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Patterns and trends in esophageal cancer mortality and incidence in Europe (1980–2011) and predictions to 2015

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Background: Over the last few decades, esophageal cancer incidence and mortality trends varied substantially across Europe, with important differences between sexes and the two main histological subtypes, squamous cell carcinoma (ESCC) and adenocarcinoma (EAC).

Patients and methods: To monitor recent esophageal cancer mortality trends and to compute short-term predictions in the European Union (EU) and selected European countries, we analyzed data provided by the World Health Organization (WHO) for 1980–2011. We also analyzed incidence trends and relative weights of ESCC and EAC across Europe using data from Cancer Incidence in Five Continents.

Results: Long-term decreasing trends were observed for male esophageal cancer mortality in several southern and western European countries, whereas in central Europe mortality increased until the mid-1990s and started to stabilize or decline over the last years. In some eastern and northern countries, the rates were still increasing. Mortality among European women remained comparatively low and showed stable or decreasing trends in most countries. Between 2000–2004 and 2005–2009, esophageal cancer mortality declined by 7% (from 5.34 to 4.99/100 000) in EU men, and by 3% (from 1.12 to 1.09/100 000) in EU women. Predictions to 2015 show persistent declines in mortality rates for men in the EU overall, and stable rates for EU women, with rates for 2015 of 4.5/100 000 men (about 22 300 deaths) and 1.1/100 000 women (about 7400 deaths). In northern Europe, EAC is now the predominant histological type among men, while for European women ESCC is more common and corresponding rates are still increasing in several countries.

Conclusion(s): The observed trends reflect the variations in alcohol drinking, tobacco smoking and overweight across European countries.

Key words: esophageal neoplasms, Europe, histologic type, incidence, mortality, trends

introduction

Esophageal cancer incidence and mortality trends varied substantially across Europe over the last few decades, with important differences between sexes and the two main histological subtypes, squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) [1].

Among men, there were marked long-term declines in mortality in southern European countries such as France and Italy, whereas upward trends were observed up to the most recent years in the UK, the Netherlands and Romania [1]. In the European Union (EU) as a whole, male age-standardized mortality rates decreased between 1990–1994 and 2000–2004 from 5.7 to 5.4/100 000, while female rates remained stable around 1.1/100 000 [2].

ESCC was the main histological type in most European countries, though steady increases in EAC incidence were observed in several regions. In the late 1990s, EAC was already more frequent than ESCC in some northern European countries, such as Denmark and Scotland [1].

To monitor recent mortality trends and to compute short-term predictions of esophageal cancer mortality rates in the EU and selected European countries, we analyzed mortality data provided by the World Health Organization (WHO). We also analyzed the trends in incidence rates of ESCC and EAC and the relative weight of these main histological types of esophageal cancer across Europe.

