Acta Oncologica, 2013; 52: 1609–1614

informa
healthcare

ORIGINAL ARTICLE

PSA testing without clinical indication for prostate cancer in relation to socio-demographic and clinical characteristics in the Danish Diet, Cancer and Health Study

RANDI V. KARLSEN[1], SIGNE B. LARSEN[1], JANE CHRISTENSEN[1], KLAUS BRASSO[2], SØREN FRIIS[1,3], ANNE TJØNNELAND[1,3] & SUSANNE OKSBJERG DALTON[1]

[1]*Danish Cancer Society Research Center, Copenhagen, Denmark,* [2]*Copenhagen Prostate Cancer Center and Department of Urology, Rigshospitalet, Copenhagen, Denmark and* [3]*Department of Public Health, University of Copenhagen, Copenhagen, Denmark*

Abstract

Background. Social differences in prostate cancer (PC) incidence and mortality might be related to testing for prostate-specific antigen (PSA). Although routine PSA screening is not recommended in Denmark, testing without clinical indication increased during the past decade. We evaluated associations between socio-demographic or clinical characteristics and PSA testing without clinical indication. *Material and methods.* In the Danish Diet, Cancer and Health Cohort, we identified 1051 men with PC diagnosed in 1993–2008. Diagnostic and clinical characteristics were obtained from medical records, and socio-demographic information was retrieved from administrative registers. We used general logistic regression analysis to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between socio-demographic or clinical characteristics and PSA testing without clinical indication. Cox regression analysis was used to examine associations with mortality. *Results.* PSA testing without clinical indication was less likely among patients >67 years (OR 0.7; 0.5–1.0). Men who were, PSA tested without clinical indication, were more likely to have vocational training (OR 1.8; 1.1–2.9) or higher education (OR 1.5; 0.9–2.5) and less likely to have advanced disease (OR 0.6; 0.4–0.9). PSA testing without clinical indication more often preceded therapy with curative intent (OR 1.8; 1.1–2.9) and less often palliative treatment (OR 0.6; 0.3–1.0). Men who were PSA tested without clinical indication had non-significantly lower overall and PC-specific mortality [hazard ratios 0.8 (0.5–1.2) and 0.6 (0.3–1.1), respectively]. *Conclusions.* PSA testing without clinical indication was associated with higher educational level. PC detected by PSA testing with no clinical indication was more often localized and treated with curative intent.

Studies of the association between socio-economic position and prostate cancer (PC) have shown a higher incidence of PC among men with higher socio-economic position [1–3] but poorer survival among PC patients with lower socio-economic position [1,3]. These differences in PC incidence and survival by socio-economic status might be related to differences in diagnostic activities (including attending PSA screening), clinical stage at diagnosis, treatment modality and lifestyle factors [2–6]. Studies indicate that higher education, living with a partner and access to health care predict use of PSA testing [7,8]. The American Cancer Society has, based on recommendations from multidisciplinary expert groups including representatives from The American Urological Association, set guidelines for early detection of PC and recommended, screening with PSA and digital rectal examination from the early 1990s until recently [9,10]. A national health survey in 2000 showed that 24% of men aged 50–54 years and 46% of those aged 70–74 years had undergone PSA screening [8].

Currently, there is intense debate about PSA screening because of questions due to the unresolved balance between the benefits of screening and the harm of diagnosing and treating men with low-risk PC who are unlikely to benefit from treatment [11]. The Danish Urological Society recommends

Correspondence: R. V. Karlsen, Survivorship, Danish Cancer Society Research Center, Strandboulevarden 49, 2100 Copenhagen, Denmark. Tel: +45 35 257665. Fax: +45 35 257734. E-mail: randi@cancer.dk

(Received 29 May 2013; accepted 30 July 2013)

ISSN 0284-186X print/ISSN 1651-226X online © 2013 Informa Healthcare
DOI: 10.3109/0284186X.2013.831474

restricting PSA testing to men with abnormal rectal exploration, lower urinary tract symptoms or other symptoms that might be due to PC, and to men who have two or more first- or second-degree family members with PC [12,13]. However, a Danish study of patients who underwent radical prostatectomy between 1997 and 2008 found that after exclusion of men with a family history, 35% were asymptomatic at the time of the diagnosis, hereby indicating a high prevalence of PSA testing without clinical indication [14].

