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Original Research

Trends in age- and sex-specific lung cancer mortality in Europe and Northern America: Analysis of vital registration data from the WHO Mortality Database between 2000 and 2017

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Abstract ***Background:*** In the context of new targeted therapies and immunotherapy as well as screening modalities for lung cancer patients, detailed mortality trends in Europe and Northern America are unknown.
Methods: Time-trend analysis using vital registration data of Northern America and Europe from the WHO Mortality Database (years 2000/2017). To assess improvements in lung cancer mortality, we performed a population-averaged Poisson autoregressive analysis. The average annual percent change (AAPC) was used as a summary measure of overall and country-specific trends in mortality. Second, we studied time trends of lung cancer incidence and smoking prevalence rates.

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Findings: In the total population of 872·5 million people between 2015 and 2017, the average annual age-standardised mortality from lung cancer was 54·6 deaths per 100 000, with substantial differences across countries. Lung cancer was reported as the primary cause of death in 5·4 cases per 100 deaths. The age-standardised mortality rate decreased constantly (AAPC −1·5%) between 2000 and 2017. While mortality in men dropped annually by an average of −2·3%, mortality in women decreased by an average of −0·3%. This slight decline was driven exclusively by the USA. In contrast, 21 out of 31 countries registered a significant increase in female lung cancer mortality between 2000 and 2017, with Spain (AAPC 4·1%) and France (AAPC 3·6%) leading the list.

Interpretation: Despite overall decreases in lung cancer mortality trends, female mortality remained unchanged or increased significantly in all countries except the USA. National mortality outcomes reflect variabilities in tobacco control, screening, therapeutic advances, and access to health care.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality with 18·0% of the total cancer deaths in the world [1]. In Europe, around 20% of all cancer deaths are caused by lung cancer [2]. The estimated Europe-wide incidence is 12% of all tumour diseases [3]. In the last decade, major improvements in survival have been established with the implementation of targeted therapies and immunotherapies [4,5]. More specifically, over 50% of patients with advanced non-small-cell lung cancer (NSCLC) may have potentially actionable molecular targets [6]. The development of targeted therapies against EGFR-activating mutations since 2003 [7–9], implementation of PD-(L)1 immune checkpoint inhibitors in 2015/2016 [10–12], and several new drugs that specifically target molecular abnormalities (e.g., ALK [13], ROS [14], BRAF [15], etc.) have paved the way for 'long-term survival' in selected patients [16,17]. Furthermore, trials in the USA and Europe have shown the potential of early detection through computerised tomography-based screening to reduce lung cancer mortality [18–20].

The precise impact of these advances in the last 20 years on current comprehensive cancer mortality outcomes in Europe and Northern America is unclear. Selected cohort data suggest that they have led to a substantial reduction in population lung cancer mortality in the USA [21]. However, it should be pointed out that analyses of western lung cancer population mortality have several limitations, making conclusions based on them prone to error. Firstly, mortality trends are frequently either outdated [22–26] or susceptible to selection bias (e.g., covering only a selected fraction of a population) [21]. In addition, outcomes may be distorted by the application of mortality predictions [27] or by the inclusion of rare but different tumour entities like 'malignant neoplasm of trachea' [23]. Therefore, we investigated age- and sex-specific trends in lung cancer mortality in Europe and Northern America. Using this data, we discuss the anticipated treatment progress in a real-world setting.

2. Materials and methods

This descriptive study was conducted using secondary data from the countries of Northern America (the USA and Canada), the European Union (EU), and the European Free Trade Association (EFTA) during the period from 2000 to 2017. Annual mortality data came from the World Health Organization (WHO) Mortality Database (latest update: June 2021) [28], which comprises deaths registered in national vital registration systems, with the underlying causes of death coded according to the International Classification of Diseases (ICD). The years after 2017 were discarded because of high proportions of missing data due to delays in the national data submission. Between 2000 and 2017, only country-years with death counts grouped according to the 10th revision of the ICD (ICD-10) were used in the analysis. Mid-year reference population sizes were extracted from United Nations data [29].

For each country, the mortality rates from lung cancer were calculated as the annual number of deaths coded as C34 in the ICD-10, divided by the population of all ages and expressed per 100 000 inhabitants. To enable comparisons between groups and over time that account for differences in age structure and population size, rates were directly standardised according to the European Standard Population, revised in 2013 by the European Commission for the EU-27 and EFTA [30]. The European Standard Population was applied for the USA and Canada as well. A total of 48 lung cancer deaths of unspecified age during the period investigated were excluded: 43 in the USA, three in Canada, one in Estonia, and one in Italy. Results were presented as average annual mortality rates for the last three years of the study period (2015/2017), and as annual mortality rates for all individual years between 2000 and 2017. Our first analysis was performed to provide a thorough description of lung cancer mortality in the last years with available data, pooling data over three years to ensure adequate precision of mortality rates in countries with small population sizes or missing counts. The second analysis was performed to investigate time trends over a period of nearly 20 years.

In the cross-sectional analysis of the three-year period from 2015 to 2017, three countries with extensive missing values were excluded: Ireland, with two missing years, and Slovakia and Liechtenstein, with no available data. If two out of three country-years were available, the missing value was imputed with the forecasts obtained from a second-order autoregressive Poisson model including restricted cubic spline terms calculated over the entire study period [31]. Subregional and overall estimates were then obtained by pooling age- and sex-specific deaths and populations of each country over the three-year period. Subregional entities were defined according to the United Nations Statistics Division geoscheme (Northern America, Eastern Europe, Northern Europe, Southern Europe, and Western Europe). The 95% confidence intervals (CIs) of the crude mortality rates were calculated using exact Poisson limits (Poisson means), while the 95% CIs of age-standardised mortality rates were calculated using a method developed by Fay and modified by Tiwari [32]. In a secondary analysis, proportionate mortality (deaths from lung cancer per 100 deaths from all causes) was investigated.

In the time-trend analysis of the 18-year period from 2000 to 2017, no imputation of missing country-years was performed, which means that each country contributed to the analysis only for the years with complete data. For reasons of consistency, Ireland, Slovakia, and Liechtenstein were also excluded from this analysis. To depict the temporal trends in lung cancer mortality for the total population of the study countries and for each subregion, we performed a population-averaged Poisson autoregressive analysis, accounting for non-linear trends by building restricted cubic splines with the knot locations recommended by Harrell [33]. The number of knots was set at seven, but a sensitivity analysis based on fewer knots (four to six) gave virtually coincident results. The average annual percent change (AAPC) was used as a summary measure of overall and country-specific trends in lung cancer mortality. The AAPC is a method that uses an underlying segmented regression in which several significant breakpoints in the time series (if any) are allowed, and is computed as a weighted average of the annual percent changes estimated over each time segment. In our analysis, the AAPCs were estimated by fitting a log-linear segmented regression model, assuming the homoscedasticity and autocorrelation of the random errors and allowing a maximum of three breakpoints over the time series. The 95% CIs of the AAPCs were calculated using a parametric approach based on the normal distribution [34].

