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Men (Aged 40–49 Years) With a Single Baseline Prostate-specific Antigen Below 1.0 ng/mL Have a Very Low Long-term Risk of Prostate Cancer: Results From a Prospectively Screened Population Cohort

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Abstract

OBJECTIVE—To study the use of a baseline prostate-specific antigen (PSA) and digital rectal examination in men (aged 40–49 years) in predicting long-term prostate cancer risk in a prospectively followed, representative population cohort.

PATIENTS AND METHODS—Since 1990, a random sample of men in Olmsted County (aged 40–49 years) has been followed up prospectively ($n = 268$), with biennial visits, including a urologic questionnaire, PSA screening, and physical examination. The ensuing risk of prostate cancer (CaP) was compared using survival analyses.

RESULTS—Median follow-up was 16.3 years (interquartile range 14.0–17.3, max 19.1). For men with a baseline PSA <1.0 ng/mL ($n = 195$), the risk of subsequent Gleason 6 CaP diagnosis by 55 years was 0.6% (95% confidence interval [CI] 0%–1.7%) and 15.7% (95% CI 6.5%–24.9%) for men with a baseline PSA ≥ 1.0 ng/mL. No man with a low baseline PSA developed an intermediate or high risk CaP, whereas 2.6% of men with a higher baseline PSA did (95% CI 0.58%–4.6%).

CONCLUSION—Men (aged 40–49 years) can be stratified with a baseline PSA. If it is below 1.0 ng/mL, there is very little risk for developing a lethal CaP, and as many as 75% of men might be able to avoid additional PSA screening until 55 years. Conversely, men aged 40–49 years with a baseline PSA level >1.0 ng/mL had a significant risk of CaP diagnosis and should be monitored more closely.

The use of prostate-specific antigen (PSA) screening for the early detection of prostate cancer (CaP) is currently an object of intense debate. Recommendations regarding PSA screening from professional societies are quite disparate and range from discussing screening with all asymptomatic men beginning at 40 years,¹ to having a discussion

regarding the benefits and harms of screening beginning at 50^{2,3} or 55 years⁴ to recommending against PSA screening altogether.⁵ The arguments revolve around the fact that although PSA screening has demonstrated a 20%–60% reduction cancer-specific death in some studies,^{6,7} others have observed no reduction.⁸ Furthermore, the absolute reduction in death is close to 1 person for 1000 men screened, whereas the number of men who would experience medical harms from PSA screening is 7 per 1000 men.⁴ Historically, the discriminating ability of PSA was superb with the area under the curve (AUC) of 0.91 in some retrospective studies.⁹ However, when PSA screening has been applied prospectively, on an annual basis, in a population, it has lost some of its discriminating ability, and over-diagnosis has become a problem. Finally, although the screening studies were not powered to detect an overall survival difference, the critics of PSA screening point out that it does not save lives when all causes of death are considered.^{6,10}

Several retrospective studies have reported that men with a higher baseline PSA in their 40s were at a significantly higher risk of subsequent development of prostate cancer 20–30 years later.^{11–15} This has led to the recommendation that perhaps routine screening should commence at 40 years to establish baseline risk of subsequent cancer. However, these studies might be biased by unequal follow-up,¹² not using representative populations,^{12,14} and relying on banked serum.^{11,13,14,16} Furthermore, these studies do not provide details on biopsy rates, negative biopsy rates, or what types of cancers were diagnosed. But, the most notable flaw of these retrospective studies in determining a prospective screening policy is that the patient and his health care provider in these studies were not able to act on the results of the baseline PSA or digital rectal examination (DRE).^{11,13,15}

Theoretically, if men could be categorized into low- or high-risk cohorts by a baseline PSA in men in their 40–50s (+/- the use of other emerging tests), this could lead to an overall reduction in PSA screening (and its associated harms) among a large portion of men at very low risk for development of a lethal cancer, whereas maximizing the benefit of screening in men at higher risk for prostate cancer development, who in turn stand to gain the most from radical therapy.

