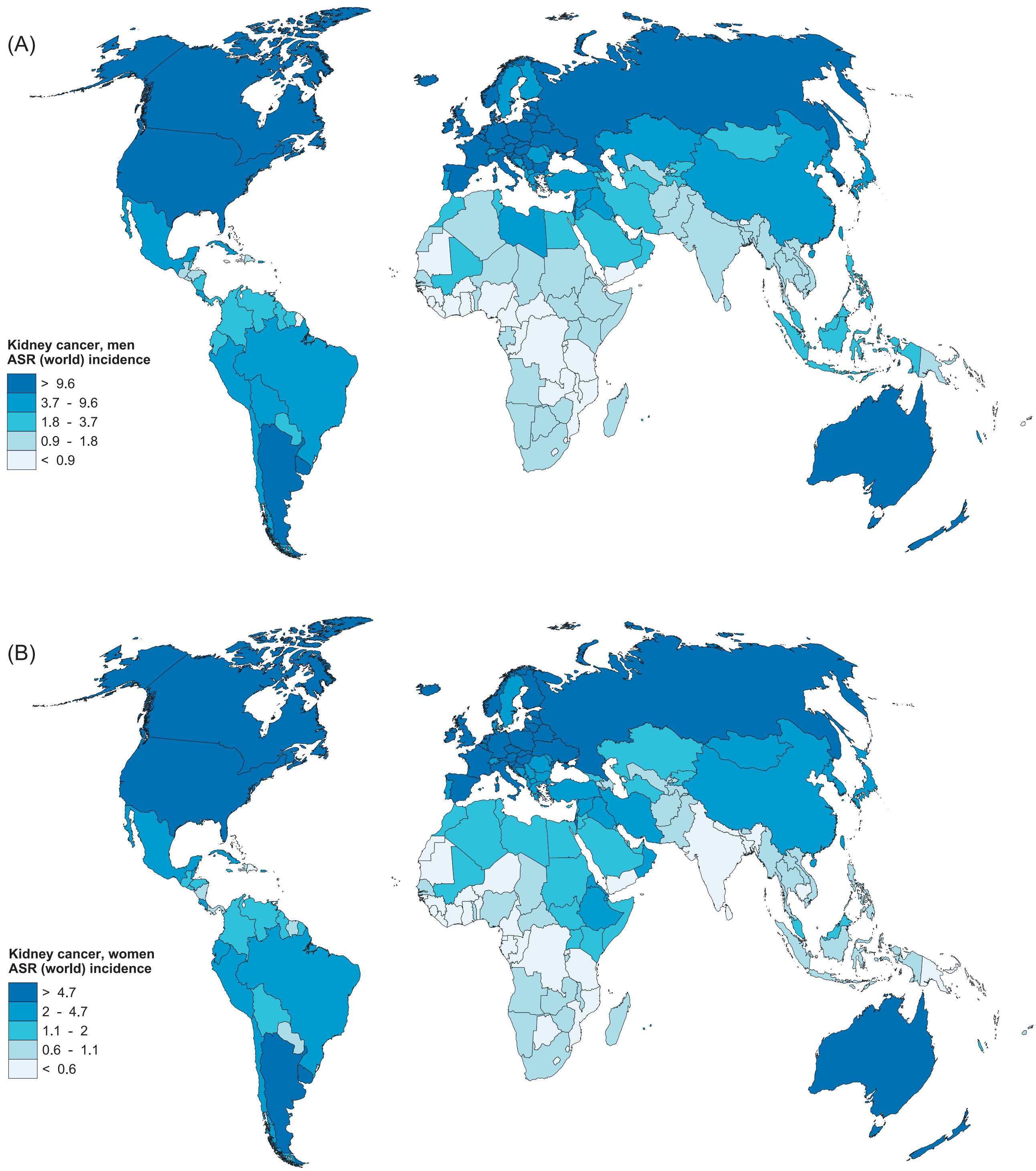

Fig. 1 – International variation in estimates of national age-standardised kidney cancer incidence rates in (A) men and (B) women [1].

Incidence rates increased with age in both sexes, with the highest incidence among the elderly (age >75 yr) in the majority of populations. The country with the highest incidence rates in all age groups in both sexes is the Czech Republic (Fig. 3).

Mortality patterns followed incidence patterns, with the highest mortality rates also observed in the Czech Republic (9.1/100 000 for men and 3.6/100 000 for women) and the Baltic countries. Comparison of incidence/mortality ratios revealed higher case fatality among men, with male mortality rates up to threefold those of females. The ratio is highest in Northern America and lowest in African countries, indicating higher survival in the former relative to the latter region (Figs. 2 and 4).

