UNIVERSITÀ DEGLI STUDI DI MILANO

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PhD in Public Health Sciences

XXXV Cycle - Study area

Medicine and Healthcare MED/01

Progress in cancer incidence, mortality, and survival

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Tesi di Dottorato di ricerca

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Academic year: 2021/2022

Main contents

ABSTRACT

Cancer mortality has declined over the last three decades in most high-income countries reflecting improvements in cancer prevention, diagnosis, treatments, and management. However, there are persisting and substantial differences in mortality, incidence, and survival worldwide.

Using the World Health Organization (WHO) database I worked on the trends and projections analysis of mortality from various cancer sites. I computed age-specific rates for each 5-year age group, calendar year, and sex globally. I then computed age-standardized mortality rates per 100,000 person-years using the direct method based on the world standard population. I performed joinpoint models to identify the years when significant changes in trends occurred and I calculated the corresponding annual percent changes. For the mortality projections, I predicted the number deaths and rates for a specific calendar year, using a logarithmic Poisson count data joinpoint regression model.

My first study on this topic aimed to provide an up-to-date overview of trends in cancer mortality, incidence, and survival among adults, retrieving data from high-quality population-based cancer registries in seven high-income countries and the European Union. Mortality from all cancers and most common cancer sites has declined over the last three decades, except for pancreas and lung (in women). The patterns for incidence were less consistent between countries, except for a steady decrease in stomach cancer in both sexes and lung cancer in men. Survival for all cancers and the selected cancer sites increased in all countries, although there is still substantial variability. Although overall cancer death rates continue to decline, incidence rates have been levelling off among males and have been moderately increasing among females. These trends reflect population changes in cancer risk factors, screening test use, diagnostic practices, and treatment advances. Many cancers can be prevented or treated effectively if they are diagnosed early. Population-based cancer incidence and mortality data can be used to inform efforts to decrease the cancer burden and regularly monitor progress toward goals.

I had the opportunity to collaborate with the University of Miami Miller School of Medicine, which provided data on cancer mortality among Italy-born Americans in California, Florida, Massachusetts, and New York Departments of Vital Statistics. The comparison of cancer mortality rates and risk factors among foreign-born populations in a host country with those in the country of origin provides insights into differences in access to care, timely diagnosis, and disease management between the two

countries. Moreover, cancer studies on specific European-born populations in the USA are scarce. Using official Italian death certificate data and resident population estimates based on the official census from the WHO, I was able to conduct a study to compare cancer mortality rates between Italians and Italy-born Americans. Generational differences in smoking prevalence patterns between the USA and Italy may explain the advantages for Italy-born Americans for lung and other tobacco-related cancers compared to their Italian male counterparts. The lower prevalence of *Helicobacter pylori*, alcohol consumption, and hepatitis B and C virus in the USA may justify the lower mortality for stomach and liver cancer, among Italy-born Americans. Earlier and more widespread adoption of cancer screening and effective treatments in the USA is likely to be influential in breast, colorectal, and prostate cancer mortality.

I then focused my studies on urologic cancer mortality over time and predictions. I carried out a time-trend analysis for selected European countries for prostate, testis, bladder, and kidney cancers over the last four decades. Prostate cancer mortality in the EU decreased over recent years and the projections are favorable. Less favourable trends were observed in eastern Europe, though starting from relatively low rates. Testicular cancer mortality declined over time in most countries, however levelling off in northern and western countries, after reaching very low rates. Bladder cancer mortality trends were less favourable in central and eastern countries compared to northern and western ones. Kidney cancer mortality reported a slight increase in men and stable rates in women over the last decade in the EU. To sum up, over the last four decades, mortality from prostate, testis, and bladder cancers but not from kidney cancer, declined in most European countries. Prostate cancer mortality rates remain lower in Mediterranean countries than in northern and central Europe. Rates for all urologic cancers remain higher in central and eastern Europe. I wrote a book chapter on the epidemiology of prostate cancer, including all the aspects I studied for my PhD.

In addition, I published as a co-author other papers on mortality over time and prediction analysis focusing on different aspects and various cancer mortality causes: mortality from soft tissue sarcomas, childhood cancer mortality, colorectal cancer mortality in young adults, and mortality from gastric and esophageal cancer, and differences between eastern and western EU cancer mortality. I submitted an abstract for the Africa Mortality Symposium on mortality cancer trends in the Republic of South Africa, the Republic of Mauritius, and Réunion and I am currently working on European prediction of cancer mortality rates for 2023. The research group I work has been publishing cancer mortality predictions annually since 2011.

Moreover, during these three years, I was involved in the CEFIC project (PI Prof. Negri from University of Bologna) titled “Incidence trends of selected endocrine-related diseases and conditions in Europe and North America, and the contribution of changes in human reproduction”. Among the endocrine-related diseases and conditions, there were four cancer sites considered: endometrium, breast, testis, and prostate. I gave my contribution to this project by evaluating the cancer incidence trends in high-income countries worldwide and reviewing the association between selected reproductive factors and the selected cancers. Thus, we investigated changes in relevant reproductive factors and estimated their influence on cancer occurrence.

During my PhD, I have been collaborating with the department of Oncology at the Mario Negri Institute. Under the supervision of Dott. Bosetti I have worked on various projects. In particular, I was involved in updating of a meta-analysis concerning aspirin use and the risk of twelve solid tumors with a dose-response analysis finalizing three publications. Moreover, the Mario Negri Institute manages the Italian Register of Multiple Sclerosis, collecting data from more than 100 Italian centers including more than 70.000 patients. Based on this real-world dataset, I have dealt with several aspects related to multiple sclerosis, being involved in the drafting of two papers one concerning two methods for measuring the disability accumulated over time and another one studying patients’ and referral centers’ characteristics in relation to multiple sclerosis phenotypes.

In my last PhD year, I worked at the Department of Quantitative Methods and Economics of the University of Las Palmas supervised by Prof. Serra-Majem for nine months. This training period aimed to gain new experience in conducting cost-effectiveness studies. I conducted a study aimed to quantify the over cost due to obesity among patients hospitalized for Covid-19. In collaboration with the Department of Public Health, I conducted an effectiveness analysis of a primary prevention intervention with a Mediterranean diet supplemented with extra-virgin olive oil or nuts using the data from PREDIMED Trial. Lastly, I took part in the WOMEDS Study, a project aimed to analyse gender inequality among medical doctors in Spain. During these months abroad, I co-wrote three papers, currently under revision.

INTRODUCTION

Descriptive epidemiology is a fundamental instrument for exploratory studies in order to generate new hypotheses and/or verify them. It is usually considered the first approach to define the purpose and scope of a research investigation.

The basic techniques of descriptive epidemiology were borrowed from demography and the key descriptive tools were morbidity and mortality rates. Their comparison and their standardization were and are still the main methods used.

Cancer is a major burden of disease in the world and the first cause of death in many countries [1]. An efficient registration system with accurate and timely information on cancer incidence and mortality is the key to policies to prevent and control cancer. Almost every country has its registry. Over the years, cancer registries have improved the quantity and the quality of data, also working on the standardization of definitions and registration procedures. Cancer incidence and mortality data are routinely recorded in cancer registries and became the basic data for cancer surveillance. Moreover, demographic data were also published on a more regular basis and became available for an increasing number of populations.

The improvement and the greater availability of epidemiological and time-based mortality and incidence data brought the development of techniques, focusing on the analysis of time series, that characterized modern descriptive epidemiology. They aimed to identify different factors that underlie the changes in rates. Historical oncologic data collected in cancer registries could provide us with rich information on the changes in cancer incidence and mortality over the years; the trends of changing rates could reflect the changes in the underlying risks.

Thus, the collection of increasingly detailed morbidity and mortality data, and the creation of data systems that allow cases and deaths to be located in time and space, have provided a solid basis for the evaluation of time series trends, in turn requiring the development of appropriate statistical methods, both explanatory and predictive [2].

Prediction of a future event is a complex process subject to large uncertainties and, for many aspects, questionable. However, in several human activities and working areas, it is useful to obtain information on future trends, even if uncertain or imprecise. Regarding cancer mortality data, the prediction of future cancer mortality rates is essential to plan the allocation of resources and evaluate strategies for prevention and cancer management.

In the following chapters, I will provide the statistical definitions and methods I used.

Mortality Rates

The death rate is an estimate of the proportion of a population that dies during a specified period. The numerator is the number of people dying during the period; the denominator is the size of the population. The death rate in a population is generally calculated by the formula:

$$mortality\ rate = \frac{n°\ of\ deaths\ during\ a\ sppecific\ period}{n°\ of\ person\ at\ risk\ of\ dying\ during\ the\ period} * 100{,}000$$

This rate is an estimate of the person-time death rate, i.e. the death rate per 100,000 person-years. This rate is also called the crude death rate.

Standardized rates

To compare two or more populations and remove as far as possible the effects of differences in age or another confounding variable, usually, the standardization of the rates is made.

The standardized rate ratios

Direct method: the specific rates in a study population are averaged, using as weights the distribution of a specific standard population. The directly standardized rate represents what the crude rate would have been in the study population if that population had the same distribution as the standard population concerning the variable(s) for which the adjustment or standardization was carried out.

The age-standardized mortality ratio (ASMR) is calculated as follows:

$$ASMR = \sum ASDR * Standard\ proportions$$

Where ASDRs are the deaths in an age group divided by the population of that age group × 100,000. While the standard error (SE) and the 95% confidence interval (CI) are obtained as follows:

$$SE = \sqrt{\sum \frac{(n°\ of\ deahts_i * Standard\ proportion_i)^2}{population_i{}^2}} * 100{,}000$$

$$95\%CI = ASMR \pm 1.96SE$$

The following are the WORLD and EU standard population distributions:

Age group	WORLD standard	EU standard 2013
0-4	0.120	0.050
5-9	0.100	0.055
10-14	0.090	0.055
15-19	0.090	0.055
20-24	0.080	0.060
25-29	0.080	0.060
30-34	0.060	0.065
35-39	0.060	0.070
40-44	0.060	0.070
45-49	0.060	0.070
50-54	0.050	0.070
55-59	0.040	0.065
60-64	0.040	0.060
65-69	0.030	0.055
70-74	0.020	0.050
75-79	0.010	0.040
80-84	0.005	0.025
85+	0.005	0.025

Indirect method: this is used to compare study populations for which the specific rates are either statistically unstable or unknown. The specific rates in the standard population are averaged, using as weights the distribution of the study population. The ratio of the crude rate for the study population to the weighted average so obtained is the standardized mortality ratio (SMR). The indirectly standardized rate itself is the product of the SMR and the crude rate for the standard population.

Joinpoint regression model

Joinpoint regression model analyses rates, proportions, or any other measure that can be considered over time in order to identify the possible time point(s) at which any given trend changes, that is the joinpoint(s), and to estimate the regression function with joinpoint(s) previously identified. The joinpoint regression model for the observations $(x_1, y_1), \dots (x_n, y_n)$, where $x_1 < x_2 < \cdots < x_n$ represents the time variable and $y_i = (i = 1, \dots n)$ is the response variable, can be written as [3]:

$$y_i = \alpha + \beta_1, x_i + \delta_1 (x_i - \tau_1)^+ + \cdots + \delta_k (x_i - \tau_k)^+ + \varepsilon_i^{(k)}$$

where:

$$(x_i - \tau_k)^+ = \begin{cases} x_i - \tau_k \; for \; x_i > \tau_k \\ 0 \; otherwise \end{cases}$$

and $\tau_1 < \cdots < \tau_k$ are the joinpoints.

Annual Percent Change

Annual Percent Change (APC) is one way to characterize trends in cancer rates over time. With this approach, the cancer rates are assumed to change at a constant percentage of the rate of the previous year. For example, if the APC is 1%, and the rate is 20/100,000 in 1990, the rate will be $20 * 1.01 = 20.2$ in 1991 and $20.2 * 1.01 = 20.402$ in 1992. Rates that change at a constant percentage every year change linearly on a log scale. For this reason, to estimate the APC for a series of data, the following regression model is used:

$$\log R_y = b_0 + b_1 y$$

Where R_y is the natural log of the rate in year y.

The APC from year y to year y+1 is

$$\frac{R_{y+1} - R_y}{R_y} * 100 =$$

$$= \frac{e^{b_0 + b_{1(y+1)}} - e^{b_0 + b_{1(y)}}}{e^{b_0 + b_{1(y)}}} * 100 =$$

$$= (e^{b_1} - 1) * 100$$

Average Annual Percent Change

While the joinpoint model computes the trend in segments whose start and end are determined to best fit the data, sometimes it is useful to summarize the trend over a fixed predetermined interval. The average annual percent change (AAPC) is a method that uses the underlying joinpoint model to compute a summary measure over a fixed pre-specified interval.

The AAPC is a summary measure of the trend over a pre-specified fixed interval. It allows us to use a single number to describe the average APCs over multiple years. It is valid even if the joinpoint

model indicates that there were changes in trends during those years. It is computed as a weighted average of the APCs from the joinpoint model, with the weights equal to the length of the APC interval. The AAPC over any fixed interval is calculated using a weighted average of the slope coefficients of the underlying joinpoint regression line with the weights equal to the length of each segment over the interval. The final step of the calculation transforms the weighted average of slope coefficients into an annual percent change. If we denote b_is as the slope coefficients for each segment in the desired range of years, and the w_is as the length of each segment in the range of years, then:

$$AAPC = (e^{\frac{\sum w_i b_i}{\sum w_i}} - 1) * 100$$

Predictive analysis

The prediction of future trends in incidence and mortality is essential to generate the epidemiological information necessary for resource allocation in health planning. Estimates of the current and future burden of cancer worldwide are needed in order to prioritize prevention actions, allocate health services and resources, and evaluate the impact of interventions and treatments [4]. Global cancer incidence projections suggest that the burden of cancer will continue to rise [5]. In developed nations, this is largely attributable to growing and ageing populations. Identifying exposures and interventions with the greatest potential impacts on reducing cancer risk will aid in implementing prevention programs and policies to combat this growing health challenge.

This is why projection methods are so important and accurate projections of the future burden of cancer are essential.

Statistical methods for cancer projections, which are commonly used when information on risk factors is not available, can be implemented in two steps:

i) using historical data to model trends of cancer risk;
ii) extrapolating the trends into the future to project the numbers and rates.

Statistical modelling of past trends allows projecting rates by extrapolating time trends from observed rates. The number of new cancer cases or deaths is calculated by applying the estimated rates to projected population numbers. Projections based on cancer incidence and mortality over time assume that trends in risk behaviour will remain stable, no intervention or screening program will be started, and there is no change in diagnostic techniques. However, this assumption of unchanged trends in rates is very strong and may not be realistic [4].

Mathematically, trends can be described as linear or non-linear, and different statistical modelling techniques including parametric, semi-parametric, and non-parametric models can be used. Because different statistical methods can result in different cancer projections, it may be difficult to determine which method is more appropriate. Thus, appropriate statistical modelling is fundamental to obtaining valid cancer projections [4].

The literature proposes many statistical models for cancer projections, each focusing on different issues and aspects. Recently, my group compared different methods to predict ASMR, showing the best predictive performance from the Poisson GLM with the identity link function [6]. Annually, my research group produced projection estimates for major cancer sites in Europe and worldwide using a simple identity model.

Joinpoint regression on the number of deaths

The trend analyses performed with joinpoint regression models can be used also to predict mortality trends, following the steps explained above:

iii) A joinpoint regression model is fit to the logarithm of the number of age-specific deaths for each 5-year age group to identify the most recent trend segments.;

iv) A regression model is applied to the mortality data for each age group over the period identified by the last segment of the joinpoint model, in order to estimate the regression coefficients. This model is then used to predict mortality for future years, to calculate the number of expected age-specific deaths and the corresponding 95% prediction intervals (PIs), that is, the confidence intervals for the prediction of each future value. These are calculated with a standard error that takes the variability of the new observation into account [7, 8];

v) Projected ASMRs, with corresponding 95% PIs, are calculated using the number of expected age-specific deaths and the projected population data for the period of interest.

APPLICATIONS

In the following subchapters, I will go deeply through three applications of descriptive epidemiology on cancer data. To this end, no ethics committee approval was necessary because I only considered public data. For all statistical analyses, I used the software R version 4.2.1 (R Development Core Team, 2017), SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), SEER*Stat (seer.cancer.gov/seerstat) version 8.4.0.1, and joinpoint version 4.9.0.0

Progress in cancer incidence mortality and survival: a global overview

From the World Health Organization (WHO) database [9], I retrieved official death certification data for the following cancer sites: stomach, pancreas, colorectum, lung, breast, uterus, ovary, prostate, bladder, leukaemias, plus all cancers combined. The list of corresponding International Classification of Diseases codes is available in **Appendix Table 1**. I derived figures for France, Germany, Italy, the United Kingdom (UK), the United States of America (USA), and Japan, over the calendar period 1990-2016, and the European Union (EU) as a whole (defined as the 28 member states). For European countries, I obtained estimates of the resident populations for the corresponding calendar periods, based on official censuses, from the same WHO database [9], and for the USA, from the Pan American Health Organization database [10]. When population data for European countries were missing, we obtained them from EUROSTAT [11]. Using the matrices of certified deaths and resident populations, we computed country- and sex-specific death rates for each 5-year age group (from 0-4 to 85+ years, and from 0-4 to 80+ for the USA) and calendar period; we then derived ASMRs at all ages, using the world standard population [2].

To identify significant changes in the linear slope (on a log scale) of death trends for the selected countries, I applied joinpoint regression model [3] to the ASMRs, allowing for up to four joinpoints. We then estimated the AAPC [12] for the whole period. For all cancers, lung, breast, colorectal, and prostate cancers, we also estimated the numbers of averted total cancer deaths over the period 1991-2016 (2015 for the EU) by comparing observed and expected deaths on the basis of the 1990 age-specific rates, i.e., the year around which the highest rates occurred in most countries and for most cancer sites considered.

We retrieved incidence data for the same cancers considered in the mortality analysis for Germany [13], England [14], the USA [15], and Japan [16]. From each of the previous countries, we derived age-standardized incidence rates at all ages, using the world standard population [2]. For France and Italy,

we extracted national estimates for the available cancer sites from cancer registries data [17, 18]. We then applied joinpoint regression analysis to the age-standardized incidence rates, and estimated AAPCs [12].

Cancer survival data for the European countries and the EU were obtained from the EUROCARE-5 database [19], which provides survival data for about 22 million records of patients diagnosed up to 2007 and followed up to December 31, 2008. For the USA, we analysed cancer survival data provided by the SEER 9 registries [15]. For Japan, we retrieved cancer survival data of patients diagnosed between 1993 and 2008 from the Japan Cancer Surveillance [20]. We retrieved age-standardized relative survival at 5 years after diagnosis by cancer site, sex, and calendar year, along with the corresponding 95% CI.

RESULTS

Mortality

Table 1 gives the ASMRs per 100,000 men and women from the selected cancer sites and all cancers in 1990 and 2016 (2015 for the EU), the number of deaths in 2016, and the AAPCs over the whole period, in the six selected countries and the EU. **Figure 1** shows the corresponding trends in mortality rates between 1990 and 2016 for each cancer site and country, for men (**a**) and women (**b**).

Table 1. Age-standardised (world population) death rates from cancer per 100,000 men and women for selected countries worldwide, plus the European Union (EU), in 1990 and 2016, number of deaths in 2016, and average annual percent changes (AAPC) over 1990-2016.

	Men				**Women**			
	1990	**2016**	**Deaths 2016[a]**	**AAPC (1990-2016)**	**1990**	**2016**	**Deaths 2016[a]**	**AAPC (1990-2016)**
Stomach								
EU [a]	15.05	6.28	34,666	-3.5[b]	6.84	2.91	22,162	-3.3[b]
France	8.67	4.16	2880	-2.8[b]	3.47	1.53	1526	-3.1[b]
Germany	14.61	5.29	5370	-3.8[b]	7.64	2.83	3861	-3.8[b]
Italy	17.12	6.73	5458	-3.6[b]	7.99	3.34	3823	-3.3[b]
UK	12.23	3.84	2867	-4.5[b]	5.05	1.73	1603	-4.1[b]
USA	4.99	2.37	6845	-2.9[b]	2.32	1.32	4588	-2.1[b]
Japan	34.13	14.57	29,854	-3.2[b]	15.01	5.58	15,677	-3.7[b]
Colorectum								
EU [a]	19.88	16.06	93,241	-0.9[b]	13.42	9.40	77,122	-1.5[b]
France	20.97	13.38	10,395	-1.8[b]	12.39	8.16	9460	-1.7[b]

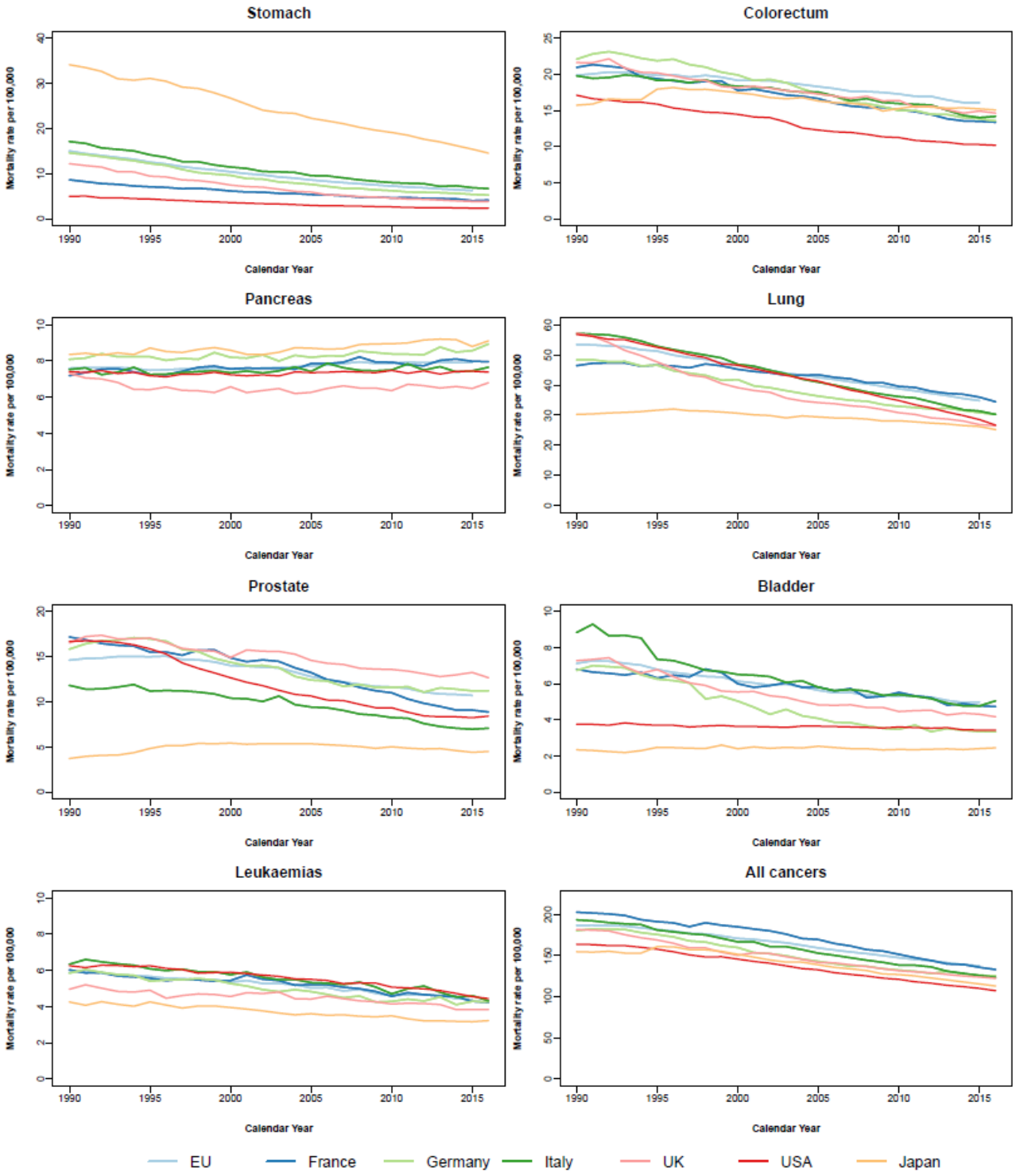
	Men				Women			
	1990	2016	Deaths 2016[a]	AAPC (1990-2016)	1990	2016	Deaths 2016[a]	AAPC (1990-2016)
Germany	22.11	13.58	14,457	-2.0[b]	16.07	8.18	12,536	-2.7[b]
Italy	19.80	14.19	11,998	-1.3[b]	13.03	8.64	10,270	-1.5[b]
UK	21.63	14.64	10,935	-1.6[b]	14.61	10.15	9618	-1.5[b]
USA	17.12	10.19	29,737	-2.0[b]	11.68	7.29	26,743	-2.0[b]
Japan	15.73	15.07	28,465	-0.1	9.91	8.73	24,098	-0.4[b]
Pancreas								
EU[a]	7.60	7.91	42,462	0.2[b]	4.65	5.53	42,201	0.7[b]
France	7.19	7.96	5501	0.4[b]	3.70	5.53	5593	1.4[b]
Germany	8.09	8.94	9008	0.2[b]	5.01	6.45	9044	0.8[b]
Italy	7.53	7.65	5834	0.1[b]	4.44	5.64	6215	0.7[b]
UK	7.31	6.79	4738	-0.2[b]	5.24	5.02	4548	0.0
USA	7.40	7.38	21,899	0.0	5.27	5.56	20,858	0.1[b]
Japan	8.36	9.11	17,060	0.3[b]	4.82	5.81	16,415	0.7[b]
Lung								
EU[a]	53.43	34.83	183,943	-1.7[b]	9.26	14.28	88,502	1.7[b]
France	46.46	34.47	22,322	-1.1[b]	5.07	12.22	9211	3.5[b]
Germany	48.39	30.26	29,324	-1.8[b]	7.86	15.44	16,481	2.6[b]
Italy	57.18	30.26	24,059	-2.4[b]	7.33	10.73	9779	1.5[b]
UK	57.26	26.52	19,357	-2.9[b]	21.02	19.40	16,328	-0.3[b]
USA	56.82	26.69	80,815	-2.9[b]	25.03	18.75	68,130	-1.1[b]
Japan	30.26	25.22	52,430	-0.7[b]	7.88	7.44	21,408	-0.3[b]
Breast								
EU[a]	-	-	-	-	20.83	14.54	93,903	-1.5[b]
France	-	-	-	-	19.63	14.72	12,434	-1.2[b]
Germany	-	-	-	-	21.87	15.79	18,570	-1.3[b]
Italy	-	-	-	-	20.62	14.21	12,616	-1.5[b]
UK	-	-	-	-	28.11	15.08	11,512	-2.5[b]
USA	-	-	-	-	22.27	12.91	41,488	-2.1[b]
Japan	-	-	-	-	6.26	9.18	14,015	1.4[b]
Uterus								
EU[a]	-	-	-	-	7.23	4.84	29,691	-1.6[b]
France	-	-	-	-	5.50	4.00	3515	-1.4[b]
Germany	-	-	-	-	6.64	3.70	4162	-2.3[b]
Italy	-	-	-	-	5.54	3.81	3130	-1.8[b]
UK	-	-	-	-	6.67	4.31	3215	-1.7[b]
USA	-	-	-	-	5.25	4.91	14,921	-0.2[b]
Japan	-	-	-	-	4.14	4.10	6345	0.0
Ovary								
EU[a]	-	-	-	-	6.49	4.78	30,213	-1.2[b]
France	-	-	-	-	5.72	3.89	3473	-1.5[b]
Germany	-	-	-	-	7.51	4.75	5674	-1.9[b]

