Risk of Prostate Cancer–related Death Following a Low PSA Level in the PLCO Trial

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ABSTRACT

Longer-than-annual screening intervals have been suggested to improve the balance of benefits and harms in prostate cancer screening. Many researchers, societies, and guideline committees have suggested that screening intervals could depend on the prostate-specific antigen (PSA) result. We analyzed data from men ($N = 33,897$) ages 55–74 years with a baseline PSA test in the intervention arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial (United States, 1993–2001). We estimated 5- and 10-year risks of aggressive cancer (Gleason ≥8 and/or stage III/IV) and 15-year risks of prostate cancer–related mortality for men with baseline PSA ≤ 0.5 ng/mL ($N = 4,862$), ≤1 ng/mL ($N = 15,110$), and 1.01–2.5 ng/mL ($N = 12,422$). A total of 217 men died from prostate cancer through 15 years, although no men with PSA ≤ 1 ng/mL died from prostate cancer within 5 years [95% confidence interval (CI), 0.00%–0.03%]. The 5-year incidence of aggressive disease was low (0.08%; 95% CI, 0.03%–0.12%) for men with PSA ≤ 1 ng/mL, and higher for men with baseline PSA 1.01–2.5 ng/mL (0.51%; 95% CI, 0.38%–0.74%). No men aged ≥65 years with PSA ≤ 0.5 ng/mL died from prostate cancer within 15 years (95% CI, 0.00%–0.32%), and their 10-year incidence of aggressive disease was low (0.25%; 95% CI, 0.00%–0.53%). Compared with white men, black men with PSA ≤ 1 ng/mL had higher 10-year rates of aggressive disease (1.6% vs. 0.4%; $P < 0.01$). Five-year screening intervals may be appropriate for the 45% of men with PSA ≤ 1 ng/mL. Men ages ≥65 years with PSA ≤ 0.5 ng/mL could consider stopping screening. Substantial risk disparities suggest appropriate screening intervals could depend on race/ethnicity.

Introduction

Death due to prostate cancer is the second leading cause of cancer-related death in U.S. men, with an estimated 31,620 deaths in 2019 (1). It is estimated that 1–2 deaths from prostate cancer are prevented per 1,000 men screened annually (2), but this benefit is considered by many to be outweighed by the harms (3). Models estimate that annual screening of men ages 50–69 (with biopsy referral at ≥4 ng/mL) would result in a 17% chance of ≥1 false-positive result, with a 13.8% probability of cancer diagnosis and 1.8% probability of overdiagnosis (4). Although the U.S. Preventive Services Task Force (USPSTF) discouraged annual prostate-specific antigen (PSA) screening in their 2012 recommendation, recent updates by the USPSTF and other organizations have shifted toward shared decision making (5–10).

Some harms of PSA screening could be safely reduced by using longer-than-annual screening intervals for men with low PSA levels (11–17). Numerous organizations produce guidelines regarding PSA-based prostate cancer screening (**Table 1**), with many recommending longer-than-annual screening for men with low PSA levels (5–10). In particular, the American Cancer Society (ACS) suggests "screening intervals can be extended to every 2 years" for men with PSA level < 2.5 ng/mL (8), while Memorial Sloan Kettering Cancer Center (MSKCC) recommended a 6- to 10-year interval for men with PSA < 1 ng/mL, and to stop screening men aged ≥60 years with PSA < 1 ng/mL (18). The 2018 USPSTF guidelines identified risk stratification tools and the use of baseline PSA level as a risk factor as research needs (10).

Over 15 years of follow-up, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial has accrued over 200 prostate cancer–related deaths. We estimated risks of prostate cancer, aggressive prostate cancer (Gleason ≥8 and/or stage III/IV), and prostate cancer–related death, among men with low baseline PSA levels, in the PSA screening arm of the PLCO (19). In addition, we consider for which men, based on PSA and age, stopping screening may be appropriate.

Materials and Methods

The PLCO was a large, multi-center, randomized controlled trial designed to assess the effectiveness of screening in

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Table 1. Prostate cancer screening guidelines.