In a secondary analysis, mortality from tracheal cancer (ICD-10 C33) was investigated [23]. Lastly, a time-trend analysis was performed on lung cancer incidence rates and smoking prevalence rates (see the appendix, pp. 13 and 19, for details).

Results were stratified by sex and five-year age group and visualised with the aid of shading matrices, line charts, and caterpillar plots. Stata 15 and Joinpoint 4.9 were used for data analysis.

3. Results

3.1. Mortality from lung cancer in 2015/2017

In the three-year period between 2015 and 2017, the population of the 31 study countries consisted of 872·5 million people. The average annual number of deaths from lung cancer was 444 398, corresponding to an average annual crude mortality of 50·9 deaths per 100 000 population (95% CI 50·8–51·0) and an average annual age-standardised mortality of 54·6 deaths per 100 000 population (95% CI 54·5–54·7).

As shown in Figs. 1 and 2, there were substantial differences in lung cancer age-standardised mortality across countries. Observed mortality ranged from 37·0 per 100 000 (95% CI 36·3–37·6) in Portugal to 91·3 per 100 000 (95% CI 90·2–92·4) in Hungary. Southern and Eastern Europe had the lowest and highest rates of mortality from lung cancer, respectively (Southern Europe: 49·4 per 100 000, 95% CI 49·2–49·7; Eastern Europe: 63·1 per 100 000, 95% CI 62·8–63·5), but with strong inter-country variability within each subregion, especially in Southern Europe (Figs. 1 and 2).

When the estimates were stratified by sex (Fig. 2, and Figures S1–2 in appendix), we found a dispersion in inter-country-specific rates that was stronger among males than females. In general, Scandinavia and Northern America had above-the-average mortality in their female populations, while no clear geographical pattern was detectable in country-specific male mortality rates.

As expected, mortality from lung cancer increased with age (Figs. 1 and 3). More specifically, there was a mortality of <10 deaths per 100 000 population up to 40–44 years of age, followed by a seemingly exponential increase from 45 to 49 years (11·6 per 100 000, 95% CI 11·5–11·8) to 75–79 years (241·2 per 100 000, 95% CI 240·1–242·2), and by a deceleration and even decrease in late life (80–84 years: 265·4 per 100 000, 95% CI 264·1–266·6; ≥85 years: 247·6 per 100 000, 95% CI 246·3–248·8). Age-specific mortality rates were consistently higher in males than females after 25 years of age.

In the total population of the 31 study countries, lung cancer was reported as the primary cause of death in 5·4 cases per 100 deaths (95% CI 5·4–5·4), with significantly higher percentages in males (6·7 per 100, 95% CI 6·7–6·7) compared to females (4·1 per 100, 95% CI

