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abstract

Trends in Breast Cancer Mortality Between 2001 and 2017: An Observational Study in the European Union and the United Kingdom

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PURPOSE Breast cancer is the most common cancer in women worldwide, representing 25.4% of the newly diagnosed cases in 2018. The past two decades have seen advancements in screening technologies, guidelines, and newer modalities of treatment. Our study reports and compares trends in breast cancer mortality in the European Union and the United Kingdom.

MATERIALS AND METHODS We used the WHO Mortality Database. We extracted breast cancer mortality data from 2001 to 2017 on the basis of the International Classification of Diseases, 10th revision system. Crude mortality rates were dichotomized by sex and reported by year. We computed age-standardized death rates (ASDRs) per 100,000 population using the world standard population. Breast cancer mortality trends were compared using joinpoint regression analysis.

RESULTS We analyzed data from 24 EU countries, including the United Kingdom. For women, breast cancer mortality was observed to be downtrending in all countries except Croatia, France, and Poland. For the most recent female data, the highest ASDR for breast cancer was identified in Croatia (19.29 per 100,000), and the lowest ASDR was noted in Spain (12.8 per 100,000). Denmark had the highest change in ASDR and the highest estimated annual percentage change of −3.2%. For men, breast cancer mortality decreased in 18 countries, with the largest relative reduction observed in Denmark with an estimated annual percentage change of −27.5%. For the most recent male data, the highest ASDR for breast cancer was identified in Latvia (0.54 per 100,000).

CONCLUSION Breast cancer mortality rates have down trended in most EU countries between 2001 and 2017 for both men and women. Given the observational nature of this study, causality to the observed trends cannot be reliably ascribed. However, possible contributing factors should be considered and subject to further study.

INTRODUCTION

Breast cancer has the highest cancer incidence rate in women worldwide.[1] On the basis of the recent WHO data, it is also the leading cause of new incident cases in both sexes combined.[2] Incidence rates vary greatly worldwide from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe.[3] The WHO reported that in 2020, the incidence of breast cancer was 2.26 million cases worldwide, and it was the cause of death in 685,000 individuals.[2] It is the most common cause of cancer deaths in women.[3]

In recent decades, we have seen notable advancements in breast cancer management. With a wider variety of evidence-based treatment options and effective early detection tools, falling breast cancer mortality has been reported in most European countries.[4] Breast cancer screening guidelines have been established in different regions. The European Commission Initiative on Breast Cancer (ECIBC) screening guidelines recommend biennial screening for all women of age 50-69 years.[5] The WHO has stated that breast cancer screening represents one of the most important tools in reducing breast cancer mortality.[2]

There is a relative lack of research focusing on male breast cancer compared with female breast cancer despite significant males' mortality. Male patients with breast cancer have a lower survival rate than their female counterparts.[6,7] Various factors have been attributed to this disparity, including different clinical characteristics of cancer itself, under-reporting, and undertreatment.[8]

This investigation compared trends in breast cancer mortality in the European nations and evaluated the difference in mortality trends between men and women. We have previously used similar methods to

CONTEXT

Key Objective

What are the breast cancer mortality rates for both sexes in 24 EU countries in 2017, and is there any improvement in survival in the past 2 decades?

Knowledge Generated

There is an overall decrease in age-standardized death rates in majority of (24 EU countries) countries in both sexes. However, we observed worsening mortality in 8 of 24 (33.3%) countries in men as compared with only 2 of 24 (8.3%) in women.

Relevance

Countries with worsening mortality rates need further regional studies to discover local factor responsible for discordant survival trends.

describe mortality trends in cardiovascular[9] and respiratory diseases.[10,11] In the current report, we use publicly available databases to assess breast cancer mortality in European countries.

MATERIALS AND METHODS

Data Sources

We used the WHO mortality database for European nations, including the United Kingdom. We extracted breast cancer mortality data from 2001 to 2017 on the basis of the International Classification of Diseases, 10th revision (ICD-10) system. The WHO evaluates the quality of the data to ensure comparability and reliability, without adjustment for under-reporting. We included 23 member states of the European Union and the United Kingdom (European Union: 27 countries as of 2020) with a quality index of > 90% to produce a defined group of analysis.[12] The WHO mortality database is available publicly on the WHO mortality website[13] and is updated annually from deaths registered by national civil registration systems, ICD coded. The data are updated regularly by the WHO, and crude mortality data are available for free downloading. Cause of death is reported as the underlying cause of death and classified according to the ICD classification system. After downloading of the raw mortality data files from the WHO website, cause of death in each country of interest and for the years of interest was age-standardized according to the world standard population. We used ICD-10 code C50 and its subcodes for data extraction. SAS coding software was used to extract the data.

Crude mortality rates were dichotomized by sex and reported by year. We computed age-standardized death rates (ASDRs) per 100,000 population using the world standard population. The age-standardized death rate, defined as mortality weighted to the distribution of mortality per 5-year age group, was calculated according to the WHO standard population and world average age structure for 1998. This removes the historical event's effects on age structure and controls for differences in age structure in populations, producing age-specific mortality rates and more representative

data.[14] The estimated level of coverage for deaths with a recorded cause for death is calculated by actual reporting divided by the estimated mortality rate. Population and birth recording in all countries exceeds 90%, as per the WHO standard for inclusion in the database.[15] Mortality data were missing in a small subset of countries for ≥ 1 calendar year. When values were not available, data from previous or subsequent years were replicated in the last observation carried forward method, and 2.7% of data were replicated from the last and subsequent observations.

