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Global trends in nasopharyngeal cancer mortality since 1970 and predictions for 2020: Focus on low-risk areas

Greta Carioli[1], Eva Negri[2], Daisuke Kawakita[3,4], Werner Garavello[5], Carlo La Vecchia[1] and Matteo Malvezzi[1,2]

[1] Department of Clinical Sciences and Community Health, Universitá degli Studi di Milano, Milan 20133, Italy
[2] Department of Epidemiology, IRCCS-Istituto di Ricerche Farmacologiche 'Mario Negri', Milan 20156, Italy
[3] Department of Otorhinolaryngology, Head and Neck Surgery, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan
[4] Division of Molecular Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan
[5] Department of Otorhinolaryngology, School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Nasopharyngeal cancer (NPC) mortality shows great disparity between endemic high risk areas, where non-keratinizing carcinoma (NKC) histology is prevalent, and non-endemic low risk regions, where the keratinizing squamous cell carcinoma (KSCC) type is more frequent. We used the World Health Organization database to calculate NPC mortality trends from 1970 to 2014 in several countries worldwide. For the European Union (EU), the United States (US) and Japan, we also predicted trends to 2020. In 2012, the highest age-standardized (world standard) rates were in Hong Kong (4.51/100,000 men and 1.15/100,000 women), followed by selected Eastern European countries. The lowest rates were in Northern Europe and Latin America. EU rates were 0.27/100,000 men and 0.09/100,000 women, US rates were 0.20/100,000 men and 0.08/100,000 women and Japanese rates were 0.16/100,000 men and 0.04/100,000 women. NPC mortality trends were favourable for several countries. The decline was −15% in men and −5% in women between 2002 and 2012 in the EU, −12% in men and −9% in women in the US and about −30% in both sexes in Hong Kong and Japan. The favourable patterns in Europe and the United States are predicted to continue. Changes in salted fish and preserved food consumption account for the fall in NKC. Smoking and alcohol prevalence disparities between sexes and geographic areas may explain the different rates and trends observed for KSCC and partially for NKC. Dietary patterns, as well as improvement in management of the disease, may partly account for the observed trends, too.

There were about 85,000 incident cases and over 50,000 deaths from nasopharyngeal carcinoma (NPC) worldwide in 2012.[1] The global distribution of incidence and mortality showed a unique disparity, with extremely high rates (over 20–30/100,000 men and 10/100,000 women) in some regions of Southern China,[2–6] Hong Kong,[7–9] Taiwan,[10] Singapore,[9] other areas of Southeast Asia,[11–13] selected Chinese migrants (mostly to North America),[9,14–17] and in North Africa.[18,19] In non-endemic areas including most western countries, Latin America and Japan, NPC is a rare malignancy with incidence rates lower than 1/100,000.[20,21]

In high risk areas, the most frequent histotype is non-keratinizing carcinoma (NKC, differentiated and undifferentiated), while keratinizing squamous cell carcinoma (KSCC) is frequent in low risk areas, although NKC is present as well.[22]

A recognized risk factor for NKC is Epstein-Barr virus (EBV) infection, although cofactors are implied.[23] Among these, there are salted fish and preserved food consumption.[24–26] Tobacco and alcohol are involved in both NKC and KSCC.[27] Some aspects of diet,[28,29] and occupational exposure to wood dust in the past have been associated with KSCC. Genetic predisposition also plays a role in both histotypes.[30,31]

Over the last decade, lifestyle and dietary habits have changed worldwide, particularly in high NKC risk populations, and NPC management and treatment has improved.[6,32,33] Therefore, we conducted a comprehensive up to date analysis of global trends in NPC mortality.

Material and Methods

We used the World Health Organization (WHO) database, available on electronic support, to obtain data on official death certification for NPC.[34] We derived figures for a total of 42 countries and the EU as a whole from 1970 to 2014 or

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Correspondence to: Eva Negri, Università degli Studi di Milano. Department of Biomedical and Clinical Sciences L.Sacco. Polo Didattico Vialba. Via G.B. Grassi, 74 20157 Milano ITALY.
E-mail: eva.negri@unimi.it

What's new?

