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Prostate cancer incidence and mortality trends in 37 European countries: An overview

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ABSTRACT

Prostate cancer has emerged as the most frequent cancer amongst men in Europe, with incidence increasing rapidly over the past two decades. Incidence has been uniformly increasing in the 24 countries with comparable data available, although in a few countries with very high rates (Sweden, Finland and The Netherlands), incidence has begun to fall during the last 3–4 years. The highest prostate cancer mortality rates are in the Baltic region (Estonia, Latvia and Lithuania) and in Denmark, Norway and Sweden. Prostate cancer mortality has been decreasing in 13 of the 37 European countries considered – predominantly in higher-resource countries within each region – beginning in England and Wales (1992) and more recently in the Czech Republic (2004). There was considerable variability in the magnitude of the annual declines, varying from approximately 1% in Scotland (from 1994) to over 4% for the more recent declines in Hungary, France and the Czech Republic. There appears little relation between the extent of the increases in incidence (in the late 1990s) and the recent mortality declines. It remains unclear to what extent the increasing trends in incidence indicate true risk and how much is due to detection of latent disease. The decreasing mortality after 1990 may be attributable to improvements in treatment and to an effect of prostate specific antigen (PSA) testing. The increase in mortality observed in the Baltic region and in several Central and Eastern European countries appear to reflect a real increase in risk and requires further monitoring.

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1. Introduction

Prostate cancer has become the most common non-skin cancer neoplasm amongst men in Europe, with an estimated 382,000 cases occurring in 2008.[1] Incidence has increased rapidly over the past two decades, and rates are influenced by early diagnosis by prostate specific antigen (PSA) testing amongst men, with or without symptoms, as well as by the detection of latent cancer in prostate surgery. PSA testing has been particularly common in certain Northern and Western European countries, an observation likely to explain much of the eightfold variation in incidence rates in Europe around 2000, with rates highest in Tyrol, Austria and lowest in Serbia.[2]

Almost 90,000 deaths from prostate cancer were estimated to have occurred in 2008 in Europe, ranking it the third most common cause of cancer death amongst men, after lung and colorectal cancers.[1]

The mortality rate is less affected by early diagnosis of asymptomatic cancers, and consequently the high death

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rates in the Nordic countries are five times those seen in several Central and Eastern European countries (such as Serbia, Russia and the Ukraine), where rates have been relatively low for decades.

This study aims to describe comprehensively the overall trends in prostate cancer incidence and mortality rates in 37 European countries by region, using published incidence data from population-based national and regional cancer registries and national death rates from the World Health Organisation (WHO) mortality databank. The temporal trends in rates are compared and discussed in light of the recent impact – within the last 15 years – of treatment with curative intent versus that of PSA testing, subsequent biopsy and treatment on mortality.

2. Data sources and methods

2.1. *Incidence*

Numbers of incident prostate cancer cases (ICD-10 C61) and the corresponding population figures were obtained from recently published reports from population-based cancer registries in Europe, with data commonly obtained from the Institutions' websites. The data for England and Wales were extracted from the Office for National Statistics website (www.statistics.gov.uk), and those from Scotland from the Information Services Division website (www.isdscotland.org). To merit inclusion, incidence data spanning 11 years or more were required, and 18 countries with national data matched this criterion (Table 1). For a further six countries, numbers of incident prostate cancer cases and corresponding population data were obtained from the Cancer Incidence in Five Continents Plus (CI5*Plus*) Dataset (ci5.iarc.fr) by registry, year of diagnosis and 5-year age group. Where appropriate, data from regional registries were aggregated to obtain an estimate of the national incidence. As the span of data available from regional registries varied, the aggregation maximised the number of registries, with as many of the regional registries involved as possible in the estimation. Finally, we analysed incidence data from 24 countries, restricting the incidence data to 1975 and thereafter to emphasise more recent trends.

2.2. *Mortality*

Prostate cancer mortality data (ICD-7 177, ICD-8/9 185 and ICD-10 C61) were extracted directly from the WHO mortality databank for 37 countries by year of death and 5-year age group, alongside national population figures from the same source. As with incidence, datasets had to span at least 11 years with a restriction to years of death from 1975. The change from ICD-8 to ICD-10 in 1995 in Switzerland caused discontinuities in trends and the Swiss data prior to 1995 and have been corrected accordingly.[3]

3. Statistical methods

The annual age-standardised rates (ASR) of prostate cancer incidence and mortality were calculated for all ages by country and period using the European standard population.[4] To provide estimated annual percentage change (EAPC), country-specific regression models of year of event were fitted to the rates using the Joinpoint regression programme version 3.4.2.[5]

Joinpoint regression is a tool for identifying sudden changes in the long-term trend in epochs, or *linear segments* of time, for which rates are relatively stable, thus avoiding the need to arbitrarily select a base for estimating the direction and magnitude of the slope. A logarithmic transformation of the rates, the standard error calculated using the binomial approximation[6] and a maximum number of three joinpoints were used in the analysis. The method identifies changes in the linear trends of incidence and mortality based on regression models with 0, 1, 2 and 3 joinpoints. The final model selected was the most parsimonious of these, with the EAPC based on the trend within each segment. The associated 95% confidence interval (95% CI) is indicative of the adequacy of the final model and the degree of random variation inherent in the underlying rates.

In order to quantify the trends over a fixed predetermined interval (*a priori* established as 1990–2004 for incidence and from 1996 to the last year available for mortality), we estimated the average annual percentage change (AAPC). The AAPC is a summary measure computed as a weighted average of the EAPCs from the joinpoint model, with the weights equal to the length of the linear segments.[7]

4. Results

4.1. *Geographical variations in incidence and mortality*

A comparison of prostate cancer incidence in 24 European countries revealed a fivefold variation in the age-adjusted rates 2001–2005, from less than 30 in the Russian Federation to more than 150 per 100,000 in Finland and Sweden (Fig. 1). Rates were high also in Iceland and Switzerland and tended to be relatively low in Belarus and Poland. Mortality rates varied by a factor of 2.5 around 2006, with rates above 30 in the Baltic countries (Estonia, Latvia and Lithuania), as well as in several Nordic countries, Slovenia and Ireland. As with incidence, low rates of prostate cancer mortality (below 15 per 100,000) were found in several Eastern European countries, including Bulgaria, Romania, the Russian Federation and the Ukraine.

Fig. 2a portrays the incidence rates 1985–1989 against mortality rates 5–10 years later (circa 1995). The correlation was reasonably strong between the two measures (Spearman's $\rho = 0.92$), with the mortality rates for a given population directly related to the prior level of incidence. In contrast, a lesser correlation was found more recently, between incidence in 1996–2000 and mortality circa 2006 (Spearman's $\rho = 0.45$), though low incidence was frequently associated with a low mortality (Fig. 2b).

4.2. *Trends in incidence and mortality by European region*

4.2.1. *General patterns*

An increasing trend in the incidence of prostate cancer was observed in all the 24 European countries included in the analysis (Fig. 3a and Table 1). The rate of increase ranged from 3% to 4% on average per annum since 1990 in The

Table 1 – Prostate cancer incidence: new cases, person-years and age-standardised (Europe) rates circa 2001–2005, data span available and joinpoint regression analysis by country within European region.

