Epidemiology of Prostate Cancer in Europe: Patterns, Trends and Determinants

Freddie Bray and Lambertus A. Kiemeney

1   Introduction

Malignant neoplasms of the prostate, hereafter referred to as prostate cancer (ICD-10 C61), usually originate in the glandular tissue. While these cancers, mainly adenocarcinomas, are often indolent, there is a subset of men who are diagnosed with highly malignant prostate cancers associated with poor prognosis. The disease poses a substantial public health burden worldwide and in Europe: it is the second most frequently diagnosed cancer and the fifth leading cause of cancer death among men globally, with an estimated 1.1 million new cases diagnosed and 307,000 deaths from the disease in 2012 [16]. Among European men, it is the most common neoplasm and third-ranked cause of cancer death, with almost 400,000 cases and over 92,000 deaths

Incidence rates of prostate cancer are heavily influenced by the diagnosis of latent cancers by serum prostate-specific antigen (PSA) testing of asymptomatic individuals, and by the detection of latent cancer in tissue removed during prostatectomy operations, or at autopsy. When PSA became commercially available in the mid-1980s in the USA and the late 1980s in Europe, the intensive use of the test by general practitioners and urologists as an early detection and diagnostic tool led to inflated incidence rates first in the USA [21] and within a few years in Greater Europe, notably in several Nordic countries [26].

During the early to mid-1990s, the detection of a substantial number of early-stage prostate cancers brought about rapid increases in population-level incidence rates across the higher-income countries of Northern, Western and Southern Europe. The extent to which prostate cancer incidence is now (as estimated in 2012) the leading form of cancer occurrence in men in these regions can be visibly grasped in Fig. 1. An East–west divide can be seen in Europe that combines differences in diagnostic intensity and the prominent cause of cancer in the region: in Central and Eastern Europe, PSA testing has been historically lower but male tobacco consumption higher and declining later, relative to elsewhere in Europe. Indeed, lung cancer remains the leading cancer in the eastern areas of Europe, prostate cancer in the west. In contrast, only in Sweden is prostate cancer the leading cause of cancer death, a country in which the male population did not take up the smoking habit like neighbouring countries; lung cancer ranks as the most important form of cancer death in men in all of the 39 remaining countries in Europe.
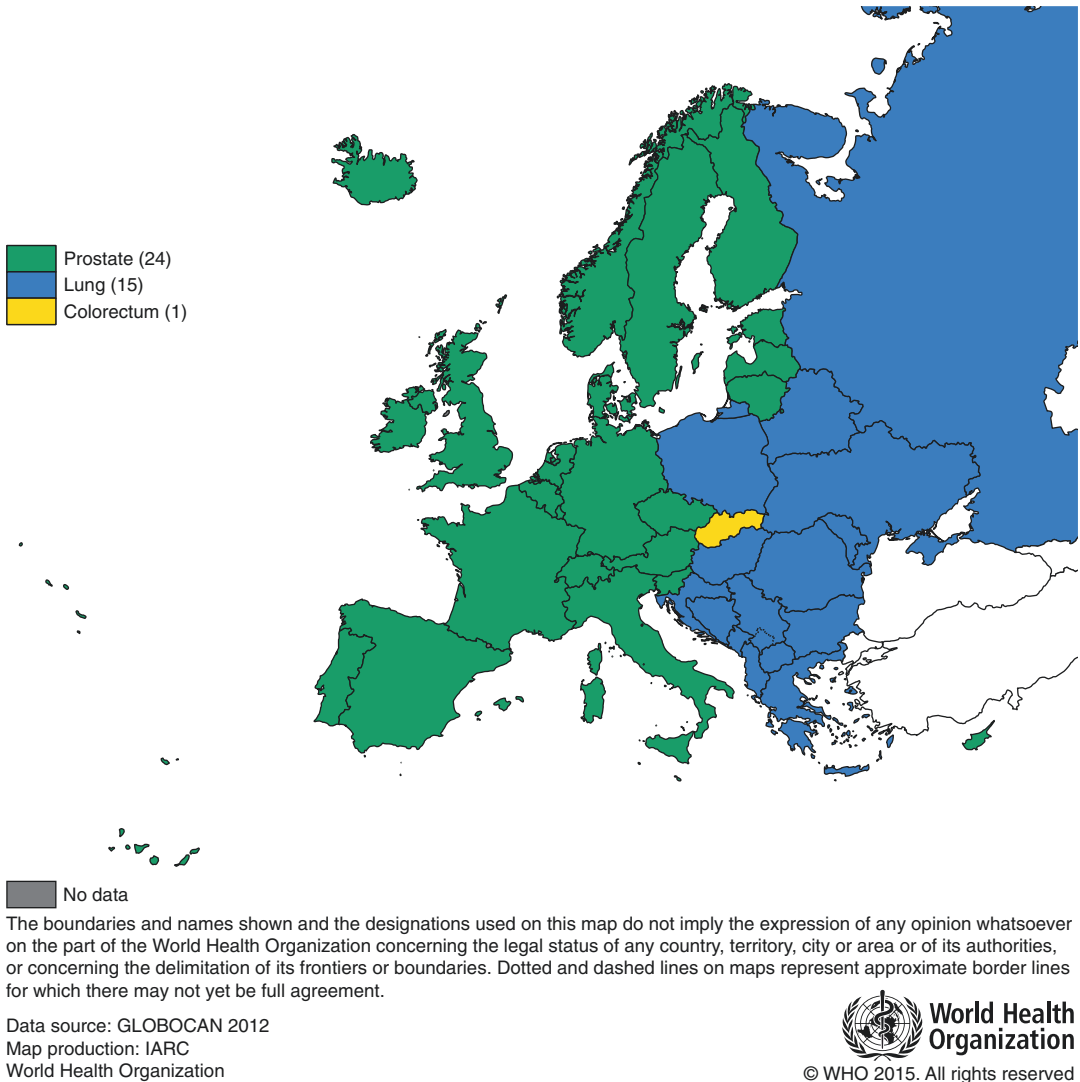
F. Bray (✉)
Section of Cancer Surveillance, International Agency for Research on Cancer, 150, Cours Albert Thomas, F-69372 Lyon Cedex, Lyon, France
e-mail: brayf@iarc.fr

L.A. Kiemeney
Radboud University Medical Center, Radboud Institute for Health Sciences, Department for Health Evidence & Department of Urology, Nijmegen, The Netherlands

Prostate (24)
Lung (15)
Colorectum (1)

No data

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Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

Fig. 1 Most common type of cancer in 40 European countries, based on the frequency of new cases as estimated in 2012 (Source: GLOBOCAN (http://globocan.iarc.fr))

Trends in incidence and mortality are not static, however, and prostate cancer incidence rates are to a great extent dependent on GP and urologist practices with respect to PSA testing. Conversely, prostate cancer mortality rates tend to be a better marker of extended disease and case fatality than of early diagnosis of asymptomatic cancers. Moderate declines in mortality rates have provided critical evidence of the favourable effect of increased curative treatment, particularly of early-diagnosed prostate cancer, within the last two decades.

1.1   Aims of Chapter

The aims of this chapter are threefold: (i) to describe the current profile of prostate cancer in Europe, (ii) to compare and contrast how recent trends in incidence and mortality are changing and (iii) to assess the factors that contribute to this evolving landscape, with a focus on the epidemiology of prostate cancer, the underlying risk factors and prospects of prevention. This chapter begins with a brief exploration of the global statistics of prostate cancer, followed by a more

thorough comparison of the incidence and mortality burden and rates across European countries by region, and within these populations over time.

1.2 Data Sources and Methods

In presenting recent geographic variations, national incidence and mortality estimates of prostate cancer were available by country, sex and age and extracted from GLOBOCAN database for the year 2012 (http://globocan.iarc.fr). Temporal comparisons make use of recorded incidence of the disease in 1975–2014 from national and regional population-based cancer registries of high quality complied in successive volumes of *Cancer Incidence in Five Continents* (http://ci5.iarc.fr) and in corresponding recorded mortality available nationally from the WHO mortality databank (http://www-dep.iarc.fr/WHOdb/WHOdb.htm); we obtained more recent data from published or online sources for a number of European populations, including the Nordic countries (http://ancr.nu) and the Netherlands (http://www.cijfersoverkanker.nl/). To enable comparison adjusted for the effects of differing age composition and population ageing over time, all incidence and mortality rates presented in this chapter are age-standardised to the world standard population [14], and are denoted *ASR*. In deciphering incidence and mortality trends over time, joinpoint regression models [25] were fitted to identify sudden linear changes in annual rates and to estimate the direction and magnitude of the slope within these distinct periods of time.
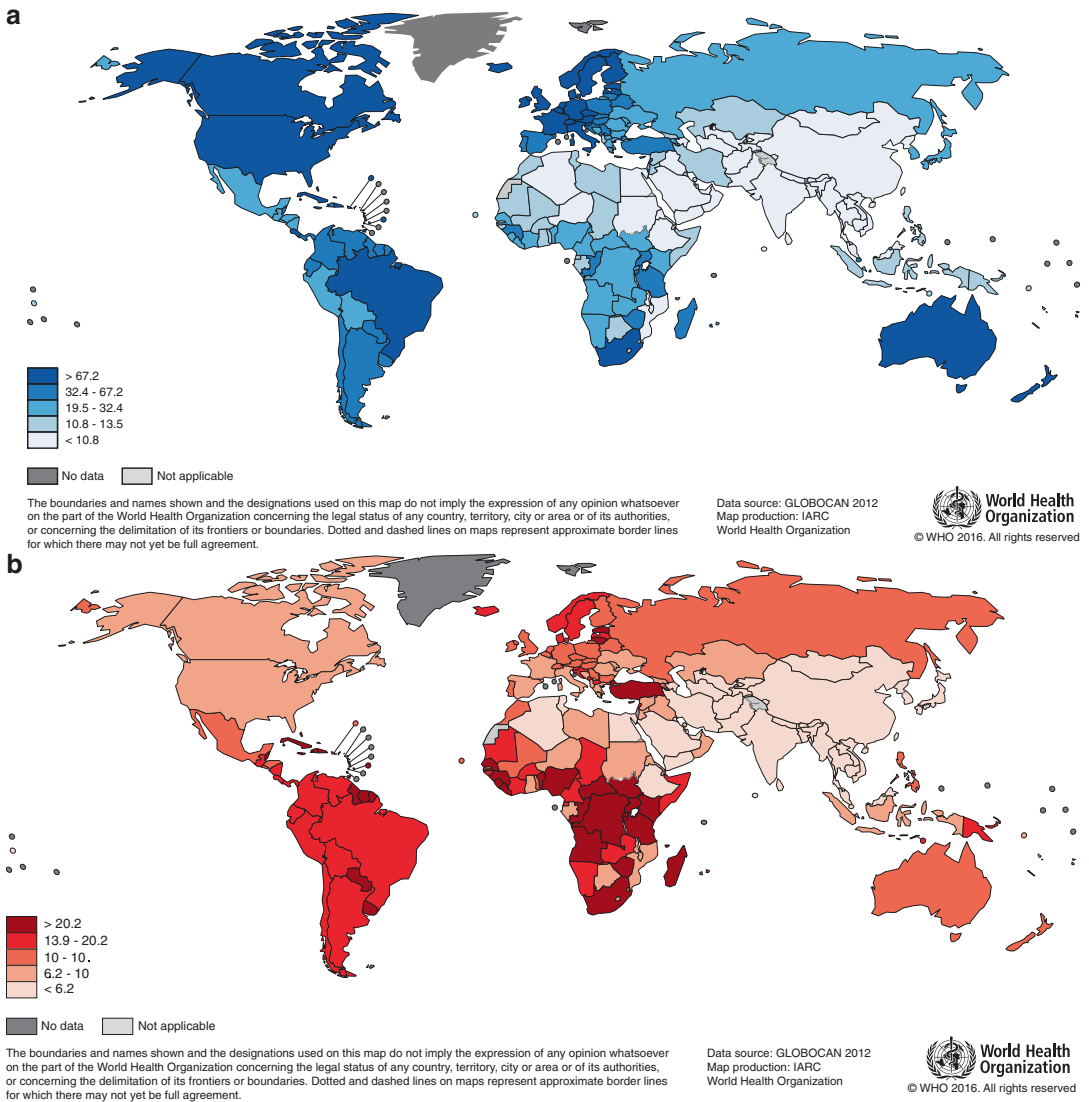
2 Prostate Cancer Incidence and Mortality