Statistical Analyses

Joinpoint regression analysis with annualized data (between 2001 and 2017, where available) was used to assess linear slope changes for mortality trends over time.[16] In brief, joinpoint analysis assesses the overall trends in mortality initially with no joinpoints and tests for significant changes in the model with the sequential addition of points where there is a significant change in the line's slope. Statistical trends were assessed by using Joinpoint software (version 4.1.1.1) provided by the US National Cancer Institute Surveillance Research Program.[17] The model also computes an estimated annual percentage change (EAPC) for each trend by fitting a regression line to the rate's natural logarithm. Relative changes in ASDR were computed for each country and each sex by calculating the difference between ASDRs at the start and the end of the observation period.

RESULTS

We analyzed data from a total of 24 EU countries, including the United Kingdom. Mortality data were available for five countries from 2001 to 2017, 12 countries from 2001 to 2016, six countries from 2001 to 2015, and one country from 2001 to 2014, accounting for a total of 898 data elements available for analysis. For the purpose of joinpoint analysis alone, 14 (1.6%) data points were imputed, as described above.

Latest Breast Cancer Mortality

Table 1 and Figure 1 show the most recent calendar year mortality data. In 2016-2017, Croatia had the highest ASDR

TABLE 1. Age-Standardized Death Rate in Men and Women

Country	Men					Women				
	Year of Diagnosis	Age-Adjusted Rate	Year of Diagnosis	Age-Adjusted Rate	Percentage Change	Year of Diagnosis	Age-Adjusted Rate	Year of Diagnosis	Age-Adjusted Rate	Percentage Change
Austria	2002	0.25	2017	0.16	−35.88	2002	19.58	2017	15.11	−29.58
Belgium	2000	0.31	2016	0.19	−40.71	2000	24.98	2016	17.85	−39.90
Bulgaria	2005	0.52	2015	0.12	−77.64	2005	18.02	2015	16.67	−8.07
Croatia	2000	0.52	2016	0.14	−73.79	2000	22.19	2016	19.29	−15.05
Cyprus	2004	0.24	2016	0.13	−44.85	2004	16.38	2016	13.46	−21.70
The Czech Republic	2000	0.30	2017	0.18	−40.48	2000	19.90	2017	13.77	−44.50
Denmark	2000	0.23	2015	0.39	66.86	2000	28.03	2015	16.70	−67.79
Estonia	2000	0.27	2016	0.14	−48.53	2000	23.52	2016	15.57	−51.06
Finland	2000	0.12	2016	0.27	129.13	2000	17.16	2016	14.28	−20.19
France	2000	0.24	2015	0.15	−39.17	2000	20.41	2015	17.44	−17.02
Germany	2000	0.34	2016	0.17	−50.56	2000	21.31	2016	17.84	−19.46
Hungary	2000	0.63	2017	0.21	−66.03	2000	25.23	2017	19.11	−31.99
Italy	2003	0.26	2015	0.22	−12.62	2003	19.07	2015	16.19	−17.84
Latvia	2000	0.14	2015	0.54	274.43	2000	19.06	2015	18.91	−0.78
Lithuania	2000	0.26	2017	0.41	56.77	2000	18.82	2017	14.14	−33.11
The Netherlands	2000	0.26	2016	0.33	26.89	2000	25.74	2016	18.58	−38.52
Poland	2000	0.16	2016	0.15	−9.86	2000	16.12	2016	17.03	5.36
Portugal	2002	0.52	2016	0.16	−69.09	2002	16.53	2016	14.67	−12.70
Romania	2000	0.28	2017	0.12	−55.61	2000	17.12	2017	17.49	2.11
Slovakia	2000	0.27	2014	0.14	−48.62	2000	19.73	2014	17.92	−10.07
Slovenia	2000	0.22	2015	0.27	19.30	2000	19.27	2015	18.87	−2.09
Spain	2000	0.18	2016	0.07	−60.74	2000	15.96	2016	12.83	−24.40
Sweden	2000	0.02	2016	0.31	1,876.40	2000	18.36	2016	13.19	−39.18
The United Kingdom	2001	0.18	2016	0.36	98.42	2001	23.86	2016	17.48	−36.53

for women across the European Union (19.29 per 100,000 [2016]), followed by Hungary (19.11 per 100,000 [2017]). Among men, Latvia had the highest mortality (0.54 per 100,000 [2015]). In 2016, Spain had the lowest mortality for women (12.83 per 100,000) as well as men (0.07 per 100,000).

Changes in Breast Cancer Mortality Between 2000 and 2017

Figure 1 and Table 1 show breast cancer mortality at the beginning and the end of the study period. The overall trend in breast cancer mortality for women across Europe decreased steadily over time. Mortality in women decreased in most countries except for Poland (+5.36%) and Romania (+2.11%). The most significant decrease in mortality was observed in Denmark (−67.79%), followed by Estonia (−51.06%). Like women, most countries observed a decrease in mortality among men, except Sweden, Latvia, Finland, the United Kingdom, Denmark, Lithuania, the Netherlands, and Slovenia. All remaining countries showed a decrease in mortality, with the highest decreases in Bulgaria (−77.64%), followed by Croatia (−77.64%).