Area	Country	Mean incident cases per year 2001–2005[A]	Person-years 2001–2005[A]	ASR (Europe) 2001–2005[A]	Observed period	JP linear segment	EAPC[B] (95% CI)
Northern	Denmark	2569	26,64,175	81.2	1975–2007	1975–1991	1.0[B] (0.6–1.5)
						1991–1995	–2.9 (–7.9 to 2.4)
						1995–2007	7.2[B] (6.7 to 7.7)
	Estonia	447	626,079	71.7	1985–2003	1985–2003	5.5[B] (4.1 to 6.9)
	Finland	4480	25,49,670	154.9	1975–2007	1975–1990	1.5[B] (0.6 to 2.4)
						1990–1995	9.3[B] (4.3 to 14.5)
						1995–2005	5.3[B] (4.3 to 6.3)
						2005–2007	–13.4[B] (–21.3 to –4.8)
	Iceland	191	145,295	140.4	1975–2007	1975–2007	3.0[B] (2.6 to 3.5)
	Ireland	2209	19,81,322	126.9	1994–2005	1994–2005	7.1[B] (5.9 to 8.3)
	Latvia	639	10,77,256	60.3	1984–2003	1984–1994	1.2 (–0.3 to 2.7)
						1994–2003	11.0[B] (9.6 to 12.4)
	Lithuania	1614	16,11,483	105.8	1986–2005	1986–1992	1.3 (–2.7 to 5.3)
						1992–2000	8.1[B] (5.4 to 10.8)
						2000–2003	21.0[B] (5.5 to 38.9)
						2003–2005	5.8 (–5.3 to 18.1)
	Norway	3317	22,63,565	130.6	1975–2007	1975–1988	1.2[B] (0.2 to 2.2)
						1988–2007	4.0[B] (3.6 to 4.5)
	Sweden	8929	44,37,639	153.9	1975–2007	1975–1996	1.7[B] (1.4 to 2)
						1996–2004	6.9[B] (5.6 to 8.2)
						2004–2007	–4.3[B] (–7.9 to –0.4)
	England/Wales	27,586	258,57,957	87.5	1980–2006	1980–2006	4.0[B] (3.7 to 4.3)
	Scotland	2490	24,40,492	84.4	1985–2007	1985–1996	5.1[B] (3.6 to 6.5)
						1996–2007	1.4[B] (0.3 to 2.5)
Eastern	Belarus	1316	46,64,603	32.9	1981–2002	1981–2002	5.5[B] (5.1 to 6.0)
	Czech Republic	3887	49,82,486	75.6	1986–2005	1986–1990	2.9 (–0.6 to 6.5)
						1990–1997	6.9[B] (5.2 to 8.5)
						1997–2000	–0.8 (–8.2 to 7.3)
						2000–2005	8.7[B] (7.1 to 10.4)
	Poland[a]	606	11,05,670	48.8	1988–2002	1988–2002	5.6[B] (4.4 to 6.7)
	Russian Federation	14,403	667,86,562	26.7	1993–2008	1993–2003	6.0[B] (5.3 to (6.7)
						2003–2008	8.8[B] (7.3 to 10.3)
	Slovakia	1134	26,12,743	55.7	1986–2005	1992–2005	4.1[B] (3.5 to 4.7)
Southern	Croatia	1334	21,35,775	57.3	1991–2005	1991–2005	6.1[B] (5.2 to 7)
	Italy[b]	2890	22,90,860	81.7	1988–2002	1988–2002	6.4[B] (6.0 to 6.8)
	Slovenia	700	976,895	68.0	1986–2005	1986–2005	4.9[B] (4.1 to 5.8)
	Spain[c]	1680	19,66,845	69.5	1985–2000	1985–2000	6.2[B] (5.5 to 6.9)
Western	France[d]	3019	26,24,555	115.0	1988–2002	1988–1993	7.5[B] (5.3 to 9.7)
						1993–2002	5.3[B] (4.7 to 5.9)
	Germany[e]	758	517,405	109.8	1975–2002	1975–1982	–3.9 (–7.9 to 0.2)
						1982–2002	4.8[B] (4.1 to 5.5)
	Switzerland[f]	679	458,065	137.8	1983–2002	1983–2002	3.9[B] (3.3 to 4.5)
	The Netherlands	8227	80,18,611	96.5	1989–2007	1989–1995	7.2[B] (4.9 to 9.6)
						1995–2001	–0.8 (–3.3 to 1.7)
						2001–2004	7 (–3.5 to 18.7)
						2004–2007	–0.9 (–5.6 to 3.9)

[A] 2001–2005 except Belarus (2001–2002); Poland (2001–2002); Estonia (2001–2003); Latvia (2001–2003); Italy (2001–2002); Spain (2000); France (2001–2002); Germany (2001–2002); and Switzerland (2001–2002).
[B] The estimated annual percent change (EAPC) is statistically significant from zero.
[a] Two Polish registries (Cracow and Warsaw).
[b] Six Italian registries (Florence; Modena; Parma; Ragusa; Romagna; Torino).
[c] Five Spanish registries (Granada; Murcia; Navarra; Tarragona; Zaragoza).
[d] Eight French registries (Bas-Rhin; Calvados; x'Doubs; Haut-Rhin; Herault; Isere; Somme; Tarn).
[e] One German registry (Saarland).
[f] Two Swiss registries (Geneva and St. Gall-Appenzell).

Netherlands, Slovakia, Switzerland and the UK to 6–7% or greater in eight countries, amongst them France, Germany, Latvia, Spain and the Russian Federation (Fig. 4). Notably, declines in prostate cancer incidence were seen during the