2.1 Global Patterns and Trends

By 2012, prostate cancer became the fourth most common cancer in the world, ranking third in importance in men, and the most frequent male cancer in 91 countries worldwide. While the estimated total annual number of 1.1 million cases represents about 15 % of all male cancers, it is a less prominent cause of cancer mortality, with just over 300,000 deaths estimated annually, or almost 7 % of male cancer deaths. The relatively low case fatality signifies many men are alive years after their initial diagnosis of prostate cancer – an estimated 3.9 million at 5 years in 2012 – making this by far the most prevalent form of cancer in men. Prostate cancer is also a cancer of the elderly, with three-quarters of a million cases diagnosed (68 %) in men aged 65 years or more.

Worldwide, recorded incidence is very high where health-seeking behaviour and health-care systems are advanced, and estimates of national incidence rates vary at least 25-fold (Fig. 2a). As a result of a substantial diagnosis of latent cancers through PSA testing of asymptomatic individuals, rates are often elevated in the high-income countries within Oceania, Northern America, and Western and Northern Europe, and low in many Asian populations, particularly in Southern Asia. Incidence rates are intermediate to high in many regions and countries in economic transition, where PSA testing is not likely to be highly prevalent, including the Caribbean, South America and Sub-Saharan Africa. A combination of genetic (ethnic) risk differences and environmental, dietary and lifestyle factors are at play, although the specific risk components are largely unknown. Clearly, rates are higher in populations where men of African-Caribbean origin is a key risk factor; in the USA, rates among blacks remain 35 % higher than those in whites.

With almost 60,000 new cases estimated in 2012, cancer of the prostate is the most frequently diagnosed cancer in Sub-Saharan African men, with the risk of developing prostate cancer before age 75 of 3.4 % (i.e. affecting almost 1 in 30 men) equivalent to the lifetime risks of breast (3.5 %) and cervical cancer (3.8 %) among women in the region [31]. While the disease is the most frequent neoplasm among men, there is a tenfold variation in prostate cancer incidence rates in Sub-Saharan countries with a cumulative risk ranging from 0.8 % in Ethiopia to greater than 8 % in the Republic of South Africa in 2012. Even in the latter country, rates are modest compared with those in men of African descent in the USA and Caribbean [16] [], although the

a

■	> 67.2
■	32.4 - 67.2
■	19.5 - 32.4
■	10.8 - 13.5
■	< 10.8

■ No data	■ Not applicable

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Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

b

■	> 20.2
■	13.9 - 20.2
■	10 - 10.
■	6.2 - 10
■	< 6.2

■ No data	■ Not applicable

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Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

Fig. 2 (**a**) Global map of prostate cancer incidence in 184 countries, based on age-standardised rates (World). Source: GLOBOCAN (http://globocan.iarc.fr). (**b**) Global map of prostate cancer mortality in 184 countries, based on age-standardised rates (World) (Source: GLOBOCAN (http://globocan.iarc.fr))

incidence is markedly increasing in a number of African populations, for example, in Kampala [35] and in the black population of Harare [10].

Mortality rates are less affected by early diagnosis of asymptomatic disease, and although a better marker of underlying risk of extended prostate cancer, they are also heavily dependent on the treatment options available in a given country (Fig. 2b). Mortality rates are high in North America, Northern and Western Europe,

Australia/New Zealand, but also in parts of Latin America (Brazil) and the Caribbean, and in much of Sub-Saharan Africa. Indeed of the 42 countries where prostate cancer is the leading cause of cancer death among men, 19 are in Sub-Saharan Africa, 13 in Central and South America and 9 are in the Caribbean. Mortality rates are low in most Asian populations and in North Africa.

Using data from population-based cancer registries, five distinct time trend patterns have been

demonstrated in prostate cancer incidence globally according to age [38]. Notably, incidence rates have been observed to peak among men aged over 75 years in most high-income populations, reflecting declining PSA screening at older ages and diagnosis at younger ages. In contrast, rates for men aged 45–54 years have not clearly stabilised or declined in most populations, and PSA testing is not likely to fully explain the rapidly rising rates of early-onset prostate cancer. In fact, decreasing overall prostate cancer mortality rates during the last decade has been reported mainly for North America, Oceania, Western Europe and parts of Northern Europe, where PSA testing has been more intensively implemented. This contrasts with the rising prostate cancer mortality rates observed in Central and Eastern Europe, and in parts of Asia and Africa [9]. The declining mortality rates may suggest that treatment and possibly earlier diagnosis have had an impact, whereas the rising rates could reflect an increasing diagnosis of prostate cancer; in both instances, the contribution of a changing prevalence and distribution of the underlying risk factors cannot be discounted.

2.2 Current Patterns in Europe

As with a global exposition of prostate cancer, the interpretation of observed variations in incidence in Europe – including any elucidation of potential risk determinants – is hampered by likely differences in the prevalence of PSA testing. Understanding the equivalent rates of mortality is also difficult given multiple contributory factors: the advent of curative treatment at about the same time as the increasing utilisation of the PSA test, and underlying this, the changing prevalence of one more (largely unknown) determinants of the disease. Each of these may have contributed to the levels of prostate cancer mortality in a given European population.

**Geographic Variations in Incidence and Mortality**

With over 400,000 new cases of prostate cancer, the disease is the leading cause of cancer in men, ahead of lung and colorectal cancer in second and third place, respectively. The disease is responsible for 22 % of the 1.8 million cancer cases among European men in 2012 and ranks fourth most frequent cancer in both sexes. Figure 3a, b, respectively, map the prostate cancer incidence and mortality rates in 2012 in 40 European countries, while Fig. 4 compares the ranking of mortality versus incidence. Rates of incidence vary tenfold in Europe, with the highest rates (125–160 per 100,000) in Lithuania, France, each of the Nordic countries as well as Switzerland and Ireland. Rates are intermediate (100–125) in Austria, Germany, Italy and England and Wales, and low (<50) in the Eastern European countries of Poland, Belarus, the Russian Federation and Bulgaria.

Approximately 92,000 deaths from prostate cancer were estimated to have occurred in 2012 in Europe, and thus the third-ranked cause of cancer death among men, after lung and colorectal cancer. In contrast to incidence, mortality rates vary only by a factor of 3, with some geographic differences observed. As with incidence, the highest mortality rates are seen in Lithuania, with their Baltic neighbours, Latvia and Estonia, ranked in second and third position. Rates are also relatively high (>25 per 100,000) in several Nordic countries (Denmark, Norway and Sweden), and in several Southern European countries (Slovenia, Croatia and Portugal) but moderate in several others (Spain, Italy and Greece); as with incidence, many of the lowest rates are seen in Central and Eastern European countries. The lowest rate is in Belarus, among the countries compared.

Clearly, there is little correlation in the present rates of prostate cancer incidence and mortality in Europe (Fig. 5). There is considerably more variability in incidence, and while the lowest and highest rates of both measures are, respectively, seen in Lithuania and Belarus, there are instances where incidence in a given country is relatively low and mortality relatively high (Latvia, Croatia), and vice versa (France). Figure 5 portrays the incidence rates in 3–5 year-periods (1983–87, 1993–97 and