In the mid-1990s, therapy with curative intent for PC was rarely used and the Danish Diet, Cancer and Health (DCH) cohort, established between December 1993 and May 1997, provides a unique data source for evaluating the characteristics of men who have undergone PSA testing without a clinical indication, in a country with free, equal, tax-supported access to health care where PSA screening has never been recommended. We examined the associations between socio-demographic characteristics (age, education and marital status) and PSA testing without clinical indication among men with PC in the DCH cohort. We also evaluated the associations between PSA testing without clinical indication and clinical characteristics, including stage at time of diagnosis, tumor aggressiveness and primary treatment, as well as overall and PC-specific mortality.

Material and methods

The population-based DCH cohort was originally established to evaluate the role of diet in risk for cancer or other chronic lifestyle diseases. The study has been described in detail elsewhere [15]. In brief, between December 1993 and May 1997, all 160 725 people aged 50–64 years who lived in the greater Copenhagen or Aarhus area with no history of cancer were invited to participate. Of these, 57 053 agreed to participate, of whom 27 179 were men. All participants filled in a food frequency questionnaire and a general questionnaire on demographic characteristics, education, medical and reproductive history, and lifestyle factors. 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.

Ascertainment of prostate cancer patients

The Danish Cancer Registry has recorded incident cases of cancer on a nationwide basis since 1943 and has been shown to have accurate and almost complete ascertainment of cancer cases [16]. Cancer diagnoses are registered according to the International Classification of Diseases, version 10 (ICD-10), and the ICD for Oncology (ICD-O-1 and -3) for topography and morphology codes.

By linkage of the DCH to the Cancer Registry through 2008, we identified 1092 men registered with a primary diagnosis of PC (ICD-10: C61) and no previous history of cancer (except non-melanoma skin cancer). We reviewed the medical records of each patient to retrieve information on PSA level at diagnosis, TNM status, Gleason score and primary treatment. In addition, we obtained information on the primary indication for PSA testing, i.e. lower urinary tract symptoms or other clinical indications for PC, or PSA testing without clinical indication. The review covered the post-diagnostic period until first initiated treatment, including active surveillance. Information on clinical stage was not available in the medical records for 21% (n = 232) of the PC patients. For these patients, information on stage was obtained from the Cancer Registry. Registration of TNM stage was initiated in the Cancer Registry in 2004 (16); previously, clinical stage was categorized as 'localized', 'regional' or 'distant' extent of disease. We defined 'aggressive PC' as T stage $\geq$T3 or PSA $>$ 10 or Gleason score $\geq$ 7 or N1 or M1 or 'regional/distant' extent of disease. 'Non-aggressive PC' was defined as $\leq$T2 or Gleason score $\leq$ 6, N0 or Nx, M0 or Mx, or 'localized' disease. The remaining cases were reviewed by one of the authors (SF) and classified on the basis of the available information.

Socio-demographic information and mortality data

By linking the personal identification numbers of the PC patients to Statistics Denmark, we obtained information on highest educational level (basic or high school, vocational training and higher education) through 1995. Information on marital status (never married, divorced or widowed, married or having a registered partner) at the time of PC diagnosis was obtained from the Civil Registration Registry. Information on overall and PC-specific mortality through 2011 was obtained by linkage to the Danish Causes of Death Registry.

Statistical analysis

We determined the distribution of socio-demographic factors and clinical characteristics according to indication status for PSA testing, i.e. testing without clinical indication, testing with clinical indication, or unknown indication. The socio-demographic factors analyzed were age and marital status at the time of diagnosis and highest obtained education up to 1995, while the clinical characteristics were disease stage, cancer aggressiveness, primary treatment, and overall and PC-specific mortality.

For analyses of PC patients with known indication status for PSA testing and no missing socio-demographic data (n = 883), we used general logistic regression models to estimate crude and adjusted odds ratios (ORs) for associations between age at diagnosis, level of education, marital status, clinical characteristics and PSA testing without clinical indication. We tested for linearity of age at time of diagnosis, with age as a continuous variable. In the adjusted models, we included age at time of diagnosis, education and marital status.

We used Cox proportional hazards regression analysis to compute hazard ratios for the associations between PSA testing without clinical indication and overall and PC-specific mortality, with follow-up time as the underlying time axis. The analyses were stratified by age at diagnosis in five-year age groups to allow for different underlying mortality rates in each age strata and adjusted for disease stage.

