VOLUME 34 · NUMBER 23 · AUGUST 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Baseline Prostate-Specific Antigen Levels in Midlife Predict Lethal Prostate Cancer

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Published online ahead of print at www.jco.org on June 13, 2016.

Support information appears at the end of this article.

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The views expressed in the submitted article are the authors' own and not an official position of any institution or funder.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/16/3423w-2705w/$20.00

DOI: 10.1200/JCO.2016.66.7527

ABSTRACT

Purpose

Prostate-specific antigen (PSA) level in midlife predicted future prostate cancer (PCa) mortality in an unscreened Swedish population. Our purpose was to determine if a baseline PSA level during midlife predicts lethal PCa in a US population with opportunistic screening.

Materials and Methods

We conducted a nested case-control study among men age 40 to 59 years who gave blood before random assignment in the Physicians' Health Study, a randomized, placebo-controlled trial of aspirin and β-carotene among 22,071 US male physicians initiated in 1982 and then transitioned into a prospective cohort with 30 years of follow-up. Baseline PSA levels were available for 234 patients with PCa and 711 age-matched controls. Seventy-one participants who developed lethal PCa were rematched to 213 controls. Conditional logistic regression was used to estimate odds ratios and the area under the receiver operating characteristic curve, with 95% CIs, of the association between baseline PSA and risk of lethal PCa.

Results

Median PSA among controls was 0.68, 0.88, and 0.96 ng/mL for men age 40 to 49, 50 to 54, and 55 to 59 years, respectively. Risk of lethal PCa was strongly associated with baseline PSA in midlife: odds ratios (95% CIs) comparing PSA in the > 90th percentile versus less than or equal to median were 8.7 (1.0 to 78.2) at 40 to 49 years, 12.6 (1.4 to 110.4) at 50 to 54 years, and 6.9 (2.5 to 19.1) at 55 to 59 years. A total of 82%, 71%, and 86% of lethal cases occurred in men with PSA above the median at ages 40 to 49, 50 to 54, and 55 to 59 years, respectively.

Conclusion

PSA levels in midlife strongly predict future lethal PCa in a US cohort subject to opportunistic screening. Risk-stratified screening on the basis of midlife PSA should be considered in men age 45 to 59 years.

J Clin Oncol 34:2705-2711. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Prostate specific antigen (PSA) screening has been shown to reduce prostate cancer (PCa) metastases and mortality.[1-4] However, PSA screening is associated with overdiagnosis and overtreatment, and it is controversial whether it does more good than harm.[5,6] Smarter screening strategies are needed to improve the accuracy of diagnosing lethal PCa while minimizing harms associated with overdiagnosis and overtreatment of indolent cancer.

One proposed strategy with potential for minimizing harm while maintaining benefit is performing a baseline PSA screening in men during midlife.[7-16] Because prostate carcinogenesis likely initiates in men during their fourth and fifth decade, the baseline PSA level at a younger age may be more accurate in predicting the presence of aggressive PCa, because it will be less confounded by benign prostate hyperplasia typical in older men.[17] Autopsy studies show that approximately 22% of white men harbor PCa by age 60 years.[18] Baseline PSA values seem to confer better predictive ability for future development of advanced PCa than do risk categories such as African American race or family history of PCa.[15,19] Studies of Swedish men demonstrated that PSA level in midlife predicts for future PCa diagnosis and metastases in unscreened populations during a median 27 years of follow-up.[10,11]

Our objective was to determine if baseline PSA level in midlife could predict future risk of lethal PCa in a population of US men, subject to opportunistic screening, with 30 years of follow-up. We hypothesized that men with a PSA level above the median in midlife will be more likely to develop lethal PCa.

MATERIALS AND METHODS

Selection and Description of Participants

The Physicians' Health Study (PHS) was a randomized, placebo-controlled trial of aspirin and β-carotene among 22,071 US male physicians initiated in 1982.[20] From 1982 to 1984, 14,916 participants (68%) age 40 to 84 years provided a blood specimen before random assignment, and these men provide the study base for the current project. All arms of the trial have ended, and participants continue to be followed as an observational cohort. The PHS was approved by the Partners HealthCare Institutional Review Board.

Technical Information

Identification of prostate cancers and deaths. Participants reported significant morbid events, including PCa, yearly in a mailed questionnaire and by postcards every 6 months. Self-reported, incident PCa cases diagnosed from 1982 to 2012 were confirmed through medical record and pathology report review by the PHS Endpoints Committee. Tumor clinical stage and occurrence of metastases were ascertained from medical records and from questionnaires sent to PCa survivors after diagnosis. Deaths were identified via family member and postal authority report and through periodic searches of the National Death Index. The Endpoints Committee determined cause of death through death certificates and medical record review and, secondarily, via next of kin.

