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Differences in the epidemic rise and decrease of prostate cancer among geographical areas in Southern Europe: an analysis of differential trends in incidence and mortality in France, Italy and Spain

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Abstract

This is a population-based study aimed at evaluating incidence and mortality trends for prostate cancer in France, Italy and Spain, during the prostate-specific antigen (PSA) era, considering elderly people aged 70 years and over and younger adults aged between 40 and 69 years. Trends were estimated by a log-linear Poisson regression model and expressed as an Estimated Annual Percent Change (EAPC). Incidence increased sharply in almost all areas. Spain showed the lowest increases. Incidence started to rise around 1985 in France and after 1990 in Italy and Spain. Mortality increased until the late 1980s in all countries, then declined in France and Italy (−2.5% in 40–69 year age group), but not in Spain. Younger people showed a much higher rise in incidence than the elderly, while mortality decreased mainly in the younger adults. The decrease in mortality was more marked in those areas and the younger age group where the rise in incidence was higher and started earlier, i.e. in France and in younger people, suggesting that the PSA test may have had a positive effect on mortality, although other clinical advances also have to be taken into account.
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1. Introduction

Prostate cancer is currently one of the most common cancers diagnosed in males in most Western countries; it usually affects elderly subjects aged 65 years or more and is a rare disease before 50 years of age.

Prostate cancer incidence is characterised by a very large geographical variability, ranging from few cases in Asiatic countries (approximately 4–7 per 100 000) to 70–100 cases per 100 000 in Nordic European countries and North America. In Italy and Spain, the rates are rather low in comparison with those registered in other Western countries, the lowest among the European Union (EU) countries, while in France, the rates are higher and intermediate between Southern and Nordic countries. In Italy and Spain, prostate cancer incidence, according to estimates in 2000, was ranked third (approximately 10% of all new diagnosed cancers), while in France it was the most common male cancer (approximately 19%). In France and Spain, prostate cancer was the second leading cause of death from cancer (approximately 11%), while in Italy it ranked fourth (approximately 8%) [1].

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The aetiology of prostate cancer is not clearly understood and the interpretation of cancer incidence and mortality trends requires an understanding of multiple interacting factors.

However, better access to health services and the introduction into the clinical routine of new therapeutic modalities such as Transurethral Resection of Prostate (TURP) and new diagnostic procedures such as Echo-Guided Biopsy (EGB), Transrectal Ultrasonography (TRUS), Prostatic Specific Antigen test (PSA) have contributed to a sharply upward incidence trend, as a result of a greater capability to detect incidental cancers that are otherwise latent [2–4].

As a consequence, in the late 1980s in the United States (US), a very large increase in newly diagnosed cases occurred, mainly due to the more widespread use of the PSA test and this was followed a few years later (between 1992 and 1993) by a subsequent fall [5,6]. The trend in mortality did not show a similar pattern: in the last 35 years, after a moderate, but steady, increase and a successive levelling off, rates started to decrease between 1990 and 1995 [7].

The present study aimed to evaluate incidence and mortality trends of prostate cancer in France, Italy and Spain. Estimates based on data collected by French, Italian and Spanish Cancer Registries (CRs) were therefore computed. In particular, incidence and mortality trends were analysed for those aged 70 years and over and for younger individuals aged between 40 and 69 years; special attention was given to differences between the two age groups that could suggest a different clinical approach according to the patient's age.

2. Patients and methods

Incidence and mortality data were obtained from the European Cancer Incidence and Mortality Database (EUROCIM), a databank of European Network of Cancer Registries (ENCR) [8].

The EUROCIM database includes both mortality and incidence data; mortality data are provided by the National Statistics Offices, whereas incidence data are collected by Cancer Registries (CRs).

French CRs monitor approximately 13% of total population, covering 11 administrative areas with disparities in urbanisation and healthcare facilities [9]. Spanish CRs observe approximately 26% of the total Spanish population. There are 13 CRs located mainly in the Northern and Eastern part of the country, most of them covering areas with less than one million resident people [10]. Italian CRs observe approximately 20% of total population, especially in Northern and Central Italy, covering 20 geographical areas of different sizes from metropolitan areas to whole regions [11].

Only the CRs, whose activity covered the years just preceding or immediately subsequent to 1990 (the time the PSA test was introduced) were included in the study. Furthermore, a minimum registration activity of 7 years was necessary for inclusion in our study.

Thus, eight CRs were selected for France and Spain and 11 for Italy.

French CRs were: Bas-Rhin, Haut-Rhin, Calvados and Somme for Northern France, Doubs, Herault, Isere and Tarn for Central-Southern France. Spanish CRs were: Asturias, Basque Country, Navarra and Tarragona for Northern Spain, Albacete, Granada, Mallorca, Murcia for Southern and Insular Spain. Italian CRs were: Genova, Parma, Torino and Varese for North-Western Italy, Ferrara, Modena, Romagna and Veneto for North-Eastern Italy, Firenze, Macerata and Ragusa for Central-Southern Italy.

Trends in mortality were computed only for the whole French, Spanish and Italian territories, using data registered from 1958 to 1997 for France and Spain and from 1958 to 1996 for Italy. In addition, the whole time period was split into two, 1958–1987 and 1988–1997 or 1996, in order to highlight the differences in trend before and after the year in which a reversal occurred.

The incidence time period considered was not the same for all of the CRs and ranged from 1975 to 1997 for the French CRs, from 1976 to 1997 for the Italian ones, from 1973 to 1997 for the Spanish ones.

The observed mortality and incidence time periods, together with related cases classified by age group and registry, are listed in Table 1a and b.

The studied populations were divided into two age groups: subjects aged 70 years or more and subjects aged between 40 and 69 years at the time of registration (death or diagnosis).

Data for estimating trends and calculating age-standardised rates were analysed by quinquennial age classes. The time trends evaluation for incidence and mortality was carried out using a log-linear Poisson regression model and expressed as the Estimated Annual Percent Change (EAPC) [12].

Age-standardised mortality and incidence rates were computed using the World population as a standard for each considered age group and CR or country.

Statistical significance ($P < 0.05$) was assessed through the likelihood ratio test [13]. The GLIM 4.0 statistical package was used to perform all analyses [14].

3. Results

3.1. Incidence trends

Tables 2–4 show incidence trends for France, Spain and Italy, respectively, by age group and each CR.

Mean age-standardised rates of the first and last 3 years of the period are also stated. In order to highlight any variation in the incidence rates that occurred over a particular time period, linear graphs have also been produced (Figs. 1–4).

Fig. 1 illustrates incidence rates for Northern and Central-Southern French CRs, Fig. 2 for Northern and Southern Spanish CRs, Fig. 3 for North-Western and North-Eastern Italian CRs, and Fig. 4 for Central-Southern Italian ones.

