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Baseline PSA measurements and subsequent prostate cancer risk in the Danish Diet, Cancer and Health cohort

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Abstract

Aim—Although prostate-specific antigen (PSA) screening reduces mortality from prostate cancer, substantial over-diagnosis and subsequent overtreatment are concerns. Early screening of men for PSA may serve to stratify the male population by risk of future clinical prostate cancer.

Methods and material—Case-control study nested within the Danish ‘Diet, Cancer and Health’ cohort of 27,179 men aged 50–64 at enrolment. PSA measured in serum collected at cohort entry in 1993–1997 was used to evaluate prostate cancer risk diagnosed up to 14 years after. We identified 911 prostate cancer cases in the Danish Cancer Registry through 31 December 2007 1:1 age-matched with cancer-free controls. Aggressive cancer was defined as T3 or Gleason score 7 or N1 or M1. Statistical analyses were based on conditional logistic regression with age as underlying time axis.

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Conflicts of interest statement:

Hans Lilja holds patents for assays for free PSA and intact PSA.

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Results—Total PSA and free-to-total PSA ratio at baseline were strongly associated with prostate cancer risk up to 14 years later. PSA was grouped in quintiles and free-to-total PSA ratio divided in three risk groups. The incidence rate ratio for prostate cancer was 150 (95% confidence interval, 72–310) among men with a total PSA in the highest quartile (>5.1 ng/ml) compared to the lowest (<0.80 ng/ml). The risk of aggressive cancer was highly elevated in men with a PSA level in the highest quintile. The results indicate that one-time measurement of PSA could be used in an individualized screening strategy, sparing a large proportion of men from further PSA-based screening.

Keywords

Prostate neoplasm; prostate-specific antigen; baseline; risk factor; nested case-control study

Introduction

Measurements of prostate-specific antigen (PSA) levels in blood are widely used to screen for prostate cancer. Most men with modestly elevated levels of PSA do not, however, have evidence of prostate cancer at biopsy and levels below the commonly used cut-off value for biopsy do not preclude malignancy¹. The incidence of prostate cancer increased steadily after the introduction of PSA screening in the late 1980s and early 1990s², followed by a concomitant decline in prostate cancer deaths attributed by some to the use of PSA in early detection³. PSA-screening has been shown to significantly reduce prostate cancer mortality by 21–44% in large randomized controlled screening trials^{4,5}. However, screening poses a risk of over-diagnosis with^{4,6–8} a significant proportion of PSA-detected tumours that would otherwise not give symptoms or lead to mortality during the man's lifetime^{9,10}.

A growing body of evidence indicates that measuring PSA early in life can predict later risk of prostate cancer^{11–17} and that it could be used in a risk-stratified approach¹⁸. However, there is a strong need for additional studies evaluating long-term prostate cancer risk in population-based cohorts of unscreened men who provided archived blood at middle age that can be used to measure PSA levels. In identifying men suitable for PSA screening, the risk of cancer with unquestionably significant features (e.g. evidence of metastasis or cause death) is more relevant than the overall risk of prostate cancer. As latent prostate cancer is prevalent among men of screening age^{19,20}, PSA screening programmes should focus on men at risk of aggressive cancer. We used measurements of total PSA and the ratio of free-to-total PSA among men aged 50–64 years to estimate risk of prostate cancer 3, 5, 8 and 14 years after entry into the Danish prospective 'Diet, Cancer, and Health' cohort. We also evaluated the association between level of PSA at baseline and aggressive cancer at time of diagnosis. Our aim was to identify men at high risk for aggressive prostate cancer, for whom early PSA-based screening at certain intervals would increase the chances of diagnosis within a window of curability.

Materials and methods

We conducted a nested case-control study within the Danish population-based prospective cohort 'Diet, Cancer and Health'. Between December 1993 and May 1997 80 996 men aged

50–64 years were invited to participate, and 27 179 men were enrolled, corresponding to 34%. The study has previously been reported in details²¹. At enrolment, all participants completed a food-frequency questionnaire and a general questionnaire including lifestyle and medical history, and anthropometric measures and biological materials, including blood samples, were collected. The study was approved by the regional ethical committees on human studies in Copenhagen and Aarhus (jr.nr.(KF)11–037/01) and by the Danish Data Protection Agency.