Joinpoint Regression for Changes in Trends

Table 2 and Figure 2 show the joinpoint analysis of breast cancer mortality in women from 2000 to 2017. For women, 19 of 24 nations reported decreasing rates of breast cancer mortality, with the exception of Croatia, France, Poland, Romania, and Slovakia. Fifteen of 24 countries had only one joinpoint trend. Of the 15 countries, all except Croatia showed a steady decline in mortality. Croatia observed a minor change of +0.1% EAPC (between 2001 and 2016). Five countries showed two joinpoint trends; of these five, Romania and Slovakia initially showed decreasing mortality till 2012 (−0.5%) and 2009 (−2.2%), respectively, followed by an increasing trend. Belgium, Estonia, and Hungary showed consistently negative EAPCs. The rates of change in breast cancer mortality were more variable in the Czech Republic, France, Italy, and Poland, with three joinpoint trends. Persistent decreases in mortality were identified in Italy. France showed a decreasing trend till 2013 (−0.2% till 2004, followed by −1.7% till 2013), followed by increasing mortality till 2015 (0.5%). The Czech Republic initially showed increasing mortality till 2005 (0.5%), followed by a
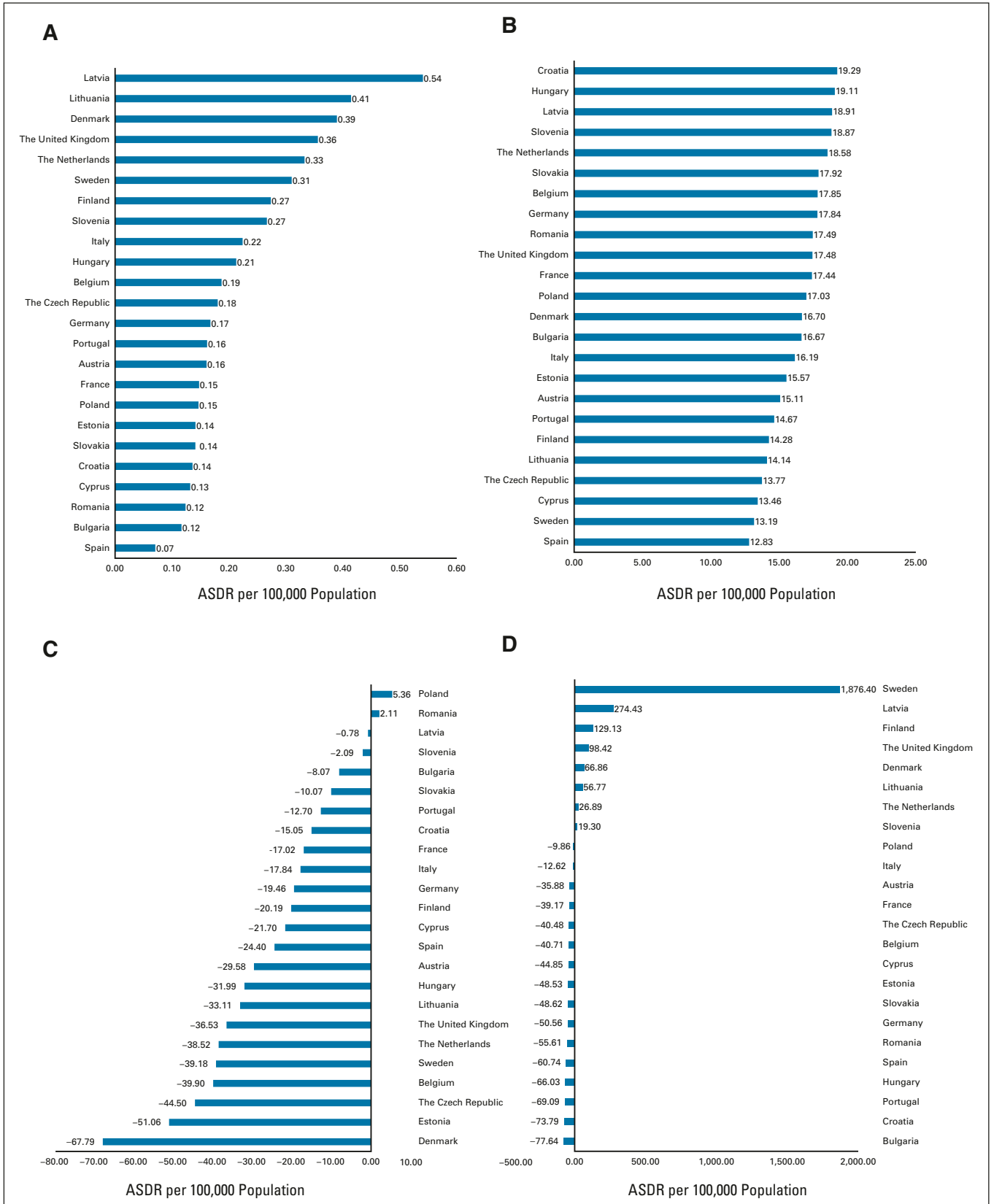
A

Country	ASDR per 100,000 Population
Latvia	0.54
Lithuania	0.41
Denmark	0.39
The United Kingdom	0.36
The Netherlands	0.33
Sweden	0.31
Finland	0.27
Slovenia	0.27
Italy	0.22
Hungary	0.21
Belgium	0.19
The Czech Republic	0.18
Germany	0.17
Portugal	0.16
Austria	0.16
France	0.15
Poland	0.15
Estonia	0.14
Slovakia	0.14
Croatia	0.14
Cyprus	0.13
Romania	0.12
Bulgaria	0.12
Spain	0.07