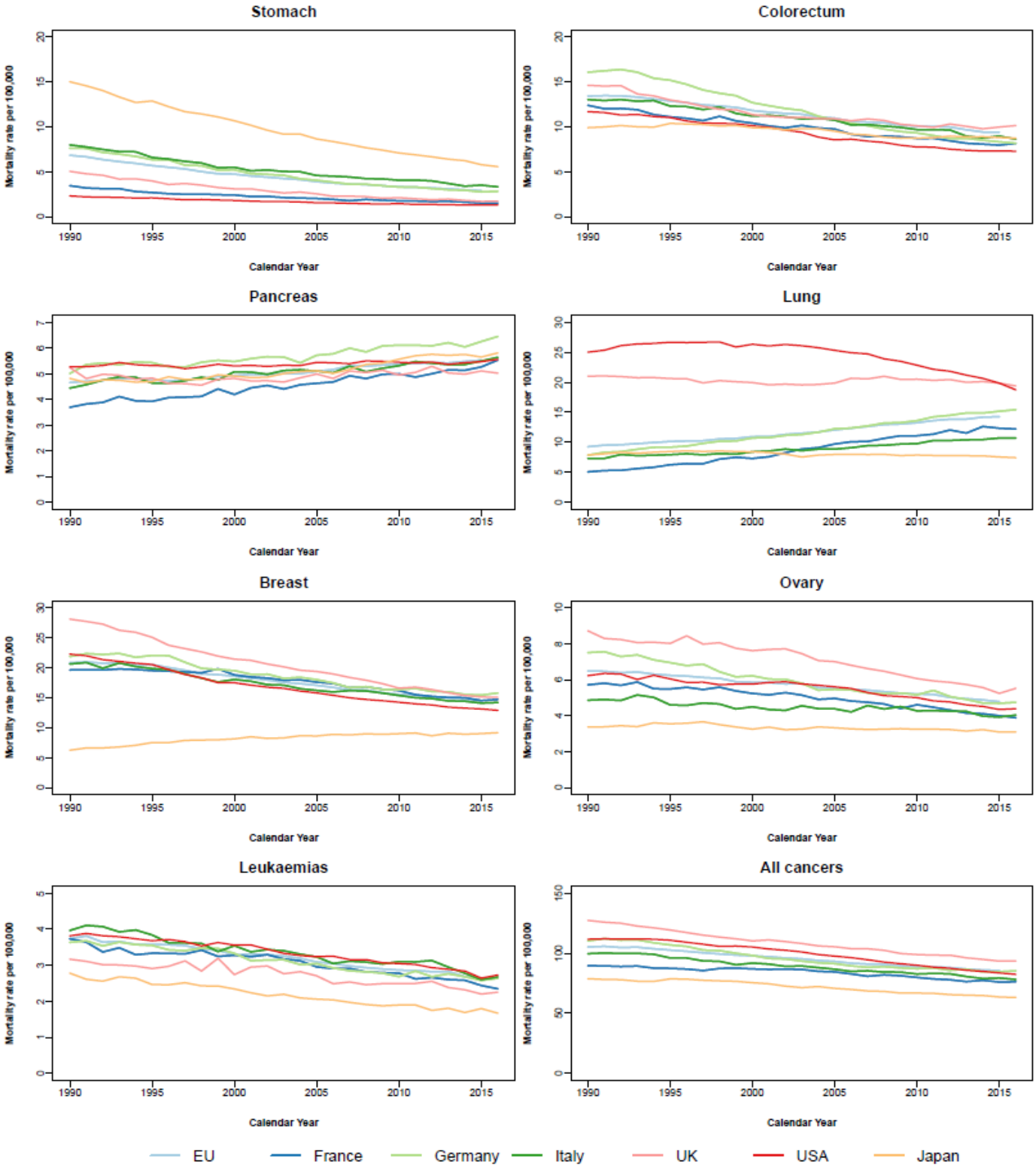
	Men				Women			
	1990	2016	Deaths 2016[a]	AAPC (1990-2016)	1990	2016	Deaths 2016[a]	AAPC (1990-2016)
Italy	-	-	-	-	4.86	4.04	3342	-0.7[b]
UK	-	-	-	-	8.72	5.52	4235	-1.7[b]
USA	-	-	-	-	6.23	4.39	14,674	-1.4[b]
Japan	-	-	-	-	3.39	3.10	4900	-0.2
Prostate								
EU[a]	14.62	10.71	74,998	-1.3[b]	-	-	-	-
France	17.17	8.88	8724	-2.6[b]	-	-	-	-
Germany	15.83	11.22	14,417	-1.4[b]	-	-	-	-
Italy	11.83	7.08	7540	-2.0[b]	-	-	-	-
UK	16.52	12.67	11,645	-1.1[b]	-	-	-	-
USA	16.69	8.42	30,370	-2.5[b]	-	-	-	-
Japan	3.73	4.50	11,803	0.6	-	-	-	-
Bladder								
EU[a]	7.13	4.99	31,938	-1.5[b]	-	-	-	-
France	6.80	4.73	4041	-1.3[b]	-	-	-	-
Germany	6.74	3.34	4049	-2.8[b]	-	-	-	-
Italy	8.84	5.05	4883	-2.4[b]	-	-	-	-
UK	7.28	4.17	3631	-2.1[b]	-	-	-	-
USA	3.75	3.43	11,941	-0.3[b]	-	-	-	-
Japan	2.35	2.45	5792	0.2	-	-	-	-
Leukaemias								
EU[a]	5.88	4.39	23,713	-1.2[b]	3.74	2.63	19,137	-1.5[b]
France	6.03	4.23	3281	-1.3[b]	3.74	2.35	2633	-1.6[b]
Germany	5.85	4.26	4542	-1.4[b]	3.64	2.64	3710	-1.4[b]
Italy	6.34	4.32	3422	-1.4[b]	3.97	2.68	2730	-1.6[b]
UK	4.96	3.83	2752	-1.1[b]	3.17	2.25	1997	-1.4[b]
USA	6.26	4.44	13,270	-1.3[b]	3.82	2.73	9859	-1.3[b]
Japan	4.25	3.22	5398	-1.3[b]	2.78	1.67	3403	-1.9[b]
All cancers								
EU[a]	186.76	137.53	760,123	-1.2[b]	105.26	85.68	603,984	-0.9[b]
France	202.87	133.02	95,440	-1.6[b]	89.59	76.26	72,811	-0.7[b]
Germany	180.45	125.37	128,942	-1.5[b]	110.34	85.33	109,619	-1.1[b]
Italy	193.52	123.60	100,166	-1.7[b]	99.62	78.14	79,533	-0.9[b]
UK	181.71	122.24	90,490	-1.6[b]	127.38	93.52	79,976	-1.2[b]
USA	163.87	107.22	323,488	-1.6[b]	111.70	82.41	291,133	-1.2[b]
Japan	154.69	112.98	226,026	-1.2[b]	78.79	63.12	158,785	-0.8[b]

[a] For the EU the last available year is 2015.

[b] Significantly different from 0 ($p < 0.05$).

Figure 1. Age-standardized mortality rates per 100,000 men and women from the selected cancer sites and all cancers over the period 1990-2016.




Stomach
Colorectum
Pancreas
Lung
Breast
Ovary
Leukaemias
All cancers
Mortality rate per 100,000
Calendar Year
1990
1995
2000
2005
2010
2015
EU
France
Germany
Italy
UK
USA
Japan

Stomach cancer

Cancer mortality steadily declined in both sexes across all countries considered. In men, the AAPCs between 1990 and 2016 ranged between -2.9% in the USA and -4.5% in the UK. In 1990, Japan had the highest rate (34.1/100,000), while the USA had the lowest one (around 5); in 2016, the corresponding figures were 14.6/100,000 in Japan and 2.4/100,000 in the USA. In women, the AAPCs varied between -2.1% in the USA and -4.1% in the UK. In 1990, rates ranged between 2.3/100,000 in the USA and 15.0 in Japan; in 2016 too, Japan had the highest death rate (5.6/100,000), and the USA had the lowest one (1.3).

Colorectal cancer

Mortality rates significantly decreased in all countries and both sexes, except in Japan where the trend was stable. In men, the AAPCs ranged between -0.1% in Japan and -2.0% in Germany and the USA. In 1990, the highest rates were around 22/100,000 in Germany and the UK and the lowest one in Japan (15.7), while in 2016 the highest rate was 16.1 in the EU and the lowest one in the USA (10.2). In women, the strongest decreases were in Germany (AAPC -2.7%), followed by the USA (-2.0%), and France (-1.7%). In 1990, the highest rate was 16.1/100,000 in Germany, the lowest one was about 10 in Japan; in 2016, female rates ranged between 7.3/100,000 in the USA and 10.2 in the UK.

Pancreatic cancer

In men, mortality rates were rising in France (AAPC +0.4%), Germany (+0.2%), Italy (+0.1%), and Japan (+0.3%), they did not change in the USA, while they decreased slightly in the UK (-0.2%). In 1990, Germany and Japan had the highest rates, over 8/100,000, and France had the lowest one, 7.2. In 2016, Japan had the highest rate (9.1/100,000), while the UK had the lowest one (6.8). Female mortality was also increasing, by 0.8% in Germany, 1.4% in France, and 0.7% in Italy and Japan. In 1990, the USA and UK had the highest rates (over 5.2/100,000) while France had the lowest one (3.7); in 2016, female rates ranged between 5/100,000 in the UK and 6.5 in Germany.

Lung cancer

In men, cancer mortality decreased in all countries, though to a different degree. The AAPCs ranged between -0.7% in Japan and -2.9% in the UK and the USA. Rates in 1990 ranged between 30.3/100,000 in Japan and around 57 in Italy, the UK, and the USA; in 2016, rates ranged between 25.2/100,000 (Japan) and 34.5 (France). In women, rates increased in France, Germany, and Italy and in the EU as a whole (AAPCs ranged between 1.5% and 3.5%) and declined in the UK, the USA, and Japan (-0.3% to -1.1%). In 1990, the highest female rate was in the USA (25.0/100,000) and the

lowest one in France (5.1); in 2016, the highest rates were in the UK and the USA (around 19/100,000), while the lowest one was in Japan (7.4).

Breast cancer

Cancer mortality decreased in all countries (AAPCs ranged between -1.2% in France and -2.5% in the UK), except in Japan (+1.4%), which however registered the lowest rates. In 1990, rates ranged between 6.3/100,000 in Japan and 28.1 in the UK; in 2016, rates ranged between 9.2/100,000 in Japan and 15.8 in Germany.

Uterine cancer

Mortality rates decreased in all the selected countries (AAPCs ranged between -0.2% in the USA and -2.3% in Germany). In 1990, death rates were between 4.1/100,000 in Japan and 6.7 in the UK; in 2016, the USA had the highest recorded rate (4.9/100,000), while Germany had the lowest one (3.7).

Ovarian cancer

Mortality levelled or declined in most of the considered countries, with AAPCs ranging from -0.7% in Italy to -1.9% in Germany. There was a nonsignificant change in Japan, which however had the lowest rates throughout the period. In 1990, death rates varied between 3.4/100,000 in Japan and 8.7 in the UK; in 2016, rates varied from 3.1/100,000 in Japan to 5.5 in the UK.

Prostate cancer

Cancer mortality declined in all countries (AAPCs ranged between-1.1% in the UK and -2.6% in France), except in Japan. In 1990, there was an over four-fold difference between the highest rate in France (17.2/100,000) and the lowest one in Japan (3.7). Over the considered period, the trends tended to converge. In 2016, the UK had the highest death rate (12.7/100,000), while Japan had the lowest one (4.5).

Bladder cancer

Mortality in men decreased in European countries (AAPCs ranged between -0.3% in the USA and -2.8% in Germany), but not in Japan where the death rates were almost stable over time. Rates varied between 2.4/100,000 in Japan and 8.8 in Italy, in 1990 and between 2.5/100,000 in Japan and 5.1 in Italy, in 2016.

Leukaemias

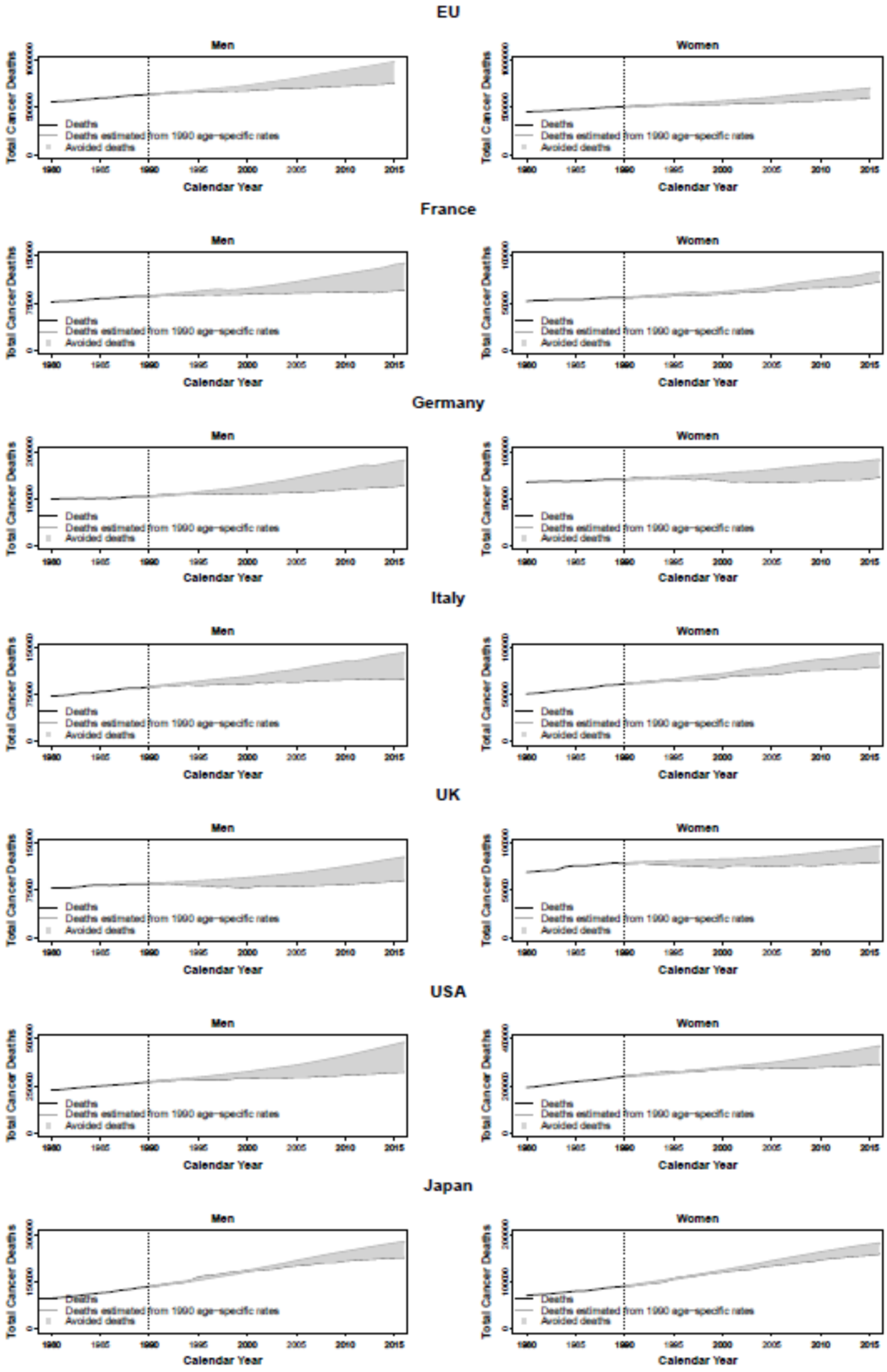
Death rates decreased across all countries and in both sexes. In men, the AAPCs ranged between -1.1% in the USA and -1.4% in Germany and Italy. In 1990, Italy had the highest male rate (6.3/100,000) and Japan had the lowest one (4.3). In 2016, rates ranged from 3.2 in Japan to 4.4/100,000 in the USA. In women, AAPCs varied between -1.3% in the USA and -1.9% in Japan. In 1990, the highest rate was for Italy, 4/100,000 women and the lowest was in Japan, 2.8. In 2016, rates ranged from 1.7/100,000 in Japan to 2.6-2.7 in Germany, Italy, and the USA.

All cancers

In both sexes and all countries, trends in mortality rates declined between 1990 and 2016. In men, the AAPCs ranged between -1.2% in Japan and the EU and -1.7% in Italy. In 1990, death rates varied from 155/100,000 in Japan to over 200 in France; in 2016, the highest rate was observed in France (133/100,000), while the lowest ones were in the USA (107) and Japan (113). In women, the AAPCs ranged between -0.7% in France and -1.1% in Germany. In 1990, rates varied between 79/100,000 in Japan and 127 in the UK; in 2016, the UK had the highest rate (about 94/100,000), while Japan had the lowest one (63).

Figure 2 shows the avoided deaths from all cancers combined for men and women in the selected countries between 1991 and 2016, assuming the age-specific rates in 1990 as constant. Over the period considered, 3,371,200 cancer deaths have been avoided in the EU. Of these 541,500 were in France, 1,008,700 in Germany, 612,200 in Italy, and 685,600 in the UK. Estimated avoided deaths were 2,173,900 in the USA and 591,100 in Japan.

Figure 2. Total avoided deaths from all cancers combined men and women between the top rate around 1990 and 2016 (light grey area); the observed number of total cancer deaths from 1990 to 2016 (or the most recent available year), and the estimated numbers of total cancer deaths by applying 1990 age-specific peak mortality rate (dark grey).



Incidence

Table 2 gives the age-standardized incidence rates per 100,000 men and women for the selected cancer sites and all cancers in 2000 and in the last year available, and the AAPCs over the period in the six selected countries. **Figure 3** shows the corresponding trends in rates since the 2000 for England, France, Germany, Italy, the USA and Japan, in men (**a**) and women (**b**).

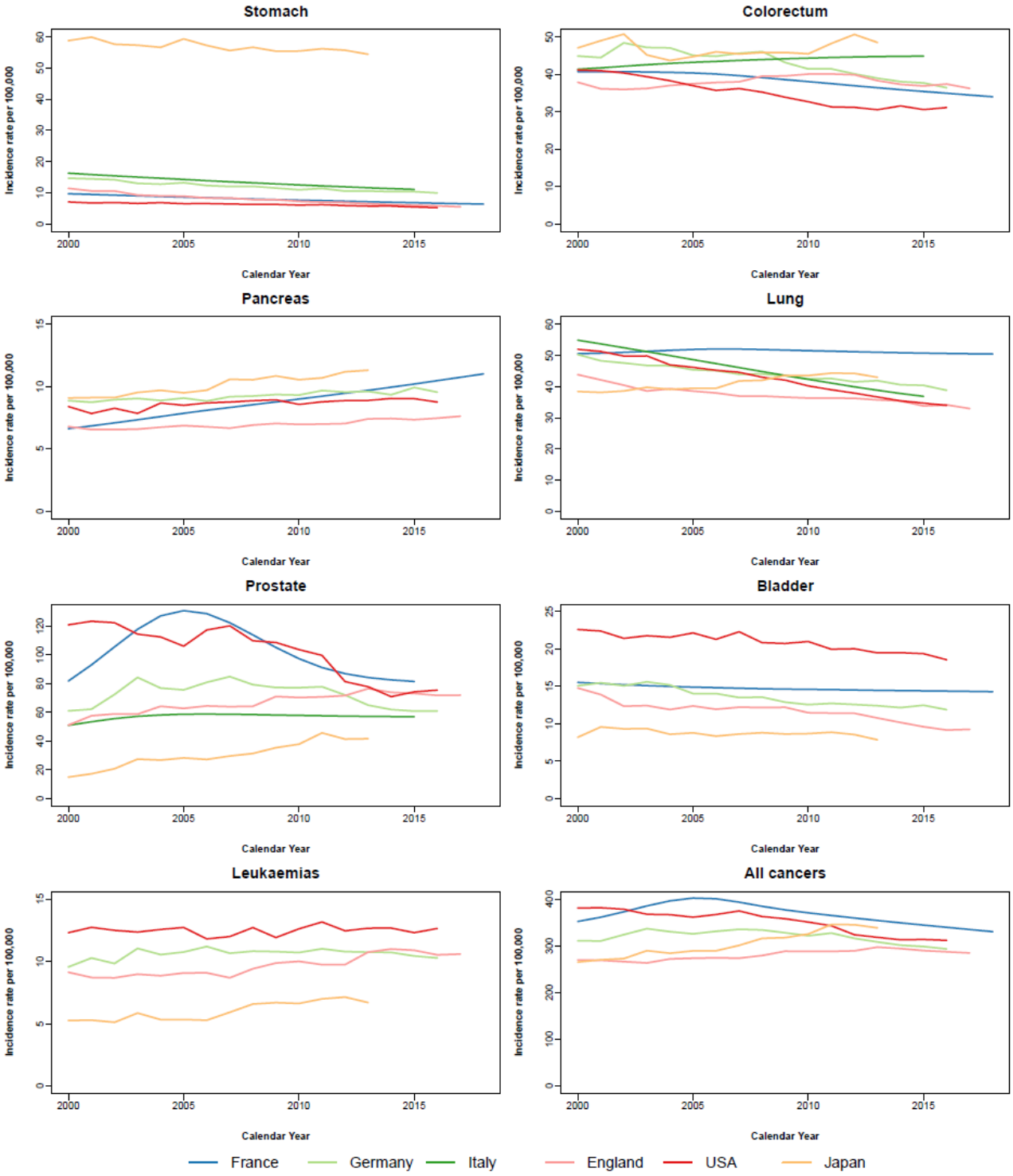
Table 2. Age-standardised (world population) incidence rates from cancer per 100,000 men and women for selected countries worldwide in 2000 and 2016 and average annual percent changes (AAPC) over 2000-2016.

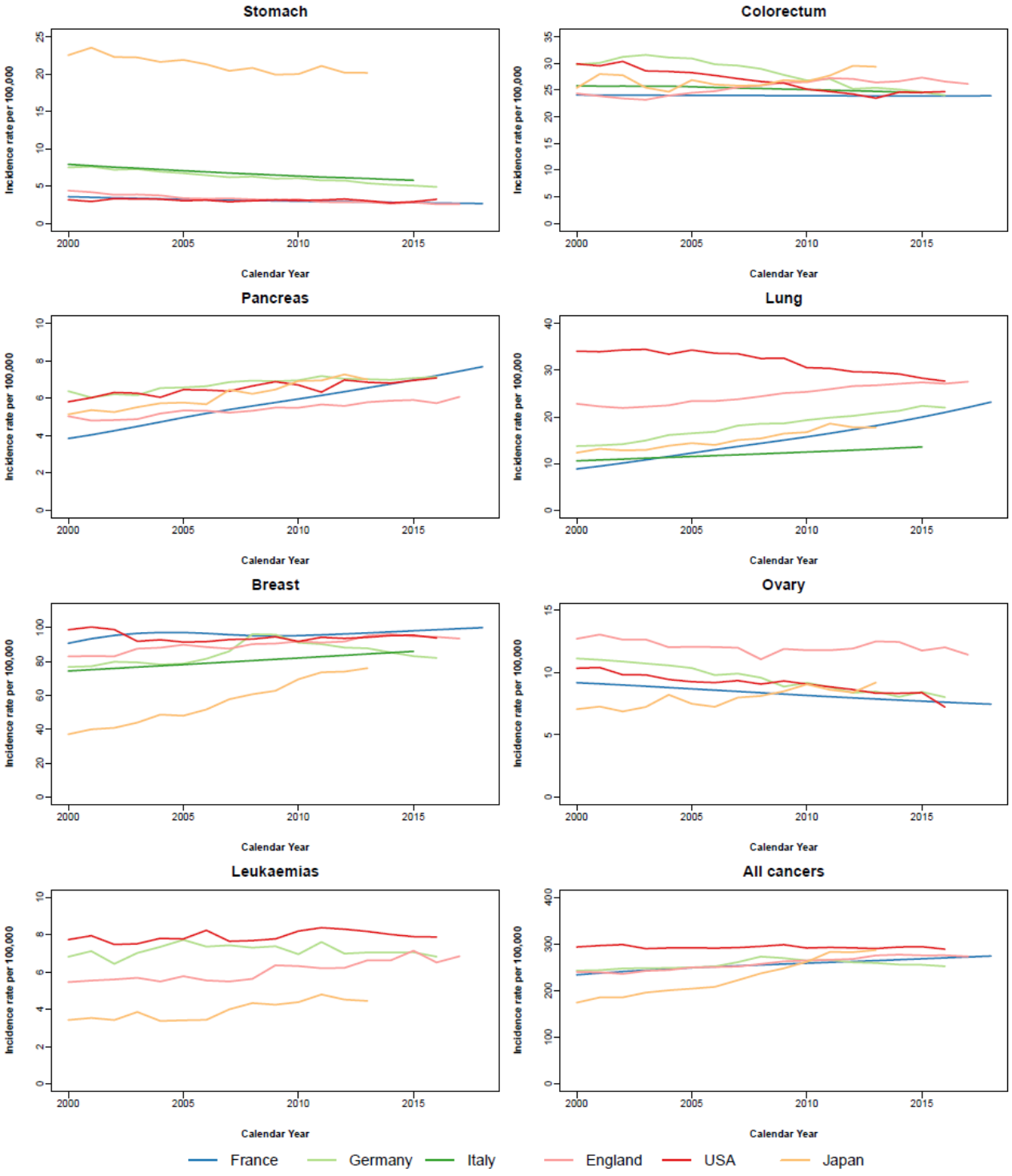
	Men			**Women**		
	2000	**2016**	**AAPC (2000-2016)**	**2000**	**2016**	**AAPC (2000-2016)**
Stomach						
England [a]	11.38	5.43	-4.0[e]	4.39	2.56	-3.0[e]
France [b]	9.65	6.31	-2.3[e]	3.57	2.65	-1.6[e]
Germany	14.63	9.90	-2.4[e]	7.49	4.88	-2.7[e]
Italy [c]	16.26	11.06	-2.5[e]	7.91	5.78	-2.1[e]
USA	7.03	5.17	-1.7[e]	3.16	3.22	-0.3
Japan [d]	58.83	54.44	-0.6[e]	22.54	20.17	-1.1[e]
Colorectum						
England [a]	37.88	36.24	-0.2	24.37	26.18	0.5[e]
France [b]	40.71	34.00	-1.0[e]	24.09	23.94	0.0
Germany	41.36	44.88	0.6[e]	25.81	24.53	-0.3[e]
Italy [c]	44.90	36.41	-1.2[e]	29.80	24.04	-1.3[e]
USA	41.16	31.11	-1.9[e]	29.93	24.72	-1.3[e]
Japan [d]	47.08	48.53	0.2	25.42	29.40	0.7[e]
Pancreas						
England [a]	6.79	7.62	0.9[e]	5.04	6.08	1.3[e]
Germany	8.87	9.55	0.7[e]	6.38	7.14	0.9[e]
USA	8.40	8.76	0.7[e]	5.81	7.09	1.0[e]
Japan [d]	9.09	11.32	1.8[e]	5.13	7.00	2.8[e]
Lung						
England [a]	43.85	32.95	-1.5[e]	22.82	27.56	1.1[e]
France [b]	50.55	50.47	0.0	8.84	23.18	5.5[e]
Germany	50.30	38.82	-1.4[e]	13.74	21.99	3.3[e]
Italy [c]	54.92	36.87	-2.7[e]	10.58	13.56	1.7[e]
USA	51.99	33.97	-2.7[e]	34.11	27.67	-1.3[e]
Japan [d]	38.43	42.99	0.9[e]	12.32	17.73	3.2[e]
Breast						
England [a]	-	-	-	82.89	93.41	0.8[e]
France [b]	-	-	-	90.66	99.90	0.5[e]
Germany	-	-	-	76.70	82.02	0.3[e]
Italy [c]	-	-	-	74.29	85.91	1.0[e]