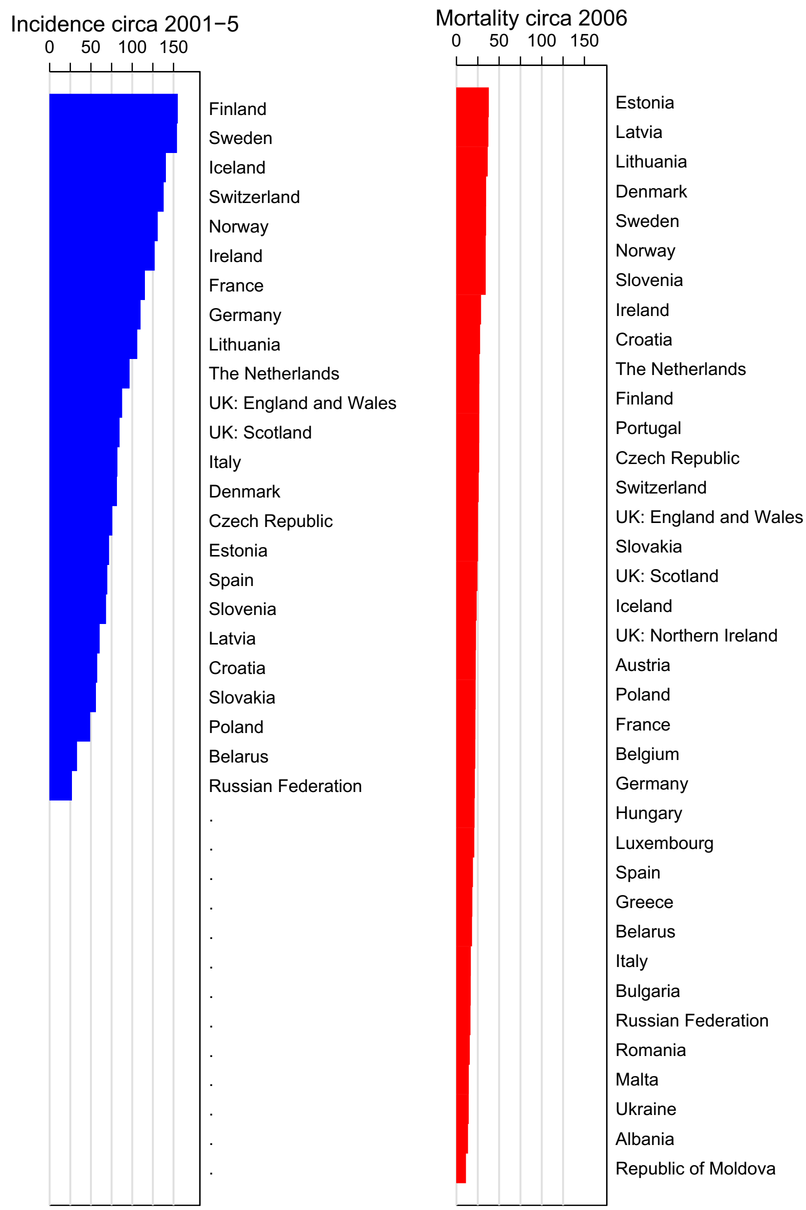

Fig. 1 – Prostate cancer incidence in 24 countries (circa 2001–2005) and mortality rates in 37 countries (circa 2006) sorted according to descending order of magnitude. Rates are combined for all ages and are standardised using the weights from the European standard. See footnotes of Table 1 for availability of data in each country.

last 3–4 years in the high incidence countries of Finland (decline observed 2005–2007), Sweden (2004–2007) and The Netherlands (2004–2007). National mortality declines of 1–3% were observed from 1996 in 13 of the 37 countries under study (Figs. 3 and 4 and Tables 2 and 3), whilst increases in mortality by 3% yearly were found in the Russian Federation as well as the three Baltic countries.

4.2.2. *Northern Europe*

In the Nordic countries of Finland, Iceland, Norway and Sweden, incidence rates were amongst the highest in Europe, and the trends in rates have been uniformly increasing, particularly during the 1990s, with Finland showing the steepest increase, 9.3% per year between 1990 and 1995 (Table 1). Significant mortality declines occurred in Finland (2.9% since 1998), Norway (2.2% since 1997) and Sweden (1.3%) since 1998 (Table 2). Incidence has also been increasing in the UK and Ireland, with the latter rates rising by over 7% per annum. Subsequent significant annual declines in mortality of around 1% were observed in the constituent countries of the UK – as early as 1992 in England and Wales (Table 3) – with a mean decline of 2.1% in Ireland (since 1997). The Baltic countries have a rather different profile, with significantly increasing rates of both incidence and mortality in the last 15 years.

4.2.3. *Eastern Europe*

Generally, the rates of increase in prostate cancer incidence in the five Eastern European countries were in keeping with those seen elsewhere in Europe (Fig. 1), with substantial recent increases in the Czech Republic and Russia, reaching

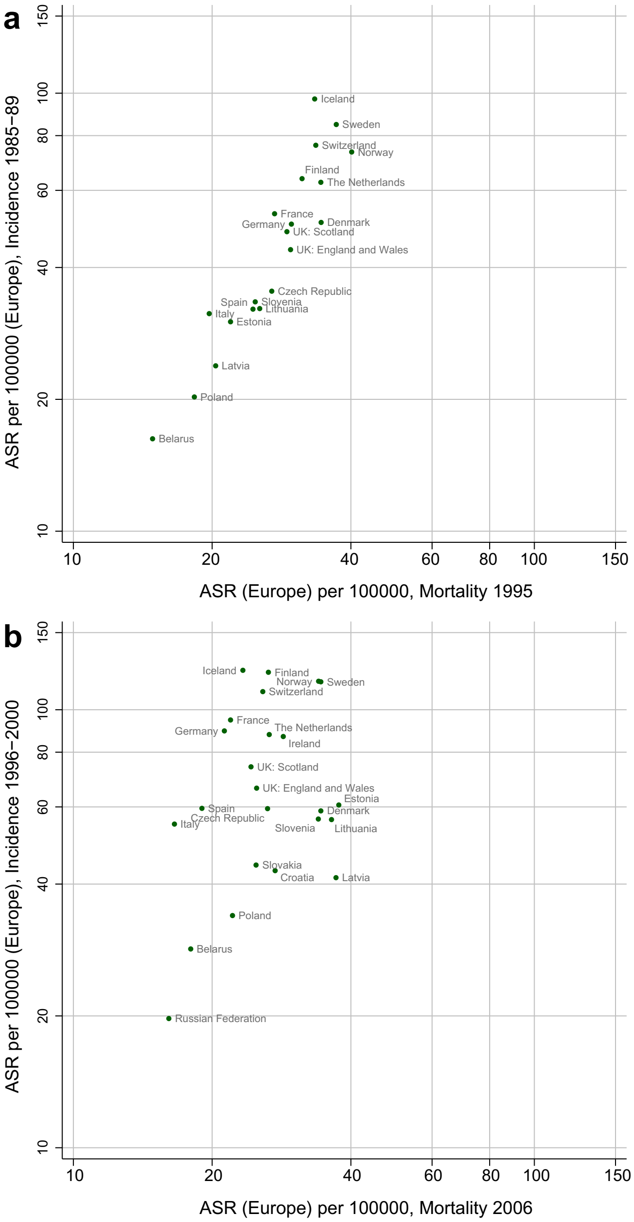

Fig. 2 – Scatterplots comparing (a) prostate cancer incidence 1985–1989 versus prostate cancer mortality circa 1995 and (b) incidence 1996–2000 versus mortality circa 2006. Rates are combined for all ages and are standardised using the weights from the European standard. See footnotes of Table 1 for availability of data in each country.

almost 9% per year during the last 5–10 years (Table 1). In terms of mortality (Tables 2 and 3), recent, yet rather rapid declines were confined to Hungary (since 1999) and the Czech Republic (since 2004).

4.2.4. *Southern Europe*

Incidence trends in the four Southern European populations studied conveyed rather constant increases in rates of 5–6% per year since the late 1980s (Table 1). The mortality trends showed more variability across the nine countries examined. Significant yearly declines of 3.7% in Spain from 1998 and 1.2% in Italy from 1994 (Tables 2 and 3) contrast with close to 2% increases in prostate cancer mortality in Albania, Croatia and the Republic of Moldova in the last decades (Table 2).

4.2.5. *Western Europe*

In France, Germany and Switzerland, rates have tended to increase about 4–5% per year since the 1990s (Fig. 1 and Table 1), with non-significant declines in incidence in The Netherlands during 1995–2001 and from 2004. Some of the largest average annual declines from 1996 – of an order of magnitude between 2.5% and 3% per annum – occurred in these countries, and were only surpassed by the mortality decrease in Austria, with a decrease of 3.8% per annum since 2000 (Tables 2 and 3).

