Value of baseline PSA in predicting prostate cancer diagnosis and death. Spanish arm of the European Randomized Study of Screening for Prostate Cancer

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Introduction Several studies have suggested that prostate-specific antigen (PSA) in young men may predict the risk of developing prostate cancer (PC). Our aim is to study baseline PSA as a prognostic factor in the lifetime risk of developing PC, clinically significant PC (csPC), and metastatic PC (mPC), as well as to assess its impact on long-term mortality.

Material and methods This study was a retrospective analysis involving 2,415 men aged 45–70 years, all participants in the Spanish arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC). These men underwent PSA testing, and prostate biopsies were performed if their PSA levels were ≥3 ng/mL. The follow-up period spanned from September 2, 1996, to February 11, 2021. Kaplan-Meier survival analysis was conducted to calculate the probability of prostate cancer diagnosis and death. The relationship between these probabilities and baseline PSA levels was assessed using the log-rank test.

Results After 25 years of follow-up, the probability of being free of a diagnosis of PC was 95.5%, 89.6%, 80.0%, and 69.4%; and of PC death: 99.6%, 99.6%, 98.9%, and 98.3% for the categories of PSA <1ng/mL, 1–1.9ng/mL, 2–2.9ng/mL, and >3ng/mL, respectively. There is an association between baseline PSA level and the probability of PC diagnosis (which is maintained in age stratification), csPC, mPC ($p < 0.001$), and PC death ($p = 0.047$).

Conclusions There is a clear relationship between baseline PSA and the probability of detection of PC, csPC and mPC during follow-up, as well as PC death, in a cohort belonging to the Spanish branch of the ERSPC, with a median follow-up of more than 23 years. Baseline PSA level can be used to define the most appropriate PC screening interval for everyone.

Key Words: prostate cancer ‹› baseline PSA ‹› prostate cancer death ‹› clinically significant prostate cancer ‹› metastatic prostate cancer

INTRODUCTION

Prostate cancer (PC) is a disease with a high incidence and notable mortality worldwide, which means that it should be considered a major health problem.

According to 2020 data from the National Statistics Institute (INE), tumors are the second leading cause of mortality (22.8% [493776] of deaths) in Spain after diseases of the circulatory system [1]. In men, PC is the third most common cause of cancer death (5922 deaths).

Globally, according to GLOBOCAN 2020 [2], PC is the second most frequently diagnosed neoplasm in men (14.1%). In terms of mortality, PC accounts for 3.8% of cancer deaths (375304 deaths per year), corresponding to eighth place. In men, it is the fifth leading cause of death from tumors (6.8%).

The westernization of Asian countries has led to an increase in the incidence of PC, which is consistent with the increase in prevalence and high-grade latent PC cases found in autopsies [3]. The prevalence of latent PC has remained stable since 1950 in Western countries but has increased over time in Asian countries.

Given its global presence, many efforts have been made over the years to provide adequate screening. However, there is much controversy about prostate-specific antigen (PSA) – based screening [4]:

- Poor specificity, with a high false positive rate and unnecessary biopsies.
- Up to 15% false negatives, so that some cancers go undiagnosed.
- The natural history of PC is highly variable. There are aggressive tumors that need treatment, but there are many slow-growing tumors that will never cause symptoms or compromise life (overdiagnosis).

Thus, although screening has been shown to reduce mortality from PC [5], many patients would receive aggressive treatment unnecessarily (overtreatment). It also has other disadvantages such as subjecting many people to unnecessary tests or treatments to potentially help a few; or giving less attention to other important health issues by primary care professionals [6]. On the other hand, several studies have suggested that a PSA test in young men can predict the subsequent risk of developing PC. These findings could be used to improve PC screening on an individual risk basis rather than universally. A recent European Randomized Study of Screening for Prostate Cancer (ERSPC) study links baseline PSA and the probability of dying from PC after 16 years of follow-up. [7]. Another recent study by the Norwegian Prostate Cancer Consortium confirms similar findings [8].

The aim of the present work is to study baseline PSA as a potential prognostic factor for the lifetime risk of developing PC, as well as clinically significant PC (csPC), metastatic PC (mPC), and its possible impact on cancer-specific mortality.