3.1.1. Absolute incidence rates

The mean age-standardised incidence rates of the last 3 years observed differed largely in the three countries

Table 1
French, Italian and Spanish Cancer Registries: (a) number of cases by age group and calendar period used for the incidence estimates, (b) number of cases by country, age group and calendar period used for the mortality estimates

(a) Incidence

		Period	No. of cases		
			40–69 years	⩾70 years	All ages
French registries					
North					
	Bas-Rhin	1975–1997	2057	3735	5796
	Calvados	1978–1997	1320	2445	3768
	Haut-Rhin	1988–1997	956	1572	2529
	Somme	1982–1997	900	1670	2571
Centre-South					
	Doubs	1978–1996	838	1584	2422
	Herault	1986–1997	1314	2699	4013
	Isere	1979–1997	1865	3527	5394
	Tarn	1982–1997	1045	2085	3130
Italian registries					
North-West					
	Genova	1986–1996	787	1808	2595
	Parma	1978–1997	639	1423	2062
	Torino	1985–1997	1218	2215	3433
	Varese	1976–1997	1269	2476	3748
North-East					
	Ferrara	1991–1997	275	489	764
	Modena	1988–1997	641	1189	1831
	Romagna	1986–1997	926	2223	3151
	Veneto	1987–1996	1591	3249	4844
Center-South					
	Firenze	1985–1997	1453	3355	4810
	Macerata	1991–1997	262	602	864
	Ragusa	1981–1997	171	572	744
Spanish registries					
North					
	Asturias	1987–1994	537	1108	1648
	Basque Country	1986–1994	945	2221	3167
	Navarra	1973–1997	872	2161	3033
	Tarragona	1980–1997	569	1519	2090
South					
	Albacete	1991–1997	174	459	633
	Granada	1985–1997	467	947	1415
	Mallorca	1988–1996	347	952	1302
	Murcia	1984–1995	490	1290	1783

(b) Mortality

	Period	No of cases		
		40–69 years	⩾70 years	All ages
France	1958–1997	49 603	219 610	269 408
Italy	1958–1996	40 058	132 428	172 679
Spain	1958–1997	25 319	96 245	121 719

and within each country. France showed the highest rates, all over 50 cases per 100 000, excepted Somme (approximately 43 cases per 100 000), without any specific geographical pattern (Table 2). Spanish incidence (Table 3) was the lowest, all values ranging from approximately 22 to 31 cases per 100 000, except Navarra (approximately 43 cases per 100 000). Tarragona and Navarra had the highest values over 30 cases per 100 000, while in North-Western and Southern rates were lower, ranging from 22 to 29 cases per 100 000. Italian incidence rates (Table 4) were inbetween those of France and Spain: Northern and Central CRs showed values between approximately 30 and 40 cases per 100 000, much higher than in the South. Indeed, Ragusa

Table 2
French incidence trends for prostate cancer by Cancer Registry and Age Group

Registries and calendar period		Age groups		
		All ages	40–69 years	⩾70 years
North				
Bas-Rhin (1975–1997)	EAPC	+5.4 ($P<0.001$)	+6.4 ($P<0.001$)	+4.9 ($P<0.001$)
	ASR	24.8–65.0	35.0–110.6	372.6–850.5
Calvados (1978–1997)	EAPC	+ 5.0 ($P<0.001$)	+5.9 ($P<0.001$)	+4.5 ($P<0.001$)
	ASR	28.1–61.0	41.5–102.9	413.0–798.6
Haut-Rhin (1988–1997)	EAPC	+2.3 ($P=0.001$)	+3.0 ($P=0.008$)	+1.8 ($P=0.048$)
	ASR	46.1–57.7	68.3–91.9	674.4–805.1
Somme (1982–1997)	EAPC	+1.8 ($P<0.001$)	+4.5 ($P<0.001$)	+0.5 ($P=0.366$)
	ASR	28.4–42.9	35.8–77.9	457.7–523.3
Centre-south				
Doubs (1978–1996)	EAPC	+4.8 ($P<0.001$)	+7.2 ($P<0.001$)	+3.6 ($P<0.001$)
	ASR	29.1–53.4	42.5–93.6	429.5–679.9
Herault (1986–1997)	EAPC	+6.2 ($P<0.001$)	+8.0 ($P<0.001$)	+5.3 ($P<0.001$)
	ASR	27.9–52.8	43.2–92.7	394.8–671.1
Isère (1979–1997)	EAPC	+5.8 ($P<0.001$)	+8.1 ($P<0.001$)	+4.8 ($P<0.001$)
	ASR	27.7–61.7	38.7–111.4	421.2–762.0
Tarn (1982–1997)	EAPC	+2.6 ($P<0.001$)	+6.1 ($P<0.001$)	+1.1 ($P=0.019$)
	ASR	32.3–60.2	46.0–122.7	485.2–645.4

EAPC, Estimated Annual Percent Change; ASR, mean Age-Standardised Rates of the first and last 3 years of the observation period. P = statistical significance of EAPC.

Table 3
Spanish incidence trends for prostate cancer by Cancer Registry and Age Group

Registries and calendar period		Age groups		
		All ages	40–69 years	⩾70 years
North				
Asturias (1987–1994)	EAPC	+2.3 ($P=0.036$)	+6.5 ($P=0.001$)	+0.4 ($P=0.745$)
	ASR	20.9–22.1	25.2–33.4	342.2–317.3
Basque country (1986–1994)	EAPC	+4.3 ($P<0.001$)	+7.9 ($P<0.001$)	+2.8 ($P<0.001$)
	ASR	21.0–26.5	21.3–33.1	374.6–430.3
Navarra (1973–1997)	EAPC	+3.6 ($P<0.001$)	+5.2 ($P<0.001$)	+3.0 ($P<0.001$)
	ASR	21.1–42.7	21.1–65.2	379.9–612.5
Tarragona (1980–1997)	EAPC	+3.2 ($P<0.001$)	+4.3 ($P<0.001$)	+2.8 ($P<0.001$)
	ASR	20.5–30.7	24.0–44.8	341.8–450.7
South				
Albacete (1991–1997)	EAPC	+3.2 ($P=0.114$)	+8.6 (p=0.030)	+1.2 ($P=0.604$)
	ASR	23.5–27.7	28.0–41.3	391.9–404.3
Granada (1985–1997)	EAPC	+6.4 ($P<0.001$)	+8.8 ($P<0.001$)	+5.2 ($P<0.001$)
	ASR	11.9–22.3	15.8–35.5	187.3–306.2
Mallorca (1988–1996)	EAPC	+4.0 ($P<0.001$)	+5.8 ($P=0.007$)	+3.2 ($P=0.014$)
	ASR	22.8–29.0	26.5–36.9	384.1–458.9
Murcia (1984–1995)	EAPC	+3.6 ($P<0.001$)	+5.5 ($P<0.001$)	+3.0 ($P<0.001$)
	ASR	16.9–24.8	16.7–28.9	302.2–418.1

EAPC, Estimated Annual Percent Change; ASR, mean Age-Standardised Rates of the first and last 3 years of the observation period. P = statistical significance of EAPC.

registered the lowest rate of any other considered CR (19.6 cases per 100 000).