The Danish Cancer Registry has recorded incident cases of cancer on a nationwide basis since 1943 and has accurate, almost complete ascertainment of cancer cases²². In the Cancer Registry, we identified 911 cohort members with an incident primary diagnosis of prostate cancer through 31st December 2007.

Medical records were used to collect information on whether the diagnosis was based on urological symptoms, PSA level at diagnosis, clinical TNM stage and Gleason score at biopsy. The information pertained to the between diagnosing and first initiated treatment, including active surveillance or watchful waiting. TNM stage was missing for 232 cases at diagnosis. For these cases, we extracted information on clinical stage from the Cancer Registry, which holds information on TNM stage since 2004; for cases before 2004, extent of disease was categorized as ‘localized’, ‘regional’ or ‘distant’. We defined ‘aggressive prostate cancer’ as T3 or Gleason score 7 or N1 or M1, or ‘regional’/‘distant’ extent of disease. ‘Non-aggressive’ prostate cancer was defined as T2 or Gleason score 6, N0 or Nx, M0 or Mx, or ‘localized’ disease. The remaining cases were reviewed by one of the authors (SF) and classified as ‘non-aggressive’ or ‘unknown’ on basis of the available information.

At time of prostate cancer diagnosis, each case was matched 1:1 by age at enrolment (for most pairs ± 6 months or ± 1 year if this was not possible) with a male control who was alive and had no previously registered cancer diagnosis (except non-melanoma skin cancer) at that time.

At baseline, 30 ml of blood were collected; plasma, serum, lymphocytes and erythrocytes were isolated, and stored at -150°C until they left the biobank and thereafter kept at -80°C until analysis. Free and total PSA levels in serum were measured with the Architect PSA chemiluminescent microparticle immunoassay on the Architect *i2000*_{SR} system (Abbott Diagnostics, Abbot Park, Illinois, USA).

Statistical analysis

The association between PSA levels at baseline and incident prostate cancer diagnosis was analysed by conditional logistic regression analysis²³. Because of the risk set matching, the calculated odds ratios were unbiased estimates of the incidence rate ratios (IRRs) that would have emerged from a cohort study in the ‘Diet, Cancer, and Health’ cohort.

Age at baseline was categorized into two groups; above or below the median age at baseline: 50–58 years and 59–64 years. The total PSA level at baseline was split into quintiles for each age group and for all men to maintain power in all groups. The ratio of free-to-total

PSA at baseline was calculated from free PSA divided by total PSA. A ratio >0.20 was considered be associated with low risk, $0.15\text{--}0.20$ with intermediate risk and <0.15 with high risk. The statistical software SAS (release 9.2, SAS Institute Inc., Cary, NC, USA) was used. $p < 0.05$ was considered to be statistically significant.

Results

We identified 911 men with an incident diagnosis of prostate cancer. Five pairs were excluded because the control had a cancer diagnosis before enrolment, which due to processing delays, had not been registered in the Cancer Registry at the time of invitation, and 32 pairs were excluded because of missing information on total or free PSA at baseline caused by lack of blood samples or failed biological analysis, leaving 874 pairs for analysis.

The median time between baseline and diagnosis was 8.6 years (interquartile range (IQR), 2.2–12.0 years). Table 1 shows the baseline characteristics of the cases and controls. The median level of total PSA at baseline (3.70 ng/ml; IQR, 2.13–7.31 ng/ml) among cases was significantly higher ($p < 0.0001$) than that among controls (1.07 ng/ml; IQR, 0.63–1.82 ng/ml). Figure 1 presents the full distribution of total PSA at baseline for cases and controls. The median ratio of free-to-total PSA (0.15; IQR, 0.10–0.21) among cases was significantly lower ($p < 0.0001$) than that among controls (0.26; IQR, 0.19–0.34) (Table 1).

On basis of clinical characteristics, 60% of the cases were defined as aggressive (Table 2). The medical records showed that 14% of cases had no urological or cancer-related symptoms at diagnosis; however, PSA at baseline was similar in asymptomatic and symptomatic men (data not shown).

Table 3 shows IRRs for prostate cancer by total PSA 3, 5, 8 and 14 years after baseline. Among all men, a total PSA in the upper quintile were associated with a high risk for prostate cancer, although numbers in the reference groups were small. Table 4 presents prostate cancer risk according to ratio of free-to-total PSA for all patients and stratified by age. Significantly higher IRRs of prostate cancer were seen for men with a free-to-total PSA ratio <0.15 than for those with a ratio >0.20 , regardless of age at baseline and time between baseline and diagnosis.