a
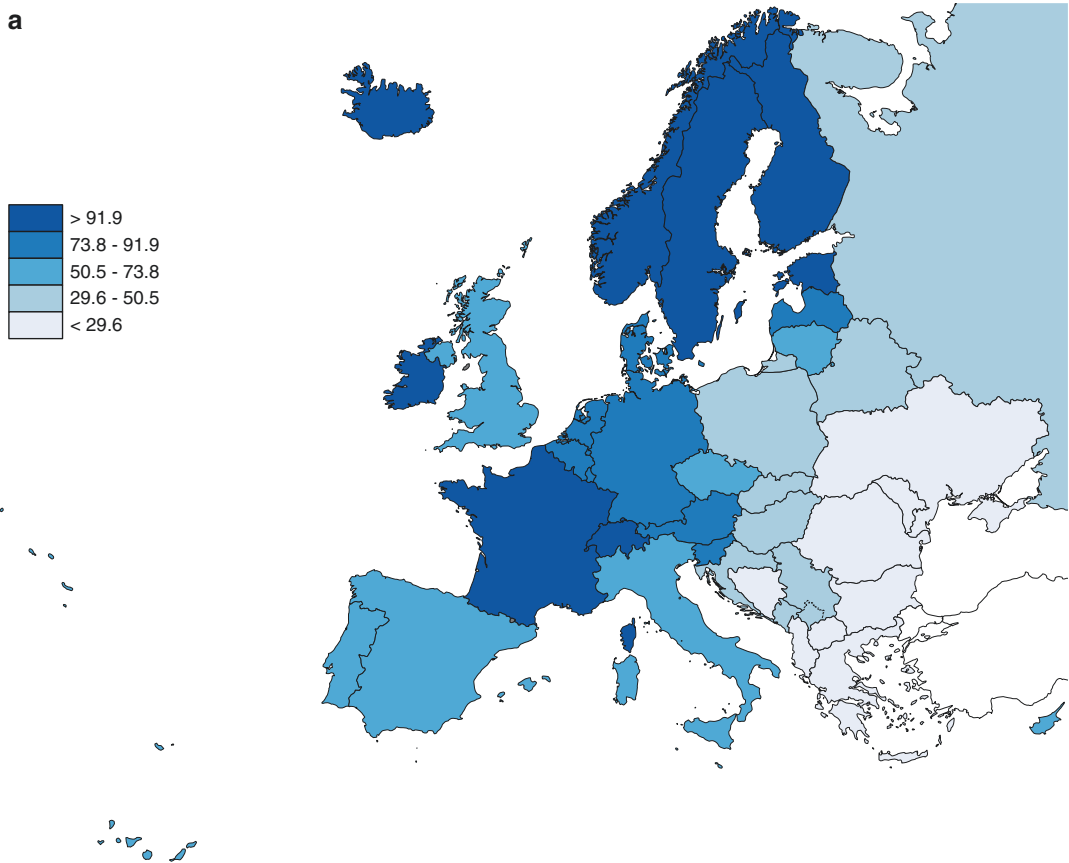
> 91.9
73.8 - 91.9
50.5 - 73.8
29.6 - 50.5
< 29.6

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Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

Fig. 3 (**a**) European map of prostate cancer incidence in 40 countries, based on age-standardised rates (World) (Source: GLOBOCAN (http://globocan.iarc.fr)). (**b**) European map of prostate cancer mortality in 40 countries, based on age-standardised rates (World) (Source: GLOBOCAN (http://globocan.iarc.fr))
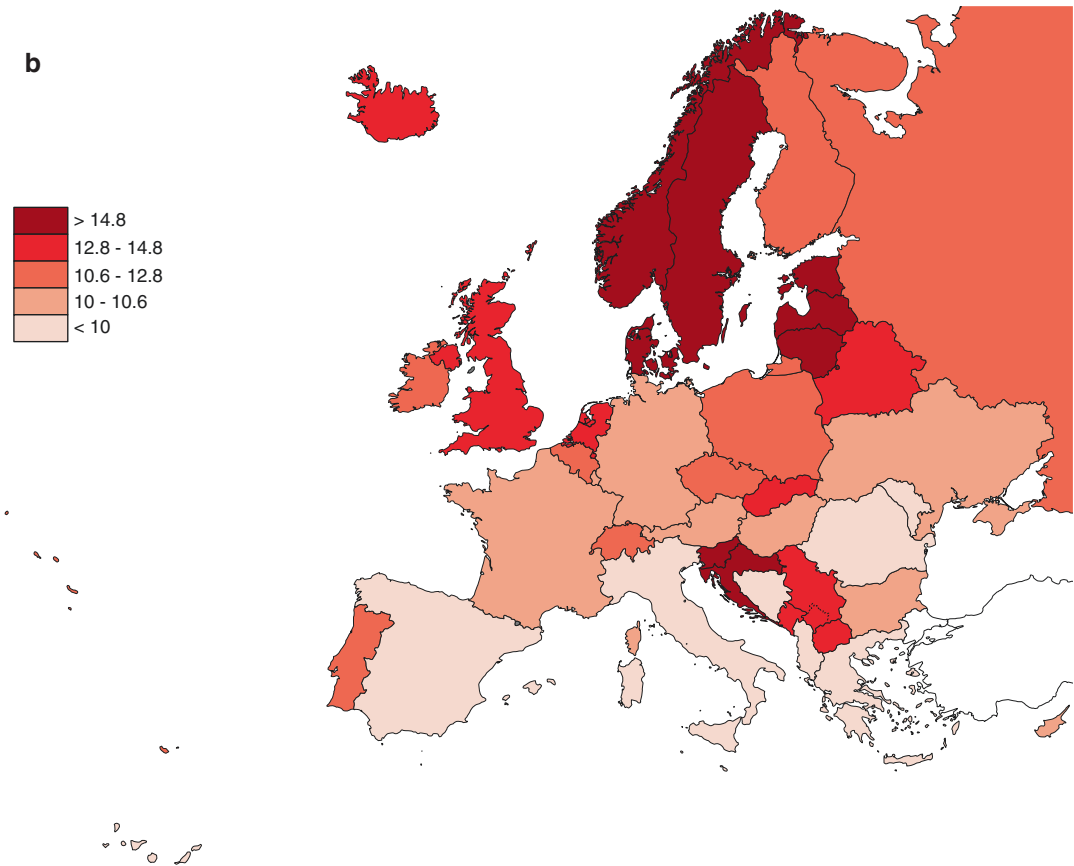
b

> 14.8
12.8 - 14.8
10.6 - 12.8
10 - 10.6
< 10

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Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

Fig. 3 (continued)

2000–04) against mortality rates 5–10 years later (circa 1993, 2003, 2010). The correlation is reasonably strong between the two measures in the 1980s diagnostic era, with the mortality rates directly related to the prior level of incidence in a given population. That correlation appears to weaken over time, however, as one enters the era of PSA availability and its expanded use as a test in Europe, during the 1990s and early 2000s.

2.3 Comparative Trends by European Region

The incidence has increased rapidly over the past two decades, and rates are influenced by early diagnosis among asymptomatic individuals, and prior to the PSA testing era, detection of latent cancer in tissue removed during prostate surgery. Examining trends in prostate cancer incidence and mortality in 32 countries, the

Fig. 4 Bar chart of prostate cancer incidence versus mortality in 32 countries, based on age-standardised rates (*Europe*), sorted by mortality in descending order (Source: Cancer Incidence in Five Continents (http://ci5.iarc.fr), WHO mortality database (http://www-dep.iarc.fr/WHOdb/WHOdb.htm))
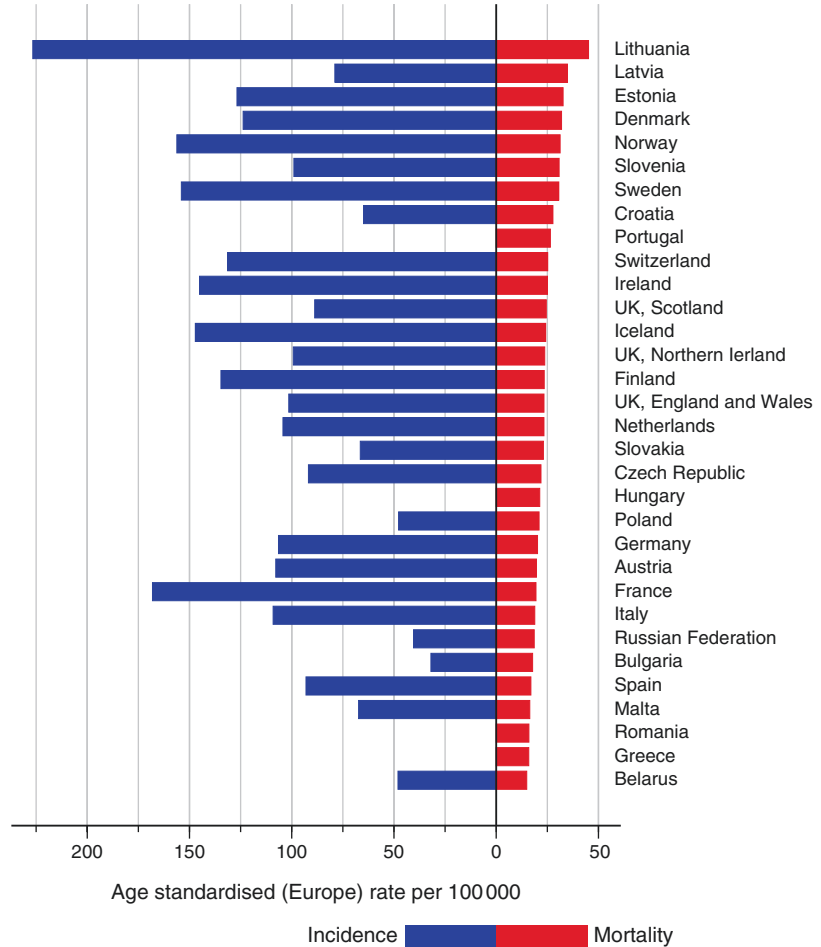

trends are presented for various years spanning 1975–2014 for 17 Northern and Western countries (Fig. 6a) and 15 Southern and European countries (Fig. 6b); the estimated annual percentage change is given.

Increasing trends in the incidence of prostate cancer have been observed in all countries from the mid-1970s through to the early 2000s, and for the period 1990–2004, the rate of increase ranged from 6 to 10 % on average per annum in France, Spain, Ireland, Italy, Slovenia, the Russian Federation and the Baltic countries (Estonia, Latvia, Lithuania) to 3–5 % in the remaining countries shown in Fig. 7. Notable are the uniform declines in prostate cancer incidence seen from the mid-2000s in almost all Northern and Western European countries, with the possible excep-

tion of countries in the Baltic region and the UK (Fig. 6a and Table 1). These recent decreases are not seen in any country within Southern or Eastern Europe, except in Italy (Fig. 6b, Table 1).