METHODS

Study Cohort and Follow-up

The study population consisted of a random sample ($n = 268$) from a larger population ($n = 1052$) of men, aged 40–49 years, living in Olmsted County, MN enrolled in a prospective cohort study entitled “Natural History of Prostatism: The Olmsted County Study” (DK058859). This cohort has been described previously.¹⁷ Beginning in 1990, 3874 men living in Olmsted County between the ages of 40 and 79 years were invited to participate; 2115 (55%) of eligible patients enrolled at baseline and completed biennial questionnaires about overall health status and urinary symptoms. A random subsample of these men ($n = 537$) was then selected as a “clinic cohort” with 476 (87%) participating in a biennial physical examination, including a DRE, PSA screening, and a transrectal ultrasound of the prostate. Men in the first few years of the study who died or were lost to follow-up were replaced during rounds 2 and 3 (in 1992 and 1994), resulting in a total of 2447 study participants and 634 clinic cohort participants (Supplementary Fig. 1). The study population

was then maintained as a closed cohort and followed up biennially. Institutional review was obtained from Mayo Clinic and Olmsted Medical Center.

For this analysis, men were excluded from the clinic cohort (3%) if they had a previous biopsy ($n = 13$) or a diagnosis of prostate cancer at their baseline visit ($n = 7$). Of the remaining 614 men, 268 were between the ages of 40 and 49 years at baseline and comprise the cohort for this analysis. Of note, none of the men between the ages of 40 and 49 had a previous biopsy or cancer diagnosis. The community medical records of all the men in the study were abstracted to obtain information on prostate cancer diagnosis (from biopsy specimens), prostate biopsy, death, and cause of death. Cause of death was also obtained from the death certificate and/or review of the medical record. Loss to follow-up was relatively low with 95% and 65% of study participants completing at least 10 and 15 years of follow-up respectively and did not differ by baseline serum PSA level (Supplementary Table 1).

If a PSA above the age-specific norm was identified during the course of the study (>2.5 for 40–49, >3.5 for 50–59, >4.5 for 60–69, and 6.5 for 70 years or older),¹⁷ a letter was sent to the patient notifying them of an abnormal PSA and suggested they seek medical attention. Furthermore, if an abnormality in texture, such as a nodule and so forth, was noted on DRE, the patient was likewise notified and advised to seek medical attention.

Initially, men were stratified according baseline PSA quartile (Figs. 1 and 2), but men in quartiles 1–3 had similar outcomes and were subsequently collapsed into 1 group. For subsequent analyses, men were categorized by baseline PSA level, dichotomizing at the 75th percentile (1.0 ng/mL), similar to a cut-point identified in a recent Swedish cohort.¹³ Differences between men with baseline PSA levels ≤ 1.0 ng/mL were analyzed by chi-square, Fisher's Exact test, or Wilcoxon Log rank as appropriate. Risk of subsequent biopsy or cancer diagnosis was calculated using Cox proportional hazard models that are presented as hazard ratios (HR), along with 95% confidence intervals (CI). Kaplan-Meier survival curves were generated, and the difference between the curves was analyzed using the log rank test. All analyses were performed using JMP 9.0.1 (SAS Institute, Cary, NC). All tests of statistical significance were 2-sided with an alpha of 0.05. Adjusted Cox-proportional hazard models were only generated when a sufficient number of events were observed; however, the cohorts were comparable at baseline (Supplementary Table 1).

RESULTS

Men with baseline PSA levels <1 ng/mL did not differ in demographic or clinical characteristics compared with men with baseline PSA ≤ 1.0 ng/mL (Supplementary Table 1). However, men with a higher baseline PSA were more likely to surpass an age-specific PSA level, receive a biopsy, and be diagnosed with prostate cancer (Tables 1 and 2). Most cancers diagnosed in this population were low risk (Gleason score <7 ; $n = 16$, 89%). There were only 2 intermediate risk cancers (and no high risk CaP) diagnosed in the entire cohort (Gleason score = 7, PSA <10 in both). These cancers were diagnosed at 11 and 17 years of follow-up (age at diagnosis was 54 and 66 years, and both men had a PSA ≤ 1.0 ng/mL at baseline). Of those with a baseline PSA <1.0 ng/mL, only 6 men (3.1%) were subsequently

diagnosed with cancer; the age range at diagnosis was 53.2–66.2 years. The difference in risk of cancer diagnosis at 16 years was 12.7% (95% CI 4.7–23.4) between those with a PSA 1.0 ng/mL vs those with a PSA <1.0 ng/mL.