Selection of cases and controls. We previously performed a nested case-control study of PSA level and PCa risk among participants with adequate plasma samples in the blood cohort.[21] In that study, there were 430 cases overall diagnosed between 1982 and 1993 and 1,642 controls among participants who had not reported a diagnosis of PCa at the time the diagnosis was reported by the corresponding case, matched by age (± 1 year) at blood draw. The current case-control analysis is restricted to the 234 cases and 711 controls age 40 to 59 years at baseline. The ratio of cases to controls was 1:3 for the majority (76%) of matched sets, 1:2 for 10%, and 1:4 for 14%.

In addition to total PCa, we studied risk of lethal PCa, defined as death from PCa or development of metastatic disease either at diagnosis or during follow-up. Among 234 original patients with PCa, 60 developed lethal PCa. Among 711 men originally selected as controls, 11 developed lethal PCa later in follow-up. Thus, there were 71 lethal cases, 65 of whom died as a result of PCa and six of whom had metastatic disease but did not die as a result of PCa during follow-up. The date of death was used as the lethal event date for men who died as a result of PCa, and the date of metastatic disease diagnosis was used for men with metastatic disease who did not die as a result of PCa during follow-up. For this analysis, the 71 lethal cases were rematched to three controls (n = 213) on the basis of age at blood draw (± 1 year), being alive at the time of lethal event in the corresponding case, and having a PSA measurement at baseline. Because our focus was lethal PCa, we did not exclude men with PCa as potential controls for these 71 cases, as long as they had not suffered a lethal event at the time of the event in the case. The alternative strategy (ie, limiting controls to men without a PCa diagnosis) would have led to an overestimate of the association between PSA levels and risk of lethal PCa.

Total PSA assay. Details of the PSA assay conducted on stored plasma samples have been described previously.[21] Briefly, total PSA levels were measured using the Tandem-R immunoradiometric assay (Hybritech, San Diego, CA). Intra- and interbatch coefficients of variation were ≤ 10% and ≤ 17%, respectively. Concentrations of total PSA stored in plasma stored at −80°C for 20 years have been shown to be comparable to concentrations in samples measured soon after blood draw.[22]

Imputed PSA values. To estimate the absolute risk of lethal PCa as a function of baseline PSA, we used the nested case-control information to impute PSA levels among the cohort of participants age 40 to 59 years who provided a blood sample at baseline (n = 11,189) using similar methodology to Vickers et al[10] (Data Supplement). Using PROC MI in SAS, PSA measurements were calculated over 10 imputations using predictive mean matching on the basis of follow-up time and stratified by baseline age (40 to 49, 50 to 54, 55 to 59 years) and case status (lethal case, nonlethal case, noncase) during follow-up from 1982 to 2012. Among this subcohort of men age 40 to 59 years who provided blood samples, n = 1,701 total incident prostate cancers were diagnosed from 1983 to 2012, including 127 lethal cases.

Statistics

Conditional logistic regression was used to estimate odds ratios (ORs) and 95% CIs for the association between baseline PSA levels and total PCa risk, comparing cases and patients with disease overall as well as by ages 40 to 49, 50 to 54, and 55 to 59 years. We used conditional logistic regression to assess the association between baseline PSA level and lethal PCa risk after rematching the controls.

The 15-, 20-, 25-, and 30-year cumulative incidence (and 95% CI) of lethal PCa according to PSA percentile was estimated within each age group. PSA levels for the full blood cohort were imputed as described above. The mean of the individual cumulative incidence estimates was calculated over the 10 imputation sets, and CIs were determined on the log-transformed scale according to Rubin's method.[23] We averaged estimates across the 10 imputation sets to plot the cumulative incidence of lethal PCa by age group and PSA level and determine the proportion of lethal PCa captured by PSA categories according to age group.

Area under the receiver operating characteristic curve (AUC) was used to evaluate the discrimination of baseline PSA for predicting total and lethal PCa using the case-control data set. All *P* values were two-sided with statistical significance at $P < .05$. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) and the R programming language.

RESULTS

Descriptive statistics of the study populations are shown in Table 1. The mean age at blood draw was 55 years. Median follow-up time from blood draw to cancer diagnosis was 9.0 years for overall cases and 8.6 years for lethal cases.

