EUROPEAN CANCER MORTALITY PREDICTIONS FOR THE YEAR 2016 WITH FOCUS ON LEUKEMIAS

M. Malvezzi[1,2], G. Carioli[2], P. Bertuccio[2], T. Rosso[2], P. Boffetta[3], F. Levi[4], C. La Vecchia[2,*], E. Negri[1]

[1]Department of Epidemiology, IRCCS-Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy

[2]Department of Clinical Sciences and Community Health, Universitá degli Studi di Milano, Milan, Italy

[3]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, NY, USA

[4]Cancer Epidemiology Unit, Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital, Lausanne, Switzerland

[*]Correspondence to: Prof. Carlo La Vecchia, Department of Clinical Sciences and Community Health, Universitá degli Studi di Milano, Via Augusto Vanzetti 5, 20122 Milan, Italy. Tel: +39-02-39-01-4527; Fax: +39-02-33-200-231; E-mail: carlo.lavecchia@unimi.it

ABSTRACT

Background: Current cancer mortality statistics are important for public health decision making and resource allocation. Age standardized rates and numbers of deaths are predicted for 2016 in the European Union.

Patients and methods: Population and death certification data for stomach, colorectum, pancreas, lung, breast, uterus, prostate, leukemia and total cancers were obtained from the World Health Organisation database and Eurostat. Figures were derived for the EU, France, Germany, Italy, Poland, Spain and the UK. Projected numbers of deaths by age group were obtained for 2016 by linear regression on estimated numbers of deaths over the most recent time period identified by a joinpoint regression model.

Results: Projected total cancer mortality trends for 2016 in the EU are favourable in both sexes with rates of 133.5/100,000 men and 85.2/100,000 women (8% and 3% falls since 2011, due to population ageing) corresponding to 753,600 and 605,900 deaths in men and women for a total number of 1,359,500 projected cancer deaths (+3% compared to 2011). In men lung, colorectal and prostate cancer fell 11%, 5% and 8% since 2011. Breast and colorectal cancer trends in women are favourable (8% and 7% falls, respectively), but lung and Pancreatic cancer rates rose 5% and 4% since 2011 reaching rates of 14.4 and 5.6/100,000 women. Leukemia shows favourable projected mortality for both sexes and all age groups with stronger falls in the younger age

groups, rates are 4.0/100,000 men and 2.5/100,000 women, with respectively falls of 14% and 12%.

Conclusion:The 2016 predictions for EU cancer mortality confirm the favourable trends in rates particularly for men. Lung cancer is likely to remain the leading site for female cancer rates. Continuing falls in mortality, larger in children and young adults, are predicted in leukemia, essentially due to advancements in management and therapy, and their subsequent adoption across Europe.

Keywords: cancer, Europe, mortality, projections, leukemia, time trends.

Key Message: "Total cancer mortality rates in the EU are predicted to fall 8% in men and 3% in women between 2011 and 2016. However, due to population aging, total number of cancer deaths will rise to 1,360,000. Mortality outlook for 2016 remains favourable, except for lung and pancreatic cancers in women. Leukemias showed favourable trends in both sexes and all age groups, with larger falls in the young."

INTRODUCTION

We previously published short-term cancer mortality predictions for the European Union (EU) as a whole, and for its six more populous countries up to the year 2015 [1-5]. On the basis of the World Health Organization (WHO) mortality database [6], here we provide the corresponding figures for the year 2016. In the present paper, we also focus specifically on leukemias, giving predicted numbers of deaths and death rate estimates for this important group of neoplasms in various age groups, and discuss their declines across sexes, countries and age groups.

MATERIALS AND METHODS

This work is an update to the previous articles on predicted European cancer mortality, hence similar methods are used [1, 5].

We obtained official death certification data from the WHO database (WHOSIS) [6] for stomach, colorectum, pancreas, lung, breast, uterus (cervix and corpus), prostate, leukemias and total cancer (malignant and benign) mortality.

Figures were derived for the EU (28 countries as of July 2013) in the period 1970-2011 and up to the most recent available year for 6 major European countries: France (2011), Germany (2013), Italy (2012), Poland (2013), Spain (2013) and the UK (2013). Details on data sources and preparation are given in the Appendix.

From the matrices of certified deaths and resident populations, we computed age-specific number of deaths and rates for each 5-year age group (from 0–4 to 85+ years) and calendar year. Age-standardised rates (world standard population) per 100 000 men and women, at all ages, were computed using the direct method, on the basis of

the world standard population [7]. For leukemias, rates for the 0-14, 15-44 and 45-69 years age-groups were also computed.