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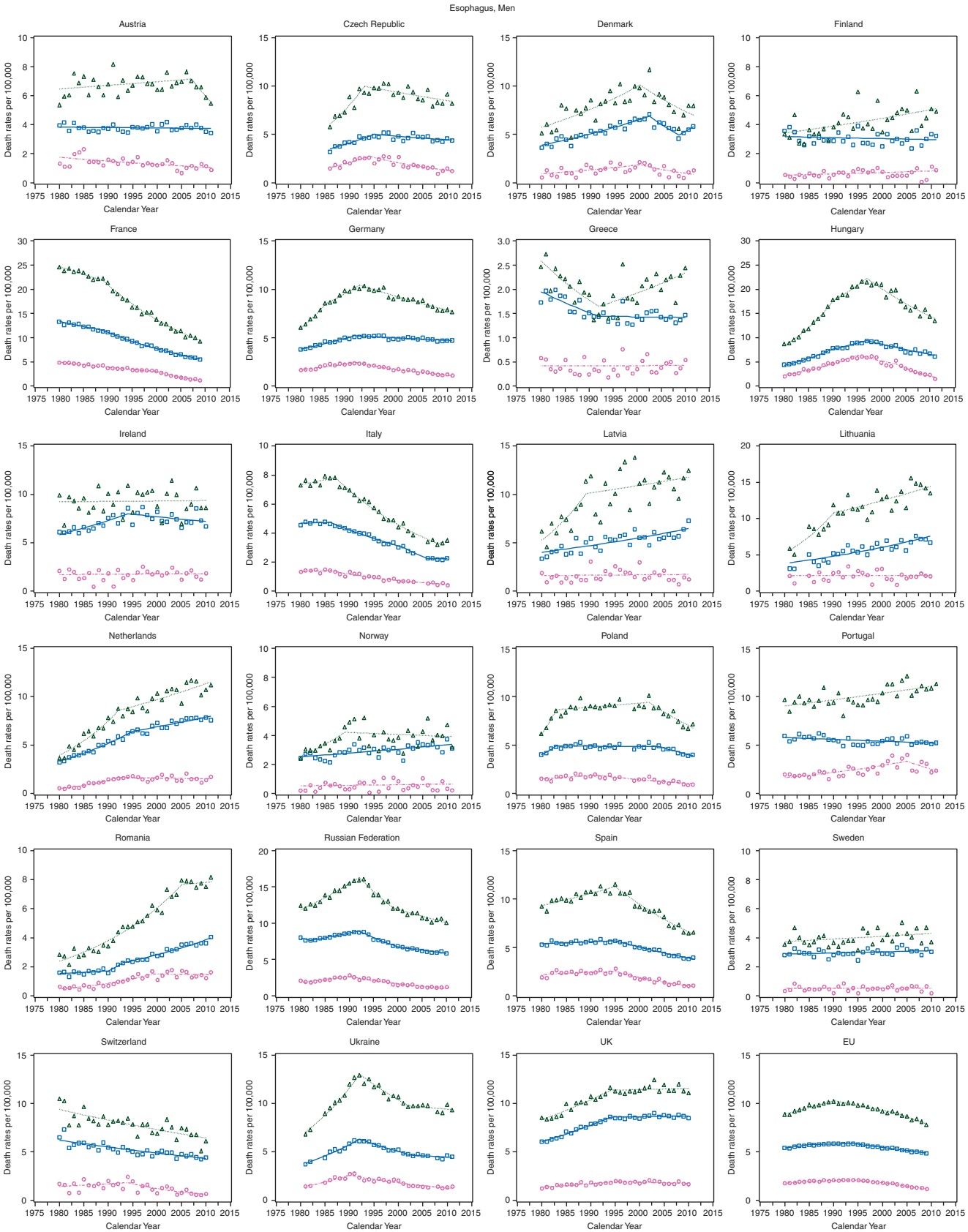

Figure 1. Joinpoint analysis for age-standardized (world population) mortality rates per 100 000 men for esophageal cancer (all ages and truncated at 25–49 and 35–64 years) in selected European countries, 1980–2011. □–□, all ages; ○– –○, 25–49 years; △–△, 35–64 years.

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methods

Official data for esophageal cancer mortality in the EU and selected European countries over the period 1980–2011, and the corresponding population figures, were derived from the WHO database [3]. Since in the period considered three different Revisions of the International Classification of Diseases (ICDs) were used to classify esophageal cancer deaths, death certification numbers corresponding to codes A046 (ICD-8) [4], B090 (ICD-9) [5] and C15 (ICD-10) [6] were extracted, as applicable. Country- and sex-specific mortality rates were computed for each 5-year age group (0–4, …, 75–79, 80+) and calendar year, and age-standardized rates were calculated at all ages and truncated at 25–49 and 35–64 years (direct method, world population). Mortality rates for the EU as a whole were computed using the aggregated number of deaths, and corresponding populations, in its 27 Member States, as defined in January 2007; Cyprus was excluded due to limited data available.

Poisson regression analysis was carried out using the Joinpoint software [7] in order to identify significant changes in the mortality trends, allowing for up to three joinpoints.

For selected European countries and the EU as a whole, we provided predicted numbers of esophageal cancer deaths and rates for the year 2015. These were derived by fitting a joinpoint model to each 5-year age-specific (age groups 0–4, …, 75–79, 80+) number of certified deaths, assuming a Poisson distribution, to identify the most recent trend segment. Then, a linear regression was carried out on mortality data for each age group over the most recent trend provided by the joinpoint model, to compute the predicted age-specific number of deaths, the corresponding 95% confidence intervals (CIs) and prediction intervals (PIs) [8]. Population figures for 2015 were obtained from EUROSTAT [9].

Incidence data were obtained from the Cancer Incidence in Five Continents (CI5) databases [10, 11] and analyzed by histological type. For countries with more than one cancer registry, data were aggregated to ensure the highest geographic coverage and the analyses were restricted to the longest common calendar period between registries.