Subregion/ Country	Annual deaths	Pop. (millions)	Crude rate (95% CI)	Age-specific rates																		Age-std. rate (95% CI)
				0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	≥85	
Northern America	169 583	359·4	47·2 (47·1–47·3)	0·0	0·0	0·0	0·0	0·1	0·1	0·4	1·1	3·3	9·4	26·6	58·1	92·5	143·3	219·2	283·4	329·0	310·3	58·3 (58·1–58·4)
Canada	20 104	36·4	55·3 (54·8–55·7)	0·0	0·0	0·0	0·0	0·1	0·1	0·4	0·9	2·5	7·1	22·8	54·3	99·6	154·6	239·9	319·1	376·9	361·4	63·5 (63·0–64·0)
United States	149 479	323·0	46·3 (46·1–46·4)	0·0	0·0	0·0	0·0	0·1	0·1	0·4	1·2	3·4	9·7	27·1	58·5	91·6	141·9	216·7	279·1	322·8	303·9	57·6 (57·4–57·8)
Eastern Europe	51 403	85·3	60·3 (60·0–60·6)	0·0	0·0	0·0	0·1	0·1	0·2	0·6	1·8	5·2	17·5	44·1	97·3	160·6	215·0	233·3	234·8	214·8	158·5	63·1 (62·8–63·5)
Bulgaria	3381	7·2	47·3 (46·4–48·2)	0·0	0·0	0·1	0·1	0·2	0·4	1·1	3·1	7·5	21·4	45·0	86·4	121·8	153·9	143·9	141·6	102·8	70·4	44·2 (43·3–45·1)
Czechia	5337	10·6	50·3 (49·5–51·0)	0·0	0·1	0·0	0·1	0·2	0·1	0·4	1·5	3·2	8·9	23·2	49·7	111·5	177·6	220·3	221·3	220·3	173·7	52·0 (51·2–52·8)
Hungary	8799	9·8	90·2 (89·1–91·3)	0·1	0·0	0·0	0·0	0·1	0·2	0·8	2·1	6·8	27·6	77·8	163·2	244·1	306·7	321·4	301·8	286·1	221·0	91·3 (90·2–92·4)
Poland	23 616	38·0	62·2 (61·7–62·6)	0·0	0·0	0·0	0·0	0·0	0·1	0·5	1·1	3·2	12·6	39·1	91·8	167·0	237·4	259·9	277·1	256·0	178·9	68·0 (67·5–68·5)
Romania	10 269	19·8	51·9 (51·3–52·5)	0·0	0·1	0·1	0·1	0·2	0·5	0·8	2·9	8·1	23·1	49·1	104·5	143·3	174·0	186·7	180·5	154·3	108·4	54·1 (53·5–54·8)
Northern Europe	50 507	99·1	51·0 (50·7–51·2)	0·0	0·0	0·0	0·1	0·1	0·2	0·4	1·0	3·3	8·4	20·8	44·8	87·7	139·9	204·8	263·3	305·5	296·1	54·0 (53·7–54·2)
Denmark	3678	5·7	64·4 (63·2–65·6)	0·0	0·0	0·0	0·0	0·1	0·3	0·4	1·0	2·9	9·0	27·5	61·7	118·7	158·9	257·7	316·6	416·7	345·5	67·4 (66·1–68·7)
Estonia	659	1·3	50·0 (47·8–52·3)	0·0	0·0	0·0	0·6	0·5	0·0	0·4	0·7	2·5	9·5	20·8	53·2	100·7	168·5	200·0	221·7	213·1	195·5	50·2 (48·0–52·5)
Finland	2252	5·5	41·0 (40·0–42·0)	0·0	0·0	0·0	0·1	0·2	0·0	0·3	0·6	1·5	4·4	13·6	33·8	69·4	109·8	159·8	192·6	197·5	193·0	39·2 (38·2–40·1)
Iceland	132	0·3	39·8 (36·0–43·9)	0·0	0·0	0·0	0·0	0·0	0·0	1·4	1·5	3·1	4·8	23·3	49·0	65·4	121·5	249·5	252·3	297·5	289·9	53·2 (48·0–58·7)
Latvia	937	2·0	47·5 (45·7–49·3)	0·0	0·0	0·0	0·4	0·0	0·5	0·7	1·6	3·2	9·7	25·9	61·7	106·9	154·9	187·4	189·8	166·8	130·6	46·2 (44·5–48·0)
Lithuania	1287	2·9	44·5 (43·2–46·0)	0·0	0·0	0·0	0·0	0·0	0·3	0·4	1·2	5·3	11·1	31·7	63·9	107·1	146·5	168·6	162·6	166·7	120·8	44·3 (42·9–45·7)
Norway	2195	5·2	41·8 (40·8–42·8)	0·1	0·0	0·0	0·0	0·0	0·0	0·5	0·4	1·9	3·7	16·7	38·2	82·4	135·9	196·7	244·0	282·8	242·7	49·2 (48·0–50·4)
Sweden	3701	9·8	37·6 (36·9–38·3)	0·0	0·0	0·0	0·0	0·0	0·0	0·2	0·7	1·3	4·6	11·2	26·7	59·8	97·2	165·0	196·1	224·3	178·6	38·0 (37·3–38·7)
United Kingdom	35 666	66·3	53·8 (53·5–54·1)	0·0	0·0	0·0	0·1	0·1	0·2	0·4	1·1	3·8	9·5	21·7	45·5	89·6	147·2	213·3	286·0	334·2	338·6	57·8 (57·5–58·2)
Southern Europe	71 609	135·8	52·7 (52·5–53·0)	0·0	0·0	0·0	0·0	0·1	0·2	0·4	1·4	4·1	11·8	28·3	59·4	98·0	140·2	179·0	212·2	237·1	215·7	49·4 (49·2–49·7)
Cyprus	266	0·9	31·2 (29·0–33·4)	0·0	0·0	0·0	0·0	0·0	0·5	0·0	1·1	3·0	8·7	11·6	31·0	84·3	106·8	164·5	172·0	187·6	154·3	38·3 (35·7–41·1)
Croatia	2882	4·2	68·5 (67·1–70·0)	0·0	0·0	0·0	0·0	0·0	0·1	0·6	1·9	4·4	19·5	46·3	99·4	177·1	215·7	229·8	235·3	244·2	170·1	65·5 (64·1–66·9)
Greece	7148	10·6	67·3 (66·4–68·2)	0·1	0·1	0·0	0·1	0·2	0·3	0·5	1·4	4·8	13·9	33·8	77·9	136·6	198·2	248·9	259·9	267·3	227·8	63·2 (62·4–64·1)
Italy	33 867	60·6	55·9 (55·5–56·2)	0·0	0·0	0·0	0·0	0·1	0·2	0·5	1·4	3·7	9·3	21·4	45·3	80·6	129·0	184·0	228·0	267·7	257·0	48·8 (48·5–49·1)
Malta	185	0·4	42·4 (38·9–46·0)	0·0	0·0	0·0	0·0	2·3	0·0	0·0	1·1	1·1	2·6	32·5	47·9	89·3	103·9	148·3	192·9	255·1	196·3	43·4 (39·9–47·2)
Portugal	4107	10·3	39·8 (39·1–40·5)	0·0	0·0	0·0	0·0	0·1	0·4	0·7	1·7	5·8	12·9	32·2	58·3	80·4	106·8	120·2	139·7	139·6	144·9	37·0 (36·3–37·6)
Slovenia	1208	2·1	58·2 (56·3–60·2)	0·0	0·0	0·0	0·0	0·0	0·3	0·2	0·4	2·0	11·0	37·7	86·3	137·9	195·3	184·9	222·2	241·0	210·6	57·8 (56·0–59·8)
Spain	21 947	46·7	47·0 (46·7–47·4)	0·0	0·0	0·0	0·0	0·1	0·1	0·3	1·3	4·2	13·9	33·8	69·7	107·0	142·2	166·2	188·2	206·8	171·8	47·9 (47·6–48·3)
Western Europe	101 296	192·9	52·5 (52·3–52·7)	0·0	0·0	0·0	0·0	0·1	0·2	0·5	1·9	5·4	14·3	33·1	69·6	113·4	149·9	178·2	203·9	214·9	193·9	50·8 (50·6–51·0)
Austria	3901	8·7	44·6 (43·8–45·4)	0·1	0·0	0·0	0·0	0·0	0·4	0·5	1·4	3·9	9·1	27·2	57·5	103·4	149·3	168·6	182·1	171·5	162·5	45·2 (44·4–46·0)
Belgium	6268	11·4	55·2 (54·4–56·0)	0·0	0·0	0·0	0·0	0·0	0·1	0·4	2·1	5·0	12·4	34·8	65·6	123·5	164·3	210·3	250·0	259·3	232·3	57·3 (56·5–58·2)
France	31 792	64·7	49·2 (48·9–49·5)	0·0	0·0	0·0	0·0	0·1	0·3	0·7	2·7	7·6	20·1	41·3	83·4	120·9	140·0	157·5	177·3	193·6	175·7	49·8 (49·5–50·1)
Germany	45 344	82·2	55·2 (54·9–55·4)	0·0	0·0	0·0	0·0	0·1	0·1	0·4	1·3	4·1	11·9	29·7	64·8	109·5	156·1	179·2	203·1	207·3	192·8	49·8 (49·5–50·1)
Luxembourg	229	0·6	39·6 (36·7–42·7)	0·0	0·0	0·0	0·0	0·0	0·0	0·7	0·0	3·8	12·0	25·9	48·5	113·0	135·4	188·1	261·0	216·8	222·9	51·1 (47·3–55·0)
Netherlands	10 497	17·0	61·8 (61·1–62·5)	0·0	0·0	0·0	0·0	0·0	0·1	0·6	2·2	5·6	14·3	32·0	67·7	118·3	169·2	241·3	296·1	354·3	304·7	65·0 (64·3–65·7)
Switzerland	3265	8·4	39·0 (38·2–39·8)	0·0	0·0	0·0	0·0	0·2	0·1	0·5	1·5	3·0	7·4	20·2	45·4	79·4	112·7	154·8	192·5	208·8	168·5	41·1 (40·3–41·9)
All populations	444 398	872·5	50·9 (50·8–51·0)	0·0	0·0	0·0	0·0	0·1	0·2	0·5	1·4	4·1	11·6	29·3	63·4	105·2	151·5	201·8	241·2	265·4	247·6	54·6 (54·5–54·7)

Fig. 1. **Average annual lung cancer mortality (×100 000 population) in Northern America, the EU, and the EFTA, overall and by country, years 2015/2017.** *Notes:* Displayed in the first columns are the average annual numbers of deaths from lung cancer and inhabitants in each country between 2015 and 2017. Countries are listed in geographical order from Northern America to Western Europe. Age-specific and age-standardised rates are coloured from lowest to highest using a decile scale. 2017 data for Norway, the UK, Belgium, and France were imputed with forecasts obtained from autoregressive Poisson regression analysis. Estimates for total and subregional populations were obtained by pooling age-specific deaths and populations of each country over the three-year period. *Abbreviations:* EU, European Union; EFTA, European Free Trade Association; CI, confidence interval; UK, United Kingdom.