Median PSA levels varied by age at baseline and were higher among older men (Table 2). Compared with men with measured PSA at or below the age-specific median, men with PSA above the median had consistently and significantly increased risk of total PCa across all age groups. The ORs were 7.3 (95% CI, 2.4 to 21.8) for 40 to 49 years, 7.6 (95% CI, 3.4 to 17.2) for 50 to 54 years, and 10.1 (95% CI, 5.2 to 19.6) for 55 to 59 years (Table 2). This was even more pronounced for men with PSA > 90th percentile, with ORs 32.4 (95% CI, 7.1 to 149.0), 34.6 (95% CI, 11.5 to 103.6), and 30.3 (95% CI, 13.5 to 67.7) for ages 40 to 49, 50 to 54, and 55 to 59 years, respectively.

The risk of lethal PCa was also strongly associated with PSA levels during midlife: the ORs comparing men with the > 90th percentile versus less than or equal to median levels of PSA were 8.7 (95% CI, 1.0 to 78.2) for 40 to 49 years, 12.6 (95% CI, 1.4 to 110.4) for 50 to 54 years, and 6.9 (95% CI, 2.5 to 19.1) for 55 to 59 years

Table 1. Characteristics of Patients With Prostate Cancer and Control Subjects, Physicians' Health Study, 1982 to 2012

Characteristic	Original Case-Control Study		Updated Case-Control Study	
	Controls (n = 711)	Total Cases (n = 234)	Controls for Lethal Cases (n = 213)	Lethal Cases (n = 71)
Study period*	1982-1993		1982-2012	
Age at blood draw, No. (%)				
40 to 44 years	20 (3)	7 (3)	3 (1)	1 (1)
45 to 49 years	84 (12)	27 (11)	28 (13)	10 (14)
50 to 54 years	202 (28)	70 (30)	51 (24)	17 (24)
55 to 59 years	405 (57)	130 (56)	131 (62)	43 (61)
BMI at baseline, No. (%)				
< 25 kg/m^2	408 (57)	123 (53)	123 (58)	31 (44)
25-30 kg/m^2	285 (40)	100 (43)	85 (40)	36 (51)
> 30 kg/m^2	18 (3)	11 (5)	5 (2)	4 (6)
White, No. (%)*	659 (94)	224 (96)	201 (95)	69 (97)
Smoking status at baseline, No. (%)				
Never	338 (48)	111 (47)	102 (48)	31 (44)
Past	314 (44)	102 (44)	98 (46)	31 (44)
Current	59 (8)	21 (9)	13 (6)	9 (13)
PSA at baseline, median (IQR)	0.89 (0.58-1.45)	2.34 (1.34-4.78)	1.04 (0.63-1.68)	2.96 (1.31-6.56)
Clinical stage, No. (%)†				
T1-T2		204 (88)		47 (66)
T3		8 (3)		4 (6)
T4/N1/M1		20 (9)		20 (28)
Gleason grade at diagnosis, No. (%)‡				
≤ 6		138 (61)		20 (31)
7		60 (27)		24 (37)
8-10		27 (12)		21 (32)

Abbreviations: BMI, body mass index; IQR, interquartile range; PSA, prostate-specific antigen.
*For the study of prostate cancer diagnosis, only cases diagnosed before 1993 were included; for the study of lethal cancer, prostate cancer deaths or metastases through 2012 were included.
†Excludes < 1% missing values.
‡Excludes < 9% missing values.

(Table 2). Of the lethal PCa events, 82%, 71%, and 86% occurred in men with PSA above the median at ages 40 to 49, 50 to 54, and 55 to 59 years, respectively (Table 3). However, there were nine cases of lethal PCa diagnosed among men with the lowest quartile of baseline PSA across all age groups.

The measured and imputed PSA values for participants who provided a blood specimen at baseline are shown in the Data Supplement. The cumulative incidence of PCa death or development of distant metastases by category of measured and imputed PSA, stratified by age at PSA measurement, is presented in Table 4. For men with PSA values below median at baseline, the absolute risk of developing lethal PCa in the next 30 years was low: 0.19% for men 40 to 44, 0.51% for men 45 to 49, 1.62% for men 50 to 54, and 0.59% for men 55 to 59 years of age.