	Men			Women		
	2000	**2016**	**AAPC (2000-2016)**	**2000**	**2016**	**AAPC (2000-2016)**
USA	-	-	-	98.63	93.80	-0.4
Japan [d]	-	-	-	36.97	75.97	5.8[e]
Uterus						
England [a]	-	-	-	18.30	21.91	1.3[e]
France [b]	-	-	-	10.70	10.99	0.1[d]
Germany	-	-	-	22.57	18.46	-1.2[e]
Italy (cervix) [c]	-	-	-	4.88	2.62	-4.1[e]
USA	-	-	-	24.16	25.83	0.4
Japan [d]	-	-	-	13.94	23.09	3.7[e]
Ovary						
England [a]	-	-	-	12.72	11.44	-0.7[e]
France [b]	-	-	-	9.19	7.47	-1.2[e]
Germany	-	-	-	11.14	8.03	-2.2[e]
USA	-	-	-	10.36	7.23	-1.6[e]
Japan [d]	-	-	-	7.06	9.21	2.0[e]
Prostate						
England [a]	51.10	71.94	1.5[e]	-	-	-
France [b]	81.78	81.47	-0.3	-	-	-
Germany	61.00	60.87	-0.5	-	-	-
Italy [c]	50.92	57.02	0.7[e]	-	-	-
USA	120.87	75.41	-2.9[e]	-	-	-
Japan [d]	14.91	41.63	7.2[e]	-	-	-
Bladder						
England [a]	14.79	9.26	-2.9[e]	-	-	-
France [b]	15.55	14.29	-0.5			
Germany	15.08	11.89	-1.4[e]	-	-	-
USA	22.62	18.57	-1.1[e]	-	-	-
Japan [d]	8.20	7.86	-0.6	-	-	-
Leukaemias						
England [a]	9.12	10.58	1.4[e]	5.45	6.84	1.5[e]
Germany	9.55	10.27	0.6	6.81	6.82	0.2
USA	12.30	12.64	0.1	7.73	7.87	0.3[e]
Japan [d]	5.25	6.69	2.7[e]	3.42	4.44	2.7[e]
All cancers						
England [a]	269.75	284.53	0.3	240.13	273.21	0.8[e]
France [b]	352.02	330.21	-0.4[e]	233.63	273.98	0.9[e]
Germany	310.48	293.27	-0.4[e]	242.75	252.04	0.2
USA	380.83	311.62	-1.2[e]	293.43	288.67	-0.1
Japan [d, f]	265.07	338.30	2.2[e]	174.05	286.97	3.8[e]

[a] For England the last available year is 2017. [b] For France the last available year is 2018. [c] For Italy the last available year is 2015. [d] For Japan the last available year is 2013. [e] Significantly different from 0 ($p < 0.05$). [f] Including non-melanoma skin cancers.

Figure 3. Age-standardized incidence rates per 100,000 men and women from the selected cancer sites and all cancers over the period 2000-2016.




Stomach
Colorectum
Pancreas
Lung
Breast
Ovary
Leukaemias
All cancers
Incidence rate per 100,000
Calendar Year
France
Germany
Italy
England
USA
Japan

Stomach cancer

In men, cancer incidence decreased in all countries considered, with AAPCs from -0.6% in Japan to -4.0% in England. The highest rates were in Japan (58.8/100,000 in 2000 and 54.4 in 2013), while the lowest ones were in the USA (7.0/100,000 in 2000 and 5.2 in 2016). Similarly, incidence trends in women declined over time, with the highest AAPCs in England (-3.0%) and Germany (-2.7%) and the lowest in Japan (-1.1%). No significant trend was observed in the USA. Again, Japan had the highest rates (22.5/100,000 in 2000 and 20.2 in 2013), while the lowest ones were in England (4.4/100,000 in 2000 and 2.6 in 2017) and the USA (3.2/100,000 in both 2000 and 2016).

Colorectal cancer

Among men, incidence rates declined over time in France (-1.0%), Italy (-1.2%), and the USA (-1.9%), while they were stable in England, Germany and Japan. The highest rates were observed in Japan (47.1/100,000 in 2000 and 48.5 in 2013), while the lowest ones were in England (37.9/100,000 in 2000 and 36.2 in 2017) and the USA (41.2/100,000 in 2000 and 31.1 in 2016) and. In women, incidence trends decreased in Germany (AAPC -0.3%), Italy (-1.3%), and the USA (-1.3%), while they increased in England (+0.5%) and Japan (+0.7%). During the latest available year, female incidence rates were around 24/100,000 in France, Germany, Italy, and the USA, 26 in England, and 29 in Japan.

Pancreatic cancer

Incidence trends rose over time in all countries and both sexes. In men, the AAPCs ranged between +0.7% in Germany and the USA and +1.8% in Japan. In the latest available year, the highest male rate was observed in Japan (11.3/100,000), while the lowest one was in England (7.6). In women, similar trends were observed with AAPCs ranging from +0.9% in Germany to +2.8% in Japan. Rates were around 6-7/100,000 women in all selected countries during the last available year.

Lung cancer

Male incidence moderately declined in all countries considered (AAPCs from -1.4% in Germany to -2.7% in Italy and the USA), except in Japan, which showed an increase of 0.9% per year and the second highest rate in 2013 (43/100,000), after France in 2018 (50.5). Conversely, female incidence trends increased over time in all countries (AAPCs ranged between +1.7% in Italy to +5.5% in France), except in the USA. The highest incidence rates over the period were registered in the USA (34.1/100,000 in 2000 and 27.7 in 2016), while the lowest ones were in Italy (10.6/100,000 in 2000 and 13.6 in 2015).

Breast cancer

The cancer incidence trend slightly increased in England (AAPC +0.8%), France (+0.5%), and Italy (+1.0%), and strongly in Japan (+5.8%). A stable trend over the whole period emerged in Germany, though it showed a decline since 2009, and the USA. In the latest available year, the highest rate was observed in France (99.9/100,000) and the lowest one in Japan (about 76).

Uterine cancer

The incidence trend declined in Germany by 1.2% per year, it was stable in France and the USA, while it increased in Japan by 3.7% and in England (+1.3%). During the last available year, the incidence rates ranged from 11/100,000 in France to 25.8 in the USA.

Ovarian cancer

Cancer incidence declined by 0.7% per year in England, by 1.2% in France, by 2.2% in Germany, and by 1.6% in the USA, but it increased by 2% per year in Japan. England reported the highest incidence rate during the last available year (11.4/100,000), while the USA had the lowest one (7.2).

Prostate cancer

Upward incidence trends were registered in England (+1.5%) and Japan (AAPC +7.2%). Conversely, the incidence decreased over time in the USA (AAPC -2.9%) and remained stable in Germany and Italy. France showed a decline since 2005. The highest rates were registered in the USA almost over the whole period (120.9/100,000 in 2000 and 75.4 in 2016), while Japan showed the lowest incidence rates (14.9/100,000 in 2000 and 41.6 in 2013).

Bladder cancer

Incidence decreased across all countries considered (AAPCs ranged between -0.5% in France and -2.9 in England. The highest rates were observed in the USA (22.6/100,000 in 2000 and 18.6 in 2016), the lowest ones in Japan (8.2/100,000 in 2000 and 7.9/100,000 in 2013).

Leukaemias

Incidence rates increased in Japan by 2.7% per year in both sexes and by 1.4-1.5% in England. No notable changes in trend were registered in the other two countries. The USA had the highest rates for both men and women in 2016 (12.6/100,000 and 7.9, respectively), while Japan had the lowest ones in both men and women in 2013 (6.7 and 4.4/100,000, respectively).

All cancers

In England male incidence trend was stable, it declined in Germany and France by 0.4% per year and in the USA by 1.2%, while Japan registered the greatest increase (AAPC +2.2%). In 2000, the highest rate was in the USA (about 380.8/100,000), the lowest one in Japan (265.1); during the last available year, the highest rate was registered in Japan (338.3/100,000), while the lowest one in England (284.5). Female trends increased by 0.8% in England, by 0.9% in France, and by 3.8% in Japan, while were stable in Germany and the USA. In 2000, the USA showed the highest rate of 293.43/100,000 women, Japan had the lowest one (174.1). During the latest year available, the USA and Japan reported the highest rates (287-288/100,000), followed by England and France (273-274), while Germany reported the lowest one (252).

Survival

Table 3 reports 5-year relative survival and the corresponding 95% confidence intervals for the selected cancer sites and all cancers in two periods of diagnosis, based on data availability, for men and women in the six selected countries and in the EU.

Table 3. Five-year relative survival, and corresponding 95% confidence interval (CI), from cancer for selected countries worldwide, plus the EU-28, in two periods of diagnosis in men and women.

	Men		**Women**	
	Earliest period (95% CI)	**Latest period (95% CI)**	**Earliest period (95% CI)**	**Latest period (95% CI)**
Stomach				
EU (95-99/00-07)	22.8 (22.6-23.12)	23.7 (23.4-24.1)	27.1 (26.8-27.5)	27.7 (27.2-28.2)
England (95-99/00-07)	15.1 (14.8-15.4)	16.4 (15.9-16.9)	18.3 (17.8-18.7)	18.3 (17.5-19.1)
France (95-99/00-07)	23.4 (22.3-24.7)	24.4 (22.9-26.1)	30.8 (29.1-32.6)	30.1 (27.7-32.8)
Germany (95-99/00-07)	27.2 (25.1-29.6)	30.5 (29.6-31.5)	28.1 (25.8-30.7)	32.6 (31.5-33.8)
Italy (95-99/00-07)	29.8 (29.3-30.3)	30.5 (29.7-31.3)	34.6 (34.0-35.2)	35.4 (34.4-36.4)
USA (97/04)	19.9 (17.2-22.7)	26.4 (23.4-29.4)	25.1 (21.4-28.9)	31.6 (27.5-35.6)
Japan (93-96/06-08)	62.1 (61.5-62.7)	65.3 (65.0-65.6)	60.4 (59.6-61.2)	63.0 (62.5-63.5)
Colorectum				
EU (95-99/00-07)	53.2 (53.0-53.4)	55.8 (55.5-56.1)	55.2 (55.0-55.4)	57.7 (57.4-57.9)
England (95-99/00-07)	49.5 (49.2-49.7)	51.3 (50.9-51.7)	51.9 (51.6-52.2)	53.2 (52.8-53.6)
France (95-99/00-07)	57.1 (56.4-57.9)	57.8 (56.8-58.7)	58.9 (58.1-59.6)	60.7 (59.7-61.7)
Germany (95-99/00-07)	56.6 (55.0-58.1)	61.0 (60.3-61.6)	57.9 (56.5-59.4)	62.9 (62.3-63.5)
Italy (95-99/00-07)	56.3 (55.9-56.7)	59.5 (59.0-60.1)	58.2 (57.8-58.6)	60.5 (60.0-61.1)
USA (97/04)	61.8 (60.2-63.4)	66.0 (64.4-67.5)	60.9 (59.3-62.5)	65.5 (63.9-67.0)
Japan (93-96/06-08)- colon	71.3 (70.4-72.2)	73.8 (73.3-74.3)	66.1 (65.1-67.1)	69.3 (68.8-69.8)

	Men		Women	
	Earliest period (95% CI)	**Latest period (95% CI)**	**Earliest period (95% CI)**	**Latest period (95% CI)**
Japan (93-96/06-08)- rectum	65.0 (63.9-66.1)	69.9 (69.3-70.5)	63.9 (62.5-65.3)	70.3 (69.5-71.1)
Pancreas				
EU (95-99/00-07)	5.0 (4.8-5.2)	6.3 (6.0-6.6)	6.3 (6.1-6.6)	7.9 (7.5-8.2)
England (95-99/00-07)	4.1 (3.9-4.3)	4.3 (3.9-4.7)	4.4 (4.1-4.7)	5.1 (4.7-5.6)
Germany (95-99/00-07)	6.4 (4.8-8.6)	8.4 (7.6-9.2)	6.5 (4.9-8.5)	9.5 (8.6-10.5)
USA (97/04)	4.7 (3.5-6.2)	5.1 (3.9-6.5)	5.2 (4.0-6.7)	6.0 (4.7-7.6)
Japan (93-96/06-08)	7.0 (6.1-7.9)	7.9 (7.4-8.4)	5.9 (4.9-6.9)	7.5 (7.0-8.0)
Lung				
EU (95-99/00-07)	11.3 (11.2-14.0)	12.0 (11.8-12.1)	13.9 (13.7-14.1)	15.9 (15.6-16.2)
England (95-99/00-07)	8.0 (7.9-8.1)	8.0 (7.8-8.2)	9.1 (8.9-9.2)	9.9 (9.7-10.2)
France (95-99/00-07)	12.1 (11.7-12.6)	13.1 (12.5-13.7)	16.8 (15.6-18.0)	16.5 (15.2-17.9)
Germany (95-99/00-07)	13.0 (12.2-14.0)	14.5 (14.1-14.9)	13.8 (12.4-15.4)	18.5 (17.8-19.2)
Italy (95-99/00-07)	12.0 (11.8-12.3)	13.2 (12.9-13.6)	15.4 (15.0-15.8)	17.3 (16.7-18.0)
USA (97/04)	13.5 (12.7-14.4)	15.0 (14.1-16.0)	16.6 (15.6- 17.7)	19.0 (17.9-20.1)
Japan (93-96/06-08)	20.8 (20.2-21.4)	27.0 (26.6-27.4)	27.1 (25.9-28.3)	43.3 (42.6-43.8)
Breast				
EU (95-99/00-07)	-	-	79.4 (79.3-79.6)	81.8 (81.6-82.0)
England (95-99/00-07)	-	-	77.3 (77.1-77.5)	79.3 (79.1-79.5)
France (95-99/00-07)	-	-	83.1 (82.6-83.7)	86.1 (85.5-86.8)
Germany (95-99/00-07)	-	-	78.3 (77.2-79.4)	83.6 (83.2-84.0)
Italy (95-99/00-07)	-	-	82.7 (82.4-82.9)	85.5 (85.1-85.9)
USA (97/04)	-	-	88.4 (87.6-89.1)	90.0 (89.3-90.6)
Japan (93-96/06-08)	-	-	84.4 (83.8-85.0)	91.1 (90.9-91.3)
Ovary				
EU (95-99/00-07)	-	-	36.5 (36.2-36.8)	37.6 (37.2-38.1)
England (95-99/00-07)	-	-	30.2 (29.9-30.6)	30.6 (30.1-31.1)
France (95-99/00-07)	-	-	35.2 (33.9-36.6)	40.1 (38.2-42.1)
Germany (95-99/00-07)	-	-	36.9 (34.6-39.4)	40.3 (39.3-41.4)
USA (97/04)	-	-	44.1 (41.5-46.7)	44.5 (41.8-47.0)
Japan (93-96/06-08)	-	-	49.4 (47.3-51.5)	58.0 (57.0-59.0)
Prostate				
EU (95-99/00-07)	76.4 (76.2-76.6)	83.4 (83.1-83.6)	-	-
England (95-99/00-07)	69.7 (69.4-70.0)	80.3 (80.0-80.6)	-	-
France (95-99/00-07)	78.3 (77.4-79.3)	88.8 (88.1-89.5)	-	-
Germany (95-99/00-07)	81.6 (79.8-83.4)	89.3 (88.7-89.8)	-	-
Italy (95-99/00-07)	79.1 (78.7-79.6)	88.4 (87.9-88.9)	-	-
USA (97/04)	97.4 (96.5-98.1)	99.7 (98.9-99.9)	-	-

	Men		Women	
	Earliest period (95% CI)	**Latest period (95% CI)**	**Earliest period (95% CI)**	**Latest period (95% CI)**
Japan (93-96/06-08)	66.8 (65.4-68.2)	97.5 (97.4-97.6)	-	-
Bladder				
EU (95-99/00-07)	72.8 (72.5-73.1)	69.4 (69.0-67.8)	-	-
England (95-99/00-07)	74.0 (73.7-74.3)	74.2 (73.8-74.6)	-	-
Germany (95-99/00-07)	79.6 (73.7-74.3)	74.0 (73.2-74.9)	-	-
USA (97/04)	79.9 (77.6-82.0)	82.1 (79.9-84.0)	-	-
Japan (93-96/06-08)	80.0 (78.7-81.3)	78.9 (78.2-79.6)	-	-
All cancers				
EU (95-99/00-07)	45.3 (45.2-45.4)	50.3 (50.2-50.4)	55.3 (55.2-55.4)	58.0 (57.9-58.1)
England (95-99/00-07)	41.2 (41.1-41.3)	46.9 (46.8-47.0)	50.4 (50.3-50.5)	52.7 (52.6-51.8)
France (95-99/00-07)	45.9 (45.6-46.2)	54.5 (54.1-54.9)	60.3 (60.0-60.6)	63.3 (62.9-63.7)
Germany (95-99/00-07)	47.6 (47.0-48.2)	56.2 (55.9-56.4)	57.1 (56.6-57.7)	62.1 (61.9-62.4)
USA (97/04)	63.2 (62.7-63.7)	68.0 (67.5-68.5)	63.5 (63.0-64.0)	66.6 (66.2-67.1)
Japan (93-96/06-08)	48.9 (48.6-49.2)	59.1 (58.9-59.3)	59.0 (58.7-59.3)	66.0 (65.8-66.2)

In men, survival rose with time in all the selected countries and for the considered cancer sites, except for bladder cancer. Considering stomach cancer, in the latest period, England had the lowest relative survival (16.4%), while Japan had the highest one (65.3%). Colorectal cancer had a survival ranging between 60 and 70% (except for England, 51.3%). For pancreatic cancer, survival ranged between 4.3% in England and 8.4% in Germany. For lung cancer, survival values ranged between 8.0% in England and 27.0% in Japan. During the latest period, prostate cancer had a survival ranging from 80.3% in England to 99.7% in the USA. For bladder cancer, survival ranged between around 74% in England and Germany and 82.1% in the USA. Five-year relative survival for all cancers combined greatly increased with time in all countries. During the latest period, the survival values ranged between 46.9% in England and 68.0% in the USA.

Similarly, female 5-year relative survival improved for all cancers considered and in all countries. Survival for stomach cancer in the most recent period ranged from 18.3% in England to 63% in Japan (**Table 3**). Colorectal cancer had a 5 survival of 60–70% in all countries (except England, 53.2%). For pancreatic cancer, survival ranged between 5.1% in England and 9.5% in Germany. For lung cancer, survival ranged between 9.9% in England and 43% in Japan. Breast cancer survival was 80% or more in all countries considered, varying between 79.3% in England and 91.1% in Japan. Survival for ovarian cancer increased slightly with time in most countries, with the lowest survival of 30.6% in England, and the highest one of 58.0% in Japan. Japan also showed the greatest increase in survival

across the two periods considered (from 49.4% to 58.0%). Five-year relative survival for all cancers combined rose in all countries, ranging from 52.7% in England to 66.6% in the USA.

DISCUSSION

The present overview of the burden of cancer in major high-income countries worldwide indicates and further quantifies that mortality from all cancers and most common cancer sites has declined over the last 25 years, except for pancreas and lung (in women). This translates to over 3,370,000 averted deaths in the EU, 2,170,000 in the USA, and about 600,000 in Japan. For incidence, the patterns are less consistent across countries, except for a steady decrease in stomach cancer in both sexes and lung cancer in men. Survival for all cancers and the selected cancer sites increased in most countries, although there is still substantial variability.

About a quarter of the overall declines in male cancer mortality is due to lung cancer alone. In addition, about 10% or more is due to other tobacco-related cancers. The declines in the prevalence of smoking across subsequent cohorts of men explain between 35 and 45% of the falls in cancer mortality [21]. Some decrease in lung cancer mortality was observed in US women, while female lung cancer mortality was upward in all other countries. As for men, this reflects the patterns in smoking prevalence across subsequent generations of women. A greater fall in mortality than the incidence of lung cancer was observed in most countries. The reductions in lung cancer mortality may be due to improvements in the diagnosis of early lesions and partly attributable to improvements in the management and treatment of the disease [22-24]. Survival showed little improvement in all countries except Japan, where lung cancer survival and its improvements were much higher. This may reflect different genetic predispositions or biological characteristics of Japanese individuals, but mainly greater attention to this disease, with organized community-based screening as well as periodical worksite health check-ups, and better surgical and radiotherapy treatment [16, 25, 26].

The favourable mortality and incidence trends for stomach cancer in men and women from all countries are attributable to increasing control of Helicobacter pylori infection, to favourable changes in modifiable risk factors, such as a more affluent and healthy diet, better food conservation, improved food handling, as well as to the reduced prevalence of tobacco use in men [27-30]. The substantial difference in Japanese rates is due to the historical exceedingly high rates in Japan, and indicates the need for further intervention on modifiable risk factors, besides the value of early diagnosis on survival [31].

Improvements in colorectal cancer management, with the increasing use of colorectal screening and the removal of precancerous adenomas, have favourably influenced the incidence and mortality for this neoplasm [23, 32, 33]. Different patterns in modifiable risk factors, such as those related to nutrition, diet, and smoking, and different access to treatments, could explain the variability across countries.

In contrast to other major cancers, incidence and mortality from pancreatic cancer are still on the rise, particularly among women, and 5-year relative survival remains very low. Pancreatic cancer is usually asymptomatic in the early stages, and without the use of invasive procedures, screening is unable to achieve an effective early diagnosis [34, 35]. The reasons for the unfavourable trends in pancreatic cancer rates remain, however, largely undefined, although the increase in the prevalence of overweight and obesity, and consequently of type II diabetes, may have played a role [36, 37].

The decline in breast cancer mortality, although incidence showed slight increases, is due to improvements in early diagnosis, through organized mammographic screening, but mainly to better management and treatment of the disease [23, 38, 39]. Only Japan did not show a favourable trend in breast cancer mortality and incidence, but rates remained lower than those observed in other areas. Breast size, favourable prenatal growth, and other hormonal factors may partly explain these comparatively low rates [40-42].

With reference to uterine cancer, mortality declined in most countries, except Japan which had, however, the lowest rates throughout the period. Such declines are largely attributable to the widespread use of Pap smear test for screening and early diagnosis [43, 44]. This may have influenced the declines in incidence rates, too.

The favourable trends in ovarian cancer incidence and mortality across all countries considered have been largely attributed to the widespread use of oral contraceptives and the decreased use of hormone replacement therapy use in post-menopause [45-47]. Survival estimates showed small improvements. Again, Japan had the lowest mortality and incidence rates, and, compared to other countries, showed the greatest increases in survival.

Improved early detection and better treatment and management for prostate cancer likely explain the declines in mortality from this neoplasm, though no consistent reductions were found in incidence. This led the 5-year relative survival for this neoplasm to be the highest among the considered cancer sites in all considered countries [23, 48].

Similarly to other tobacco-related cancers, trends were favourable for male bladder cancer also, with an associated high 5-year relative survival. This reflects the decline in smoking prevalence in men and the lower exposure to occupational carcinogens over the last few decades [21, 49].

Although incidence for leukaemias showed rising trends in all countries and for both sexes, mortality registered favourable patterns. This is mainly explained by therapeutic advancements, including better diagnosis, adoption of modern protocols for chemotherapy and immunotherapy assisted by toxicity-limiting therapies, and improved radiotherapy [50, 51].

In conclusion, our analysis confirms that cancer mortality is decreasing globally, with declines for the most common cancers, except pancreatic cancer in both sexes and lung cancer in women. Mortality and incidence rates for lung, colorectal, breast, prostate, and bladder cancers are related to favourable changes in risk factor exposures. This study underlines the increasing need for tobacco control to reduce female lung cancers worldwide. Disparities in mortality, incidence, and survival among countries persist, likely due to variable cancer determinants, diagnosis, and management. Among these, smoking cessation in both sexes, interventional on other major recognize cancer risk factors, advancement in early diagnosis and organized screening, and access to innovative treatments will further improve cancer incidence, mortality, and survival globally.

Cancer mortality in Italian populations: differences between Italy and the USA

Among specific immigrant populations, cancer mortality rates tend to deviate from those in the countries of origin and approach rates of the majority population in the host country at different times, sometimes taking generations. Aside from changes in lifestyle habits, diets, and risk factor exposures, this transition/trajectory may be influenced by host country healthcare-related dependent factors such as access to cancer care and screening, timely diagnosis, and adequate treatment [52, 53].

Previous studies have examined the differences and similarities in cancer patterns between either Italy and the US or between Italy-born Americans and non-Italian US Whites using group data from the 1970s and 1980s [54-56]. However, an analysis between Italian populations only, directly comparing the diaspora (Italy-born Americans) -using individual-level data rather than areas with a high density of Italians - and those in the country of origin, Italy, has never been carried out. The rationale for the current study is that there is genetic similarity between these two populations but differences in lifestyle habits as well remarkable differences in health care systems (a universal health system in Italy, while one linked to employment and social programs in the US) also impact cancer patterns.