3.1.2. Time trends

Incidence for all ages increased in every French CR, with highly statistically significant trends (Table 2). A large variability in the magnitude of the increase was observed, EAPCs ranging from approximately +2 in Somme and +6 in Herault.

In Spain, the lowest upward trends were observed, even if the rise was statistically significant in all areas but Albacete. EAPCs ranged from approximately +2 and +4 in all CRs, excluding the largest rise observed in Granada (EAPC +6.4) (Table 3).

Statistically significant upward trends were observed for all of the Italian CRs (Table 4), with the exception of Ferrara in the North-Eastern and the Southern CR, Ragusa. Four CRs in the North presented EAPCs around +7, but also in the other areas notable increases were registered, often higher than 3% per year.

When attention is focused on trends for the two specific age groups it is possible to note a rather well defined pattern of increasing incidence in almost all of the CRs of the three countries: middle-aged adults (aged 40–69 years), showed larger increases than the elderly. Ragusa in Italy was the only exception. In France, such a difference was particularly marked in Somme (+4.5% in the younger age group and no significant trend in the elderly) and Tarn (+6.1% versus +1.1%). In Spain, Albacete and Asturias registered the highest variations (+8.6% and +6.5%, respectively) in the younger age group versus no statistically significant trends in the older group. The ratio between the mean EAPC of people aged between 40 and 69 years and those aged ⩾70 years was 1.5 in Italy, 1.9 in France and 2.4 in Spain.

Different incidence time trends were observed among the countries in the linear graphs in Figs. 1–4. In France, incidence started to increase around the middle of 1980s, earlier than in the other two countries where trends first started to rise in the 1990s. For the most recent years considered, in several French CRs, in particular Doubs, a levelling off or a real decrease was observed, but this phenomenon was less marked in the CRs in Italy and Spain. In addition, in France, all CRs showed a similar pattern of trend. In France and Italy, in the older group, a levelling off or decrease in incidence in the most recent years was more commonly observed than in the younger age group where in several cases, the incidence continued to rise until 1997.

Table 4
Italian incidence trends for prostate cancer by Cancer Registry and Age Group

Registries and Calendar period		Age groups		
		All ages	40–69 years	⩾70 years
North-west				
Genova	EAPC	+7.5 ($P<0.001$)	+9.9 ($P<0.001$)	+6.5 ($P<0.001$)
(1986–1996)	ASR	21.9–38.3	26.9–56.1	359.6–565.6
Parma	EAPC	+2.9 ($P<0.001$)	+4.1 ($P<0.001$)	+2.3 ($P<0.001$)
(1978–1997)	ASR	19.1–32.4	30.2–58.4	266.8–401.8
Torino	EAPC	+7.0 ($P<0.001$)	+9.8 ($P<0.001$)	+5.6 ($P<0.001$)
(1985–1997)	ASR	21.2–41.2	28.5–66.5	329.3–566.0
Varese	EAPC	+4.0 ($P<0.001$)	+5.2 ($P<0.001$)	+3.4 ($P<0.001$)
(1976–1997)	ASR	23.2–43.9	28.5–69.0	380.4–611.1
North-east				
Ferrara	EAPC	+2.4 ($P=0.196$)	+2.9 ($P=0.348$)	+2.1 ($P=0.361$)
(1991–1997)	ASR	22.6–27.3	36.3–45.6	311.6–361.4
Modena	EAPC	+5.5 ($P<0.001$)	+7.7 ($P<0.001$)	+4.3 ($P<0.001$)
(1988–1997)	ASR	23.9–34.8	36.4–58.5	343.0–460.8
Romagna	EAPC	+7.2 ($P<0.001$)	+8.5 ($P<0.001$)	+6.6 ($P<0.001$)
(1986–1997)	ASR	21.0–41.5	28.3–62.0	326.0–601.3
Veneto	EAPC	+6.9 ($P<0.001$)	+8.7 ($P<0.001$)	+6.1 ($P<0.001$)
(1987–1996)	ASR	24.5–38.3	33.6–57.0	375.7–556.6
Centre-South				
Firenze	EAPC	+5.0 ($P<0.001$)	+8.3 ($P<0.001$)	+3.7 ($P<0.001$)
(1985–1997)	ASR	22.1–36.3	27.4–58.1	356.8–501.2
Macerata	EAPC	+5.8 ($P=0.001$)	+6.3 ($P=0.048$)	+5.6 ($P=0.008$)
(1991–1997)	ASR	27.9–37.4	42.8–55.0	398.1–549.1
Ragusa	EAPC	+0.8 ($P=0.307$)	+0.4 ($P=0.782$)	+0.9 ($P=0.310$)
(1981–1997)	ASR	18.2–19.6	23.9–25.6	289.0–310.5

EAPC, Estimated Annual Percent Change. ASR, mean Age-Standardised Rates of the first and last 3 years of the observation period. P = statistical significance of EAPC.

3.2. Mortality trends

Mortality trends for each country, the whole calendar period and age group, are presented by means of three linear graphs in Fig. 5. Fig. 6 gives the EAPCs relating to the two sub-periods 1958–1987 and 1988–1997 (or 1996), by country and age.

3.2.1. Absolute mortality rates

Mean rates of the last 3 years considered differed geographically to a lesser extent than the comparable incidence rates (Fig. 5). For all ages, mortality rates were 11, 14, 17 cases per 100 000 in Italy, Spain and France, respectively, for people aged 40–69 years they ranged from 9 to 13 cases, while for those aged ⩾70 years they were more variable, 213, 271 and 322 cases per 100 000.

3.2.2. Time trends

Mortality in the younger age groups, after a fairly stable trend from 1960 to 1970, and a slight increase during the early 1980s (that was common to all three countries) started to decline in France and Italy, but not in Spain (Fig. 5). The older age group showed a very different picture: rates rose slowly, but steadily, with a similar pattern being observed in all three countries until the late 1980s. Then, mortality began to decrease in France and to level off in Italy, whereas it continued to rise in Spain. In the first time period, 1958–1987, EAPCs computed for all ages were around +1 in Italy and Spain and +0.6 in France (Fig. 6). A striking difference between the two age groups was noted, increase in the mortality being limited to people over 70 years of age. 1987 represented the join point with a mortality peak in France and Italy. In the second time period,

