Estimates of prostate cancer burden in Italy

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ABSTRACT

Age-standardized incidence rates of prostate cancer (PC) sharply increased during the period 1990–2005 in Italian areas covered by cancer registries, while corresponding mortality rates remained nearly constant. The latest observations have reported on a reversal of the incidence trend with decreasing values after 2005. We provided incidence, mortality, and prevalence estimates at national and geographical area levels, together with time projections up to the year 2020.

We applied the MIAMOD method, using as input national mortality data for the years 1970–2010 and population-based survival data for the period of diagnosis (1985–2002). We assumed relative survival of prostate cancer remained constant after the year of diagnosis (2005).

The age-standardized incidence rates of PC were estimated to increase during the period 1984–2005, from 31 per 100,000 in 1984 to 93 per 100,000 in 2005. From 2005 onwards, the estimated rates declined to 71 in 2015 and to 62 in 2020. Age-standardized mortality rates slightly increased from 1970 up to about 19 per 100,000 in 1999 and then started to decrease with an estimated reduction of about 2.3% per year. Mortality projections indicated a continuing reduction, with a predicted age-standardized rate of about 12 per 100,000 in 2020. Prevalence was estimated to continuously increase up to a crude prevalence value of 1.2% in the year 2020.

The results indicate that the epidemic peak of PC was reached around the year 2005 followed by declining incidence rates, while a substantial decrease in mortality, starting during the early 2000s, is expected to continue during the 2010s.

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1. Introduction

Prostate cancer (PC) is the leading cancer in the male European population, with about 420,000 new cases in 2012 [1]. By contrast, PC mortality – with about 101,000 deaths in 2012 – ranks third after those of lung cancer and colorectal cancer [1]. While PC incidence rates increased rapidly during the 1990s, mortality rates changed only modestly, with a tendency to decrease in the late 1990s in most European countries [2]. In Italy, 20% of all cancers occurring in the male population arise in the prostate gland [3]. Data from the pool of Italian population-based cancer registries (CRs), which covered around 30% of the Italian population, showed annual incidence percentage changes of about 4% during the period 2003–2005, and even bigger changes during the periods 1991–1994 (10%) and 1994–2003 (7%). However, these data did not completely describe PC occurrence at a national level; CRs were not active in all Italian regions, and the North was more represented than the South.

Prevalence and incidence estimates and time projections for PC are valuable in health planning. Actually, the vast majority of new diagnoses concern men with organ-confined disease; these men may benefit from radiation or surgery with radical intent. Those with low- and very-low-risk disease may require active surveillance only. On the other hand, treated patients can hardly be considered as cured, since 10 or 15 years after diagnosis they can still have an extra risk of dying with respect to the general population [4]. Thus, all PC patients require a lifelong follow-up with periodical clinical examination, prostate-specific antigen (PSA) testing and, in some cases, imaging examinations for the early detection of progression of clinical and biochemical recurrence.

From the public health point of view, it is reasonable to provide complete incidence data for each region, and for Italy as a whole.

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Estimates of PC incidence, prevalence, and mortality, as well as time projections up to the year 2015, have previously been published [5]. They were based on mortality data available in Italy at regional and national levels and on PC survival estimates up to 2002. Those estimates showed, for the first time, a tendency of PC incidence to stop or to reduce the steep increase observed up to the early 2000s. However, the regional and national estimates were based on official mortality data updated at the latest to the calendar year 2003, a fact that prevented the identification of a possible reversal of incidence trends in the most recent years. In that analysis a preliminary step of mortality projection was then necessary before the application of the usual MIAMOD modeling procedure [6]. In order to overcome this limitation, and to include the latest available data in the analyses, the present study aims to provide more detailed incidence, prevalence, and mortality estimates for PC, also based on updated population and mortality data up to the year 2010.

2. Materials and methods

Mortality data for PC, general mortality and population data by age, calendar year, and geographical macro-area (North-West, North-East, Center, and South Islands) for the period 1970–2010 were obtained from the Italian National Institute of Statistics (ISTAT) [7,8]. Cause-specific mortality was missing for the years 2004 and 2005 and was imputed by linear interpolation (by age class) between the previous and the following years. Population data for the years 2009–2010 were estimated on the basis of the ISTAT previous with central scenario. These data were added to the data available from 1970 to 2008.