After exclusion of non-aggressive prostate cancer-cases, IRRs for aggressive cancer remained substantially higher for men in the top quintiles of total PSA compared to bottom quintiles (Table 5). A lower ratio of free-to-total PSA was also strongly associated with increased risk of aggressive prostate cancer (Table 6).

Discussion

We found that both total PSA and the ratio of free-to-total PSA measured at baseline were strongly associated with prostate cancer risk up to 14 years following baseline. Both measures were also strongly associated with risk of aggressive prostate cancer.

The main strength of our study was that the male study subjects were enrolled in the cohort in 1993–1997 when there was only little focus on early detection of prostate cancer in

Denmark and thus limited opportunistic PSA testing. Therefore, it can be presumed that very few if any of the participants were tested for PSA before enrolment. Furthermore, our study had accurate and virtually complete follow-up due to the unique personal identification number assigned to all Danish citizens since 1968.

Participants in the 'Diet, Cancer and Health' study were enrolled at age 50–64 years. Before age 50, the risk of clinical prostate cancer is low²⁴ and this age group would thus appear more appropriate for estimating subsequent risk of prostate cancer. However, there is no consensus as when to start PSA-testing, but PSA testing may be valuable before the age of 50 in high risk individuals, although there is no rationale for testing before the age of 40¹². Our study indicated that PSA levels below the threshold for prostate cancer work-up (4 ng/ml in Denmark) also predict the subsequent risk of prostate cancer men over 58 years. A Swedish study reported strong associations between PSA measured at age 60 and death from prostate cancer even after more than 25 years of follow-up¹³. Measuring 'baseline' PSA in men age 60 or older would, however, risk missing early cases.

In Denmark, PSA testing is recommended only for men with symptoms or findings that make prostate cancer a diagnostic possibility and for men with two or more first- or second-degree relatives with this cancer²⁵. Nevertheless, increased non-systematic use of PSA during the past decade has led to a marked rise in the incidence of prostate cancer also in Denmark²⁶. A recent study showed that 35% of patients treated by radical prostatectomy in Denmark between 1997 and 2008 had been referred without prostate-related symptoms²⁷, and in a Swedish study 28% of prostate cancer cases diagnosed in 2005 were based on PSA testing during health examinations²⁸. An impact of opportunistic screening should therefore also be considered in our study. In our study population, 14% were asymptomatic at diagnosis, and although it is likely that this reflected a PSA based diagnosis, other reasons for biopsy also exist, such as an unrecorded abnormal digital rectal examination. Anyway, in our study, PSA based detection of prostate cancer among asymptomatic men was uncommon (*i.e.*, 14% or less) and at least 86% of our cases were diagnosed based on clinical symptoms. Conceivably, PSA based diagnoses of prostate cancer would likely result in an overestimated association between PSA and prostate cancer risk, since the decision to recommend a prostate biopsy and the likelihood of work-up for prostate cancer are correlated to the level of total PSA. Furthermore, the level of opportunistic PSA testing in our study does not necessarily reflect that in the background population, as the participants in the 'Diet, Cancer and Health' study are generally healthier and have a higher socioeconomic position than non-participants^{21,29}. The male study subjects might therefore be more aware of their health and better informed about health care services, such as the benefits and harms of PSA testing. Furthermore, we had no information as to the proportion of men who had undergone a PSA test, which did not lead to a prostate cancer diagnosis, and use of non-systematic PSA testing for early diagnosis was not accurately recorded in the medical records. We used the absence of urological symptoms at the time of diagnosis as a proxy for PSA testing; however, the number of cases diagnosed on the basis of PSA alone may have been underestimated.

Previous studies have demonstrated that total PSA in frozen serum remains stable, even after long storage at –20°C, whereas free PSA shows greater random variation³⁰. As our serum

samples were archived at temperatures far below -20°C , the time between baseline and analysis would probably not have affected the level of total PSA significantly. These assumptions are supported by the age-specific median levels of total PSA and the ratio of free-to-total PSA support, which are similar to previously reported data¹³. Although it is difficult to exclude that minor degradation of total and free PSA might have occurred, any misclassification of PSA levels would likely be non-differential.