ASDR per 100,000 Population

B

Country	ASDR per 100,000 Population
Croatia	19.29
Hungary	19.11
Latvia	18.91
Slovenia	18.87
The Netherlands	18.58
Slovakia	17.92
Belgium	17.85
Germany	17.84
Romania	17.49
The United Kingdom	17.48
France	17.44
Poland	17.03
Denmark	16.70
Bulgaria	16.67
Italy	16.19
Estonia	15.57
Austria	15.11
Portugal	14.67
Finland	14.28
Lithuania	14.14
The Czech Republic	13.77
Cyprus	13.46
Sweden	13.19
Spain	12.83

ASDR per 100,000 Population

C

Country	ASDR per 100,000 Population
Poland	5.36
Romania	2.11
Latvia	-0.78
Slovenia	-2.09
Bulgaria	-8.07
Slovakia	-10.07
Portugal	-12.70
Croatia	-15.05
France	-17.02
Italy	-17.84
Germany	-19.46
Finland	-20.19
Cyprus	-21.70
Spain	-24.40
Austria	-29.58
Hungary	-31.99
Lithuania	-33.11
The United Kingdom	-36.53
The Netherlands	-38.52
Sweden	-39.18
Belgium	-39.90
The Czech Republic	-44.50
Estonia	-51.06
Denmark	-67.79

ASDR per 100,000 Population

D

Country	ASDR per 100,000 Population
Sweden	1,876.40
Latvia	274.43
Finland	129.13
The United Kingdom	98.42
Denmark	66.86
Lithuania	56.77
The Netherlands	26.89
Slovenia	19.30
Poland	-9.86
Italy	-12.62
Austria	-35.88
France	-39.17
The Czech Republic	-40.48
Belgium	-40.71
Cyprus	-44.85
Estonia	-48.53
Slovakia	-48.62
Germany	-50.56
Romania	-55.61
Spain	-60.74
Hungary	-66.03
Portugal	-69.09
Croatia	-73.79
Bulgaria	-77.64

ASDR per 100,000 Population

FIG 1. Age-standardized death rate of men and women: (A) end point for men, (B) end point for women, (C) percentage change in mortality in men, and (D) percentage change in mortality in women. ASDR, age-standardized death rate.

TABLE 2. Joinpoint Analysis for Breast Cancer Mortality of Women in 24 EU Countries and the United Kingdom From 2000 to 2017, Where Data Are Available

Country	Trend 1			Trend 2			Trend 3		
	Years	EAPC	CI of EAPC	Years	EAPC	CI of EAPC	Years	EAPC	CI of EAPC
Cyprus	2004-2016	−1.6	−2.4 to −0.8						
Austria	2002-2017	−1.9	−2.2 to −1.6						
Belgium	2000-2011	−1.4	−1.8 to −1.1	2011-2016	−3.2	−4.3 to −2.1			
Bulgaria	2005-2015	−0.3	−1.7 to 1.2						
Croatia	2000-2016	0.1	−0.5 to 0.6						
The Czech Republic	2000-2005	0.4	−2 to 2.8	2005-2008	−7.3	−16.7 to 3.1	2008-2017	−1.5	−2.5 to −0.6
Denmark	2000-2015	−3.2	−3.6 to −2.8						
Estonia	2000-2003	−9.3	−17.9 to 0.2	2003-2016	−1	−2 to 0.1			
Finland	2000-2016	−1.5	−1.9 to −1						
France	2000-2004	−0.2	−1 to 0.6	2004-2013	−1.7	−2 to −1.4	2013-2015	0.5	−2 to 3.2
Germany	2000-2016	−1.3	−1.5 to −1.1						
Hungary	2000-2007	−2.8	−4.2 to −1.4	2007-2017	−0.5	−1.3 to 0.3			
Italy	2003-2005	−2.1	−4 to −0.1	2005-2008	−0.1	−2.1 to 1.9	2008-2015	−1.7	−1.9 to −1.4
Latvia	2000-2015	−0.3	−0.9 to 0.3						
Lithuania	2000-2017	−1.2	−1.8 to −0.5						
The Netherlands	2000-2016	−2.2	−2.5 to −2						
Poland	2000-2006	0.3	−0.3 to 0.9	2006-2010	−1.6	−3.4 to 0.2	2010-2016	1.7	1.1 to 2.4
Portugal	2000-2016	−1.2	−1.5 to −0.8						
Romania	2000-2012	−0.5	−0.9 to −0.1	2012-2017	1.3	−0.1 to 2.8			
Slovakia	2000-2009	−2.2	−3.6 to −0.8	2009-2014	3.2	−0.2 to 6.8			
Slovenia	2000-2015	−1.4	−2.3 to −0.6						
Spain	2000-2010	−1.4	−1.6 to −1.2						
Sweden	2000-2016	−2	−2.3 to −1.6						
The United Kingdom	2001-2016	−2.2	−2.3 to −2						

Abbreviation: EAPC, estimated annual percentage change.

constant decline till 2017 (−1.5%). Poland showed a notable trend of an initial rise in mortality until 2006 (0.3%), followed by a decline till 2010 (−1.6%) and an increase in mortality until 2016. The most rapid increases in breast cancer mortality were identified in Slovakia between 2009 and 2014 (+3.2%) and Poland between 2010 and 2016 (+1.7%). The most rapid decreases in mortality identified through joinpoint regression were in Belgium between 2011 and 2016 (−3.2%) and Denmark between 2000 and 2015 (−3.2%).