4.3. *Relative changes in incidence versus changes in mortality*

Fig. 4 presents the mean annual change in incidence between 1990 and 2004 compared to mortality trends from 1996 and thereafter. Recent prostate cancer mortality declines were observed in 13 of the 22 countries, for which incidence and mortality series were available, with the estimated mean declines between 2% and 3% per annum in Germany, Spain, France, The Netherlands and Switzerland. Incidence rates increased by 3% or more per year on average from 1990–2004 in each country studied. There appears to be little relation between the extent of the increases in prostate cancer incidence (from 1990) and the subsequent mortality declines (after 1996).

4.4. *Timing and extent of mortality declines*

Table 3 indicates for the 17 countries where prostate cancer mortality rates showed a recent decline, the year (e.g. the last joinpoint) and the extent of the decrease in terms of the EAPC. The first declines in prostate cancer mortality rates were seen in England and Wales in 1992 and the latest in the Czech Republic in 2004 but in most countries the declines began during the mid- to late-1990s. There was considerable variability in the magnitude of the year-on-year decreases, varying from approximately 1% in Scotland (from 1994) to over 4% for the more recent declines observed in Hungary, France and the Czech Republic.

5. Discussion

For all the 24 countries included in this analysis, an increase in prostate cancer incidence during the study period was observed. In Sweden, Finland and The Netherlands – countries with the highest incidence – rates reached a plateau or even started to decline towards the end of the observation period (after 2005, having reached ASRs approaching 200 per 100,000). The highest prostate cancer mortality rates were in the Baltic region (Estonia, Latvia and Lithuania) and in the Nordic countries (Denmark, Norway and Sweden). Mortality rates have been decreasing in 13 of the 37 countries analysed, predominantly since the mid-1990's, and mostly in higher-resource countries in Western Europe (e.g. Great Britain, France, Germany and The Netherlands), the Nordic countries (e.g. Finland and Norway). Mortality increased in several Eastern

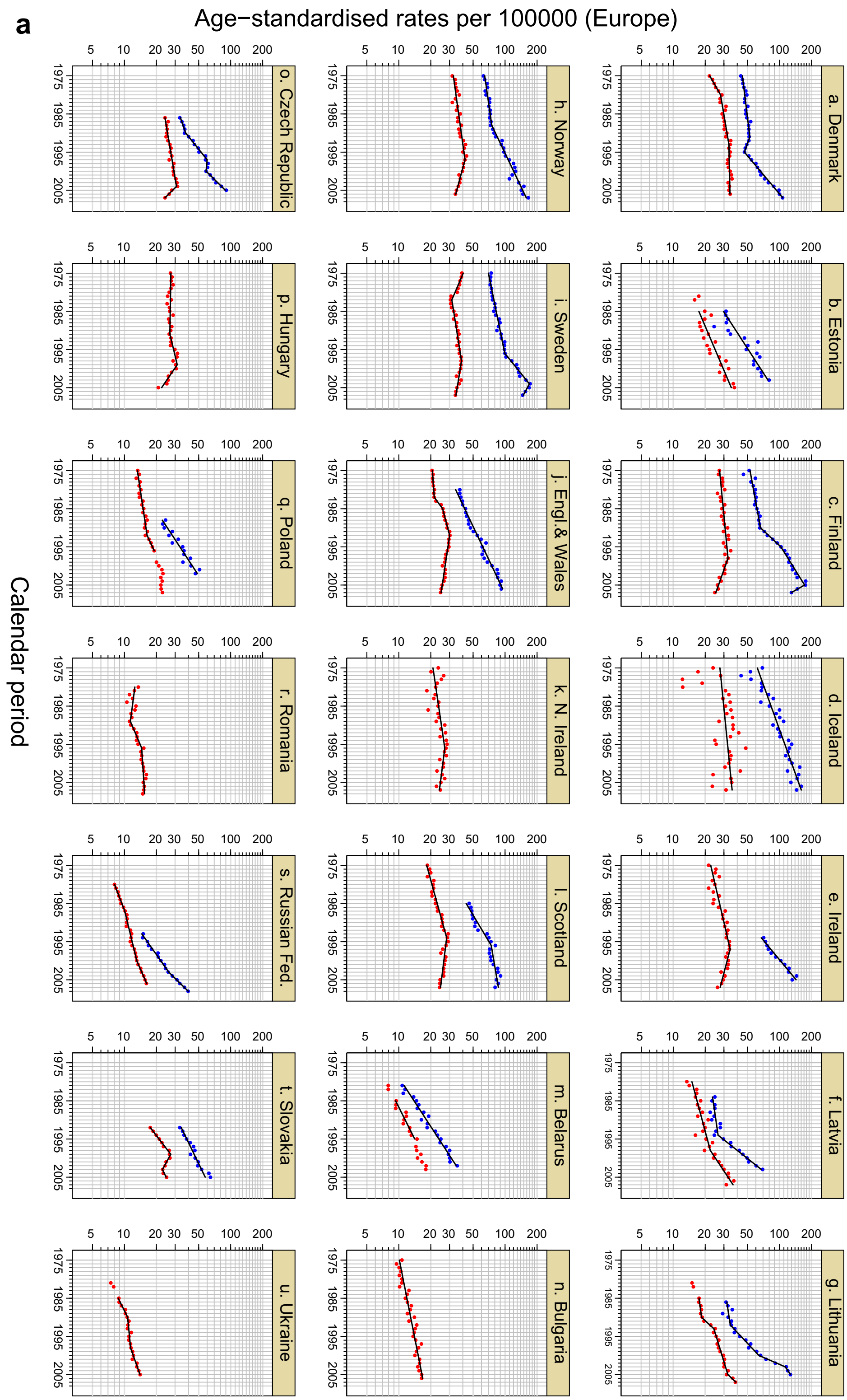

Fig. 3 – Fitted annual trends based on joinpoint regression (solid lines) and corresponding observed incidence (blue circles) and mortality rates (red circles) for (a). Northern (countries a. to l.) and Eastern (m. to u.) Europe and (b) Southern (a. to i.) and Western Europe (j. to p.). Rates are combined for all ages and are standardised using the weights of the European standard. See footnotes of Table 1 for availability of data in each country.

European countries (including several former Soviet countries), in stark contrast to the decline observed in Hungary and the Czech Republic.

In contrast to cervix and breast cancer, there are few, if any, population-based organised programmes for prostate cancer in Europe. Opportunistic testing (case-finding)