The number of negative initial biopsies is reported in Table 1. Most men biopsied (80.5%), regardless of baseline PSA, were found not to have cancer at their initial biopsy. Men with a baseline PSA <1.0 ng/mL were slightly more likely to have a benign biopsy (86% vs 74%), although this difference was not statistically significant (HR = 1.15, 95% CI 0.9–1.5).

The receiver operator characteristic curve for prostate cancer diagnosis based on a single baseline PSA obtained in men aged 40–49 years is presented in Supplementary Figure 2. This demonstrates that a PSA above the median (0.7 ng/mL) as previously reported^{11,12} was not as discriminatory as a PSA above the 75th percentile (1.0 ng/mL). Although men above the PSA median were at higher risk for cancer, most of this risk is derived from the top PSA quartile (Table 2). Men with a baseline PSA 1.0 ng/mL were 5 times as likely to be diagnosed with cancer in the ensuing 15–20 years (HR = 5.1, 95% CI 2.0–13.0) compared with those with a PSA <1.0 ng/mL. The sensitivity and specificity for subsequent CaP diagnosis were 67% and 74% respectively, for baseline PSA cutoff of 1.0. The AUC for a single baseline PSA was 0.73 ($P = .0005$). The limited number of intermediate to high-risk cancers precludes stable estimates; however, we note that a PSA of 1.1 ng/mL provided the best discrimination for these higher risk cancers with an AUC of 0.85, comparable with previous reports.^{18,19} None of the 203 patients in this cohort with a baseline PSA <1.1 ng/mL developed an intermediate to high-risk cancer during the ensuing follow-up (median 16.2 years, interquartile range 10–17.3).

An abnormal baseline DRE was not associated with increased risk of cancer diagnosis during follow-up (HR = 0.48, 95% CI 0.08–1.7). Men with an abnormal baseline DRE were more likely to get a biopsy during follow-up; however, this result was not significant (HR 1.9, 95% CI 0.92–3.5). Baseline DRE was also not predictive of subsequent cancer diagnosis. In fact, of the 27 men with an abnormal baseline examination, only 10 subsequently underwent a biopsy, and only 1 of these 10 was found to have cancer anytime during follow-up, for a positive predictive value of 3.7%.

COMMENT

PSA screening for the early detection of prostate cancer has a confusing past and an unclear future. This has led clinicians and researchers alike to fall on either side of the argument over its usefulness in saving lives and preventing harm.^{3,5,20} The heart of the arguments both for and against PSA screening can be distilled to a few key points: (1) radical treatment of clinically detected prostate cancer improves all cause mortality.²¹ (2) It is unclear whether radical treatment of screen-detected prostate cancer improves all cause mortality,²² but it appears to improve cancer-specific mortality.⁶ (3) Patients whose cancers have grown outside of the prostate at surgery are more likely to die from prostate cancer than those who have localized cancer.²¹ (4) PSA screening, as used in the past (annual or semiannual screening with a biopsy trigger at a PSA of 4.0 ng/mL or lower, or for a DRE finding or PSA velocity), led to the diagnosis of many men with low-risk localized cancer; however,

these men were extremely unlikely to derive any survival benefit from treatment.^{18,22} (5) PSA was, is, and could continue to be a valuable marker in identifying men at risk for death from prostate cancer if used differently.²³

Our data suggest that a baseline PSA level in men in their 40s might be able to help risk stratify men. Men with a PSA below 1.0 ng/mL did not develop an intermediate or high-risk cancer during the ensuing 15–20 years and were at an extremely low risk to develop cancer by 55 years (Fig. 2C). This risk stratification can be pivotal in tipping the balance of the benefits and harms of PSA testing in a positive direction by limiting screening (and subsequent diagnosis of indolent cancers) in men at very low risk of developing a lethal cancer and maintaining appropriate vigilance in men at higher risk.