Table 3 and Figure 3 show the joinpoint analysis of breast cancer mortality in men from 2000 to 2017. Because of low mortality in men, we report significant trend changes in the data and the mortality EAPCs for the periods covered by each trend. For men, there is a generally favorable trend in mortality across Europe, except Estonia (+19%, 2008-2016), Finland (+18.2%, 2008-2016), France (+17%, 2012-2015), Slovenia (+2.4%, 2000-2015), Sweden (+2.2, 2000-2016), Poland (+1.7%, 2000-2016), Romania (+1.6%, 2000-2017), and Cyprus (+1.6%, 2004-2016). Denmark had the most rapid recent mortality declines

(−27.5%, 2013-2015), followed by Spain (−16.7%, 2013-2016) and Italy (−16.5%, 2013-2015). Sixteen of 24 countries had only one joinpoint trend for the study period. Estonia, Finland, and Italy showed two joinpoint trends. Estonia and Finland showed a decrease in mortality from 2000 to 2008 (Estonia −16.9% and Finland −14.9%), followed by an increase in mortality from 2008 to 2016 (Estonia 19% and Finland 18.2%). In contrast, Italy showed a constant decline of −1.9% from 2003 to 2013, followed by a rapid decline of −16.5% from 2013 to 2015. Spain had three joinpoint trends, with an initial decline of −0.7% from 2000 to 2010 followed by an increase till 2013 and a decline of 16.7% till 2016. Denmark and France had four joinpoint trends with high variability in the trend throughout the study period (Table 3).

