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RESEARCH ARTICLES

Characteristics and outcome of prostate cancer with PSA <4 ng/ml at diagnosis: a population-based study

Marta Bonet · Arnaud Merglen · Gérald Fioretta · Elisabetta Rapiti · Isabelle Neyroud-Caspar · Roberto Zanetti · Raymond Miralbell · Christine Bouchardy

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Abstract
Introduction This population-based study aims to assess prognosis of prostate cancer diagnosed with prostate-specific antigen (PSA) levels <4 ng/ml in routine care.
Materials and methods We compared prostate cancer patients with low PSA values (n=59) with other prostate cancer patients (n=1330) by logistic regression and the Cox model using data from the Geneva Cancer Registry.
Results Patients with low PSA values more frequently had early-stage and well differentiated tumours. Nevertheless, 35% presented with aggressive tumour characteristics or metastases. After adjustment for other prognostic factors, prostate cancer-specific mortality was similar for both groups (hazard ratio: 1.1; 95%CI: 0.6–2.2).
Conclusion We conclude that cancer with low PSA values at diagnosis is not indolent.

Keywords Prostate cancer · Prostate-specific antigen · Tumour characteristics · Survival · Mortality

M. Bonet · R. Miralbell
Division of Radiation Oncology
Geneva University Hospitals
Avenue de la Roseraie 53
1205 Geneva, Switzerland

M. Bonet
Hospital Universitari Arnau de Vilanova de Lleida
Lleida, Spain

A. Merglen · G. Fioretta · E. Rapiti · I. Neyroud-Caspar · C. Bouchardy (✉)
Geneva Cancer Registry
Institute for Social and Preventive Medicine
Geneva University
55 Boulevard de la Cluse
1205 Geneva, Switzerland
e-mail: christine.bouchardymagnin@unige.ch

R. Zanetti
Piedmont Cancer Registry
CPO, Via San Francesco da Paola 31
10123 Turin 1, Italy

Introduction

Prostate-specific antigen (PSA) screening is widely used in North America and Europe. Health professionals in Geneva follow international guidelines, setting the threshold for biopsy referral at PSA ≥4 ng/ml [1]. Unless there is clinical suspicion (abnormal rectal examination), no further investigations are recommended for men presenting with PSA values <4 ng/ml.

Prostate cancer in men with PSA levels <4.0 ng/ml is not unusual when systematically investigated. The reported prevalence of biopsy-confirmed prostate cancer discovered in men presenting with "normal PSA" values range from approximately 2 to 26% depending on the threshold of PSA value considered [2–8]. However, in routine care these cancers are less frequent as they are only discovered fortuitously during endoscopic resection for prostate hyperplasia or following additional investigations in case of clinical suspicion. Recent results from the Rotterdam section of the European randomised study of screening for prostate cancer showed a 2% detection rate of cancer among men with PSA <4 ng/ml referred for sextant biopsies after abnormal digital or ultrasound rectal examination [9]. In a Swedish population-based cohort study, prostate cancer diagnosed with PSA <4 ng/ml represented only 6% of all prostate cancers diagnosed in routine care [10].

Pathological characteristics and the impact of cancer diagnosed with low PSA values are not well known. Few studies have raised these specific questions by reporting on both tu-

mour characteristics and prognosis among patients with PSA levels <4 ng/ml at diagnosis, showing contradictory results [11–23]. Some of the studies reported that tumours diagnosed at low PSA levels have better prognostic characteristics [2, 12, 13, 16–18, 20–23], while other studies reported they had similar characteristics to other prostate tumours [8, 14, 19].

Most studies were limited to operated or irradiated patients with localised prostate cancer [11–15, 17, 23] or used biological failure to evaluate prognosis (increasing post-treatment PSA level), non-pertinent for tumours with low PSA production [11, 13, 14, 17, 18, 23].

To our knowledge, no previous studies have used population-based data to evaluate occurrence, characteristics and mortality of prostate cancer among patients with low PSA values in routine care. This is the aim of our study.