We fit a logarithmic Poisson count data joinpoint regression model to the numbers of certified deaths for each 5-year age group to identify the most recent trend segment (see Appendix) [8].

We applied a linear regression to mortality data for each 5-year age group over the most recent trend segment identified by the joinpoint model in order to compute the predicted age-specific certified numbers of deaths and the corresponding 95% prediction intervals (PIs) [9]. Predicted age-specific numbers of deaths and the predicted population data from Eurostat were used to compute the predicted age standardized death rates with 95% PIs [10].

RESULTS

Table 1 shows the total numbers of predicted cancer deaths (rounded to the nearest hundred) and the death rate predictions with corresponding 95% PIs for the selected neoplasm for 2016, in the EU as a whole, as well as the 2011 recorded data. Overall, 1 359 500 EU citizen are projected to die of cancer in 2016 (753 600 men and 605 900 women), compared with the 1 314 787 cancer deaths recorded in 2011 (734 259 men and 580 528 women). These figures correspond to age-standardised rates of 133.5/100 000 men and 85.2/100 000 women predicted for 2016, compared with 144.6 men and 88.1 women recorded in 2011. Thus, a 7.7% fall in rates for men and a 3.3% one in women are predicted between 2011 and 2016, despite an increase of about 45 000 (+3.3%) in the absolute number of cancer deaths.

Figure 1A shows bar plots of death rates per 100 000 population and numbers of deaths from all cancers for the year 2011 for EU men and women, and the predicted values for 2016 with corresponding 95% PIs. **Figure 1B** shows bar plots of death rates per 100 000 population for 2011 and the predicted rates for 2016 with 95% PIs for the eight neoplasm sites considered for the EU (in men and women).

Lung cancer is responsible for nearly 274 000 predicted deaths in both sexes combined in 2016, corresponding to over 20% of total cancer deaths, and it has the highest predicted rates in both sexes, in men 34.0/100 000, corresponding to 183 800 predicted deaths (24.4% of total male cancer deaths), despite a 10.7% fall in rates since 2011. In women, mortality from lung cancer is still rising and it is likely to be the neoplasm with the highest mortality rate in the EU in women in 2016, with a predicted rate of 14.4/100 000, corresponding to 89 700 predicted deaths (14.8% of total female cancer deaths), and to a 5.4% rise in rates since 2011.

Breast cancer has the second highest projected rate (14.3/100 000, with a 7.6% fall from 2011), but the total number of deaths remains highest for this neoplasm (92 300). Between the ages of 55 and 79 years, more deaths from female lung than breast cancer were predicted, while in elderly women an excess in breast cancer deaths persisted.

The cancer with the second largest impact in men is that of colorectum, with a predicted rate of 16.2/100 000 corresponding to a 4.6% fall, followed by prostate cancer, with a predicted rate of 10.6/100 000 men with a 7.8% fall since 2011. In women colorectal cancer shows the third highest predicted rate (9.3/100 000, with a

7.0% fall from 2011); deaths from this cancer represent 12.8% of total cancer deaths in the EU in 2016, with 173 400 projected deaths.

Pancreatic cancer shows rising predicted death rates in women (5.6/100 000, +3.9%), while the predicted rate of 7.9/100 000 in men only shows a 0.5% fall compared to 2011. The corresponding total deaths are 85 600, that is 6.3% of all predicted cancer deaths. Cancer of the uterus, stomach and leukemias each represent <5% of total cancer deaths, and show persistent declines.

Figure 2 illustrates trends in all age standardised cancer mortality rates for men and women in quinquennia centred from 1972 to 2007, and the predicted rates for 2016 with PIs for all cancers. Trends in total cancer mortality in the EU are favourable in both sexes; in men rates have been falling since the late 1980s, while in women they have been favourable over the entire period, though in recent years the falls in women were less pronounced than in men.

Figure 3 gives corresponding trends for major cancer sites. Stomach cancer mortality shows the greatest falls over the whole period. In men, lung cancer also showed appreciable falls in mortality since the late 1980s as did breast cancer in women. The only exceptions to these generally favourable trends in the EU are pancreatic cancer in both sexes and lung cancer in women: pancreatic cancer mortality rates have been showing steady rises in women, while in men it seems to have stabilized. Over the last decades female lung cancer has shown strong rises. See supplementary Appendix for individual country data and analyses (supplementary **Tables S1–S9** and **Figure S1**, available at Annals of Oncology online).