There appears to be little relation between the extent of the increases in prostate cancer incidence (as estimated from 1990) and the subsequent mortality declines (as estimated from 1996, Tables 1 and 2). National mortality declines in prostate cancer mortality were observed from 1996 in 19 of the 27 countries where both incidence and mortality measures are available (Fig. 7); these ranged from 2 to 3 % declines in Austria, France, Switzerland, Germany, the Netherlands, Finland, Spain and Norway to less than 1 % declines in Denmark and Slovakia. In contrast, increases in mortality of 0.5 % (Poland)
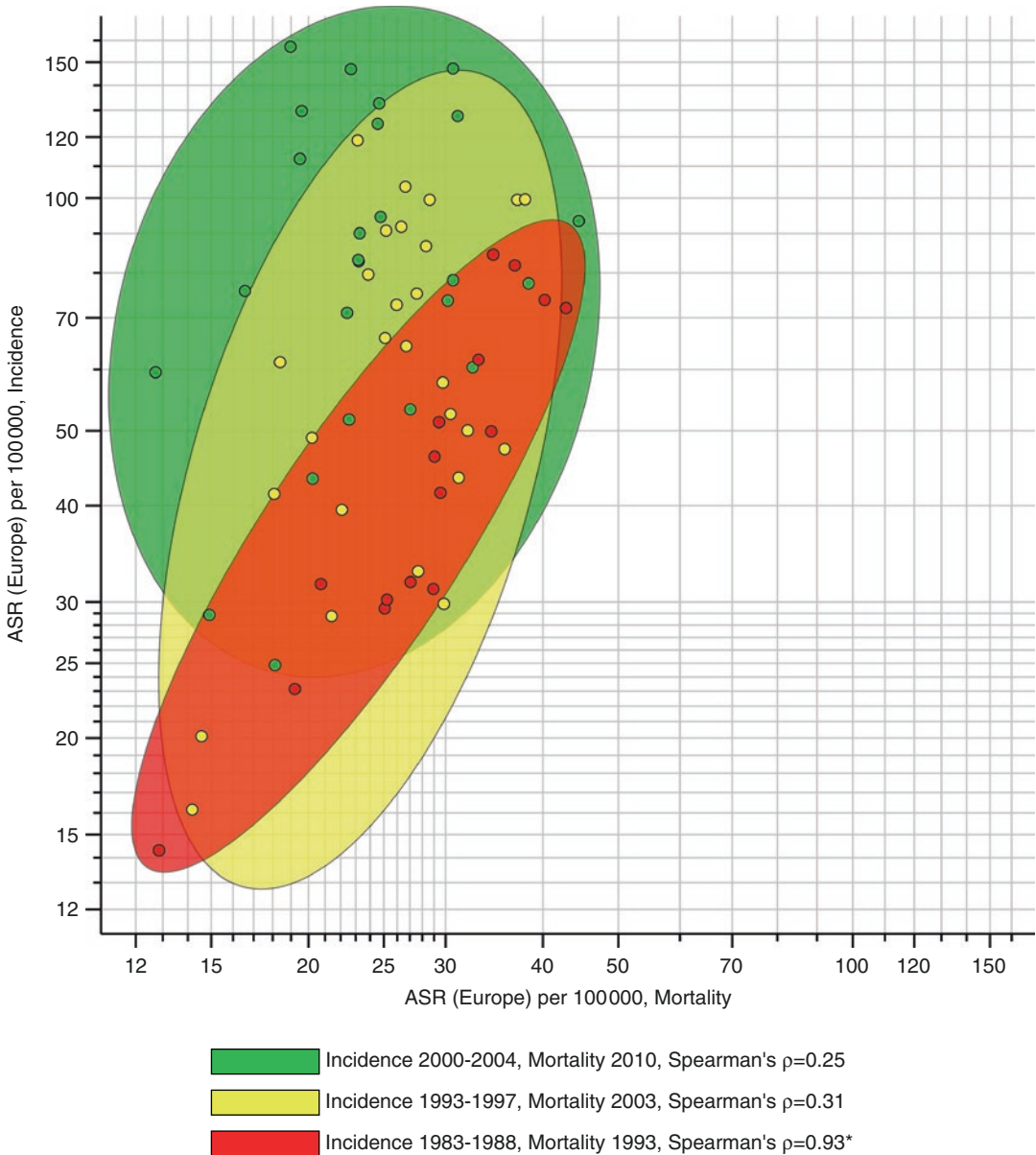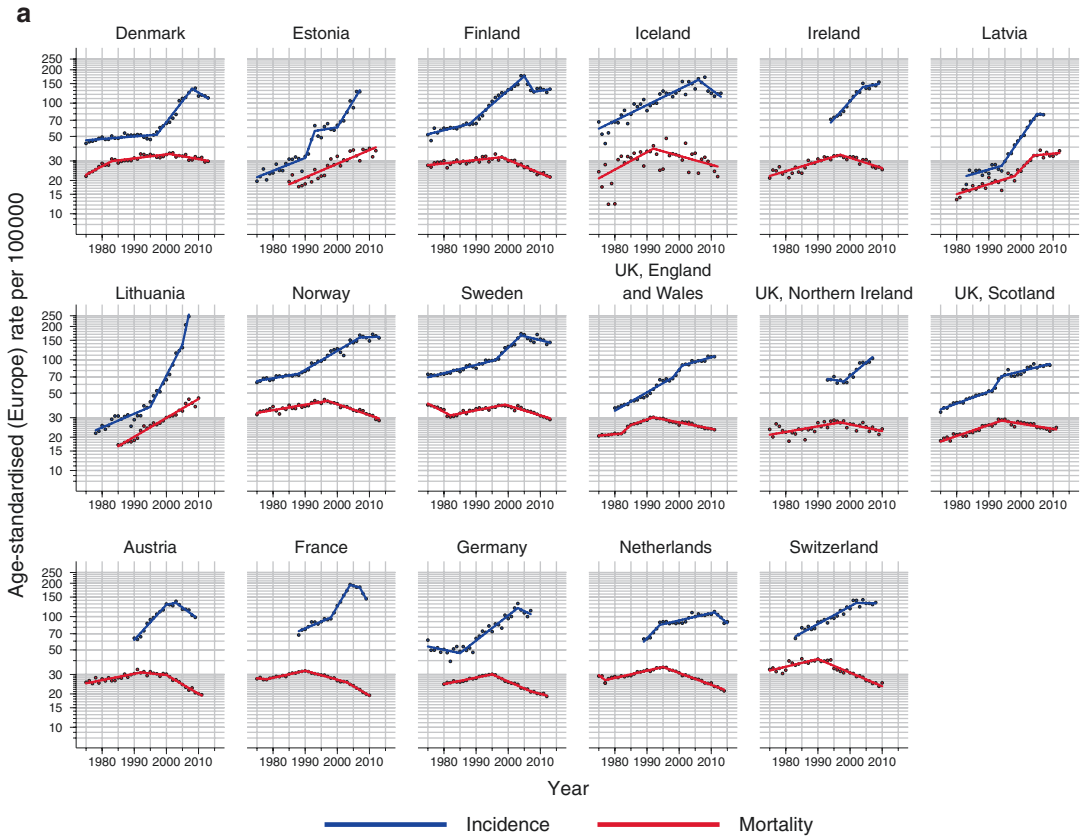
Fig. 5 Scatterplot of prostate cancer incidence versus mortality rates for three recent periods (Source: Cancer Incidence in Five Continents (http://ci5.iarc.fr), WHO mortality database (http://www-dep.iarc.fr/WHOdb/WHOdb.htm))

through to 4 % (Lithuania) are seen in the remaining eight countries in the Baltic region, Southern or Eastern Europe. Below is a more detailed exposition of the trends by region.

Northern Europe
In the five Nordic countries, rates have been uniformly increasing during the 1990s (Fig. 6a and

Table 1). Notable are the very recent declines in rates seen during period 2004–8, although incidence rates in Finland subsequently increased in 2008 following a short-term decline from 2005. Significant mortality declines of 2–3 % per annum are observed in all Nordic countries (Table 2), with the declines beginning in 1992 in Iceland, through to 1998 in Sweden (Table 3).

Fig. 6 (**a**) Line graphs of prostate cancer incidence versus mortality rates 1975–2014 in Northern and Western Europe. *Circles*: observed rates; Solid lines: trends based on Joinpoint regression (Source: Cancer Incidence in Five Continents (http://ci5.iarc.fr), WHO mortality database (http://www-dep.iarc.fr/WHOdb/WHOdb.htm)). (**b**) Line graphs of prostate cancer incidence versus mortality rates 1975–2014 in Southern and Eastern Europe. *Circles*: observed rates; *Solid lines*: trends based on Joinpoint regression (Source: Cancer Incidence in Five Continents (http://ci5.iarc.fr), WHO mortality database (http://www-dep.iarc.fr/WHOdb/WHOdb.htm))
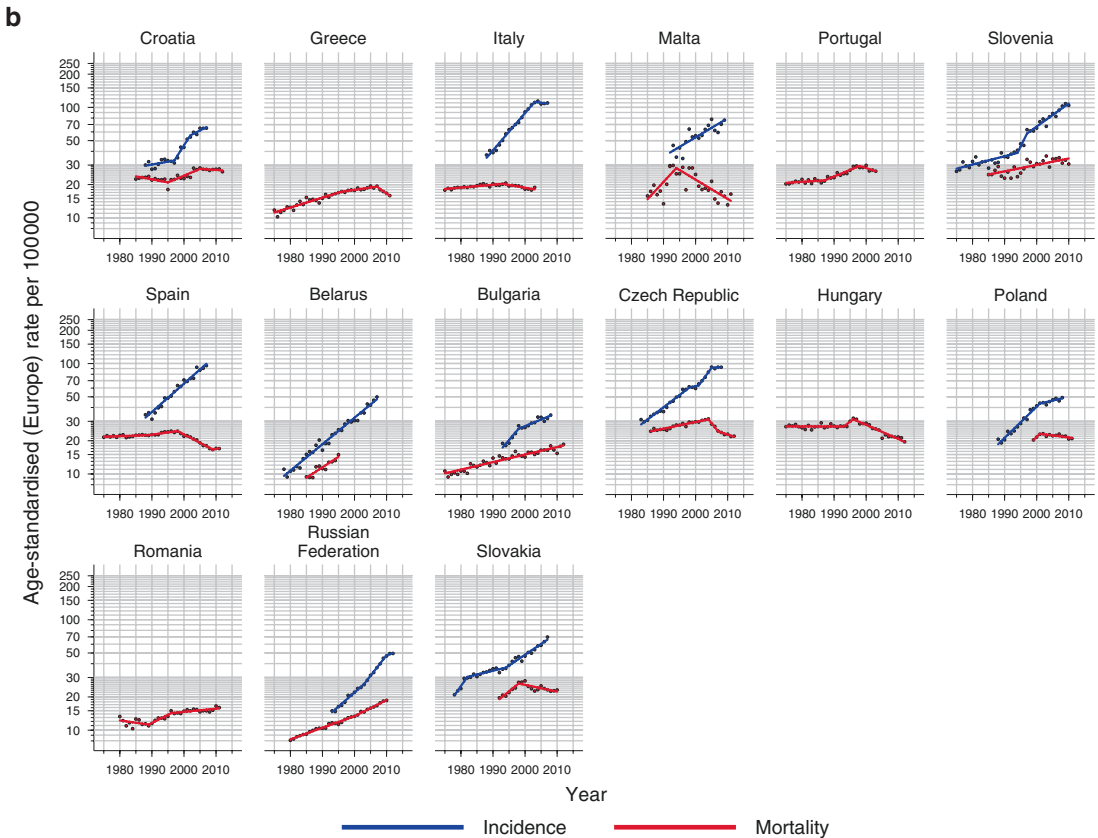
Fig. 6 (continued)

The incidence has also been increasing in the UK and Ireland but unlike their Nordic counterparts, no recent incidence declines are seen. Significant annual declines in mortality of slightly over 1 % were observed in the constituent countries of the UK. – as early as 1992 in England and Wales (Table 3) – with mean declines of 2.1 % observed in Ireland (since 1997). The Baltic countries have a very different prostate cancer profile, with significantly increasing rates of both incidence and mortality observed in the last decades; these correspond to 3 % in Estonia and 4 % in Lithuania (Fig. 6b and Table 2). A suggestion of a stabilisation of mortality rates can be observed in Latvia from 2004.