MATERIAL AND METHODS

This study was a retrospective analysis of 2,415 men aged 45–70 years, enrolled in the screening arm of the Spanish section of ERSPC. These participants underwent PSA testing, and those with PSA levels ≥3 ng/mL were randomized to receive sextant prostate biopsies guided by transrectal ultrasound. Additional biopsy cores were taken if suspicious areas were identified on the ultrasound images. The follow-up period for this study extended from September 2, 1996, to February 11, 2021.

In the Spanish section of the ERSPC [9]: 18,612 men between 45 and 70 years of age registered in the municipalities of Getafe and Parla (C. Madrid, Spain) were invited to participate. Those with a life expectancy of less than 10 years or a previous diagnosis of PC were excluded. The study included 4,276 men who were randomized to screening arm (serum PSA determination) and control arm. The screening interval was 4 years if PSA levels were normal, and 1 year if previous elevated PSA level and negative biopsy result. The last PSA determination was performed in October 2005, although the cohort was followed up to register new cancers and their characteristics, as well as mortality and its causes. The identification and follow-up of the PCs detected was carried out by cross-referencing databases with the Pathology Anatomy Departments of the University Hospitals of Getafe and Infanta Cristina (Madrid, Spain). The date and fundamental cause of death were obtained from the death certificates, by means of an agreement with the Spanish National Statistics Institute (INE). The cause of death in patients diagnosed with PC was contrasted with the clinical history data and assigned by consensus of a local cause of death committee created for this purpose, according to ERSPC guidelines.

The variables included in the analysis were

- date of birth
- date and baseline PSA level (PSA level at the start of the study)
- date of diagnosis of:
  - PC
  - csPC (according to NCCN guidelines [10] defined as non-clinically significant cancer: T1 or T2a + Gleason 3+3 + PSA <10 mg/ml; and the rest as clinically significant)
  - mPC (documented M1, or with PSA >100 ng/ml regardless of documentation of metastases) [11]
- date of death from PC
- follow-up time to each event

Descriptive analysis was performed for the variables baseline PSA, age at baseline PSA and follow-up time to PC death. The Kolmogorov-Smirnov normality test was applied.

Kaplan-Meier survival analysis was used to calculate the probability of diagnosis of PC, csPC, mPC and death from PC. Comparison between the probability of these events and the baseline PSA level category using the log-rank test.

Any difference with p <0.05 was considered statistically significant. Data processing and analysis was performed using Microsoft Access and SPSS v17.0.

RESULTS

Median baseline PSA, age at baseline PSA and follow-up time were 0.9 ng/ml, 56.9 and 23.3 years, respectively. None of these conformed to a normal distribution.

We stratified according to categories of baseline PSA level (ng/ml): <1, 1–1.9, 22–.9 and ≥3; and age (years): 45–50, 50–55, 55–60, ≥60.

The probabilities of remaining free of each event shown below, after 25 years of follow-up, were as follows:

- For the diagnosis of PC, the probability was 95.5%, 89.6%, 80.0%, and 69.4% for PSA (ng/ml) categories <1, 1–1.9, 2–2.9, and ≥3, respectively.
- For the diagnosis of csPC, the probability was 96.7%, 93.4%, 88.1%, and 83.9% for PSA categories (ng/ml) <1, 1–1.9, 2–2.9 and ≥3, respectively.
- In the diagnosis of mPC, the probability was 99.8%, 99.7%, 100%, and 97.2% for PSA categories (ng/ml) <1, 1–1.9, 2–2.9 and ≥3, respectively.
- The probability of being free of death from PC was 99.6%, 99.6%, 98.9%, and 98.3% for PSA categories (ng/ml) <1, 1–1.9, 2–2.9 and ≥3, respectively.

The detailed description for each follow-up time point is shown in Table 1.

A significant relationship was found between baseline PSA categories and subsequent diagnosis of PC (p <0.001), csPC (p <0.001), mPC (p <0.001) and PC death (p = 0.047), throughout follow-up.

In age stratification, the odds of remaining free of a PC diagnosis based on baseline PSA after 25 years of follow-up were as follows:

- For age category 45–50; in those with PSA <1 ng/ml it was 95.8% versus 72.5% if PSA ≥3 ng/ml.