Annual data for the period 1980–2002 (the last available year) were derived from the CI5-plus database [10], and 3-year moving averages were used to represent the histology- and sex-specific incidence trends in age-standardized incidence rates (direct method, world standard population).

Grouped incidence data, referring mostly to the period 1998–2002, provided by CI5 volume IX (CI5-IX) [11] were also retrieved, and used to describe the geographical distribution of esophageal cancer histological types across Europe, using ArcGIS [12].

results

In the EU as a whole, male esophageal mortality rates decreased since the early 1990s (all ages: APC = −1.2% in 1994–2009) with steeper declines since the early 2000s in younger age groups. Decreases in overall male mortality trends were observed in France, Greece, Italy, Portugal and Switzerland. Over the most recent calendar years, trends have also been decreasing or leveling off in the Czech Republic, Germany, Hungary, Ireland, Poland, the Russian Federation, Spain,

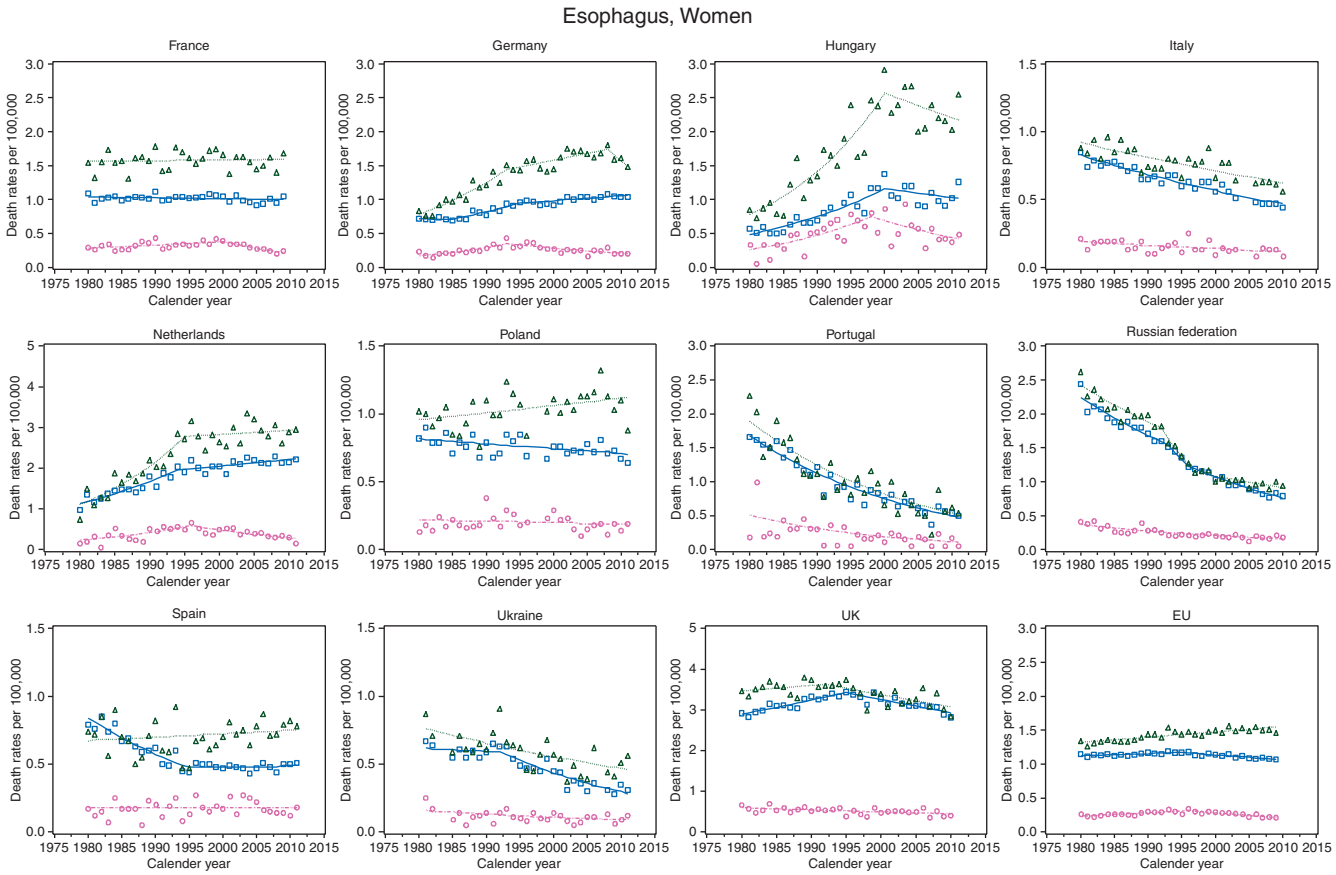

Figure 2. Joinpoint analysis for age-standardized (world population) mortality rates per 100 000 women for esophageal cancer (all ages and truncated at 25–49 and 35–64 years) in selected European countries, 1980–2011. □–□, all ages; ○–○, 25–49 years; △–△, 35–64 years.