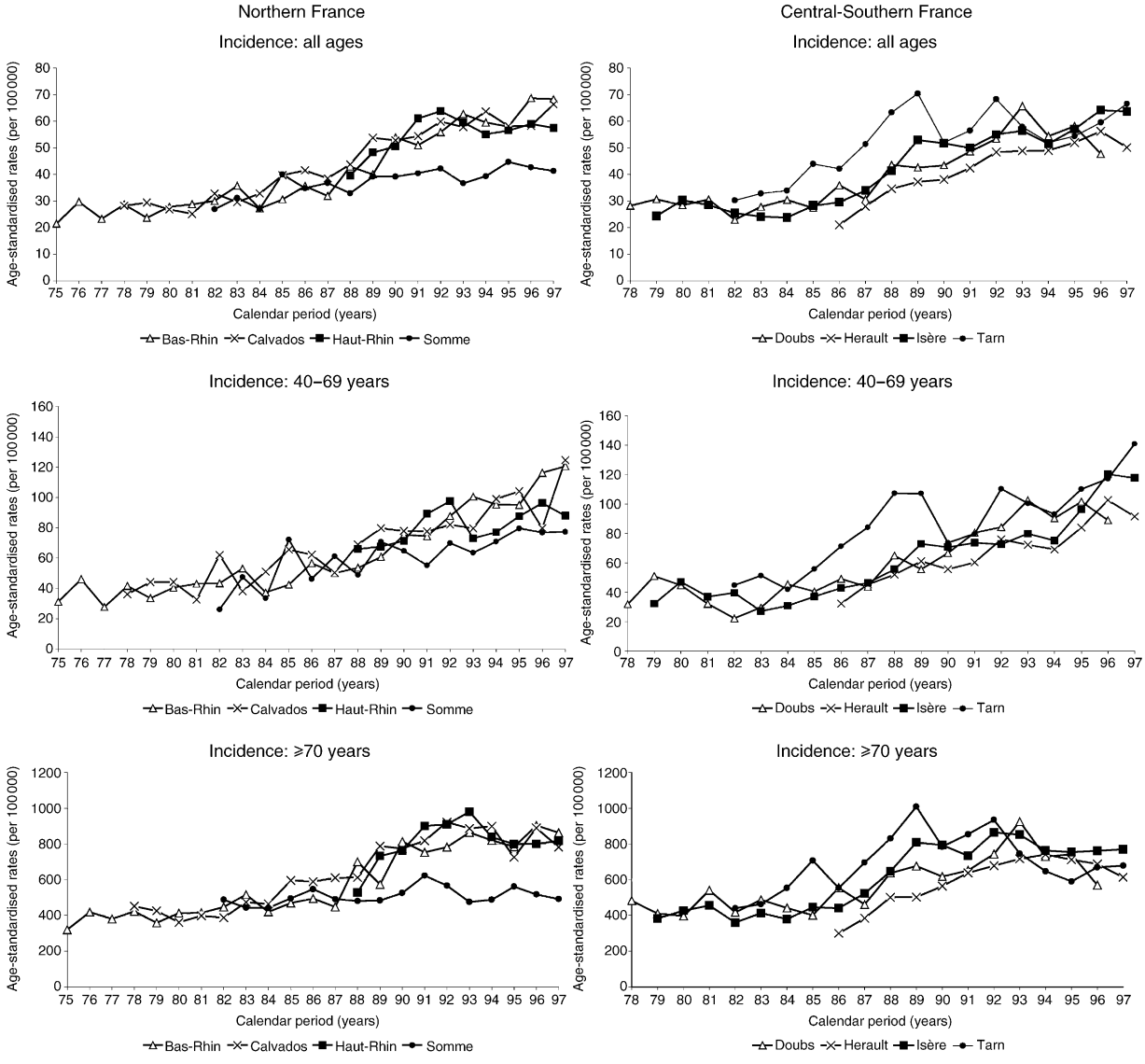

Fig. 1. Incidence trends for prostate cancer in Northern and Central-Southern France by Cancer Registry and Age Group.

there was a reversal in the mortality trend: for all ages EAPCs were −0.6 in Italy and −1.7 in France, whilst mortality was still increased in Spain.

This decline was more notable in the younger age group (approximately −2.5% both in France and Italy), while in the elderly a decline was evident only in France.

4. Discussion

Striking upward trends in the incidence of prostate cancer were observed in all of the three countries, with a few exceptions for some of the CRs. In the most recent years of the observed time period, a reversal in these trends appeared. The younger age group had much larger increases in incidence than the older one.

In general, geographical and ethnic differences in incidence and changes in time trends all around the world have been well documented [15]. Even if no one single factor has been proposed for these differences, diet, androgen metabolism and genetics are among the strongest hypotheses for the aetiology of prostate cancer [2]. Changes in the prevalence of risks factors might be partially responsible for the increase in prostate cancer incidence, but variations in clinical practices have been considered the most important determinants of the time trends of recent years [6].

Indeed, the increased incidence reported here occurred during a period of major changes in diagnostic techniques. This strong period-effect was likely to be principally due to a higher detection rate following the introduction of the PSA test, rather than a real change in the prevalence of risk factors. A larger number of