Organization	Year of recommendations	Age range	Screening recommendations
American Urological Association (9)	2018	Shared decision-making for men ages 55–69 years at "average risk"	"A routine screening interval of 2 years or more may be preferred over annual screening"
National Comprehensive Cancer Network (7)	2018	Shared decision-making for men ages 45–75 years	PSA < 1 ng/mL (DRE normal, if done): 2–4 year interval PSA 1–3 ng/mL (DRE normal, if done): 1–2 year interval
USPTF (38)	2018	Men ages 55–69 years "should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision"	"PSA-based screening for prostate cancer every 2 or 4 years instead of annually appears to provide a good trade-off between a reduction in overdiagnosis and a small reduction in mortality benefit."
American Academy of Family Physicians (AAFP) (39)	2018	n/a	"The AAFP does not recommend routine PSA-based screening for prostate cancer. For men aged 55 through 69 who are considering periodic prostate cancer screening, clinicians should discuss the risks and benefits and engage in shared decision-making that enables an informed choice." "The AAFP recommends against screening for prostate cancer in men aged 70 and older."
EAU-ESTRO-SIOG (6)	2017	After counselling, men on potential risks and benefits, men aged 50+ years at average risk with a life expectancy of at least 10–15 years	PSA > 1 ng/mL at age 40 years: 2-year interval. PSA >2 ng/mL at age 60 years: 2-year interval. Otherwise 8-year interval.
American College of Physicians (5)	2013	Shared decision-making for men ages 50–69 years at "average risk" with a life expectancy of more than 10–15 years.	"Longer (than annual) intervals may be indicated."
ACS (8)	2010	Shared decision-making for men aged 50+ years at "average risk" with ≥10 years life expectancy	PSA<2.5 ng/mL: "screening intervals can be extended to every 2 years." Annual screening for PSA ≥2.5 ng/mL.

reducing disease-specific mortality. We restrict our analyses to men ages 55–74 years randomized to the intervention arm [PSA testing at baseline and five further annual PSA screens, and a digital rectal exam (DRE) at baseline and three further annual DRE screens] between 1993 and 2001. Each institution received approval from its institutional review board, ensuring the study was carried out in accordance with the Declaration of Helsinki. All participants signed informed consent documents prior to randomization. Relevant exclusion criteria for the PLCO included history of prostate cancer, surgical removal of the entire prostate, participation in another cancer screening or primary prevention study, and use of finasteride in the previous 6 months. From April 1995, men were also excluded if they reported more than one PSA test in the past 3 years. At baseline, participants completed a questionnaire to collect demographic and risk factor information. A PSA level >4 ng/mL or abnormal DRE was considered a positive screen. Screening test results were reported to men and their physicians, who together determined diagnostic follow-up.

Details on the ascertainment of incident cancers and prostate cancer–specific mortality have been published previously (20, 21). Incident cancers and deaths were ascertained primarily by an annual study update form; to obtain more complete mortality data, this was supplemented by periodic linkage to the National Death Index. Cancers were confirmed with medical records. Causes of death were reviewed by an end-point adjudication process (20). Subjects were followed for cancer incidence through December 31, 2009 or 13 years of follow-up, whichever came first, and for mortality through December 31, 2012, providing some participants with up to 20 years of follow-up for mortality (21). For prostate cancer incidence, events were any prostate cancer diagnosis, and subjects were censored at the earliest of date of cancer diagnosis, death or December 31, 2009; for aggressive disease events were any prostate cancer incidence with Gleason ≥8 and/or stage III/IV, and subjects were censored at Gleason 2–7 diagnosis, unless the cancer stage was III/IV. Gleason scores from the first biopsy at which cancer was diagnosed were used, as this was available for almost all participants. When available, pathologic cancer stage was used, otherwise clinical stage. Because we did not know whether the Gleason 7 was 4 + 3 or 3 + 4, we chose a cutoff of 8 and above for aggressive disease, as we know that is aggressive. For mortality, events were deaths from prostate cancer, and subjects were censored at death or December 31, 2012.

We calculated cumulative incidences of prostate cancer diagnosis and aggressive disease at 2, 5, and 10 years, and prostate cancer–specific mortality at 2, 5, 10, and 15 years, for men with baseline PSA (i) ≤0.5 ng/mL, (ii) ≤1 ng/mL (including ≤0.5 ng/mL), and (iii) 1.01–2.5 ng/mL. These thresholds were chosen based on current screening guidelines, where 1 ng/mL is a common cutoff for determining the screening interval (e.g.,

NCCN (7); and European Association of Urology (EAU)-European Society for Radiotherapy and Oncology (ESTRO)-International Society of Geriatric Oncology (SIOG (6); guidelines), and a cutoff of 2.5 ng/mL is currently used by the ACS (22). We generated Kaplan–Meier cumulative incidence curves for the three primary endpoints. Analyses for men with baseline PSA ≤ 1 ng/mL were also stratified by (i) age (<60, 60–64, 65–69, and ≥70 years) and (ii) race/ethnicity (white, black, Hispanic, and Asian). These provide risk estimates for aggressive disease in the absence of nonaggressive disease, and of prostate cancer–related mortality in the absence of death from other causes. Log-rank tests were used to test for differences in incidence curves between races. Confidence intervals (CI) when there were zero events were calculated using an exact binomial test.

In addition, we provide information on what benefits may have been missed and harms prevented had there been 5-yearly screening for men with baseline PSA ≤ 1 ng/mL.

Data Availability

Deidentified PLCO data are available for researchers to access through the Cancer Data Access System.