It is recognized that radical prostatectomy vs watchful waiting in men in which the large majority of prostate cancer was clinically detected, demonstrated a significant survival benefit with a reduction in prostate cancer-specific and all cause mortality at 12 years (0.62, 95% CI 0.44–0.87 and 0.75, 0.61–0.92, respectively). The number needed to treat (NNT) to prevent once prostate cancer death was 7.²¹ Men with cancer who had the best survival were those whose tumors were localized to the prostate at surgery. The men whose tumors grew out of the prostate before prostatectomy were nearly 7 times more likely to die from their cancer than men with organ-confined disease (HR = 6.9; 95% CI 2.6–18.4), suggesting that theoretically men would benefit from earlier detection and provided a basis for early detection of prostate cancer.

However, screen-detected CaP and clinically detected CaP appear to be very different, with screen-detected CaP being on average a less aggressive disease (and patients with screen-detected cancer stand to benefit less from treatment), which explains why the NNT in the European randomized screening study was higher (NNT = 37) and they did not find any reduction in death from any cause, HR = 0.99 (0.97–1.0).⁶ Furthermore, the PIVOT trial, found no significant reduction in prostate cancer death or death from any cause in older men (median age 71 years) with screen-detected cancers treated by radical prostatectomy (HR = 0.63, 95% CI 0.36–1.09 and 0.88, 95% CI 0.71–1.08).²² What clearly could reconcile the discrepancy between the lack of survival advantage observed in screen-detected cancers and the advantage observed in clinically detected cancers is the number of men with low-risk cancer. If the lowest risk men forego subsequent annual PSA testing according to baseline PSA, we could potentially maximize the benefit and minimize the harm of PSA screening.

Our data suggest that annual screening in men in their 40s might not be necessary even in the highest risk patients. In our cohort, men received a PSA test every 2 years. The PLCO study suggests that annual PSA screening offers no survival advantage over routine care, which often meant periodic PSA screening in >50% of the controls. Annual PSA screening did, however, result in a 22% increase in CaP diagnoses in that study (n = 478; RR = 1.22; 95% CI 1.16–1.29), most of which were Gleason 6 or lower cancers (n = 476).²⁴ Our data suggest that annual screening (as suggested by the NCCN guidelines)²⁵ or even biennial screening (as in our study) might still be too frequent, because 75% of the men who went on to have CaP diagnosed did not do so for at least 8 years. Furthermore, with the increasing awareness of the harms of biopsy (sepsis, drug resistant bacteria, pain, hematuria, and so

forth), a high proportion of negative biopsies should be avoided. In this cohort, 80% of initial biopsies were negative, and of those that were positive, the vast majority was low-risk cancers (89%).

Baseline DRE was not associated with subsequent prostate cancer diagnosis. Almost 10% of DREs were abnormal by nodularity ($n = 10$) or symmetry ($n = 17$), and although it did not help identify any prostate cancers, it increased the risk of biopsy by almost 2-fold. Given the low pretest probability of prostate cancer in US men in their 40s (0.0006%)²⁶ and the poor positive predictive value of an abnormal examination with 15 years of follow-up, it seems reasonable to forgo DRE as part of an early prostate cancer detection protocol of asymptomatic men in this age group.