Table 1. *Probability of remaining free of a diagnosis of PC, csPC, mPC and death according to PSA categories throughout follow-up.*

	PSA CATEGORIES (ng/mL)						
	<1						
Follow-up time (start of interval, years)		0	5	10	15	20	25
Cumulative probability of remaining free of the event at the end of the interval	PC	99.3%	99.3%	98.5%	97.3%	95.5%	95.5%
	csPC	99.7%	99.6%	99.1%	98.0%	96.7%	96.7%
	mPC	100%	99.8%	99.8%	99.8%	99.8%	99.8%
	Death from PC	100%	99.9%	99.9%	99.6%	99.6%	99.6%
	1–1,9						
Follow-up time (start of interval, years)		0	5	10	15	20	25
Cumulative probability of remaining free of the event at the end of the interval	PC	98.0%	96.3%	93.9%	91.8%	89.6%	89.6%
	csPC	99.1%	98.2%	97.0%	95.5%	93.3%	93.3%
	mPC	99.8%	99.8%	99.8%	99.7%	99.7%	99.7%
	Death from PC	99.8%	99.8%	99.8%	99.7%	99.7%	99.7%
	2–2,9						
Follow-up time (start of interval, years)		0	5	10	15	20	25
Cumulative probability of remaining free of the event at the end of the interval	PC	92.8%	90.0%	84.0%	82.3%	80.0%	80.0%
	csPC	97.3%	95.9%	91.4%	90.3%	88.1%	88.1%
	mPC	100%	100%	100%	100%	100%	100%
	Death from PC	100%	100%	99.5%	98.9%	98.9%	98.9%
	≥3						
Follow-up time (start of interval, years)		0	5	10	15	20	25
Cumulative probability of remaining free of the event at the end of the interval	PC	76.7%	73.0%	70.9%	70.4%	69.4%	69.4%
	csPC	89.5%	86.2%	84.5%	84.0%	84.0%	84.0%
	mPC	99.2%	99.2%	99.2%	98.3%	97.3%	97.3%
	Death from PC	100%	98.8%	98.8%	98.3%	98.3%	98.3%

PC – prostate cancer; mPC – metastatic prostate cancer; csPC – clinically significant prostate cancer; PSA – prostate-specific antigen

- In males 50–55; it was 95.5% and 65.8% for PSA <1 ng/ml and PSA ≥3 ng/ml categories respectively.
- In the 55–60 group; probability of 94.3% and 66.5% for PSA categories <1 ng/ml and PSA ≥3 ng/ml respectively.
- Finally, in the ≥60; it was 96.5% for PSA <1 ng/ml versus 75.9% if PSA ≥3 ng/ml.

The rest of the data are shown in Figure 1.
A significant difference was found (p <0.001 in all four cases), finding an association between PSA levels and PC development for all age groups.

DISCUSSION

In the present study, we observed a clear relationship between baseline PSA and the probability of PC detection throughout follow-up, which is maintained in the age stratification, as well as for the detection of csPC, mPC and PC death, in a cohort belonging to the Spanish arm of the ERSPC, with a median follow-up of more than 23 years.
We found that the probability of detection of PC with baseline PSA levels <1 ng/ml was 4.5% versus 30.6% with PSA ≥3 ng/ml at 25 years. In the case of csPC detection, the probability found was 3.3% and 16%; and in the diagnosis of mPC it was 0.2% and 2.7%, respectively.
Other studies allude to the association between baseline PSA level and possible subsequent development of PC:
Gann et al. [12] found a RR = 5.5 of subsequent development of PC in men with PSA levels between 2.0 and 3.0 ng/ml versus those with levels below 1.0 ng/ml.