4·1–4·1). Stratification by age group (Fig. 4) revealed that proportionate mortality from lung cancer reached its peak of 10·9 per 100 deaths (95% CI 10·9–10·9) in the strata of population aged 60–69 years, with a similar difference between males (11·2 per 100, 95% CI 11·2–11·3) and females (10·4 per 100, 95% CI 10·3–10·4). The only subregion where age-specific percentages differed between males and females to a substantial extent was Southern Europe.

3.2. Time trends in mortality from lung cancer between 2000 and 2017

As shown in the appendix (Fig. S3) and depicted in Figs. 5 and 6, the estimated age-standardised lung cancer mortality rate in the total population of Northern America, the EU, and the EFTA decreased at a constant pace from 69·9 per 100 000 in 2000 to 53·9 per 100 000 in 2017, corresponding to an AAPC of −1·5% (95% CI −1·5, −1·5). Northern America was the subregion with the strongest decrease in lung cancer mortality, and the USA exhibited a particularly steep decline from 82·7 deaths per 100 000 in 2000 to 54·9 deaths per 100 000 in 2017, corresponding to an AAPC of −2·4% (95% CI −2·5, −2·3). The only countries that showed significant increases in lung cancer mortality over the 18-year study period were Cyprus (AAPC 1·9%; 95% CI 0·9, 2·8), Portugal (AAPC 0·8%; 95% CI 0·5, 1·1), and Romania (AAPC 0·7%; 95% CI 0·4, 1·0).

As shown in the appendix (Figs. S4–5) and depicted in Figs. 5 and 6, sex-specific trends in estimated age-standardised lung cancer mortality were diverse and convergent. Overall male mortality dropped annually by an average of −2·3% (95% CI −2·3, −2·3), from 110·6 per 100 000 in 2000 to 74·4 per 100 000 in 2017, while overall female mortality only decreased by an average of −0·3% (95%−0·3, −0·4), from 40·7 per 100 000 in 2000 to 38·3 per 100 000 in 2017. This slight decline was driven exclusively by the USA, which was the only country with a significant decline in female lung cancer mortality during this period (AAPC −1·6%; 95% CI −1·8, −1·5). Of note, in 2000, the USA had the highest lung cancer mortality rate for females (60.9 per 100 000) among all countries with available data (Fig. 5, and Figure S5 in appendix), as well as the highest incidence of lung cancer compared to all other countries (see the next subsection). Conversely, 21 out of 31 countries registered significant increases in female lung cancer mortality between 2000 and 2017, with Spain (AAPC 4·1%, 95% CI 3·9, 4·3) and France (AAPC 3·6%, 95% CI 3·3, 3·9) leading the list. A visual illustration of the negative correlation that exists between country-specific AAPCs and starting levels of lung cancer age-standardised mortality is provided in Figure S6 in appendix.

Between 2000 and 2017, estimated mortality from lung cancer decreased or levelled off in all age groups except for the ≥85-year group; in particular, in this age group the female mortality rate went from 139·0 per 100 000 in 2000 to 164·2 per 100 000 in 2017 (Figures S7–9 in appendix). This pattern was confirmed in all subregions.

Figure S10 in appendix illustrates the results of the time-trend analysis performed on deaths from tracheal

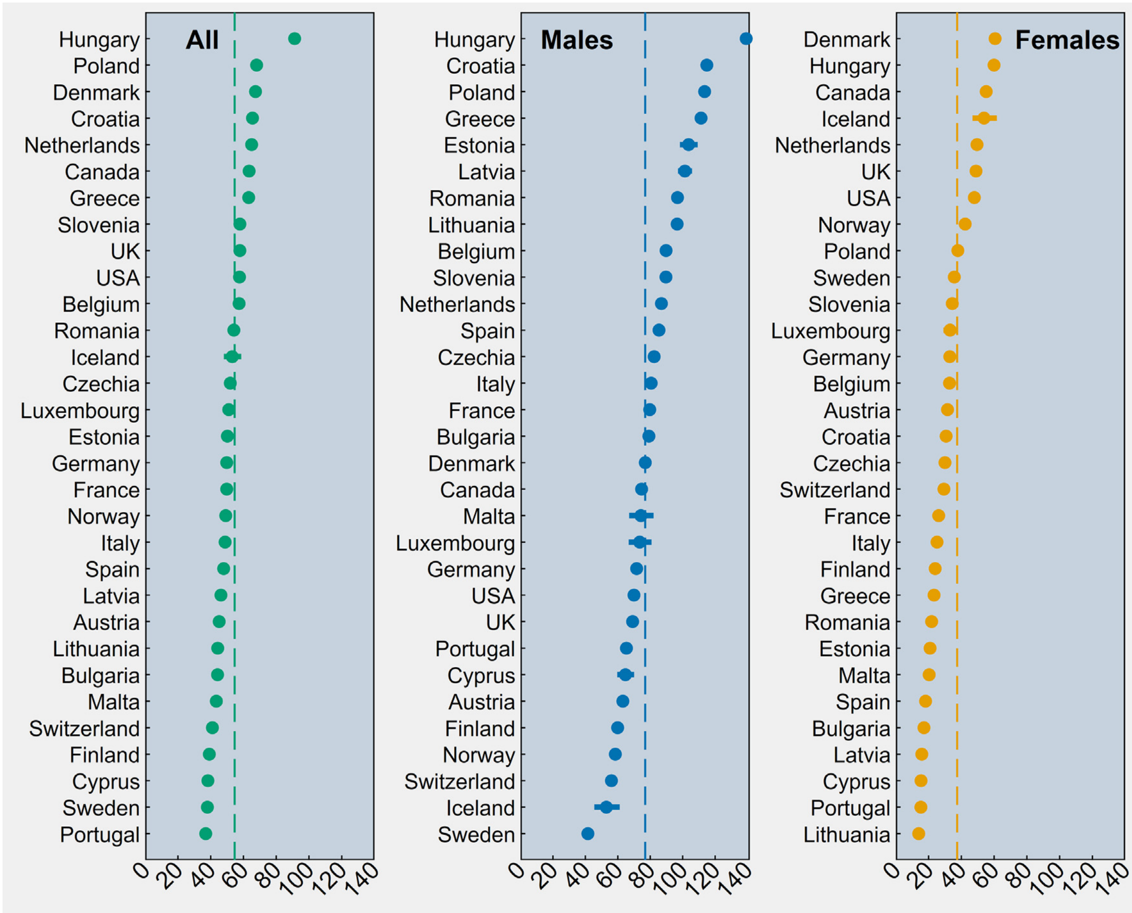

Fig. 2. **Average annual lung cancer age-standardised mortality (×100 000 population) for each country of Northern America, the EU, and the EFTA, overall and by sex, years 2015/2017.** *Notes:* Point estimates of age-standardised mortality are presented along with 95% confidence intervals. The dashed line is the international average for the years 2015/2017 obtained by pooling all data from individual countries. Countries are sorted into descending order based on their mortality rates. *Abbreviations:* EU, European Union; EFTA, European Free Trade Association; UK, United Kingdom; USA, United States of America.

cancer between 2000 and 2017. Estimated age-standardised mortality for both sexes combined went from 0·82 per 1 000 000 population in 2000 to 0·51 per 1 000 000 population in 2017, with an AAPC of −2·7% (95% CI −2·9, −2·6).