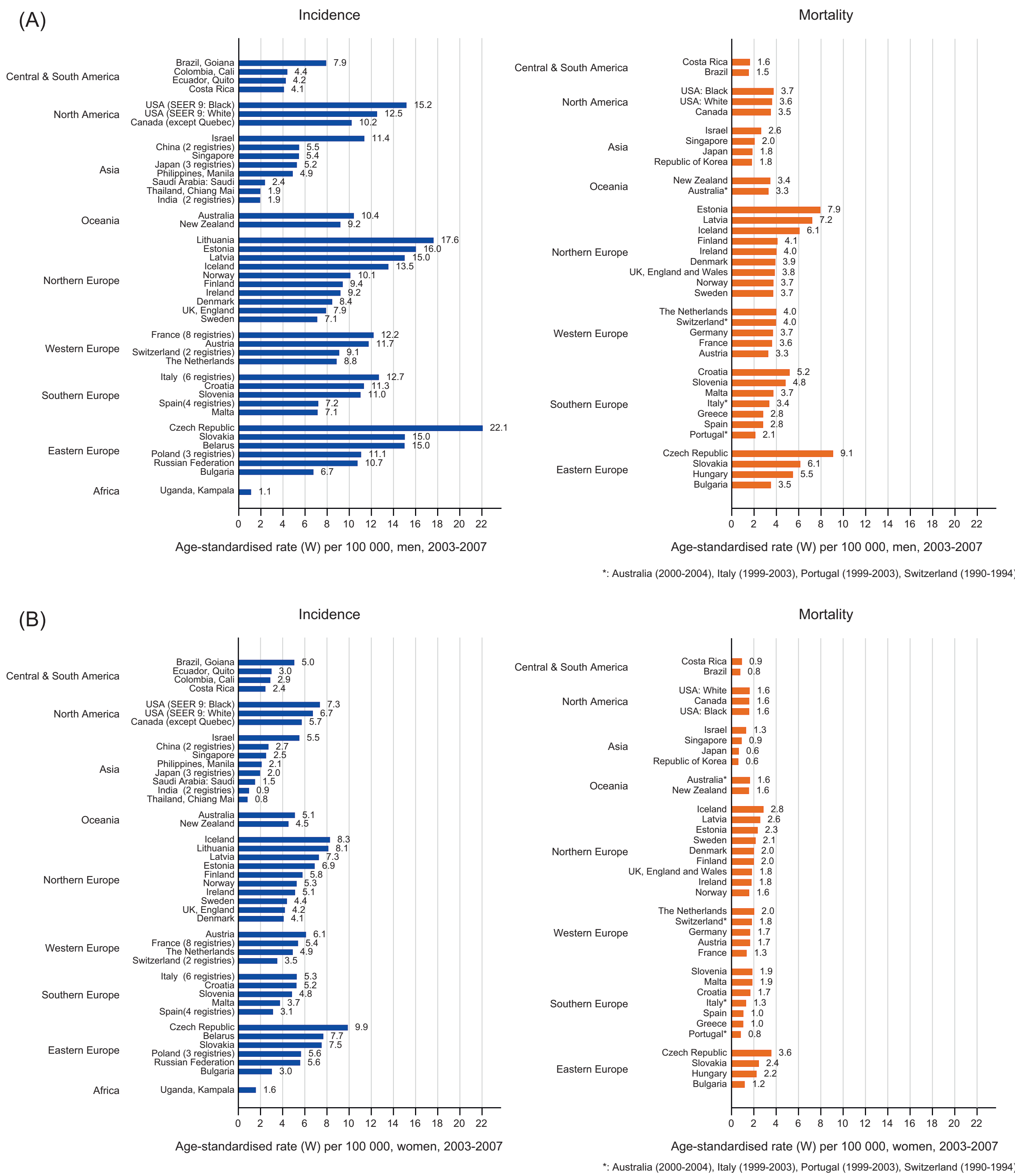

Fig. 2 – Renal cell carcinoma incidence rates (2003–2007) in selected cancer registries [22] and mortality rates (2003–2007) in selected countries [23] in (A) men and (B) women. ASR (W) = age-standardised rate (world); SEER = Surveillance Epidemiology and End Results.

3.2. *Incidence and mortality trends*

During the most recent 10-yr period, RCC incidence has been increasing in most of the countries under study, more markedly among men than women. Recently observed mortality trends are stable in most countries for both sexes, but have been decreasing in Western Europe and in most Northern European countries (AAPC −1% to −3%), as well as

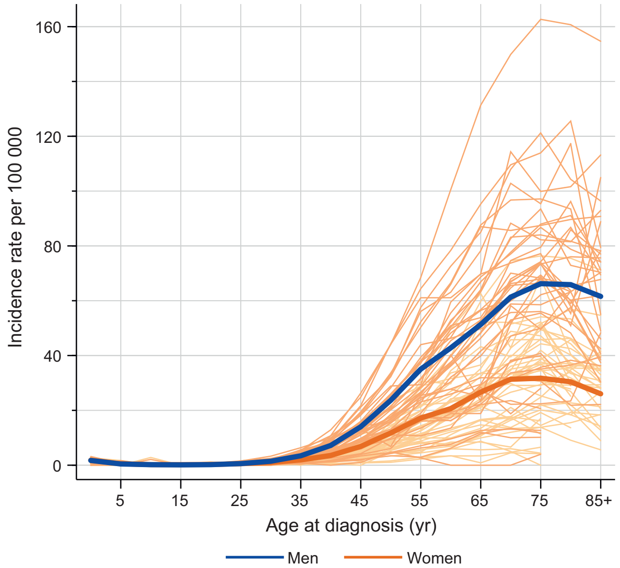

Fig. 3 – Age-specific renal cell carcinoma incidence (2003–2007) rates per 100 000 by country and sex. Thick lines represent the overall age-specific rates for men and women.

the USA and Australia. In the majority of countries, mortality has been decreasing at a faster rate in women compared with men (Figs. 5 and 6).