The MIAMOD method [6,9] was used for the estimation of PC incidence and prevalence. This statistical method is based on a back-calculation approach to estimate incidence and prevalence of chronic irreversible diseases starting from population mortality and patient survival. The method relies on the mathematical relationships between mortality, prevalence, incidence, and survival. The model estimation is based on mortality data from ISTAT for the period 1970–2010, with cause of death coded according to the International Classification of Diseases, 9th revision, (ICD-9) [10]. Relative survival of cancer patients was estimated from observed CR data by means of parametric cure models of the Weibull type at macro-area level.

PC relative survival data for the period of diagnosis 1985–2002 were obtained from the EUROCare-4 study [11]. Data referred to the populations covered by 21 CRs in Italy jointly covering about 25% of the national population. A linearly increasing trend was fitted up the year of diagnosis 2005, after which, constant relative survival (set at the value of 2005) was assumed.

All estimates were carried out up to age 99 years. Age-adjusted incidence and mortality rates were based on the standard European population. Model-based incidence estimates were checked for consistency with the observational data available from the Italian Association of Cancer Registries (AIRTUM) database and from the published trend of incidence for the pool of AIRTUM CRs [12].

3. Results

A synthesis of the checking procedure is shown in Fig. 1, presenting age-standardized PC incidence trends estimated in the whole country, together with the corresponding observed trends from the pool of nine Italian CRs (i.e., Latina, Modena, Naples, Parma, Reggio Emilia, Salerno, Sassari, Umbria, Varese) covering the incidence period 1995–2009. Estimated rates were up to 20% higher than the observed ones during the period 1990–2000, characterized by a very sharp incidence rise. However, they fit well the subsequent flattening and decreasing tail of the incidence trend reported by the CRs.

Figs. 2–6 show, for Italy and for the four geographic macro-areas, time trends of annual age-standardized PC incidence rates (Fig. 2), age-standardized and age-specific PC mortality rates (Figs. 3 and 4), and PC prevalence proportions (Figs. 5 and 6) between 1970 and 2020. In Italy, the age-standardized incidence trend of PC was estimated to increase sharply, in particular during the period 1990–2005, from 40 to 93 per 100,000 men/year (Table 1 and Fig. 1). In 2005 the estimated rates reached a peak and declined to 71 per 100,000 in 2015 and to 62 per 100,000 men/year in 2020 (Table 1 and Fig. 1). The North West regions reached the highest incidence estimates in the years 2003–2004 (age-standardized incidence about 109 per 100,000 men/year), followed by the North East (102), the Center (about 98), and the South Islands with the lowest estimates (72) (Fig. 2). From 2006, the estimated incidence of PC decreased in all the Italian macro-areas, and the drop was particularly steep in the Northern regions. Forecasted age-standardized rates by 2020 were between 58 and 72 per 100,000 men/year in all the macro-areas.

The mortality for PC (Fig. 3) slightly increased from 15 per 100,000 in 1970 to about 19 per 100,000 men/year in 1999 and then started to decrease, down to 15 per 100,000 men/year in 2010, with an annual reduction of about 2.3% with respect to the 1999 level. Model projections have forecast a persisting reduction, with a predicted age-standardized rate of about 12 per 100,000 men/year in 2020. Mortality trends were similar among the various geographical areas, except for the South Islands. Beginning with different death risks in 1970, from 10 in the South-Islands to approximately 20 per 100,000 men/year in the other macro-areas, mortality rates increased up to the mid 1980s. Then, rates started to decrease in the North and Center, but not in the South-Islands, to converge to similar levels in the mid-2000s. After 2000, mortality started to decrease in all macro-areas, with observed rates ranging between 13 and 16 per 100,000 men/year in 2010 and predicted rates of 10 (Northern regions), 12 (Center) and 14 (South) per 100,000 men/year by the year 2020.

Observed mortality rates (Fig. 4) decreased in all the age groups during the period 2000–2010. The annual percentage mortality changes were particularly marked for the age classes under 55 (3.7%), 55–64 (4.4%), and 65–74 years (3.9%), whereas they were lower for age classes 65–74 (2.3%) and 85+ years (1.0%). Predicted mortality rates for 2020 were extremely low for ages below 55 years (0.23 per 100,000 men/year), moderate for the central age classes 55–74 years, and very high (423.3) for the oldest one. Also considering the demographic phenomenon of
population ageing, our estimates indicate that PC mortality will in the future be an event more and more related to old age.

Prevalence estimates (Fig. 5) rose consistently with increasing incidence, to reach the predicted level of 1.2% of Italian men living in 2020 after a PC diagnosis. They increased in all the Italian areas, with the highest proportions for the Center and North and the lowest in the South Islands. This latter proportion was estimated to be almost the half (800 versus 1400 per 100,000 men/year) of those from the North and Center.