DISCUSSION

This observational study outlines trends in cancer mortality in the European Union and the United Kingdom. Among women, mortality has declined in most countries except Poland and Romania. The most significant decline in
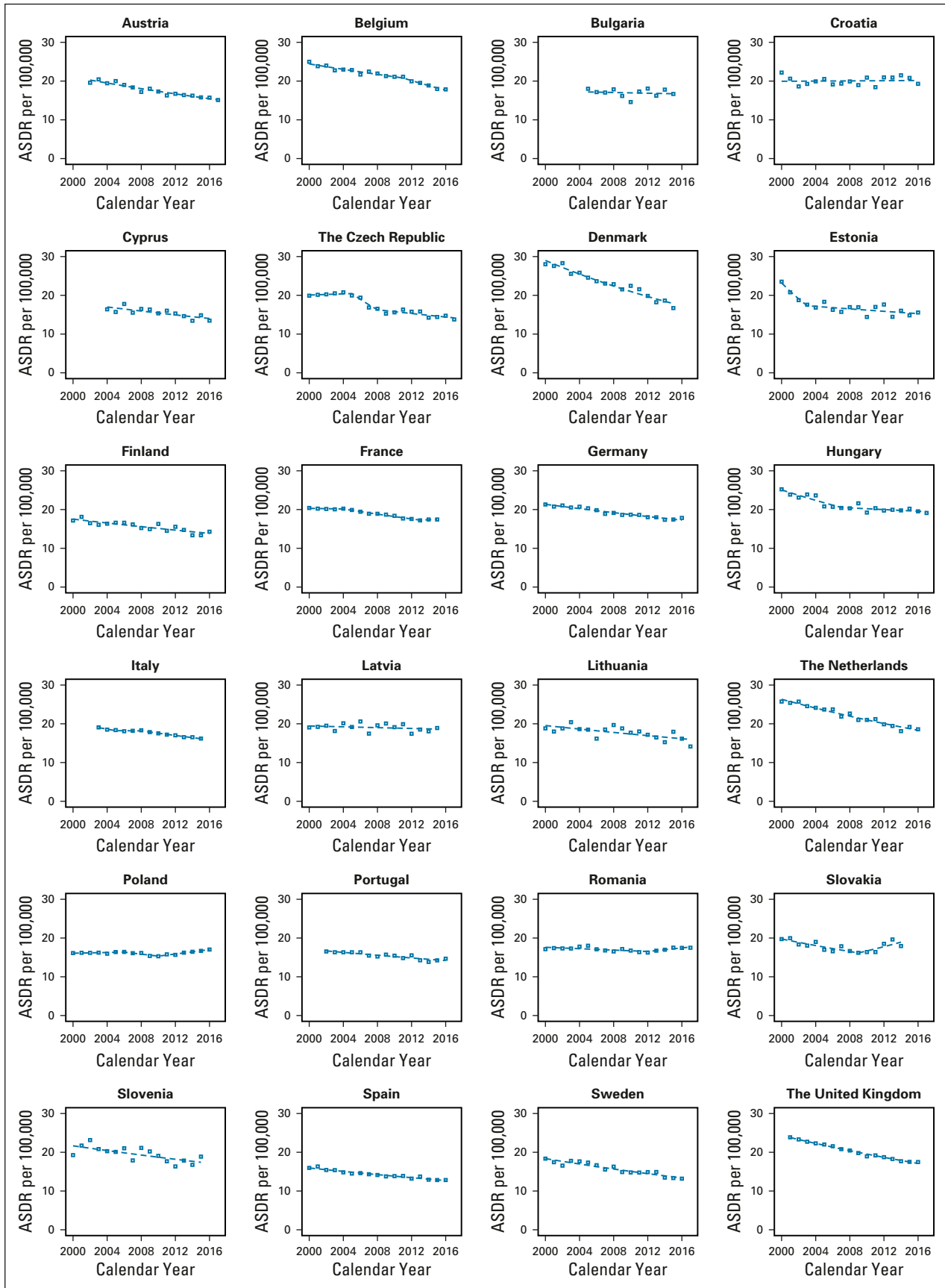
FIG 2. Trends in age-standardized death certification rates per 100,000 for breast cancer in women. ASDR, age-standardized death rate.
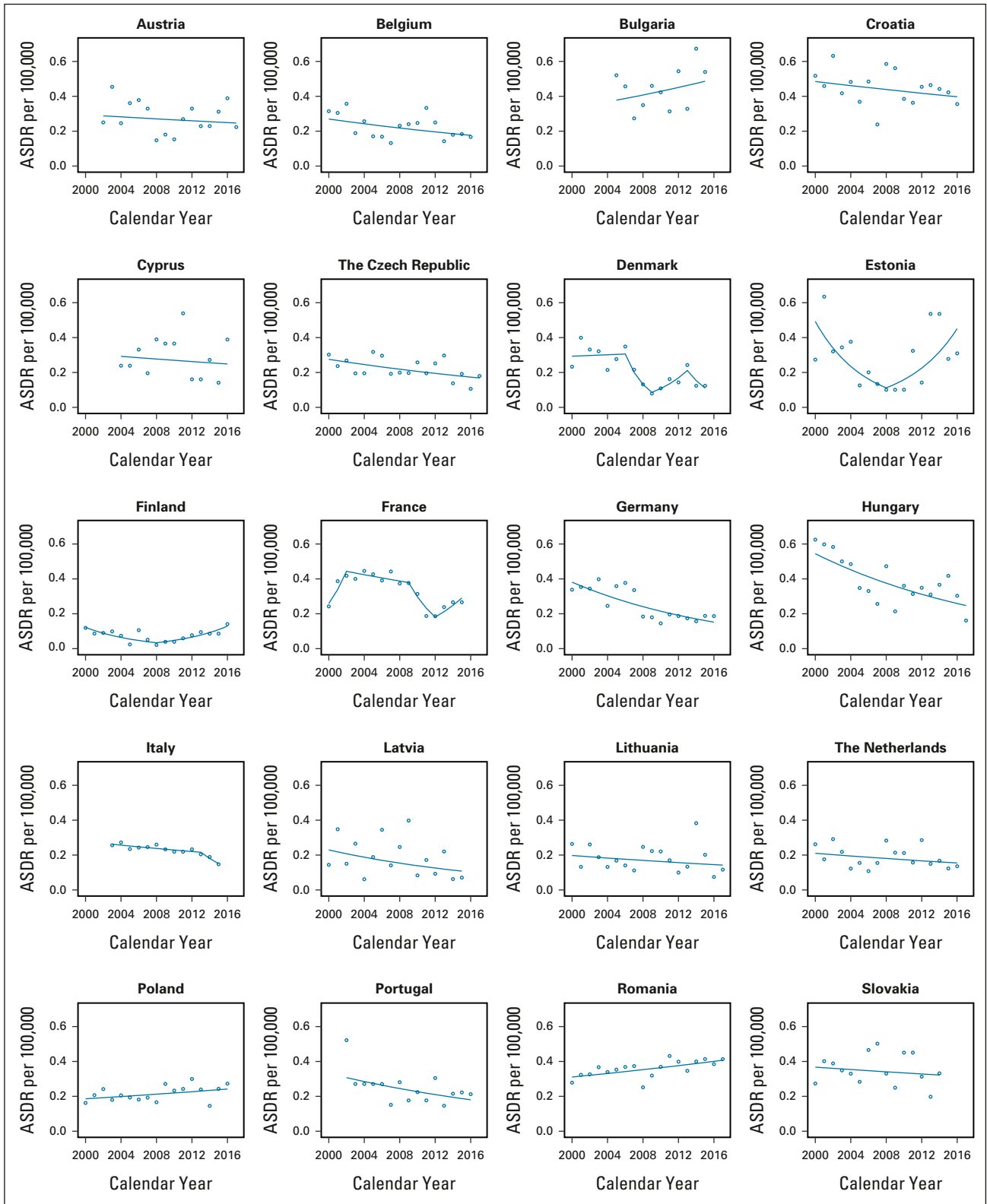
FIG 3. Trends in age-standardized death certification rates per 100,000 for breast cancer in men. ASDR, age-standardized death rate.(continued on following page)
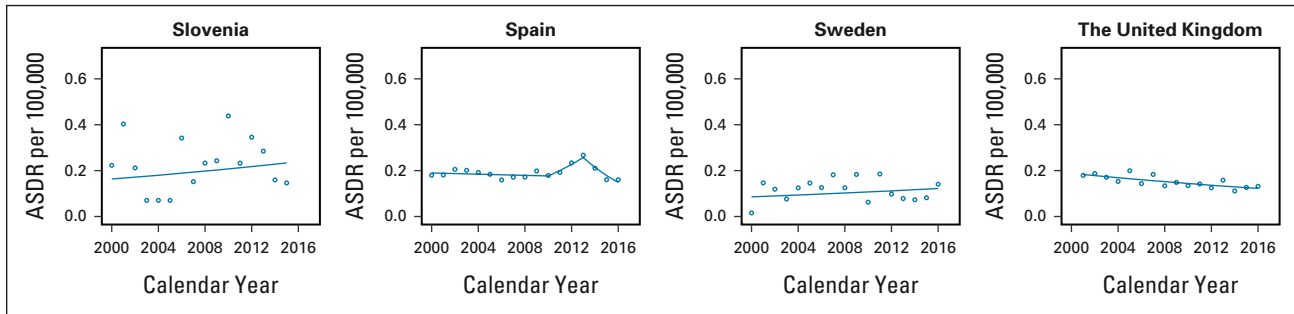
FIG 3. (Continued)