3.2.1. Northern America

RCC incidence has been increasing in both sexes in Canada and the USA. The most prominent increases in incidence were observed in the US black population (AAPC 2.7% annually in both men and women). The corresponding mortality trends have been declining in both countries. In the USA, the declines were more pronounced for blacks, starting from the 1990s (Figs. 5 and 6).

3.2.2. Central and South America

Regionally, the greatest increases in RCC incidence were in Central and South America (AAPC ranging from 3.0% to 6.8% in men and from 2.5% to 6.4% in women). Mortality rates have been significantly increasing in both sexes in Brazil (AAPC 2.5% in men and 1.1% in women), but rather stable in Costa Rica (Figs. 5 and 6).

3.2.3. Europe

In Northern Europe, male RCC incidence has been stable in Estonia and Finland, but increasing in all other countries, with such rises generally less pronounced in women. Mortality trends began to diverge from incidence in the late 1990s, with the greatest declines observed in Nordic countries, and more prominently in women. The only Northern European country with increasing RCC mortality in both sexes is Ireland (AAPC 1.3% in men and 0.7% in women).

In the other high-incidence area, Eastern Europe, increases of incidence have stabilised in the Czech Republic, but are continuing in both sexes in Belarus, Bulgaria, the Russian Federation, and Slovakia. Mortality declines have been observed in several Eastern European countries including the Czech Republic and Hungary. In Western Europe, incidence trends differ across countries, although mortality began to decline across countries in the 1990s. In Southern Europe, however, increases in RCC incidence rates have been observed, with mortality significantly increasing in both sexes in Croatia (AAPC 3.0% in men and 1.5% in women), in men in Slovenia, Portugal, and Greece (AAPC 1.7%, 1.6% and 1.2%, respectively), and in Spanish women (AAPC 0.6%). Declines in RCC mortality were only observed in Italy (Figs. 5 and 6).

3.2.4. Asia

RCC incidence has been increasing in most Asian countries among men, most notably in China (AAPC 7.6%; represented by two registries, Hong Kong and Shanghai). In Asian women, significant increases have been observed in India (AAPC 2.0%; represented by Chennai and Mumbai) and in Singapore (AAPC 2.4%). Mortality trends have been more stable, with declines apparent in Israel and Japan (both sexes) from the mid-1990s (Figs. 5 and 6).

3.2.5. Africa

No significant changes in incidence or mortality have been observed in African populations in the most recent period (Figs. 5 and 6).

3.2.6. Oceania

RCC incidence has been increasing in both sexes in Australia and New Zealand, with mortality stable in New Zealand but decreasing modestly among Australian men (AAPC −0.5%), and more markedly in women, at −2.0% on average annually (Figs. 5 and 6).

4. Discussion

We observed great disparities in RCC incidence rates worldwide, ranging from 22/100 000 in Czech men to <1/100 000 in African countries. Furthermore, over the most recent 10-yr period, incidence increased in 33 out of 43 populations under study in men and in 21 populations in women, most prominently in Latin American populations, where annual increases of over 3% were observed in both sexes. By contrast, mortality trends have been more favourable, with rather few concomitant increases in mortality in most of the populations studied. In high-resource settings, such as in Northern and Western Europe, North America, and Australia, mortality trends have actually uniformly declined since the 1990s.

The predominant lifestyle factors associated with RCC are smoking and obesity [4,5]. Although some authors have hypothesised that declines in mortality in Europe may be driven by prior decreases in smoking prevalence [20], this appears to be contrary to the rising trends in incidence. The main temporal profile of largely increasing RCC incidence contrasts with the tobacco-driven patterns of decreasing male but increasing female lung cancer incidence over the same period, and with the corresponding trends in smoking prevalence in many high-income settings [27,28].