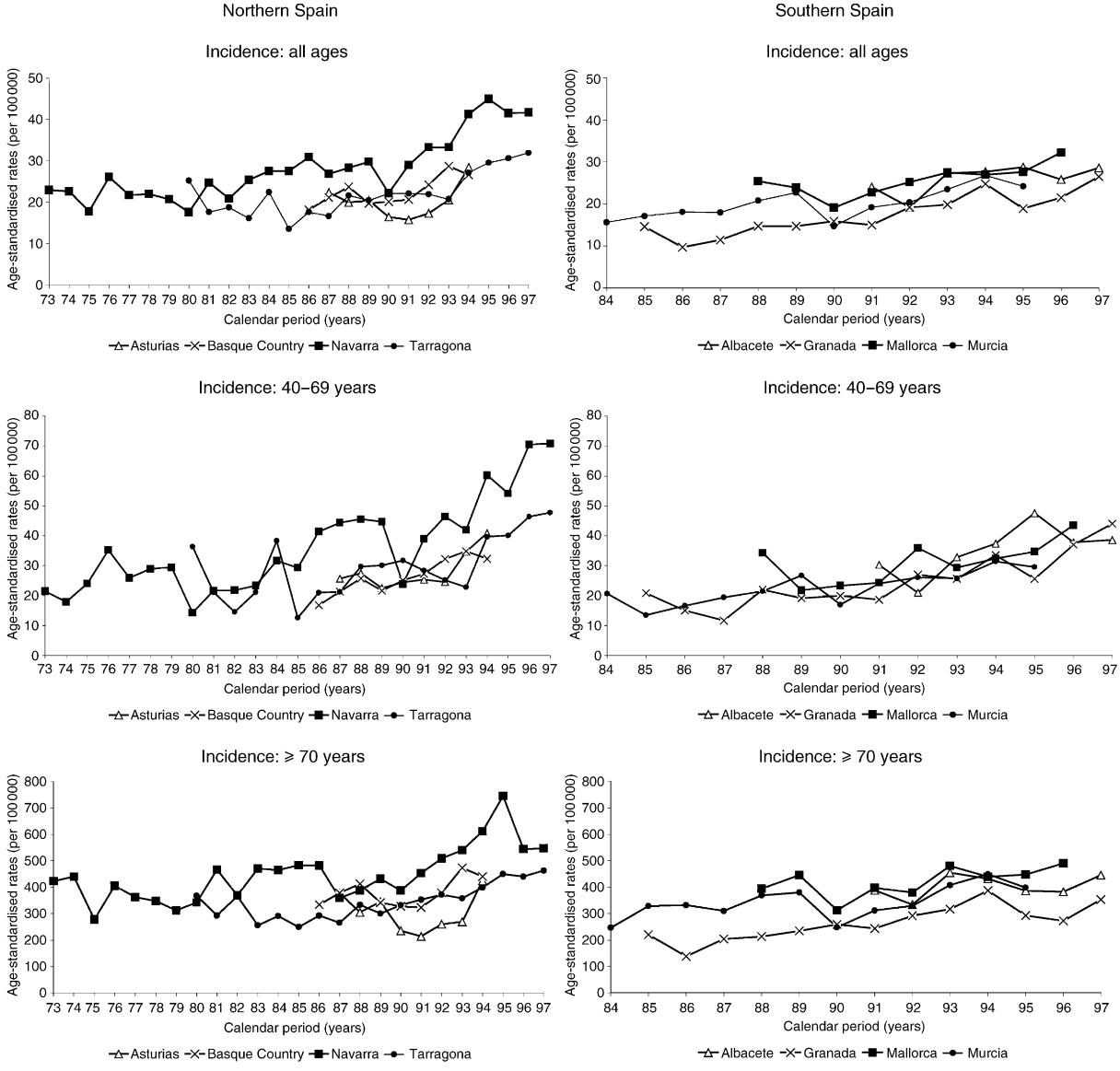

Fig. 2. Incidence trends for prostate cancer in Northern and Southern Spain by Cancer Registry and Age Group.

cancers, which otherwise are clinically silent, are now diagnosed because of the widespread use of the serum PSA assay [2].

Our findings are consistent with those in North America and with the upward trends described more recently in Europe [3,6,16]. Present data indicate that in France incidence started to increase in the mid-1980s in almost all of the CRs. In Italy and Spain, the use of the PSA test began after 1990 and, for some Spanish areas, a little later still. In France, the earlier rise could be due to an earlier introduction of TRUS and PSA [17,18].

In Italy, Ragusa did not show any rise, representing an important exception since it is the only CR in Southern Italy.

Incidence trends could be influenced by different attitudes of urological departments in adopting the PSA assay. This behaviour could be due to the lack of consensus with regard to diagnostic practices and opportunistic screening as well as optimal treatment strategies to be adopted. Furthermore, in Italy, differences in trends could also be due to difficulties related to the availability of medical technologies or a reduced awareness or attention to the disease, which is typical of areas where it is less common, as is probably the case in Ragusa and other Southern Italian areas.

In France, a much lower EAPC was observed for the Somme region: the incidence rate did not rise as in all the other CRs. Perhaps, the cause is an under-registration due to the proximity of this region to Paris with some patients migrating to the capital to seek care.

In the Spanish CRs, the increase in incidence was lower than in France or Italy. Spain is one of the EU countries with the lowest occurrence of prostate cancer [10] and a reduced awareness for the detection of this

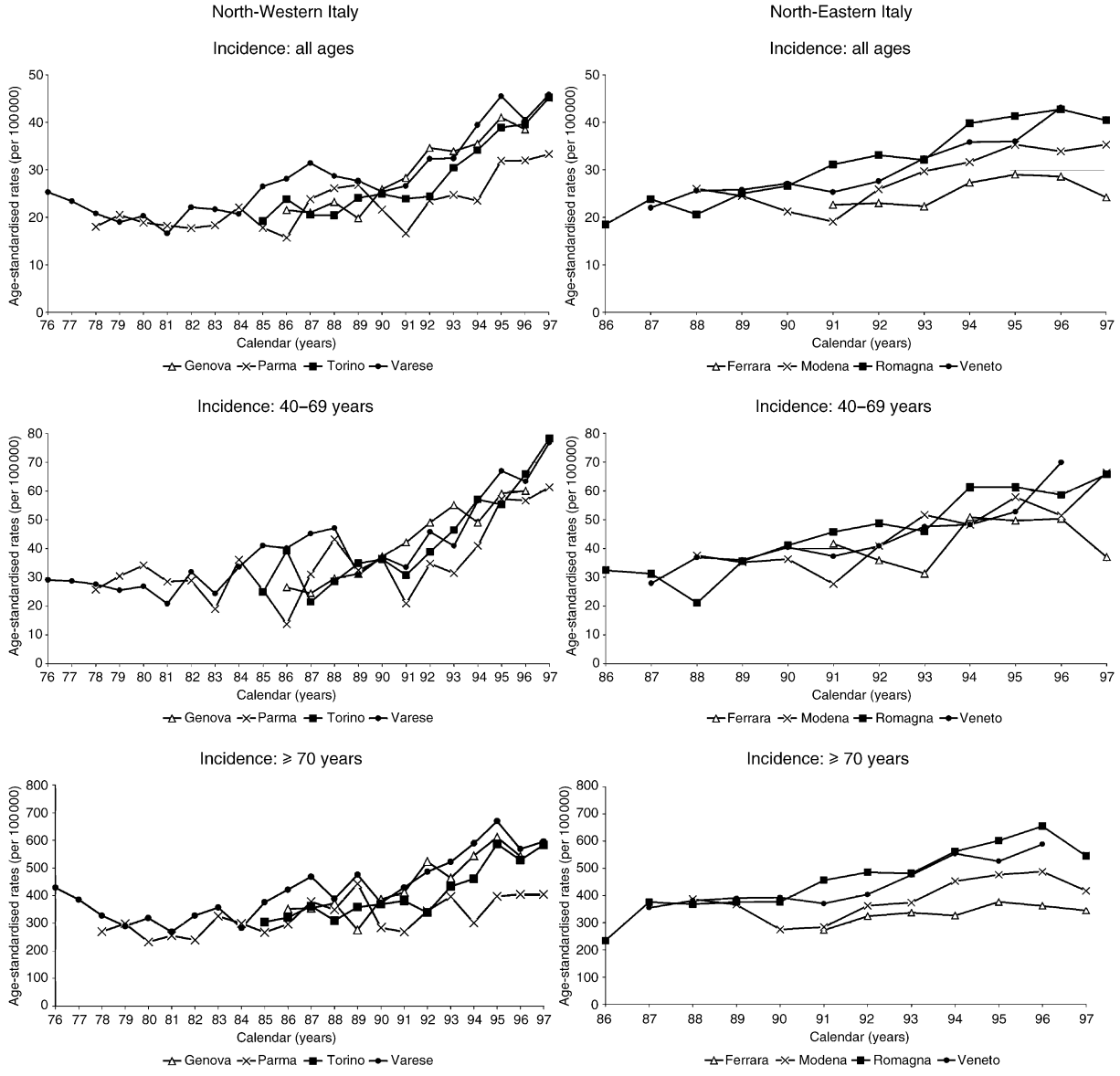

Fig. 3. Incidence trends for prostate cancer in North-Western and North-Eastern Italy by Cancer Registry and Age Group.

tumour could be possible. In addition, both the Spanish Association of Primary Health Care and the Spanish Association Against Cancer have not recommended PSA screening for asymptomatic patients [19].