Nasopharyngeal cancer (NPC) shows major variations between high and low-risk areas. Over the last decade, lifestyle and dietary habits have changed worldwide, particularly in high-risk populations, and NPC management and treatment has improved. Here, the authors used the World Health Organization database to calculate NPC mortality trends from 1970 to 2014 in several countries worldwide. Declines in mortality were observed in most areas of the world for the major histological types, following patterns that are predicted to continue in the near future. Decreased salted fish and preserved food consumption and tobacco smoking may partly or largely explain these trends.

the most recent available year. Due to accuracy, completeness and availability issues, for Spain we only considered data since 1984, for Mexico since 1998 and for the Republic of Korea since 1995.[35] We included countries which met either of the following two criteria: 5 million or more inhabitants, at least 50 deaths recorded in 2005–2009, and provided data for the 2000s. We considered the European Union (EU) as a whole (28 countries as of July 2013, minus Cyprus due to data unavailability), 25 separate European countries (EU and non-EU), 10 countries from the Americas, and 7 other countries or economic areas worldwide.

We did not perform extrapolation for missing data, except for the calculation of the EU rates where, when data were not available for one or more years for a country, we used the nearest available data.

During the calendar period considered, three Revisions of the International Classification of Diseases (ICD) were used.[36–38] NPC deaths were recoded for all countries according to the 10th Revision of the ICD (ICD 10 code C11).

We used resident population estimates, based on official censuses, from the WHO database. When population data were missing, we obtained them from EUROSTAT and the Pan American Health Organization (PAHO) databases.[39,40] PAHO provided data stratified by sex and 5-year age groups (from 0 to 4, to 80+ years) for selected years only (1995, 2000 and 2005) and stratified by sex and broader age groups (<1, 1–4, 5–14, 15–44, 45–64 and 65+ years) for the remaining years. We, therefore, obtained estimates for the 5-year age groups interpolating data from 1995, 2000 and 2005.

Using certified deaths and resident population, we calculated age-specific NPC death rates for each 5-year age group (from 0–4 to 85+ years and from 0–4 to 80+ for the Americas) and calendar year or quinquiennium. We then computed age-standardized mortality rates per 100,000 people, based on the world standard population.[41]

To identify significant changes in mortality trends, we used joinpoint regression models, allowing for a maximum of three jointpoints.[42] For major countries worldwide (including the EU as a whole) we calculated estimated annual percent changes (APC) and the average annual percent change (AAPC) over the entire considered period.[43,44]

For the EU as a whole, the United States and Japan, we predicted NPC number of deaths and rates for the year 2020. We fitted joinpoint regression models, allowing for up to five joinpoints. In this case, we considered the number of certified deaths in each 5-year age group, with the aim to identify the most recent trend slope. Subsequently, we applied a linear regression to various age groups over the period identified by the joinpoint model to calculate the predicted age-specific certified number of deaths, and the corresponding 95% prediction intervals. Using the predicted population data from EUROSTAT, the United States Census Bureau, and from the Japanese National Institute of Population and Social Security Research databases we computed predicted age-standardized mortality rates.[39,45,46]

Results

Table 1 gives, for all the countries considered and the EU as a whole, mortality rates and number of deaths from NPC, for men and women, at all ages around 2002 (2000–2004 quinquiennium), 2007 (2005–2009 quinquiennium) and 2012 (single year; when missing we considered the closest available year—*i.e.*, 2011 for the EU, France, Canada, Australia and New Zealand), and numbers of deaths for the year 2012 (or closest available). Table 1 also gives the percent change between 2012 and 2002.

Between 2002 and 2012, NPC mortality rates decreased from 0.32 to 0.27/100,000 men (−14.7%) in EU. Most major European countries showed favourable trends, except Belgium, Germany, Greece and Portugal.

The decline was −11.7% in the United States (0.20/100,000 men in 2012). Across major Latin American countries, Colombia, Cuba and Mexico showed downward trends. Mexico had one of the lowest NPC mortality rates in 2012, 0.07/100,000 men. Argentina, Brazil, Chile and Venezuela showed upward trends.

Mortality rates in Hong Kong were the highest among the available areas, 4.5/100,000 in 2012. However, Hong Kong and Japan (that had much lower rates, 0.16/100,000) showed substantial declines, with percent changes of −30.0%. Other Eastern and Pacific countries considered showed favourable trends.

NPC mortality rates in women were systematically lower than in men. Change in the EU was −5.4%, and the rate was 0.09/100,000 women. France and Italy showed the greatest falls among major European countries. Female NPC mortality trends were also downwards in most smaller countries.