Table 2 gives age standardised leukemia mortality rates in 2000–2004 and 2005–2009,

predicted mortality rate for 2016 and the percent difference between the 2016

prediction and 2007 (2005-2009 quinquennium), for all ages, 0–14, 15–44 and 45–69

years age groups, for male and female, in the six studied countries and the EU as a

whole. In 2000-2004, leukemia mortality rates for all ages in men were between 5 and

6/100 000, and showed favourable trends in all countries and the EU as a whole, giving

predicted rates for 2016 between 4 (Spain and UK) and 5/100 000 (Poland and Italy).

Similarly, in women, in 2000-2004, leukemia mortality rates for all ages in women were

around 3/100 000, and predicted rates for 2016 are between 2 and 3/100 000 (UK and

Italy). The overall decline between 2007 and 2016 approached 16% in women and 19%

in men. The falls, however were greatest in children (38% in males, 20% in females)

and young adults (26% in males, 22% in females). The predicted rates for 2016 in the

EU are favourable compared with 2011, with values of 4 at all ages, 0.5 at 0–14 years,

1 at 15–44 years and 6.8 /100 000 at 45–69 year in men, and values of 2.5, 0.6, 0.7 and

4.2/100 000 in women, respectively.

Figure 4 illustrates joinpoint analysis of EU leukemia mortality rates for men and

women in the four age groups considered, with predictions for 2016 and relative PIs. In

both sexes, rates for all age groups display a similar pattern with important falls over

the whole studied period, except for men aged 45-69 and all ages, where xxx

favourable trends start in the late 70s.

DISCUSSION

The 2016 projections confirm the favourable outlook for total cancer mortality previously reported [3-5]. Total cancer mortality rates in the EU are projected to decrease in both sexes, in spite of the slight rise in number of deaths due to the ageing of the European population [11]. In fact, the median age of the total EU population was 41 in 2011 and rose to 42 in 2016, corresponding median ages for men were 39 in 2011 and 41 in 2016, and in women 42 in 2011 and 44 in 2016. The greater falls seen, over the studied period, in men (over 10%) as compared to women (about 3%), are mainly driven by the different trends in cancer related to tobacco smoking between the sexes [12]. The fall in tobacco related cancer mortality is the main driver for the fall in overall cancer mortality in men, while in women the fall is mainly due to cancers amenable to treatment and subject to early diagnosis, i.e. cancers of the breast and uterus (as well as stomach and colorectum), whereas lung cancer trends remain upwards [4, 5].

Lung cancer mortality reflects the differences between smoking prevalence trends between the sexes and European countries [12].

The 2016 projection confirms the steady declines of lung cancer mortality in men and the increases in women, with lung cancer rates much higher than breast cancer rates in young and middle age women, indicating that the excess lung cancer mortality is likely to be greater in the near future. In the UK where female projections for this cancer have been unstable, updated data to 2013 brought about a downward projected trend, this would be in line with lung cancer age-period-cohort analyses for this country [13].

Improved therapeutic procedures, and advancements in diagnosis and screening have determined favourable trends in several cancer sites and are among the main drivers of the decline in cancer mortality in women, including breast and cervical cancer. However, a slowdown in the falls in uterine cancer mortality is apparent for several countries. The exception to these descending rates is the UK, particularly in elderly women and hence likely due to endometrial cancer linked to overweight and diabetes [14]. National mortality data do not allow separate analysis of cervix and corpus uteri cancers.

Prostate cancer trends are also descending, albeit with variable degrees across countries. The role of screening practices is still debated, but it may have had a role in the measured and projected falls in mortality.[15, 16]. Effective modern therapies, including radiotherapy and anti-androgens, and management protocols are, however, the major determinants of the favourable trends, not only in the middle aged, but also in the elderly [15]. The excess in mortality for elderly Polish men is likely due to delayed adoption of these therapies.

EU colorectal cancer mortality reductions are brought mainly by northern and western European countries thanks to better awareness of the disease, screening, early diagnosis and patient management protocols and treatments [17, 18]. However, projected rises in Spain and particularly in Poland (which has the highest rates in Europe), highlight the need to rationalize these strategies in southern and eastern Europe.

The favourable trends in mortality from stomach cancer are projected to continue into 2016. Thus, gastric cancer remains one of the main drivers of the total favourable

trends in both sexes; the most probable determinants of these trends are a more affluent varied diet, better food conservation and the fall in Helicobacter Pylori infection across generations [19, 20]. However, falls seem to be slowing down, particularly in women and in countries where rates are already low [20, 21]. This suggests that mortality levels of this tumour are reaching an asymptote. National mortality data do not allow to discriminate cardias versus corpus and pyloric cancer. It is therefore possible that such a levelling in rates is due to lack of declines in cardias and cardio-esophageal-junction cancer mortality.