In Granada, the increase was bigger than in any other Spanish area. This could be due (in part) to improvements in the primary health care system in the 1980s and the diagnosis of prostate cancer in older people living in rural areas that in the past would never have been diagnosed.

The decrease in the rates, particularly evident in France, has also been registered in North American areas [5]. This could be a consequence of effective screening of the population that decreases the possible number of detectable cases [20] or to a higher scepticism for the use of the PSA test, leading to a reduction in its use, as has been claimed by some authors [21]. In France, for instance, the consensus conference held in December 1989 recommended that the PSA test should not be used as a screening tool [22]. This may have contributed to changes in the behaviour of urologists.

Differences according to the subject's age were observed, in addition to geographical variations. Comparing the incidence trends for the two age groups, a common pattern emerged: younger adults had a steeper increase in incidence than the elderly subjects. This important difference could reflect a lower diagnostic intensity in elderly people and a different attitude of practitioners towards elderly patients.

Mortality, estimated at the national level, presented a slow, steady increase until the late 1980s, followed by a decrease in France and Italy, but not in Spain. Unlike incidence, mortality decreased to a larger extent in the younger than the older age group and only in France was there also a decline in the older age group.

This phenomenon was consistent with the mortality trends observed in the US over the time period of 1990–1995 and was also in agreement with data relating to other European countries [7,16].

It is conceivable that the increase in mortality from 1958 until the late 1980s was more marked in individuals over 70 years and corresponded to a real increase in risk. This result is consistent with the slight, steady increase in mortality observed in several Western countries before the 1990s [23,24]. Dutch and Spanish authors, investigating the possible reason for this trend, explained that the rise in mortality was principally due to a birth cohort effect [25,26]. Some other possible interpretations of this increase in mortality include a fall in mortality from prostate hyperplasia and the related larger attribution of mortality cases to prostate cancer thanks either to a better diagnosis or because more urologists perform TURP [27].

Interesting observations can be made by considering the relationships between incidence and mortality. The decrease in mortality occurred principally when incidence increased. Furthermore, the fall in mortality concerned mostly the younger age group for which the rise in

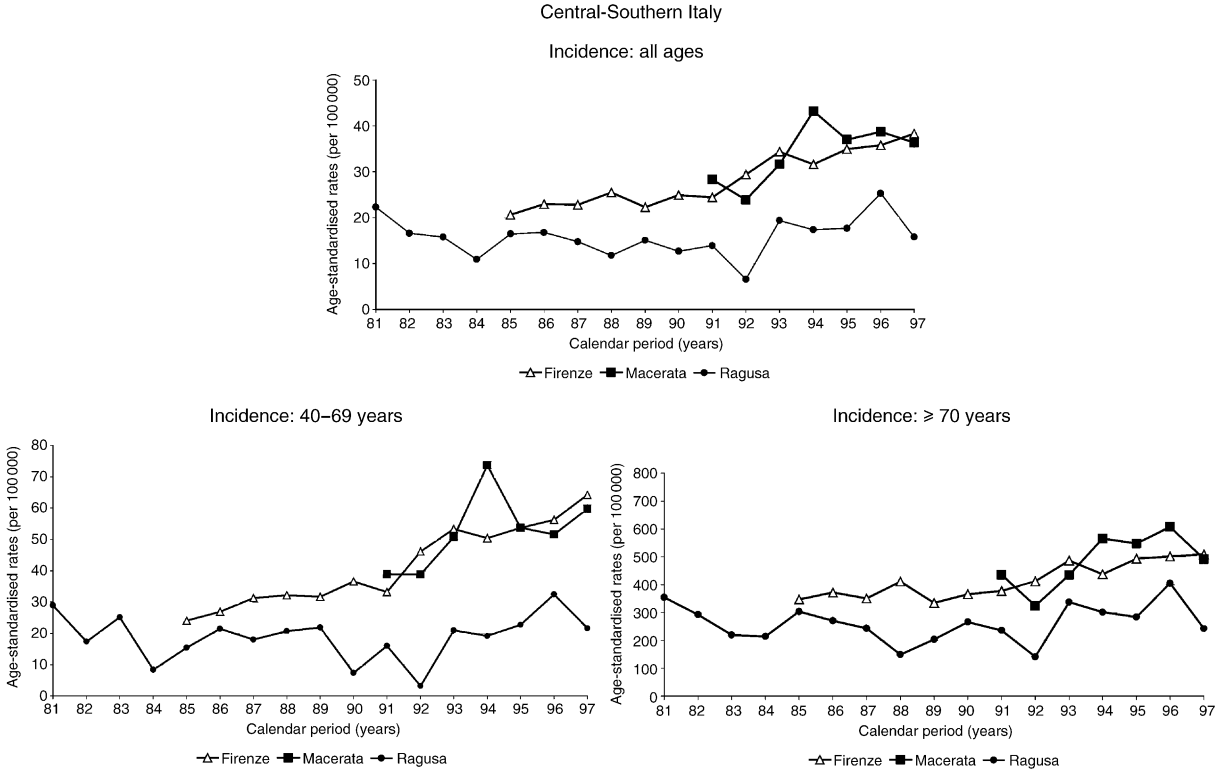

Fig. 4. Incidence trends for prostate cancer in Central-Southern Italy by Cancer Registry and Age Group.

incidence was higher. Therefore, it is reasonable to think that such improvements in the mortality rates could be due, at least partially, to a positive effect of the PSA test and other related diagnostic methods. Other causes have to be taken into account owing to the small delay between the first increase in incidence and the beginning of the mortality fall and considering that a lead time of 3 years has been computed for the PSA assay [28].

As claimed by different experts, the improvement in prognosis could be caused by some advances and the increased use of already known treatments, as well as due to the introduction of new therapies [29,30].

A larger number of patients now undergo radical prostatectomy and curative radiotherapy, because the number of localised cancers, that are potentially curable, has risen and more refined techniques are being adopted [29].

Moreover, orchiectomy has been rapidly replaced by the use of gonadotropin-releasing hormone (GnRH) analogues, making hormonal therapy more acceptable [31].