3.3. Time trends in incidence of lung cancer between 1998 and 2012

The following results are presented in Figures S12–16 in appendix. Overall age-standardised lung cancer incidence among males decreased from 130·0 per 100 000 in 1998 to 102·0 per 100 000 in 2012 (AAPC −1·7%; 95% CI −1·8, −1·7). This decline was observed in all the 22 countries with available data except Cyprus, Norway, Bulgaria, and France. On the contrary, there was an increase in overall age-standardised female incidence from 62·4 per 100 000 in 1998 to 67·5 per 100 000 in 2012 (AAPC 0·5%; 95% CI 0·5, 0·6), with the only exception of the USA, which registered a slight non-significant decline in the same observation period.

3.4. Time trends in the prevalence of cigarette smoking between 1946 and 2015

The prevalence of male smoking has been decreasing over the last 70 years, while female prevalence exhibited different patterns of change in the six study countries with available data (Figure S17 in appendix). In the USA, cigarette smoking among women began to decrease in the early 1980s, while in Denmark and Norway, this decline started with a 20-year delay. Italy, Austria, and Germany had lower prevalence rates of female smokers, and no clear decline was observed between 1946 and 2015.

4. Discussion

This comprehensive analysis of trends in age- and sex-specific lung cancer mortality among 872·5 million people in Europe and Northern America documents heterogenous mortality outcomes in the new millennium. Besides therapeutic advances, country-specific trends reflect national differences in tobacco control

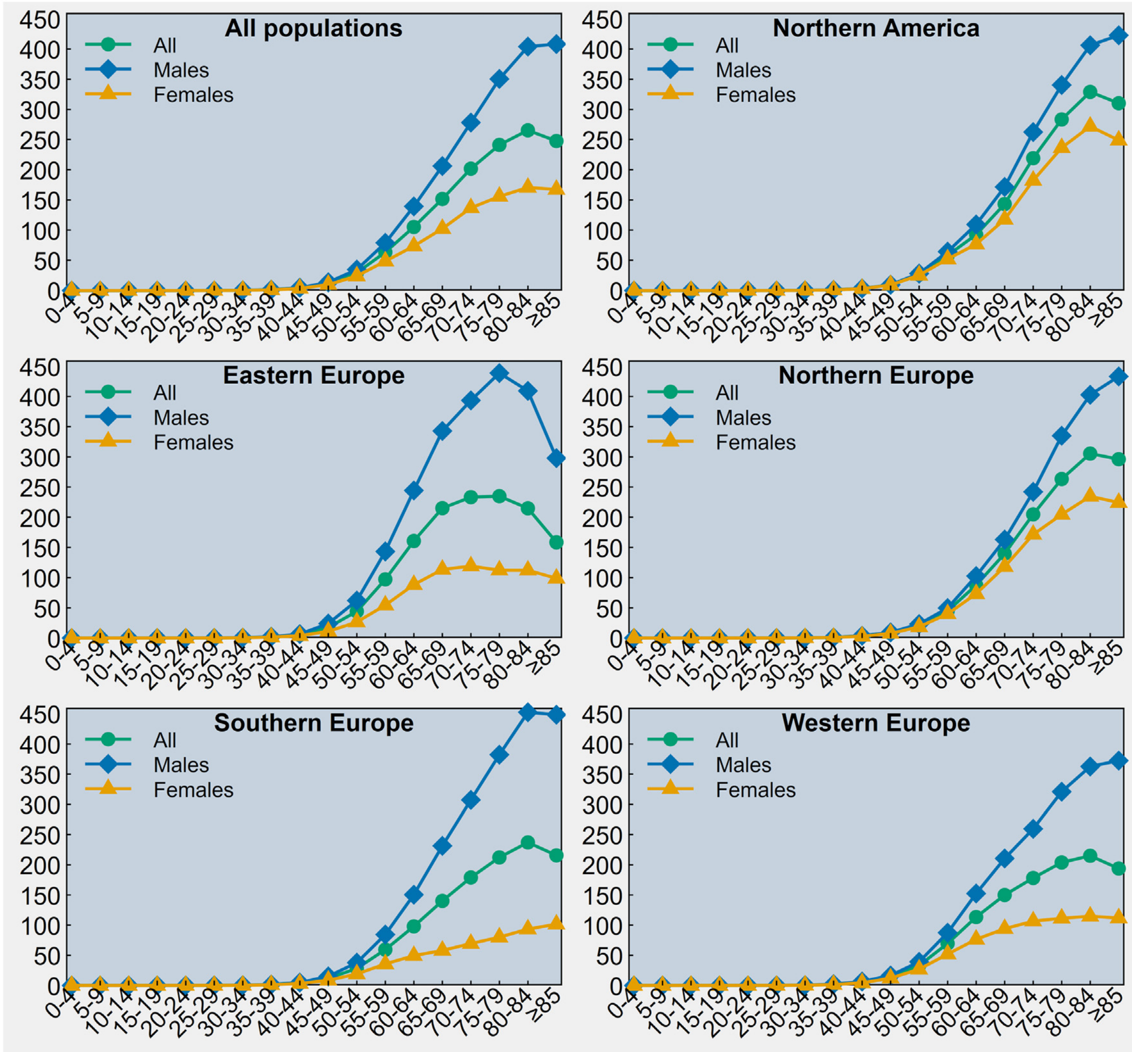

Fig. 3. **Average annual lung cancer age-specific mortality (×100 000 population) in Northern America, the EU, and the EFTA, overall and by sex and subregion, years 2015/2017.** *Notes:* Northern America includes Canada and the USA; Eastern Europe includes Bulgaria, Czechia, Hungary, Poland, and Romania; Northern Europe includes Denmark, Estonia, Finland, Iceland, Latvia, Lithuania, Norway, Sweden, and the UK; Southern Europe includes Cyprus, Croatia, Greece, Italy, Malta, Portugal, Slovenia, and Spain; Western Europe includes Austria, Belgium, France, Germany, Luxembourg, the Netherlands, and Switzerland. *Abbreviations:* EU, European Union; EFTA, European Free Trade Association; USA, United States of America; UK, United Kingdom.