In this study, we assess site-specific differences in cancer mortality between two Italian ancestry populations (Italy-born Americans and Italians in Italy), using individual-level mortality data available from Italy and four American states: California, Florida, New York, and Massachusetts, which combined represent over 25% of the US population. The population of Italy-born Americans (approximately 440,000) predominantly consists of elderly individuals in age groups for which cancer is a common cause of death, reflecting the Italian migration to the US up until the late 1960s.

Data Source

Italy-born Americans

Individual-level mortality data by sex and age for all cancers combined and for 20 select cancer sites for Italy-born Americans were obtained from the California, Florida, Massachusetts, and New York Departments of Vital Statistics from 2008-2018. These states were common destinations for the Italian diaspora in the US during the twentieth century. State mortality datasets have close to 99% completeness in terms of country of birth for all deceased subjects [57]. The combined population totals (rate denominators) stratified by five-year age group and sex for the same years were obtained based

on the "non-Hispanic White Race" and "country of birth Italy" categories from the single-year American Community Survey data for the four states combined and pooled for years 2008-2018 [58].

Italians

For the same period of time, we retrieved corresponding official death certificate data and resident population estimates for Italians in Italy (hereafter referred to as Italians), from the WHO database [59].

Cancers of interest

We focused our work on the following 20 cancer sites: stomach, pancreas, colorectum, lung, breast, uterus, ovary, prostate, bladder, leukaemias, plus all cancers combined. See **Supplementary Table 1** for the list of ICD codes used.

RESULTS

Table 1 shows the age-standardized (EU standard population) death rates by sex for the Italy-born American (2008-2018) and the Italian populations (2008-2016). The all-combined cancer death rate in Italy-born Americans was 260.3/100,000 and 154.6/100,000 for men and women, respectively, while for Italians it was 345.7/100,000 for men and 192.4/100,000 for women.

Table 1. Age-adjusted (European standard population) mortality rates per 100,000 for various cancers for all ages and both sexes, 2008-2018.

	Men				**Women**			
	Italy-born Americans		**Italians[a]**		**Italy-born Americans**		**Italians[a]**	
	ASMR	**Deaths[a]**	**ASMR**	**Deaths**	**ASMR**	**Deaths[a]**	**ASMR**	**Deaths**
Oral cavity and pharynx	2.89	63	7.03	17,819	1.69	43	2.31	7912
Esophagus	4.05	91	4.91	12,336	1.00	33	1.18	4126
Stomach	10.24	253	20.86	51,431	4.61	124	10.36	36,903
Colorectal	23.43	554	42.28	103,324	17.26	468	25.14	90,004
Primary liver cancer	14.06	328	22.93	57,465	6.32	183	8.61	30,416
Gallbladder	1.25	31	1.29	3165	1.40	38	1.92	6631
Pancreas	16.96	395	18.95	47,431	13.82	410	14.49	50,402
Lung	73.26	1756	89.52	223,537	23.23	611	23.74	78,739

Skin melanoma	3.40	74	3.89	9864	1.66	34	2.09	6902
Breast	‡	‡	‡	‡	25.66	593	32.73	109,576
Cervix	‡	‡	‡	‡	1.23	23	1.23	3877
Corpus	‡	‡	‡	‡	5.20	134	6.72	22,481
Ovary	‡	‡	‡	‡	8.54	208	9.11	29,685
Prostate	24.22	586	28.58	66,389	‡	‡	‡	‡
Bladder	14.93	382	16.85	40,181	2.42	89	2.96	11,019
Kidney	7.55	125	10.14	25,082	1.89	56	3.64	12,766
Brain and CNS	7.47	156	7.57	19,571	5.40	107	5.01	15,857
Non-Hodgkin's lymphomas	9.98	244	9.07	22,527	6.12	190	5.60	19,507
Multiple myeloma	4.96	124	5.86	14,421	3.80	107	4.03	14,138
Leukemia	12.79	310	12.28	30,141	7.73	180	6.93	24,144
All malignant cancers	260.33	6168	345.69	851,923	154.55	4101	192.39	661,937

Abbreviations: ASMR, Age standardized mortality rate; CNS, Central Nervous System.

[a] 2008-2016 for Italy (WHO data).

‡ Not reported; rate calculated from observations fewer than 10.

Among Italy-born American males, the ranking top causes of cancer death in decreasing order were lung, prostate, colorectal, pancreas, and bladder. For Italian males, it was lung, colorectal, prostate, liver, and stomach. Italian males showed higher cancer mortality rates compared to Italy-born Americans for all sites except non-Hodgkin's lymphoma and leukemia. Among Italy-born American females, the top causes of cancer death were breast, lung, colorectal, pancreas, and ovary. For Italian women, the rank order was breast, colorectal, lung, pancreas, and stomach. Despite the different rank order, second and third among Italy-born Americans and Italians, respectively, mortality rates for lung cancer in the groups of interest are quite similar: 23.2 in Italy-born American females and 23.7 per 100,000 in Italians.

Table 2 reports the SMRs of select cancer sites for Italy-born Americans compared to the general population of Italy. Among Italy-born Americans, the SMR for all cancer deaths was 0.75 (95% CI 0.73-0.77) in men and 0.78 (95% CI 0.76-0.80) in women. For most cancers, the SMRs were below 1 and were particularly low for neoplasms of the digestive tract: 0.42 in men and 0.69 in women for oral and pharyngeal cancer; 0.51 for men and 0.40 for women for the stomach; 0.54 for men and 0.61 for women for colorectal; 0.62 for men and 0.72 for women for liver cancer. Among Italy-born American males, lower mortality was observed for kidney (SMR: 0.52, 95% CI 0.43-0.62), prostate (SMR: 0.78, 95%CI 0.72-0.84), lung (SMR: 0.83, 95% CI 0.79-0.87), and bladder cancer (SMR: 0.89, 95% CI 0.80-0.98). Among females, the SMRs were lower than 1 for kidney (SMR: 0.53, 95% CI 0.40-0.68), skin melanoma (SMR: 0.70, 95% CI 0.49-0.96), breast (SMR: 0.73, 95% CI 0.67-0.79) and corpus uteri (SMR: 0.78, 95% CI 0.65-0.91). Non-Hodgkin's lymphoma (NHL) was the only

neoplasm with a SMR significantly above one for both sexes (SMR: 1.16, 95% CI 1.02-1.31 males and 1.21, 95% CI 1.04-1.39 females).

Table 2. Standardized mortality ratios for select cancers in Italy-born Americans versus Italians for both sexes, 2008-2018.

	Males		Females	
	Italy-born Americans		Italy-born Americans	
	SMR	95% CI	SMR	95% CI
Oral cavity and pharynx	0.42	0.32-0.53	0.69	0.50-0.91
Esophagus	0.83	0.67-1.01	0.98	0.67-1.34
Stomach	0.51	0.45-0.57	0.40	0.33-0.48
Colorectal	0.54	0.50-0.59	0.61	0.56-0.67
Primary liver cancer	0.62	0.55-0.69	0.72	0.62-0.83
Gallbladder	0.99	0.67-1.36	0.70	0.50-0.94
Pancreas	0.90	0.82-1.00	0.99	0.90-1.09
Lung	0.83	0.79-0.87	1.02	0.94-1.10
Skin melanoma	0.90	0.70-1.11	0.70	0.49-0.96
Breast	‡	‡	0.73	0.67-0.79
Cervix	‡	‡	0.99	0.62-1.43
Corpus	‡	‡	0.78	0.65-0.91
Ovary	‡	‡	0.97	0.84-1.10
Prostate	0.78	0.72-0.84	‡	‡
Bladder	0.89	0.80-0.98	0.90	0.72-1.10
Kidney and other urinary sites	0.52	0.43-0.62	0.53	0.40-0.68
Brain and CNS	1.05	0.89-1.22	1.00	0.82-1.20
Non-Hodgkin's lymphomas	1.16	1.02-1.31	1.21	1.04-1.39
Multiple myeloma	0.87	0.72-1.03	0.91	0.75-1.09
Leukemia	1.08	0.96-1.20	0.93	0.80-1.07
All malignant cancers	0.75	0.73-0.77	0.78	0.76-0.80

Abbreviations: SMR, Standardized mortality ratio; CI, Confidence Interval; CNS, Central Nervous System.

When we stratified mortality data in people younger than 75 and people aged 75 or older we did not find differences in the SMRs, except for cancers of the stomach, lung, brain and CNS, and NHL whose SMRs were lower among men younger than 75 (data not shown). Among females, the SMR for all cancers combined was 0.80 (95% CI 0.76-0.84) for those below 75 years of age and 0.77 (95% CI 0.74-0.80) for women ages 75 years old or more. No significant differences in SMRs were observed between age-groups for women.

DISCUSSION

Mortality rates for all cancers combined and for most major sites were lower in Italy-born Americans compared to Italians. Overall, cancer mortality of the digestive tract (oral, stomach, colorectal, liver), tobacco-related cancers (lung and bladder) among males, as well as kidney and breast cancer were

lower in Italy-born Americans compared to Italians. NHL was the only cancer for which Italy-born Americans showed higher mortality rates than Italians for both sexes.

In the two countries, mortality patterns for tobacco-related cancers, particularly lung cancer, follow the smoking prevalence patterns observed across generations. In US males, the smoking prevalence has been decreasing since 1964 [60], much earlier than in Italy, with subsequent declines in lung cancer death rates after three decades (i.e., around the early 1990s) [61, 62]. In the US, women started smoking earlier and at higher rates than in Europe; however, smoking prevalence has stabilized and even declined slightly in recent years, also earlier than in Europe [21]. Therefore, female lung cancer trends started to decline around the 2000s in the US, while in most European countries the female lung cancer epidemic is still developing [61-63]. In 2020, lung cancer rates in Italy approach 13/100,000 (world standard), having never reached the highest rates of about 26/100,000 observed among US females during the early 1990s [64]. These differences in time and magnitude of smoking prevalence trends by sex explain the significant differences found here for tobacco-related cancers such as lung and bladder cancer in men (with higher rates in Italy), and the lack of difference between women of Italian ancestry in the US and Italy.

Italy-born Americans had particularly low rates for other tobacco-related cancers, such as kidney and oral cancer in comparison to Italians. For kidney cancer, obesity and hypertension are important risk factors aside from smoking [65]. The prevalence of obesity in Italy is lower than that in the US [66, 67]. However, the most recent data available for 2014 has shown that 55% of adults suffer from hypertension in comparison to 42% of adults in the US for that year [68, 69], and management of hypertension may be less effective in Italy. Along with the observed differences in smoking patterns amongst countries, this could partly account for the findings in our study. For oral cancer, it is known that tobacco and alcohol use increases the risk of developing this malignancy. Our findings parallel the smoking patterns observed in both countries, and they are in contrast to the greater alcohol per capita consumption and prevalence of heavy episodic drinking in the US compared to Italy [70]. However, specific data for alcohol consumption among Italy-born Americans is non-existent.

Colorectal cancer is the second or third most common cause of cancer deaths among Italy-born Americans and Italians of both sexes. Widespread screening for colorectal cancer started earlier in the US [71], reaching the participation of about 40% of the target population in 2012 [72]. Meanwhile, in Italy, organized screening was introduced in select regions around 2005 and less than 30% of the target population participated in 2014 [73]. This can partly explain the lower mortality among Italy-born Americans. Moreover, there has been notable progress in the management and treatment of

colorectal cancer in the US [72, 73] while variations in access to effective treatment between the US and Italy can explain some of these differences.

Breast cancer is the second major cause of cancer death among US women after lung cancer [74]. However, it is the leading cause of cancer deaths in both Italy-born American and Italian women. Over the last three decades, rates for this cancer site have declined by about 40% in the US and 30% in Italy [75, 76]. This decline has been mainly driven by improvements in treatments as well as uptake of mammographic screening over the past several decades [62, 73], which has been earlier on and more widespread in the US and consequently among Italy-born Americans [72, 77]. As is the case for colorectal cancer, data suggest that breast cancer screening prevalence is higher in the US, approaching nearly 73%, compared to 39% of women in Italy who participate in organized breast cancer screening programs [78, 79].

Italy-born Americans also had lower mortality compared to Italians for some infection-related cancers such as stomach and liver. *Helicobacter pylori* (*H. pylori*) is the key risk factor for gastric cancer. Differences in gastric mortality between Italy-born Americans and Italians are attributable to the variations in the prevalence of infection. Indeed, *H. pylori* prevalence in the US general population is around 30% [80], while in Italy it is much higher, around 56% [81], particularly among the elderly [82]. For liver cancer, the high rates in Italians are attributable to a higher prevalence of chronic infection with hepatitis B (HBV) and C (HCV) viruses [83] and possibly higher regular alcohol consumption in Italy [84, 85]. Overall, HCV and HBV prevalence are 5.9% and 0.7% in Italy, which are higher when compared to the US population corresponding estimates of 1.0 % and 0.3% [86-88]. In the US, the mortality and incidence for liver cancer and hepatocellular carcinoma (HCC), specifically, is predominantly HCV-related [89] while in Western European countries, a high proportion of liver cancer cases are related to alcohol and/or metabolic conditions [90-92]. There were no significant differences in mortality for cervical cancer amongst Italy-born American and Italian women. This parallels the similar prevalence of human papillomavirus (HPV) among women in the general population in Italy and the US, with 4.1% and 3.3%, respectively [93, 94]. Unlike in the US, in Italy, there is no organized screening program for cervical cancer, since a large portion of young and middle-aged women undergo voluntary screening. However, despite our findings, compared to the US, the proportion of women who participate in cervical cancer screening in Italy, remains low [78, 79].

Over the last two decades, favorable mortality rates for prostate cancer are attributed to improvements in treatments (surgery, radiotherapy, as well as the use of newer androgen deprivation therapies) and more widespread use of prostate-specific antigen (PSA) testing, particularly in the US. The

combination of wider use of PSA testing and more aggressive treatment in the US may well justify this advantage for Italy-born Americans in comparison to Italians. Substantial advantages in mortality rates for prostate cancer among US immigrant populations in comparison to their countries of origin are also found for other nationalities in the USA [95].

Strengths of this study include its population-based design and the granular nature of its data, namely the availability of individual-level death data for Italy-born Americans and the availability of specific denominators for Italy-born populations in the USA through the American Community Survey. Mortality certification in both the USA and Italy is valid for most cancers, and changes in classification, coding, and registration are unlikely to affect our results. Moreover, death certificate criteria did not change over time and are similar between the USA and Italy. Therefore, the observed differences in cancer mortality between Italy-born Americans and Italians are unlikely to be affected by major bias. However, our study is not without limitations. This includes the lack of specific data on socio-economic status and risk factors, particularly for the Italy-born American population; the only data available is for the non-Hispanic White USA population. The healthy immigrant effect could account for a baseline inherent difference between the two populations, with an advantage for those who emigrate (i.e., Italy-born Americans). However, when considering cancer, a chronic disease for which the latency periods between risk factor exposures and actual diagnosis may take decades, this healthy immigrant advantage in relation to those in the country of origin has not been observed on a population basis [95].

As a whole, the overall lower mortality rates in Italy-born Americans can be attributed to lower levels of smoking prevalence earlier on (especially among males), earlier and greater adoption of modern effective treatments, and a higher screening coverage for selected neoplasms [72, 73]. This line of reasoning can be applied to several cancer sites [76] including tobacco-related cancers such as lung and bladder as well as screening-related cancers like breast, colorectal, and prostate. It is of interest that despite the worldwide accepted beneficial effects of the Mediterranean diet (albeit more so for heart disease), possibly more prevalent in Italy as a Mediterranean country, this "advantage" is not reflected in the cancer mortality rates shown here for digestive cancers as a whole. Italians showed higher rates for most digestive cancers in comparison to Italy-born Americans, a group that could have possibly adopted different dietary preferences over time given the assimilation to a new environment. Having said that, mortality rates capture both incidence and survival, and referred factors such as accessibility to treatment and screening may impact the current rates by means of improved survival; therefore, more detailed studies are necessary. In agreement with this, survival statistics for recent calendar

periods show that the five-year relative survival for major cancer sites, except for stomach cancer, is higher in the USA than in Italy [63].

In conclusion, despite the absence of a national health service in the US, cancer mortality was lower for Italy-born Americans than Italians. Our mortality data suggests that, based on the comparison of patterns in populations of Italian descent, on a population basis, cancer prevention, screening, and management seem more effective in the USA as compared to Italy. More detailed studies focusing on comparisons of population-based indicators in more homogenous populations, in terms of ancestry, socio-economic status, and race-ethnicity are essential in order to more clearly ascertain the end results of different health systems.

Following the same structure of this article, I conducted the analyses for an article that compares cancer mortality between Germans and Germany-born Americans. We are now finalizing the article for submitting it.

Mortality trends from urologic cancers in Europe over 1980-2017 and a projection to 2025

Working on this project, I had the opportunity to learn how to project temporal trends of a specific cause of death. Under the supervision of my tutor, we analyzed temporal trends from prostate, testis, bladder, and kidney cancers [96]. Using the join point program, we also predict mortality rates for the calendar year 2025.

Over the last two decades, urologic cancers, including prostate, testis, and bladder showed declines in mortality in most of Europe, with some exceptions in eastern and central European countries [61, 97]. Trends were more difficult to interpret for kidney cancer. Therapeutic advances for testicular and also prostate cancer, reductions in exposure to tobacco smoking, and occupational carcinogens for bladder cancer mostly contributed to the observed favorable patterns.
We updated figures for mortality trends in Europe using the WHO database over the period 1980-2017. We carried out a time-trend analysis for 36 European countries using the official WHO database.

We extracted the number of deaths and population data and calculated ASMRs for each cancer considered, sex, country, and the EU (27), at all ages and at age 35-64 for prostate, bladder, and kidney, and 20-44 for testis, over the 1980-2017 period. For selected major countries, we carried out a joinpoint regression analysis to identify significant changes in trends. We also predicted the number of deaths and rates for 2025, using a logarithmic Poisson count data joinpoint regression model.

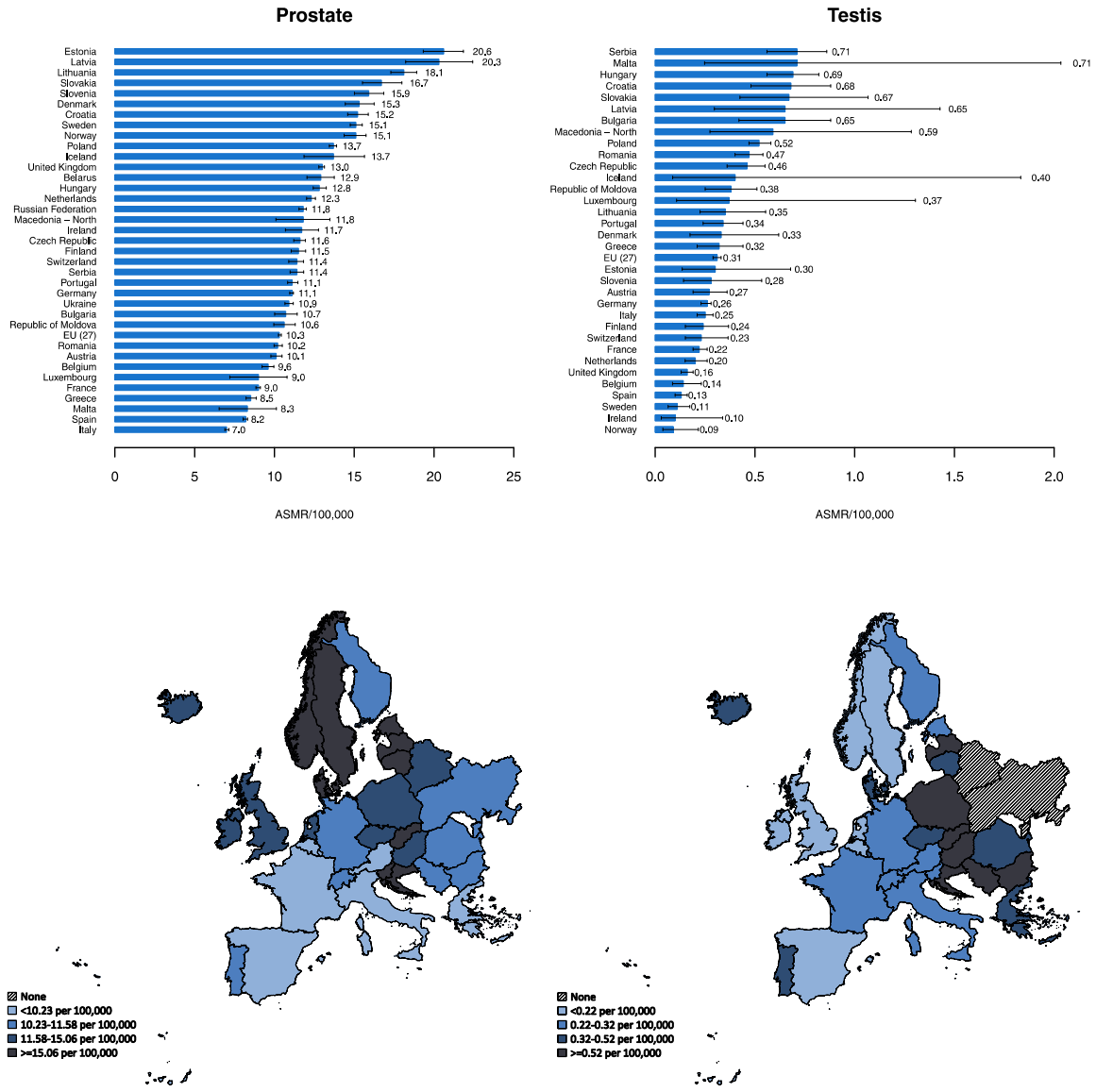
RESULTS

Prostate cancer mortality in the EU decreased over recent years, reaching a rate of 10.3/100,000 in 2015 and a projected rate of 8.9 in 2025. Less favourable trends were observed in eastern Europe, though starting from relatively low rates. Testicular cancer mortality declined over time in most countries, however levelling off in northern and western countries, after reaching very low rates. EU testicular cancer mortality rate in 2015 was 0.31/100,000 at all ages and 0.56 at 20-44. Bladder cancer mortality trends were less favourable in central and eastern countries compared to northern and western ones. The EU rates in 2015 were 5.1/100,000 men and 1.1 women. Kidney cancer mortality showed less favourable trends, with a slight increase in men and stable rates in women over the last decade in the EU.

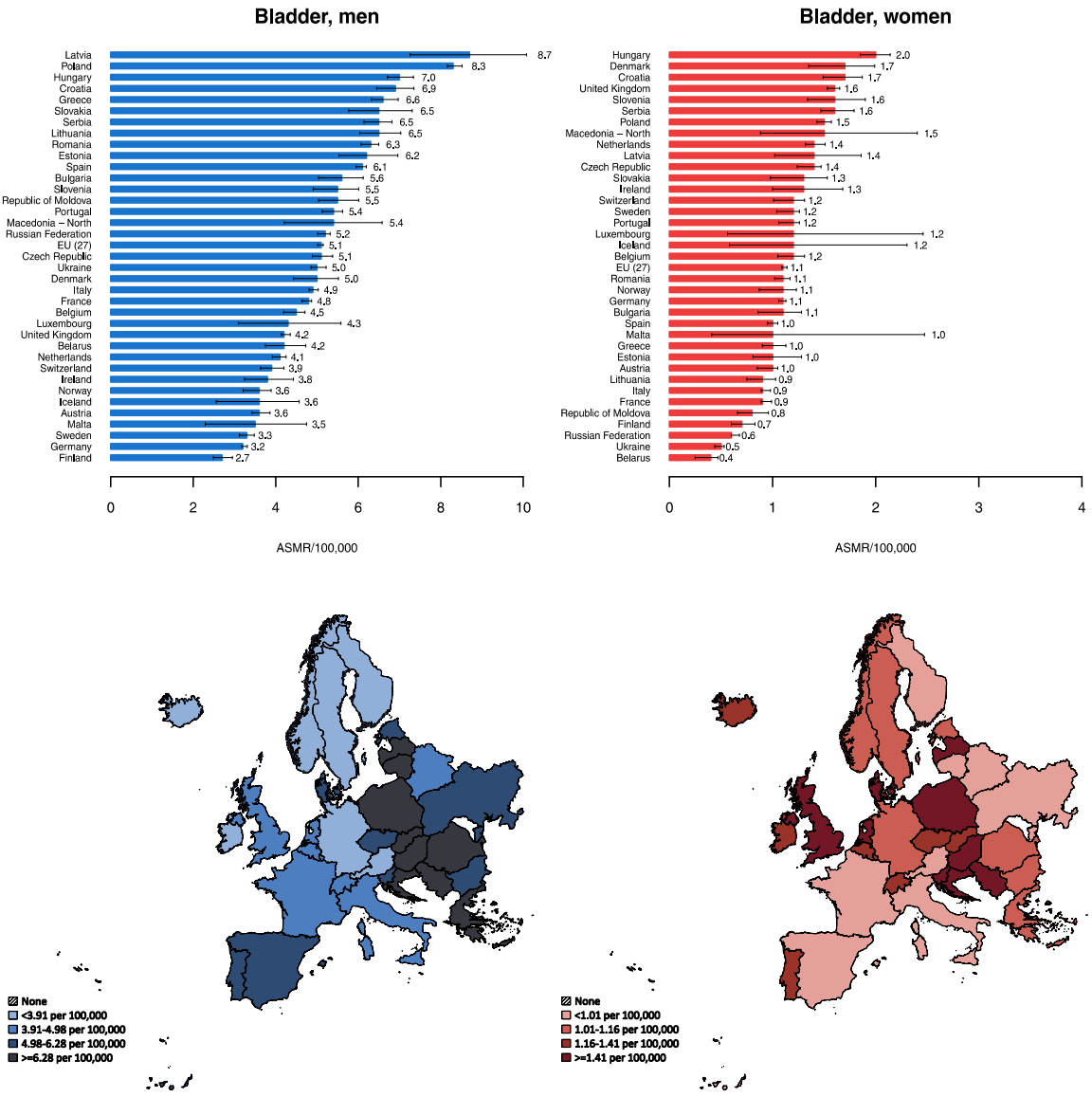
Figure 1. Age-standardized mortality (world population) mortality rates per 100,000 and the corresponding 95% confidence intervals (CI) in the 36 European countries and the EU (27), in 2015-

2017 (according to data availability), for cancers of prostate and testis (panel A), bladder (panel B), and kidney and other urinary organs (panel C).