Although our numbers are small, taken in the setting of existing literature, our data suggest that men could be effectively risk stratified with a baseline PSA in their 40s, potentially preserving the benefits of PSA screening and minimizing the harm. The AUC for the baseline PSA correctly identifying subsequent prostate cancer was 0.73 (Supplementary Fig. 2), which is comparable with previous studies.¹⁵ If the baseline PSA is below 1.0 ng/mL, it appears that men in their 40s might safely forego additional screening until at least the age of 55 or 60 years with a minimal risk of missing a lethal cancer that would be prevented by annual screening. If a repeat PSA is obtained at 55 years and it continues to be low (<1.0 ng/mL), data from the European screening trial suggest that these men might never benefit from additional screening.¹⁹ Conversely, it appears that men with a baseline PSA ≥ 1.0 ng/mL in their 40s could have a repeat PSA in 6–8 weeks to determine if the elevation was transient; if it continues to be over 1.0 ng/mL, these men should be watched more closely, every 2–4 years. This algorithm is similar to one recently proposed in an editorial²⁷ and would likely reduce the number of low-risk prostate cancers detected with minimal risk of missing potentially lethal cancers that annual screening would prevent.

Our study is limited by size and events, making some of the estimates unstable and the confidence intervals wide. We also acknowledge that this is technically not a PSA-screening study, but a subanalysis of a larger study of prostatism and aging. We note that transrectal ultrasound is not the part of any prostate cancer screening protocol (nor should it be); however, all referral letters for medical attention were based on an elevated PSA level or an abnormal DRE. Finally, Olmsted County is a relatively homogeneous population, and our results might not be applicable to other populations. We note, however, that others have demonstrated that PSAs in both young white and black men similarly predict subsequent CaP¹⁴; therefore, our results should be generalizable and can serve as a guide until similar studies are carried out among more diverse populations. Finally, we were unable to comment on the risk of prostate cancer–specific mortality because there were no prostate-specific deaths in this cohort. Despite these limitations, we believe this to be the only PSA-screened, prospectively followed up, population-based cohort of men in their 40s. Although we have nearly 20 years of follow-up, this still might not be enough to determine the lifetime risk of CaP or risk of death from CaP. Nevertheless, the lessons we can learn from these data can significantly inform the current PSA debate.

CONCLUSION

Men with a baseline PSA below 1.0 ng/mL in their 40s are at a very low risk for subsequent CaP diagnosis. This suggests that potentially 75% of men in their 40s could safely avoid PSA screening until at least 55 years with minimal risk of developing a lethal cancer. DRE in these setting does not appear to help detect cancer, rather it might increase the risk of a prostate biopsy. Conversely, men aged 40–49 years with a baseline PSA at or above 1.0 ng/mL had a significant long-term risk of prostate cancer and should be monitored more closely.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. National Comprehensive Cancer Network. [Accessed March 27, 2013.] NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer Early Detection, version 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf
2. Brawley OW, Ankerst DP, Thompson IM. Screening for prostate cancer. *CA Cancer J Clin.* 2009; 59:264–273. [PubMed: 19564245]
3. Brawley OW, Gansler T. Introducing the 2010 American Cancer Society prostate cancer screening guideline. *CA Cancer J Clin.* 2010; 60:68–69. [PubMed: 20200111]
4. Carter, HB.; Albertsen, P.; Barry, MJ., et al. American Urological Association. [Accessed May 31, 2013.] Early detection of prostate Cancer: AUA guideline. Available at: <http://www.auanet.org/common/pdf/education/clinical-guidance/Prostate-Cancer-Detection.pdf>
5. Chou R. Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2011
6. Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med.* 2012; 366:981–990. [PubMed: 22417251]
7. Hanley JA. Measuring mortality reductions in cancer screening trials. *Epidemiol Rev.* 2011; 33:36–45. [PubMed: 21624962]
8. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst.* 2012; 104:125–132. [PubMed: 22228146]
9. Whittemore AS, Lele C, Friedman GD, Stamey T, Vogelmann JH, Orentreich N. Prostate-specific antigen as predictor of prostate cancer in black men and white men. *J Natl Cancer Inst.* 1995; 87:354–360. [PubMed: 7531773]
10. Schroeder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med.* 2009; 360:1320–1328. [PubMed: 19297566]
11. Fang J, Metter EJ, Landis P, et al. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging. *Urology.* 2001; 58:411–416. [PubMed: 11549490]