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Ukraine and the UK, whereas increasing trends were still observed in Latvia, Lithuania, the Netherlands, Norway and Romania (Figure 1 and supplementary Table S1, available at *Annals of Oncology* online).

Among EU women, esophageal cancer mortality started to decline in the mid-1990s at all ages (APC = −0.6 in 1995–2009) and in the age group 25–49 years (APC = −2.9 in 1996–2009), while for the 35–64 year age group a slight upward trend was observed over the period 1980–2009 (APC = 0.5%). Long-term decreasing trends were observed for overall female mortality in Italy, Poland, Portugal, the Russian Federation and Ukraine, and more recent declines (since the mid/late 1990s) were observed in Hungary and in the UK, whereas in Germany, the Netherlands and Spain increasing mortality trends were still observed over the most recent calendar years (Figure 2 and supplementary Table S1, available at *Annals of Oncology* online).

Between 2000–2004 and 2005–2009, in the EU as a whole, esophageal cancer mortality fell by 7% at all ages among men (from 5.34 to 4.99/100 000) and by 3% among women (from 1.12 to 1.09/100 000). The UK, particularly Scotland, had the highest overall mortality rate in 2005–2009 for both sexes, whereas Greece showed the lowest one among men (1.38/100 000) (Tables 1 and 2).

Table 1. Age-standardized (world population) mortality rates from esophageal cancer per 100 000 men (at all ages and truncated at 25–49 and 35–64 years) in selected European countries and in the European Union (EU) in the periods 2000–2004 and 2005–2009 (unless otherwise mentioned in parenthesis), and corresponding percent changes

	All ages			25–49 years			35–64 years		
	2000–2004	2005–2009	% change	2000–2004	2005–2009	% change	2000–2004	2005–2009	% change
Austria	3.81	3.88	2	1.24	1.03	−17	6.81	6.96	2
Belarus (2000–2003/2007–2009)	5.27	5.59	6	1.57	1.55	−1	10.57	11.15	5
Belgium (2003–2004)	5.47	5.20	−5	1.74	1.44	−17	9.01	8.64	−4
Bulgaria	1.99	2.43	22	0.79	0.98	24	3.89	4.78	23
Croatia	5.35	5.02	−6	1.84	1.39	−24	9.60	9.40	−2
Czech Republic	4.74	4.48	−5	1.90	1.38	−27	9.24	8.51	−8
Denmark	6.44	5.39	−16	1.63	0.93	−43	9.64	7.34	−24
Estonia	4.67	5.22	12	1.16	1.17	1	8.63	9.84	14
Finland	2.90	2.92	1	0.51	0.48	−6	4.46	4.67	5
France	7.19	5.99	−17	2.46	1.46	−41	12.58	10.24	−19
Germany	4.94	4.80	−3	1.57	1.30	−17	8.97	8.21	−8
Greece	1.49	1.38	−7	0.42	0.40	−5	2.08	2.09	0
Hungary	8.28	7.08	−14	4.55	3.00	−34	19.32	15.77	−18
Iceland	3.76	5.28	40	1.13	0.66	−42	4.52	6.72	49
Ireland	7.62	7.36	−3	1.96	1.57	−20	9.51	8.79	−8
Italy (2000–2003/2006–2009)	2.87	2.22	−23	0.66	0.52	−21	4.27	3.37	−21
Latvia	5.47	5.79	6	1.83	1.31	−28	10.72	11.17	4
Lithuania	6.35	6.85	8	1.89	2.03	7	12.60	14.14	12
Luxembourg	4.99	5.21	4	1.70	1.15	−32	8.51	8.97	5
Macedonia	1.75	1.67	−5	0.88	0.61	−31	3.10	2.85	−8
Malta	2.41	3.24	34	0.76	0.53	−30	4.20	3.58	−15
The Netherlands	7.13	7.71	8	1.64	1.49	−9	10.44	10.88	4
Norway	3.01	3.23	7	0.49	0.57	16	3.64	4.22	16
Poland	4.92	4.40	−11	1.43	1.14	−20	9.16	7.79	−15
Portugal	5.51	5.35	−3	3.29	2.99	−9	10.94	10.95	0
Republic of Moldova	3.06	3.14	3	1.04	0.64	−38	6.02	5.66	−6
Romania	3.01	3.57	19	1.44	1.48	3	6.54	7.79	19
Russian Federation	6.57	6.07	−8	1.45	1.16	−20	11.54	10.53	−9
Slovakia	7.23	6.48	−10	3.68	2.17	−41	15.43	13.69	−11
Slovenia	4.91	4.40	−10	2.05	1.13	−45	8.17	7.51	−8
Spain	4.82	4.13	−14	1.66	1.21	−27	8.88	7.26	−18
Sweden	3.09	3.08	−0	0.52	0.55	6	4.24	4.26	0
Switzerland	4.83	4.56	−6	1.04	0.72	−31	7.28	6.67	−8
Ukraine (2005–2006, 2008–2009)	4.85	4.45	−8	1.62	1.34	−17	9.99	9.44	−6
UK	8.71	8.71	0	1.92	1.74	−9	11.67	11.57	−1
UK, England and Wales	8.53	8.54	0	1.86	1.71	−8	11.35	11.25	−1
UK, Northern Ireland	7.80	8.28	6	2.62	1.83	−30	10.93	12.14	11
UK, Scotland	10.93	10.63	−3	2.33	2.02	−13	15.16	14.61	−4
EU (27)	5.34	4.99	−7	1.68	1.30	−23	9.03	8.25	−9