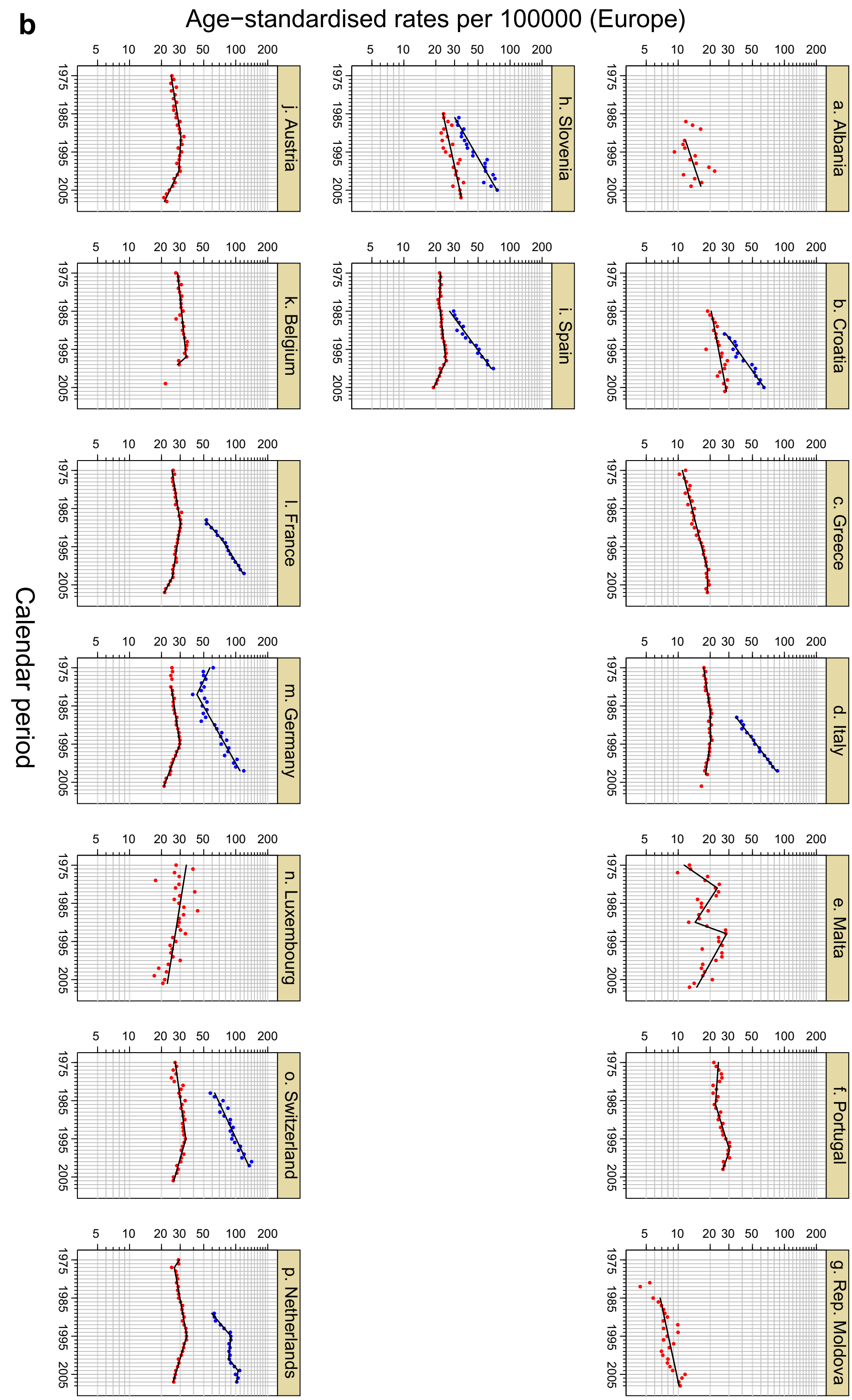

Fig 3. *(continued)*

amongst men with or without urological symptoms is however common in Europe, and we use the expression *PSA testing* as a synonym for such practices. The term *screening* is used only in the context of the randomised trials examining the impact of PSA-based screening on prostate cancer mortality.

The disappearance of the correlation between incidence and mortality towards the end of the study period is consistent with the overdiagnosis or detection of indolent tumours, most likely attributable to PSA testing. The highest incidence rates in the countries with highest standards of living and health care expenditure also supports this notion. In

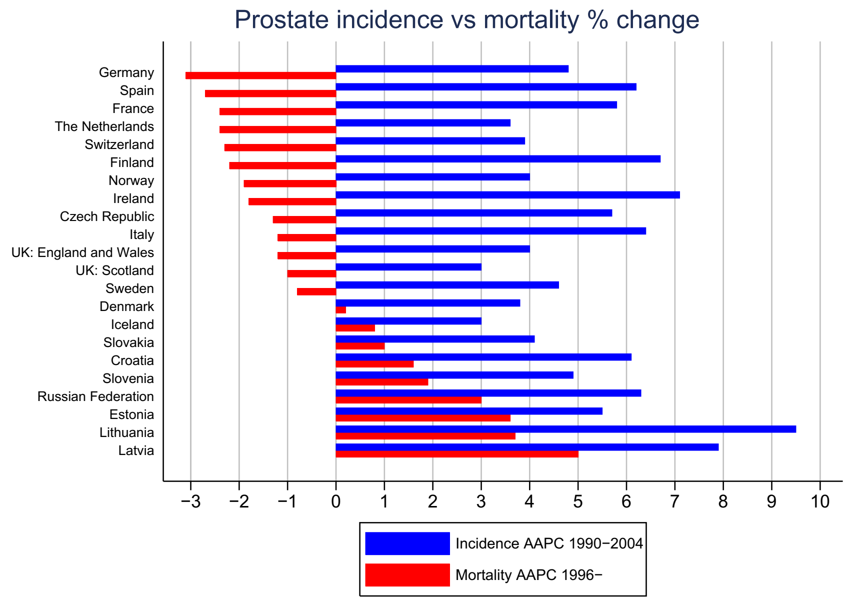

Fig. 4 – Average annual percentage change (AAPC) in incidence trends 1990–2004 and mortality from 1996 to last year available. AAPC is computed as a weighted average of the EAPCs based on the joinpoint model (see Methods). Rates are combined for all ageand are standardised using the weights of the European standard. See footnotes of Table 1 for availability of data in each country.

countries with low incidence rates, correlation with mortality seemed to persist.

A downturn in incidence trends, as observed earlier in the United States of America (USA), was found for some countries, notably including several participating in the European Randomised Study of Screening for Prostate Cancer (ERSPC) trial[8], although only a small proportion of the male population was screened within the trial. This may be due to a genuine reduction in risk factors or saturation of PSA testing with an extensive early diagnosis of the pool of pre-clinical disease.

The decreasing mortality after 1990 may be generally attributable to improvements in the treatment and an effect of PSA testing. Overall, prostate cancer survival has improved during the past decades in several countries[9,10], with 5-year relative survival proportions approaching 100% particularly for localised disease. Brachytherapy and hormonal treatment of localised prostate cancer have become more common during the past two decades and higher doses are being used in external beam radiotherapy.[11] Yet, active surveillance for early disease is also becoming more frequent. For locally advanced cancer, combined modality treatment with prolonged androgen suppression has been shown to improve the outcome[12–14] and early endocrine therapy has been adopted in advanced disease as well as second-line treatment of recurrent disease. Another contributing factor may be the protective effect of statin use; several studies have shown a decreased risk of advanced prostate cancer and prostate cancer death amongst statin users.[15,16]

The aetiology of prostate cancer remains elusive, with established risk factors explaining only a fraction of the variation in disease occurrence. Whilst there are promising leads, few risk factors have been established for prostate cancer besides age, ethnicity and family history.[17] Despite a high heritability shown in twin studies[18], known susceptibility genes (including HPC1/RNASEL, HPC2/ELAC2 and MSR1) are associated with small increases in risk (OR 1.1–1.2) and are involved in only some 10% of cases.[19,20] Findings regarding the role of various dietary factors are conflicting, with most consistent evidence for selenium and lycopene.[21,22] With respect to chemoprevention, 5-alpha reductase inhibitors such as finasteride and dutasteride have been shown to reduce prostate cancer risk in randomised trials.[23,24]