12. Loeb S, Roehl KA, Antenor JAV, et al. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. *Urology*. 2006; 67:316–320. [PubMed: 16442597]
13. Ulmert D, Cronin AM, Björk T, et al. Prostate-specific antigen at or before age 50 as a predictor of advanced prostate cancer diagnosed up to 25 years later: A case-control study. *BMC Medicine*. 2008; 6:6–14. [PubMed: 18279502]
14. Whittemore AS, Cirillo PM, Feldman D, Cohn BA. Prostate specific antigen levels in young adulthood predict prostate cancer risk: results from a cohort of black and white Americans. *J Urol*. 2005; 174:872–876. [PubMed: 16093978]
15. Lilja H. Prediction of significant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50. *Cancer*. 2011; 117:1210–1219. [PubMed: 20960520]
16. Lilja H, Ulmert D, Bjork T, et al. Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. *J Clin Oncol*. 2007; 25:431–436. [PubMed: 17264339]
17. Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men: Establishment of age-specific reference ranges. *JAMA*. 1993; 270:860–864. [PubMed: 7688054]
18. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986–2005. *J Natl Cancer Inst*. 2009; 101:1325–1329. [PubMed: 19720969]
19. Roobol MJ, Roobol DW, Schröder FH. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population-based screening setting? (ERSPC, section Rotterdam). *Urology*. 2005; 65:343–346. [PubMed: 15708050]
20. Greene KL, Albertsen PC, Babaian RJ, et al. Prostate Specific Antigen Best Practice Statement: 2009 Update. *J Urol*. 2009; 182:2232–2241. [PubMed: 19781717]
21. Bill-Axelsson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2011; 364:1708–1717. [PubMed: 21542742]
22. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med*. 2012; 367:203–213. [PubMed: 22808955]
23. Vickers AJ, Lilja H. We need a better marker for prostate cancer. How about renaming PSA? *Urology*. 2011
24. Andriole GL, Grubb RL, Buys SS, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*. 2009; 360:1310–1319. [PubMed: 19297565]
25. Mohler J, Bahnson RR, Boston B, et al. Prostate cancer: clinical practice guidelines in oncology™. *J Natl Compr Canc Netw*. 2010; 8:162–200. [PubMed: 20141676]
26. Surveillance Epidemiology and End Results. [Accessed November 5, 2012.] Prostate Cancer SEER Incidence and U.S. Death Rates, Age-Adjusted and Age-Specific Rates, by Race. Available at: http://seer.cancer.gov/csr/1975_2009_pops09/browse_csr.php?section=23&page=sect_23_table.07.html
27. Vickers AJ, Lilja H. Predicting prostate cancer many years before diagnosis: how and why? *World J Urol*. 2011; 30:131–135. [PubMed: 22101902]

APPENDIX

Supplementary Data: Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.urology.2013.06.074>.

Figure 1.

Risk of surpassing an age-specific cut-point (**A**), undergoing a prostate biopsy by PSA quartile (**B**), or being diagnosed with prostate cancer (**C**) stratified by baseline PSA quartiles (Q1 0–0.4, Q2 0.5–0.69, Q3 0.7–0.9, Q4 > 1.0 ng/mL). PSA, prostate-specific antigen. (Color version available online.)

Figure 2.

Risk of surpassing an age-specific cut-point (A), undergoing a prostate biopsy by PSA quartile (B), or being diagnosed with prostate cancer (C) stratified by baseline PSA. PSA, prostate-specific antigen. (Color version available online.)

Table 1

Proportion of men who developed an elevated prostate-specific antigen level, underwent prostate biopsy and prostate cancer diagnosis stratified according to baseline prostate-specific antigen in men in their 40s