We used a dichotomous classification of aggressive and non-aggressive prostate cancer. In other studies death due to prostate cancer was used as an indication of clinically significant prostate cancer. Because of the nested case-control design of our study with 1:1 matching at time of diagnosis, we were unable to use death as indicator of aggressive cancer. We used the characteristics of the disease at diagnosis (*i.e.*, clinical stage cT3 or higher, Gleason score 7 or higher at biopsy, or evidence of skeletal or lymph node metastasis) as indicators of aggressive cancer. After a maximum period of 14 years from baseline and a median of 8.6 years between baseline and diagnosis, 282 cases had died, and 195 of these from prostate cancer corresponding to almost 70%. Among cases with non-aggressive prostate cancer, only 13 died of prostate cancer, indicating that our definition of aggressive prostate cancer was strongly correlated with the subsequent risk of prostate cancer mortality. We found that 60% of cases had aggressive prostate cancer at the time of diagnosis. This stage distribution is compatible with a low level of opportunistic PSA screening in Denmark and further corroborated by the lower incidence and survival after prostate cancer compared to the neighbouring countries Norway and Sweden²⁴, in which PSA screening is more frequent.

Our study confirms the usefulness of a single PSA measurement at baseline to predict later risk of prostate cancer diagnosis. We show that men with a PSA level of 5 ng/ml or higher at baseline could be candidates for careful surveillance with repeat prostate cancer testing, whereas men with a PSA level of 1.5 ng/ml or lower may not benefit importantly from repeated testing. Although the results provide some indication of which men that would benefit from regularly screening, uncertainty still remains with regard to the distinction between aggressive and non-aggressive prostate cancer. Although the ratio of free-to-total PSA strongly predicts subsequent aggressive prostate cancer, a ratio >0.20 does preclude aggressive prostate cancer. A combination of total PSA level and PSA ratio might yield further information; however, in this study we did not have sufficient power to evaluate this. Further studies are warranted to improve identification of men at risk of aggressive prostate cancer.

Conclusion

Our study shows that PSA levels measured at baseline predict subsequent prostate cancer risk up to 14 years later. PSA measurements may therefore be useful in an individualized, risk-based screening strategy. Our findings do not allow definition of at what age to commence such pre-screening and with what screening intervals. These questions along with other potential initiatives towards individualized screening strategies need to be evaluated in randomized trials.

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Figure 1.
Distribution and density of total PSA at baseline among cases and controls

Table 1

Baseline characteristics of 874 matched cases and their controls in the Danish 'Diet, Cancer and Health' cohort.

	Cases		Controls	
	N (%)	Median (IQR)	N (%)	Median (IQR)
Age (years)		58 (54–61)		58 (54–61)
Total PSA (ng/ml)		3.70 (2.13–7.31)		1.07 (0.63–1.82)
Total PSA grouped (ng/ml)				
0.0–0.5	9 (1)		144 (16)	
0.5–1.0	45 (5)		266 (30)	
1.0–1.5	69 (8)		178 (20)	
>1.5	751 (86)		286 (33)	
Total PSA in quintiles (ng/ml)				
<0.8	35 (4)		299 (34)	
0.8–1.5	88 (10)		289 (33)	
1.5–2.7	168 (19)		173 (20)	
2.7–5.1	261 (30)		87 (10)	
>5.1	322 (36)		26 (3)	
Free PSA grouped (ng/ml)		0.55 (0.37–0.89)		0.27 (0.18–0.43)
0.0–0.2	53 (6)		272 (31)	
0.2–0.4	207 (24)		354 (41)	
0.4–0.6	225 (26)		143 (16)	
>0.6	389 (45)		105 (12)	
Free-to-total PSA ratio grouped		0.15 (0.10–0.21)		0.26 (0.19–0.34)
>0.20	263 (30)		629 (72)	
0.15–0.20	184 (21)		143 (16)	
<0.15	427 (49)		101 (12)	

Prostate specific antigen (PSA), free-to-total PSA ratio (free PSA/total PSA), quintiles are based on cases and controls together.