Pancreatic cancer is the tumour with the least favourable outlook in both sexes. However, in men, projections for the EU give a stable mortality rate rather than a rising one, while in women the unfavourable trend is confirmed [3-5]. Aetiology for this cancer is still largely uncertain, but smoking plays a relevant role accounting for 20 to 30% of cases in various populations [22-24]. Consequently, the observed differences in trends between sexes may well be explained by the different smoking trends. The other relevant recognized risk factors are obesity and diabetes, whose prevalence has increased over recent years in most populations [25].

Inferences on leukemia mortality are complicated by the nature of this heterogeneous group of diseases; national mortality data does not allow for their individual separation and analysis. Projections for these cancers in 2016 are favourable in both sexes for most age groups and countries, but the falls are appreciably larger at younger ages. Therapeutic advancements are the main drivers of these trends; these include better diagnosis, multidrug chemotherapy and immunotherapy protocols assisted by toxicity limiting therapies and improved radiotherapy [26, 27].

The distribution of leukemias by type varies by age. Children are generally affected by

acute lymphoblastic leukemia (ALL) that is also frequent in adolescents and young

adults. In contrast chronic leukemias, in particular chronic lymphocytic leukemia (CLL)

is common in the elderly. ALL is mostly curable and 5-year survival in children has

reached over 90% in optimum conditions [28]. Improvements have also been observed

in adolescents and adults; these are attained through improved disease management

and, in recent years, relapse control using allogenic hematopoietic stem cell

transplants and immunotherapy, as well as using pediatric inspired regimens in young

adults [29-33]. Stem cell transplants and new chemotherapy regimens have also

brought improvements in acute myelogenous leukemia (AML) that is relatively

common in adult and elderly patients [34, 35]. Chronic leukemia is hardly curable, but

long term survival has been achieved in chronic myeloid leukemia, since the

introduction of tyrosine kinase inhibitors [36-39]. Some improvement in survival in

Europe, though not as strong as in the USA [40], has also been observed in CLL even

though it is mainly in patients under 75 years of age. These improvements are due to

better diagnosis, management and therapy including anti-CD20 antibodies like

Obintuzimab combined with Chlorambucil [41, 42].

Given large size of the underlying population, EU cancer mortality predictions should

not be affected by random oscillations or major unexpected factors. However, if some

factors were to determine changes within the last few years the model would not be

able to account for them. Also the linear models used tend to underestimate future

rates, particularly under certain conditions (eg. asymptotic behaviours after strong

descending trends); hence, in some scenarios predictions may be overly optimistic within a global picture of declining trends [43].

Updated data from the WHO made it possible to compute EU age standardised mortality rates for 2011, and compare these data with our predictions [1]. All estimates, with the exceptions, in women, for stomach and uterine cancers and leukemias, are within a 5% difference. Stomach and uterine cancer trends fall within the model's predictive limits, while for leukemia, discrepancy between predicted and observed rates affects the younger age groups that are weighted heavily in the world standard population.

In conclusion EU cancer mortality predictions for 2016 confirm the favourable trends in rates (although in the absence of a decline in the absolute number of deaths) particularly for men. This is essentially due to larger declines in tobacco smoking in men than in women in recent decades. Despite the steady favourable trends in breast and uterine (mainly cervix) cancer mortality, they also confirm that lung cancer is likely to be the leading site for cancer rates in EU women. With specific reference to leukemia, they confirm the favourable trends in mortality due to the advancement in therapy, particularly for acute leukemia in children and young adults.