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Persisting favorable trends in overall male esophageal cancer mortality rates are predicted up to 2015 (Figure 3): in the EU, the predicted age-standardized mortality rate is 4.46/100 000, corresponding to ~22 300 esophageal cancer deaths. The predicted rates are 4.24/100 000 for France, 4.17/100 000 for Germany, 1.67/100 000 for Italy, 3.14/100 000 for Poland, 3.52/100 000 for Spain and 8.51/100 000 for the UK. Among EU women, the predicted age-standardized mortality rate is 1.07/100 000, corresponding to ~7400 esophageal cancer deaths.

Among men (Figure 4), increasing EAC incidence trends were observed in most countries, while ESCC trends have been decreasing or stabilizing over the last few decades. In Denmark, the Netherlands, England and Scotland, the increases in male EAC trends were among the steepest observed, and the EAC incidence is now higher than that of the ESCC. In central and southern Europe, smaller rises in EAC were observed and ESCC remains the predominant histological type among men.

Trends were less stable among women (supplementary Figure S1, available at *Annals of Oncology* online), as very low histology-specific incidence rates were observed. ESCC was the predominant histological type among women in all registration areas considered and still presented increasing trends in Austria, Denmark, Estonia, Slovakia and Switzerland.

Table 2. Age-standardized (world population) mortality rates from esophageal cancer per 100 000 women (at all ages and truncated at 25–49 and 35–64 years) in selected European countries and in the European Union (EU) in the periods 2000–2004 and 2005–2009 (unless otherwise mentioned in parenthesis), and corresponding percent changes