In the United States, the fall was −9.2%, from 0.09/100,000 to 0.08/100,000 between 2002 and 2012. Colombia also had a similar fall, and Cuba showed a decline from

Table 1. Age-standardized (world population) mortality rates per 100,000 men and women from nasopharyngeal cancer at all ages in selected countries around 2002 (2000–2004 quinquennium), 2007 (2005–2009 quinquennium) and in 2012 (or closest available), corresponding percent change (2012 *vs.* 2002) and number of deaths for 2012

	Men					Women				
	Death rate/100,000			% change	Number of	Death rate/100,000			% change	Number of
	2002	2007	2012	(2012/2002)	deaths 2012	2002	2007	2012	(2012/2002)	deaths 2012
EU (2011)	0.32	0.28	0.27	−14.7	1103	0.09	0.09	0.09	−5.4	441
Austria	0.24	0.24	0.25	3.3	18	0.10	0.06	0.03	−64.2	3
Belgium	0.18	0.13	0.18	0.6	15	0.04	0.04	0.05	33.3	5
Bulgaria	0.21	0.40	0.34	59.4	19	0.06	0.09	0.12	95.2	10
Croatia	0.36	0.33	0.52	44.8	22	0.14	0.09	0.04	−74.3	4
Czech Republic	0.32	0.27	0.27	−16.9	23	0.07	0.08	0.04	−43.7	6
Denmark	0.17	0.15	0.10	−43.9	5	0.09	0.10	0.03	−62.5	2
France (2011)	0.25	0.20	0.21	−16.9	104	0.06	0.06	0.04	−35.5	28
Germany	0.15	0.14	0.16	1.9	117	0.05	0.06	0.05	3.9	44
Greece	0.51	0.50	0.56	10.6	52	0.16	0.12	0.17	5.7	17
Hungary	0.59	0.48	0.51	−13.0	36	0.12	0.14	0.07	−41.9	11
Italy	0.39	0.28	0.31	−20.9	168	0.10	0.09	0.06	−42.2	38
Netherlands	0.18	0.15	0.16	−9.5	22	0.07	0.08	0.07	0.0	8
Poland	0.39	0.39	0.31	−19.4	89	0.15	0.12	0.13	−11.6	42
Portugal	0.52	0.50	0.66	27.3	55	0.14	0.14	0.16	15.6	15
Romania	0.95	0.81	0.93	−1.5	138	0.26	0.24	0.26	−0.8	44
Slovakia	0.56	0.44	0.49	−13.0	18	0.07	0.09	0.10	38.6	5
Spain	0.53	0.44	0.36	−32.5	143	0.12	0.11	0.10	−14.2	55
Sweden	0.16	0.17	0.10	−38.5	8	0.04	0.06	0.03	−17.1	3
UK	0.19	0.17	0.15	−24.2	82	0.07	0.06	0.08	9.7	39
Israel	0.43	0.27	0.12	−73.0	5	0.13	0.08	0.04	−72.9	2
Kyrgyzstan	0.40	0.47	0.53	32.6	12	0.15	0.21	0.12	−21.8	2
Norway	0.12	0.12	0.12	−4.0	4	0.07	0.02	0.02	−67.6	1
Republic of Moldova	1.19	1.05	1.00	−16.3	22	0.41	0.39	0.29	−30.7	8
Serbia	0.30	0.36	0.47	56.6	28	0.08	0.13	0.15	82.7	13
Switzerland	0.16	0.14	0.09	−47.2	7	0.06	0.04	0.05	−10.2	4
Canada (2011)	0.31	0.28	0.23	−26.9	62	0.11	0.11	0.10	−4.6	28
United States	0.22	0.21	0.20	−11.7	454	0.09	0.08	0.08	−9.2	212
Argentina	0.16	0.16	0.17	6.8	40	0.04	0.05	0.06	68.6	17
Brazil	0.20	0.21	0.21	5.0	219	0.07	0.07	0.08	12.5	92
Chile	0.06	0.07	0.09	44.1	8	0.02	0.02	0.03	35.0	3
Colombia	0.17	0.16	0.16	−4.2	36	0.07	0.07	0.06	−9.2	15
Costa Rica	0.63	0.48	0.35	−44.7	9	0.20	0.15	0.17	−13.1	4
Cuba	0.47	0.49	0.47	−1.1	42	0.14	0.15	0.09	−32.1	10
Guatemala	0.02	0.05	0.12	495.0	6	0.02	0.05	0.01	−39.1	1
Mexico	0.07	0.08	0.07	−8.3	33	0.04	0.03	0.05	19.5	29
Uruguay	0.36	0.45	0.21	−40.9	4	0.12	0.17	0.06	−47.1	2
Venezuela	0.17	0.18	0.26	47.7	34	0.08	0.08	0.06	−31.3	10
Hong Kong	6.57	5.47	4.51	−31.3	255	1.77	1.54	1.15	−35.1	74
Japan	0.23	0.20	0.16	−30.0	230	0.06	0.05	0.04	−31.0	74
Republic of Korea	0.42	0.41	0.36	−12.5	127	0.10	0.12	0.07	−32.0	29
Australia (2011)	0.27	0.25	0.24	−8.3	41	0.10	0.09	0.07	−32.7	14
New Zealand (2011)	0.33	0.31	0.51	52.1	16	0.13	0.14	0.08	−42.0	3