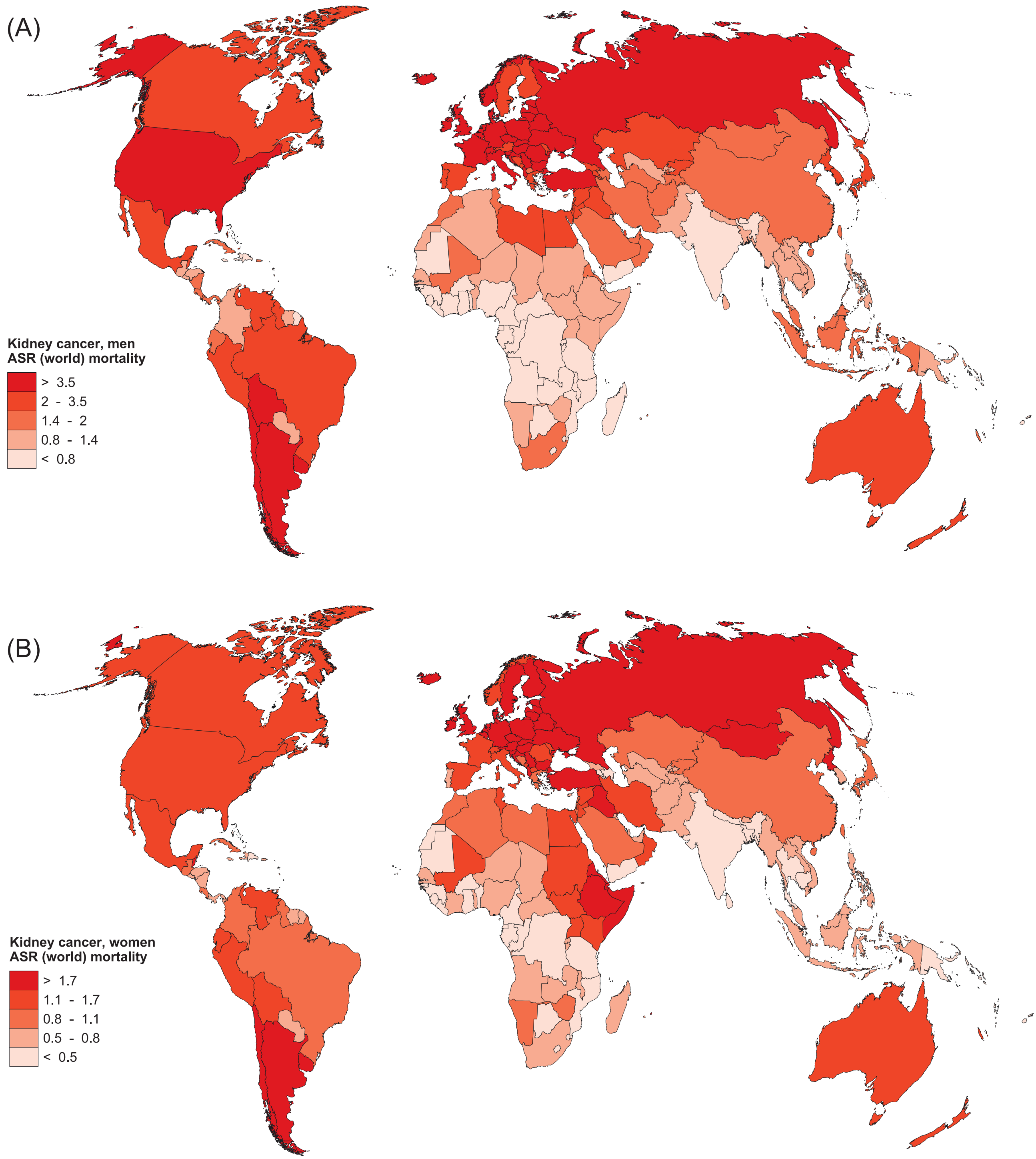

Fig. 4 – International variation in estimates of national age-standardised kidney cancer mortality rates in (A) men and (B) women [1].

A more common reason to which the rising incidence of RCC over the last decades in Western populations has been attributed is the increased use of imaging techniques, which can result in incidental findings of small renal masses, reported to contribute as much as 50% to the overall incidence [18,19]. However, it remains unclear whether increased utilisation of medical services may explain the increases in RCC incidence consistently observed in low- to medium-resource settings, such as Latin American countries.

Obesity also appears to have an important role in RCC incidence patterns and trends [5]. From a rudimentary ecological perspective, regions with the lowest average BMI, such as sub-Saharan Africa and India, are largely the areas with the lowest RCC incidence. One could speculate that the