Western Europe

Increasing incidence rates are observed in all five countries since the mid-1980s, ranging from around 3 % per annum for the period 1990–2004 (Switzerland, the Netherlands) to almost 7 % (France). As seen in the Nordic countries, incidence rates have uniformly declined in Western Europe, with the decrease beginning during the period 2002–4 (Fig. 6a and Table 1). Some of the largest decreases in prostate cancer mortality in European men are seen in the region (Fig. 7), notably the close to 4 % rate declines in Austria and France, beginning in 2000 and 2003, respectively (Fig. 6b and Table 2).
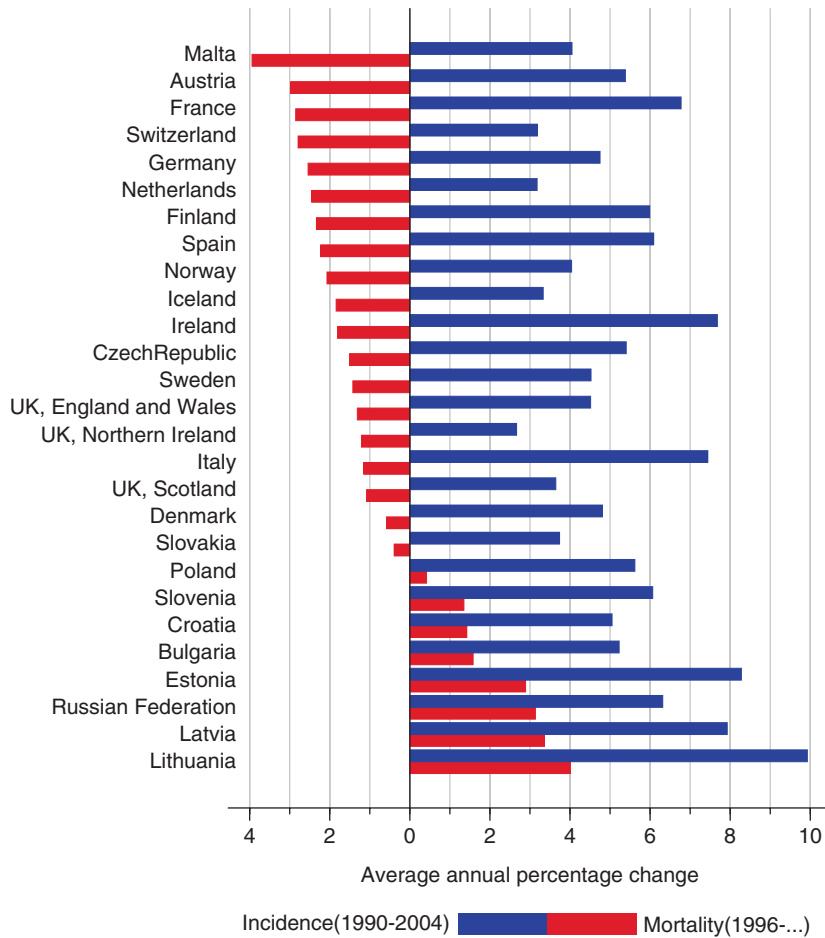
Fig. 7 Average annual percentage changes in prostate cancer incidence (1990–2004) and mortality trends (1996-) based on the joinpoint regression, sorted in ascending order of mortality trends (Source: Cancer Incidence in Five Continents (http://ci5.iarc.fr), WHO mortality database (http://www-dep.iarc.fr/WHOdb/WHOdb.htm))

Southern Europe

Incidence trends in the four Southern European countries are increasing rapidly, particularly in Italy, Slovenia and Spain where the mean annual increases are 6–7% per annum from 1990 to 2004 (Fig. 6b and Table 1). The mortality trends showed more variability across the six countries examined, although decreasing rates are seen in all countries except Slovenia. Among the most impressive declines are the 3.4% and 3.9% per annum reductions in Spain 1998–2009 and Malta 1994–2011, respectively (Fig. 6b and Table 2).

Eastern Europe

Some of the largest rate increases in prostate cancer incidence are observed in the five Eastern European countries, including the Czech Republic and Russia, where the rates rose 9–10% per year during the 2000s, although the increases have attenuated subsequently in very recent years (Fig. 6b and Table 1). In terms of mortality, there is greater variability; the long-term increases in the Russian Federation and Bulgaria of 2–3% per annum contrast with the rapid declines of the same order of magnitude in Hungary (since 1996) and more recently in the Czech Republic and Slovakia (Fig. 6b and Table 2).

Table 1 Prostate cancer incidence: new cases, person and age-standardised (Europe) rates circa 2006–2010, data span available and joinpoint regression analysis by country within European region

Country	Mean incidence cases per year 2006–2010	Person-years 2006–2010	ASR (Europe) 2006–2010	Observed period	JP linear segment	EAPC CI (95%)
Europe	129 210	153 918 116				
Northern Europe	65 260	46 532 428				
Denmark	4 256	2 719 803	123.8	1975–2013	1975–1997 1997–2008 2008–2013	0.5[a] (0.0; 1.0) 9.1[a] (7.9; 10.3) −4.0[a] (−6.3; −1.6)
Estonia	691	620 195	106.3	1975–2007	1975–1990 1990–1993 1993–2000 2000–2007	2.7[a] (0.8; 4.7) 20.6 (−14.3; 69.6) 1.1 (−3.8; 6.1) 11.7[a] (8.6; 14.8)
Finland	4 479	2 604 531	134.6	1975–2013	1975–1988 1988–2005 2005–2008 2008–2013	1.7[a] (0.4; 3.0) 6.0[a] (5.4; 6.6) −10.2 (−19.5; 0.2) 1.0 (−1.3; 3.4)
Iceland	225	159 570	147.1	1975–2013	1975–2006 2006–2013	3.3[a] (2.8; 3.9) −4.9[a] (−7.9; −1.8)
Ireland	2 741	2 154 884	143.3	1994–2009	1994–2004 2004–2009	7.7[a] (6.5; 8.8) 1.3 (−1.0; 3.6)
Latvia	824	1 059 911	75.1	1983–2007	1983–1994 1994–2005 2005–2007	1.9[a] (0.5; 3.4) 10.3[a] (9.0; 11.6) −0.8 (−11.0; 10.6)
Lithuania	2 555	1 592 521	163.3	1978–2007	1978–1995 1995–2005 2005–2007	2.9[a] (1.7; 4.1) 13.8[a] (11.9; 15.8) 36.7[a] (23.4; 51.5)
Norway	4 264	2 377 718	156.2	1975–2013	1975–1988 1988–2007 2007–2013	1.2[a] (0.1; 2.2) 4.0[a] (3.5; 4.5) 0.2 (−1.7; 2.2)
Sweden	9 510	4 585 718	154.0	1975–2013	1975–1996 1996–2004 2004–2013	1.7[a] (1.3; 2.1) 6.6[a] (4.8; 8.4) −1.7[a] (−2.7; −0.7)
UK, England and Wales	32121	25 326 450	101.4	1980–2011	1980–1998 1998–2001 2001–2011	3.9[a] (3.4; 4.4) 8.7 (−2.7; 21.5) 1.9[a] (1.2; 2.7)

(continued)

Table 1 (continued)

Country	Mean incidence cases per year 2006–2010	Person-years 2006–2010	ASR (Europe) 2006–2010	Observed period	JP linear segment	EAPC CI (95%)
UK, Northern Ireland	841	845 796	96.1	1993–2007	1993–1998 1998–2007	−1.1 (−6.1; 4.2) 5.8[a] (4.0; 7.7)
UK, Scotland	2 753	2 485 331	88.0	1975–2009	1975–1991 1991–1994 1994–2009	2.5[a] (1.8; 3.2) 10.5 (−3.7; 26.7) 1.7[a] (1.2; 2.2)
Western Europe	22 847	16148 556				
Austria	5 224	4 038 612	109.4	1990–2009	1990–2000 2000–2003 2003–2009	7.6[a] (6.5; 8.8) 1.3 (−9.1; 12.8) −4.7[a] (−6.5; −2.9)
France	5 992	2 984 699	172.2	1988–2009	1988–1998 1998–2004 2004–2007 2007–2009	2.9[a] (1.9; 3.9) 11.9[a] (9.8; 14.1) −1.9 (−8.6; 5.3) −11.1[a] (−17.6; −4.0)
Germany	837	511456	113.2	1975–2007	1975–1985 1985–2003 2003–2007	−1.4 (−3.9; 1.2) 5.4[a] (4.5; 6.3) −3.2 (−8.4; 2.3)
Netherlands	10 075	8 144 299	104.3	1989–2015	1989–1994 1994–2011 2011–2015	7.3[a] (3.1; 11.5) 1.5[a] (1.0; 2.1) −5.5[a] (−8.9; −2.0)
Switzerland	719	469 490	133.4	1983–2008	1983–2002 2002–2008	3.7[a] (3.2; 4.3) −0.1 (−2.5; 2.2)
Southern Europe	8 001	7172 636				
Croatia	1517	2138 032	62.2	1988–2007	1988–1997 1997–2002 2002–2007	1.2 (−0.7; 3.2) 11.1[a] (5.3; 17.2) 3.5[a] (0.5; 6.6)
Italy	3447	2 080 603	109.9	1988–2007	1988–2003 2003–2007	8.1[a] (7.6; 8.6) −0.9 (−3.3; 1.6)
Malta	156	203 268	69.2	1992–2009	1992–2009	4.1[a] (2.6; 5.5)
Slovenia	1146	997 043	99.0	1975–2010	1975–1994 1994–1997 1997–2010	1.8[a] (0.9; 2.6) 14.4[a] (−7.3; 41.3) 4.9[a] (4.2; 5.7)
Spain	1735	1753 690	87.9	1988–2007	1988–2007	6.1[a] (5.5; 6.6)
Eastern Europe	33102	84 064496				