	All ages			25–49 years			35–64 years		
	2000–2004	2005–2009	% change	2000–2004	2005–2009	% change	2000–2004	2005–2009	% change
Austria	0.65	0.61	−6	0.16	0.09	−44	1.02	0.93	−9
Belarus (2000–2003/2007–2009)	0.35	0.30	−14	0.14	0.08	−43	0.44	0.38	−14
Belgium (2003–2004)	1.46	1.32	−10	0.42	0.19	−55	2.47	1.93	−22
Bulgaria	0.48	0.39	−19	0.23	0.13	−43	0.70	0.62	−11
Croatia	0.64	0.61	−5	0.21	0.11	−48	0.84	0.71	−15
Czech Republic	0.60	0.64	7	0.24	0.10	−58	0.93	1.06	14
Denmark	1.91	1.71	−10	0.49	0.29	−41	2.49	2.40	−4
Estonia	0.48	0.43	−10	0.07	0.16	129	0.56	0.71	27
Finland	0.87	0.97	11	0.06	0.08	33	0.77	1.08	40
France	1.01	0.98	−3	0.34	0.24	−29	1.57	1.53	−3
Germany	1.00	1.04	4	0.25	0.23	−8	1.65	1.67	1
Greece	0.31	0.27	−13	0.09	0.07	−22	0.30	0.23	−23
Hungary	1.17	0.96	−18	0.64	0.45	−30	2.58	2.16	−16
Iceland	1.07	1.22	14	0.00	0.00	.	0.38	0.77	103
Ireland	3.16	2.84	−10	0.45	0.37	−18	3.14	2.57	−18
Italy (2000–2003/2006–2009)	0.56	0.47	−16	0.12	0.12	0	0.71	0.62	−13
Latvia	0.44	0.59	34	0.09	0.04	−56	0.62	0.88	42
Lithuania	0.50	0.65	30	0.15	0.28	87	0.74	1.15	55
Luxembourg	0.98	1.02	4	0.00	0.21	.	0.69	1.90	175
Macedonia	0.42	0.25	−40	0.10	0.05	−50	0.64	0.31	−52
Malta	0.41	0.84	105	0.00	0.00	.	0.41	0.73	78
The Netherlands	2.09	2.17	4	0.47	0.35	−26	2.83	2.91	3
Norway	0.86	0.81	−6	0.17	0.05	−71	1.14	1.13	−1
Poland	0.74	0.75	1	0.20	0.17	−15	1.08	1.15	6
Portugal	0.72	0.55	−24	0.15	0.13	−13	0.73	0.54	−26
Republic of Moldova	0.43	0.34	−21	0.16	0.11	−31	0.68	0.54	−21
Romania	0.41	0.46	12	0.17	0.17	0	0.60	0.81	35
Russian Federation	0.99	0.84	−15	0.19	0.17	−11	1.01	0.95	−6
Slovakia	0.62	0.59	−5	0.35	0.20	−43	1.15	0.98	−15
Slovenia	0.67	0.59	−12	0.10	0.10	0	0.52	1.00	92
Spain	0.47	0.48	2	0.21	0.16	−24	0.72	0.78	8
Sweden	0.94	0.89	−5	0.25	0.10	−60	1.16	1.14	−2
Switzerland	1.03	1.13	10	0.21	0.15	−29	1.44	1.52	6
Ukraine (2005–2006, 2008–2009)	0.39	0.31	−21	0.09	0.10	11	0.48	0.47	−2
UK	3.20	3.04	−5	0.49	0.46	−6	3.26	3.26	0
UK, England and Wales	3.12	2.96	−5	0.50	0.46	−8	3.20	3.20	0
UK, Northern Ireland	2.84	2.69	−5	0.30	0.37	23	2.92	3.06	5
UK, Scotland	4.04	3.97	−2	0.52	0.52	0	3.99	3.90	−2
EU (27)	1.12	1.09	−3	0.28	0.22	−21	1.51	1.51	0

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Among men, most countries in northern and western Europe showed a higher proportion of EAC than any other histological type and presented the lowest values of the ESCC/EAC ratio, whereas in southern, central/eastern Europe the proportions of ESCC were generally higher (supplementary Figure S2 and Table S2, available at *Annals of Oncology* online). Among women (supplementary Figure S3 and Table S2, available at *Annals of Oncology* online), the proportion of ESCC incident cases was higher than that of EAC in all large countries. Central and eastern European countries showed the highest proportions of unspecified esophageal cancers in both sexes.

discussion

This updated analysis of esophageal cancer mortality trends in Europe confirms the long-term downward mortality rates observed for male esophageal cancer in several western countries, while in central European countries mortality trends were upwards until mid-1990s and started to stabilize or decline only over recent years. However, in some eastern and northern countries, male esophageal cancer mortality is still increasing. Mortality rates among European women remained comparatively low and showed stable or decreasing trends in some countries.

Regarding incidence, the EAC rates rose substantially among men in northern Europe and surpassed ESCC ones over the last decade, whereas ESCC remains the predominant histological type among European women and rates are still increasing in several countries. Such trends are unlikely to be attributable to a better classification of cases, as the unspecified esophageal cancer rates were low and did not appreciably decline in those countries. However, incidence trends must be interpreted with caution, since in some European countries incidence data had only a limited coverage of population.

Improvements in disease management may have somewhat influenced esophageal cancer mortality, as some increase in relative survival has been observed across Europe in the last few decades [13]. However, the heterogeneity in esophageal cancer incidence and mortality trends mostly reflects the differences in the exposure to the main determinants of EAC and ESCC cancer and their variations with time and across populations.