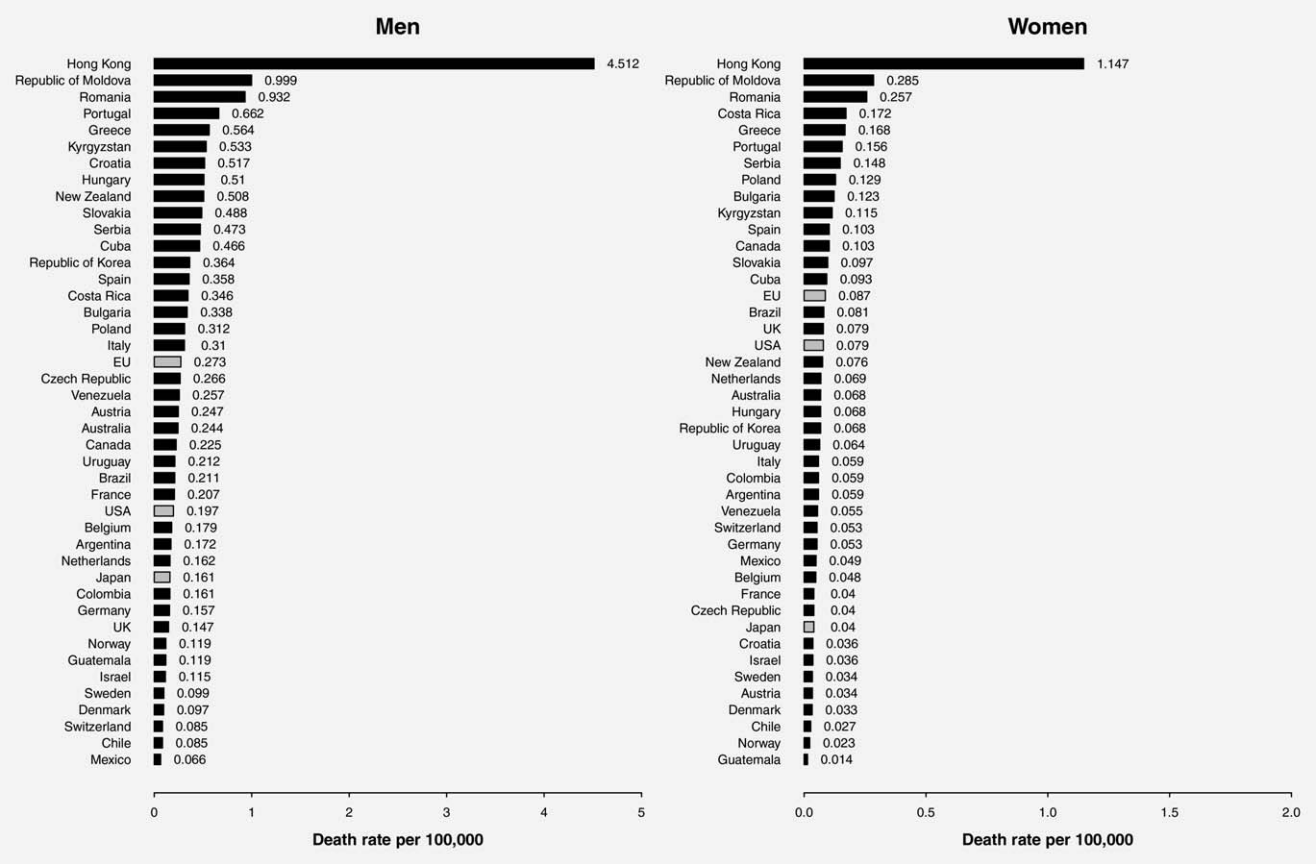

Figure 1. Age-standardized (world population) death certification rates from nasopharyngeal cancer in men and women from 42 selected countries worldwide plus the EU as a whole in 2012, or the last available year.