Table 2

Characteristics of 874 prostate cancer patients at diagnosis based on information from hospital records

Characteristic	Cases
	N (%)
Age (years)	
<60	91 (10)
60–70	588 (67)
>70	195 (22)
Total PSA (ng/ml)	
0–4	35 (4)
4–10	280 (32)
10–50	341 (39)
>50	163 (19)
Missing	55 (6)
Clinical stage	
T1	216 (25)
T2	210 (24)
T3	200 (23)
T4	22 (3)
Unknown/Missing	226 (26)
Positive lymph nodes	
N1	61 (7)
N0/missing/unknown	813 (93)
Metastasis	
M1	156 (18)
M0/missing/unknown	718 (82)
Gleason grade	
2–5	99 (11)
6	226 (26)
7	217 (25)
8–10	189 (22)
Missing	143 (16)
Cancer type	
Non-aggressive	309 (35)
Aggressive	521 (60)
Unknown	44 (5)
Method of detection	
PSA test	123 (14)

Characteristic	Cases
	N (%)
Symptoms	612 (70)
Missing/unknown	139 (16)

Prostate specific antigen (PSA)

Aggressive prostate cancer is defined as T3 or Gleason score ≥ 7 or N1 or M1, or “regional”/“distant” extent of disease as recorded in the Danish Cancer Registry.

Table 3

Risk of prostate cancer by PSA level in quintiles among cases and controls stratified by age at baseline

Age	Total PSA ng/ml	Time after baseline									
		3 years		5 years		8 years		14 years			
		N	Cases	IRR (95% CI)	Cases	IRR (95% CI)	Cases	IRR (95% CI)	Cases	IRR (95% CI)	Cases
All men	0.80	334	3	Reference	4	Reference	11	Reference	35	Reference	
	0.81–1.50	377	3	0.38 (0.04–3.73)	7	0.68 (0.15–3.14)	21	1.08 (0.43–2.70)	88	2.57 (1.56–4.22)	
	1.51–2.70	341	5	3.77 (0.37–38.)	11	3.01 (0.49–19)	41	5.36 (2.00–14)	168	8.85 (5.26–15)	
	2.71–5.10	348	9	8.98 (0.83–97)	38	35 (5.29–238)	104	33 (11–97)	261	34 (19–61)	
	>5.10	348	63	146 (9.38–2259)	125	218 (28–1691)	218	257 (71–934)	322	150 (72–310)	
58	0.70	197	3	Reference	3	Reference	7	Reference	23	Reference	
	0.71–1.30	201	2	-	4	-	10	0.39 (0.07–2.13)	42	1.78 (0.93–3.40)	
	1.31–2.10	178	1	1.50 (0.07–31)	4	1.36 (0.08–23)	15	2.30 (0.54–9.85)	87	5.89 (3.14–11)	
	2.11–4.00	196	1	1.69 (0.08–36)	18	13 (1.15–154)	57	60 (7.32–656)	152	24 (12–49)	
	>4.00	186	23	20 (1.32–333)	50	56 (4.57–689)	93	264 (23–2968)	172	74 (32–175)	
>58	1.00	154	1	Reference	2	Reference	6	Reference	17	Reference	
	1.01–1.90	155	0	-	1	0.89 (0.05–15)	8	1.38 (0.40–4.81)	30	1.95 (0.93–4.09)	
	1.91–3.20	161	5	-	13	20 (0.83–465)	30	4.74 (1.54–15)	85	7.21 (3.45–15)	
	3.21–6.90	163	8	-	18	12 (0.94–164)	54	14 (4.39–47)	117	21 (9.31–47)	
	>6.90	157	39	-	72	-	115	179 (33–977)	149	133 (44–403)	

Prostate specific antigen (PSA), confidence interval (CI)

Table 4
Risk of prostate cancer by free-to-total PSA ratio among cases and controls stratified by age at baseline