Alcohol consumption is associated with an increased risk of ESCC [14] but not of EAC [15], whereas tobacco smoking is a risk factor for both ESCC and EAC, the association being, however, stronger for ESCC [16, 17]. EAC is also associated with overweight/obesity and gastro-esophageal reflux disease [18], and it is inversely related to *Helicobacter pylori* infection [19]. Dietary aspects (i.e., low consumption of fruit and vegetables and high intake of meat, saturated fats and refined carbohydrates) are also related to esophageal cancer risk [20], and a non-negligible fraction of incident cases may be attributable to these factors [21, 22].

Trends and patterns in alcohol consumption have been largely heterogeneous across Europe, with widely debated rises in several Nordic and central European countries, Russia and the UK, and not so widely appreciated decreases in southern European countries [23]. Favorable trends observed in male mortality rates in countries from southern Europe followed the steady fall in alcohol consumption over the last few decades [23, 24], similarly to what has been observed for oral and pharyngeal cancers [25, 26]. Such favorable trends may also be due to changes in the composition of alcoholic beverages, including a reduction in acetaldehyde levels in most of these countries [27]. ESCC rates reflected the trends in alcohol consumption, decreasing in southern countries (e.g., France, Italy and Spain), and stabilizing in northern countries (e.g., Denmark and the UK), while EAC followed more consistently the trends in overweight/obesity, with more appreciable increases in northern Europe than in southern countries [28, 29].

Tobacco consumption has steadily declined in men from most European countries over the last few decades. However, changes in smoking have been less notable than those in alcohol drinking in southern Europe. Furthermore, alcohol and tobacco have a synergistic effect on esophageal cancer risk and the relative risks for combined exposures are one or two orders of magnitude greater than that of nonsmokers and nondrinkers [30]. Thus, limitation of one of these factors leads to the avoidance of a substantial proportion of cases on a population level [21].

Esophageal cancer trends in women are more difficult to interpret in terms of changes in exposure to risk factors, also on account of their much lower rates. Still, EAC was proportionally much less common than ESCC in women compared with men. This has long been recognized, but it is still surprising given that

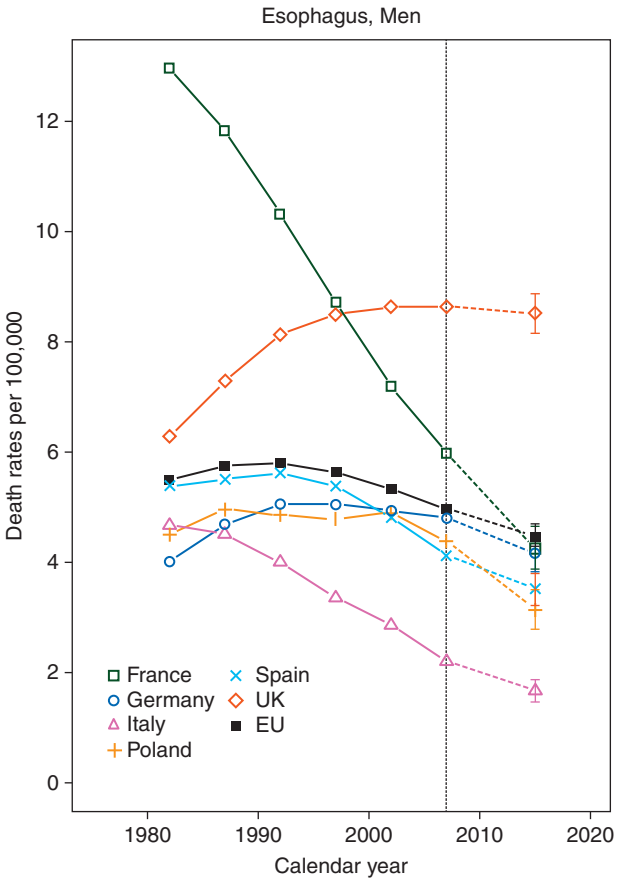

Figure 3. Trends in age-standardized (world population) mortality rates per 100 000 men for esophageal cancer in the European Union (EU) as a whole and selected European countries from 1980 to 2011, and predicted rates for 2015.

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women drink and smoke less than men. A possible explanation is the lower frequency of abdominal obesity in women, with consequently less gastro-esophageal reflux [31]. Another reason may be that women use less frequently tight belts and wear dresses [32].