The statistical analyses were performed with the SAS statistical software package release 9.1.

Results

Medical records were retrieved for 1051 (96%) of the 1092 patients with PC in the DCH cohort. Of these, 170 (16%) had had a preceding PSA test with no clinical indication, 714 (67%) had had a preceding PSA test because of symptoms, and for 167 (16 %), clinical indication for PSA testing was unknown (Table I). The age distribution was similar in the three categories. Patients who had undergone PSA testing without clinical indication had a slightly higher educational level, with slightly more men with vocational training (52.9% vs. 45.2%) and fewer with basic/high school only (15.3 vs. 22.8%). No differences in marital status were observed between the men tested without clinical indication and men who were PSA tested based on clinical indication (Table I).

The prevalence of localized PC was higher among patients who had undergone PSA testing without clinical indication than among those with a diagnosis

Table I. Socio-demographic and clinical characteristics by PSA testing status among 1051 men with prostate cancer in the Diet Cancer and Health Study.

Characteristics	PSA testing without clinical indication n = 170 (16%)	PSA testing with clinical indication n = 714 (68%)	Indication for PSA testing unknown n = 167 (16%)
Age at diagnosis (years)			
Mean	67.1	66.5	67.5
Range	53.6–77.6	52.0–79.6	55.5–78.2
Education [n (%)]			
Basic or high-school	26 (15)	163 (23)	44 (26)
Vocational training	90 (53)	323 (45)	72 (43)
Higher	54 (32)	228 (32)	51 (31)
Marital status [n (%)]			
Married/registered partner	138 (81)	573 (80)	132 (79)
Divorced/widowed	25 (15)	113 (16)	29 (17)
Never married	6 (4)	28 (4)	6 (4)
Missing data	1 (1)	0	0
Disease stage TNM [n (%)]			
Localized	116 (68)	367 (51)	79 (47)
Advanced	34 (20)	188 (26)	42 (25)
Missing data	20 (12)	159 (22)	46 (28)
Cancer type [n (%)]			
Non-aggressive	52 (31)	261 (37)	36 (22)
Aggressive	113 (66)	432 (61)	96 (58)
Missing data	5 (3)	21 (3)	35 (21)
Treatment [n (%)]			
Active surveillance	29 (17)	133 (19)	22 (13)
Curative treatment	108 (64)	314 (44)	61 (37)
Surgery	72 (42)	238 (33)	34 (20)
Radiation	37 (22)	77 (11)	25 (15)
Cryotherapy	0	2 (0)	1 (0)
Missing data	61 (36)	397 (56)	107 (64)
Palliative care	29 (17)	244 (34)	52 (31)
Unknown/missing data	26 (15)	23 (3)	32 (19)
Mortality [n (%)]			
Prostate cancer-specific	14 (8)	165 (23)	32 (19)
Other	16 (9)	86 (12)	24 (14)

based on clinical indication (68.2% vs. 51.4%) (Table I). Accordingly, treatment with curative intent was more often carried out among PC patients diagnosed by PSA testing without clinical indication (63.5 vs. 44.0%). In line with these findings, both overall and PC-specific mortality were substantially lower among men who had undergone PSA testing without clinical indication than among men PSA tested with clinical indication (9.4% vs. 12.0% and 8.2% vs. 23.1%, respectively) (Table I).

In a direct comparison of men PSA tested without clinical indication and men tested with clinical indication PC patients (n = 883), PSA testing without clinical indication was less likely among older (> 67 years) than younger (≤ 67 years) patients (OR, 0.7; 95% CI 0.5–1.0) (Table II). The adjusted ORs for vocational training and higher education compared with basic/high school education were 1.8 (95% CI 1.1–2.9) and 1.5 (95% CI 0.9–2.5), respectively, whereas the point estimates for marital status were close to unity.

We also found an inverse association between PSA testing without clinical indication and advanced disease (OR 0.6; 95% CI 0.4–0.9) (Table II). Furthermore, curative treatment was more likely offered among patients PSA tested without clinical indication (OR 1.8; 95% CI 1.1–2.9), and fewer of these patients received palliative treatment only (OR 0.6; 95% CI 0.3–1.0).