PSA levels in midlife predicted future risk of PCa overall as well as risk of lethal PCa with good discrimination (Table 5). For lethal disease using measured PSA levels, the AUC was 0.75 (95% CI, 0.53 to 0.97) for men 40 to 49 years, 0.72 (95% CI, 0.55 to 0.89) for men 50 to 54 years, and 0.76 (95% CI, 0.67 to 0.84) for men 55 to 59 years.

DISCUSSION

In this prospective study among US men, we found that a single baseline PSA level measured during midlife predicted subsequent development of lethal PCa with good accuracy over 30 years of follow-up. Opportunistic PSA screening occurred during our follow-up time, which spanned cases diagnosed during pre-PSA and PSA eras. Assuming that opportunistic screening was at least somewhat effective in reducing mortality,[24] our results are likely to underestimate the association between baseline PSA and lethal PCa in the absence of any screening. These data identify subgroups of men, on the basis of their PSA levels at a given age, with widely divergent lifetime risk of PCa death, who therefore could benefit from screening intervals tailored to their actual magnitude of risk. An increased risk of lethal PCa was present for men with PSA levels above the median and especially in men with PSA levels above the 75th and 90th percentiles. In our data, one of seven men with PSA > 3.0 ng/mL at 55 to 59 years and one of 12 men with PSA > 2.1 ng/mL at 50 to 54 years died as a result of PCa within 30 years. These results support prior studies showing value of baseline PSA conducted among unscreened men in Sweden.[10,11]

These findings do not necessarily imply that prostate biopsy or definitive treatment is immediately required in younger men with higher PSA levels at baseline, because this could lead to overdiagnosis, but only that they undergo more intensive PSA screening to enable earlier identification of cancer and potential cure while still possible. If baseline PSA is markedly elevated (> 90th percentile) for age, cumulative incidence for lethal PCa at 30 years is substantial, with rates of 4.5%, 8.4%, and 14.1% for men age 45 to 49, 50 to 54, and 55 to 59 years, respectively.

Table 2. Association of PSA Levels With Prostate Cancer Risk by Age Groups, Physicians' Health Study

Age at Blood Draw (years)	Upper Percentiles *v* Below Median PSA				Lower Percentiles *v* Above Median PSA			Total Cases/ Controls
	≤ 50th Percentile (referent)	> 50th Percentile	> 75th Percentile	> 90th Percentile	≤ 25th Percentile	> 25th to ≤ 50th Percentile	> 50th Percentile (referent)	
Total prostate cancer (original case-control study)								
40 to 49								
PSA level (ng/mL)	≤ 0.68	> 0.68	> 1.04	> 1.68	≤ 0.52	> 0.52 to ≤ 0.68	> 0.68	
Cases/controls	4/51	30/50	29/25	20/10	4/26	0/25	30/50	34/101
OR (95% CI)	1.00	7.3 (2.4 to 21.8)	10.7 (3.4 to 33.6)	32.4 (7.1 to 149.0)	0.3 (0.1 to 0.8)	NE	1.00	
50 to 54								
PSA level (ng/mL)	≤ 0.88	> 0.88	> 1.40	> 1.96	≤ 0.59	> 0.59 to ≤ 0.88	> 0.88	
Cases/controls	9/107	61/104	47/51	40/21	6/56	3/51	61/104	70/211
OR (95% CI)	1.00	7.6 (3.4 to 17.2)	11.9 (5.0 to 28.5)	34.6 (11.5 to 103.6)	0.2 (0.1 to 0.4)	0.1 (0.03 to 0.3)	1.00	
55 to 59								
PSA level (ng/mL)	≤ 0.96	> 0.96	> 1.64	> 2.88	≤ 0.60	> 0.60 to ≤ 0.96	> 0.96	
Cases/controls	12/200	118/199	90/97	63/39	6/102	6/98	118/199	130/399
OR (95% CI)	1.00	10.1 (5.2 to 19.6)	16.8 (8.2 to 34.7)	30.3 (13.5 to 67.7)	0.1 (0.04 to 0.2)	0.1 (0.04 to 0.3)	1.00	
All ages, 40 to 59*								
Cases/controls	25/358	209/353	166/173	123/70	16/184	9/174	209/353	234/711
OR (95% CI)	1.00	8.7 (5.5 to 13.9)	14.1 (8.6 to 23.3)	31.1 (17.3 to 56.1)	0.1 (0.1 to 0.3)	0.1 (0.04 to 0.2)	1.00	
Lethal prostate cancer (updated case-control study using rematched controls)								
40 to 49								
PSA level (ng/mL)	≤ 0.68	> 0.68	> 1.04	> 1.68	≤ 0.52	> 0.52 to ≤ 0.68	> 0.68	
Cases/controls	2/13	9/20	9/14	6/5	2/8	0/5	9/20	11/33
OR (95% CI)	1.00	2.9 (0.5 to 15.7)	5.6 (0.6 to 48.7)	8.7 (1.0 to 78.2)	0.5 (0.1 to 3.0)	NE	1.00	
50 to 54								
PSA level (ng/mL)	≤ 0.88	> 0.88	> 1.40	> 1.96	≤ 0.59	> 0.59 to ≤ 0.88	> 0.88	
Cases/controls	5/22	12/29	11/17	11/8	5/13	0/9	12/29	17/51
OR (95% CI)	1.00	1.9 (0.6 to 6.7)	2.9 (0.8 to 10.7)	12.6 (1.4 to 110.4)	1.1 (0.3 to 4.5)	NE	1.00	
55 to 59								
PSA level (ng/mL)	≤ 0.96	> 0.96	> 1.64	> 2.88	≤ 0.60	> 0.60 to ≤ 0.96	> 0.96	
Cases/controls	6/53	37/76	30/39	22/25	2/27	4/26	37/76	43/129
OR (95% CI)	1.00	4.0 (1.6 to 10.0)	6.0 (2.3 to 15.8)	6.9 (2.5 to 19.1)	0.2 (0.04 to 0.7)	0.3 (0.1 to 1.0)	1.00	
All ages, 40 to 59*								
Cases/controls	13/88	58/125	50/70	39/38	9/48	4/40	58/125	71/213
OR (95% CI)	1.00	3.1 (1.6 to 6.1)	4.8 (2.3 to 9.7)	7.4 (3.3 to 16.6)	0.4 (0.2 to 0.9)	0.2 (0.1 to 0.6)	1.00	