Patients and methods

We used data from the population-based Geneva cancer registry, which records all incident cancer cases occurring in the canton (approximately 435,000 inhabitants). The registry collects information from various sources and is considered exhaustive, as attested by its low percentage (<2%) of patients recorded from death certificates only. All hospitals, pathology laboratories and practitioners are requested to report every cancer case. Registrars systematically abstract data from medical and laboratory files. Physicians regularly receive questionnaires to secure missing clinical and therapeutic data. Death certificates are consulted systematically.

Recorded data include sociodemographic information, method of discovery, type of confirmation, tumour histology and grade (coded according to the International Classification of Diseases for Oncology) [24], stage of disease at diagnosis, treatment during the first six months after diagnosis, survival status and cause of death.

The cancer registry regularly assesses survival, taking as reference date the date of confirmation of diagnosis or the date of hospitalisation (if it preceded the diagnosis and was related to the disease). In addition to passive follow-up (standard examination of death certificates and hospital records), active follow-up is performed yearly using the files of the Cantonal Population Office in charge of the registration of the resident population. Cause of death is taken from clinical records and coded according to the World Health Organization's classification.

Between 1989 and 2000, 2267 men were diagnosed with invasive prostate cancer among the resident population. We excluded patients with previous or synchronous invasive cancer (except non-melanoma skin cancer) (n=224), patients with cancer discovered at death (n=11), unknown stage at diagnosis (n=461) and unknown PSA value at diagnosis (n=353). The study finally included 1383 patients.

Tumour stage was based on the TNM classification system. We used pathological stage or, when absent, clinical stage. Stage was classified as T1 (clinically inapparent tumour not palpable or visible by imaging), T2 (tumour confined within the prostate), T3 (tumour extends through the prostate capsule with or without invasion of the seminal vesicles), T4 (tumour is fixed or invades adjacent structures) or M1 (distant metastasis). Lymph node invasion was classified as negative, positive or unknown [25].

Differentiation was classified as Grade 1 (well differentiated: Gleason 2–4), Grade 2 (moderately differentiated: Gleason 5–6), Grade 3–4 (poorly differentiated, undifferentiated: Gleason 7–10) or unknown [25].

We considered all treatments given during the first six months after prostate cancer diagnosis. Surgical treatment included radical, retropubic or perineal prostatectomy. We could not distinguish between chemical and hormonal castration. Radiotherapy consisted in external radiotherapy. Brachytherapy was not administered during the study period.

Statistical analysis

We used a case-control approach to compare patient and tumour characteristics between patients diagnosed with low PSA values (PSA <4 ng/ml) vs. elevated PSA values (PSA ≥4 ng/ml). To identify sociodemographic and pathological characteristics clinically linked to PSA value at diagnosis we used unconditional logistic regression analyses.

Prostate cancer-specific survival was estimated by the actuarial method (intervals in days and standard error according to Greenwood) [26]. To establish if low PSA level was independently linked to prognosis, we compared the risk of prostate cancer-specific mortality between the two groups using Cox proportional hazards analysis adjusted for other prognostic factors. All analyses were done with SPSS software (Version 14; SPSS Inc, Chicago, IL, USA).

Results

Only 53 (3.8%) prostate cancer patients had PSA values <4 ng/ml at diagnosis. Mean age of patients was 71 years (range 55–92) in the <4 ng/ml group and 70 years (range 44–97) in the ≥4 ng/ml PSA group.

Table 1 lists patient and tumour characteristics according to PSA level at diagnosis. Crude logistic regressions showed that patients with low PSA levels were more often diagnosed in public care (p<0.001) and that the majority of patients (51%) had fortuitous discovery, usually following pathological findings of prostate cancer after endoscopic prostate surgery. Furthermore, patients with low PSA levels more often had earlier stage at diagnosis ((p<0.001) and less aggressive tumours ((p<0.010). The proportion of well differentiated tumours was 34% in patients with low PSA values and 12% among patients with elevated PSA values. However, six (11%) of the 53 patients presenting with low

Table 1 Patient and tumour characteristics and associated odds ratio for low PSA level at diagnosis