As regards geographical distribution, it is possible to note a North–South gradient for the incidence and mortality rates. The highest rates were registered in

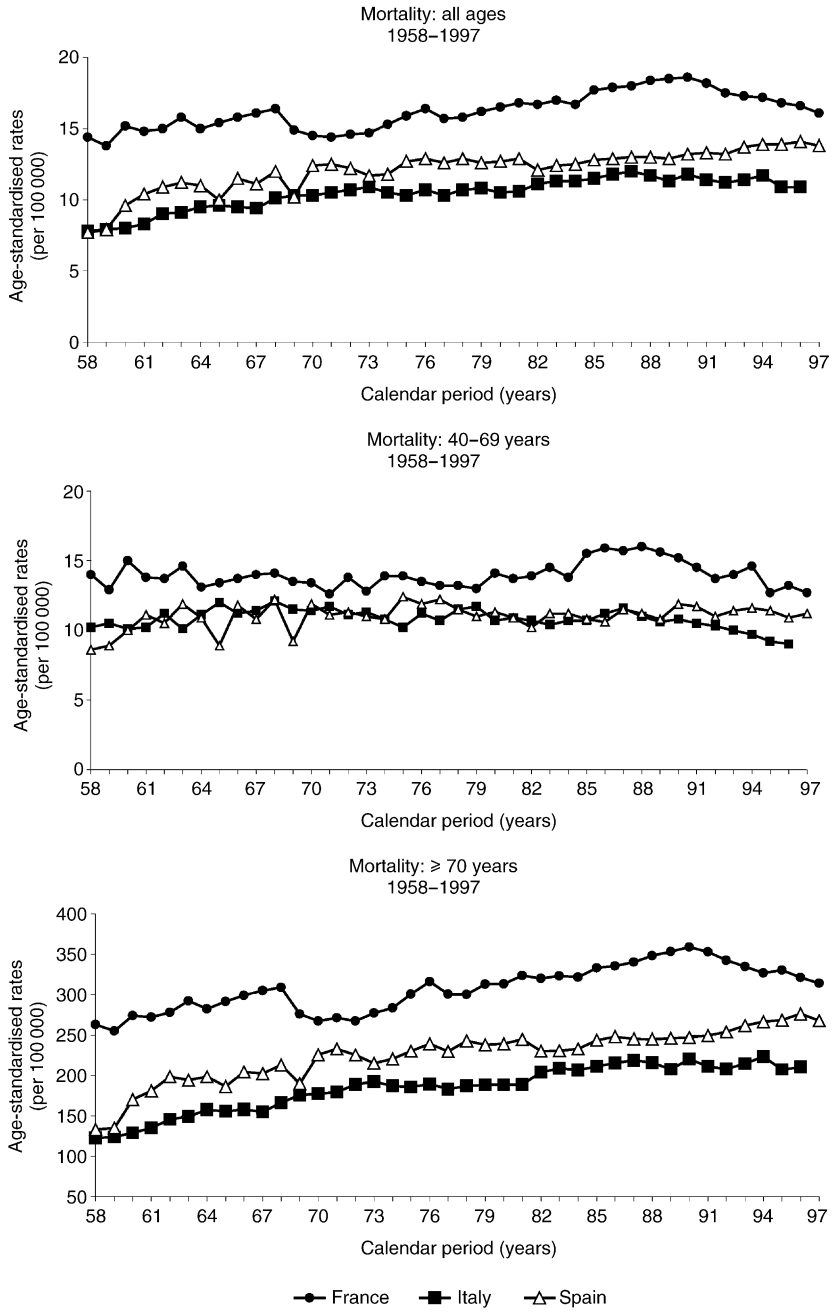

Fig. 5. Mortality trends for prostate cancer in France, Italy and Spain by Age Group.

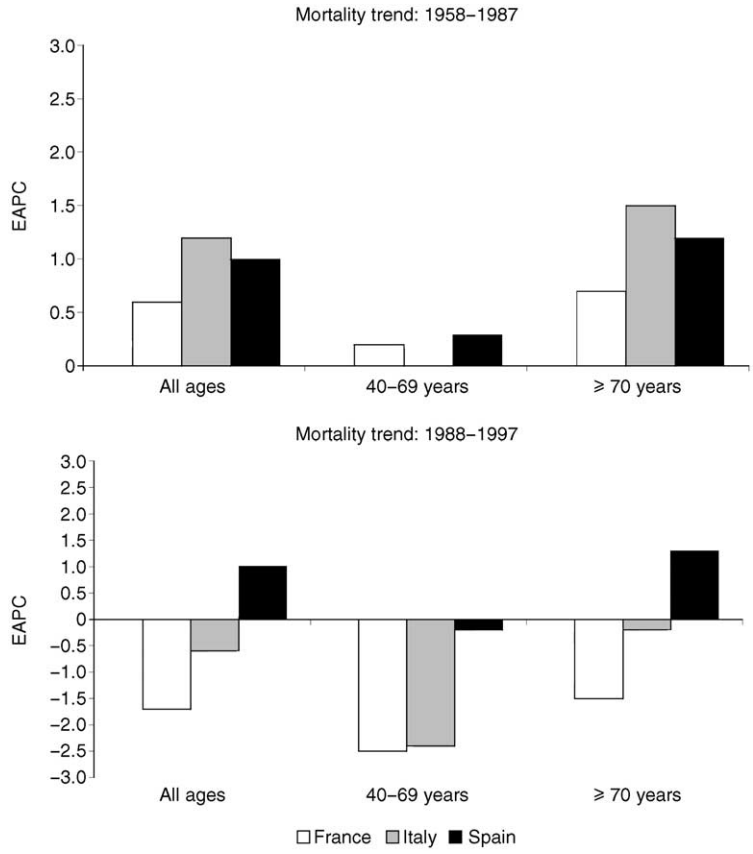

Fig. 6. Mortality trends of prostate cancer in France, Italy and Spain for two calendar periods (1958–1987, 1988–1997) by Age Group, according to Estimated Annual Percent Change (EAPC).

France and, within each country, in the Northern areas. This finding would seem to be consistent with the hypothesis that a lack of vitamin D and sunlight represent risk factors [32]. A similar gradient appeared also for the trends: the rise in incidence and the fall in mortality were greater in the Northern CRs.

This investigation has some inherent limitation. For mortality, issues related to death certification, demographic and incidence data, could make the analysis of rates in the oldest old subjects (over 85 years) less reliable [33]. Anyway, the presented results seem to be consistent, at least from a clinical point of view, with the pattern emerging within each age class for the different CRs in all three countries.

Another limitation concerns the variability of the observed time period which could make geographical comparability more difficult. However, for all CRs a time period around 1990 was chosen, in order to have at our disposal the largest number of geographical areas and to focus attention on the time period including major clinical changes.

In conclusion, the decrease in mortality, more marked in those areas and the age group with the higher increases in incidence, could be indirect evidence that the introduction of the PSA test and early diagnosis had a favourable impact on mortality. However, the results of randomised trials on mass screening are still lacking. We therefore have to be cautious and take into consideration other clinical advances. We did not observe any decrease in mortality for Spain, perhaps as a consequence of a delayed and lower increase in incidence, particularly in the elderly. An improvement is also expected in this country, since from the late 1980s there was substantial development of the Spanish Public Health Service and as a consequence, the availability of health care facilities was more consistent in the different regions.

Further studies are warranted in order to determine if the elderly could also benefit from early detection and treatment, without there being useless interventions, over-diagnosis and over-treatment.