[35], disparities in the access to and application of effective evidence-based treatments and health care programs [36–41], and differences in lung cancer screening plans [19,42].

Despite recent advances in screening and treatment, lung neoplasms still account for the highest mortality of all tumours [3,43]. We found a constant significant decrease in lung cancer mortality (−1·5% per year) in the overall population from the beginning of our study period in 2000. Several explanations have been suggested for this observed trend. Howlader *et al.* suggested that '*a reduction in incidence along with treatment advances – particularly approvals for and use of targeted therapies – is likely to explain the reduction in mortality*' from 2013 to 2016 [21]. The correlation of the treatment advances with short-term mortality trends might be difficult because the time interval from treatment implementation is too short. Broad testing for molecular analyses of lung cancers started in 2013, and large-scale lung cancer screening has not been implemented in Europe to date [44]. Moreover, in western countries outside the USA, targeted therapies generally achieved wide applicability later (e.g., gefitinib was approved in 2003 in the USA *vs.* in 2009 in the EU), therefore, not being relevant for the reduction in lung cancer mortality observed already in the 2000s in this study [7].

Smoking prevalence is highly associated with lung cancer incidence [45]. We must not forget that, irrespective of treatment advances, smoking rates in high-income countries began dropping considerably in the 1990s [46,47]. In the so-called 'smoking epidemic', patterns of nicotine consumption follow a wave-shaped

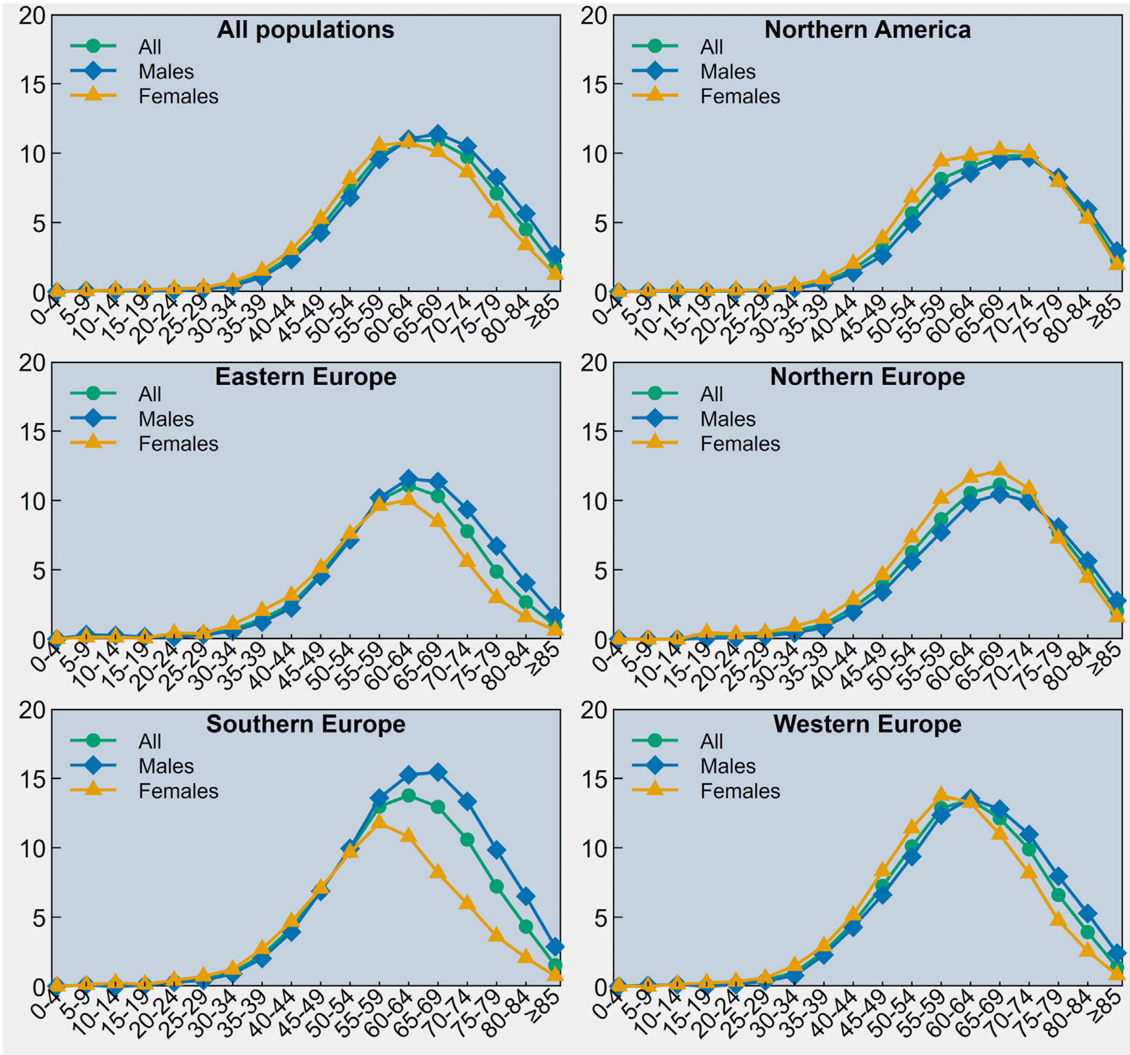

Fig. 4. **Lung cancer proportionate mortality (deaths from lung cancer ×100 deaths) in Northern America, the EU, and the EFTA, overall and by sex and subregion, years 2015/2017.** *Notes:* Northern America includes Canada and the USA; Eastern Europe includes Bulgaria, Czechia, Hungary, Poland, and Romania; Northern Europe includes Denmark, Estonia, Finland, Iceland, Latvia, Lithuania, Norway, Sweden, and the UK; Southern Europe includes Cyprus, Croatia, Greece, Italy, Malta, Portugal, Slovenia, and Spain; Western Europe includes Austria, Belgium, France, Germany, Luxembourg, the Netherlands, and Switzerland. *Abbreviations:* EU, European Union; EFTA, European Free Trade Association; USA, United States of America; UK, United Kingdom.

trend of increase and decline [48]. An investigation of smoking-attributable mortality beginning with birth cohorts before the 19th century suggests that changes in mortality occur approximately three decades after the relevant changes in smoking prevalence [45]. Different time points of smoking peaks for men and women, as well as changes in incidence rates among younger men and women and sex differences in carcinogens, influenced mortality trends significantly [45,47,49,50]. Moreover, as suggested by our data, smoking peaks and turnarounds occurred at different time points and likely reflect inter-country variability in mortality outcomes as of 2015/2017. These observations are highly relevant for the lung cancer mortality trends described in this study. Despite widespread enthusiasm for advances in targeted therapy and immunotherapy, our data suggest that a more differentiated view may be warranted [17].