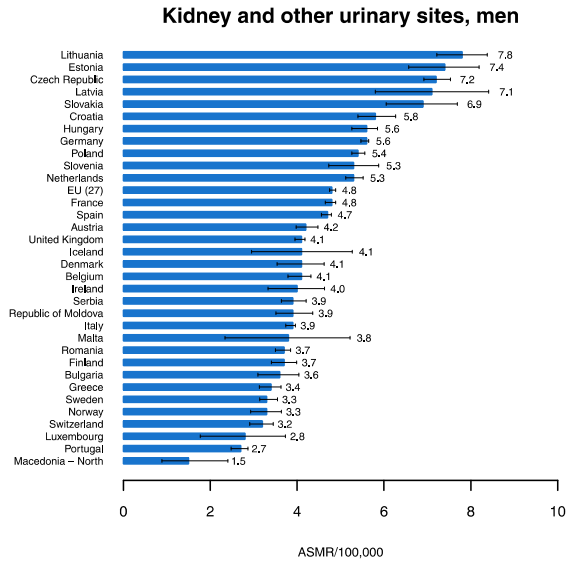
Panel A)

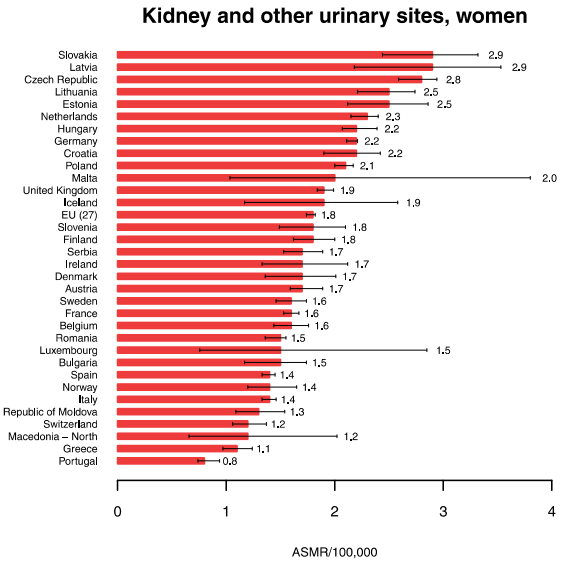


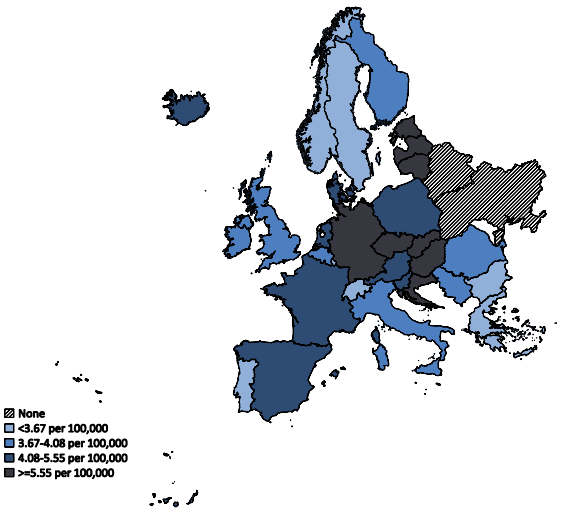
Panel B)


Bladder, men
Latvia 8.7
Poland 8.3
Hungary 7.0
Croatia 6.9
Greece 6.6
Slovakia 6.5
Serbia 6.5
Lithuania 6.5
Romania 6.3
Estonia 6.2
Spain 6.1
Bulgaria 5.6
Slovenia 5.5
Republic of Moldova 5.5
Portugal 5.4
Macedonia – North 5.4
Russian Federation 5.2
EU (27) 5.1
Czech Republic 5.1
Ukraine 5.0
Denmark 5.0
Italy 4.9
France 4.8
Belgium 4.5
Luxembourg 4.3
United Kingdom 4.2
Belarus 4.2
Netherlands 4.1
Switzerland 3.9
Ireland 3.8
Norway 3.6
Iceland 3.6
Austria 3.6
Malta 3.5
Sweden 3.3
Germany 3.2
Finland 2.7
0 2 4 6 8 10
ASMR/100,000
Bladder, women
Hungary 2.0
Denmark 1.7
Croatia 1.7
United Kingdom 1.6
Slovenia 1.6
Serbia 1.6
Poland 1.5
Macedonia – North 1.5
Netherlands 1.4
Latvia 1.4
Czech Republic 1.4
Slovakia 1.3
Ireland 1.3
Switzerland 1.2
Sweden 1.2
Portugal 1.2
Luxembourg 1.2
Iceland 1.2
Belgium 1.2
EU (27) 1.1
Romania 1.1
Norway 1.1
Germany 1.1
Bulgaria 1.1
Spain 1.0
Malta 1.0
Greece 1.0
Estonia 1.0
Austria 1.0
Lithuania 0.9
Italy 0.9
France 0.9
Republic of Moldova 0.8
Finland 0.7
Russian Federation 0.6
Ukraine 0.5
Belarus 0.4
0 1 2 3 4
ASMR/100,000
None
<3.91 per 100,000
3.91-4.98 per 100,000
4.98-6.28 per 100,000
>=6.28 per 100,000
None
<1.01 per 100,000
1.01-1.16 per 100,000
1.16-1.41 per 100,000
>=1.41 per 100,000

Panel C)


Kidney and other urinary sites, men
Lithuania 7.8
Estonia 7.4
Czech Republic 7.2
Latvia 7.1
Slovakia 6.9
Croatia 5.8
Hungary 5.6
Germany 5.6
Poland 5.4
Slovenia 5.3
Netherlands 5.3
EU (27) 4.8
France 4.8
Spain 4.7
Austria 4.2
United Kingdom 4.1
Iceland 4.1
Denmark 4.1
Belgium 4.1
Ireland 4.0
Serbia 3.9
Republic of Moldova 3.9
Italy 3.9
Malta 3.8
Romania 3.7
Finland 3.7
Bulgaria 3.6
Greece 3.4
Sweden 3.3
Norway 3.3
Switzerland 3.2
Luxembourg 2.8
Portugal 2.7
Macedonia – North 1.5
0 2 4 6 8 10
ASMR/100,000


Kidney and other urinary sites, women
Slovakia 2.9
Latvia 2.9
Czech Republic 2.8
Lithuania 2.5
Estonia 2.5
Netherlands 2.3
Hungary 2.2
Germany 2.2
Croatia 2.2
Poland 2.1
Malta 2.0
United Kingdom 1.9
Iceland 1.9
EU (27) 1.8
Slovenia 1.8
Finland 1.8
Serbia 1.7
Ireland 1.7
Denmark 1.7
Austria 1.7
Sweden 1.6
France 1.6
Belgium 1.6
Romania 1.5
Luxembourg 1.5
Bulgaria 1.5
Spain 1.4
Norway 1.4
Italy 1.4
Republic of Moldova 1.3
Switzerland 1.2
Macedonia – North 1.2
Greece 1.1
Portugal 0.8
0 1 2 3 4
ASMR/100,000


None
<3.67 per 100,000
3.67-4.08 per 100,000
4.08-5.55 per 100,000
>=5.55 per 100,000

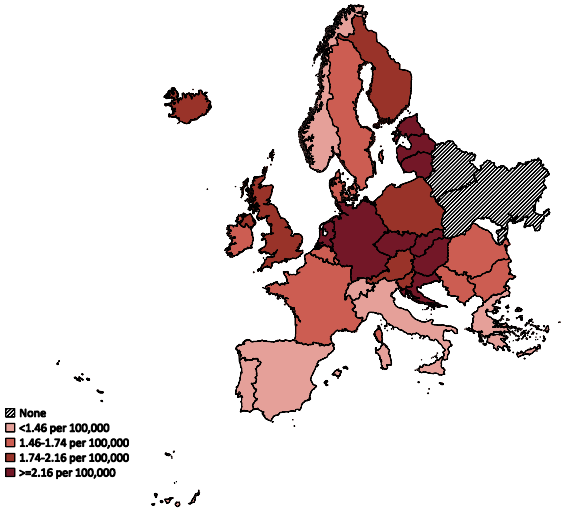
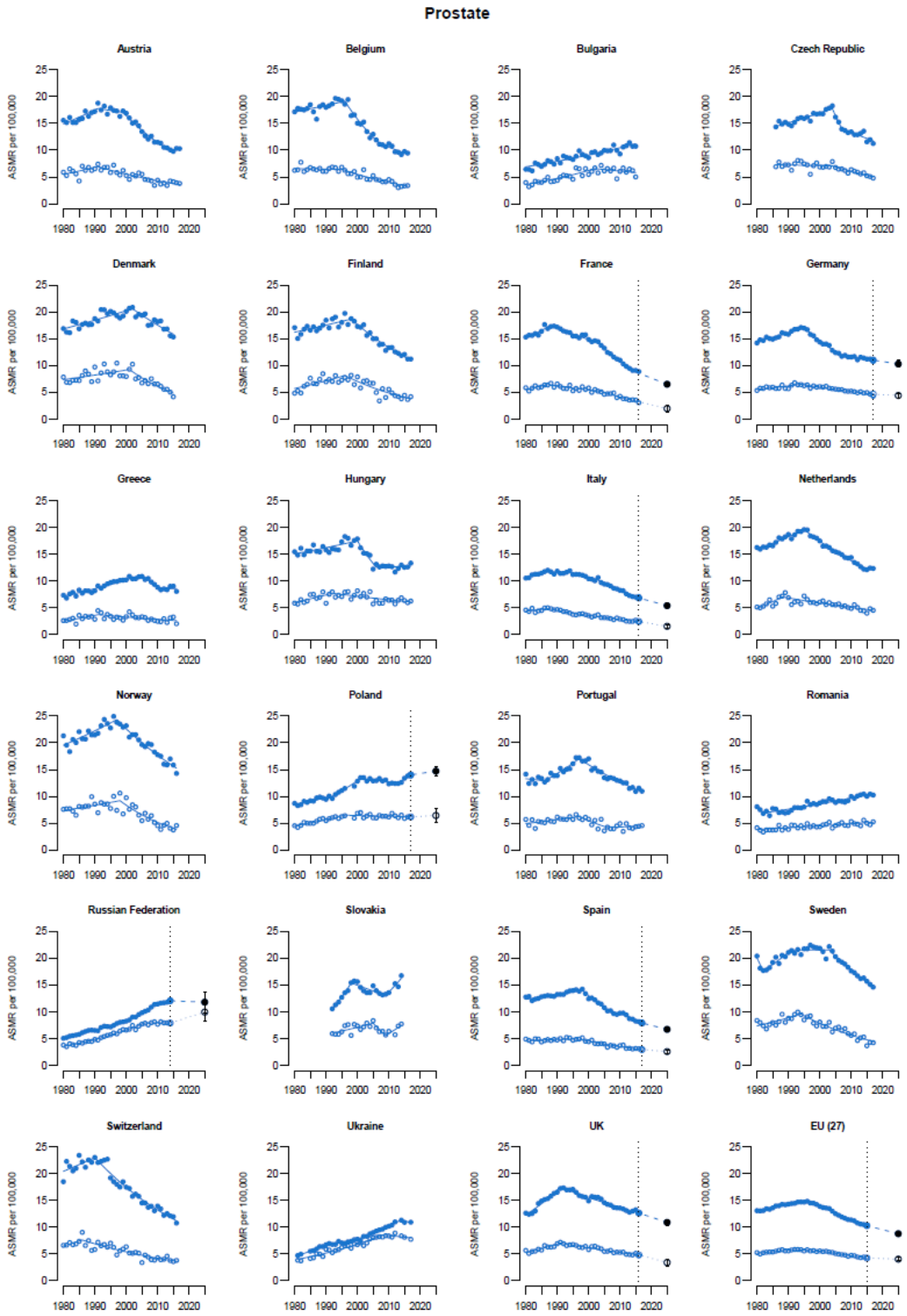
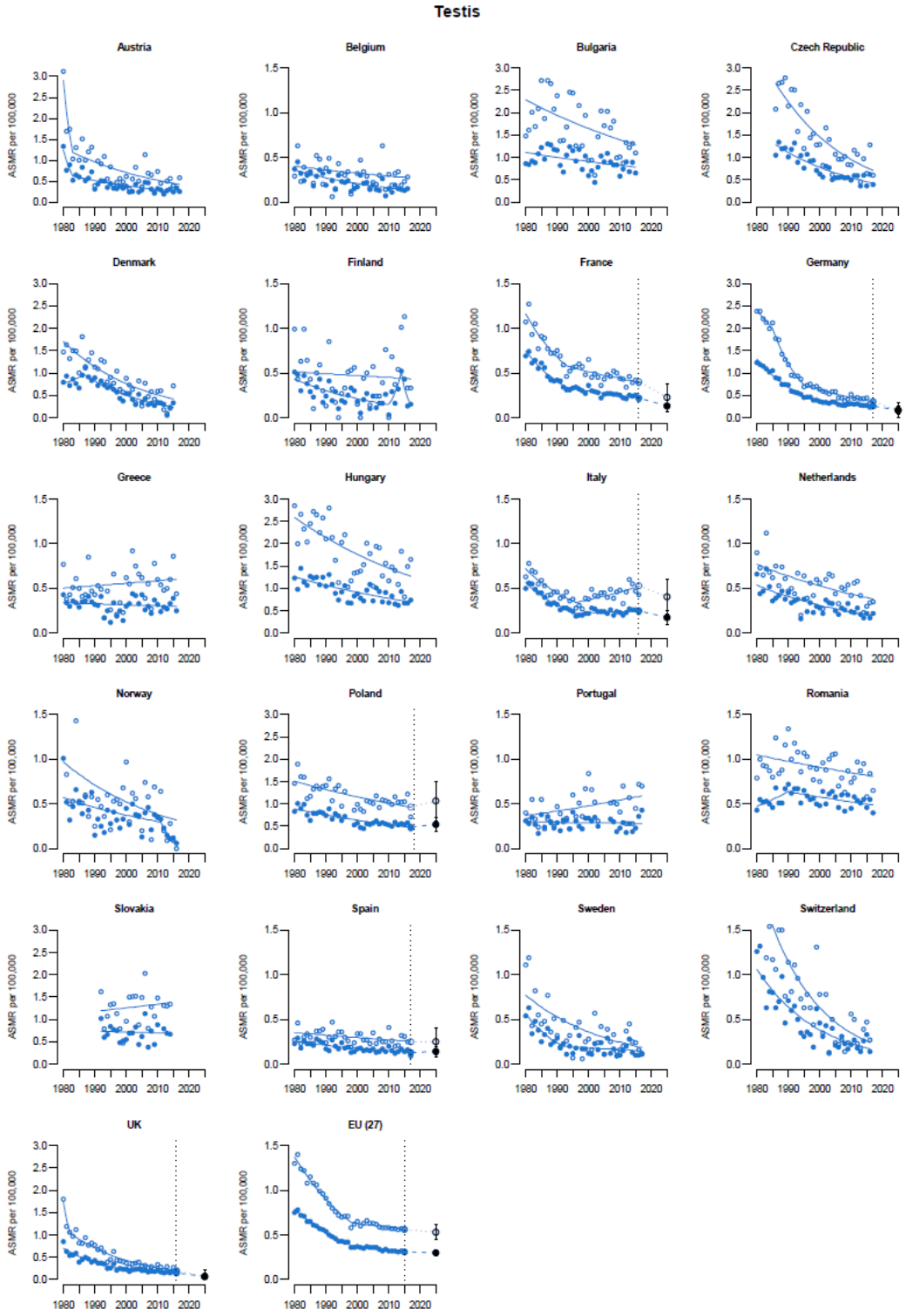
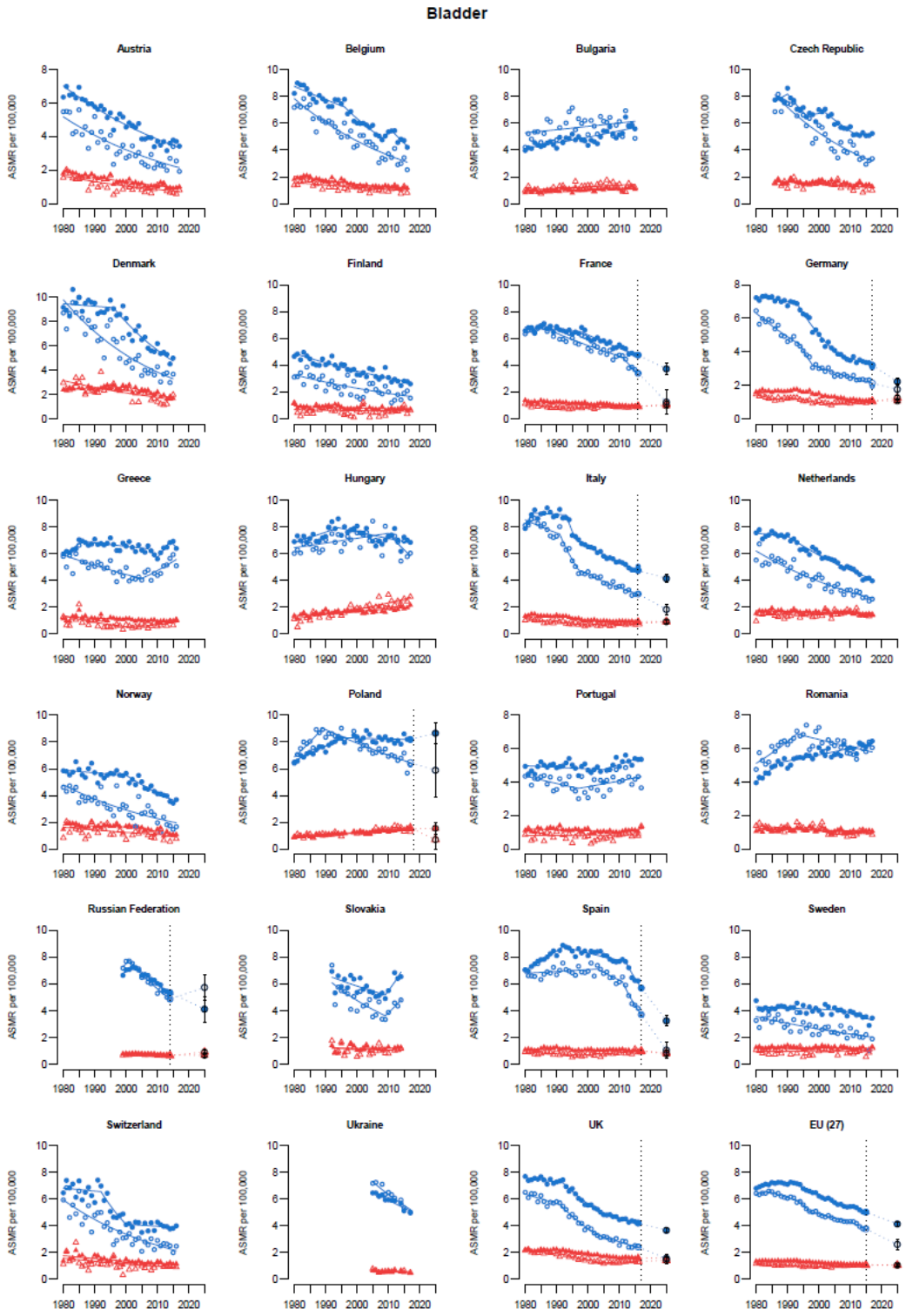

None
<1.46 per 100,000
1.46-1.74 per 100,000
1.74-2.16 per 100,000
>=2.16 per 100,000

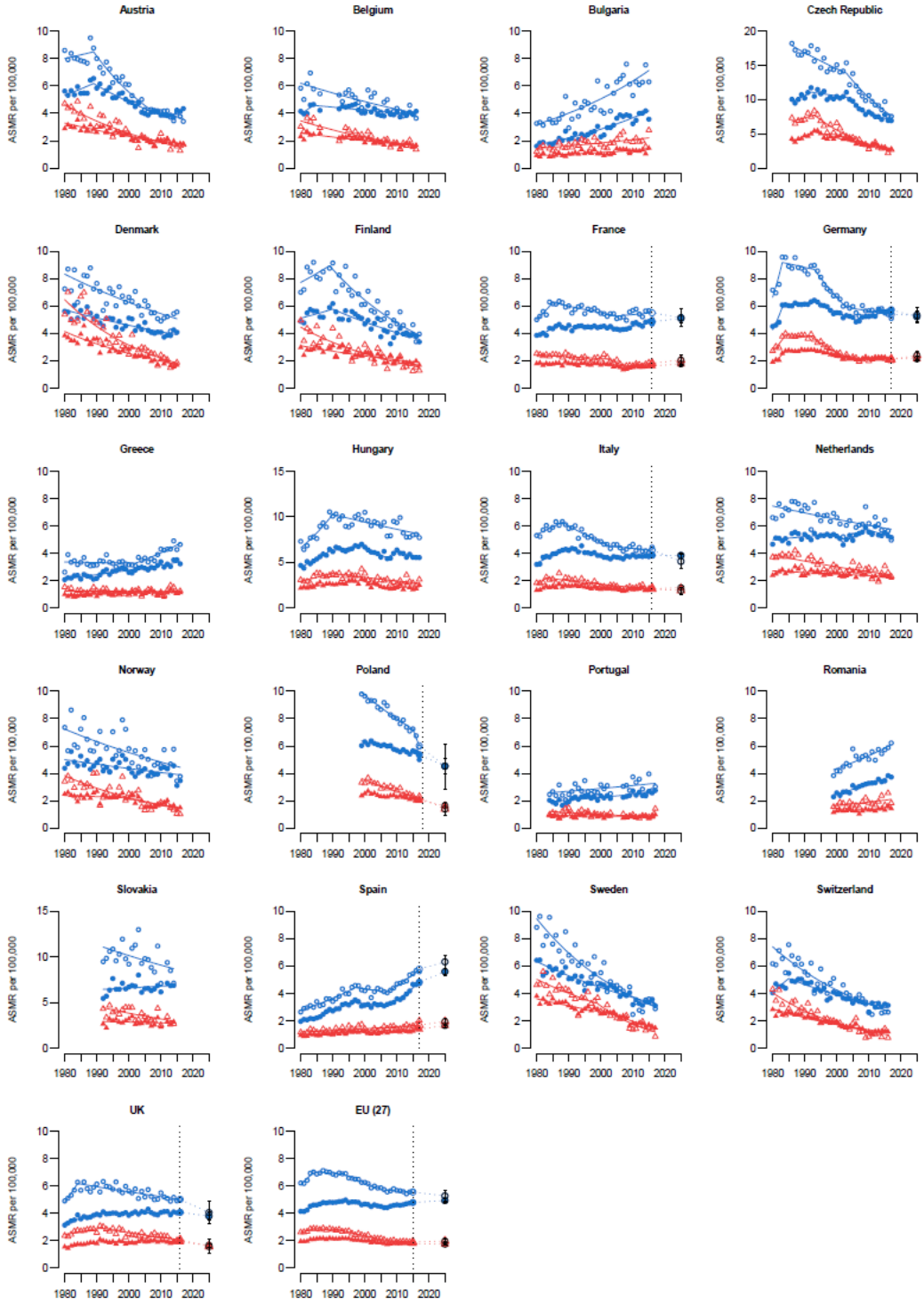
Figure 2. Joinpoint analysis for mortality from the urologic cancers sites in 24 selected major European countries during the period 1980–2017, and the predicted rates for France, Germany, Italy, Poland, the Russian Federation, the UK and the EU (27) for the year 2025.




Testis
Austria
Belgium
Bulgaria
Czech Republic
Denmark
Finland
France
Germany
Greece
Hungary
Italy
Netherlands
Norway
Poland
Portugal
Romania
Slovakia
Spain
Sweden
Switzerland
UK
EU (27)
ASMR per 100,000
1980 1990 2000 2010 2020


Bladder
Austria
Belgium
Bulgaria
Czech Republic
Denmark
Finland
France
Germany
Greece
Hungary
Italy
Netherlands
Norway
Poland
Portugal
Romania
Russian Federation
Slovakia
Spain
Sweden
Switzerland
Ukraine
UK
EU (27)
ASMR per 100,000
1980 1990 2000 2010 2020

Kidney and other urinary sites



DISCUSSION

In the EU (27), mortality rates from prostate and male bladder cancer continued to decline while those from testicular, female bladder, and kidney cancers were less consistent. There are appreciable differences among European countries, with less favourable trends generally taking place in some eastern countries.

In most countries considered, the decline in prostate cancer mortality rates is consistent over time [61, 98]. These favourable trends reflect the adoption of prostate-specific antigen (PSA) and advances in prostate cancer therapy and management [48, 99]. A decline in incidence trends and a levelling of mortality ones were observed in the US [100, 101], where there was a major decline in the introduction of PSA, following the US Preventive Services Task Force upgraded recommendations in 2018 [101, 102]. A recent study conducted in US on prostate incidence trends for different stages, found an increase of more advanced stages than local ones, according to the lower usage of PSA-based screening [103]. Appreciable decreases in mortality are evident in most western European countries, while countries from eastern Europe still show unfavourable trends, though starting from relatively low rates. Moreover, there are unexplained differences in rates among the high-income countries considered. Northern countries have rates twofold higher than Italy or other Mediterranean countries, which reported the lowest rates. This geographical variability in trend over time remains largely unexplained but may be in part due to a delayed and still limited access to modern effective treatments in selected central and eastern European countries [61, 104-106].

Testicular cancer is a relatively common neoplasm among young men at age 20-44. However, this neoplasm is highly curable and, though the incidence has been increasing [107], mortality continues to decline in most of Europe since the introduction of effective treatments in the 1970s. However, there was a recent tendency to level off in northern and western countries, as in North America and Japan [108], after reaching very low rates (less than 0.25/100,000). This pattern lagged in eastern European countries, likely due to inadequate availability and adoption of effective treatments [109]. The relative

5-year survival estimated in eastern European countries was estimated ten points lower than that in the other areas (82% vs 90-93% in 2005-2007) [110]. These persistent geographical disparities reinforce the need to ensure equity in testicular cancer care across Europe [111].

Incidence and mortality trends from bladder cancer have been declining in men in most European countries, although small increases were observed in selected southern and eastern European countries, as well as in the Baltic ones [49, 63], while there were some increasing trends among women. The favourable trends in mortality from this neoplasm are due to improvements in treatment [101, 112], such as endoscopic resection, adjuvant instillation chemotherapy, and intravesical immunotherapy [113]. Tobacco smoking and past occupational exposure to carcinogens remain the major determinants of bladder cancer [101, 114]. Thus, differences in mortality between sexes and countries analysed could be explained by the past and current prevalence of those two risk factors [115].

Some declines in mortality from kidney cancer started in the 1990s in most northern and western European countries, but it has been slowing down during the last decade, with an increase by about 7% in the EU rates in men over the last decade. However, substantial geographical differences remain, with the most favourable trends observed in selected Nordic countries, while the unfavourable ones are in eastern countries. Patterns in kidney cancer mortality can be linked to tobacco smoking and obesity [116-118]. Although the reduction of the prevalence of tobacco smoking can at least partly explain the long-term decreases in mortality in men since the 1990s, it remains among the most contributors accounting for about one-third of the male kidney cancer deaths [119]. In eastern European countries, the increasing mortality can be a consequence of the increasing prevalence of smokers in successive birth cohorts [117, 120]. Obesity can partly explain unfavourable patterns, particularly in women [118, 119]. Other risk factors, such as hypertension [121], occupational exposures [122], and selected dietary factors [123], may also have a role in mortality from kidney cancer, but their impact remains unquantified [124].