	PSA <4 ng/ml *N*=53 Cases	PSA ≥4 ng/ml *N*=1330 Controls	Crude odds ratio
Age			
<60 years	5 (9%)	182 (14%)	1[a]
60–69 years	17 (32%)	511 (38%)	1.2 (0.4–3.3)
70–79 years	20 (38%)	409 (31%)	1.8 (0.7–4.8)
≥80 years	11 (21%)	228 (17%)	1.8 (0.6–5.1)
Country of birth			
Switzerland	34 (64%)	888 (67%)	1[a]
Mediterranean	11 (21%)	233 (18%)	1.2 (0.6–2.5)
Other	8 (15%)	209 (16%)	1.0 (0.5–2.2)
Civil status			
Married	39 (74%)	1008 (76%)	1[a]
Widowed	5 (9%)	146 (17%)	0.9 (0.3–2.3)
Divorced	7 (13%)	106 (8%)	1.7 (0.7–3.9)
Single	2 (4%)	70 (5%)	0.7 (0.2–3.1)
Social class			
High	12 (23%)	360 (27%)	1[a]
Middle	22 (42%)	567 (43%)	1.2 (0.6–2.4)
Low	18 (34%)	376 (28%)	1.4 (0.7–3.0)
Unknown	1 (2%)	27 (2%)	1.1 (0.1–8.9)
Period of diagnosis			
1989–1991	11 (21%)	160 (12%)	1[a]
1992–1994	10 (19%)	245 (18%)	0.6 (0.2–1.4)
1995–1997	15 (28%)	418 (31%)	0.5 (0.2–1.2)
1998–2000	17 (32%)	507 (38%)	0.5 (0.2–1.1)
Method of discovery			
Symptoms	19 (36%)	542 (41%)	1[a]
Fortuitous	27 (51%)	174 (13%)	4.4*** (2.4–8.2)
Screening[b]	7 (13%)	614 (46%)	0.3* (0.1–0.8)
Sector of care			
Private	16 (30%)	784 (59%)	1[a]
Public	37 (70%)	546 (41%)	3.3*** (1.8–6.0)
Stage			
T1	21 (40%)	198 (15%)	1[a]
T2	19 (36%)	400 (30%)	0.4* (0.2–0.9)
T3	7 (13%)	430 (32%)	0.2*** (0.1–0.4)
T4	0 (–%)	51 (4%)	–
M1	6 (11%)	251 (19%)	0.2** (0.1–0.6)
Lymph nodes			
Negative	27 (51%)	732 (55%)	1a
Positive	5 (9%)	145 (11%)	0.9 (0.4–2.5)
Unknown	21 (40%)	453 (34%)	1.3 (0.7–2.3)
Differentiation			
Grade 1	18 (34%)	162 (12%)	1[a]
Grade 2	10 (19%)	543 (41%)	0.2*** (0.1–0.4)
Grade 3–4	15 (28%)	439 (33%)	0.3** (0.2–0.6)
Unknown	10 (19%)	186 (14%)	0.5 (0.2–1.1)
Histology			
Adenocarcinoma	50 (94%)	1254 (94%)	1[a]
Other	3 (6%)	76 (6%)	1.0 (0.3–3.2)

[a]Reference category
[b]Only digital rectal examination (DRE) for cases, DRE+PSA for controls
*p<0.05, **p<0.01, ***p<0.001

PSA values at diagnosis had metastatic disease. All six had poorly differentiated tumours. Table 2 shows treatments delivered to patients according to their PSA values. Patients with low PSA values were more frequently managed with watchful waiting than patients with higher PSA levels (49% vs. 24%, (p<0.01).

Table 2 Treatment options for prostate cancer and associated odds ratio for low PSA level at diagnosis

	PPSA <4 ng/ml *N*=53 Cases	PSA ≥4 ng/ml *N*=1330 Controls	Crude odds ratio
Prostatectomy	12 (23%)	407 (31%)	1[a]
Radiotherapy[b]	8 (15%)	286 (22%)	0.9 (0.4–2.4)
Watchful waiting	26 (49%)	323 (24%)	2.7** (1.4–5.5)
Hormone therapy	3 (6%)	165 (12%)	0.6 (0.2–2.2)
Other[c]	4 (8%)	149 (11%)	0.9 (0.3–2.9)