Northern America was the region with the strongest lung cancer mortality decrease from 2000 to 2017 (AAPC −2·4% in the USA and −1·3% in Canada). The USA started with one of the highest mortality rates at the turn of the millennium, but by 2017, the mortality rate had dropped by a third. Lung cancer mortality rates in Europe, meanwhile, were characterised by strong inter-country variability within each subregion, especially in Southern Europe. In contrast to the general mortality reduction trend of our analysis, Hungary had the highest mortality rates by far, with the highest reported mortality and incidence rates worldwide [51,52]. Northern Europe saw the smallest drop in mortality as compared to all the

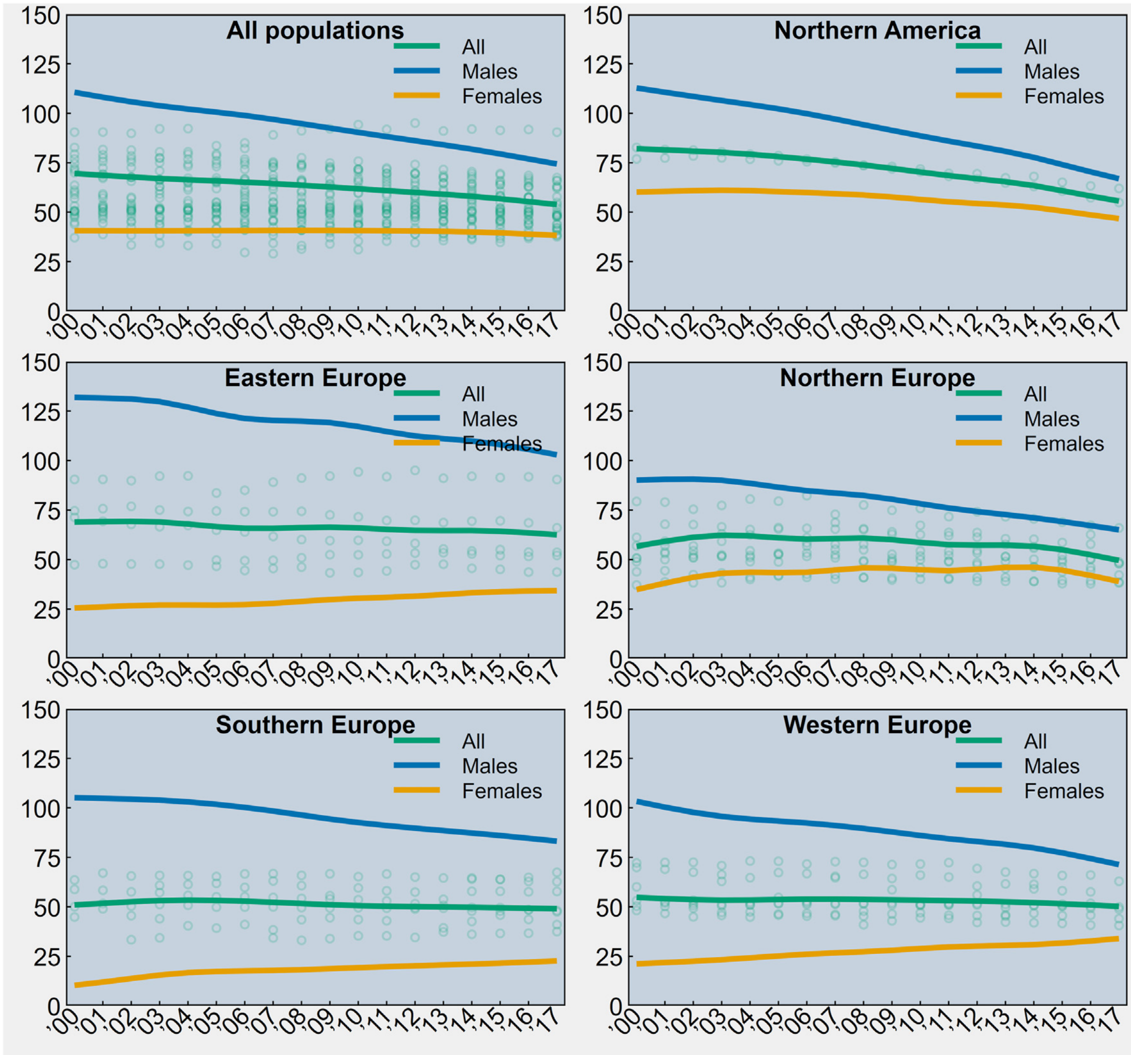

Fig. 5. **Time trends in lung cancer age-standardised mortality (×100 000 population) between 2000 and 2017 in Northern America, the EU, and the EFTA, overall and by sex and subregion.** *Notes:* Overall rates (males plus females) observed in all country-years are displayed in the background of each plot, below population-averaged cubic splines. Northern America includes Canada and the USA; Eastern Europe includes Bulgaria, Czechia, Hungary, Poland, and Romania; Northern Europe includes Denmark, Estonia, Finland, Iceland, Latvia, Lithuania, Norway, Sweden, and the UK; Southern Europe includes Cyprus, Croatia, Greece, Italy, Malta, Portugal, Slovenia, and Spain; Western Europe includes Austria, Belgium, France, Germany, Luxembourg, the Netherlands, and Switzerland. *Abbreviations:* EU, European Union; EFTA, European Free Trade Association; USA, United States of America; UK, United Kingdom.

other subregions, whereby the low starting value in 2000 must also be taken into account here. Variability in mortality rates across countries may be influenced by significant inequalities in access to lung cancer care. In Central and South-Eastern Europe, physicians report the unavailability of novel lung cancer drugs, despite perennial approval and guideline recommendation, due to national reimbursement problems [39]. Oncologists report suboptimal molecular testing with worse testing percentages in Europe compared to Northern America [53]. The heterogeneous outcomes observed suggest that there is progress in cancer care in the USA and Europe, but that opportunities are missed as well.

Our investigation revealed notable differences in lung cancer mortality when data were stratified according to sex. In general, Scandinavia and Northern America had higher-than-average mortality in their female populations, while no clear geographic pattern was evident in the country-specific mortality rates for males. In contrast to the gradual decline in overall male mortality of −2·3% per year, overall female mortality rates declined by only −0·3% between 2000 and 2017. Our results show an overall incidence decrease in male mortality and an increase in female mortality, supporting a different female-to-male incidence ratio [54]. Indeed, the slight decline in lung cancer mortality among women was solely attributable to the USA, which was the only country where female lung cancer mortality dropped between 2000 and 2017. In all other countries, we found no improvement in female mortality, making preliminary enthusiasm bound