Mortality from prostate, testis, and bladder but not kidney declined in most European countries, but with less favourable trends in most eastern countries.

After we finalized the publications, I had the opportunity to write a chapter titled *Epidemiologia del tumore alla prostata nello scenario europeo* [125] as a part of the book "Tumore alla prostata. Stato dell'arte e nuove prospettive" (Libro bianco 2022 - Fondazione Onda). I wrote a global epidemiology overview of prostate cancer, describing the incidence, mortality, and survival nowadays and over time in Europe. Moreover, I discussed artifacts, risk factors, and advances in diagnosis, treatments, and management of prostate cancer.

OTHER PROJECTS RELATED TO MORTALITY TRENDS

Oral and pharyngeal cancer incidence and mortality [126]

Main points

Changes in tobacco and alcohol exposure in men over the last decades likely explain the favourable trends in oral and pharyngeal cancer mortality and incidence observed in selected countries worldwide, while increased HPV infection is likely responsible for the rise in oropharyngeal cancer incidence.

Childhood cancer mortality trends in the Americas and Australasia: An update to 2017 [127]

Main points

Advances in childhood cancer management have substantially improved the burden of these neoplasms over the past 40 years, particularly in high-income countries. Our study aimed to monitor recent trends in America and Australasia, using mortality data from the World Health Organization. Trends in childhood cancer mortality continued to decline in high-income countries, by around 2-3% per year in Japan, Korea, and Australia, and 1-2% in North America. Only a few Latin American countries showed favourable trends, including Argentina, Chile, and Mexico, whereas other countries with limited resources still lag behind.

Colorectal Cancer Mortality in Young Adults Is Rising in the United States, Canada, United Kingdom, and Australia but Not in Europe and Asia [128]

Main points

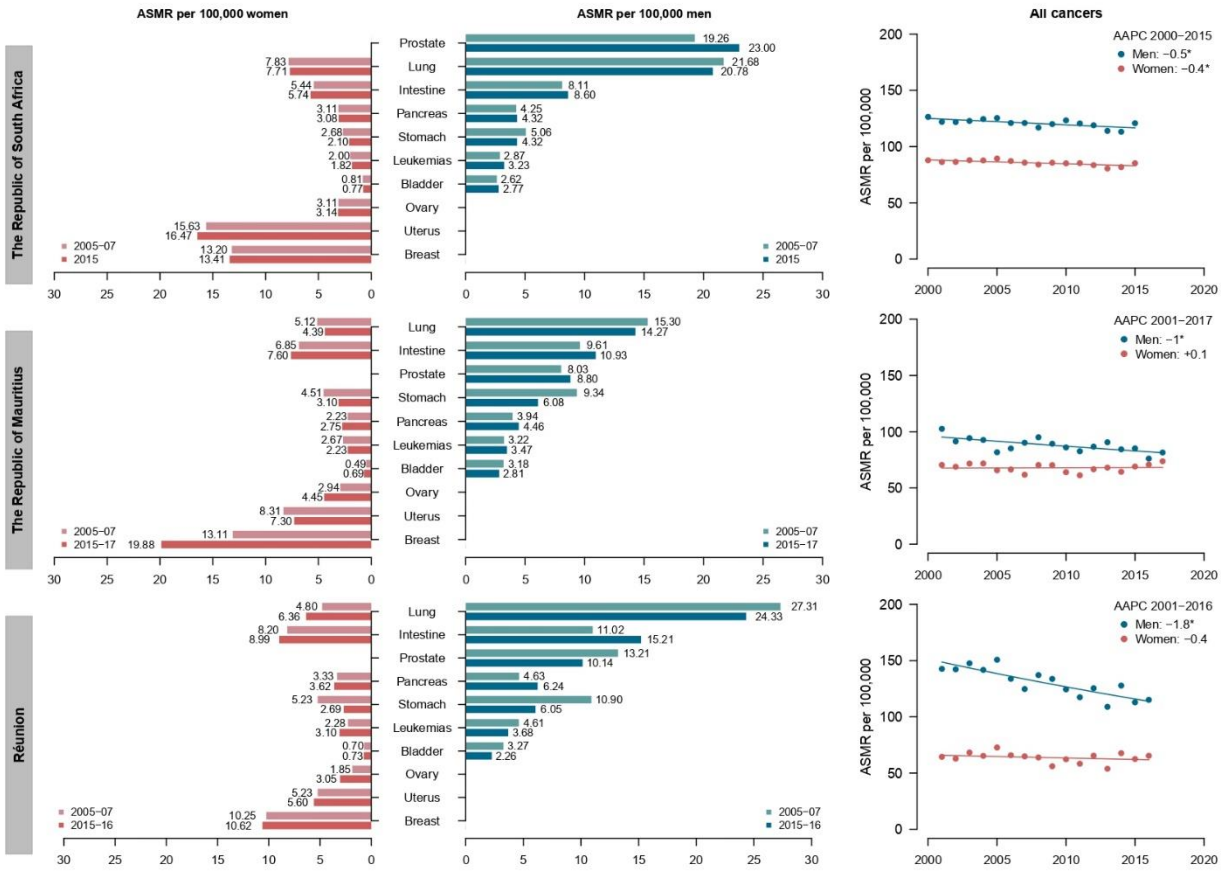
the rising trends in young adult colorectal cancer are confirmed by mortality data in the USA, Canada, Australia, and the UK, but not in other selected countries. Due to their cohort nature, a smaller

increase in overweight and obesity and declining alcohol drinking in some European countries may, at least in part explain the observed trends.

Trends in cancer mortality in the Republic of South Africa, the Republic of Mauritius and Réunion

Main points

We analysed cancer mortality figures in the Republic of South Africa, the Republic of Mauritius, and Réunion over the last two decades. Control of tobacco smoking and perhaps indoor pollution in man is likely a driver of the moderately favourable trends in lung and total cancer mortality observed over the last decades. Mortality rates from breast, prostate, colorectum, and (cervix) uteri are relatively high on a global scale, despite undefined validity of cancer death certification. Screening and HPV vaccination are priorities to control cervical cancer.



Persisting cancer mortality gap between western and eastern Europe [129]

Main points

Over the last three decades, cancer mortality has shown favourable patterns in Europe. Patterns and trends however have been less favourable for most eastern countries. Differences in lifestyle patterns, mainly smoking and alcohol, besides different roll-out of improvements in cancer diagnosis and management are the key determinants of the persisting difference in cancer mortality between western and eastern Europe. There is no evidence for the gap to close.

Mortality patterns of soft tissue sarcomas worldwide up to 2018, with predictions for 2025 ***(accepted)***

Main points

The epidemiological evidence on soft tissue sarcoma (STS) mortality is inconsistent in geographic and time coverage. This study provides mortality trends for STSs in selected countries worldwide over the last two decades, together with predicted figures for 2025. In addition to improvements in STSs registration, unfavourable mortality rates reported in this study reflect inadequate referral of patients with STSs to high-volume multidisciplinary centres, as well as insufficient advancements in STS prevention, diagnosis, and treatments.

Global trends in gastric cancer mortality 1990-2019, with predictions to 2025, and incidence by subtype ***(submitted)***

Main points

The incidence of gastric cancer (GC) is heterogeneously declining worldwide. We aimed to calculate updated mortality trends for GC. Observed and predicted GC mortality trends declined in most countries in both sexes, with few exceptions, likely due to the control of GC risk factors, in particular *Hp* infection.

CEFIC PROJECT

I have been involved since I started my PhD on a CEFIC project titled "Incidence trends of selected endocrine-related diseases and conditions in Europe and North America, and the contribution of changes in human reproduction" (PI Prof. Negri from the University of Bologna). Among the endocrine-related diseases and conditions, there were four cancer sites considered: breast, endometrium, testis, and prostate. I gave my contribution to this project by evaluating the cancer incidence trends in high-income countries worldwide and reviewing the association between selected reproductive factors and the selected cancers. Thus, we investigated changes in relevant reproductive factors and estimated their influence on cancer occurrence.

I have mainly worked on work packages 1 and 2, which aimed to evaluate incidence trends, and systematically analyse the literature on the possible determinants, including in particular artefacts and risk factors. Here I show the main results of my contribution.

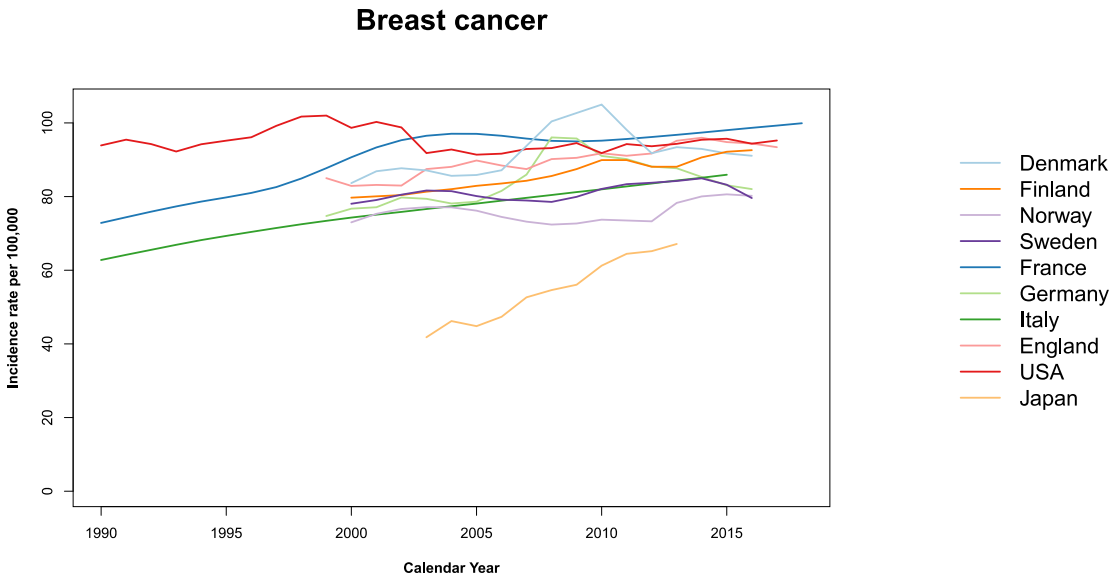
BREAST CANCER

Data sources and availability

Data were derived from National cancer registries or associations of registries providing national estimates. We retrieved estimates of national incidence rates in women for all countries, except Canada, for which we considered data from Ontario. For comparison, we also retrieved data from Japan. The period of availability was between 1943-2016 for Nordic countries, and later for the other countries. We considered the period from 2000 to 2016, where data were available for all countries.

Trends

Between 2000 and 2016 incidence rates increased about 10-20% in most countries, with the exceptions of Sweden, the USA, Canada (Ontario) where rates were flat, and Japan, where rates more than doubled.



Artefacts and other factors possibly influencing trends

We did not conduct a search to identify potential artefacts, since we considered that the major artefact influencing trends is the increased adoption of mammographic screening, either opportunistic or within an organized breast cancer screening program. While decreasing breast cancer mortality, mammographic screening also leads to diagnostic anticipation and overdiagnosis, this inflating incidence rates. Its effect on incidence rates has been quantified in an increase of around 20-30%, although these estimates may be specific for a country and period. Changes in risk factors that may have led to an increase in rate include decreased parity, increased age at first birth, obesity prevalence, and alcohol consumption. A decrease in (long-term) use of hormone replacement therapies in several countries may have favourably influenced rates.

The modest increase observed in most, but not all countries, can be attributed to increases in mammographic screening, as well as to unfavourable trends in other major risk factors.

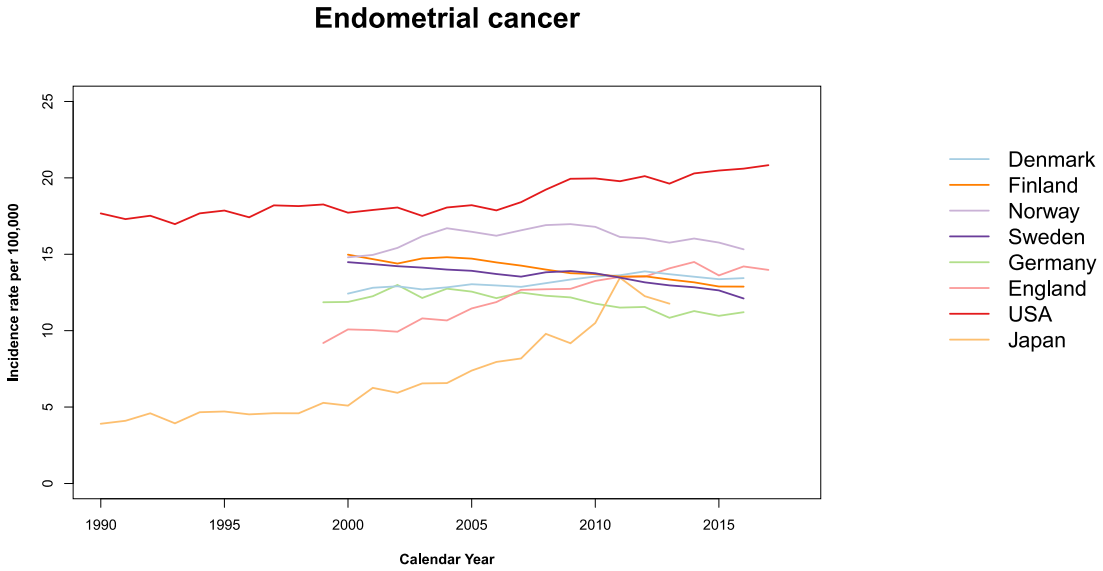
ENDOMETRIAL CANCER

Data sources and availability

Data were derived from National cancer registries, or associations of registries providing national estimates (e.g. Cancer statistics for the Nordic countries, NORDCAN, and the Global Cancer Observatory). For comparison, we also analysed data from Japan, based on the national registry. The period of availability was 1943-2016 for Nordic countries, and later for the other countries. We considered the period from 2000 to 2016, where data were available for all countries.

Trends

Different trends emerged in different countries. In the United States, Canada and UK increasing incidence rates were observed. In the Nordic countries (Sweden, Finland, Germany, Norway) endometrial cancer incidence decreased or was stable (Denmark). In the other considered countries (France, Germany, Italy and Spain), endometrial cancer incidence was essentially stable.



Artefacts and other factors possibly influencing trends

The main identified artefact is the changed prevalence of hysterectomy.

Potential risk factors for endometrial cancer include low or null parity, early age at menarche, and never using oral contraceptives, while late age at last birth appeared inversely related to endometrial cancer.

Trends were heterogeneous, with increases only observed in North America and the UK.

Risk factors and artefacts

Databases: PubMed and Embase

Search string: (((Endometr AND (cancer* OR neoplasm* OR tumor* OR tumour*)) AND (epidemiolog* OR statistic*) AND (review* OR meta-analys* OR metaanalys*))) OR (((Endometr* AND (cancer* OR neoplasm* OR tumor* OR tumour*)) AND trend* AND (Europe OR Germany OR*

France OR Italy OR Spain OR UK OR Sweden OR Finland OR Norway OR Denmark OR USA OR California OR Texas OR Florida OR New York OR Canada)))

Data: 14/09/2020

Inclusion/exclusion criteria: last 10 years

Results

Articles retrieved: 5329 (1150 duplicates), 4179 unique articles.

Table 1. Identified reviews and reported potential artifacts/risk factors.

Authors, year, type of article*	**Reported potential artifacts/risk factors**	**Quantification of effects on trends**
Constantine GD, et al. (2019) [130] Type: DESCR	HRT, compounded bioidentical HT, early age at menarche, later age at menopause, low parity, no history of OC use	
Doll KM. and. Winn A. N (2019) [131] Type: DESCR	Hysterectomy prevalence may be an artifact	When considering only women at risk (i.e. who did not undergo hysterectomy) endometrial cancer incidence nearly doubles
Lortet-Tieulent J, et al. (2018) [132] Type: DESCR	Exogen extrogen use (in peri- and post-menopause) and endogenous extrogen exposure (nulliparity, few pregnancy, early age at menarche, obesity)	
Raglan O, et al. (2019) [133] Type: REVIEW	Strong evidence for parity. Suggestive evidence for age at last birth, age at menarche, OC	
Setiawan VW, et al. (2012) [134] Type: ANALYTIC	Age at last birth	
Wartko P, et al. (2013) [135] Type: DESCR	HRT use; interaction between HRT use and overweight/obesity	
Williams CL, et al. (2018) [136] Type: ANALYTIC	No association with ART	
Wu QJ, et al. (2015) [137] Type: REVIEW	Parity	

* Type: REVIEW (review article/systematic review/meta-analysis), DESCR (descriptive observational study), ANALYTIC (analytic observational study), OTHER.

Potential risk factors for endometrial cancer include low or null parity, early age at menarche, and never using oral contraceptives, while late age at last birth appeared inversely related to endometrial cancer.

Table 2. Synthesis of the reported artifacts/risk factors.

Reported artifact	***Studies***
Hysterectomy prevalence	Doll KM and Winn AN (2019) [131]
Risk factors	
Parity	Raglan O, et al. (2019) [133] Wu QJ, et al. (2015) [137]
Early age at menarche	Constantine GD, et al. (2019) [130] Lortet-Tieulent J, et al. (2018) [132] Raglan O, et al. (2019) [133]
Age at last birth	Raglan O, et al. (2019) [133] Setiawan VW, et al. (2012) [134]

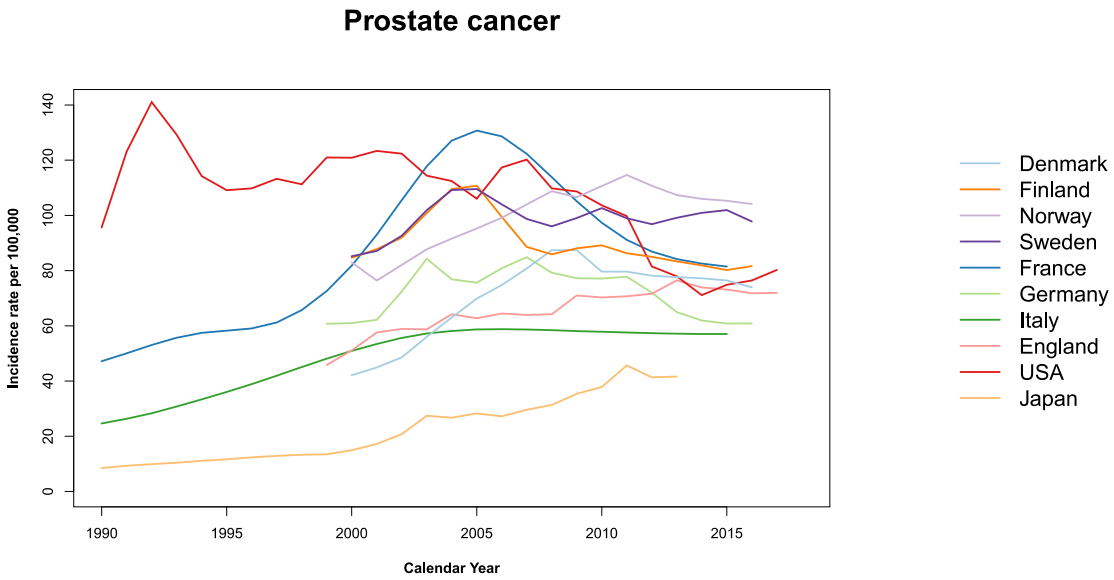
PROSTATE CANCER

Data sources and availability

Data were derived from National cancer registries or associations of registries providing national estimates. We retrieved estimates of national incidence rates in men for all countries, except Canada, for which we considered data from Ontario. For comparison, we also retrieved data from Japan. The period of availability was 1943-2016 for Nordic countries, and later for the other countries. We considered the period from 2000 to 2016, where data were available for all countries.

Trends

Over the observed period, upward incidence trends were registered in most of the countries considered: Denmark, the UK, Italy, Norway, Spain, Sweden (and Japan). Conversely, the incidence decreased over time in Finland, Ontario (Canada), and the USA, and remained stable in Italy. France showed a decline since 2005. The highest rates were registered in the USA almost over the whole period, while Japan showed the lowest incidence rates.



Artefacts and other factors possibly influencing trends

Differences in incidence trends across various geographical areas reflect differences in the use of diagnostic testing (according to GLOBOCAN 2018 estimates, variations in incidence rates were 190-fold across worldwide countries). The initial trend peak in prostate cancer incidence has been attributed to a depletion of previously undiagnosed and accumulated cases from the pool of prevalent preclinical cases from previous years. Around 20-40% of the prostate cases in the USA and Europe could be due to overdiagnosis through extensive prostate-specific antigen (PSA) testing. The United States Preventive Services Task Force in 2008 recommended against screening for men 75 and older, and in 2012 for men of all ages. In more recent years, decreased rates of PSA screening have likely contributed to the observed decreased incidence of prostate cancer.

The upward incidence trends observed in most countries are attributed to the widespread use of PSA screening.

Risk factors and artefacts

Databases: Medline and Embase

Search string: ((Prostat AND (cancer* OR neoplasm* OR tumor* OR tumour*)) AND (epidemiolog* OR statistic*) AND (review* OR meta-analys* OR metaanalys*)) AND ((Prostat* AND (cancer* OR neoplasm* OR tumor* OR tumour*)) AND trend* AND (Europe OR Germany OR France OR Italy OR Spain OR UK OR Sweden OR Finland OR Norway OR Denmark OR USA OR California OR Texas OR Florida OR New York OR Canada)) - 14/09/2020*

Further restriction: search up to 5 years ago

Results:

Articles retrieved: 8749 (and 2261 duplicates).

Table 1. Identified reviews and reported potential artifacts/risk factors.

Authors, year, type of article*	**Reported potential artifacts/risk factors**	**Quantification of effects on trends**
Han MA, et al. (2020) [138] REVIEW	Higher birth order (RF)	1.38 (1.23-1.55)
Zhou CK, et al. (2016) [139] REVIEW + ANALYTIC	Birthweight (RF)	National Survey of Health and Development results*: $OR_{per\ kg\ increase}$=0.84 (95% CI 0.56-1.27)* Meta-analysis results: *OR=1.02 (95% CI 1.00-1.05)*
Rawla P. (2019) [140] REVIEW	PSA (Artifact)	20-40% of prostate cancer cases in the USA and Europe could be due to overdiagnosis through extensive PSA testing

* type: REVIEW (review article/systematic review/meta-analysis), DESCR (descriptive observational study), ANALYTIC (analytic observational study), OTHER.

Table 2 shows the summary of results reported in the identified articles. The systematic review and meta-analysis on the impact of maternal and reproductive factors on cancer risks of offspring suggested that higher birth order may result in a very small increase in prostate cancer incidence[138]. Another systematic review and meta-analysis provided evidence that heavier birth weight may be associated with modest increased risks of total and aggressive/lethal prostate cancer [139]. Notwithstanding these considerations, the role of birth order and birthweight on prostate cancer risk should be considered only marginal. Indeed, the time period between exposure and onset of the disease makes it unlikely that a strong association exists between these two considered risk factors and prostate cancer. Differences in incidence trends across various geographical areas reflect differences in the use of diagnostic testing (considering GLOBOCAN 2018 estimates, variation in incidence rates were 190-fold across worldwide countries). The initial trend peak in prostate cancer incidence has been attributable to a depletion of previously undiagnosed and accumulated cases from the pool of prevalent preclinical cases from previous' years. Around 20 to 40% of the prostate cancer cases in the USA and Europe could be due to overdiagnosis through extensive PSA testing.

The United States Preventive Services Task Force (USPSTF) in 2008 recommended against screening for men 75 and older, and in 2012 for men of all ages. In more recent years, including the USPSTF

2008, decreased rates of PSA screening have likely contributed to the observed decreased incidence of prostate cancer.

Table 2. Synthesis of the reported artifacts/risk factors.

Reported risk factors	***Studies***
Birth order	Han MA, et al.(2020) [138].
Birthweight	Zhou CK, et al (2016) [139]
Reported artifact	***Studies***
PSA (prostate-specific antigen) screening	Rawla P. (2019) [140]
TURP (transurethelial resection of the prostate)	

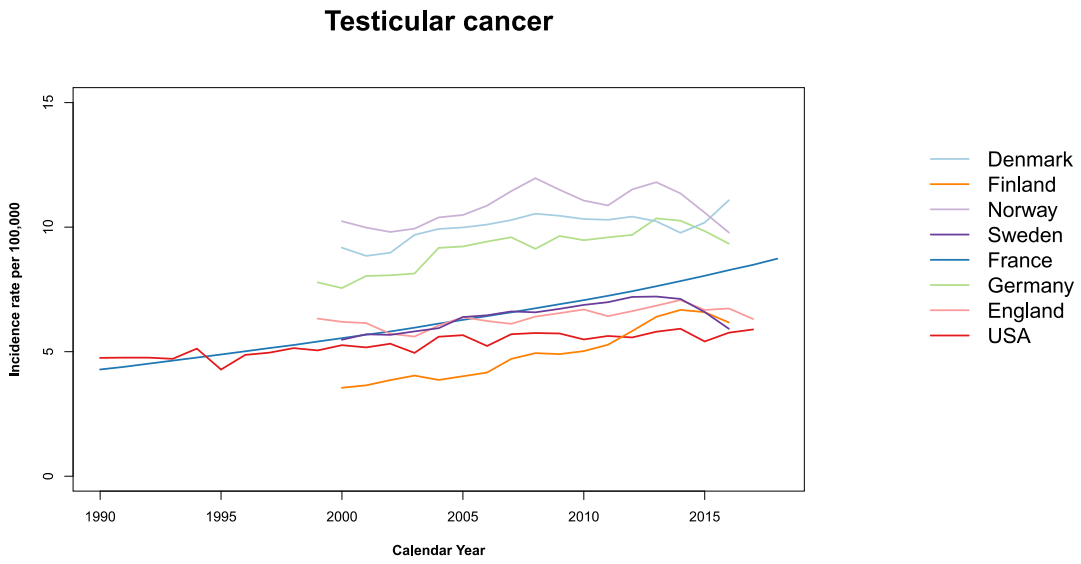
TESTICULAR CANCER

Data sources and availability

Data were derived from National cancer registries, or associations of registries providing national estimates (e.g. the Cancer statistics for the Nordic countries, NORDCAN, and the Global Cancer Observatory). For comparison, we also analysed data from Japan, based on the national registry. The period of availability was 1943-2016 for Nordic countries, and later for the other countries. We considered the period from 2000 to 2016, where data were available for all countries.