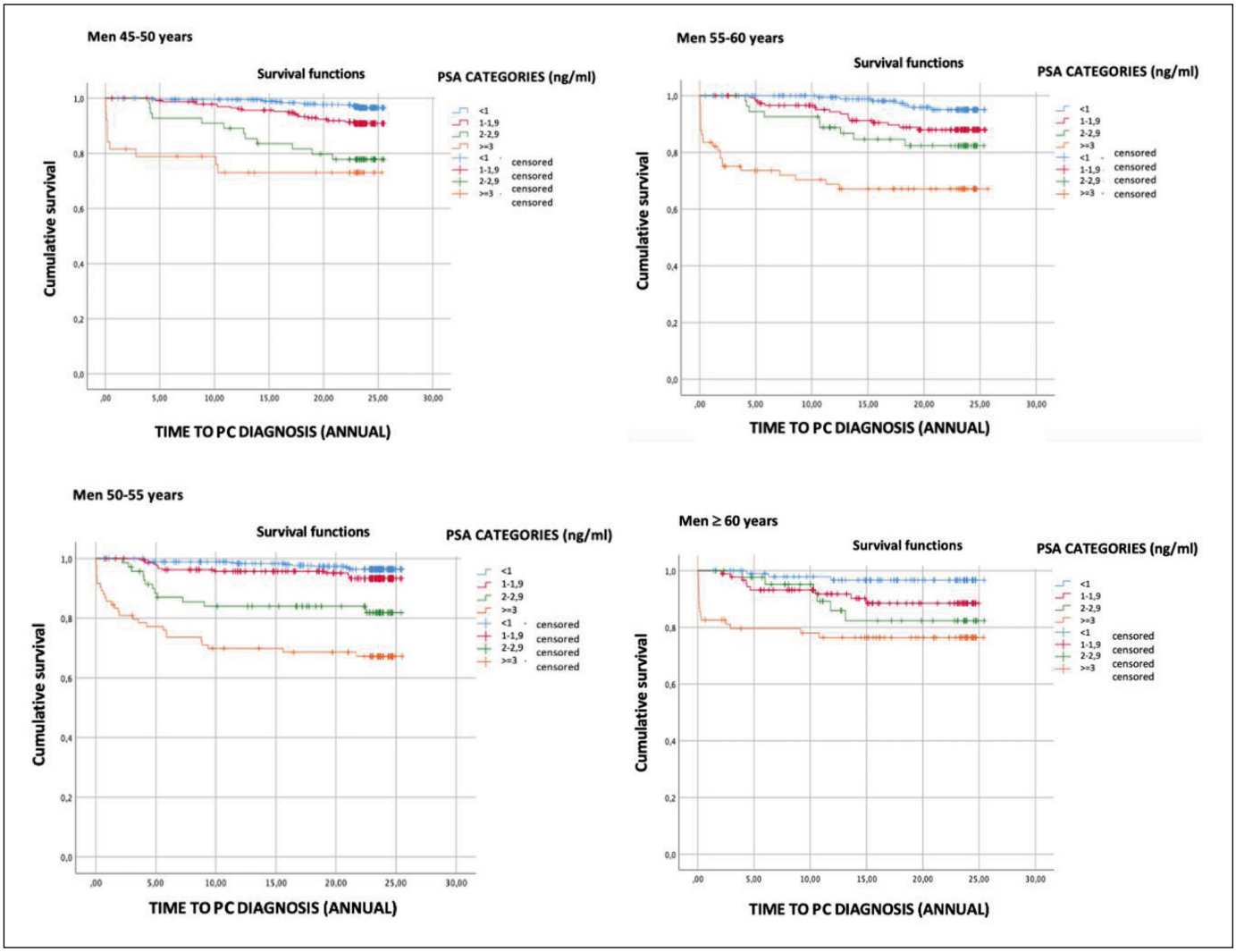

Figure 1. *Probability of remaining free of prostate cancer diagnosis according to prostate-specific antigen categories throughout follow-up in men aged 45–50 years, 50–55 years, 55–60 years and ≥60 years.*

PC – prostate cancer

Junyong Fang et al. [13] found an increased risk of PC at age 25 years in men with baseline PSA at or above the median for each age group studied (0.60 ng/ml in men 40–49.9 years, and 0.71 ng/ml in men 50–59.9 years), with RRs ranging from 3.7 to 3.5 depending on age category.

Loeb et al. [14] showed that a baseline PSA level between the median (0.7 ng/ml in men aged 40–49 years and 0.9 ng/ml in the 50–59 age group) and 2.5 ng/ml was associated with a 14.6 and 7.6 times higher risk of PC in men in the aforementioned age categories, respectively.