Results

Of 38,340 men randomized to the intervention arm, 33,897 men with an adequate baseline PSA test were included in this analysis. Through 13 years of follow-up for cancer incidence (median 11.6 years), 4,204 prostate cancers were diagnosed (median time to diagnosis 5.2 years) and 812 aggressive disease cases (median time to diagnosis 5.0 years), and through a median of 14.8 years of follow-up for prostate cancer–related mortality, there were 217 prostate cancer–related deaths in the analysis cohort (median time to death 11.4 years; **Table 2**). PSA values increased with increasing age (Supplementary Table S1). The distributions of PSA levels were similar between races/ethnicities for men with PSA ≤ 2.5 ng/mL (Supplementary Table S2). A total of 81.2% of men had a baseline PSA ≤2.5 ng/mL.

PSA ≤ 1 ng/mL

Overall, 44.6% of men (n = 15,110) had baseline PSA ≤ 1 ng/mL (**Table 2**), none of whom died of prostate cancer within 5 years (95% CI, 0.00%–0.03%). The 5-year cumulative incidences of prostate cancer and aggressive disease were 0.51% (95% CI, 0.39%–0.62%) and 0.08% (95% CI, 0.03%–0.12%), respectively (**Fig. 1**; **Table 3**). A total of 15.7% of men (N = 34, 0.23% of 15,110 with PSA ≤ 1 ng/mL) who died from prostate cancer had PSA ≤ 1 ng/mL (**Table 2**). The cumulative incidences of prostate cancer, aggressive disease, and prostate cancer–related mortality by age are presented in Supplementary Table S3. There were no significant differences by age in aggressive disease incidence at 5 or 10 years (P = 0.53 and P = 0.43, respectively). For prostate cancer incidence, there was no significant difference by age within 5 years (P = 0.12), although differences appear at 10 years (P = 0.004; **Fig. 2**).

MSKCC recommends discontinuing screening in men aged ≥60 years with PSA < 1 ng/mL (18). In our study, 40.7% of men aged ≥60 years (N = 9,449) had baseline PSA ≤ 1 ng/mL, and their 10-year cumulative incidence of aggressive disease was 0.48% (95% CI, 0.33%–0.62%), while prostate cancer–related mortality was 0.07% (95% CI, 0.01%–0.13%; **Table 3**). Within 15 years, prostate cancer–related mortality in men aged ≥60 years was 0.31% (95% CI, 0.18%–0.45%).

If we instead consider men aged ≥65 years with PSA ≤ 1 ng/mL, the results for the 36.6% of men (N = 4,553) who had baseline PSA < 1 ng/mL were very similar to the results for men aged ≥60 years with PSA < 1 ng/mL. The 10-year cumulative incidence of aggressive disease was 0.53% (95% CI, 0.30%–0.76%), and prostate cancer–related mortality was 0.08% (95% CI, 0.00%–0.16%). Within 15 years, prostate cancer–related mortality was 0.29% (95% CI, 0.10%–0.48%; **Table 3**).

Only 1.0% (153/14,780) of men with baseline PSA ≤ 1 ng/mL had at least one (mean of 3.5 further tests in the following four screening rounds) further PSA test exceed 4 ng/mL during the following four screening rounds, of whom 44 (29%) had a biopsy during the first 5 years of follow-up, before they would have been screened again with a 5-year screening interval. Eleven of these men were diagnosed with cancer within 5 years of their baseline PSA, of whom three had aggressive disease. Three of these 11 men died from prostate cancer at 6, 10, and 14 years after the baseline PSA test (2/3 of the men with aggressive disease, and one with nonaggressive disease at diagnosis). Therefore, at most eight prostate cancer–related deaths were prevented by screening men with baseline PSA ≤ 1 ng/mL annually.

PSA ≤ 0.5 ng/mL

We consider PSA ≤ 0.5 ng/mL as an alternative to PSA ≤ 1 ng/mL for the question of when it may be appropriate to stop screening. When restricted to men aged ≥65 years, 11.7% of men (N = 1,454) had baseline PSA ≤ 0.5 ng/mL. None of these men died from prostate cancer within 15 years (95% CI, 0.00%–0.59%), and only three aggressive cancers were diagnosed within 10 years, corresponding to a 10-year cumulative incidence of 0.25% (95% CI, 0.00%–0.53%; **Table 3**).

The results for the 13.1% of men (N = 3,048) aged ≥60 years were similar to the results for the men aged ≥65 years; the 15-year cumulative incidence of prostate cancer–related mortality was 0.13% (95% CI, 0.00%–0.28%), and the 10-year cumulative incidence of aggressive disease was 0.32% (95% CI, 0.10%–0.54%; eight cancers).