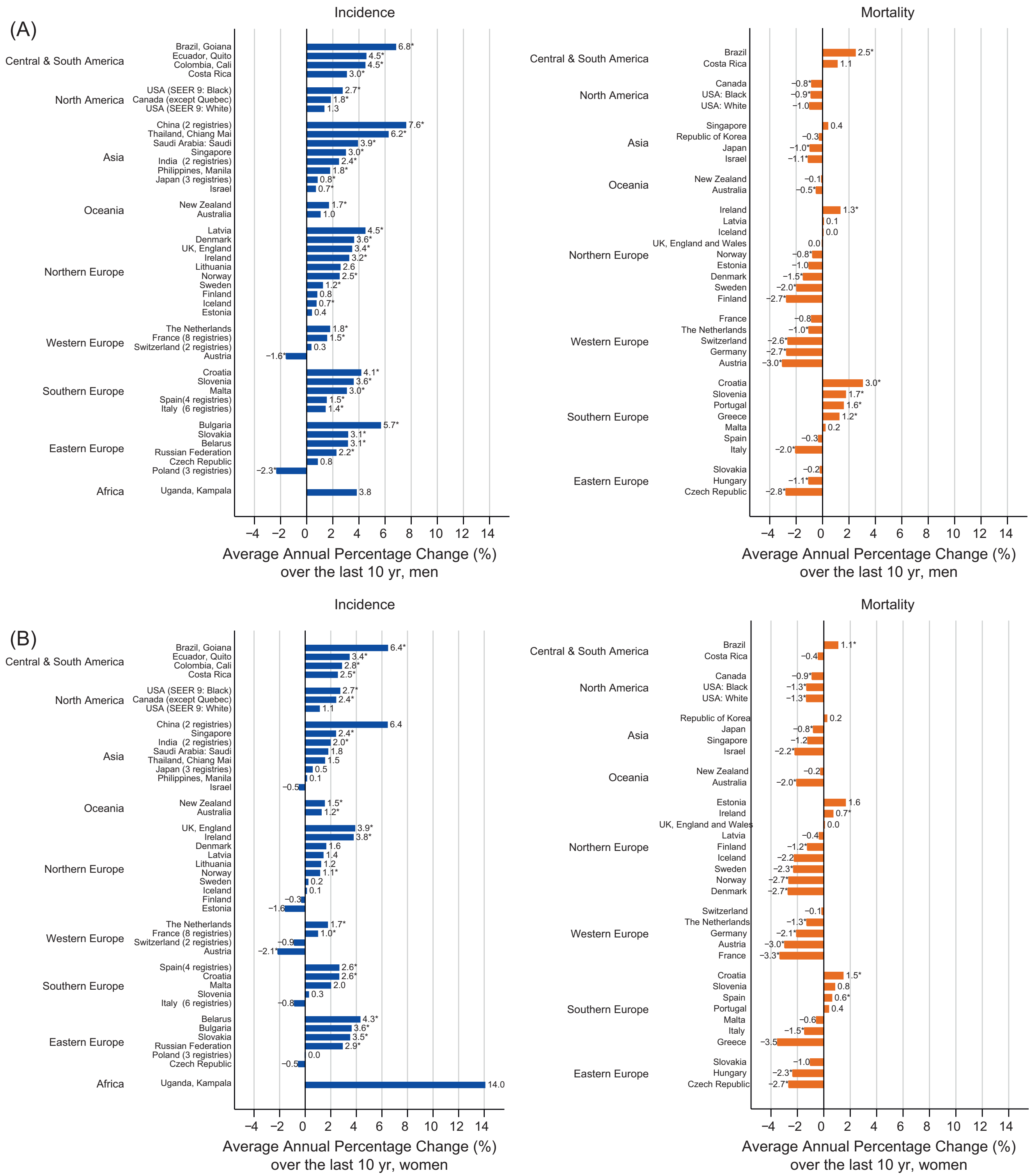

Fig. 5 – Average annual percentage change (AAPC) in RCC incidence and mortality rates for the last 10 yr of available data by region in (A) men and (B) women. * Statistically significant.

increasing obesity trends observed worldwide are, to some extent, mirrored by equivalent RCC incidence trends [29].

In the context of these known risk factors and possible artefacts, it remains unclear why RCC incidence in the Czech Republic remains the highest worldwide. Several explanations have been offered, including arsenic exposure and a high prevalence of smoking and obesity; however, the differences in risk factors compared to neighbouring countries such as Slovakia do not appear to be large enough to explain the higher level of incidence [28,29].

In comparison to previous studies reporting increases in kidney cancer mortality worldwide, it is evident that some progress has been made given the stabilisation or decline in mortality trends observed in recent years in a number of countries globally [3,19,30]. However, a gap in survival between areas with higher and lower resources is also evident, with greater mortality declines in Western versus Eastern Europe and North versus South America; these are noted for other urologic cancers, including testicular and prostate cancer [31,32]. One paradox is the decreasing and more favourable mortality trends in US blacks compared to whites as previously reported [33] and confirmed by our