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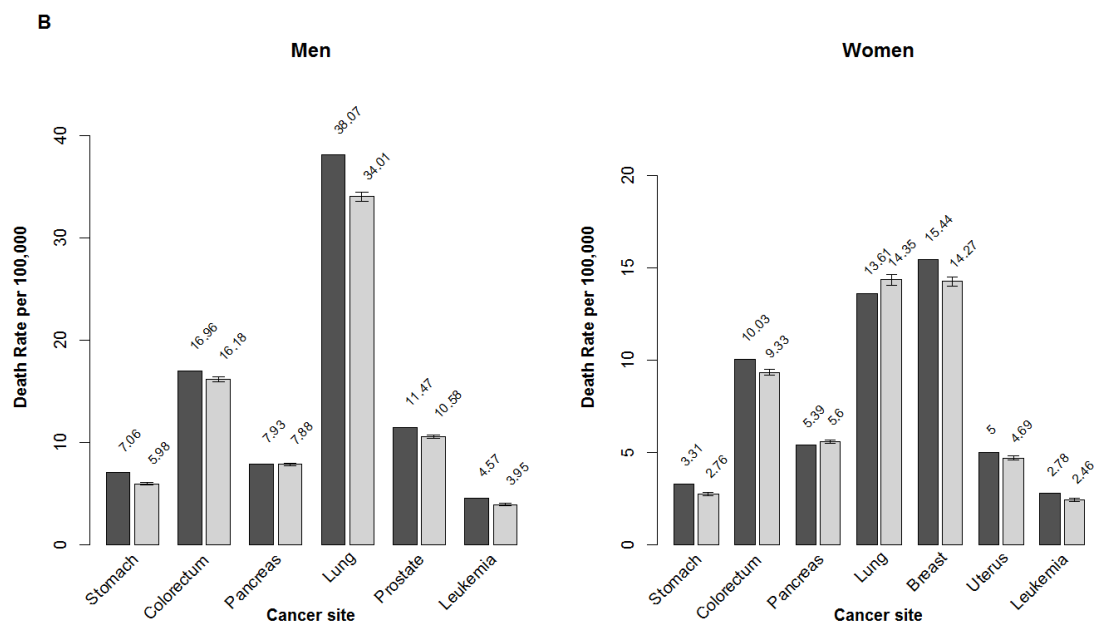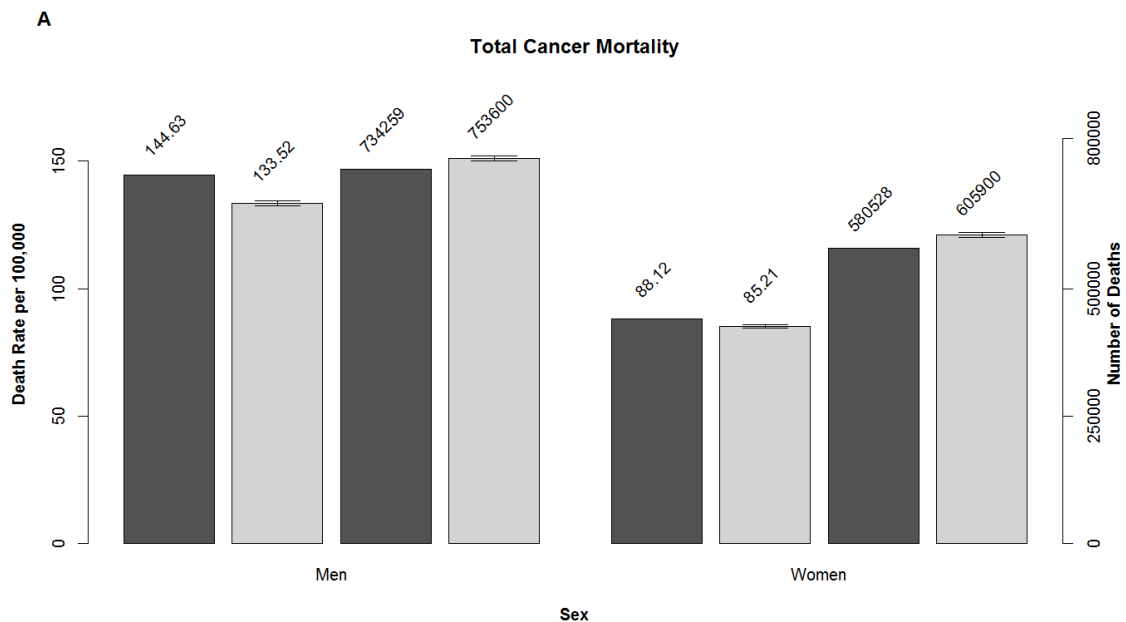
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Figure 1A Bar-plots of age-standardized (world population) death rates per 100 000

and number of deaths for the year 2011 (dark gray) and predicted rates and number of

deaths (predicted numbers of deaths are rounded to the nearest hundred) for 2016

(light gray) with 95% prediction intervals (PIs) for total cancer mortality in the EU in

men and women. **B** Bar-plots of age-standardized death rates per 100 000 population

for year 2011 (dark gray) and predicted rates for 2016 with 95% PIs (light gray) in the