Trends

Among the countries considered, testicular cancer is still showing increasing trends in incidence. In some northern European countries (i.e. UK, Norway and Sweden) incidence rates appear to have stabilized over the period.



Artefacts and other factors possibly influencing trends

No particular artefact influencing rates emerged from the literature. Perinatal factors and development abnormalities may play a role in testicular cancer etiology, including LBW, low gestational age, and cryptorchidism. Changes in those factors may likely explain the increasing trends. In addition, birth order has been inversely associated to testicular cancer risk. It has been estimated that an increase of 26% in testicular cancer is attributable to the temporal change in birth order between 1950 and 2015 in the Netherlands.

Increasing trends in incidence rates of testicular cancer have been partly attributed to decreasing parity. Cryptorchidism is the strongest risk factor identified, and may also have influenced trends. However, a quantification of its role is still undefined.

Risk factors and artefacts

Databases: Medline and Embase

Search string: (((Testicular OR testis) AND (cancer OR neoplasm* OR tumor* OR tumour*)) AND (epidemiolog* OR statistic*) AND (review* OR meta-analys* OR metaanalys*))) OR (((Endometr* AND (cancer* OR neoplasm* OR tumor* OR tumour*)) AND trend* AND (Europe OR Germany OR France OR Italy OR Spain OR UK OR Sweden OR Finland OR Norway OR Denmark OR USA OR California OR Texas OR Florida OR New York OR Canada)))*

Data: 14/09/2020

inclusion/exclusion criteria: last 10 years

Results

Articles retrieved 1766 (86 duplicates), 1680 unique articles

Table 1. Identified reviews and reported potential artifacts/risk factors.

Authors, year, type of article*	**Reported potential artifacts/risk factors**	**Quantification of effects on trends**
Richiardi L, et al. (2007) [141] Type: REVIEW	This article reported an increase in risk for low birth weight.	**Low birth weight**: OR=1.28 (95% CI 0.99–1.65)
Cook MB, et al. (2009) [142] Type: REVIEW	This systematic review and meta-analysis has found evidence for associations of birth order with risk of testicular cancer. No association was found for maternal age.	**Birth order:** **primiparous vs not,** OR=1.08 (95% CI 1.01–1.16) **second vs first**, OR=0.94 (95% CI 0.88–0.99) **third vs first,** OR=0.91 (95% CI 0.83–1.01) **fourth vs first,** OR=0.80 (95% CI 0.69–0.94)
McGlynn KA and Cook MB. (2009) [143] Type: REVIEW	Factors such as low birth weight, low gestational age and low and high maternal age might also influence the risk of testicular cancers but the results are often inconsistent.	
Cook MB, et al. (2010) [144] Type: REVIEW	Rates of testicular cancer have been associated with cryptorchidism, low birth rate, short gestational age, inguinal hernia, and twinning, suggesting a common etiology such as a hormonal factor in utero.	**Low birth weight**: OR=1.34 (95% CI 1.08–1.67) **Low gestational age**: OR=1.31 (95% CI 1.07–1.59)
Stephansson O, et al. (2011) [145] Type: ANALYTIC	There was a weak, positive association between high (≥4000 g) birth weight and childhood testicular germ-cell and a correspondingly elevated risk for low birth weight.	**High birth weight (≥4000 g):** OR=1.25 (95% CI: 0.83-1.90) **Low birth weight (<2500)**: OR=1.41; (95% CI: 0.43-4.56) **Birth order (first vs later):** OR=1.40; (95% CI: 0.96-2.05)
Crump C, et al (2012) [146] Type: ANALYTIC	These findings suggest that extreme but not later preterm birth may be independently associated with testicular cancer in later life.	**Preterm Birth (22–29 weeks):** OR: 3.95 (95% CI: 1.67–9.34)
Piltoft JS, et al. (2017) [147] Type: ANALYTIC	Birth weight was inversely associated with testicular cancer and no clear association with birth order was observed.	**Low birth weight (<2500):** 1.48 (1.00–2.17)
Levine H, et al. (2017) [148] Type: ANALYTIC	Increasing paternal age at birth was linearly associated with lower risk of testicular cancer.	**Paternal age:** $HR_{per\ year}$ = 0.98; (95% CI: 0.97-0.99) **Maternal age:** $HR_{per\ year}$ = 0.98; (95% CI: 0.97-0.99)

Swaen G, et al. (2018) [149] Type: REVIEW	Boys born from nulliparous mothers (firstborn boys) are at an increased risk for testicular cancer, compared to boys from multiparous mothers, irrespective of the gender of the siblings. This association is found in several studies, but not all, and it seems to be the case in particular in the earlier birth cohorts.	
Znaor A, et al. (2020) [150] Type: DESCR	The aetiology of testicular cancer remains elusive, in part due to difficulties in obtaining robust exposure data related to the perinatal period.	

* type: REVIEW (review article/systematic review/meta-analysis), DESCR (descriptive observational study), ANALYTIC (analytic observational study), OTHER.

Table 2. Synthesis of the reported artifacts/risk factors.

Reported artifact	**Studies**
Improving education awareness or better diagnostic procedures?	Le Cornet C, et al. (2014) [151] Nigam M, et al. (2015) [152] Znaor A, et al. (2020) [150]
Decrease in parity over the last decades	Swaen G, et al. (2018) [149]
Risk factors	
Low birth weight	Richiardi L, et al. (2007) [141] Cook MB, et al. (2010) [144] Stephansson O, et al. (2011) [145] Piltoft JS, et al. (2017) [147]
Birth order	Cook MB, et al. (2009) [142] Stephansson O, et al. (2011) [145] Piltoft JS, et al. (2017) [147]
Parity	Swaen G, et al. (2018) [149]
Preterm birth	Crump C, et al (2012) [146]
Paternal age	Levine H, et al. (2017) [148]
Maternal age	Cook MB, et al. (2009) [142] Levine H, et al. (2017) [148]

Risk factors for testicular cancer include undescended testis (cryptorchidism), personal or family history of testicular cancer, age, ethnicity, and infertility. Several epidemiological studies have investigated the relationship between variables related to prenatal exposures and testicular cancer, but results are often inconsistent, suggesting an etiology poorly understood. McGlynn and Cook in 2009 reassumed very clearly several aspects that may influence the risk of testicular cancer. “Maternal age has been both inversely and directly associated with testicular cancer risk. Moreover, several studies have reported no association. Low maternal parity and low birth order have been linked to testicular cancer risk in some while other articles not.” Cook et al. in 2010 performed a meta–analysis on perinatal variables in relation to the risk of testicular cancer. Most of the published articles analysed

which reported an evidence was not very recent. In a recent publication by Znaor and colleagues in 2020, suggested that the aetiology of testicular cancer remains elusive, probably due to difficulties in obtaining robust exposure data related to the perinatal period.

For this reason, we are now conducting a systematic review to update the most recent meta-analysis (Cook et al. in 2010) on exposure related to the perinatal period, hoping that more recent articles can lead to a deeper understanding of the etiology of testicular cancer.

MARIO NEGRI INSTITUTE EXPERIENCE

During my PhD, I have been collaborating with the department of Oncology belonging to the Mario Negri Institute. Under the supervision of Dott. Bosetti I worked on various projects. We updated a meta-analysis concerning aspirin use and the risk of twelve solid tumors with a dose-response analysis finalizing three publications [153-155]. Moreover, the Mario Negri Institute manages the Italian Register of Multiple Sclerosis, collecting data from more than 100 centers in Italy on more than 70.000 patients. Based on this real-world dataset, I have dealt with several aspects related to multiple sclerosis, being involved in the drafting of two papers one concerning two methods for measuring the disability accumulated over time [156] and another one studying patients' and referral centers' characteristics in relation to multiple sclerosis phenotypes [157].

Detection of disability worsening in relapsing-remitting multiple sclerosis patients: a real-world roving Expanded Disability Status Scale reference analysis from the Italian Multiple Sclerosis Register [156]

Main points

In relapsing-remitting multiple sclerosis patients (RRMS) disability progressively accumulates over time. To compare the cumulative probability of 6-month confirmed disability-worsening events using a fixed baseline or a roving Expanded Disability Status Scale (EDSS) reference, in a real-world setting.

A cohort of 7964 RRMS patients followed for 2 or more years, with EDSS scores recorded every 6 months, was selected from the Italian Multiple Sclerosis Register. The overall probability of confirmed disability-worsening events and of confirmed disability-worsening events unrelated to relapse was evaluated using as reference a fixed baseline EDSS score or a roving EDSS score in which the increase had to be separated from the last EDSS assessment by at least 6 or 12 months.

Using a fixed baseline EDSS reference, the cumulative probability of 6-year overall confirmed disability-worsening events was 33.2%, and that of events unrelated to relapse was 10.9% (33% of overall confirmed disability-worsening events). Using a roving EDSS, the proportions were respectively 35.2% and 21.3% (61% of overall confirmed disability-worsening events).

In a real-world setting, roving EDSS reference scores appear to be more sensitive for detecting confirmed disability-worsening events unrelated to relapse in RRMS patients.

Do patients' and referral centers' characteristics influence multiple sclerosis phenotypes? Results from the Italian multiple sclerosis and related disorders register [157]

Main points

Multiple sclerosis (MS) is characterized by phenotypical heterogeneity, partly resulting from demographic and environmental risk factors. Socioeconomic factors and the characteristics of local MS facilities might also play a part. This study included patients with a confirmed MS diagnosis enrolled in the Italian MS and Related Disorders Register in 2000-2021. Patients at the first visit were classified as having a clinically isolated syndrome (CIS), relapsing-remitting (RR), primary progressive (PP), progressive-relapsing (PR), or secondary progressive MS (SP). Demographic and clinical characteristics were analyzed, with centers' characteristics, geographic macro-areas, and Deprivation Index. We computed the odds ratios (OR) for CIS, PP/PR, and SP phenotypes, compared to the RR, using multivariate, multinomial, mixed effects logistic regression models. In all 35,243 patients from 106 centers were included. The OR of presenting more advanced MS phenotypes than the RR phenotype at first visit significantly diminished in relation to calendar period. Females were at a significantly lower risk of a PP/PR or SP phenotype. Older age was associated with CIS, PP/PR, and SP. The risk of a longer interval between disease onset and first visit was lower for the CIS phenotype, but higher for PP/PR and SP. The probability of SP at first visit was greater in the South of Italy. Differences in the phenotype of MS patients first seen in Italian centers can be only partly explained by differences in the centers' characteristics. The demographic and socio-economic characteristics of MS patients seem to be the main determinants of the phenotypes at first referral.

Use of preventive drugs during the last year of life in older adults with cancer or chronic progressive diseases [158]

Main points

We aimed to evaluate the prescription of preventive medications with questionable usefulness in community dwelling elderly adults with cancer or chronic progressive diseases during the last year of life. We used the healthcare databases of the Lombardy region, Italy, identifying two retrospective cohorts of patients aged 65 years or more, who died in 2018 and had a diagnosis of either a solid cancer (N=19,367) or a chronic progressive disease (N=27,819). We estimated prescription of eight major classes of preventive drugs 1 year and 1 month before death; continuation or initiation of preventive drug use during the last month of life was also investigated.

Over the last year of life, in both oncologic and non-oncologic patients, we observed a modest decrease in the prescription of blood glucose-lowering drugs, anti-hypertensives, lipid-modifying agents, and bisphosphonates, and a slight increase in the prescription of vitamins, minerals, antianemic drugs, and antithrombotic agents (among oncologic patients only). One month before death, the prescription of preventive drugs was still common, particularly for anti-hypertensives, antithrombotics, and antianemics, with more than 60% of patients continuing to be prescribed most preventive drugs and an over 10% starting a therapy with an antithrombotic, an antianemic, or a vitamin or mineral supplement. These findings support the need for an appropriate drug review and improvement in the quality of drug prescription for vulnerable populations at the end-of-life.

I took part in this paper by conducting analyses on the healthcare databases of the Lombardy region and reviewing and editing the original article.

Factors for Timely Identification of Possible Occurrence of Delirium in Palliative Care: A Prospective Observational Study [159]

Main points

Delirium occurs in 50-80% of end-of-life patients but is often misdiagnosed. Identification of clinical factors potentially associated with delirium onset can lead to a correct early diagnosis. To this aim, we conducted a prospective cohort study on patients from an Italian palliative care unit (PCU) admitted in 2018-2019. We evaluated the presence of several clinical factors at patient admission and compared their presence in patients who developed delirium and in those who did not develop it during follow-up. The study indicates that some clinical factors, such as setting of care (hospice vs home care), presence of breathlessness, and administration of psychoactive drugs (haloperidol) are associated with the probability of delirium onset. Their evaluation in PC patients could help healthcare professionals to identify the development of delirium in those patients in a timely manner.

Risk factors of locoregional recurrence after surgical resection of non-small cell lung cancer: a meta-analysis (still ongoing)

Main points

In collaboration with Dr Varlotto, from the Marshall University, Radiation Oncology, with the Medtronic Advanced Surgical Instruments, and the Unit of Cancer Epidemiology, Mario Negri

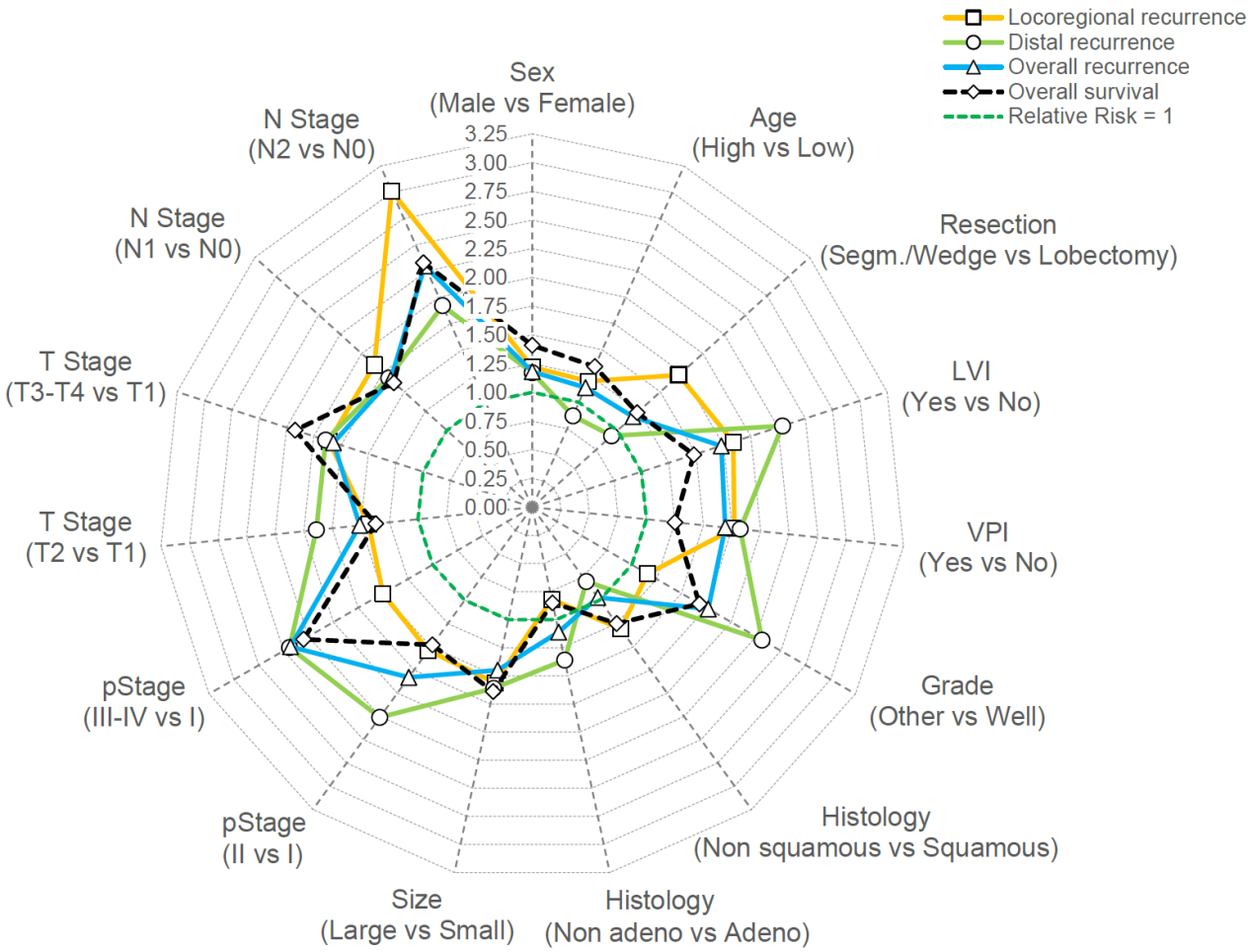
Institute, held by Dr Bosetti, we conducted a meta-analysis to study the risk factors associated with locoregional recurrence in patients with resected non-small cell lung cancer. This work started in September 2020 and we are finalizing the paper for submission.

Abstract

We conducted a systematic review and meta-analysis to identify all original studies that assessed risk factors for LR after surgical resection of NSCLC published between 01/01/2000 and 10/08/2020. Eighty-one studies were selected for inclusion. Sixteen risk factors were considered, including patient's characteristics, treatment variables, histopathologic, and staging variables.

This large-scale meta-analysis indicates that LR is influenced predominantly by nodal stage, T stage, lymphovascular invasion, and visceral pleural involvement. DR and OS are more strongly associated with pathological stage and treatment variables.

Figure 1. Radar plot showing the pooled risk estimates for major risk factors for locoregional recurrence, distal recurrence, overall recurrence, and overall survival after surgical resection of non-small cell lung cancer.



UNIVERSITY OF LAS PALMAS EXPERIENCE

In my last PhD year, I worked at the Department of Quantitative Methods and Economics of the University of Las Palmas supervised by Prof. Serra-Majem for nine months. This training period aimed to gain new experience in conducting cost-effectiveness studies. I conducted a study aimed to quantify the over cost due to obesity among patients hospitalized for Covid-19. In collaboration with the Department of Public Health, I conducted an effectiveness analysis of a primary prevention intervention with a Mediterranean diet supplemented with extra-virgin olive oil or nuts using the data from PREDIMED Trial. Lastly, I took part in the WOMEDS Study, a project aimed to analyse gender inequality among medical doctors in Spain. During these months abroad, I co-wrote three papers, currently under revision.

Gender inequality in the medical profession: the women doctors in Spain (WOMEDS) study (submitted)

The Women Doctors in Spain (WOMEDS) project analyzes the different aspects of the medical specialties from a gender perspective in order to detect possible gender gaps, compare results among different medical specialties, and propose corrective actions for the discriminatory inequalities that eventually would be encountered. It focuses on the clinical setting but has necessary ramifications for professional organizations, academia, and research. For this study I build three indicators concerning women in i) health care, ii) medical councils, medical associations, and medical conferences, and iii) research and academy, created a Tableau page (available at: (https://public.tableau.com/app/profile/gender.medicine), as well as wrote the paper - currently submitted - as first and corresponding author.

Clinical and economic impact of COVID-19 on people with obesity in a Spanish cohort during the first pandemic peak (under review)

This study aimed to assess the prevalence of obesity and obesity-associated comorbidities in COVID-19 patients and the association between obesity and key relevant outcomes of COVID-19 in a Spanish hospital. We also evaluated the economic impact of the combination of obesity and COVID-19 disease, which we foretell to be significantly higher than the impact of COVID-19 infection itself. I

took part in this project building various scenarios for missing data imputation. I have also helped write the final manuscript.

Cost-effectiveness analysis of a primary prevention intervention with Mediterranean diet supplemented with extra-virgin olive oil or nuts (ongoing)

Reducing primary cardiovascular events is a significant public health concern. The PREDIMED study is the largest primary prevention trial showing an inverse association between adherence to the Mediterranean diet and the incidence of several major chronic diseases in subjects at high cardiovascular risk [160]. However, the cost-effectiveness study of these interventions has yet to be calculated. In this study, I estimated the costs and cost-effectiveness of PREDIMED interventions as well as changes in quality of life during the follow-up in patients recruited in Guía, Gran Canaria.

COURSES AND OTHER ACTIVITIES

Transferable skills and courses from PhD catalogue

During my PhD, I attended the following mandatory courses:

- Fondamenti di Academic writing;
- Language coaching: interpersonal skills - presentation skills;
- Open science;
- Lezione propedeutica base su IP e brevetti;
- Comunicazione e nuovi media;
- La valutazione della ricerca;
- Introduzione alla valorizzazione della ricerca;
- Research Integrity I;
- Research Integrity II;
- Academic Writing: Research Papers;
- Language coaching: Interpersonal Skills - Interview Skills;
- Grantmanship Parte I;
- Grantmanship Parte II;
- Competenze e occupabilità dei dottori di ricerca (Self branding);
- Laboratorio per la preparazione di un piano di disseminazione/comunicazione;
- Valorizzare creando impresa: fare spin-off all'Università degli Studi di Milano;
- Lezione avanzata sull'utilizzo dell'IP per fare innovazione;
- CV e tecniche di selezione: come compilare un buon CV e approcciarsi alle tecniche di selezione aziendale;
- Tensioni e conflitti nella transizione di carriera.

Moreover, I attended the following courses:

- Mediation analysis and causal inference, hold by Prof. Edefonti and Prof. Valeri;
- Statistica per le decisioni in Sanità Pubblica, hold by Prof. La Vecchia and Dott. Bitetto;
- Approccio One Health al controllo delle zoonosi emergenti, hold by Prof. Zecconi;
- Power calculation and sample size optimization, hold by Prof. Carlo La Vecchia and Prof. Cristian Ricci;

— Criminologia clinica, medicina legale e diritto: conoscenza e prevenzione per i professionisti della sanità, hold by Prof. Merzagora;
— Ricerca clinica: valutazione della qualità e credibilità dei risultati della ricerca; origini di bias, hold by Prof. Moja;
— Revisioni sistematiche con meta-analisi: metodi statistici ed interpretazione dei risultati, hold by Prof. Casazza;
— Disegni di Studi Osservazionali, hold by Prof. La Vecchia.

Supplementary activities for study programmes - art. 45

In accordance with the article n. 45 cod. 742, 918, and 1103 of the University General Regulations, I obtained a collaboration with the Department of Biomedical, Surgical and Dental Sciences for teaching activities (tutoring, exercises, drills and tutorials) for the course of Medical Statistics held by the Prof. Monica Ferraroni for three consecutive years.

Supplementary material

Supplementary Table 1. List of malignant neoplasms.

Neoplasm	ICD-10 code
Oral cavity and pharynx	C00-C14
Esophagus	C15
Stomach	C16
Colorectal	C18-C20 and C26
Primary liver cancer	C22
Gallbladder	C23
Pancreas	C25
Lung	C33-C34
Skin melanoma	C43
Breast	C50
Cervix	C53
Corpus	C54-C55
Ovary	C56
Prostate	C61
Bladder	C67
Kidney and other urinary sites	C64-C66 and C68
Brain and CNS	C70-C72
Non-Hodgkin's lymphomas	C82-C85
Multiple myeloma	C90
Leukemia	C91-C95
All malignant cancers	C00-C97

ICD, International Classification of Diseases;
CNS: Central Nervous System.

REFERENCES

1. McCleskey BC, Epstein JI, Albany C, et al. The Significance of Lymphovascular Invasion of the Spermatic Cord in the Absence of Cord Soft Tissue Invasion. *Arch Pathol Lab Med.* Jun 2017;141(6):824-829.

2. Esteve J, Benhamou E, Raymond L. Statistical methods in cancer research. Volume IV. Descriptive epidemiology. *IARC Sci Publ.* 1994(128):1-302.

3. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med.* Feb 15 2000;19(3):335-351.

4. Qiu Z, Jiang Z, Wang M, Hatcher J. Long-Term Projection Methods: Comparison of Age-PeriodCohort Model-Based Approaches. *Prepared by Alberta Health Services for the Canadian Partnership Against Cancer.* 2010.

5. Bray F, Moller B. Predicting the future burden of cancer. *Nat Rev Cancer.* Jan 2006;6(1):63-74.

6. Carioli G. Cancer mortality data analysis and prediction. PhD Thesis. 2019.

7. Faraway JJ. *Linear models with R*: Chapman and Hall/CRC; 2004.

8. Verzani J. *Using R for introductory statistics*: Chapman and Hall/CRC; 2004.

9. World Health Organization Statistical Information System. WHO mortality database: Estimated coverage of mortality data. Geneva: World Health Organization. Available from: https://www.who.int/data/data-collection-tools/who-mortality-database [Last accessed Jan 2022].

10. Pan American Health Organization (PAHO).Health Information Platform for the Americas. Available from: http://wwwpahoorg/data/indexphp/en/indicators/demographics-core/308-poblacion-nac-enhtml [Last accessed Jan 2022].

11. Alarcón-Capel E, Ruano-Ravina A, Barros-Dios JM. [Radon exposure and genitourinary cancer in miners]. *Gac Sanit.* Oct 29 2019.

12. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. *Stat Med.* Dec 20 2009;28(29):3670-3682.

13. Arndt V, Holleczek B, Kajuter H, et al. Data from Population-based Cancer Registration for Secondary Data Analysis: Methodological Challenges and Perspectives. Gesundheitswesen. Available at: https://www.krebsdaten.de/Krebs/EN/Home/homepage_node.html. Oct 29 2019.

14. Henson KE, Elliss-Brookes L, Coupland VH, et al. Data Resource Profile: National Cancer Registration Dataset in England. *Int J Epidemiol.* Apr 23 2019.

15. Surveillance Epidemiology and End Results Program (SEER). SEER Registries.Available from: https://seer.cancer.gov/registries/ [Last accessed Jan 2022].

16. Hori M, Matsuda T, Shibata A, et al. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol.* Sep 2015;45(9):884-891.

17. Gautier Defossez, Sandra Le GuyaderPeyrou, Zoé Uhry, et al. National estimates of cancer incidence and mortality in metropolitan France between 1990 and 2018. Volume 1 – Solid tumours. Available at: https://www.e-cancer.fr/; 2019.

18. Cragg WJ, Cafferty F, Diaz-Montana C, et al. Early warnings and repayment plans: novel trial management methods for monitoring and managing data return rates in a multi-centre phase III randomised controlled trial with paper Case Report Forms. *Trials.* Apr 27 2019;20(1):241.

19. Rossi S, Baili P, Capocaccia R, et al. The EUROCARE-5 study on cancer survival in Europe 1999-2007: Database, quality checks and statistical analysis methods. *Eur J Cancer.* Oct 2015;51(15):2104-2119.

20. Matsuda T, Ajiki W, Marugame T, et al. Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: a chronological and international comparative study. *Jpn J Clin Oncol.* Jan 2011;41(1):40-51.

21. Collaborators GBDT. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the Global Burden of Disease Study 2015. *Lancet.* May 13 2017;389(10082):1885-1906.