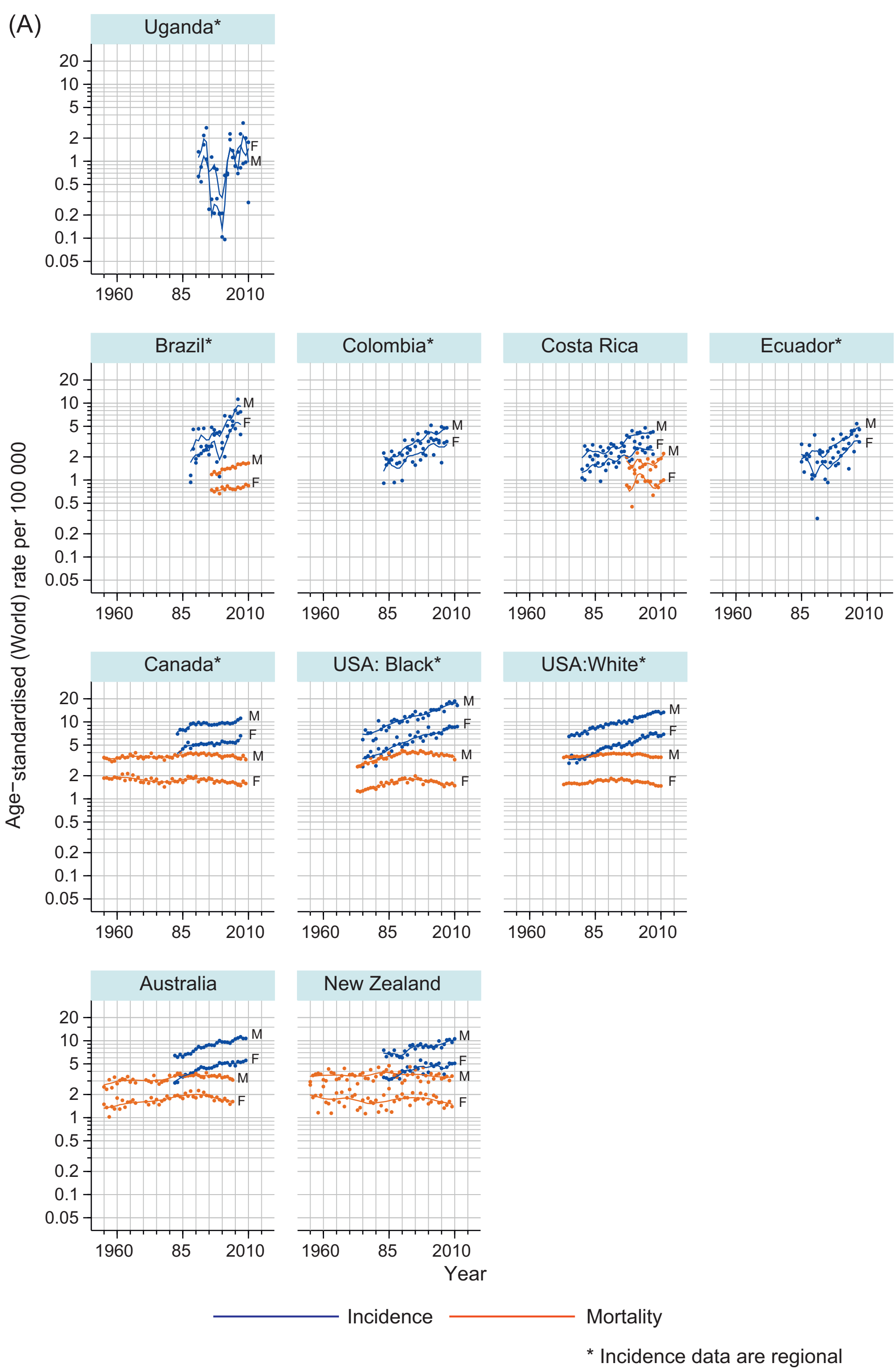

Fig. 6 – Trends in RCC age-standardised (World) incidence (regional or national) [22] and mortality (national) rates [23] for men and women. Rates ≤0.05 per 100 000 are not plotted.

study. Until the mid-2000s, the standard treatment for RCC was surgical excision and immunotherapy, mostly consisting of interferon or interleukin regimens [34,35]. These treatments are expensive, so they have not been universally available across countries, with surgery being the only treatment option in lower-resource settings [34]. Increasing proportions of incidentally discovered masses in areas of very high and high income have put a focus on the management of small renal masses (up to 7 cm) [35]. Because radical nephrectomy often results in impairment of function or failure of the contralateral kidney, the preferred procedure for small kidney cancers is partial nephrectomy. This procedure has now been included in both the US and European urology society guidelines, but it is still not widely implemented, even in the USA [36,37].

The currently observed disparities in reducing renal cell cancer mortality are likely to increase even further following the introduction of targeted therapies with tyrosine kinase and mTOR inhibitors since the mid-2000s [34]. Access to targeted therapies varies even within Europe, and is not available in most lower-resource countries [34,38]. The 2012 Asian Oncology Summit provided guidelines for management of kidney cancer in Asia according to a four-tier resource-stratified framework [34]. Such an approach appears adequate for other similarly resourced countries, in terms of optimising outcomes given limited resources.

Interpreting RCC outcomes (mortality and survival) is particularly challenging given that higher survival proportions may reflect overdiagnosis rather than a true survival benefit [39]. The 5-yr relative survival for European kidney cancer patients diagnosed between 2000 and 2007 is reported as 60.6%, in comparison to 72.4% according to Surveillance Epidemiology and End Result (SEER) data for 2004–2010. The survival advantage for the US population may reflect a high proportion of localised cancers (64%), but comparative information on stage distribution is not available from the EUROCARE-5 study [40,41].