Belarus	1750	4 572 634	43.3	1978–2007	1978–2007	5.7[a] (5.4; 6.0)
Bulgaria	1590	3 733 526	32.2	1993–2008	1993–1998	8.2[a] (4.2; 12.3)
					1998–2008	2.8[a] (1.7; 3.9)
Czech Republic	4 949	5 027 528	90.5	1983–2008	1983–1998	5.2[a] (4.7; 5.8)
					1998–2001	1.6 (−8.1; 12.3)
					2001–2005	9.6[a] (5.0; 14.5)
					2005–2008	0.3 (−3.4; 4.2)
Poland	1096	2 365 394	47.0	1988–2008	1988–2001	6.7[a] (5.9; 7.6)
					2001–2008	1.6[a] (0.1; 3.0)
Russian Federation	22 385	65 749 763	40.4	1993–2012	1993–2003	6.1[a] (5.3; 6.8)
					2003–2010	9.0[a] (7.9; 10.1)
					2010–2012	2.2 (−2.8; 7.4)
Slovakia	1 332	2615651	60.7	1978–2007	1978–1982	10.0[a] (3.7; 16.8)
					1982–1994	1.6[a] (0.6; 2.7)
					1994–2007	4.6[a] (4.0; 5.2)

CI confidence interval
[a]Statistically significant

Table 2 Prostate cancer mortality: new deaths, person and age-standardised (Europe) rates circa 2006–2010, data span available and joinpoint regression analysis by country within European region

Country	Mean incidence cases per year 2006–2010	Person-years 2006–2010	ASR (Europe) 2006–2010	Observed Period	JP linear segment	EAPC CI (95%)
Europe	79 487	314 570 696				
Northern Europe	17 497	47 822 287				
Denmark	1 136	2 724 046	31.6	1975–2013	1975–1983	3.6[a] (2.1; 5.2)
					1983–2001	0.8[a] (0.4; 1.2)
					2001–2013	−1.2[a] (−1.7; −0.6)
Estonia	230	605 582	35.7	1985–2012	1985–2012	2.9[a] (2.3; 3.4)
Finland	807	2 606 774	24.2	1975–2013	1975–1998	0.7[a] (0.4; 1.0)
					1998–2013	−2.7[a] (−3.2; −2.3)
Iceland	49	159 355	28.4	1975–2012	1975–1992	3.7[a] (1.2; 6.3)
					1992–2012	−1.8[a] (−3.3; −0.3)
Ireland	525	2 162 832	26.6	1975–2010	1975–1997	2.0[a] (1.6; 2.5)
					1997–2010	−2.1[a] (−2.9; −1.3)
Latvia	365	979 270	34.4	1980–2012	1980–1998	2.1[a] (1.3; 2.9)
					1998–2004	7.4[a] (3.0; 12.0)
					2004–2012	0.6 (−1.1; 2.4)
Lithuania	547	1 456 969	41.6	1985–2010	1985–2010	4.0[a] (3.7; 4.3)
Norway	1 064	2 380 853	33.7	1975–2013	1975–1997	1.1[a] (0.9; 1.4)
					1997–2013	−2.3[a] (−2.6; −1.9)
Sweden	2 450	4 590 870	33.2	1975–2013	1975–1982	−3.5[a] (−4.8; −2.2)
					1982–1999	1.3[a] (1.0; 1.7)
					1999–2013	−2.0[a] (−2.4; −1.6)
UK, England and Wales	9 297	26 785 718	24.3	1975–2011	1975–1982	0.6 (−0.5; 1.7)
					1982–1985	6.2 (−1.2; 14.1)
					1985–1992	2.3[a] (1.2; 3.4)
					1992–2011	−1.3[a] (−1.5; −1.1)
UK, Northern Ireland	226	869 855	23.0	1975–2010	1975–1997	1.2[a] (0.6; 1.8)
					1997–2010	−1.4[a] (−2.5; −0.3)
UK, Scotland	801	2 500 163	23.7	1975–2011	1975–1994	2.3[a] (1.9; 2.7)
					1994–2011	−1.1[a] (−1.4; −0.7)
Western Europe	25 518	86 364 688				

Country				Period	APC (95% CI)
Austria	1 117	4 059 464	21.5	1975–2011	
				1975–1992	1.3[a] (0.9; 1.7)
				1992–2000	−0.6 (−2.0; 0.7)
				2000–2011	−3.8[a] (−4.5; −3.2)
France	8 986	30 225 670	20.8	1975–2010	
				1975–1978	−0.7 (−3.1; 1.7)
				1978–1990	1.5[a] (1.2; 1.8)
				1990–2003	−1.8[a] (−2.1; −1.6)
				2003–2010	−3.9[a] (−4.3; −3.4)
Germany	12 010	40 815 102	20.7	1980–2012	
				1980–1995	1.4[a] (1.1; 1.6)
				1995–2007	−2.9[a] (−3.2; −2.6)
				2007–2012	−1.8[a] (−2.8; −0.7)
Netherlands	2 095	7 504 334	29.7	1975–2014	
				1975–1977	−5.0 (−10.5; 0.8)
				1977–1995	1.5[a] (1.3; 1.7)
				1995–2014	−2.4[a] (−2.6; −2.3)
Switzerland	1 310	3 760 118	25.0	1975–2010	
				1975–1990	1.6[a] (0.9; 2.3)
				1990–2010	−2.8[a] (−3.2; −2.4)
Southern Europe	17 095	63 803 923			
Croatia	660	2 101 797	27.4	1985–2012	
				1985–1995	−1.3[a] (−2.3; −0.2)
				1995–2005	2.9[a] (1.8; 4.0)
				2005–2012	−0.4 (−1.8; 0.9)
Greece	1 574	5 464 094	18.0	1975–2011	
				1975–1996	2.1[a] (1.8; 2.4)
				1996–2007	1.0[a] (0.2; 1.7)
				2007–2011	−4.6[a] (−7.2; −2.0)
Italy	7 197	27 744 064	18.4	1975–2003	
				1975–1993	0.6[a] (0.4; 0.8)
				1993–2003	−1.1[a] (−1.6; −0.7)
Malta	31	209 869	14.9	1985–2011	
				1985–1994	7.5[a] (2.4; 12.9)
				1994–2011	−3.9[a] (−5.5; −2.3)
Portugal	1 712	4 997 329	27.7	1975–2003	
				1975–1987	0.4 (−0.4; 1.3)
				1987–1998	2.8[a] (2.0; 3.6)
				1998–2003	−2.2[a] (−4.1; −0.2)
Slovenia	350	1 002 387	32.9	1985–2010	
				1985–2010	1.3[a] (0.8; 1.9)

(continued)

Table 2 (continued)

Country	Mean incidence cases per year 2006–2010	Person-years 2006–2010	ASR (Europe) 2006–2010	Observed Period	JP linear segment	EAPC CI (95%)
Spain	5 571	22 284 383	17.3	1975–2011	1975–1989	0.3 (−0.1; 0.6)
					1989–1998	0.9[a] (0.3; 1.5)
					1998–2009	−3.4[a] (−3.8; −3.0)
					2009–2011	1.2 (−3.6; 6.2)
Eastern Europe	19 377	116 579 798				
Belarus	441	4 797 846	12.9	1985–1995	1985–1995	4.5[a] (3.1; 5.9)
Bulgaria	820	3 654 124	16.5	1975–2012	1975–2012	1.6[a] (1.4; 1.8)
Czech Republic	1 317	5 097 845	24.0	1986–2012	1986–2004	1.4[a] (1.2; 1.6)
					2004–2007	−8.0[a] (−14.0; −1.7)
					2007–2012	−2.3[a] (−3.7; −0.8)
Hungary	1 186	4 769 849	21.9	1975–2012	1975–1993	−0.0 (−0.4; 0.4)
					1993–1996	5.2 (−6.3; 18.0)
					1996–2012	−2.9[a] (−3.3; −2.5)
Poland	3 897	18 456 675	21.9	1999–2011	1999–2001	6.7 (−2.7; 17.0)
					2001–2011	−0.8[a] (−1.5; −0.2)
Romania	1 789	10 709 460	15.2	1980–2011	1980–1989	−1.0 (−2.4; 0.5)
					1989–1996	3.5[a] (1.0; 6.0)
					1996–2011	0.7[a] (0.2; 1.2)
Russian Federation	9 419	66 463 516	17.5	1980–2010	1980–2000	2.4[a] (2.3; 2.6)
					2000–2010	3.4[a] (3.0; 3.8)
Slovakia	508	2 630 483	23.0	1992–2010	1992–1998	5.6[a] (3.0; 8.3)
					1998–2010	−1.4[a] (−2.1; −0.6)

CI confidence interval
[a]Statistically significant

Table 3 Summary of recent declines in national prostate mortality in Europe: year which the downturn was first observed and the estimated annual per cent change (EAPC)