Abbreviations: NE, not estimable; OR, odds ratio; PSA, prostate-specific antigen.
*Using age-specific cut points for percentiles.

Table 3. Proportion of Lethal Prostate Cancers Captured by Percentiles of Measured PSA Levels at Age 40 to 49, 50 to 54, and 55 to 59 Years

Stratification	PSA Concentration (ng/mL)	Proportion of Lethal Prostate Cancers in PSA Category (%)
Age 40 to 49 years at blood draw (n = 11 lethal events)		
Top 10th percentile	≥ 1.68	55
Quartile 4	≥ 1.04	82
Above median	≥ 0.68	82
Below median	< 0.68	18
Age 50 to 54 years at blood draw (n = 17 lethal events)		
Top 10th percentile	≥ 1.96	65
Quartile 4	≥ 1.40	65
Above median	≥ 0.88	71
Below median	< 0.88	29
Age 55 to 59 years at blood draw (n = 43 lethal events)		
Top 10th percentile	≥ 2.88	51
Quartile 4	≥ 1.64	70
Above median	≥ 0.96	86
Below median	< 0.96	14

Abbreviation: PSA, prostate-specific antigen.

PSA screening guidelines typically recommend screening take place between ages 55 to 69 years, because there is no published randomized trial of PSA screening in men younger than the age of 50 years and because incidence of PCa in younger ages is quite low. Before age 45 years, the cumulative incidence of lethal PCa at 15 years is low, and metastatic cancer is rarely diagnosed. Our results showed no PCa deaths within 15 years in men younger than 45 years with a PSA level below the median at baseline. These findings may inform discussions of an appropriate age range for screening initiation, because men younger than 45 years see little benefit, and lethal disease is likely to be caught early enough at a subsequent screen.

The ideal screening interval for men depending on baseline PSA level in midlife is unknown. We found that risk of developing lethal PCa in the next 30 years among those with baseline PSA levels below the median was < 2% at ages 40 to 59 years. Although risk was small, it remained present, and so screening should be continued, albeit with longer intervals. It seems that baseline PSA level below the median at age 45 years followed by repeat measurements at 5-year intervals would capture most lethal cases, given that the 15-year cumulative incidence for lethal PCa at age 40 to 44 years is zero and in the 45 to 49 year age group only 0.07%.