In conclusion, esophageal cancer mortality has been stabilizing or decreasing in most European countries, and it is expected to decrease further in the next few years. Among men, EAC is now the predominant histological type in northern countries, while ESCC remains the most common subtype in women.

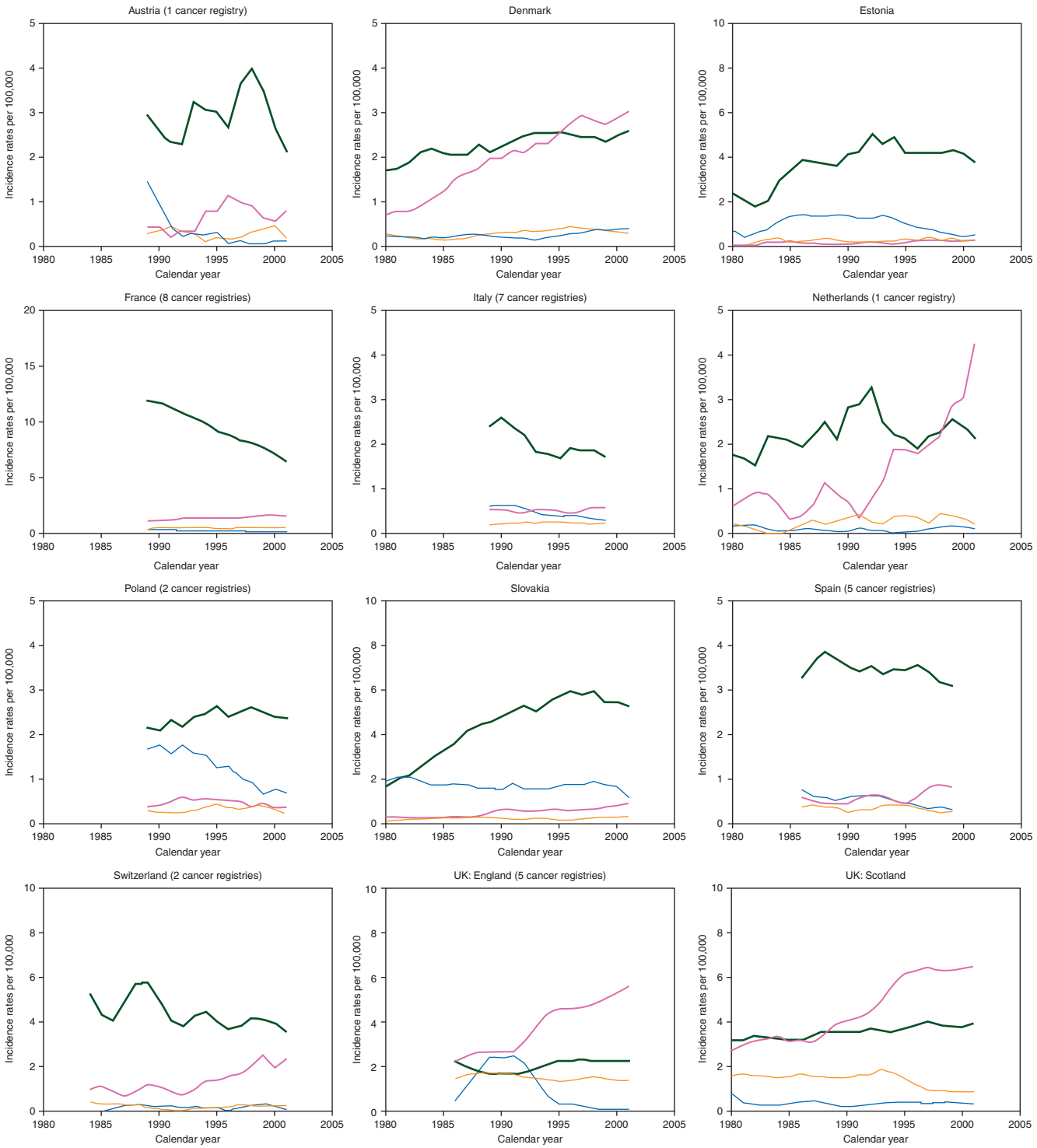

Figure 4. Trends in age-standardized (world population) incidence rates per 100 000 men for esophageal cancer by histological types in selected European countries, 1980–2002. —esophageal squamous cell carcinoma; —esophageal adenocarcinoma; —unspecified esophageal cancers; —other esophageal cancers.

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disclosure

The authors have declared no conflicts of interest.

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