Latent disease is common, as autopsy studies have revealed indolent prostate cancer in more than half of the male population aged 70 or older.[25–27] Similarly, prostate cancer can be demonstrated in 25–45% of cystoprostatectomy specimens removed for bladder cancer.[28] The natural history of prostate cancer is not understood to the extent that we could accurately predict which lesions would progress and which would remain indolent throughout the lifetime of a man harbouring a latent carcinoma.[29]

The effect of prostate cancer testing on the observed trends in incidence and mortality can be evaluated here only indirectly, as no information on the extent of PSA testing was available. The relationship between decreasing mortality trends and advances in treatment in combination with early detection by PSA has been the subject of much debate.[30] The testing of men for PSA can affect prostate cancer incidence dramatically, as lead-time has been estimated as 6–12 years and overdiagnosis up to 40%.[31] In the USA, prostate cancer testing is more common than in Europe; Up to 70% of the men in the USA have been tested at least once, whilst in most European countries figures around 10–20% have been published[32,33], even though no large and systematic analyses have been conducted. In the USA, a sharp increase in the prostate cancer incidence was noted in the 1990's followed by a decline.[34] Almost simultaneously with the increase in incidence, a decrease in prostate cancer mortality also

Table 2 – Prostate cancer mortality: deaths, person-years and age-standardised (Europe) rates circa 2001–2005, data span available and joinpoint analysis by country within European region.

Area	Country	Mean deaths per year 2001–2005[A]	Person-years 2001–2005[A]	ASR (Europe) 2001–2005[A]	Observed period[B]	JP linear segment	EAPC[a] (95% CI)
Northern	Denmark	1113	26,64,175	34.2	1975–2006	1975–1980	4.8[a] (1.9 to 7.8)
						1980–1993	1.4[a] (0.8 to 2.0)
						1993–2006	0.2 (–0.3 to 0.7)
	Estonia	189	623,870	32.6	1981–2005	1985–2005	3.6[a] (2.7 to 4.4)
	Finland	785	25,49,670	28.5	1975–2007	1975–1998	0.8[a] (0.5 to 1.1)
						1998–2007	–2.9[a] (–3.9 to –1.9)
	Iceland	50	145,295	33.5	1975–2007	1975–2007	0.8 (–0.1 to 1.8)
	Ireland	530	19,81,322	30.8	1975–2007	1975–1997	1.9[a] (1.5 to 2.4)
						1997–2007	–2.1[a] (–3.4 to –0.9)
	Latvia	307	10,71,499	30.4	1980–2007	1980–1998	2.2[a] (1.4 to 3.1)
						1998–2007	5.6[a] (3.8 to 7.5)
	Lithuania	448	16,11,483	31.0	1981–2007	1985–1990	1.1 (–1.2 to 3.4)
						1990–1993	9.3 (–0.3 to 20)
						1993–2005	2.6[a] (2 to 3.1)
						2005–2007	9.1[a] (2 to 16.7)
	Norway	1058	22,63,565	36.7	1975–2006	1975–1997	1.2[a] (0.9 to 1.4)
						1997–2006	–2.2[a] (–3.1 to –1.3)
	Sweden	2487	44,37,639	36.6	1975–2007	1975–1982	–3.5[a] (–4.8 to –2.1)
						1982–1998	1.3[a] (0.9 to 1.7)
						1998–2007	–1.3[a] (–2.1 to –0.5)
	England and Wales	9055	258,57,957	26.8	1975–2007	1975–1982	0.6 (–0.5 to 1.7)
						1982–1985	6.2 (–1.5 to 14.6)
						1985–1992	2.2[a] (1.1 to 3.3)
						1992–2007	–1.2[a] (–1.5 to –1.0)
	Northern Ireland	217	833,372	25.3	1975–2007	1975–1996	1.2[a] (0.5 to 1.9)
						1996–2007	–1.0 (–2.5 to 0.4)
	Scotland	781	24,40,492	26.2	1975–2007	1975–1994	2.3[a] (1.9 to 2.7)
						1994–2007	–1.0[a] (–1.6 to –0.5)
Eastern	Belarus	685	46,51,056	17.5	1981–2003	1985–1995	4.2[a] (2.8 to 5.6)
	Bulgaria	749	38,04,157	15.7	1975–2006	1975–2006	1.6[a] (1.4 to 1.9)
	Czech Republic	1420	49,82,486	30.0	1986–2007	1986–2004	1.4[a] (1.1 to 1.7)
						2004–2007	–8.0[a] (–11.4 to –4.5)
	Hungary	1265	48,14,088	25.1	1975–2005	1975–1991	–0.1 (–0.6 to 0.4)
						1991–1999	2.0[a] (0.3 to 3.8)
						1999–2005	–5.5[a] (–7.5 to –3.4)
	Poland	3483	185,44,438	22.5	1975–2007	1975–1992	1.3[a] (1.0 to 1.6)
						1992–1996	3.9[a] (1.7 to 6.2)
	Romania	1615	106,62,679	15.5	1975–2008	1980–1989	–1.1 (–2.5 to 0.3)
						1989–1996	3.6[a] (1.1 to 6.1)
						1996–2008	0.5 (–0.2 to 1.3)
	Russian Federation	7615	667,86,562	14.6	1980–2006	1980–1987	3.2[a] (2.2 to 4.3)
						1987–2000	2.0[a] (1.7 to 2.4)
						2000–2006	3.7[a] (2.8 to 4.5)
	Slovakia	491	26,12,743	23.9	1992–2005	1992–1999	6.5[a] (5.5 to 7.6)
						1999–2003	–4.4[a] (–7.6 to –1)
						2003–2005	4.0 (–3.0 to 11.4)
	Ukraine	2800	220,78,237	13.2	1981–2005	1985–1990	4.2[a] (2 to 6.5)
						1990–1998	0.8 (–0.3 to 1.9)
						1998–2005	2.9[a] (1.9 to 4)
Southern	Albania	134	15,43,312	13.9	1987–2004	1992–2004	2.8 (–1.0 to 6.8)
	Croatia	559	21,35,775	26.4	1985–2006	1985–2006	1.6[a] (1.0 to 2.2)
	Greece	1404	54,57,954	19.0	1975–2007	1975–2001	2.1[a] (1.9 to 2.3)
						2001–2007	0.0 (–1.4 to 1.5)
	Italy	7319	278,48,299	18.3	1975–2006	1975–1986	1.3[a] (0.8 to 1.8)
						1986–1994	0.2 (–0.7 to 1)
						1994–2003	–1.2[a] (–1.7 to –0.7)
	Malta	36	197,409	17.8	1975–2007	1975–1981	12.7[a] (1.2 to 25.6)
						1981–1990	–5.2 (–10.3 to 0.2)
						1990–1993	25.5 (–19.4 to 95.6)
						1993–2007	–4.5[a] (–6.4 to –2.6)

Table 2 – (*continued*)