Lilja et al. [15] demonstrated a strong association between PSA measurement at age 50 years or earlier and subsequent PC diagnosis ($p < 0.0005$, AUC 0.719), as well as for the development of advanced PC (AUC 0.75). They determined a risk of developing PC of 1-5% in those men with PSA level (measured between 44–50 years) <0.5 ng/ml; rising to 8–15% for PSA 0.75–1.25 ng/ml; and >20% in those with PSA >1.50 ng/ml, with a median follow-up of 23 years.

The data from these studies are consistent with those found in our experience, highlighting the importance of baseline PSA as a determinant factor in the subsequent development of PC.

These findings may help us to define appropriate PC screening intervals for patients based on their baseline PSA. In fact, the European Association of Urology (EAU) guidelines for PC 2022 [4], include baseline PSA as one of the relevant factors in defining PC screening, and recommend offering a risk-adapted strategy (based on baseline PSA level), with follow-up intervals of 2 years for men with a PSA level >1 ng/ml at age 40; and for men with a PSA level >2 ng/ml at age 60; and postponing follow-up to 8 years for those with lower PSA levels. Other groups, such as ther German PROBASE [16] also advocate risk-based screening strategies based on baseline PSA in young men (45–50 years).

Regarding the relationship between baseline PSA level and death from PC during follow-up, we found a significant association ($p = 0.047$), although it should be noted that the magnitude of these differences is small: 0.4% probability with PSA levels <1 ng/ml at 25 years of follow-up and 1.7% if PSA ≥3 ng/ml; both values are well below what would be expected.

Such low values for PC mortality in our series have already been observed in previous updates of our results [9] where PC mortality accounted for 1.9% of all deaths, meaning that only 0.3% of the recruited population died from PC after almost 16 years of follow-up. The study found that, of the 334 cancer deaths, PC was the tenth most common cause of death: only 12 patients (3.6%) died from PC. Potential underestimation of PC as a cause of death, or incorrect assignment of causes of death on death certificates, were ruled out as possible causes of the low mortality from PC in our series [17] as all INE procedures comply with Spanish and European regulations (including EUROSTAT methodology) [18]. A study to check the quality of cancer death certificates in Spain found a correct assignment of cause of death between 84.6 and 91.4% (based on direct comparison with information from hospital records) [19]. In addition, the ERSPC study has centralized and local cause of death committees where the correct allocation of mortality data is protocolized and monitored [20].

A recent study [7] with the pooled analysis of all participating centres in the ERSPC group analyzed the relationship between baseline PSA and the probability of death from PC, with results similar to those shown in our data. With 16 years of follow-up, the probability of csPC as a function of baseline PSA ranged from 1.2–1.5% for men with PSA <1.0 ng/ml and 13.3–13.8% if PSA ≥3.0 ng/ml, results similar to those found in our study. Ninety-two per cent of PC deaths occurred in the group of men with PSA above the median (1.21 ng/ml).

Furthermore, they show that with 8 years of additional follow-up in the 60–61 year-old group with PSA <2 ng/ml, a period in which 42% of patients attended a subsequent screening visit, no deaths from PC occurred in the group, therefore questioning the value of repeat PSA screening in men aged 68–70 years and PSA <2.0 ng/ml, even in cases with a life expectancy of more than 15 years.

Another study refers to the predictive value of baseline PSA for death from PC [8], also found an association between baseline PSA and the probability of PC diagnosis and death. At 16 years of follow-up, the probability of PC diagnosis among 40-49 years old with PSA <1 ng/ml was 4.3% versus 17.7% if PSA 3–3.9 ng/ml; and of PC death 0% versus 0.6% for these baseline PSA categories, respectively. In the 65–69 age group, the probability of PC with PSA <1 ng/ml was 3.6% versus 22% if PSA 3–3.9%; and of PC death 0.7% versus 5.6%, respectively.

Limitations of our study include the low mortality from PC in the area studied, as well as the limited sample size.

CONCLUSION

With this study we highlight the clear relationship between baseline PSA and the probability of PC detection throughout follow-up, which is maintained

for all age categories. Baseline PSA also correlates with the probability of detecting csPC, mPC, and dying from PC in a cohort belonging to the Spanish ERSPC branch, with a median follow-up of more than 23 years.
Baseline PSA level can help to customize the appropriate PC screening interval for each individual.
The authors declare that they have no conflicts of interest.

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CONFLICTS OF INTEREST
The authors declare no conflict of interest.

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