0.14 in 2002 to 0.09/100,000 in 2012 (−32.1%). In Hong Kong, the fall was −35% from 1.77 to 1.15/100,000 women. Trends were inconsistent in other countries, possibly due to low numbers of deaths.

Figure 1 displays all age NPC mortality rates in 2012. The highest rates were in Hong Kong (4.51/100,000 men and 1.15/100,000 women), followed by selected Eastern European countries (Moldova and Romania). The lowest rates were in Northern Europe and Latin American countries. EU rates were 0.27/100,000 men and 0.09/100,000 women, US rates were 0.20/100,000 men and 0.08/100,000 women and Japanese rates were 0.16/100,000 men and 0.04/100,000 women.

Figure 2 and the corresponding Table 2 show joinpoint analysis results for NPC mortality trends in 20 selected larger countries worldwide between 1970 and the most recent available year. The EU showed an increasing trend for men (1.7 APC) until the 1990s, then a fall (−2 APC). Women had an inconsistent trend up to 1986, and a decline thereafter (−1.9 APC).

The United States showed declines in both sexes with AAPCs of −1.8 for men and −2.3 for women. Hong Kong trends appreciably declined across the whole studied period, with AAPCs of −2.9 in men and of −4.2 in women. NPC mortality rate trends in Japanese men rose up to 1996 and then declined significantly; in women, the decline started in 1985.

Figure 3 and supplementary Table 1 shows NPC mortality trend predictions for the year 2020 in the EU, the United States and Japan. The favourable patterns in mortality are predicted to continue, with the only exception of Japanese men, where they appear to have reached a plateau.

Discussion

In this up to date global analysis, we found a downward trend in NPC mortality for most countries worldwide. There were inconsistent trends in some European and Latin American countries, possibly attributable to random variation from low numbers of deaths, improved diagnosis and validity of cause of death certification.

Tobacco smoking and alcohol drinking are associated with KSCC,[27,47] which tends to be comparatively more frequent in non-endemic regions, although NKC is observed in those areas, too.[8,22,48] Aspects of diet may also influence KSCC. A diet rich in fruit and vegetables and a Mediterranean dietary pattern has been favourably related to KSCC risk. The RR was around 0.5 for the highest versus the lowest adherence to the pattern in a multicentric Italian study.[49,50] Occupational exposure to wood dusts, leather,