We investigated whether one low PSA level at age 40 to 49 years is sufficient to allow men to be exempted from further screening. We found that compared with men having PSA levels above the median of 0.68 ng/mL, men age 40 to 49 years with PSA levels below the 25th percentile of 0.52 ng/mL were at a decreased risk, albeit nonsignificant, of lethal PCa (OR, 0.36; 95% CI, 0.04 to 3.30). However, despite this low PSA level, two men with baseline levels below 0.52 ng/mL died as a result of PCa during follow-up. The cumulative incidence of lethal PCa for men age 40 to 44 and 45 to 49 years with a PSA level below the 25th percentile (0.53 ng/mL) at 30 years is 0.37% (95% CI, 0.05 to 1.70) and 0.97% (95% CI, 0.30 to 2.49), respectively. Thus, it would be prudent to conduct another PSA test during the lifetime of men age 40 to 49 years, even if the first measure is exceptionally low, because there still exists a small risk of PCa death.

We then sought to determine whether it is safe to stop PSA screening at age 60 years. We found that men age 55 to 59 years with PSA levels below the median of 0.96 ng/mL were at low risk of lethal PCa. The cumulative incidence of lethal PCa in this age group was 0.59% (95% CI, 0.25 to 1.22) for PSA levels below the median at 30 years. Fully 86% of lethal cases occur in men with PSA above the median. This suggests white men with PSA level below 1.0 ng/mL at age 60 years might reasonably forgo further PSA screening. This requires further study but is consistent with a study comparing a nonscreened population (Malmö) with a screened population (Göteborg screening trial) that showed no reduction in PCa mortality, but an important increase in overdiagnosis, for rescreening men with a PSA level < 1.0 ng/mL at age 60 years.[25] In contrast, rescreening men with PSA levels > 2.0 ng/mL at age 60 years had a large reduction in PCa mortality with minimal overdiagnosis: only 23 men needed to be screened and six diagnosed to avoid one PCa death at 15 years.[1,25]

In our analysis of the ability of PSA at midlife to predict total and lethal PCa, the AUCs were higher for predicting total (AUC, 0.83 for 40 to 49 years) versus lethal (AUC, 0.75 for 40 to 49 years) PCa. In contrast, in the Malmö Preventive Project, the baseline PSA values in men age < 50 years more strongly predicted advanced PCa (AUC, 0.75) compared with total (AUC, 0.72) risk, likely due to the absence of routine screening in Sweden.[11] The higher discrimination of PSA for total cancer in the current study is likely a function of verification bias. In a screened population, men with higher PSA are more likely to be subject to biopsy and thus have an accordingly higher risk of diagnosis. The lower discrimination of PSA for lethal cancer is best explained in terms of risk reduction associated with screening: a man with a higher PSA who is destined to develop lethal cancer may have that cancer detected early because of opportunistic screening, leading to cure.

There are few study populations available in any country that have access to baseline blood samples, excellent accounting of lethal PCa outcomes, and the extensive follow-up required to investigate this question. Furthermore, because this is a US population subject to opportunistic PSA screening, it is generalizable to a contemporary population. A similar case-control design was previously used among Swedish men age 27 to 56 years with extremely low PSA testing rates in the Malmö Preventive Project.[10] They found risk of death from PCa was also strongly associated with baseline PSA: 44% (95% CI, 34% to 53%) of deaths occurred in men with PSA concentration in the highest 10th of the distribution of concentrations at age 45 to 49 years (≥ 1.6 ng/mL), with a similar proportion for the highest 10th at age 51 to 55 years (≥ 2.4 ng/mL; cumulative incidence, 44%; 95% CI, 32% to 56%).[10]

Our study is subject to limitations. Despite decades of follow-up, we have limited lethal events, especially in younger age groups, contributing to wider CIs. However, it is worth noting that the wide CIs are due, in part, to the fact that PSA is so strongly related to lethal disease risk, resulting in a small number of events in the reference group with low PSA levels. An unknown proportion of case-control participants might have undergone opportunistic PSA testing before study inclusion in 1993. Even though approval of the

Table 4. Cumulative Incidence (%) and 95% CI of Prostate Cancer Death or Development of Distant Metastases, Stratified by Categories of Imputed PSA Levels and Age at Blood Draw