Overall and PC-specific mortality were inversely associated with PSA testing without clinical indication [hazard ratios of 0.5 (95% CI 0.4–0.8) and 0.4 (95% CI 0.2–0.7)]. After adjustment for potential confounders, however, the hazard ratios for both overall (0.8; 95% CI 0.5–1.2) and PC-specific (0.6; 95% CI 0.5–1.2) mortality were closer to unity.

Table II. Crude and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CI) for PSA testing without clinical indication among men with prostate cancer in the Danish Diet Cancer and Health Study.

Characteristic	Crude OR (95% CI)	Adjusted OR (95% CI)
Age at diagnosis (years) (n = 883)		
≤ 67	Reference	Reference
> 67	0.7 (0.5–1.0)	0.7(0.5–1.0)*
Education (n = 883)		
Basic or high school	Reference	Reference
Vocational training	1.7 (1.1–2.8)	1.8 (1.1–2.9)†
Higher	1.5 (0.9–2.5)	1.5 (0.9–2.5)†
Marital status (n = 883)		
Married/registered partner	Reference	Reference
Divorced/widowed	0.9 (0.6–1.5)	1.0 (0.4–2.6)‡
Never married	0.9 (0.4–2.2)	1.0 (0.4–2.5)‡
Disease stage TNM (n = 704)		
Localized	Reference	Reference
Advanced	0.6 (0.4–0.9)	0.6 (0.4–0.9)§
Cancer type (n = 883)		
Non-aggressive	Reference	Reference
Aggressive	1.3 (0.9–1.8)	1.2 (0.8–1.7)§
Treatment (n = 864)		
Active surveillance	Reference	Reference
Curative treatment	1.6 (1.0–2.5)	1.8 (1.1–2.9)§
Palliative care	0.5 (0.3–0.9)	0.6 (0.3–1.0)§

CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen.

*Adjusted for marital status and education; †Adjusted for age at diagnosis and marital status; ‡Adjusted for age at diagnosis and education; §Adjusted age at diagnosis, marital status and education.

Discussion

We found that PSA testing without clinical indication was associated with higher educational level. PC detected by PSA testing without clinical indication was more often localized and treated with curative intent, associated with non-significantly reduced overall and PC-specific mortality. To the best of our knowledge, no previous study has examined these associations in a country in which all residents have free, equal access to health care and in which no general PC screening program has been implemented. Thus, we had a unique opportunity to investigate the use of the PSA test without clinical indication within a well-defined, predominately PSA-naive population.

The proportion of men PSA tested without clinical indication in our study (16.2%) was lower than in other studies [7,8], primarily because of the conservative Danish policy regarding PSA testing. Furthermore, although we performed a detailed medical record review, we were unable to obtain complete information on PSA testing in the general practitioner setting. Thus, the prevalence of PSA testing without clinical indication in our study is probably underestimated. The proportion of men PSA tested without clinical indication, who underwent surgery with curative intent in our study, was nevertheless close to that reported in a previous Danish study (42% vs. 35%) [14].

It has been reported that the proportion of men who participate in PSA screening increases with age, with the highest participation rate among men aged 60–79 years [7,8]. Although more than 90% of the men PSA tested without clinical indication in our study were over 60 years, such testing was less likely among men over 67 years, indicating a somewhat different relationship between age and PSA testing without clinical indication in our study than in others.

Our finding, that men who underwent PSA testing without clinical indication had a higher educational level is compatible with other reports [4,5,17]. Marital status was, however, unrelated to

PSA testing without clinical indication, perhaps because of the composition of the DCH cohort, in which most men were married or cohabiting [15]. Our finding with regard to educational level probably reflects greater health literacy and health-oriented behavior [18]. This finding should be interpreted in the context of the increased proportion of PSA tests that are performed in general practice in Denmark, which increased from 39% to 66% out of the total PSA tests performed between 1996 and 2008 [19]. A substantial part of these tests were consecutive among men with previously normal tests, clearly indicating that PSA testing without clinical indication is carried out to some extent in general practice, despite the recommendations against [19]. It is unknown whether the increase in PSA testing without clinical indication is due to recommendations by general practitioners or to more patient requests.