Stratification Parameter	Characteristics	All Men (n = 268)		PSA <1.0 (n = 192)		PSA 1.0 (n = 76)		P Value [†]
		N (%) [*]	N (%) [*]	N (%) [*]	N (%) [*]			
DRE	Developed an abnormal DRE during follow-up	81 (30.2%)		60 (31.3%)		21 (27.6%)		.3
PSA	Developed PSA above age-specific cut-point during follow-up	31 (11.6%)		10 (5.2%)		21 (27.6%)		<.0001
Prostate biopsy	Number of men getting at least one biopsy in 20 y of follow-up	66 (24.6%)		35 (18.2%)		31 (40.8%)		.0003
	Number of negative initial biopsies (% of total initial biopsies without cancer)	53 (80.3%)		30 (85.7%)		23 (74.2%)		.2
	Median time to prostate biopsy (IQR)	14.7 (11.1, 16.8)		14.9 (12.6, 16.9)		13.7 (9.6, 16.5)		.0497
	Median age at first prostate biopsy years (IQR)	59.4 (56.3, 61.6)		59.6 (56.8, 67.8)		58.3 (54.4, 61.2)		.16
Prostate cancer	Prostate cancer diagnosis	18 (6.7%)		6 (3.1%)		12 (16%)		.0006
	Median time to diagnosis of CaP, y (IQR)	12.2 (8.1–15.7)		14.6 (10.3–16.8)		10.3 (7.9–15.2)		.6
	Median age at CaP diagnosis, y (IQR)	57.1 (54.5–60.0)		58.8 (54.9–62.2)		56.6 (54.0–59.7)		.6
	Type of cancer diagnosed by risk group							
	Low (PSA <10, GS = 6)	16 (6%)		2.7% (0.1–5.4) [‡]		11.8% (4.0–19) [‡]		.003
	Med (PSA 10–20 or GS = 7)	2 (0.7%)		0		2 (2.6%)		-
	High (PSA >20, GS >7, or both medium criteria met)	0		0		0		-
	Death from CaP	0		0		0		-
	Death from any cause	7 (2.6%)		6 (3.1%)		1 (1.3%)		.3

CaP, prostate cancer; DRE, digital rectal examination; GS, Gleason score; IQR, interquartile range; PSA, prostate-specific antigen.

* N and % unless otherwise noted.

[†] P value from Wilcoxon Rank sum test (Median age, median time to biopsy and cancer diagnosis) Cox proportional hazards models (abnormal DRE, elevated PSA, prostate biopsy, and cancer diagnosis, death) Chi-square (negative initial biopsy).

[‡] Fifteen-year estimated risk (95% confidence interval), hazard ratio 4.4 1.6–13.0, *P* = .0033.

Table 2
Risk of exceeding an age-specific PSA cutpoint, prostate biopsy, and cancer diagnosis by various PSA cutoffs

Baseline PSA by Quartile	Risk of Exceeding Age-specific PSA Cutpoint		Risk of Prostate Biopsy		Risk of Prostate Cancer	
	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)
Quartile 1 (<0.5 ng/mL), n = 42	0	0	5	(referent)	1	(referent)
Quartile 2 (0.5–0.69 ng/mL), n = 76	3	(referent)	13	1.4 (0.55–4.5)	2	1.03 (0.1–22)
Quartile 3 (0.7–0.99 ng/mL), n = 74	7	2.3 (0.63–10.6)	17	1.9 (0.77–5.9)	3	1.4 (0.2–29)
Quartile 4 (≥ 1.0 ng/mL), n = 76	21	7.0 (2.4–29.6)	31	3.8 (1.6–11.3)	12	6.3 (1.23–114)
Baseline PSA cutpoint median						
PSA <0.7 ng/mL, n = 118	3	(referent)	18	(referent)	3	(referent)
PSA ≥ 0.7 ng/mL, n = 150	28	7.2* (2.6–30.3)	48	2.2 [†] (1.3–3.9)	15	3.7 (1.2–16.0)
Baseline PSA cutpoint 75th percentile						
PSA <1.0 ng/mL, n = 192	10	(referent)	35	(referent)	6	(referent)
PSA ≥ 1.0 ng/mL, n = 76	21	5.4* (2.6–12.0)	31	2.7 [†] (1.6–4.5)	12	5.3 (2.0–15.1)

CI, confidence interval; HR, hazard ratio; other abbreviation as in Table 1.

* Adjusted for age and family history of prostate cancer.

[†] Adjusted for age, digital rectal examination, and family history of prostate cancer.