Stratification	PSA Concentration (ng/mL)	Cumulative Risk of Lethal Prostate Cancer Within			
		15 Years	20 Years	25 Years	30 Years
Age 40 to 44 years at blood draw					
Screening cut point	> 4	0 (NE)	2.3 (0.2 to 10.4)	3.5 (0.3 to 14.5)	9.4 (< 0.01 to 59.2)
Top 10th percentile	≥ 1.70	0 (NE)	0.6 (0.1 to 2.6)	1.24 (0.3 to 3.5)	3.4 (1.1 to 8.0)
Quartile 4	≥ 1.15	0 (NE)	0.2 (0.03 to 0.1)	0.5 (0.1 to 1.3)	1.4 (0.4 to 3.7)
Quartile 3	0.72-1.14	0 (NE)	0 (NE)	0.1 (0.01 to 0.7)	0.1 (0.01 to 0.7)
Above median	≥ 0.72	0 (NE)	0.1 (0.01 to 0.5)	0.2 (0.07 to 0.7)	0.6 (0.2 to 1.4)
Below median	< 0.72	0 (NE)	0.03 (NE)	0.09 (0.01 to 0.5)	0.2 (0.02 to 0.9)
Quartile 2	0.53-0.71	0 (NE)	0 (NE)	0 (NE)	0 (NE)
Quartile 1	< 0.53	0 (NE)	0.06 (NE)	0.18 (0.02 to 0.9)	0.4 (0.05 to 1.7)
Age 45 to 49 years at blood draw					
Screening cut point	> 4	4.6 (0.9 to 13.8)	8.5 (2.5 to 19.1)	9.6 (2.8 to 21.4)	15.7 (0.2 to 56.8)
Top 10th percentile	≥ 1.70	0.9 (0.2 to 2.9)	2.5 (0.9 to 5.4)	3.3 (1.4 to 6.6)	4.5 (1.6 to 9.6)
Quartile 4	≥ 1.23	0.7 (0.2 to 1.6)	1.3 (0.6 to 2.6)	1.7 (0.8 to 3.1)	2.3 (0.9 to 4.7)
Quartile 3	0.72-1.22	0.06 (NE)	0.3 (0.03 to 1.1)	0.3 (0.04 to 1.2)	0.4 (0.04 to 1.8)
Above median	≥ 0.72	0.4 (0.1 to 0.8)	0.8 (0.4 to 1.4)	0.9 (0.5 to 1.7)	1.2 (0.6 to 2.1)
Below median	< 0.72	0.07 (NE)	0.3 (0.1 to 1.0)	0.5 (0.2 to 1.2)	0.5 (0.2 to 1.3)
Quartile 2	0.53-0.71	0 (NE)	0 (NE)	0 (NE)	0 (NE)
Quartile 1	< 0.53	0.15 (NE)	0.6 (0.2 to 1.8)	0.9 (0.3 to 2.2)	0.1 (0.3 to 2.5)
Age 50 to 54 years at blood draw					
Screening cut point	> 4	11.4 (3.3 to 25.2)	13.4 (4.6 to 26.9)	18.6 (7.6 to 33.4)	18.6 (7.6 to 33.4)
Top 10th percentile	≥ 2.10	2.4 (0.9 to 5.0)	3.7 (1.8 to 6.9)	5.1 (2.6 to 8.6)	8.4 (3.4 to 16.2)
Quartile 4	≥ 1.43	1.2 (0.5 to 2.4)	1.7 (0.9 to 3.1)	2.2 (1.2 to 3.7)	3.4 (1.7 to 6.0)
Quartile 3	0.89-1.42	0.2 (0.02 to 1.0)	0.2 (0.02 to 1.0)	0.2 (0.02 to 1.0)	0.2 (0.02 to 1.0)
Above median	≥ 0.89	0.7 (0.3 to 1.3)	0.9 (0.5 to 1.6)	1.2 (0.7 to 1.9)	1.6 (0.9 to 2.7)
Below median	< 0.89	0.3 (0.06 to 0.8)	0.3 (0.08 to 0.9)	0.8 (0.4 to 1.4)	1.6 (0.8 to 3.1)
Quartile 2	0.59-0.88	0 (NE)	0 (NE)	0 (NE)	0 (NE)
Quartile 1	< 0.59	0.5 (0.1 to 1.6)	0.6 (0.2 to 1.8)	1.6 (0.8 to 3.0)	2.3 (1.6 to 6.9)
Age 55 to 59 years at blood draw					
Screening cut point	> 4	4.7 (2.0 to 9.1)	7.6 (4.0 to 12.9)	12.6 (7.3 to 19.4)	17.3 (8.4 to 29.0)
Top 10th percentile	≥ 3.02	3.1 (1.3 to 6.0)	5.5 (3.0 to 9.2)	9.4 (5.7 to 14.2)	14.1 (8.1 to 21.8)
Quartile 4	≥ 1.78	1.6 (0.8 to 2.9)	3.3 (2.0 to 5.0)	6.1 (4.2 to 8.4)	9.4 (6.4 to 13.1)
Quartile 3	1.02-1.77	0.6 (0.1 to 1.7)	0.9 (0.2 to 2.4)	2.3 (1.1 to 4.1)	4.8 (2.6 to 8.2)
Above median	≥ 1.02	1.1 (0.6 to 1.9)	2.2 (1.4 to 3.2)	4.4 (3.2 to 5.8)	7.4 (5.5 to 9.6)
Below median	< 1.02	0.3 (0.09 to 0.8)	0.4 (0.1 to 0.9)	0.6 (0.3 to 1.2)	0.6 (0.3 to 1.2)
Quartile 2	0.63-1.01	0.2 (0.03 to 1.2)	0.2 (0.03 to 1.2)	0.7 (0.2 to 1.8)	0.7 (0.2 to 1.8)
Quartile 1	< 0.63	0.4 (0.07 to 1.2)	0.5 (0.2 to 1.5)	0.5 (0.2 to 1.5)	0.5 (0.2 to 1.5)