[a]Reference category

[b]Including 1 man treated with radiotherapy and hormone therapy among men with low PSA, and 125 men treated with radiotherapy and hormone therapy among men with elevated PSA

[c]All men with low PSA values had prostatectomy, 2 were also treated with hormone therapy, 2 others had also radiotherapy. All men with elevated PSA values had prostatectomy, 80 were also treated with hormone therapy, 32 others had also radiotherapy and 37 others underwent prostatectomy, radiotherapy and hormone therapy

**$p<0.01$

Table 3 presents the risk of prostate cancer-specific mortality. Figure 1 shows the 5-year cancer-specific survival curve, according to PSA level at diagnosis. Five-year survival was slightly higher in patients presenting with low PSA values: 86% (95%CI: 76–96%) vs. 78% (95%CI: 76–80%) (p=0.351) and the risk of prostate cancer-specific mortality associated with PSA values <4 ng/ml was slightly lower (HR: 0.6; 95%CI: 0.3–1.2).The prognosis was similar for patients with low or elevated PSA levels (HR: 1.1; 95%CI: 0.6–2.2 after adjusting for factors significantly related to prognosis in crude Cox models, i.e., age, stage, grade and treatment.

Discussion

This is one of the rare population-based studies that provides data on frequency and outcome of prostate cancer diagnosed with low PSA values in routine care. Prostate cancer with low PSA values represented less than 4% of all prostate cancers diagnosed in the population. The majority of these cancers were discovered fortuitously by pathological examination of the prostate after endoscopic resection or following symptoms. Compared with cancers diagnosed with high PSA levels, tumours with low PSA values were more often localised and well differentiated. However, nearly 35% of the tumours with low PSA values had aggressive characteristics or had already metastasised at diagnosis. Low PSA values were not associated with lowered risk of prostate cancer-specific mortality.

The main limitation of our study is the low number of patients, because prostate cancer with PSA values <4 ng/ml at diagnosis is unusual in routine care practice. In fact, most previous observational studies reported series of less than 60 patients [2, 5, 13, 19, 21–23, 27, 28]. Another limitation is that, despite having information on numerous patient and tumour characteristics, we cannot exclude bias linked to putative poorer assessment of grade or other prognostic factors among patients with low PSA levels. To take into account other putative confounders, we adjusted for sociodemographic characteristics such as social class, civil status, nationality and period of diagnosis, as they have been associated with PSA screening, stage at diagnosis, treatment and/or prognosis [29–33].

Our aim is not to question the efficacy of screening or optimal cut-off threshold PSA values, but to provide clinicians with non-biased information on the significance and prognosis of prostate cancer in patients diagnosed with "normal" PSA values.

For patients presenting with PSA levels <4.0 ng/ml, prostate cancer is usually investigated only among men presenting with symptoms or clinical indications, resulting in a prevalence of approximately 2% [9]. However, this prevalence is much higher if systematically investigated in routine care [2, 3, 5–8].

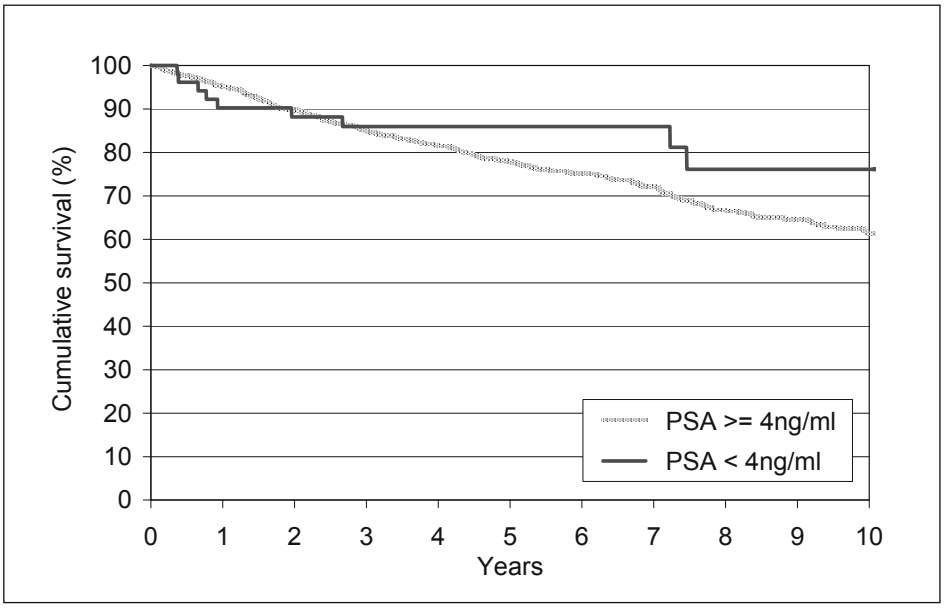
The main concern is the prognostic significance of this type of cancer. Even though few studies showed no differ-