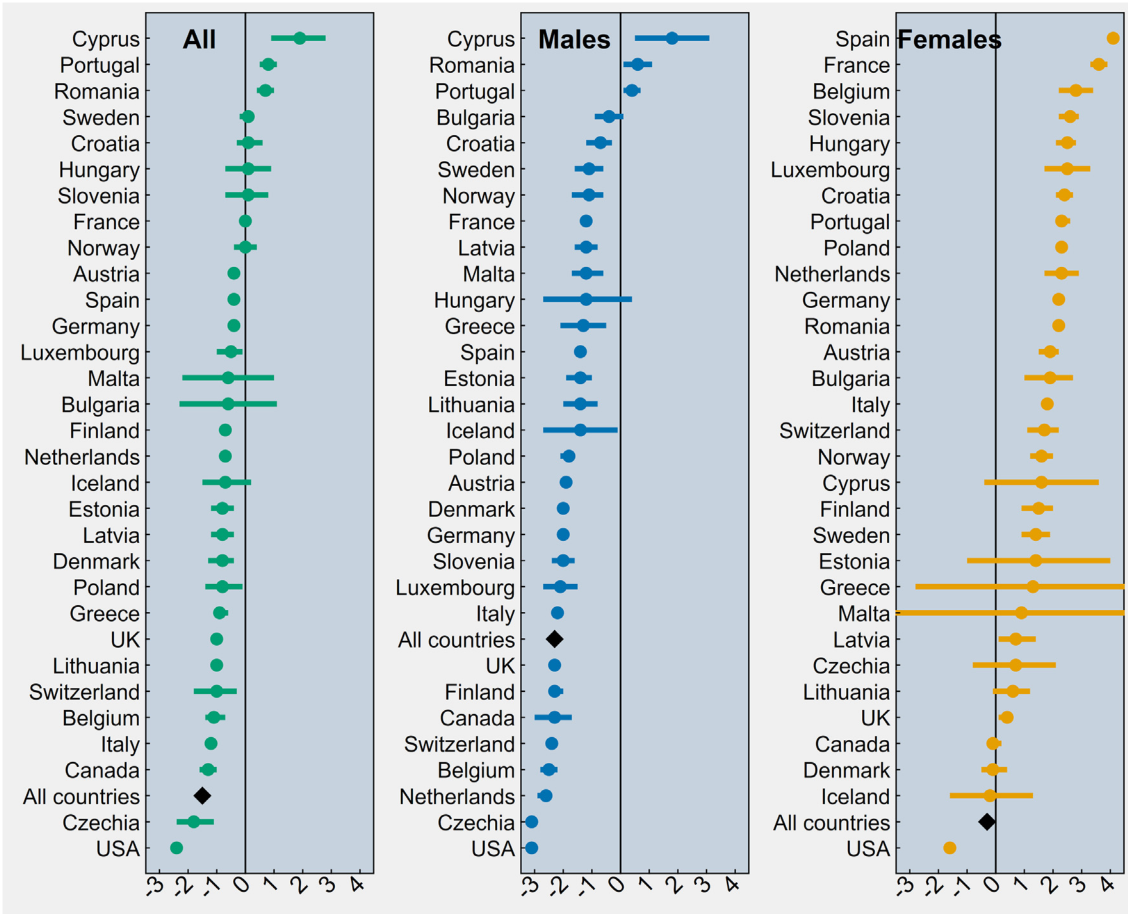

Fig. 6. **Average annual percent change (AAPC) in lung cancer age-standardised mortality between 2000 and 2017 for each country of Northern America, the EU, and the EFTA, overall and by sex**. *Notes:* All AAPCs were obtained from segmented regression analysis are presented along with 95% confidence intervals (CIs) and are sorted into descending order. If the 95% CI does not cross the vertical zero-line, the AAPC is statistically significant. Greece's and Malta's 95% CIs for female mortality were trimmed for the sake of convenience. Year-specific rates used to compute the AAPCs for the total population of the 31 countries (black diamonds) were obtained from population-averaged regression analysis with spline terms. *Abbreviations:* EU, European Union; EFTA, European Free Trade Association; UK, United Kingdom; USA, United States of America.

to be limited [21]. One possible explanation is sex-specific differences in smoking habits: while men reached the peak of smoking-attributed mortality fractions approximately in the 1990s, after which mortality continuously decreased, present and future projections for women suggest that the peak has only just been reached or will be reached in the next decades [47]. The concordant changes in sex-specific mortality highlighted by our study fit with sex-based differences in tobacco consumption over time and underline the further urgent need for continuous smoking reduction.

Results indicate that lung cancer mortality decreased in all age groups except those over 84 years, and especially among women over 84 years. This is in line with the findings of other investigators and might be explained by the limited therapeutic options for elderly, frail, and multimorbid patients, including limited utilisation of guideline-based and novel therapies [55,56].

A number of limitations should be considered when interpreting the results of our study. As with any secondary data, the accuracy of the mortality rates is dependent upon the quality of death certification, which means that there is always the potential for the true cause of death to be different from that recorded. Although we used data from the WHO Mortality Database, which ensures data quality through careful evaluation prior to inclusion, international variations in diagnosis and process of death certification have the potential to bias the comparison of mortality trends across countries. Moreover, our analysis did not account for mortality disparities within countries that were attributable to ethnicity, race, socioeconomic status, or geographic residence, since our data source did not include this information. Another limitation is that the WHO Mortality Database does not provide data on the number of diagnosed cases, which are necessary for estimating case fatality trends. The study found that mortality rates from tracheal cancer are very low, and trends are difficult to compare to lung cancer rates. This suggests that these cancer entities should be documented and analysed separately.

Taken together, this work shows decreasing lung cancer mortality trends in Europe and Northern America from the turn of the millennium until 2017. The overall decrease in female lung cancer mortality was driven solely by the USA, while in all other countries, female mortality remained unchanged or increased significantly. The diversity of national lung cancer mortality outcomes may reflect intercountry differences in tobacco control, access to cancer care, application of effective guideline-based treatments, and implementation of lung cancer screening plans.

Author contributions

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Hauke Winter M.D. – supervision.

Martin E Eichhorn M.D. – writing review & editing.

Romina M Roesch M.D. – writing review & editing.

Samantha Taber M.D. – writing original draft.

Petros Christopoulos M.D. – investigation, writing review & editing.

Armin Wiegering M.D. – writing review & editing.

Jacopo Lenzi Ph.D. – conceptualisation, methodology, formal analysis, investigation, writing original draft, writing review & editing.

Data sharing

Statistical source code used to generate estimates can be obtained from the study statistician (Dr. Jacopo Lenzi). Source data can be downloaded from the WHO website (WHO Mortality data).

Conflict of interest statement

Petros Christopoulos: research funding from AstraZeneca, Novartis, Roche, Takeda, and advisory board/lecture/educational fees from AstraZeneca, Boehringer Ingelheim, Chugai, Kite, Novartis, Pfizer, Roche, and Takeda. Martin E. Eichhorn: research funding from MSD Oncology and advisory board/lecture/educational fees from MSD Oncology, AstraZeneca, Bristol Myers Squibb, Roche Pharma AG and Intuitive Surgical. Hauke Winter: research funding from Intuitive Surgical and advisory board/lecture/educational fees from AstraZeneca and Intuitive Surgical.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.05.011.

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