Area	Country	Mean deaths per year 2001–2005[A]	Person-years 2001–2005[A]	ASR (Europe) 2001–2005[A]	Observed period[B]	JP linear segment	EAPC[a] (95% CI)
	Portugal	1685	50,15,239	26.8	1975–2003	1975–1986	–0.6 (–1.8 to 0.7)
						1986–1998	2.6[a] (1.7 to 3.5)
						1998–2003	–2.9[a] (–5.2 to –0.4)
	Republic of Moldova	106	17,31,246	9.0	1981–2008	1985–2008	1.8[a] (1.0 to 2.6)
	Slovenia	284	976,895	32.5	1985–2007	1985–2007	1.9[a] (1.3 to 2.4)
	Spain	5630	206,29,672	20.8	1975–2005	1975–1983	–0.3 (–1.0 to 0.4)
						1983–1998	0.9[a] (0.7 to 1.2)
						1998–2005	–3.7[a] (–4.3 to –3.1)
Western	Austria	1144	39,44,550	26.1	1975–2008	1975–1991	1.3[a] (0.9 to 1.8)
						1991–2000	–0.5 (–1.6 to 0.6)
						2000–2008	–3.8[a] (–4.9 to –2.8)
	Belgium	1374	50,65,258	21.8	1975–2004	1975–1997	0.8[a] (0.6 to 1.1)
						1997–1999	–8.8 (–18.5 to 1.9)
	France	9208	292,15,226	24.9	1975–2007	1975–1989	1.3[a] (1.0 to 1.6)
						1989–2003	–1.2[a] (–1.6 to –0.9)
						2003–2007	–4.3[a] (–6.1 to –2.4)
	Germany	11,284	403,14,615	23.3	1975–2006	1980–1995	1.3[a] (1.1 to 1.5)
						1995–2006	–3.1[a] (–3.4 to –2.8)
	Luxembourg	44	223,240	20.6	1975–2006	1975–2006	–1.3[a] (–2.0 to –0.6)
	Switzerland	1294	35,94,636	28.1	1975–2006	1975–1995	1.2[a] (0.8 to 1.5)
						1995–2006	–2.3[a] (–3.1 to –1.5)
	The Netherlands	2332	80,18,611	28.2	1975–2007	1975–1977	–5.2 (–10.2 to 0.1)
						1977–1995	1.5[a] (1.3 to 1.7)
						1995–2007	–2.4[a] (–2.7 to –2.2)

[A] 2001–2005 except Belarus (2001–2003); Albania (2001–2004); Italy (2001–2003); Portugal (2001–2003); Belgium (2004).
[B] Missing years Belarus (1983, 1984, and 1996); Poland (1997 and 1998); Romania (1979); Russian Federation (1983 and 1984); Ukraine (1983 and 1984); Estonia (1983 and 1984);Lithuania (1983 and 1984); Albania (1990 and 1991); Italy (2004 and 2005); Republic of Moldova (1983 and 1984); Belgium (2000–2003); Germany (1979).
[a] The estimated annual percent change (EAPC) is statistically significant from zero.

Table 3 – Summary of recent declines in national prostate cancer mortality in Europe: year for which the downturn was first observed and the estimated annual percent change (EAPC) (based on overall decline in AAPC – see Fig. 4).

Country	Year decline identified	EAPC (95% CI)
England and Wales	1992	–1.2[a] (–1.5 to –1.0)
Italy	1994	–1.2[a] (–1.7 to –0.7)
Scotland	1994	–1.0[a] (–1.6 to –0.5)
Germany	1995	–3.1[a] (–3.4 to –2.8)
Switzerland	1995	–2.3[a] (–3.1 to –1.5)
The Netherlands	1995	–2.4[a] (–2.7 to –2.2)
Northern Ireland	1996	–1.0 (–2.5 to +0.4)
Ireland	1997	–2.1[a] (–3.4 to –0.9)
Norway	1997	–2.2[a] (–3.1 to –1.3)
Finland	1998	–2.9[a] (–3.9 to –1.9)
Portugal	1998	–2.9[a] (–5.2 to –0.4)
Spain	1998	–3.7[a] (–4.3 to –3.1)
Sweden	1998	–1.3[a] (–2.1 to –0.5)
Hungary	1999	–5.5[a] (–7.5 to –3.4)
Austria	2000	–3.8[a] (–4.9 to –2.8)
France	2003	–4.3[a] (–6.1 to –2.4)
Czech Republic	2004	–8.0[a] (–11.4 to –4.5)

[a] The estimated annual percent change (EAPC) is statistically significant from zero.

occurred. This is consistent with an effect of wide-scale opportunistic testing, prompting an earlier diagnosis of prostate cancers that otherwise would have been detected later. As the test based on serum prostate-specific antigen (PSA) became more commonly used at this time, a beneficial effect of the intervention has been put forward as the explanation. Yet, no similar pattern has been observed in other populations and no correlation between the extent of PSA testing and declines in prostate cancer mortality have been demonstrated in most population-level (ecological) analyses or case–control studies.[35–43] Further, simulation studies have suggested that PSA testing alone is unlikely to explain the decrease.[44–46] A recent Dutch study has suggested that only the increases from 2001 in prostate cancer incidence were likely attributable predominantly to PSA testing, with the decreasing mortality rates from 1996 were likely the result of an increased detection of cT2-tumours between 1989 and 1995.[47]

A 20% reduction in prostate cancer mortality due to PSA screening was recently shown in a large European randomised trial within 9 years of follow-up[8], though no such effect was observed in a smaller USA trial.[24] The difference between the trials may be due to statistical power and the persistence of variability between the arms, e.g. an inability to compare screened and unscreened groups in accordance with the allocation due to non-compliance and contamination. Nevertheless, the ERSPC trial showed that under ideal conditions, PSA screening can reduce mortality, with an effect within 10 years since the commencement of screening and potentially a larger longer-term effect. The screening trial also indicated materially increased incidence due to screening with a 1.7-fold cumulative risk in the screening arm compared with the control arm.

There are some methodological shortcomings in joinpoint regression.[48] The overall trend can be unduly influenced by the last data points, and additionally, arbitrary slopes can be obtained for populations with large random variation. Such techniques do, however, permit quantification of the linear trends of rates of a disease, where the trends in incidence have been rapidly changing with time. Further, as prostate cancer is principally a disease of old men, underreporting of incident cancer cases in elderly patients in different time periods is a possible source of bias. Finally for six countries, sub-national incidence data were available based on an aggregation of regional registry datasets; we used these data series assuming that the pertaining cancer registries collectively represented national patterns and trends. This is a large and untested assumption, and is particularly vulnerable where registry coverage is low within a country and the catchment population may be non-representative, e.g. the Saarland registry representing incidence rates of Germany.

In summary, we found consistent increases in prostate cancer incidence throughout Europe. In general, there was a geographical gradient with higher occurrence in the North and lowest in the East. It remains unclear to what extent the increasing trends in incidence indicate true risk or represent increased detection of latent disease, and indeed such comparisons of incidence are equivocal without population-based information on the basis of the prostate cancer diagnoses. With respect to prostate cancer mortality, there is substantial heterogeneity across populations. Whilst it is likely that there are geographical and temporal variations in the quality of reporting of the underlying cause of death in Europe, regional patterns emerge, with downward turns in several Western, Northern and lately, Eastern European countries. There appears however little relation between the increasing incidence and decreasing mortality in the recent past, consistent with an effect of overdiagnosis or detection of indolent tumours via PSA testing. In contrast, uniformly increasing mortality trends persist in a number of Central and Eastern European countries, other than the Czech Republic and Hungary. It remains unclear as to what extent such trends reflect true changes in risk or are a result of increasing detection of latent disease.