Prevalence estimates increased in all age groups (Fig. 6). The increment was remarkable for men aged 85+ years. In this group of the population, one out of ten men was estimated to have had a diagnosis of PC by 2015.

Table 1 shows standardized incidence and mortality rates for PC, the corresponding number of PC cases and number of PC deaths and prevalence in 1990, 1995, 2000, 2005, 2010, 2015 and 2020. From 1990 to 2005 the estimated number of new annual PC diagnoses increased by a three-fold factor up to about 38,000 cases
in 2005. Thereafter, it started to decrease slightly down to about 33,000 predicted cases in 2020. Deaths from PC increased from about 5500 in 1990 to 7450 in 2005 and thereafter were estimated to remain approximately constant up to 2015 and to decrease down to 7150 deaths in 2020. Prevalence was estimated as dramatically increasing from 1990 to 2020, with almost a 10-fold increase in the number of men living with a PC diagnosis. However, the rate of increase was estimated to slow down after 2005, so that a plateau could be expected to be reached by 2025.
4. Discussion

The analyses presented in this paper indicate a marked decline, in all Italian areas, in PC incidence rates since the year 2005 after the continuous and steeply rising trends observed in the previous decade (1995–2004). The sharp increase in PC incidence can be in large part attributed to lead time bias, plus an increasing detection of non-lethal tumors (i.e., over-diagnosis) [13]. The effect has certainly intensified during the PSA testing era [2]. The two rounds of a survey carried out in Italy [14] reported a prevalence of recourse to PSA testing in asymptomatic men of 31% (36% in the North and 29% in the South) in 2002 and of 46% (51% in the North-Center and 38% in the South) in 2008. Early diagnosis and curative treatments may also have had some impact in improving survival of patients with lethal cancers. In Italy, the annual number of new PC diagnoses quadrupled between 1990 and 2015, and in the same period prevalence became 10-fold higher. Due to the very good prognosis of PC, prevalence was about 11-fold higher than incidence.

Incidence in the South was estimated as about one half that in the North during the 1970s, well before the introduction of PSA and also before the use in Italy of trans-urethral resection (TURP) for the treatment of benign prostate hyperplasia. Recent indications on a probable causal role of body fatness and adult height [15], historically higher in Northern Italy, are consistent with these estimates, even if the contribution of a higher diagnostic aggressiveness in the North with respect to the South can be hypothesized. Our estimates show converging incidence trends after the year 2000 with similar levels expected around the year 2020. The delayed spread of PSA testing in the South [14] probably explains in large part the differences in time trends [2], but also changes in risk factors in the South Islands might have played a role.

The temporal pattern of incidence observed in Italy was also described in many other developed countries. In particular, a
recent decline in PC incidence has become evident in Nordic European countries [16], and a clear decline was also observed in the USA [17], and Australia [18]. The decrease was attributed to the declines in PSA testing [19]. In 2008, the US Preventive Services Task Force recommended against PC screening for men aged 75 years or more [20], and similar indications were given by health authorities and consensus panels in other countries such as the UK [21] and Canada [22]. These changing recommendations anticipated, and might also have determined, the decline in both PSA testing [19] and PC incidence rates among older men (aged \( \geq 75 \) years), especially with regard to early-stage PC, which is most likely to be detected by screening [20]. Indeed, from 2009 through 2010, the incidence rates of localized PC decreased, whereas incidence rates of regional PC stabilized, and rates of distant PC increased in the US male population [17]. In the Nordic countries, incidence trends increased from around 1990 (with a 5-year delay due to the conservative attitude of urologists in Denmark) up to 2003 then rates rapidly converged [16]. A decline in incidence was apparent in Finland, Norway and Sweden, the countries with the highest figures. In Sweden and Norway the use of PSA testing was seen to be closely related with PC incidence [16]. A slightly decreasing incidence was detected in most recent years in France and Netherlands but was still not described in other South European countries [2].

Another relevant result of our study is that PC mortality in Italy is decreasing. For the age classes from 55 to 84 years, the mortality decline was observed throughout the period 1985–2010, although this was more accentuated from 2000 onwards. Conversely, for the youngest (<55 years) and the oldest (\( \geq 85 \) years) age classes, the trend was at first increasing and then, only after the early 2000s, started to decline, though more slowly compared with the trends in other age classes. Also in the countries considered above a mortality decline was observed after a long period of sharp increases in incidence rates.