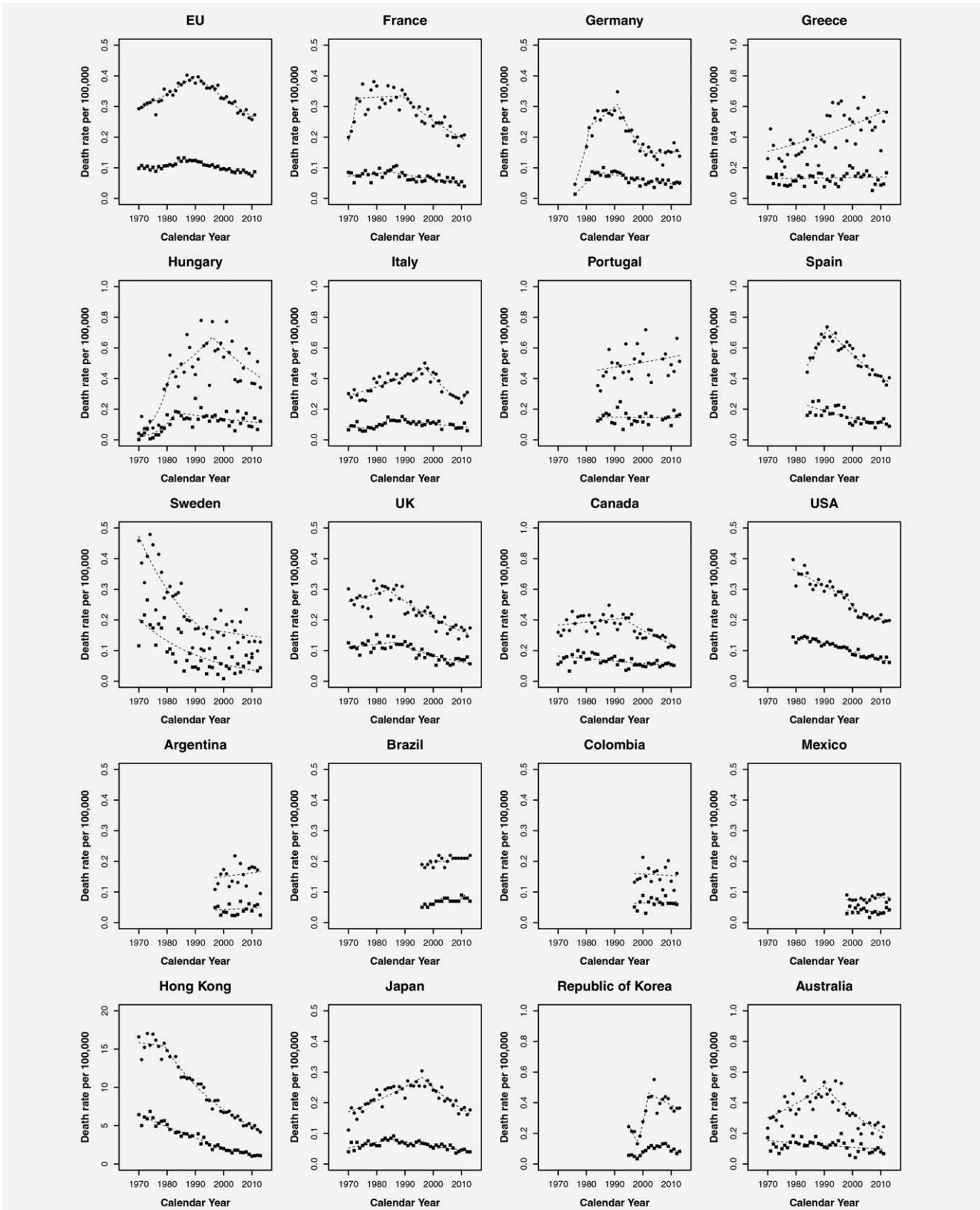

Figure 2. Joinpoint analysis for all ages nasopharyngeal cancer mortality in men (circles) and women (squares) in 19 selected countries and the EU as a whole, 1970–2014.

Table 2. Joinpoint analysis for nasopharyngeal cancer at all ages in selected countries worldwide, 1970–2013