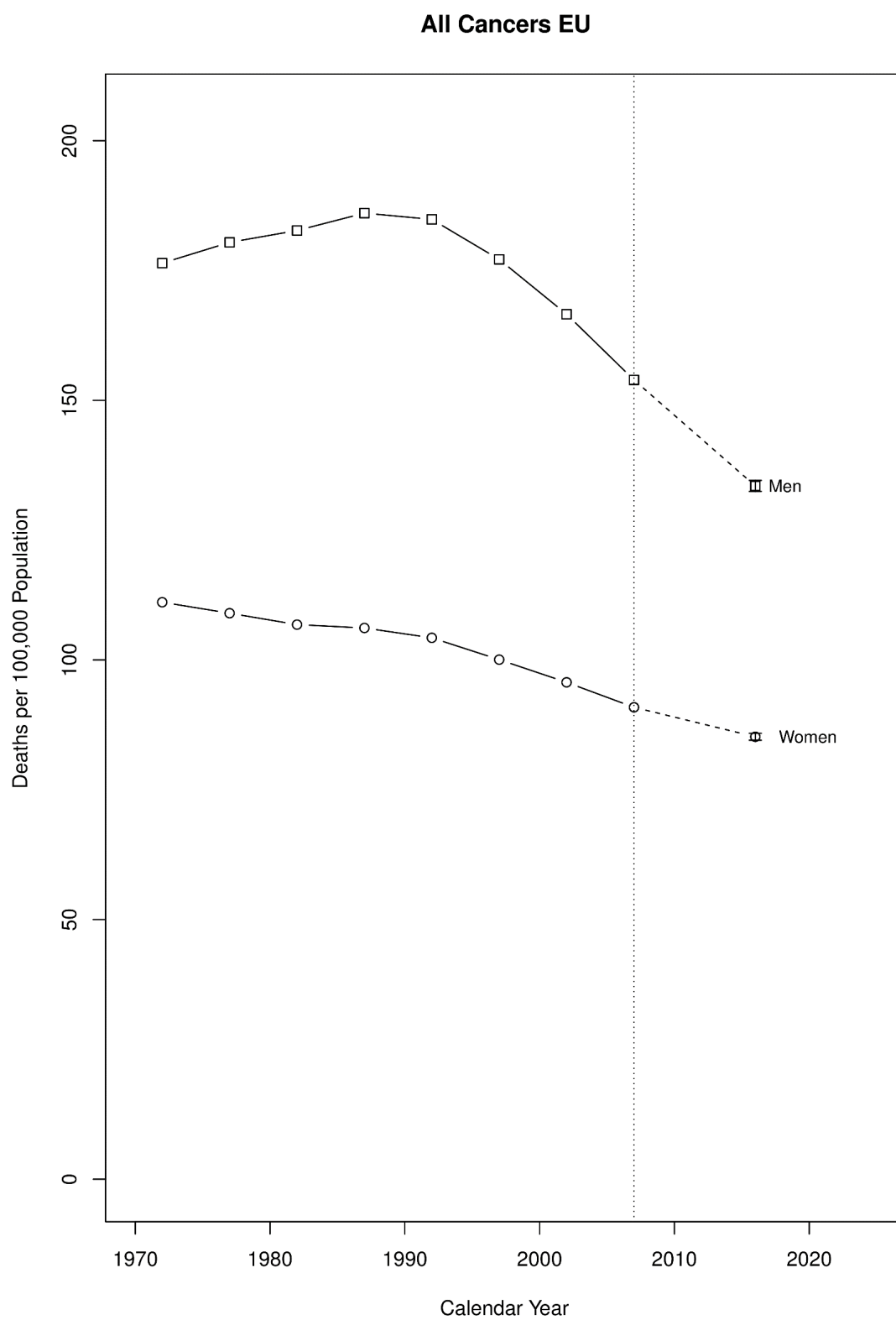EU in men and women for selected cancer sites.

Figure 2 Age-standardized (world population) total cancer mortality rate trends in