Age	PSA ratio	Time after baseline											
		3 years			5 years			8 years			14 years		
		Free/total	N	Cases	IRR (95% CI)	Cases	IRR (95% CI)	Cases	IRR (95% CI)	Cases	IRR (95% CI)	Cases	IRR (95% CI)
All men	>0.20	892	20	Reference	34	Reference	79	Reference	263	Reference	2.96 (2.19–4.01)	184	Reference
	0.15–0.20	327	11	2.08 (0.70–6.23)	25	2.52 (1.17–5.44)	74	4.34 (2.56–7.35)	184	20 (11–35)	10. (7.30–14)	427	2.96 (2.19–4.01)
	<0.15	528	52	17 (4.91–56)	126	25 (9.72–63)	242	20 (11–35)	427	10. (7.30–14)			
58	>0.20	515	7	Reference	14	Reference	40	Reference	162	Reference	2.79 (1.88–4.16)	104	Reference
	0.15–0.20	171	5	1.31 (0.24–7.06)	12	2.00 (0.66–6.03)	38	4.97 (2.28–11)	104	18 (7.60–41)	6.91 (4.64–10)	210	2.79 (1.88–4.16)
	<0.15	271	18	15 (1.88–113)	53	22 (5.21–92)	104	18 (7.60–41)	210	6.91 (4.64–10)			
>58	>0.20	377	13	Reference	20	Reference	39	Reference	101	Reference	3.32 (2.03–5.43)	80	Reference
	0.15–0.20	156	6	2.87 (0.66–12)	13	3.11 (1.05–9.19)	36	3.46 (1.67–7.18)	80	22 (9.84–49)	18 (10–33)	217	3.32 (2.03–5.43)
	<0.15	257	34	18 (3.87–87)	73	28 (7.84–99)	138	22 (9.84–49)	217	18 (10–33)			

Prostate specific antigen (PSA), confidence interval (CI)

Table 5
Risk of non-aggressive and aggressive prostate cancer among cases and controls by PSA level at diagnosis stratified by age

Age	Risk group at diagnosis					
	Total PSA ng/ml	Non-aggressive		Aggressive		
	Quintile	Cases	IRR (95% CI)	Cases	IRR (95% CI)	
All men	0.80	9	Reference	24	Reference	
	0.81–1.50	34	3.48 (1.40–8.68)	54	2.44 (1.30–4.58)	
	1.51–2.70	72	22 (7.46–63)	86	5.96 (3.14–11)	
	2.71–5.10	105	99 (30–332)	152	23 (11–46)	
	>5.10	89	355(80–1570)	205	100 (42–235)	
58	0.70	6	Reference	16	Reference	
	0.71–1.30	14	2.11 (0.67–7.29)	28	1.74 (0.78–3.86)	
	1.31–2.10	44	13 (3.76–47)	39	3.99 (1.82–8.75)	
	2.11–4.00	67	83 (18–386)	82	14 (6.29–32)	
	>4.00	54	169 (30–958)	110	50 (18–136)	
>58	1.00	5	Reference	11	Reference	
	1.01–1.90	8	1.66 (0.42–6.50)	21	2.22 (0.87–5.69)	
	1.91–3.20	35	8.69 (2.31–33)	46	6.89 (2.68–18)	
	3.21–6.90	44	22 (5.47–91)	71	24 (8.39–71)	
	>6.90	32	18 (17–1895)	97	110 (29–410)	

Prostate specific antigen (PSA), confidence intervals (CI). Aggressive prostate cancer is defined as T3 or Gleason score 7 or N1 or M1, or “regional”/“distant” extent of disease as recorded in the Danish Cancer Registry.

Table 6

Risk of non-aggressive and aggressive prostate cancer among cases and controls by free-to-total PSA ratio at diagnosis stratified by age

Age	Free-to-total PSA ratio	Risk group at diagnosis					
		Non-aggressive			Aggressive		
		N	IRR (95% CI)	N	IRR (95% CI)	N	IRR (95% CI)
All men	>0.20	113	Reference	133	Reference		
	0.15–0.20	79	3.11 (1.92–5.04)	96	3.02 (2.01–4.55)		
	<0.15	126	5.81 (3.59–9.41)	262	14.1 (8.98–22)		
58	>0.20	75	Reference	80	Reference		
	0.15–0.20	48	3.48 (1.81–6.70)	51	2.43 (1.48–4.09)		
	<0.15	68	4.06 (2.31–7.15)	130	11 (5.87–19)		
>58	>0.20	38	Reference	53	Reference		
	0.15–0.20	31	2.70 (1.25–5.87)	45	4.52 (2.23–9.19)		
	<0.15	58	13 (4.69–34)	132	23 (11–51)		

Prostate specific antigen (PSA), confidence intervals (CI). Aggressive prostate cancer is defined as T3 or Gleason score 7 or N1 or M1, or “regional”/“distant” extent of disease as recorded in the Danish Cancer Registry.