Country	Years	APC 1	Years	APC 2	Years	APC 3	Years	APC 4	AAPC	Years	APC 1	Years	APC 2	Years	APC 3	Years	APC 4	AAPC
EU	1970–1990	1.7*	1990–2011	−2*					−0.2*	1970–1976	−1.5	1976–1986	3.1*	1986–2011	−1.9*			−0.7*
France	1970–1973	20.2*	1973–1989	0.2	1989–2011	−2.5*			0.1	1970–1985	1.2	1985–2011	−2.1*					−0.9*
Germany	1976–1981	38.5*	1981–1991	2.7*	1991–2001	−7.1*	2001–2013	0.4	3.3*	1976–1982	34.3*	1982–2013	−2.3*					2.9*
Greece	1970–2012	1.5*							1.5*	1970–2012	0.2							0.2
Hungary	1970–1981	21.9*	1981–1996	3	1996–2013	−2.9*			5.1*	1970–1983	19.4*	1983–2013	−1.6*					4.3*
Italy	1970–1997	1.8*	1997–2010	−4.7*	2010–2012	11.9			0.2	1970–1979	−2.3	1979–1984	14	1984–2012	−1.8*			−0.1
Portugal	1984–2013	0.7							0.7	1984–2013	−0.1							−0.1
Spain	1984–1991	6*	1991–2013	−3*					−0.9*	1984–2013	−2.8*							−2.8*
Sweden	1970–1992	−4.5*	1992–2013	−0.9					−2.7*	1970–2013	−4.2*							−4.2*
UK	1970–1984	1	1984–2013	−2.3*					−1.2*	1970–1986	0.9	1986–2013	−2.9*					−1.5*
Canada	1970–1993	0.5	1993–2011	−3*					−1.1*	1970–2011	−1.1*							−1.1*
United States	1979–1998	−1.5*	1998–2002	−6.1	2002–2013	−0.7			−1.8*	1979–1992	−1.2*	1992–2013	−2.9*					−2.3*
Argentina	1997–2013	0.8							0.8	1997–2013	1							1
Brazil	1996–2013	0.8*							0.8*	1996–2004	5.7*	2004–2008	−4.6	2008–2011	9.4	2011–2013	−8.2	2.1
Colombia	1997–2012	−0.3							−0.3	1997–2012	0.6							0.6
Mexico	1998–2013	0.6							0.6	1998–2013	−0.5							−0.5
Hong Kong	1970–1979	−0.3	1979–2013	−3.6*					−2.9*	1970–1989	−3.1*	1989–2013	−5.1*					−4.2*
Japan	1970–1996	2*	1996–2013	−3.2*					−0.1	1970–1985	2.9*	1985–2013	−2.3*					−0.5
Republic of Korea	1995–1998	−16.4	1998–2002	32.5*	2002–2013	−2.3			1.8	1995–1998	−10.7	1998–2002	26.2	2002–2008	2.4	2008–2013	−10.6*	0.9
Australia	1970–1990	2.7*	1990–2011	−4.3*					−1	1970–2011	−1.1*							−1.1*

*Significantly different from 0 ($p < 0.05$).
APC, estimated annual percent change.
AAPC, estimated average annual percent change.