Country	Year decline identified	EAPC CI (95 %)
Northern Europe		
Denmark	2001	−1.2[a] (−1.7; −0.6)
Finland	1998	−2.7[a] (−3.2; −2.3)
Iceland	1992	−1.8[a] (−3.3; 0.3)
Ireland	1997	−2.1[a] (−2.9; −1.3)
Norway	1997	−2.3[a] (−2.6; −1.9)
Sweden	1999	−2.0[a] (−2.4; −1.6)
UK, England and Wales	1992	−1.3[a] (−1.5; −1.1)
UK, Northern Ireland	1997	−1.4[a] (−2.5; −0.3)
UK, Scotland	1994	−1.1[a] (−1.4; −0.7)
Western Europe		
Austria	1992	−0.6 (−2.0; 0.7)
France	1990	−1.8[a] (−2.1; −1.6)
Germany	1995	−2.9[a] (−3.2; −2.6)
Netherlands	1995	−2.4[a] (−2.6; −2.3)
Switzerland	1990	−2.8[a] (−3.2; −2.4)
Southern Europe		
Croatia	2005	−0.4 (−1.8; 0.9)
Greece	2007	−4.6[a] (−7.2; −2.0)
Italy	1993	−1.1[a] (−1.6; −0.7)
Malta	1994	−3.9[a] (−5.5; −2.3)
Portugal	1998	−2.2[a] (−4.1; −0.2)
Spain	1998	−3.4[a] (−3.8; −3.0)
Eastern Europe		
Czech Republic	2004	−8.0[a] (−14.0; −1.7)
Hungary	1996	−2.9[a] (−3.3; −2.5)
Poland	2001	−0.8[a] (−1.5; −0.2)
Slovakia	1998	−1.4[a] (−2.1; −0.6)

CI confidence interval
[a]Statistically significant

Lastly, Table 3 indicates the 24 countries where prostate cancer mortality rates have declined, the year the downturn began and the extent of the decrease per annum. The first declines in prostate cancer mortality rates were seen in France and Switzerland in 1990, while the latest are observed in Greece in 2007, but in most countries rates began to fall during the mid- to late-1990s. There was considerable variability in the timing and order of magnitude of the year-on-year decreases, varying from approximately 0.6 % in Austria (from 1992) to 4–8 % for the quite recent declines observed in the Czech Republic and Greece.

2.4   Key Determinants of the Cancer Burden

Towards one-quarter (22 %) of all cancers diagnosed in men in Europe today are cancers of the prostate, compared with 11 % estimated in 1995 [5]. While the true impact of prostate cancer screening can be only evaluated indirectly, incidence rates are clearly heavily influenced by the radical changes in diagnostic capabilities and practice over the last decades. The increasing rates

in European men can be partly attributed to TURP in the 1970s and 1980s, while the more marked upsurge in incidence over the last 15–20 years (as identified in many countries via the joinpoint analyses) can be largely attributed to the greater use of PSA testing and subsequent biopsy. The initial rise in PSA testing in the late 1980s, closely followed by increasing prostate cancer incidence rates, has been clearly demonstrated in the Nordic countries [24]; given the consistent observation of increases in incidence in European countries – ranging from 3 to 10 % per annum from the early to mid-1900s – it is likely that such practices have prevailed in all regions of Europe. Of note are the recent accelerations in the historically lower rates observed in Southern and Eastern Europe, including Croatia, Slovenia, the Czech Republic and Slovakia.

There is little correlation between incidence and mortality rates in different European populations, nor in the evolution in trends in the last 15 years. Where observable, the slow and steady increases in prostate cancer mortality in the 1970s and 1980s have been replaced uniformly by declining mortality rates that are now apparent in 24 countries in Europe, with only the Baltic countries, where mortality rates are stable or rising, the clear exception. The underlying reasons for the fall in mortality across Europe are likely to imitate those conjectured in the USA, at least in part; Brawley [5] has noted possible explanations for the rate declines since 1991 in the USA that include an effect of screening and treatment, changes in the attribution of cause of death, or improved treatment resulting in a genuine postponement of death for some men with metastatic disease. Ecologic studies have revealed that declines in prostate cancer mortality rates are seen too early to be solely attributed to PSA testing; some have postulated they may be the result of improving treatment of both localised and high-risk disease [18]. The extent to which underlying changes in the prevalence and distribution of risk factors contribute to these trends remains largely unexplored and unknown.

Still, incidence varies tenfold and detectable falls in incidence have occurred recently in many higher-income countries, particularly in Northern and Western Europe. The changing but persistent influence of PSA on incidence relates to the perceptions and practices of health-care professionals regarding its utility as a prognostic test as well as public awareness of the controversy surrounding prostate cancer screening; in France, public perceptions of screening have been observed to vary by age and socioeconomic status [20]. The evidence of the benefits and harms of screening have become increasingly evident, as has the question of whether PSA can reduce prostate cancer mortality via the European Randomised Study of Screening for Prostate Cancer (ERSPC) trial. Schroder et al. [32] have reported a 22 and 21 % risk reduction from PSA screening at 11 or 13 years of follow-up, respectively, although in absolute terms, one death from prostate cancer was prevented for every 781 men invited for screening at 13 years follow-up. With three-fifths of screen-detected cancers in the ERSPC trial classified as low risk, experts have stressed that decision-making must be informed by tools that are able to stratify risk of low or high grade cancers on biopsy; the extent to which the trial findings will influence PSA testing practices and PSA screening awareness in Europe will reveal itself in the temporal patterns of prostate cancer incidence in due course.

2.5   Caveats in Interpretation

There are several points of caution we should note in the above analysis linked to the availability and quality of the data sources and the methods applied. GLOBOCAN was utilised to present cancer incidence and mortality maps for 2012 worldwide and for Europe. These are estimates that rely upon the best available data on cancer incidence and mortality in a given country. In Europe, the methods used to estimate national rates involve projections of recent trends, where annual data are available prior to 2012 [17]. Incidence data derive from population-based cancer registries which may cover national populations or subnational areas; estimates in France, Spain and Italy are all based on national estimates

based on regional rather than national coverage, for example. An aggregation of regional registry datasets was required, assuming that the pertaining cancer registries collectively represented national patterns and trends. Where no recorded incidence data were available or when they were considered to be lacking sufficient quality, as was the case in nine countries in Europe including Greece, Hungary and Romania, modelled estimates were derived by applying available national mortality to regional data from other countries. In Europe, almost all countries have national mortality data through death registration systems compiled in the WHO mortality database, the exceptions being Bosnia Herzegovina and Montenegro.

To further compare patterns and trends in prostate cancer in Europe, we focussed on 32 countries, predominantly with high quality incidence and mortality, the former measure based mainly on registries included in the recent volumes of the *Cancer Incidence in Five Continents* (CI5) series. Those compiled in these volumes have been assessed as having high quality incidence data following a peer-reviewed assessment of their comparability, completeness and accuracy; yet for a number of countries – including Germany, Italy and Spain – regional registries are used to convey national profiles. These regional proxies may be more or less representative in certain countries than others. Given the difficulties in interpreting contemporary rates of prostate cancer incidence and mortality in Europe, comparative data on PSA use, treatment modalities and stage information may have provided insight, but were not available.

One methodological shortcoming is the use of joinpoint regression [23]. Quantification of the trends within linear segments can be unduly influenced by the last data points, while joinpoints and arbitrary slopes are sometimes identified by the regression where the underlying data are subject to substantial random variation. The technique is, however, particularly suitable for prostate cancer, permitting, in this chapter, quantification of the rather abrupt linear trends in incidence and mortality in Europe over time.

3 Epidemiology and the Prospects for Prevention

This chapter closes with a review of the epidemiology of prostate cancer and by extension, the potential to reduce the burden via removal or reduction of the causes of the disease through primary prevention strategies. The first thing to note is that, for a disease as prevalent and incident as prostate cancer, relatively little is known about its exact aetiology. Convincing evidence has been produced for only a few risk factors: ageing, genetic predisposition, ethnicity and body fatness. Numerous scientific papers have suggested a long list of other risk factors, of which those most intensely investigated will be reported in this section. Results of these studies are quite inconsistent which makes any definitive conclusions difficult. Apart from the general problems in observational studies on risk factors for disease, in prostate cancer the definition of the disease is arbitrary. Because of the large impact of PSA testing on prostate cancer incidence and the differences between indolent and potentially lethal prostate cancers, epidemiological studies should preferably study the latter subgroup of tumours in order to validly identify risk factors for the disease [21].

Ageing

The most well-known risk factor for prostate cancer is ageing, as evidenced by the age-specific incidence rates in the previous paragraphs. Prostate cancer is rarely diagnosed before the age of 45. In most western communities the peak in the incidence rates lies between 65 and 75 years of age. In a recent review of postmortem studies, the estimated mean cancer prevalence in men who died from other causes increased in a nonlinear fashion from 5% (95% CI: 3–8%) at age <30 years to 59% (95% CI: 48–71%) by age >79 years [3]. This underlines one of the greatest dilemmas in prostate cancer diagnostics nowadays: most men who have prostate cancer will die with the disease, not from the disease. The pivotal issue of research in prostate cancer is the identification of discriminative tests that can

accurately predict invalidating and lethal prostate cancer.

Family History and Genetics

Besides age, a positive family history of prostate cancer is the most well-established risk factor for prostate cancer. First-degree relatives of affected men carry a two- to threefold increased risk of being diagnosed with the disease themselves. It is estimated that 5–10 % of prostate cancers have a true genetic cause. But the identification of the genes underlying these Mendelian forms of prostate cancer has appeared to be much more problematic than in, for example, breast cancer. Apparently, familial prostate cancer is a far more heterogeneous disease with contributions from many more genetic loci than familial breast cancer [28]. Mutations in the few high-penetrance genes are so rare that testing in families with hereditary prostate cancer, that is, families with three or more first-degree relatives (or 2 first-degree relatives of young age) with prostate cancer [8] is not useful, possibly with the exception of two genes: *BRCA2* and *HOXB13*. Male carriers of a *BRCA2* mutation have a two- to sixfold increased risk of prostate cancer, occurring earlier in life and with a more aggressive phenotype. The G84E (rs138213197) mutation in *HOXB13* is something like a middle-penetrance mutation with a quite high population frequency of about 0.1–1.3 % and a fairly high risk ratio of 3.5–7 for prostate cancer [21, 25]. More and more clinical genetics centres around the world are starting to test for these genes in men at increased prostate cancer risk.

In addition to the handful of high-penetrance genes, since 2007, genome-wide association studies have identified approximately 100 low-penetrance genetic polymorphisms (single nucleotide polymorphisms – SNPs) that are associated with an increased risk of prostate cancer [28]. Some of these SNPs are in or near genes, for example, the *HNF1B* gene, the *KLK3* gene (PSA) and the *MSMB* gene, but many if not most are in intergenic regions with unknown functions. The 8q24 region is a good example of the latter type, containing multiple SNPs that

are significantly associated with prostate cancer and other cancer types. Because of the design of the GWAS studies, the prevalence of these SNPs in the population is high. The direct consequence, however, is that their effect is weak: typically, odds ratios of 1.1–1.3 are found. Using combinations of SNPs, polygenic risk scores are being developed to aid in predicting the individual risk of prostate cancer. With such scores, it is possible to discriminate men with a very high or a very low risk Table 4 [1]. The problem, however, is that the proportion of men with a clinically relevant increased risk is still quite small while all men have to be genotyped to identify this small group. The challenge is how to counsel the men who are not in the highest risk category. Nevertheless, at some point in the near future, such polygenic risk scores will probably be used to individualise population screening programmes for prostate cancer.