Table 3 Risk of prostate cancer-specific mortality (hazard ratio) according to PSA level at diagnosis

PSA	Patients, *N*=1383	Deaths, *N*=368	Crude hazard ratio	Multiadjusted hazard ratio[a]
≥4 ng/ml	133	358	1[b]	1[b]
<4 ng/ml	53	10	0.6 (0.3–1.2)	1.1 (0.6–2.2)

[a]Adjusted for age, stage, differentiation and treatment regimens

[b]Reference category



Men at risk at the beginning of each year

Year	1	2	3	4	5	6	7	8	9	10
PSA <4 ng/ml	53	46	42	36	34	32	23	18	13	11
PSA ≥4 ng/ml	1330	1214	1094	981	895	704	525	391	250	165

The comparison between these two groups was not statistically significant (Log-rank test p=0.15).

Fig. 1 Prostate cancer-specific survival according to PSA level at diagnosis

ence in tumour characteristics among patients with low and elevated PSA levels [8, 14, 19], most studies reported that patients presenting with low PSA levels more often had well differentiated tumours, a Gleason score <7 or organ-confined disease [2, 12, 13, 16–18, 20–23]. Nevertheless, high-grade cancers are not uncommon in men with low PSA values [2–4, 6, 8, 11–13, 15, 17, 18, 21, 23]; low PSA values do not exclude aggressive tumour characteristics. We report that 35% of these tumours are poorly differentiated. When we consider moderate and high histological grade tumours together, this proportion increases to 58%.

The usefulness of PSA as a marker of disease activity and its correlation with survival remains controversial [34]. Several studies have evaluated if men with low PSA levels at diagnosis presented with similar prognosis as men with elevated PSA values [10–18, 35–37]. Some studies reported that men presenting with low PSA values had poorer outcome [15], some similar outcome [14, 18] and others reported non-significantly better outcome [11, 13] or significantly better outcome [12, 16, 17, 23, 28, 35–37]. However, results are difficult to compare because of differences in patient selection, range of PSA values and methods of analyses. Also, some studies considered only biological failure [11, 13, 14, 17, 18, 23, 28] or short-term overall survival [12] and not prostate cancer-specific mortality. Interesting results from a large population-based cohort study reported that patients presenting with PSA levels <4 ng/ml had the best 10-year disease-specific survival, but PSA values were not an independent prognostic factor in multiadjusted analysis [10]. However, this analysis considered all PSA values <10 ng/ml together and the authors gave no detailed characteristics of tumours with lower PSA values. We found no other studies evaluating prostate cancer-specific mortality between men with "normal" vs. elevated PSA at diagnosis in a non-selected population-based setting, adjusting for confounders and including treatment options.

Finally, some data suggested that certain high-grade cancers produce less PSA than low-grade cancers [38]. In our study, among the six patients presenting with metastatic disease in the low PSA group, all presented with poorly differentiated histological adenocarcinoma. Thus for patients presenting with low PSA values we can exclude neither prostate cancer nor metastatic disease.

Despite the fact that these cancers are generally localised and well differentiated tumours, a non-negligible proportion of these patients have poorly differentiated or metastatic disease. Low PSA level per se is not an indicator of good prognosis in terms of survival. Therefore it should not influence therapeutic decisions.

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Conflict of interest There is no conflict of interest.

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