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Appendix

The Cancer Registries from the Eurocim Group: France: Bas-Rhin (M. Velten), Calvados (J. Mace-Lesech), Doubs (P. Arveux), Haut-Rhin (A. Buemi), Herault (J.P. Daurès), Isère (F. Ménégoz), Somme (A. Dubreuil), Tarn (M. Sauvage). Italy: Ferrara (S. Ferretti), Firenze (E. Paci), Genova (M. Vercelli), Macerata (F. Pannelli), Modena (M. Federico), Parma (V. De Lisi), Ragusa (R. Tumino), Romagna (F. Falcini), Torino (R. Zanetti), Varese (P. Crosignani), Veneto (P. Zambon). Spain: Albacete (E. Almar), Asturias (A. Cañado), Basque Country (M.I. Izarzugaza), Granada (C. Martinez), Mallorca (I. Garau), Murcia (C. Navarro), Navarra (E. Ardanaz), Tarragona (J. Galceran).

References

1. Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, version 1.0. IARC CancerBase no., 5*. IARC Press, Lyon, 2001.
2. Mettlin C. Recent developments in the epidemiology of prostate cancer. *Eur J Cancer* 1997, **33**, 340–347.
3. Merril RM, Potosky AL, Fewer EJ. Changing trends in U.S. prostate cancer incidence rates. *J Natl Cancer Inst* 1996, **88**, 1683–1685.
4. Potosky AL. Rise in prostatic cancer incidence associated with increased use of transurethral resection. *J Natl Cancer Inst* 1990, **82**, 1624–1628.
5. Stephenson RA, Smart CR, Mineau GP, James BC, Janerich DT, Dibble R. The fall in incidence of prostate carcinoma. *Cancer* 1995, **77**, 1342–1348.
6. Potosky AL, Feuer EJ, Levin DL. Impact of screening on incidence and mortality of prostate cancer in the United States. *Epidemiol Rev* 2001, **1**, 181–186.
7. Surveillance, Epidemiology, and End Results (SEER) Program. Age-adjusted U.S. cancer death rates. *J Natl Cancer Inst* 1997, **89**, 12.
8. Ferlay J, Bray F, Sankila R, Parkin DM. European Network of Cancer Registries. *EUROCIM User Manual*, 3rd edn. Lambda-Plus Software Product, 1998.
9. Comité national des registres. *Rapport d'activité 1996–1999*. Paris, INSERM, 2000.
10. Miñarro R, Black RJ, Martinez C, *et al*. *Cancer Incidence and Mortality in Spain: Patterns and Trends [Incidencia y mortalidad de cáncer en España: Patrones y tendencias]. IARC Technical Report No. 36*. Lyon, International Agency for Research on Cancer, 2000.
11. Falcini F, Paci E, La Rosa F, *et al*. The Italian Network of cancer registries. In Zanetti R, Gafà L, Pannelli F, Conti E, Rosso S, eds. *Cancer in Italy. Incidence Data from Cancer Registries 1993–1998, vol. 3*. Rome, Il Pensiero Scientifico, 2002, 3–12.
12. Esteve J, Benhamou E, Raymond L. *Statistical Methods in Cancer Research Volume IV Descriptive Epidemiology. IARC Scientific Publications No. 128*. Lyon, International Agency for Research on Cancer, 1994 170–211.
13. Kleinbaum DG, Kupper LL, Muller KE. *Applied Regression Analysis and Other Multivariable Methods*. PWS-KENT Publishing Company, 1988, 68, 167–168, 206–217, 497–512.
14. Francis B, Green M, Payne C. *GLIM 4.0 The Statistical System for Generalized Linear Interactive Modelling*. Oxford University Press, 1994, 266–278.
15. Coleman MP, Estève J, Damiecki P, Arslan A, Renard H. *Trends in Cancer Incidence and Mortality. IARC Scientific Publications No. 121*. Lyon, International Agency for Research on Cancer, 1993.
16. Vercelli M, Quaglia A, Marani E, Parodi S. Prostate cancer incidence and mortality trends among elderly and adult Europeans. *Crit Rev Onc Hem* 2000, **35**, 133–144.
17. Chirpaz E, Colonna M, Menegoz F, *et al*. Incidence and mortality trends for prostate cancer in 5 French areas from 1982 to 1996. *Int J Cancer* 2002, **97**, 372–376.
18. Menegoz F, Colonna M, Exbrayat C, Mousseau M, Orfeuvre H, Schaerer R. A recent increase in the incidence of prostatic carcinoma in a French population: role of ultrasonography and prostatic specific antigen. *Eur J Cancer* 1995, **31**, 55–58.
19. Castillejom M, Cierco Peguera P, Bonfill Cosp X. Cribado de cáncer de próstata. *Atención primaria* 2002, **28**, 468–471.
20. Gann PH. Interpreting recent trends in prostate cancer incidence and mortality. *Epidemiology* 1997, **8**, 117–120.
21. Legler JM, Feuer EJ, Potosky AL, Merril RM, Kramer BS. The role of prostate specific antigen (PSA) testing patterns in the recent prostate cancer incidence decline in the United States. *Cancer Causes Control* 1998, **9**, 519–527.
22. Conférence de Consensus 1990. Conférence de consensus : le dépistage du cancer localisé de la prostate, Paris le 8 et 9 décembre 1989. *Annales d'Urologie* 1990, **24**, 5–8.
23. Post PN, Kil PJM, Crommelin MA, Schapers RFM, Coebergh JWW. Trends in incidence and mortality rates for prostate cancer before and after prostate-specific antigen introduction. A registry based study in Southeastern Netherlands, 1971–1995. *Eur J Cancer* 1998, **34**, 705–709.
24. Zaridze DG, Boyle P, Smans M. International trends in prostatic cancer. *Int J Cancer* 1984, **33**, 223–230.
25. Cayuela A, Lacalle JR, Gili M. Analysis of cohort mortality from prostatic cancer in Spain, 1951–1983. *J Epidemiol Comm Health* 1989, **43**, 249–252.
26. Post PN, Straatman H, Kiemeney LA, Coebergh JWW. Increased risk of fatal prostate cancer may explain the rise in mortality in The Netherlands. *Int J Epidemiol* 1999, **28**, 403–408.
27. La Vecchia C, Levi F, Lucchini F. Mortality from benign prostatic hyperplasia: worldwide trends 1950–92. *J Epidemiol Comm Health* 1995, **49**, 379–384.
28. Etzioni R, Legler JM, Feuer EJ, Merril RM, Cronin KA, Hankey BF. Cancer surveillance series: interpreting trends in prostate cancer—part III: quantifying the link between population prostate-specific antigen testing and recent declines in prostate cancer mortality. *J Natl Cancer Inst* 1999, **91**, 1033–1039.
29. Mettlin C, Murphy GP. Why is the prostate cancer death rate declining in the United States? *Cancer* 1998, **82**, 249–251.
30. Mettlin C. Changes in patterns of prostate cancer care in the United States: results of American College of Surgeons Commission on Cancer Study, 1974–1993. *Prostate* 1997, **32**, 221–226.
31. Small EJ. Advances in prostate cancer. *Curr Opin Oncol* 1999, **11**, 226–235.
32. Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality. *Cancer* 1992, **70**, 2861–2869.
33. Bain MRS, Harvey JC, Muir CS. Epidemiology research in aging: perspectives and limitations. In Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology*. Amsterdam, The Netherlands, Harwood Academic, 1998, 105–114.