Recently, it has been shown that the prevalence of low-penetrance SNPs is about the same, or a little bit higher, in patients from hereditary prostate cancer families as in patients from the general population [13]. This may be interpreted as evidence that the clustering of such SNPs rather than high-penetrance genes may cause a clustering of patients in families. The alternative explanation is, however, that so-called hereditary prostate cancer families are not strongly genetically determined but merely the result of increased awareness and PSA testing of men in such families. The finding that prostate cancer patients in these families have a better prognosis than patients from the general population supports this alternative explanation [12]. This emphasises the importance of considering the aggressiveness and method of diagnosis of prostate cancers in families before deciding that unaffected men in these families should be tested in order to avoid overdiagnosis.

Ethnicity

As shown in the previous section on incidence, enormous differences in prostate cancer incidence exist between ethnic populations. The lowest incidence is found in men of Asian descent, whereas men who live in North America and Northern

Table 4 Estimation of a Polygenic Risk Score (PRS) using 100 prostate cancer risk variants and comparison of risk by PRS percentiles (iCOGS data)

Percentiles (%)	OR (using PRS)	OR (using iCOGS)
<1	1 (baseline)	0.19 (0.13–0.27)
1–10	1.68 (1.13–2.50)	0.31 (0.28–0.35)
10–25	2.78 (1.88–4.10)	0.52 (0.48–0.55)
25–75	5.39 (3.67–7.92)	1 (baseline)
75–90	9.57 (6.50–14.09)	1.78 (1.68–1.88)
90–99	15.78 (10.71–23.26)	2.93 (2.75–3.12)
≥99	30.47 (20.14–46.09)	5.65 (4.83–6.62)

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Europe have a very high prostate cancer risk. Particularly men of African-American heritage have a very high risk of prostate cancer. Ethnic differences are most probably caused by a combination of genetic factors, exposure to environmental risk factors and factors related to health-seeking behaviour. This is illustrated most clearly by the results of migration studies, which looked at prostate cancer incidence trends in Asian men (low incidence) who migrated to the USA (high incidence); prostate cancer incidence in these men increased markedly and significantly, but to a level that was intermediate between the incidence in the Japanese and the original American population [11]. A similar phenomenon was found for Japanese men who emigrated to Brazil [20].

Diet

It has long been thought that diet is an important factor in the development and progression of prostate cancer. And it probably is, considering the observation that second and following generation migrants adopt the risks of their new countries, combined with the fact that there are no other lifestyle factors that can easily explain this observation. The paradox here is that the strongest evidence for the role of diet comes from the weakest study designs, such as migrant studies. Designs that are supposedly stronger such as prospective cohort studies and randomised trials have yielded inconsistent results. A clear example of this is the SELECT trial (Selenium and Vitamin E Cancer

Prevention Trial) [25]. This large prospective trial, in which 31,000 men were included, studied the effect of vitamin E, selenium, and the combination of both vs. placebo. No effect on prostate cancer incidence was found for administering selenium, either alone or in combination. This refuted the result found in the Nutrition Prevention of Cancer (NPS) trial [15], which observed a 50 % reduction in prostate cancer incidence in men randomised to selenium supplements. The Continuous Update Program of the World Cancer Research Fund brings expert nutritional epidemiologists together from around the globe and continuously reviews the literature on diet and cancer in a meticulous way. It concluded in 2014 that there is no diet or nutritional factor that is convincingly or probably associated with prostate cancer [36] (http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports/prostate-cancer). On the contrary, the CUP project concludes that there is strong evidence that beta-carotene, either through food or supplements, is unlikely to have a substantial risk on the risk of prostate cancer. So, the numerous studies on dietary fats, red and processed meat, vitamin E, selenium, lycopene, cruciferous vegetables, green tea, tomato products and many other nutritional factors have not resulted in any clarity about the role of diet in prostate cancer. The recent report [36] specifically concludes that:

- The evidence that a higher consumption of dairy products increases the risk of prostate cancer is limited.
- The evidence that diets high in calcium increase the risk of prostate cancer is limited.
- The evidence that low plasma alpha-tocopherol concentration (vitamin E) increases the risk of prostate cancer is limited.
- The evidence that low plasma (blood) selenium concentrations increases risk of prostate cancer is limited.

One has to question, however, whether the best designs to study aetiology are really the best designs in the field of nutritional epidemiology. For example, most randomised trials on supplements and cohort studies on nutritional factors

start with study populations over 50 years of age. If diet has its most important effect in puberty or even earlier in childhood or pre-conception, these designs will not be able to validly assess any effect. Other problems have to do with misclassification of food intake over the years, variable within-person eating habits, arbitrary dosages of interventions in trials and so forth. Possibly, the weakest study designs (ecological migrant studies) are the best when it comes to nutritional epidemiology. Unfortunately, these designs cannot come up with any specific conclusion beyond typical diets in certain parts of the world.

Body Fatness

In its 2014 report on prostate cancer, the World Cancer Research Fund concludes that greater body fatness (marked by BMI, waist circumference and waist-hip ratio) is probably a cause of advanced prostate cancer. In a meta-analysis of 23 studies ($N=11,149$) on advanced prostate cancer, a statistically significant 8 % increased risk was found per 5 kg/m2 increase in body mass index (BMI) [36]. A meta-analysis of four studies on waist circumference ($N=1,781$) showed a statistically significant 12 % increased risk per 10 cm and a meta-analysis of 4 studies on waist-hip ratio resulted in a significant 15 % higher risk per 0.1 unit increase. It is not entirely clear what the mechanism is behind this association. Obesity influences the levels of quite a few hormones and growth factors such as insulin and leptin, which can promote the growth of cancer cells. In men, obesity is associated with lower testosterone levels, although the importance of this is not really clear. Serum testosterone levels do not seem to have a strong effect on prostate cancer risk but because it is essential for differentiation of prostate epithelium, decreased levels may facilitate the growth of a less differentiated, aggressive prostate cancer phenotype. Obesity is also associated with a low-grade chronic inflammatory state which can promote cancer development. Obese adipose tissue is characterised by macrophage infiltration, an important source of inflammation. Fat cells produce pro-inflammatory factors, leading to elevated concentrations of circulating TNF-alpha, IL-6 and CRP.

Adult Attained Height

In a meta-analysis of 34 studies ($N=79,387$), the WCRF report found a statistically significant 4 % increased risk per 5 cm taller height: RR 1.04 (95 % CI 1.03–1.05). Adult height is related to the rate of growth during foetal life and childhood. Health and nutrition status in the neonatal period and childhood may impact on the age of sexual maturity. Resulting effects on circulating levels of growth factors, insulin, and other endocrine or tissue specific mediators may influence cancer risk.

Diabetes

Most data on the association between diabetes and prostate cancer come from studies on diabetes type 2. The results from epidemiological studies are somewhat inconsistent but, overall, there seems to be a reduced risk [30]. This contradicts the finding that body fatness is a risk factor for prostate cancer. Because the link between diabetes type 2 and prostate cancer is mainly observed in studies from the PSA era, diabetes is known to decrease the serum PSA value, and the association is stronger for low-grade than for high-grade prostate cancer; it is possible that the association is caused by detection bias. In addition, it is extremely difficult to disentangle the effects of diabetes and its treatment.

In a recent cohort study using five nationwide registers of persons with type 1 diabetes (Australia, Denmark, Finland, Scotland and Sweden), 553 prostate cancers were diagnosed among 2 million male person-years of follow-up. A reduced risk of prostate cancer was found ($HR=0.56$; 95 % CI 0.51–0.61) [7].

Androgens

Because the function of the prostate is so dependent on androgens and because hormonal treatment is used in metastasised prostate cancer, it has long been believed that having higher levels of testosterone in the blood may increase the risk of prostate cancer. And indeed, clinical trials with 5-alpha reductase inhibitors (5-ARIs), the Prostate Cancer Prevention Trial (PCPT), in which men were treated with finasteride 5 mg daily or placebo for 7 years, and the REduction by DUtasteride of pros-

tate Cancer Events (REDUCE) trial, in which patients were treated with dutasteride 0.5 mg daily or placebo for 4 years [2, 34] suggested a decrease in risk (see Chapter 2 by Bertrand Tombal). However, the results of these trials may have been influenced by several factors such as end-of-study biopsies. In the non-trial situation, a link between androgens and prostate cancer development is not clear [31]. Recently, a large prospective study from Finland, Sweden and Norway confirmed the absence of an association between prediagnostic serum testosterone levels and prostate cancer development [27]. More research is needed to clarify the link between diabetes and prostate cancer.

Vasectomy

Several recent meta-analyses of the association between vasectomy and prostate cancer have concluded that there is no link between the two (e.g. [37]). US-based studies found a positive association (RR = 1.54) but non-USA studies did not (RR = 0.74). Probably, some studies that did find a positive association have suffered from bias due to differences in health-seeking behaviour by vasectomised and non-vasectomised men.

Aspirin

There is some evidence in the literature that aspirin and other NSAIDS slightly reduce the risk of prostate cancer. However, a recent analysis of the Health Professionals Follow-up Study among 48,000 men did not find any effect of regular aspirin use on prostate cancer risk [6].

Physical Activity

It is not clear whether being more physically active reduces the risk of prostate cancer. A review and meta-analysis of 43 studies did report a decreased risk (pooled RR = 0.90; 95 % CI 0.84–0.95) but because many low-quality studies were included, a definitive conclusion is impossible [26].

Prostatitis

Despite the fact that a definitive causative infectious agent or agents has yet to be identified, accumulating evidence both in human studies and in animal models indicate that infections may contribute to potentially tumour-promoting chronic prostatic inflammation [33].

In conclusion, because ageing, genetic predisposition and ethnicity are not modifiable, until harder evidence becomes available on other suspected risk factors, maintaining a healthy weight is the only lifestyle factor that can lower the risk of prostate cancer.

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