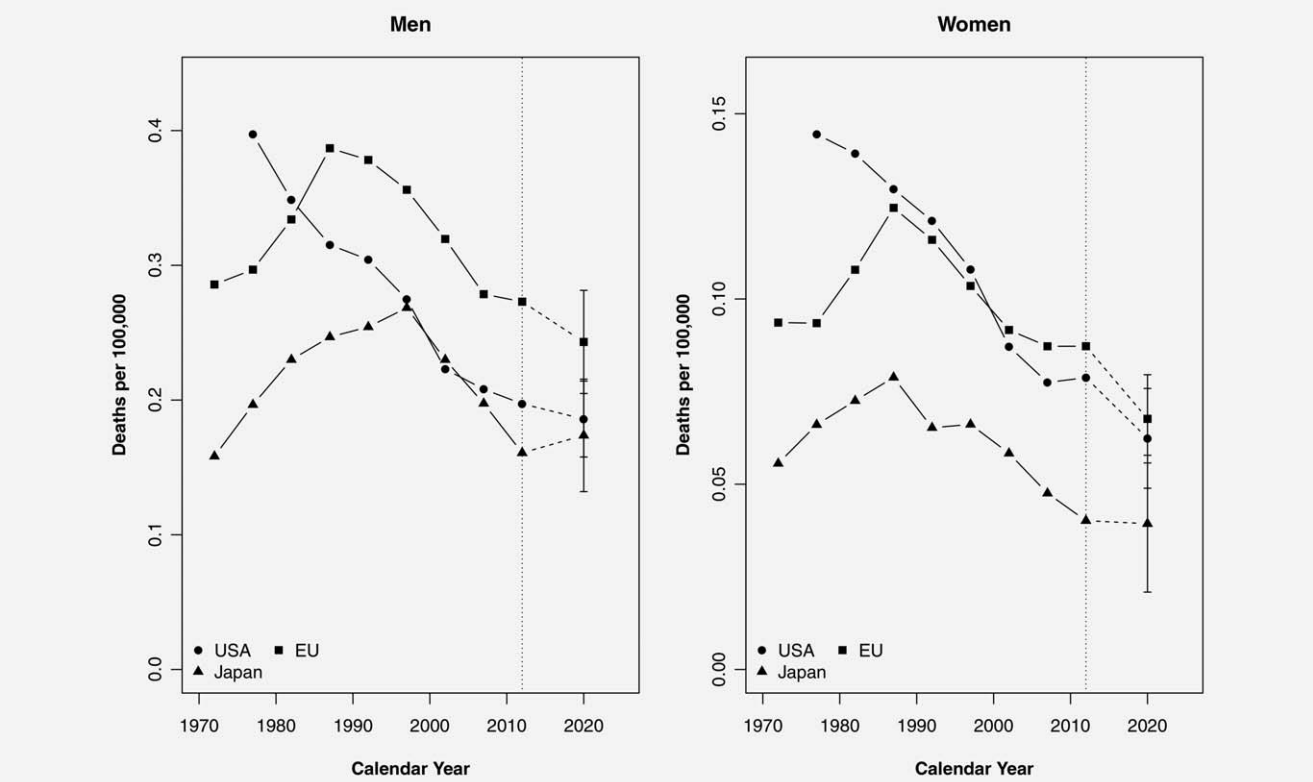

Figure 3. Age-standardized (world population) quinquennial nasopharyngeal cancer death rates in the EU as a whole, the United States and Japan in 1972–2012, and predicted rates to 2020 with corresponding prediction intervals.

nickel and possibly formaldehyde,[28,51,52] were reported as KSCC risk factors, although quantification, and hence, the public health impact for these factors, remains undefined.[47] Still, exposure control to these occupational risk factors over the last decades may also account for part of NPC mortality declines. Family history of NPC and selected genetic factors, including human leukocyte antigen locus, have been associated with NPC risk.[47] In several European countries and North America, the prevalence of tobacco smoking showed a decreasing trend in men (but not consistently in women) over the last few decades.[53–55] Other smoking-related cancers, including laryngeal and lung cancer, showed decreasing trends mainly in men.[56–58] Likewise, the decline in NPC mortality was greater for men than for women over the last decade. The smoking pattern in the two sexes can also explain the earlier rises in men for the EU and several European countries,[54] with a subsequent decline, as well as the earlier declines in the UK and the United States for both sexes.[59,60] Alcohol drinking has also been associated with NPC risk.[27,61] Alcohol drinking increased up to more recent years in countries of central and eastern Europe, but has been declining in Southern Europe.[60] Thus, alcohol drinking disparity in Europe might explain at least part of the declining trends in NPC mortality in selected southern European countries.[60] Changes in tobacco smoking, and alcohol drinking (as well as salted fish consumption in high risk areas) are related to NPC risk and hence incidence, although their impact or mortality remains difficult to quantify in various countries.

The NPC mortality rate in Latin American is relatively low. Hence, it is possible that random variation due to low numbers of deaths and variable cancer death certification validity partly or largely explain some of the observed inconsistent trends.

EBV, in interaction with salted fish and preserved food consumption, which are high in nitrous compounds and volatile nitrosamines, induces carcinogenic development for NKC,[24] the predominant histology in endemic areas.[8,22] In several high risk areas, a noticeable decline in NPC incidence has been reported.[7,9–12,18,19,62] Our study showed a significant decreasing NPC mortality in Hong Kong. In other endemic areas, declining trends were also reported, including Taiwan,[10] Singapore,[9] Southeast Asia[11,12] and North Africa.[18,19] In contrast, Sinui, Cangwu[2] and Zhongshan[3] showed a stable NPC mortality trend, with rates over 20/100,000 among men and over 10/100,000 among women.[2,3] We used national mortality data from the WHO database. Thus, we were unable to provide specific trends for Southern China (except Hong Kong) and Malaysia, two areas with high salted fish consumption. Data for Malaysia were available for 2007 and 2008 only. NPC all ages mortality was 2.1/100,000 men and 0.6/100,000 women.

Lifestyle and dietary habits have changed in the last decade, particularly in selected high mortality areas, and may account for the favorable trends observed. A study from Hong Kong investigated the incidence trend according to histology type,[8] and a declining trend was observed in KSCC, too. This supports the notion that the decreasing trend in smoking prevalence in men might partly account for the downward trend in NPC mortality in high risk areas as well.

Improved management has also been associated with the decline in NPC mortality.[33,63] Diagnostic imaging accuracy improved and intensity modulated radiotherapy (IMRT) is established as the standard NPC treatment.[33] IMRT can decrease the comorbidity of treatment and improve treatment compliance.[32] Improvements in accessibility to medical care may well have favorably influenced mortality trends, particularly in high income countries, including Hong Kong.

In conclusion, NPC mortality showed favorable trends over the last few decades in most countries, both in high and low incidence areas. These favourable trends are predicted to continue in the near future in major countries worldwide.

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