mortality was observed in Denmark and Estonia. Among men, Bulgaria and Croatia saw the most significant reduction in mortality. Given the observational nature of this study, causality to the observed trends cannot be reliably ascribed. However, possible contributing factors should be considered.

The incidence of breast cancer in Western European countries has been decreased or plateaued, contrasting to the trend seen in Eastern European countries, which have been increasing. Romania, Poland, Bulgaria, Latvia, and Slovakia have seen increasing incidence from 1990 to 2015.[18] Two of these countries (Romania and Slovakia) have a biphasic pattern of mortality trends, with a decreasing trend noted from 2000 to 2012 in Romania and 2000 to 2009 in Slovakia and then an increasing trend. Poland also has a biphasic pattern but with an increasing trend noted from 2000 to 2006 and then a decreasing trend from 2006 to 2010. The Czech Republic, Slovenia, and Hungary have a biphasic pattern of incidence; an increasing trend is noted from 1990 to 2005, whereas a decreasing trend is noted from 2005 to 2015.[18] Of these, only the Czech Republic has the mortality trend exactly mirroring the incidence trend. Slovenia and Hungary have a decreasing trend of mortality from 2001 to 2017.

The introduction of screening programs and better access to medical care may have led to the earlier detection of breast cancer at a more localized stage. New surgical techniques and tailored adjuvant treatment regimens are now available. The successful implementation of breast cancer screening programs is considered one of the most critical factors in decreasing breast cancer mortality in women.[1-3] Significant variability in the target population, age, screening techniques, and participation rates exists between nations.[19] According to the International Agency for Cancer Research, participants in organized screening programs, where 50- to 69-year-old women are invited to undergo mammography at 2-year intervals, are 35% less likely to die from breast cancer.[20] The European Union recommends a 70%-75% participation rate among the eligible population. The slight increase in breast cancer mortality in Romania could be attributed to a lack of screening where the lowest proportion of eligible women

(13.5%) underwent screening in 2010, compared with the European Union at an average of 46%.[21] Poland introduced screening in 2006, and by 2010, uptake was 45.5%.[22] However, despite increasing uptake of screening, mortality continued to grow between 2010 and 2016. Of note, Polish breast screening programs do not include women age 40-49 and 70-74 years,[22] and perhaps these variations in inclusion criteria might account for the observed trend. In contrast, Estonia, which has seen the second largest reduction in breast cancer mortality, expanded its target population from 45- to 59-year-olds with health care coverage to all 50- to 65-year-olds.[23] Estonia has seen a significant increase in screening uptake from 41% in 2004 to 58% in 2014.[24]

Significant advances in breast cancer management have occurred in recent decades. Performing sentinel lymph node biopsy in patients with early disease and clinically negative axillary examination has enabled the identification of patients suitable for systemic chemotherapy and axillary lymph node dissection.[25,26] This has led to a reduction in morbidity and mortality.[27] Neoadjuvant systemic therapy[28] is now often used before locally advanced breast cancer surgery to improve breast conservation without compromising survival outcomes. Better molecular testing has enabled the more widespread use of hormonal therapy. Patients with hormone receptor–positive cancers now benefit from endocrine therapy, and patients with human epidermal growth factor receptor 2–positive cancers benefit from human epidermal growth factor receptor 2–directed treatment such as trastuzumab.[29] Advanced genetic testing helps identify candidates at high risk for breast cancer and individuals suitable for risk-reducing mastectomy, endocrine therapy, or increased surveillance. These factors may contribute to the decrease in breast cancer mortality observed in countries with robust screening programs in place by 2000 (which marks the beginning of our study period). Such nations include Denmark, which experienced the most significant reduction in breast cancer mortality between 2000 and 2017, followed by Estonia and the Czech Republic, which started screening programs in 2002.[19] In contrast, Poland with highest positive change started breast

TABLE 3. Joinpoint Analysis for Breast Cancer Mortality of Men in 24 EU Countries and the United Kingdom From 2000 to 2017, Where Data Are Available