We found that localized PC was more prevalent among men who underwent PSA testing without clinical indication and also that PC detected by such testing was more often managed by curative intended therapy and these findings are consistent with other studies [4,5]. Decisions about treatment are also influenced by information on treatment options, physicians' recommendations and patients' preferences, which may be influenced by educational level and patients' perceptions of the risks and benefits of treatment options [20,21].

Randomized trials indicate that PSA screening reduces mortality from PC, but the results are equivocal [22,23]. The mortality reduction associated with PSA screening is modest, and screening has been associated with substantial overdiagnosis, which may lead to unnecessary treatment [9,24]. Observational studies indicate that the social inequality in survival may be related to a difference in the use of PSA testing among men with high versus low socioeconomic status. In our study, higher educational level was associated with more PSA testing without clinical indication and modestly reduced statistically non-significant risks for overall and PC-specific mortality which might be attributable to lead-time bias for which we could not adjust. Estimates from the European Randomized Study on Prostate Cancer Screening [25] indicate that the lead-time may be ≥ 8 years. PSA testing without clinical indication per se may therefore not reduce PC-specific mortality but instead be an indicator of greater use of the healthcare system, mediated by a higher educational level and other socio-demographic factors. The tendency to lower clinical stages and better survival found in men having PSA testing without clinical indication might reflect lead-time bias. On the other hand PSA testing without clinical indication was associated with aggressiveness of tumor. Stage is based on TNM, whereas aggressiveness also includes Gleason score and PSA level at diagnosis. Thus it seems like PSA testing without clinical indication lead to diagnosis of more early stage tumors but also to diagnosis of more aggressive tumors.

The strengths of this study include the use of a population-based cohort of men included in a time-period when Denmark was a primarily PSA-naive country, the continuously updated and complete nationwide registries, and the detailed medical record review. Using these comprehensive data sources, we obtained detailed information on diagnosis and treatment, education and marital status as well as cause of death.

Our study had a number of limitations. The categorization according to PSA testing status might have been subject to misclassification, as the medical records did not provide complete information on diagnostic activities in the primary healthcare sector and we were unable to determine screening status on a substantial group of 167 men. This may have led to an underestimation of the proportion of PC cases detected by PSA testing without clinical indication. The risk stratification of the cancer cases used in the present study reflects clinical practice in Denmark and the information on clinical stage and tumor characteristics were collected from different sources, as cases where no information on TNM was available from medical records were categorized based on the Danish Cancer Registry. This registry generally has a high degree of completeness in regard to incident cancer cases, but no studies have assessed the correlation between clinical information and register data on prostate cancer stage. Any misclassification must be considered non-differential and unlikely to influence the results. Also, we did not control for family history of PC or for lifestyle or environmental factors that might increase awareness of PC and of the PSA test. Further, although men who were invited to participate in the DCH study were a random sample of the Danish population, the participants constituted only one third of the invited population and probably differ from the general population [15,26] in terms of health consciousness and use of the healthcare system. This might have resulted in a higher proportion of men being PSA tested without clinical indication compared to the general population. However, we have no reason to believe that the positive association between education and PSA testing without clinical indication found in this study, would not be present in the general population, although the association might be weaker. Thus, our results should be interpreted cautiously with regard to the relation between socioeconomic level and use of PSA testing without clinical indication in the general population.

Although PSA screening is not recommended in Denmark, our findings indicate that there is a considerable PSA testing without clinical indication, which is related to socio-economic parameters, notably education. It remains unclear whether the decision to perform PSA testing without indication is initiated by patients or by general practitioners, and further studies are warranted to clarify the use of PSA testing without clinical indication in Denmark.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

This study was funded by the Danish Cancer Society and the collection of medical charts was funded by The Danish Council for Independent Research – Medical Science [grant number 271-07-0609] and The Health Insurence Foundation [grant number 2006B095]. We thank Katja Boll for technical support.

References

[1] Dutta RS, Philip J, Javle P. Trends in prostate cancer incidence and survival in various socioeconomic classes: A population-based study. Int J Urol 2006;13:1364.

[2] Lund Nilsen TI, Johnsen R, Vatten LJ. Socio-economic and lifestyle factors associated with the risk of prostate cancer. Br J Cancer 2000;82:1358–63.

[3] Marsa K, Johnsen NF, Bidstrup PE, Johannesen-Henry CT, Friis S. Social inequality and incidence of and survival from male genital cancer in a population-based study in Denmark, 1994–2003. Eur J Cancer 2008;44:2018–29.