Abbreviations: NE, not estimable; PSA, prostate-specific antigen.

PSA test for the purpose of screening asymptomatic men for PCa by the US Food and Drug Administration did not occur until 1994, uptake in the United States was present before this, and it is estimated that PSA testing increased from < 5% of white men in 1989 to approximately 40% in 1994.[26] The impact of this opportunistic screening is likely limited, because our primary study outcome was lethal PCa and not incidence.

It is also important to note that the cumulative incidence of PCa mortality in this study was 4.9% in 2012. This is higher than the general population because of decreased cardiac mortality among this physician group. Finally, the study population consisted primarily of white men. Although studies have shown midlife PSA to be predictive of PCa diagnosis in African American men, no study has evaluated risk of PCa metastases or death,

Table 5. AUC and 95% CI for Total and Lethal Prostate Cancer by Measured Baseline PSA at Age 40 to 49, 50 to 54, and 55 to 59 Years

Measured PSA Levels From Case-Control Study, 1982-1993	No. of Cases	No. of Controls	AUC	95% CI
Total prostate cancer				
40 to 49 years	34	101	0.83	0.73 to 0.92
50 to 54 years	70	211	0.80	0.74 to 0.87
55 to 59 years	130	399	0.80	0.76 to 0.85
Lethal prostate cancer				
40 to 49 years	11	33	0.75	0.53 to 0.97
50 to 54 years	17	51	0.72	0.55 to 0.89
55 to 59 years	43	129	0.76	0.67 to 0.84

Abbreviations: AUC, area under the receiver operating characteristic curve; PSA, prostate-specific antigen.

despite there being a greater risk of diagnosis and mortality compared with white men.[9,27,28]

In conclusion, PSA levels in midlife predict strongly for subsequent development of lethal PCa in a cohort of American men subject to opportunistic PSA screening. Risk-stratified screening on the basis of midlife PSA should be considered in men age 45 to 59. Men with PSA below median at age 60 years (< 1.0 ng/mL) are unlikely to develop lethal disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Support

The Physicians' Health Study was supported by the National Institutes of Health Grants No. CA-097193, CA-34944, CA-40360, HL-26490, and HL-34595. This work was also supported by the Department of Defense Prostate Cancer Research Program Grant No. W81XWH-12-1-0072 (J.L.B.), Dana-Farber Cancer Institute Mazzone Awards Program (J.L.B. and M.A.P.), and the Prostate Cancer Foundation Young Investigator Award (L.A.M.); M.A.P. is an American Urological Association Urology Care Foundation Scholar. Additional funding support provided from the National Cancer Institute Grants No. R33 CA127768-02, P50-CA92629, and P50-CA090381; Swedish Cancer Society Grant No. 3455; Fundaçion Federico; the Sidney Kimmel Center for Prostate and Urologic Cancers; David H. Koch through the Prostate Cancer Foundation; and a Cancer Center Support Grant from the National Cancer Institute made to Memorial Sloan Kettering Cancer Center Grant No. P30-CA008748 (S.C., D.S., and A.V.; PI: Craig B. Thompson).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Baseline Prostate-Specific Antigen Levels in Midlife Predict Lethal Prostate Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

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No relationship to disclose

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Research Funding: Myriad Genetics
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No relationship to disclose

Acknowledgment

We thank Meir Stampfer for his valuable insight and guidance. We also thank the participants of the Physicians' Health Study for their dedicated participation in the study. The co-first authors M.A.P. and J.L.B. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.