Prevalence, the major indicator of patients’ needs, is not expected to stop as incidence and mortality. In Italy, in 2014, about 360,000 men were estimated to live with a PC diagnosis, representing a large proportion of the male population, especially among the elderly. This increasing number of PC patients requires specific health services, and they suffer from the physical and psychological sequela due mainly to radical treatment. Although a large part of the prevalence is due to increasing age, it must be kept in mind that PC incidence is heavily affected by overdiagnosis [13]: this may be relevant to the efficiency of the healthcare system. Indeed, for PC additional efforts should be undertaken to increase the appropriateness of treatment prescription and to improve treatment outcomes, also minimizing side effects and the related healthcare costs.

The present estimates and forecasts of PC incidence rates and new cases in Italy were, for the period 2000–2015, about 10% lower than those provided in 2013 [5]. This difference can be ascribed to the use of more updated mortality data for the model estimation. Actually, projected mortality in the period 2003–2010 from the previous analysis was higher than the corresponding levels subsequently observed for the same period.

Forecasting disease trends in periods subsequent to the period of data availability is a difficult task, heavily dependent on the model specification and on the unpredictable future validity of the hypotheses made. This is particularly true in the case of PC.

A common problem in the parametric models, such as those needed to provide time projections, is the difficulty in capturing very sudden changes in the described phenomena; that is exactly what happened during the period 1990–2010 with the jump, the peak, and the subsequent rebound in prostate cancer incidence. Furthermore, very careful survival modeling is needed when the expected incidence changes are not reflected in mortality rates and are mainly associated with survival changes, as for PC. We used model-based relative survival rates fitted on data for the period of diagnosis 1985–2002 as input for the MIAMOD estimation, assuming survival trend to be linearly increasing up to 2005 and remaining constant thereafter. More updated data, subsequently published from EUROCARE-5 [23] and AIR-TUM [12], are consistent with both these assumptions. Another limitation of the methodology used is the assumption of independent age and period effect, apart from the simple linear interaction represented by birth cohort. For example, different shapes of age-specific trends, such as those depicted for mortality in Fig. 4, cannot be captured by such models. Therefore, we decided not to present here age-specific incidence trends, as they would be approximately parallel simply due to an effect of the model specification.

Another weakness in PC trends forecasting derives from the large influence on incidence and survival of unplanned changes in health and clinical practice. The spread of early diagnosis, for which we have no monitoring activity at the population level, is the most important of such uncertainty factors. The PSA threshold for recommending a prostate biopsy is another example. It has been estimated that lowering the PSA threshold from 4.1 to 2.6 ng/mL (an option that is actually considered by many urologists) would double the number of incident cases [24], with the additional cases expected to have on average a very good prognosis. This phenomenon could for example explain the wave-shaped incidence trend of PC reported in Australia [18].

Alternative modeling approaches to the same estimation problem addressed here have been applied under the Bayesian framework. Bayesian models can be adapted to different situations taking into account relevant prior information. For example, incidence data collected by CRs, here considered as an external independent validation, can be directly used in modeling national incidence rates [25].

Despite these difficulties, comparison of estimated versus observed incidence from Italian CRs was quite good for the period 2003–2008, the last years of availability of empirical incidence data. This supports the accuracy of estimation procedures and also indirectly indicates that, at least for PC, the pool of CRs used to provide time trends were fairly representative of the Italian situation. In any case, due to the continuously evolving scenario and to the burden for the individuals and for society as a whole, a continuous monitoring of the epidemiological indicators for PC is deemed necessary.

These data support the hypothesis that prostatic cancer diagnosis was conditioned by a pronounced lead time anticipation and over-diagnosis. It is not clear, however, to what extent the reduced incidence could be due to having reached the natural upper limit of screening case detection capacity, or to the consequence of physicians’ compliance with the health authorities recommendations [26] against the mass recourse to PSA testing, or their consciousness that an excess of diagnoses have been made after the introduction of PSA testing. On the other hand, the decreased mortality could be the effect both of an early diagnosis of significant disease as well as the result of improved treatment strategies.

**Conflicts of interest**

All authors declare no conflict of interest.

**Author contributions**

Study conception and design: Riccardo Capocaccia and Gemma Gatta; Acquisition of data: Roberto Foschi;
Analysis and interpretation of data: Roberto Foschi, Riccardo Capocaccia and Antonella Zucchetto; Drafting of manuscript: Riccardo Capocaccia, Gemma Gatta and Roberto Foschi; Critical revision: Riccardo Valdagni, Massimo Maffezzini, Nicola Nicolai and Antonella Zucchetto.

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