quinquennia from 1970-74 to 2005-09 and predicted rates for 2016 with 95%

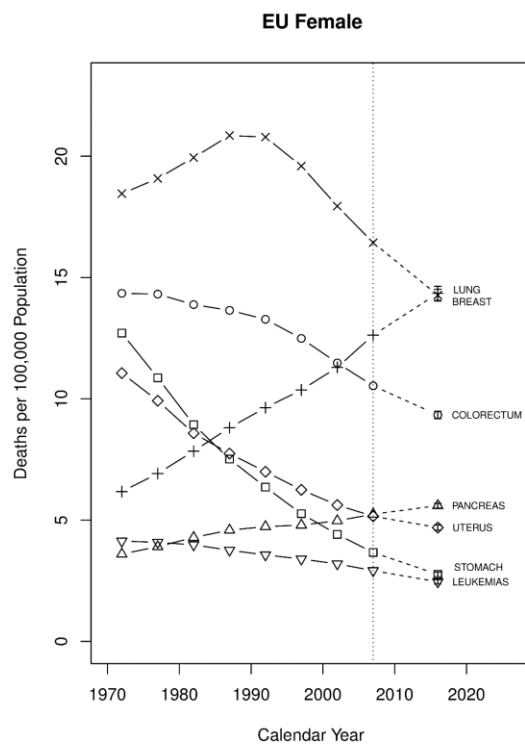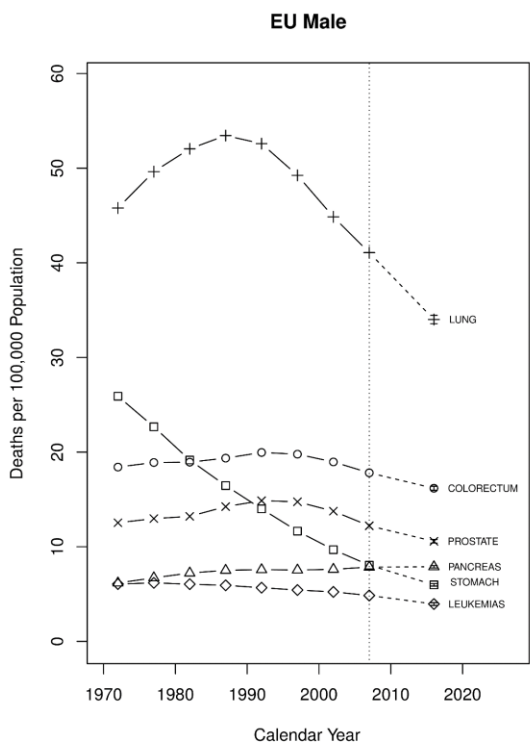prediction intervals (PIs), for men (squares) and women (circles) in the EU.

Figure 3 Age-standardized (world population) EU male and female cancer mortality

rate trends in quinquennia from 1970-74 to 2005-09 and predicted rates for 2016 with

95% prediction intervals (PIs). Men: stomach (squares), colorectum (circles), pancreas

(triangles), lung (crosses), prostate (xs) and leukemias (diamonds). Women: stomach

(squares), colorectum (circles), pancreas (triangles), lung (crosses), breast (xs), uterus (diamonds) and leukemias (inverted triangles).

Figure 4 Annual leukemias age-standardized (world population) death rates in the EU per 100,000 for all-ages, 0-14, 15-44 and 45-69 years age groups from 1970 to 2009, the resulting joinpoint regression models, and predicted rates for the year 2016 with 95% PIs. On the left, men and women all-ages (full squares and full circles, respectively) and men and women 0-14 years (empty squares and empty circles, respectively), on the right, men and women 15-44 years (full squares and full circles, respectively) and men and women 45-69 (empty squares and empty circles, respectively).

A

Total Cancer Mortality

B

Men

Women

All Cancers EU

EU Male

EU Female

Leukemias

All ages and 0–14 years · 15–44 and 45–69 years

Deaths per 100,000 Population · Calendar Year

Men all ages · Women all ages · Men 0–14 · Women 0–14 · Men 45–69 · Women 45–69 · Men 15–44 · Women 15–44
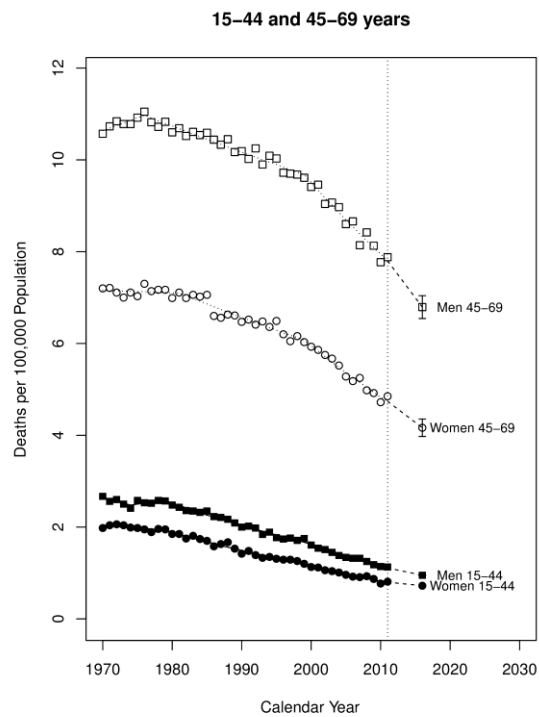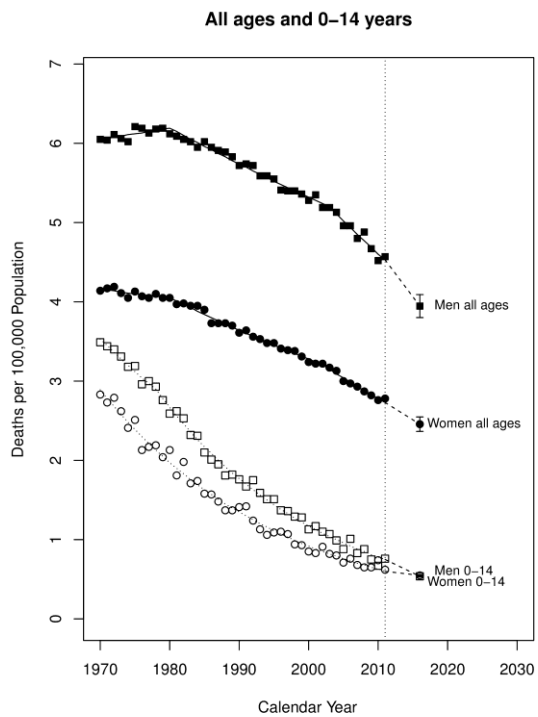
TABLE 1