Country	Trend 1			Trend 2			Trend 3			Trend 4		
	Years	EAPC	CI of EAPC	Years	EAPC	CI of EAPC	Years	EAPC	CI of EAPC	Years	EAPC	CI of EAPC
Austria	2002-2017	−1	−4.9 to 3									
Belgium	2000-2016	−2.6	−5.5 to 0.3									
Bulgaria	2005-2015	2.6	−3.4 to 8.9									
Croatia	2000-2016	−1.2	−3.6 to 1.2									
Cyprus	2004-2016	1.6	−2 to 5.4									
The Czech Republic	2000-2017	−2.9	−5.1 to −0.5									
Denmark	2000-2006	0.7	−13.4 to 17.1	2006-2009	−34.4	−73.1 to 60	2009-2013	25.2	−19.9 to 95.6	2013-2015	−27.5	−70.3 to 76.9
Estonia	2000-2008	−16.9	−29.3 to −2.3	2008-2016	19	1.3 to 39.9						
Finland	2000-2008	−14.9	−24.5 to −4	2008-2016	18.2	4.8 to 33.4						
France	2000-2002	30.9	1.3 to 69.2	2002-2009	−2.2	−6.4 to 2.1	2009-2012	−21.8	−39.5 to 1.1	2012-2015	17	2.9 to 33
Germany	2000-2016	−5.6	−7.7 to −3.4									
Hungary	2000-2017	−4.5	−7 to −2									
Italy	2003-2013	−1.9	−3.2 to −0.6	2013-2015	−16.5	−29.8 to −0.6						
Latvia	2000-2015	−4.9	−11.3 to 1.9									
Lithuania	2000-2017	−1.9	−5.7 to 2									
The Netherlands	2000-2016	−1.9	−5.1 to 1.4									
Poland	2000-2016	1.7	−0.4 to 3.7									
Portugal	2000-2016	−3.7	−7.2 to −0.2									
Romania	2000-2017	1.6	0.5 to 2.7									
Slovakia	2000-2014	−0.9	−4.3 to 2.5									
Slovenia	2000-2015	2.4	−4.6 to 9.9									
Spain	2000-2010	−0.7	−2.8 to 1.5	2010-2013	13.3	−14.1 to 49.5	2013-2016	−16.7	−27.5 to −4.3			
Sweden	2000-2016	2.2	−4.1 to 8.9									
The United Kingdom	2001-2016	−2.7	−3.9 to −1.4									

Abbreviation: EAPC, estimated annual percentage change.

cancer screening program in 2006, almost 4-6 years later than other countries.[19]

Fewer medical resources in Central and Eastern European (CEE) countries have led to inequalities in cancer care compared with Western European nations.[30] Of note, CEE countries' survival rates are typically 10%-15% lower than the European average (81.8%; 95% CI, 81.6 to 82.0).[31] The causes of these disparities are undoubtedly multifactorial.[32] However, improving access to high-quality breast cancer treatment in Central and Eastern Europe is clearly a priority.[33] Another area where significant disparities exist across Europe is cancer registries (CRs). CRs allow public health and cancer control entities to estimate breast cancer incidence and mortality and identify high-risk groups, early diagnosis, and treatment. CRs in Europe have progressed consistently since 1990 and have increased to nearly 200, which covers approximately 60% of the European population. However, significant disparities in terms of population coverage, data quality, and data output were seen, especially in South-Eastern Europe.[32,34,35] Future efforts to widen access to screening, minimizing barriers to treatment, and increasing the availability of diagnostic and therapeutic resources would help continue this trend. Developing the economic, political, and scientific infrastructure would help tackle regional disparities in cancer mortality across Europe, particularly in CEE countries.

Male breast cancer is rare. The latest male breast cancer mortality ranged from 0.07 to 13.2 in the European countries included in our study. Lack of breast cancer screening argues against any impact of screening on the male breast cancer mortality. Other factors can be influencing these trends. Male breast cancers are typically diagnosed later and at a more advanced stage than females and are associated with higher mortality rates.[8,36] However, the disparity in mortality rate is not solely explained by delayed presentation.[8] This suggests that biological characteristics and treatment may also play a role. Male and female breast cancers have significantly different genetic profiles. BRCA2 mutations are twice as common in male breast cancer (12% v 5%),[4,7] and CYP17 gene aberration is common in men, but rare in women,[37] and male breast cancer is highly associated with the Klinefelter syndrome.[38] Yet, much of the current treatment recommendations are extrapolated from female breast cancer clinical trials.[39] There are also subgroups of breast cancer that exclusively occur in men including the luminal M1 and luminal M2. This is also a major difference between men and women that might also be playing a role in the differences.[40] The lack of effective treatment and standard of care for male breast cancers contributes to the significantly higher mortality rate in men versus women.

Strengths of this study include the use of annual mortality data collected from national surveillance statistics from the WHO for men and women. Over a long observation period, assessing population-level trends has enabled comparison in trends rather than absolute annual mortality rates. This is one of the first studies to comment on breast cancer mortality in men. Significant limitations of this study are as follows: First, on the basis of the quality of the available data, we included only 24 countries from the European Union. Second, we did not attempt to assess the incidence and prevalence of morbidity associated with breast cancer as our primary aim was to understand mortality changes. Third, we combined subtypes of breast cancers as mortality data are not recorded for each pathological subtype. Finally, as with any observational study, causal statements regarding the observed trends cannot be made. The discussion will assist future researchers, policymakers, and public health experts in focusing their efforts.

In conclusion, breast cancer mortality rates have down trended in most EU countries between 2001 and 2017 for both men and women. This observational study outlines trends in cancer mortality in the European Union and the United Kingdom. Among women, mortality has declined in most countries except Poland and Romania. The most significant decline in mortality was observed in Denmark and Estonia. Among men, Bulgaria and Croatia saw the most significant absolute reduction in mortality. Given the observational nature of this study, causality to the observed trends cannot be reliably ascribed. However, possible contributing factors should be considered and subject to further study.

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