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REFERENCES

1. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010;**46**:765–81.
2. Curado MP, Edwards BK, Shin HR, et al. Cancer incidence five continents, vol. IX. Lyon: IARC Scientific Publications No.160, IARC; 2007.
3. Lutz JM, Pury P, Fioretta G, Raymond L. The impact of coding process on observed cancer mortality trends in Switzerland. *Eur J Cancer Prev* 2004;**13**:77–81.
4. Doll R, Cook P. Summarizing indices for comparison of cancer incidence data. *Int J Cancer* 1967;**2**:269–79.
5. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;**19**:335–51.
6. Boyle P, Parkin DM. Cancer registration: principles and methods. In: Statistical methods for registries, vol. 95. IARC Sci. Publ.; 1991. p. 126–158.
7. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. *Stat Med* 2009;**28**:3670–82.
8. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;**360**:1320–8.
9. Berrino F, De Angelis R, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. *Lancet Oncol* 2007;**8**:773–83.
10. Rachet B, Maringe C, Nur U, et al. Population-based cancer survival trends in England and Wales up to 2007: an assessment of the NHS cancer plan for England. *Lancet Oncol* 2009;**10**:351–69.
11. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol* 2010;**28**:1117–23.
12. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009;**373**:301–8.
13. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009;**360**:2516–27.
14. Bria E, Cuppone F, Giannarelli D, et al. Does hormone treatment added to radiotherapy improve outcome in locally advanced prostate cancer?: meta-analysis of randomized trials. *Cancer* 2009;**115**:3446–56.
15. Murtola TJ, Tammela TL, Maattanen L, et al. Prostate cancer and PSA among statin users in the Finnish prostate cancer screening trial. *Int J Cancer* 2010.
16. Bonovas S, Filioussi K, Sitaras NM. Statin use and the risk of prostate cancer: a metaanalysis of 6 randomized clinical trials and 13 observational studies. *Int J Cancer* 2008;**123**:899–904.
17. Signorello LAHO. Prostate cancer. In: Adami HO, Hunter D, Trichopoulos D, editors. *Textbook of cancer epidemiology*. Oxford: Oxford University Press; 2002. p. 188–211.
18. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer – analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000;**343**:78–85.
19. Christensen GB, Baffoe-Bonnie AB, George A, et al. Genome-wide linkage analysis of 1233 prostate cancer pedigrees from the International Consortium for Prostate Cancer Genetics using novel sumLINK and sumLOD analyses. *Prostate* 2010;**70**:735–44.
20. Eeles RA, Kote-Jarai Z, Al Olama AA, et al. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. *Nat Genet* 2009;**41**:1116–21.
21. Etminan M, Takkouche B, Caamano-Isorna F. The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:340–5.
22. Etminan M, FitzGerald JM, Gleave M, Chambers K. Intake of selenium in the prevention of prostate cancer: a systematic review and meta-analysis. *Cancer Causes Control* 2005;**16**:1125–31.
23. Thompson IM, Basler J, Hensley D, et al. Prostate cancer prevention: what do we know now and when will we know more? *Clin Prostate Cancer* 2003;**1**:215–20.
24. Andriole GL, Crawford ED, Grubb III RL, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;**360**:1310–9.
25. Breslow L, Agran L, Breslow DM, Morganstern M, Ellwein L. Cancer control: implications from its history. *J Natl Cancer Inst* 1977;**59**:671–86.
26. Yatani R, Chigusa I, Akazaki K, et al. Geographic pathology of latent prostatic carcinoma. *Int J Cancer* 1982;**29**:611–6.
27. Konety BR, Bird VY, Deorah S, Dahmoush L. Comparison of the incidence of latent prostate cancer detected at autopsy before and after the prostate specific antigen era. *J Urol* 2005;**174**:1785–8.
28. Pritchett TR, Moreno J, Warner NE, et al. Unsuspected prostatic adenocarcinoma in patients who have undergone radical cystoprostatectomy for transitional cell carcinoma of the bladder. *J Urol* 1988;**139**:1214–6.
29. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst* 2010;**102**:605–13.
30. Weir HK, Thun MJ, Hankey BF, et al. Annual report to the nation on the status of cancer, 1975–2000, featuring the uses of surveillance data for cancer prevention and control. *J Natl Cancer Inst* 2003;**95**:1276–99.
31. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst* 2009;**101**:374–83.
32. Ross LE, Berkowitz Z, Ekwueme DU. Use of the prostate-specific antigen test among US men: findings from the 2005 National Health Interview Survey. *Cancer Epidemiol Biomarkers Prev* 2008;**17**:636–44.
33. Gavin A, McCarron P, Middleton RJ, et al. Evidence of prostate cancer screening in a UK region. *BJU Int* 2004;**93**:730–4.
34. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986–2005. *J Natl Cancer Inst* 2009;**101**:1325–9.
35. Lu-Yao G, Albertsen PC, Stanford JL, et al. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. *BMJ* 2002;**325**:740.
36. Perron L, Moore L, Bairati I, Bernard PM, Meyer F. PSA screening and prostate cancer mortality. *CMAJ* 2002;**166**:586–91.
37. Oliver SE, May MT, Gunnell D. International trends in prostate-cancer mortality in the "PSA ERA". *Int J Cancer* 2001;**92**:893–8.
38. Coldman AJ, Phillips N, Pickles TA. Trends in prostate cancer incidence and mortality: an analysis of mortality change by screening intensity. *CMAJ* 2003;**168**:31–5.
39. Vutuc C, Waldhoer T, Madersbacher S, Micksche M, Haidinger G. Prostate cancer in Austria: impact of prostate-specific

antigen test on incidence and mortality. *Eur J Cancer Prev* 2001;**10**:425–8.
40. Bartsch G, Horninger W, Klocker H, et al. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. *Urology* 2001;**58**:417–24.
41. Concato J, Wells CK, Horwitz RI, et al. The effectiveness of screening for prostate cancer: a nested case–control study. *Arch Intern Med* 2006;**166**:38–43.
42. Kvale R, Auvinen A, Adami HO, et al. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. *J Natl Cancer Inst* 2007;**99**:1881–7.
43. Marcella SW, Rhoads GG, Carson JL, Merlino F, Wilcox H. Prostate-specific antigen screening and mortality from prostate cancer. *J Gen Intern Med* 2008;**23**:248–53.
44. Etzioni R, Tsodikov A, Mariotto A, et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. *Cancer Causes Control* 2008;**19**:175–81.
45. Telesca D, Etzioni R, Gulati R. Estimating lead time and overdiagnosis associated with PSA screening from prostate cancer incidence trends. *Biometrics* 2008;**64**:10–9.
46. Tsodikov A, Szabo A, Wegelin J. A population model of prostate cancer incidence. *Stat Med* 2006;**25**:2846–66.
47. Cremers RG, Karim-Kos HE, Houterman S, et al. Prostate cancer: trends in incidence, survival and mortality in The Netherlands, 1989–2006. *Eur J Cancer* 2010;**46**:2077–87.
48. Baade PD, Coory MD, Aitken JF. International trends in prostate-cancer mortality: the decrease is continuing and spreading. *Cancer Causes Control* 2004;**15**:237–41.