Number of predicted cancer deaths and mortality rates for the year 2016 and comparison figures for most recent data for the EU as a whole, with 95% prediction intervals.

European Union		Observed number of deaths 2011	Predicted number of deaths 2016	Lower prediction limit (95%)	Upper prediction limit (95%)	Observed ASR[a] 2011	Predicted ASR[a] 2016	Lower prediction limit (95%)	Upper prediction limit (95%)
Sex	Cancer								
Men	STOMACH	36332	33800	33105	34585	7.06	5.98	5.84	6.11
	COLORECTUM	90412	95600	94432	96707	16.96	16.18	15.96	16.40
	PANCREAS	39056	42600	41974	43250	7.93	7.88	7.76	8.01
	LUNG	185707	183800	181553	186115	38.07	34.01	33.57	34.45
	PROSTATE	72330	75800	74672	76999	11.47	10.58	10.39	10.77
	LEUKEMIAS	22694	23000	22453	23465	4.57	3.95	3.80	4.09
	ALL NEOPLASMS (malignant and benign)	734259	753600	748212	759068	144.63	133.52	132.46	134.58
Women	STOMACH	23883	21400	20740	22015	3.31	2.76	2.67	2.86
	COLORECTUM	77478	77800	76641	78953	10.03	9.33	9.18	9.49
	PANCREAS	38693	43000	42376	43587	5.39	5.60	5.50	5.69
	LUNG	79474	89700	88177	91144	13.61	14.35	14.05	14.64
	BREAST	91291	92300	91060	93544	15.44	14.27	14.03	14.52
	UTERUS (CERVIX AND CORPUS)	28614	28900	28287	29485	5.00	4.69	4.58	4.80
	LEUKEMIAS	18751	19100	18661	19529	2.78	2.46	2.37	2.55
	ALL NEOPLASMS (malignant and benign)	580528	605900	601438	610265	88.12	85.21	84.54	85.87

[a] ASR, standardized using the World Standard Population

ASR, age-standardized mortality rates

TABLE 2

Age-standardised leukemia mortality rates for all ages in selected European countries and the EU as a whole, in men and women, for all ages, 0-14, 15-44 and 45-69 years in the quinquennia 2000-04, 2005-09 and the predicted rates for 2016, with percentage differences between 2016 and 2007 (2005-09 quinquennium).

		Men				Women			
		ASR* 2000-04	ASR* 2005-09	Predicted ASR* 2016	% Difference 2016 vs 2007	ASR* 2000-04	ASR* 2005-09	Predicted ASR* 2016	% Difference 2016 vs 2007
Selected European countries	France	5.46	5.06	4.00	-0.21	3.22	2.87	2.31	-0.20
	Germany	5.02	4.56	4.13	-0.09	3.15	2.88	2.50	-0.13
	Italy	5.69	5.24	4.49	-0.14	3.44	3.07	2.78	-0.09
	Poland	5.63	5.53	4.53	-0.18	3.36	3.20	2.53	-0.21
	Spain	4.79	4.31	3.56	-0.17	2.87	2.50	2.20	-0.12
	United Kingdom	4.66	4.40	3.74	-0.15	2.85	2.53	2.12	-0.16
European Union	All ages	5.23	4.85	3.95	-0.19	3.20	2.92	2.46	-0.16
	0-14 years**	1.10	0.87	0.54	-0.38	0.85	0.69	0.55	-0.20
	15-44 years**	1.50	1.28	0.95	-0.26	1.07	0.92	0.72	-0.22
	45-69 years	9.19	8.39	6.79	-0.19	5.74	5.12	4.16	-0.19

*ASR, age-standardized mortality rates using the World Standard Population

** Predictions estimated with a log-linear model