22. Pastorino U, Silva M, Sestini S, et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial: new confirmation of lung cancer screening efficacy. *Ann Oncol.* Jul 1 2019;30(7):1162-1169.

23. Henley SJ, Thomas CC, Lewis DR, et al. Annual Report to the Nation on the Status of Cancer, part II: Progress toward Healthy People 2020 objectives for 4 common cancers. *Cancer.* Mar 12 2020.

24. Martin-Sanchez JC, Lunet N, Gonzalez-Marron A, et al. Projections in Breast and Lung Cancer Mortality among Women: A Bayesian Analysis of 52 Countries Worldwide. *Cancer Res.* Aug 1 2018;78(15):4436-4442.

25. Inage T, Nakajima T, Yoshino I, Yasufuku K. Early Lung Cancer Detection. *Clin Chest Med.* Mar 2018;39(1):45-55.

26. Nawa T, Fukui K, Nakayama T, et al. A population-based cohort study to evaluate the effectiveness of lung cancer screening using low-dose CT in Hitachi city, Japan. *Jpn J Clin Oncol.* Feb 1 2019;49(2):130-136.

27. Balakrishnan M, George R, Sharma A, Graham DY. Changing Trends in Stomach Cancer Throughout the World. *Curr Gastroenterol Rep.* Aug 2017;19(8):36.

28. Ferro A, Peleteiro B, Malvezzi M, et al. Worldwide trends in gastric cancer mortality (1980-2011), with predictions to 2015, and incidence by subtype. *Eur J Cancer.* May 2014;50(7):1330-1344.

29. Poorolajal J, Moradi L, Mohammadi Y, Cheraghi Z, Gohari-Ensaf F. Risk factors for stomach cancer: a systematic review and meta-analysis. *Epidemiol Health.* 2020;42:e2020004.

30. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ.* May 20 2014;348:g3174.

31. Huang RJ, Sharp N, Talamoa RO, Ji HP, Hwang JH, Palaniappan LP. One Size Does Not Fit All: Marked Heterogeneity in Incidence of and Survival from Gastric Cancer among Asian American Subgroups. *Cancer Epidemiol Biomarkers Prev.* Mar 9 2020.

32. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin.* Mar 5 2020.

33. Issa IA, Noureddine M. Colorectal cancer screening: An updated review of the available options. *World J Gastroenterol.* Jul 28 2017;23(28):5086-5096.

34. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* Jan 2018;68(1):7-30.

35. Lucas AL, Malvezzi M, Carioli G, et al. Global Trends in Pancreatic Cancer Mortality From 1980 Through 2013 and Predictions for 2017. *Clin Gastroenterol Hepatol.* Oct 2016;14(10):1452-1462 e1454.

36. Gallus S, Lugo A, Murisic B, Bosetti C, Boffetta P, La Vecchia C. Overweight and obesity in 16 European countries. *Eur J Nutr.* Aug 2015;54(5):679-689.

37. Bosetti C, Rosato V, Li D, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. *Ann Oncol.* Oct 2014;25(10):2065-2072.

38. Cuzick J. Preventive therapy for cancer. *Lancet Oncol.* Aug 2017;18(8):e472-e482.

39. Giordano SB, Gradishar W. Breast cancer: updates and advances in 2016. *Curr Opin Obstet Gynecol.* Feb 2017;29(1):12-17.

40. Hulka BS, Stark AT. Breast cancer: cause and prevention. *Lancet.* Sep 30 1995;346(8979):883-887.

41. Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. *Lancet.* Oct 24 1992;340(8826):1015-1018.

42. Kusano AS, Trichopoulos D, Terry KL, Chen WY, Willett WC, Michels KB. A prospective study of breast size and premenopausal breast cancer incidence. *Int J Cancer.* Apr 15 2006;118(8):2031-2034.

43. Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. *Lancet.* Jul 17-23 2004;364(9430):249-256.

44. Cuzick J. Long-term cervical cancer prevention strategies across the globe. *Gynecol Oncol.* May 2010;117(2 Suppl):S11-14.

45. Collaborative Group on Epidemiological Studies of Ovarian C, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet.* Jan 26 2008;371(9609):303-314.

46. Yang HP, Anderson WF, Rosenberg PS, et al. Ovarian cancer incidence trends in relation to changing patterns of menopausal hormone therapy use in the United States. *J Clin Oncol.* Jun 10 2013;31(17):2146-2151.

47. La Vecchia C. Ovarian cancer: epidemiology and risk factors. *Eur J Cancer Prev.* Jan 2017;26(1):55-62.

48. Carroll PH, Mohler JL. NCCN Guidelines Updates: Prostate Cancer and Prostate Cancer Early Detection. *J Natl Compr Canc Netw.* May 2018;16(5S):620-623.

49. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. *Eur Urol.* Jan 2017;71(1):96-108.

50. Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2016 with focus on leukaemias. *Ann Oncol.* Apr 2016;27(4):725-731.

51. Davis JR, Benjamin DJ, Jonas BA. New and emerging therapies for acute myeloid leukaemia. *J Investig Med.* Dec 2018;66(8):1088-1095.

52. McCredie M. Cancer epidemiology in migrant populations. *Recent Results Cancer Res.* 1998;154:298-305.

53. Arnold M, Razum O, Coebergh JW. Cancer risk diversity in non-western migrants to Europe: An overview of the literature. *Eur J Cancer.* Sep 2010;46(14):2647-2659.

54. Geddes M, Balzi D, Buiatti E, Khlat M, Parkin D. Cancer in Italian migrants. *Cancer Causes Control.* Mar 1991;2(2):133-140.

55. La Vecchia C, Harris RE, Wynder EL. Comparative epidemiology of cancer between the United States and Italy. *Cancer Res.* Dec 15 1988;48(24 Pt 1):7285-7293.

56. Bernstein L, Flannery J, Reynolds P. Cancer in Italian migrant populations. The United States of America. *IARC Sci Publ.* 1993(123):67-94.

57. Pinheiro P, Callahan K, Kobetz E. Disaggregated Hispanic Groups and Cancer: Importance, Methodology, and Current Knowledge. In: Ramirez AG, Trapido EJ. Advancing the Science of Cancer in Latinos ed. Cham: Springer International Publishing, 2020:17-34. .

58. Ruggles S, Flood S, Goeken R. IPUMS USA: Version 9.0 [dataset]. In: IPUMS, ed. Minneapolis, MN, 2019.

59. Cift A, Yucel MO. Comparison of inflammatory markers between brucella and non-brucella epididymo-orchitis. *Int Braz J Urol.* Jul-Aug 2018;44(4):771-778.

60. Thun M, Peto R, Boreham J, Lopez AD. Stages of the cigarette epidemic on entering its second century. *Tob Control.* Mar 2012;21(2):96-101.

61. Carioli G, Bertuccio P, Boffetta P, et al. European cancer mortality predictions for the year 2020 with a focus on prostate cancer. *Ann Oncol.* May 2020;31(5):650-658.

62. Islami F, Siegel RL, Jemal A. The changing landscape of cancer in the USA - opportunities for advancing prevention and treatment. *Nat Rev Clin Oncol.* Oct 2020;17(10):631-649.

63. Santucci C, Carioli G, Bertuccio P, et al. Progress in cancer mortality, incidence, and survival: a global overview. *Eur J Cancer Prev.* Sep 2020;29(5):367-381.

64. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. 2020:Available from: https://gco.iarc.fr/today, accessed [05 May 2021].

65. Pinheiro PS, Medina HN, Callahan KE, et al. Kidney cancer mortality disparities among Hispanics in the US. *Cancer Epidemiol.* Jun 2021;72:101938.

66. DiBonaventura M, Nicolucci A, Meincke H, Le Lay A, Fournier J. Obesity in Germany and Italy: prevalence, comorbidities, and associations with patient outcomes. *Clinicoecon Outcomes Res.* 2018;10:457-475.

67. Ghoshal A, Garmo H, Arthur R, et al. Serum biomarkers to predict risk of testicular and penile cancer in AMORIS. *Ecancermedicalscience.* 2017;11:762.

68. Tocci G, Muiesan ML, Parati G, et al. Trends in Prevalence, Awareness, Treatment, and Control of Blood Pressure Recorded From 2004 to 2014 During World Hypertension Day in Italy. *J Clin Hypertens (Greenwich).* Jun 2016;18(6):551-556.

69. Zhang Y, Moran AE. Trends in the Prevalence, Awareness, Treatment, and Control of Hypertension Among Young Adults in the United States, 1999 to 2014. *Hypertension.* Oct 2017;70(4):736-742.

70. Pedersen MR, Bartlett EC, Rafaelsen SR, et al. Testicular microlithiasis is associated with ethnicity and socioeconomic status. *Acta Radiol Open.* Aug 2017;6(8):2058460117723676.

71. Doubeni CA. The impact of colorectal cancer screening on the US population: is it time to celebrate? *Cancer.* Sep 15 2014;120(18):2810-2813.

72. Barlow WE, Beaber EF, Geller BM, et al. Evaluating Screening Participation, Follow-up, and Outcomes for Breast, Cervical, and Colorectal Cancer in the PROSPR Consortium. *J Natl Cancer Inst.* Mar 1 2020;112(3):238-246.

73. Giorgi Rossi P, Carrozzi G, Federici A, Mancuso P, Sampaolo L, Zappa M. Invitation coverage and participation in Italian cervical, breast and colorectal cancer screening programmes. *J Med Screen.* Mar 2018;25(1):17-23.

74. IARC. Cancer Today. *https://gco.iarc.fr/today/home.* Last accessed Jan 2021.

75. Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2019 with focus on breast cancer. *Ann Oncol.* May 1 2019;30(5):781-787.

76. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin.* May 2019;69(3):184-210.

77. Howard DH, Richardson LC, Thorpe KE. Cancer screening and age in the United States and Europe. *Health Aff (Millwood).* Nov-Dec 2009;28(6):1838-1847.

78. Bieniek JM, Juvet T, Margolis M, Grober ED, Lo KC, Jarvi KA. Prevalence and Management of Incidental Small Testicular Masses Discovered on Ultrasonographic Evaluation of Male Infertility. *J Urol.* Feb 2018;199(2):481-486.

79. Sabatino SA, White MC, Thompson TD, Klabunde CN, Centers for Disease C, Prevention. Cancer screening test use - United States, 2013. *MMWR Morb Mortal Wkly Rep.* May 8 2015;64(17):464-468.

80. IARC Working Group. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. *IARC.* 2012;100 B(Biological Agents).

81. Hooi JKY, Lai WY, Ng WK, et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. *Gastroenterology.* Aug 2017;153(2):420-429.

82. Roberts SE, Morrison-Rees S, Samuel DG, Thorne K, Akbari A, Williams JG. Review article: the prevalence of Helicobacter pylori and the incidence of gastric cancer across Europe. *Aliment Pharmacol Ther.* Feb 2016;43(3):334-345.

83. Baecker A, Liu X, La Vecchia C, Zhang ZF. Worldwide incidence of hepatocellular carcinoma cases attributable to major risk factors. *Eur J Cancer Prev.* May 2018;27(3):205-212.

84. Franceschi S, Montella M, Polesel J, et al. Hepatitis viruses, alcohol, and tobacco in the etiology of hepatocellular carcinoma in Italy. *Cancer Epidemiol Biomarkers Prev.* Apr 2006;15(4):683-689.

85. La Vecchia C, Bosetti C, Bertuccio P, Castro C, Pelucchi C, Negri E. Trends in alcohol consumption in Europe and their impact on major alcohol-related cancers. *Eur J Cancer Prev.* Jul 2014;23(4):319-322.

86. Zengerling F, Kunath F, Jensen K, Ruf C, Schmidt S, Spek A. Prognostic factors for tumor recurrence in patients with clinical stage I seminoma undergoing surveillance-A systematic review. *Urol Oncol.* Oct 2018;36(10):448-458.

87. Rosenberg ES, Rosenthal EM, Hall EW, et al. Prevalence of Hepatitis C Virus Infection in US States and the District of Columbia, 2013 to 2016. *JAMA Netw Open.* Dec 7 2018;1(8):e186371.

88. Lim JK, Nguyen MH, Kim WR, Gish R, Perumalswami P, Jacobson IM. Prevalence of Chronic Hepatitis B Virus Infection in the United States. *Am J Gastroenterol.* Sep 2020;115(9):1429-1438.

89. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology.* May 2012;142(6):1264-1273 e1261.

90. Pinheiro PS, Callahan KE, Jones PD, et al. Liver cancer: A leading cause of cancer death in the United States and the role of the 1945-1965 birth cohort by ethnicity. *JHEP Rep.* Sep 2019;1(3):162-169.

91. Borie F, Tretarre B, Bouvier AM, et al. Primitive liver cancers: epidemiology and geographical study in France. *Eur J Gastroenterol Hepatol.* Sep 2009;21(9):984-989.

92. Liu Y, Ding Z. Obesity, a serious etiologic factor for male subfertility in modern society. *Reproduction.* Oct 2017;154(4):R123-r131.

93. Carré J, Gatimel N, Moreau J, Parinaud J, Léandri R. Does air pollution play a role in infertility?: a systematic review. *Environ Health.* Jul 28 2017;16(1):82.

94. McQuillan G, Kruszon-Moran D, Markowitz LE, Unger ER, Paulose-Ram R. Prevalence of HPV in Adults Aged 18-69: United States, 2011-2014. *NCHS Data Brief.* Apr 2017(280):1-8.

95. Pinheiro PS, Callahan KE, Stern MC, de Vries E. Migration from Mexico to the United States: A high-speed cancer transition. *Int J Cancer.* Feb 1 2018;142(3):477-488.

96. Bertuccio P, Santucci C, Carioli G, Malvezzi M, La Vecchia C, Negri E. Mortality Trends from Urologic Cancers in Europe over the Period 1980-2017 and a Projection to 2025. *Eur Urol Oncol.* Oct 2021;4(5):677-696.

97. Bosetti C, Bertuccio P, Chatenoud L, Negri E, La Vecchia C, Levi F. Trends in mortality from urologic cancers in Europe, 1970-2008. *Eur Urol.* Jul 2011;60(1):1-15.

98. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. *Eur Urol.* Jan 2020;77(1):38-52.

99. Litwin MS, Tan HJ. The Diagnosis and Treatment of Prostate Cancer: A Review. *JAMA.* Jun 27 2017;317(24):2532-2542.

100. Negoita S, Feuer EJ, Mariotto A, et al. Annual Report to the Nation on the Status of Cancer, part II: Recent changes in prostate cancer trends and disease characteristics. *Cancer.* Jul 1 2018;124(13):2801-2814.

101. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* Feb 4 2021.

102. Force USPST, Grossman DC, Curry SJ, et al. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA.* May 8 2018;319(18):1901-1913.

103. Jemal A, Culp MB, Ma J, Islami F, Fedewa SA. Prostate Cancer Incidence 5 Years After US Preventive Services Task Force Recommendations Against Screening. *J Natl Cancer Inst.* Jan 4 2021;113(1):64-71.

104. Huncharek M, Haddock KS, Reid R, Kupelnick B. Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. *Am J Public Health.* Apr 2010;100(4):693-701.

105. Gallus S, Lugo A, La Vecchia C, et al. Pricing Policies And Control of Tobacco in Europe (PPACTE) project: cross-national comparison of smoking prevalence in 18 European countries. *Eur J Cancer Prev.* May 2014;23(3):177-185.

106. Haque R, Van Den Eeden SK, Wallner LP, et al. Association of body mass index and prostate cancer mortality. *Obes Res Clin Pract.* Jul-Aug 2014;8(4):e374-381.

107. Gurney JK, Florio AA, Znaor A, et al. International Trends in the Incidence of Testicular Cancer: Lessons from 35 Years and 41 Countries. *Eur Urol.* Nov 2019;76(5):615-623.

108. Znaor A, Lortet-Tieulent J, Jemal A, Bray F. International variations and trends in testicular cancer incidence and mortality. *Eur Urol.* Jun 2014;65(6):1095-1106.

109. Znaor A, Bray F. Thirty year trends in testicular cancer mortality in Europe: gaps persist between the East and West. *Acta Oncol.* Sep 2012;51(7):956-958.

110. Trama A, Foschi R, Larranaga N, et al. Survival of male genital cancers (prostate, testis and penis) in Europe 1999-2007: Results from the EUROCARE-5 study. *Eur J Cancer.* Oct 2015;51(15):2206-2216.

111. Znaor A, Skakkebaek NE, Rajpert-De Meyts E, et al. Testicular cancer incidence predictions in Europe 2010-2035: A rising burden despite population ageing. *Int J Cancer.* Aug 1 2020;147(3):820-828.

112. Nadal R, Bellmunt J. Management of metastatic bladder cancer. *Cancer Treat Rev.* Jun 2019;76:10-21.

113. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol.* Oct 2013;64(4):639-653.

114. Cumberbatch MGK, Jubber I, Black PC, et al. Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018. *Eur Urol.* Dec 2018;74(6):784-795.

115. Bafunno D, Catino A, Lamorgese V, et al. Tobacco control in Europe: A review of campaign strategies for teenagers and adults. *Crit Rev Oncol Hematol.* Jun 2019;138:139-147.

116. Huang J, Leung DK, Chan EO, et al. A Global Trend Analysis of Kidney Cancer Incidence and Mortality and Their Associations with Smoking, Alcohol Consumption, and Metabolic Syndrome. *Eur Urol Focus.* Jan 23 2021.

117. Perez-Farinos N, Lopez-Abente G, Pastor-Barriuso R. Time trend and age-period-cohort effect on kidney cancer mortality in Europe, 1981-2000. *BMC Public Health.* May 3 2006;6:119.

118. Levi F, Ferlay J, Galeone C, et al. The changing pattern of kidney cancer incidence and mortality in Europe. *BJU Int.* Apr 2008;101(8):949-958.

119. Dy GW, Gore JL, Forouzanfar MH, Naghavi M, Fitzmaurice C. Global Burden of Urologic Cancers, 1990-2013. *Eur Urol.* Mar 2017;71(3):437-446.

120. Molarius A, Parsons RW, Dobson AJ, et al. Trends in cigarette smoking in 36 populations from the early 1980s to the mid-1990s: findings from the WHO MONICA Project. *Am J Public Health.* Feb 2001;91(2):206-212.

121. Weikert S, Boeing H, Pischon T, et al. Blood pressure and risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. *Am J Epidemiol.* Feb 15 2008;167(4):438-446.

122. Moore LE, Boffetta P, Karami S, et al. Occupational trichloroethylene exposure and renal carcinoma risk: evidence of genetic susceptibility by reductive metabolism gene variants. *Cancer Res.* Aug 15 2010;70(16):6527-6536.

123. Dalmartello M, Bravi F, Serraino D, et al. Dietary Patterns in Italy and the Risk of Renal Cell Carcinoma. *Nutrients.* Jan 2 2020;12(1).

124. Bai X, Yi M, Dong B, Zheng X, Wu K. The global, regional, and national burden of kidney cancer and attributable risk factor analysis from 1990 to 2017. *Exp Hematol Oncol.* 2020;9:27.

125. Tyrrell HEJ, Church DN, Joseph J, et al. Changing Practice Evaluation-Stage 1 Seminoma: Outcomes With Adjuvant Treatment Versus Surveillance: Risk Factors for Recurrence and Optimizing Follow-up Protocols-Experience From a Supraregional Center. *Clin Genitourin Cancer.* Jun 2018;16(3):240-244.

126. Bosetti C, Carioli G, Santucci C, et al. Global trends in oral and pharyngeal cancer incidence and mortality. *Int J Cancer.* Aug 15 2020;147(4):1040-1049.

127. Malvezzi M, Santucci C, Alicandro G, et al. Childhood cancer mortality trends in the Americas and Australasia: An update to 2017. *Cancer.* Sep 15 2021;127(18):3445-3456.

128. Santucci C, Boffetta P, Levi F, La Vecchia C, Negri E, Malvezzi M. Colorectal Cancer Mortality in Young Adults Is Rising in the United States, Canada, United Kingdom, and Australia but Not in Europe and Asia. *Gastroenterology.* Apr 2021;160(5):1860-1862 e1862.

129. Santucci C, Patel L, Malvezzi M, et al. Persisting cancer mortality gap between western and eastern Europe. *Eur J Cancer.* Apr 2022;165:1-12.

130. Constantine GD, Kessler G, Graham S, Goldstein SR. Increased Incidence of Endometrial Cancer Following the Women's Health Initiative: An Assessment of Risk Factors. *J Womens Health (Larchmt).* Feb 2019;28(2):237-243.

131. Doll KM, Winn AN. Assessing endometrial cancer risk among US women: long-term trends using hysterectomy-adjusted analysis. *Am J Obstet Gynecol.* Oct 2019;221(4):318 e311-318 e319.

132. Lortet-Tieulent J, Ferlay J, Bray F, Jemal A. International Patterns and Trends in Endometrial Cancer Incidence, 1978-2013. *J Natl Cancer Inst.* Apr 1 2018;110(4):354-361.

133. Raglan O, Kalliala I, Markozannes G, et al. Risk factors for endometrial cancer: An umbrella review of the literature. *Int J Cancer.* Oct 1 2019;145(7):1719-1730.

134. Setiawan VW, Pike MC, Karageorgi S, et al. Age at last birth in relation to risk of endometrial cancer: pooled analysis in the epidemiology of endometrial cancer consortium. *Am J Epidemiol.* Aug 15 2012;176(4):269-278.

135. Wartko P, Sherman ME, Yang HP, Felix AS, Brinton LA, Trabert B. Recent changes in endometrial cancer trends among menopausal-age U.S. women. *Cancer Epidemiol.* Aug 2013;37(4):374-377.

136. Williams CL, Jones ME, Swerdlow AJ, et al. Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: Data linkage study including 2.2 million person years of observation. *BMJ (Online).* 2018;362.

137. Wu QJ, Li YY, Tu C, et al. Parity and endometrial cancer risk: a meta-analysis of epidemiological studies. *Sci Rep.* Sep 16 2015;5:14243.

138. Han MA, Storman D, Al-Rammahy H, et al. Impact of maternal reproductive factors on cancer risks of offspring: A systematic review and meta-analysis of cohort studies. *PLoS One.* 2020;15(3):e0230721.

139. Zhou CK, Sutcliffe S, Welsh J, et al. Is birthweight associated with total and aggressive/lethal prostate cancer risks? A systematic review and meta-analysis. *Br J Cancer.* Mar 29 2016;114(7):839-848.

140. Rawla P. Epidemiology of Prostate Cancer. *World J Oncol.* Apr 2019;10(2):63-89.

141. Richiardi L, Pettersson A, Akre O. Genetic and environmental risk factors for testicular cancer. *Int J Androl.* Aug 2007;30(4):230-240; discussion 240-231.

142. Cook MB, Akre O, Forman D, Madigan MP, Richiardi L, McGlynn KA. A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer--experiences of the mother. *Int J Epidemiol.* Dec 2009;38(6):1532-1542.

143. McGlynn KA, Cook MB. Etiologic factors in testicular germ-cell tumors. *Future Oncol.* Nov 2009;5(9):1389-1402.

144. Cook MB, Akre O, Forman D, Madigan MP, Richiardi L, McGlynn KA. A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer--experiences of the son. *Int J Epidemiol.* Dec 2010;39(6):1605-1618.

145. Stephansson O, Wahnstrom C, Pettersson A, et al. Perinatal risk factors for childhood testicular germ-cell cancer: a Nordic population-based study. *Cancer Epidemiol.* Dec 2011;35(6):e100-104.

146. Crump C, Sundquist K, Winkleby MA, Sieh W, Sundquist J. Gestational age at birth and risk of testicular cancer. *Int J Cancer.* Jul 15 2012;131(2):446-451.

147. Piltoft JS, Larsen SB, Dalton SO, et al. Early life risk factors for testicular cancer: a case-cohort study based on the Copenhagen School Health Records Register. *Acta Oncol.* Feb 2017;56(2):220-224.

148. Levine H, Keinan-Boker L, Leiba A, Derazne E, Rais A, Kark JD. Paternal age and risk of testicular germ cell tumors: a cohort study of 1,000,000 men. *Andrology.* Nov 2017;5(6):1124-1130.

149. Swaen GMH, Boffetta P, Zeegers M. Impact of changes in human reproduction on the incidence of endocrine-related diseases. *Crit Rev Toxicol.* Oct 2018;48(9):789-795.

150. Znaor A, Skakkebæk NE, Rajpert-De Meyts E, et al. Testicular cancer incidence predictions in Europe 2010–2035: A rising burden despite population ageing. *International Journal of Cancer.* 2020;147(3):820-828.

151. Le Cornet C, Lortet-Tieulent J, Forman D, et al. Testicular cancer incidence to rise by 25% by 2025 in Europe? Model-based predictions in 40 countries using population-based registry data. *Eur J Cancer.* Mar 2014;50(4):831-839.

152. Nigam M, Aschebrook-Kilfoy B, Shikanov S, Eggener S. Increasing incidence of testicular cancer in the United States and Europe between 1992 and 2009. *World J Urol.* May 2015;33(5):623-631.

153. Santucci C, Gallus S, Martinetti M, La Vecchia C, Bosetti C. Aspirin and the risk of nondigestive tract cancers: An updated meta-analysis to 2019. *Int J Cancer.* Mar 15 2021;148(6):1372-1382.

154. Bosetti C, Santucci C, Gallus S, La Vecchia C. Reply to the Letter to the Editor 'Aspirin to prevent gastrointestinal cancer - but recent trial data don't fit' by Jacobsen and colleagues. *Ann Oncol.* Sep 2020;31(9):1263.

155. Bosetti C, Santucci C, Gallus S, Martinetti M, La Vecchia C. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. *Ann Oncol.* May 2020;31(5):558-568.

156. Lepore V, Bosetti C, Santucci C, et al. Detection of disability worsening in relapsing-remitting multiple sclerosis patients: a real-world roving Expanded Disability Status Scale reference analysis from the Italian Multiple Sclerosis Register. *Eur J Neurol.* Feb 2021;28(2):567-578.

157. Bergamaschi R, Beghi E, Bosetti C, et al. Do patients' and referral centers' characteristics influence multiple sclerosis phenotypes? Results from the Italian multiple sclerosis and related disorders register. *Neurol Sci.* Sep 2022;43(9):5459-5469.

158. Bosetti C, Santucci C, Pasina L, et al. Use of preventive drugs during the last year of life in older adults with cancer or chronic progressive diseases. *Pharmacoepidemiol Drug Saf.* Aug 2021;30(8):1057-1065.

159. Corli O, Santucci C, Uggeri S, et al. Factors for Timely Identification of Possible Occurrence of Delirium in Palliative Care: A Prospective Observational Study. *Adv Ther.* Aug 2021;38(8):4289-4303.

160. Estruch R, Ros E, Salas-Salvado J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med.* Jun 21 2018;378(25):e34.