There is a lack of survival information for lower-resource countries; instead, the mortality/incidence ratio provides an indication of cancer outcome. Patel et al [42] analysed such ratios in the context of development and concluded that kidney cancer survival is higher in the most developed populations. However, the low incidence/mortality ratios in less developed populations may reflect not only lower survival but also less frequent use of imaging and

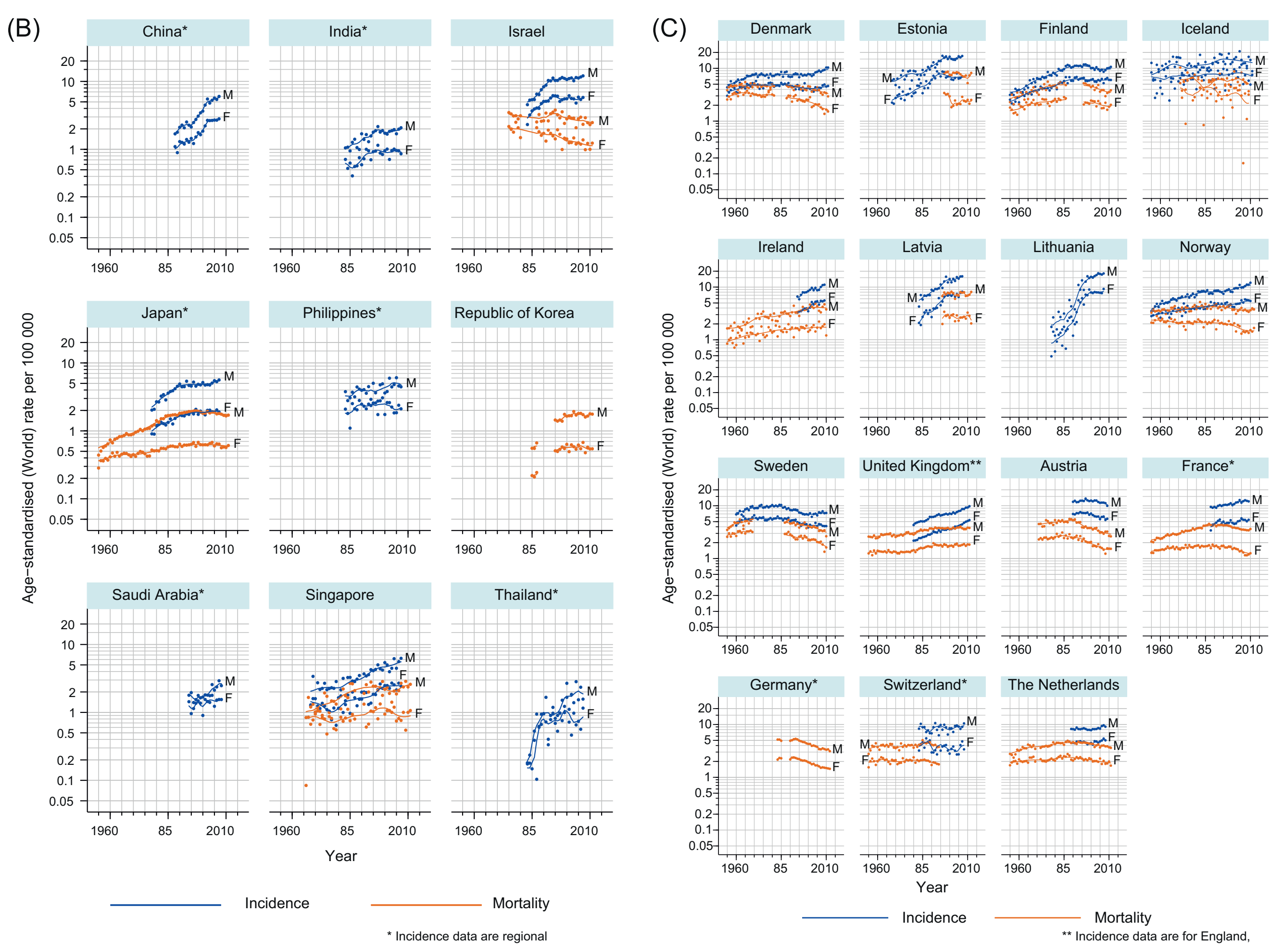

Fig. 6. (*Continued*)