[4] Rapiti E, Fioretta G, Schaffar R, Neyroud-Caspar I, Verkooijen HM, Schmidlin F, et al. Impact of socioeconomic status on prostate cancer diagnosis, treatment, and prognosis. Cancer 2009;115:5556–65.

[5] Hoffman RM, Stone SN, Espey D, Potosky AL. Differences between men with screening-detected versus clinically diagnosed prostate cancers in the USA. BMC Cancer 2005; 5:27.

[6] Jonsson H, Holmstrom B, Duffy SW, Stattin P. Uptake of prostate-specific antigen testing for early prostate cancer detection in Sweden. Int J Cancer 2011;129:1881–8.

[7] Drazer MW, Huo D, Schonberg MA, Razmaria A, Eggener SE. Population-based patterns and predictors of prostate-specific antigen screening among older men in the United States. J Clin Oncol 2011;29:1736–43.

[8] Ross LE, Coates RJ, Breen N, Uhler RJ, Potosky AL, Blackman D. Prostate-specific antigen test use reported in the 2000 National Health Interview Survey. Prev Med 2004;38:732–44.

[9] Chou R, Croswell JM, Dana T, Bougatsos C, Blazina I, Fu R, et al. Screening for prostate cancer: A review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2011;155:762–71.

[10] Mettlin C, Jones G, Averette H, Gusberg SB, Murphy GP. Defining and updating the American Cancer Society guidelines for the cancer-related checkup: Prostate and endometrial cancers. CA Cancer J Clin 1993;43:42–6.

[11] Lin K, Lipsitz R, Miller T, Janakiraman S. Benefits and harms of prostate-specific antigen screening for prostate cancer: An evidence update for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149:192–9.

[12] Brasso K, Friis S, Kjaer SK, Jorgensen T, Iversen P. Prostate cancer in Denmark: A 50-year population-based study. Urology 1998;51:590–4

[13] The Danish Urological Society. DACROPA. Available from: http://ducg dk/prostata/retningslinjer/2011. [cited 5 May 2013].

[14] Borre M. Screening by lower urinary tract symptoms vs asymptomatic prostate-specific antigen levels leading to radical prostatectomy in Danish men: Tumour characteristics and treatment outcome. Br J Urol Int 2009; 104:205–8.

[15] Tjonneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, et al. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: A population-based prospective cohort study of 57,053 men and women in Denmark. Scand J Public Health 2007;35:432–41.

[16] Gjerstorff ML. The Danish Cancer Registry. Scand J Public Health 2011;39:42–5.

[17] Finney Rutten LJ, Meissner HI, Breen N, Vernon SW, Rimer BK. Factors associated with men's use of prostate-specific antigen screening: Evidence from Health Information National Trends Survey. Prev Med 2005;40:461–8.

[18] Goldman DP, Smith JP. Can patient self-management help explain the SES health gradient? Proc Natl Acad Sci U S A 2002;99:10929–34.

[19] Mukai TO, Bro F, Pedersen KV, Vedsted P. [Use of prostate-specific antigen testing]. Ugeskr Laeger 2010;172:696–700.

[20] Schymura MJ, Kahn AR, German RR, Hsieh MC, Cress RD, Finch JL, et al. Factors associated with initial treatment and survival for clinically localized prostate cancer: Results from the CDC-NPCR Patterns of Care Study (PoC1). BMC Cancer 2010;10:152.

[21] Kane CJ, Lubeck DP, Knight SJ, Spitalny M, Downs TM, Grossfeld GD, et al. Impact of patient educational level on treatment for patients with prostate cancer: Data from CaPSURE. Urology 2003;62:1035–9.

[22] Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360: 1310–9.

[23] Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010;11:725–32.

[24] Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012;366:981–90.

[25] Finne P, Fallah M, Hakama M, Ciatto S, Hugosson J, de KH, et al. Lead-time in the European randomised study of screening for prostate cancer. Eur J Cancer 2010;46: 3102–8.

[26] Larsen SB, Dalton SO, Schuz J, Christensen J, Overvad K, Tjonneland A, et al. Mortality among participants and non-participants in a prospective cohort study. Eur J Epidemiol 2012;27:837–45.