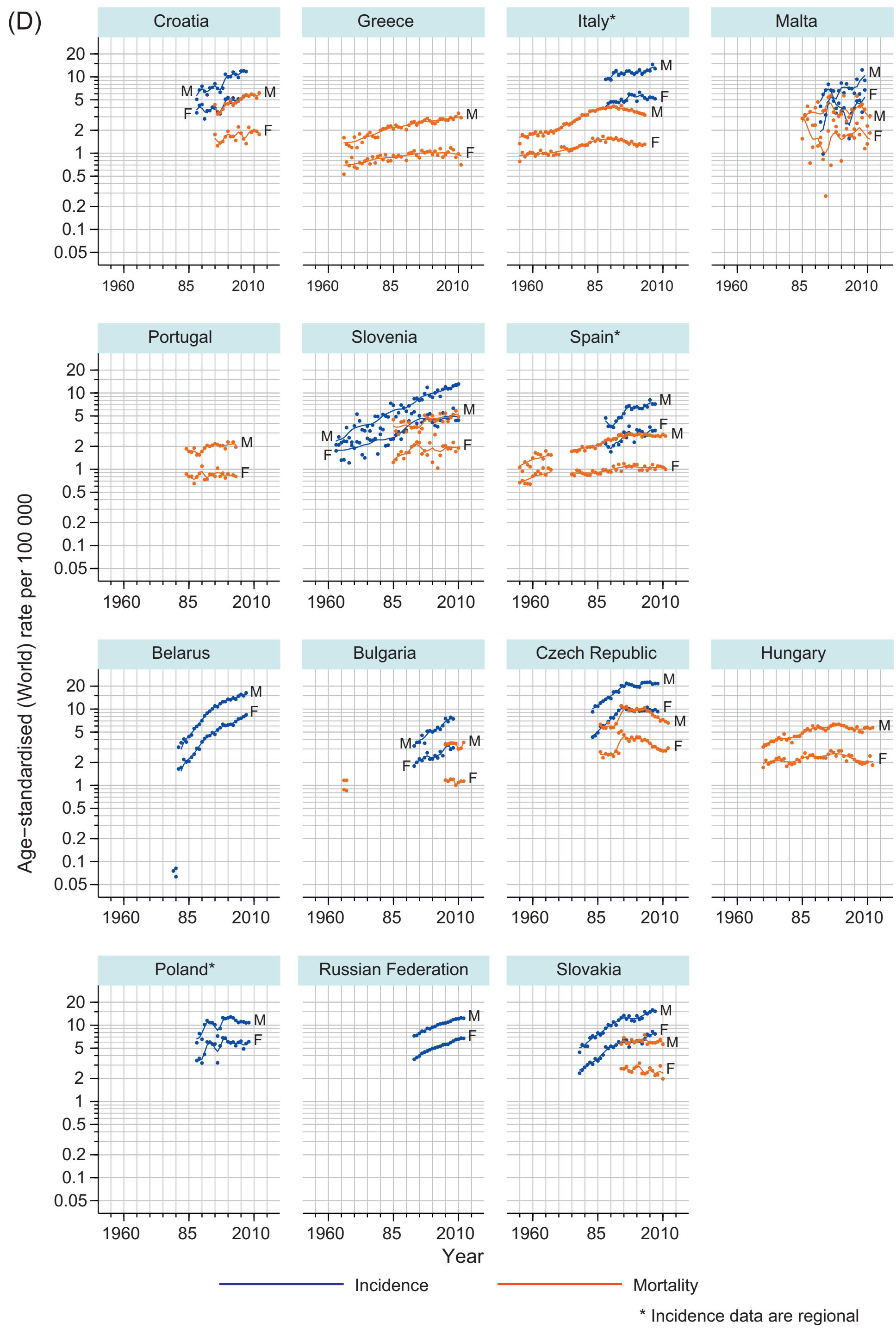

Fig. 6. (*Continued*).

consequently fewer incidental diagnoses, as well as possible under-registration of new RCC cases. In the current framework, mortality trends may remain the best indicator of progress of kidney cancer care, although incidence and survival are important in jointly assessing complex interactions between changes in the prevalence and distribution of key risk factors, the extent to which medical interventions are in place, and the level of quality and access to adequate cancer care.

A limitation of our study is the lack of availability of RCC data in many low- and middle-income settings. This should change, as the International Agency for Research on Cancer (IARC) is putting intense efforts into increasing the coverage and quality of cancer registration in low- and middle-income countries via the Global Initiative for Cancer Registration (GICR) programme (http://gicr.iarc.fr). For 17 countries, the incidence was obtained from regional registries, with population coverage ranging from 1% and

75% (Supplementary Table 1). Therefore, there may be some issues with regard to the representativeness of these registry data in truly depicting national incidence rates.

5. Conclusions

The study of RCC confirms a need for continued surveillance and in particular for analysis of patterns and trends in incidence, mortality, and survival in parallel given the synergy between these indicators. Disentangling the effects of smoking and obesity remains complex, and the documented risk factors for RCC are exclusively those reported for developed settings. Obesity levels, as measured in terms of BMI, have been increasing worldwide, and smoking is on the rise in countries in developmental transition, with efforts to introduce antismoking policies in these countries facing insurmountable pressure from the tobacco industry [43].

The levels of RCC mortality are highly dependent on the organisation of urologic oncology and treatment availabilities in a given country. The contrast is stark between advances in providing therapies that target specific molecular pathways via oncology centres in the Western world and rural hospitals in the least developed areas of the world, where nephrectomy might be the only treatment option. The long-term best-practice approach must include primary prevention of smoking and obesity, alongside careful monitoring of trends using high-quality population-based cancer registries and corresponding national registration sources.

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, Laversanne.
Analysis and interpretation of data: Znaor, Laversanne, Lortet-Tieulent, Jemal, Bray.
Drafting of the manuscript: Znaor, Bray.
Critical revision of the manuscript for important intellectual content: Znaor, Lortet-Tieulent, Laversanne, Jemal, Bray.
Statistical analysis: Laversanne.
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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.2014.10.002.

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