Overall, 14.3% of men had baseline PSA ≤ 0.5 ng/mL, none of whom died from prostate cancer within 5 years (95% CI, 0.00%–0.08%). The 10-year cumulative incidences of prostate cancer and aggressive disease were 0.76% (95% CI, 0.50%–1.02%) and 0.29% (95% CI, 0.13%–0.46%). Six men (2.8%) who died from prostate cancer over 15 years had baseline PSA ≤ 0.5 ng/mL (Supplementary Table S3), a cumulative incidence of 0.10% (95% CI, 0.00%–0.20%).

Table 2. Demographic information for men without a prostate cancer diagnosis, incidence, aggressive disease, and mortality.

Age	No cancer ($n = 29,693$) *n* (%)	Incidence ($n = 4,204$) *n* (%)	Aggressive disease ($n = 812$) *n* (%)	Mortality ($n = 217$) *n* (%)	Total ($N = 33,897$) *n* (%)
<60	9,737 (32.8)	957 (22.8)	160 (19.7)	27 (12.4)	10,694 (31.5)
60–64	9,327 (31.4)	1,436 (34.2)	285 (35.1)	71 (32.7)	10,763 (31.8)
65–69	6,742 (22.7)	1,204 (28.6)	243 (29.9)	65 (30.0)	7,946 (23.4)
70+	3,887 (13.1)	607 (14.4)	124 (15.3)	54 (24.9)	4,494 (13.3)
Prior PSA					
Prior PSA	13,293 (44.8)	2,070 (49.2)	366 (45.1)	97 (44.7)	15,363 (45.3)
No prior PSA	13,709 (46.2)	1,795 (42.7)	385 (47.4)	106 (48.8)	15,504 (45.7)
Unknown	2,691 (9.1)	339 (8.1)	61 (7.5)	14 (6.5)	3,030 (8.9)
Race/ethnicity					
White, non-Hispanic	26,368 (88.8)	3,770 (89.7)	709 (87.3)	189 (87.1)	30,138 (88.9)
Black, non-Hispanic	1,173 (4.0)	232 (5.5)	54 (6.7)	19 (8.8)	1,405 (4.1)
Asian	1,229 (4.1)	108 (2.6)	27 (3.3)	3 (1.4)	1,337 (3.9)
Hispanic	626 (2.1)	63 (1.5)	12 (1.5)	4 (1.8)	689 (2.0)
Other	225 (0.8)	27 (0.6)	9 (1.1)	1 (0.5)	252 (0.7)
Unknown	72 (0.2)	4 (0.1)	1 (0.1)	1 (0.5)	76 (0.2)
Family history					
Family history	2,075 (7.0)	463 (11.0)	87 (10.7)	17 (7.8)	2,538 (7.5)
No family history	26,848 (90.4)	3,637 (86.5)	705 (86.8)	194 (89.4)	30,485 (89.9)
Unknown	770 (2.6)	104 (2.5)	20 (2.5)	6 (2.8)	874 (2.6)
Year of enrollment					
1993–1995	9,020 (30.4)	1,656 (39.4)	343 (42.2)	110 (50.7)	10,676 (31.5)
1996–1998	13,642 (45.9)	1,860 (44.2)	353 (43.5)	83 (38.2)	15,502 (45.7)
1999–2001	7,031 (23.7)	688 (16.4)	116 (14.3)	24 (11.1)	7,719 (22.8)
Positive baseline DRE					
DRE positive	1,889 (6.4)	560 (13.3)	146 (18.0)	53 (24.4)	2,449 (7.2)
DRE negative	27,804 (93.6)	3,644 (86.7)	666 (82.0)	164 (75.6)	31,448 (92.8)
Prior biopsy					
Prior biopsy	1,304 (4.4)	320 (7.6)	50 (6.2)	14 (6.5)	1,624 (4.8)
No prior biopsy	28,324 (95.4)	3,881 (92.3)	762 (93.8)	202 (93.1)	32,205 (95.0)
Unknown	65 (0.2)	3 (0.1)	0 (0.0)	1 (0.5)	68 (0.2)
PSA category					
≤0.5 ng/mL	4,809 (16.2)	53 (1.3)	23 (2.8)	6 (2.8)	4,862 (14.3)
≤1 ng/mL	14,730 (49.6)	380 (9.0)	99 (12.2)	34 (15.7)	15,110 (44.6)
1–2.5 ng/mL	10,922 (36.8)	1,500 (35.7)	266 (32.8)	66 (30.4)	12,422 (36.6)
2.5–4 ng/mL	2,625 (8.8)	1,050 (25.0)	165 (20.3)	41 (18.9)	3,675 (10.8)
>4 ng/mL	1,416 (4.8)	1,274 (30.3)	282 (34.7)	76 (35.0)	2,690 (7.9)
≤0.5 ng/mL, age ≥60	3,009 (10.1)	39 (0.9)	17 (2.1)	5 (2.3)	3,048 (9.0)
≤0.5 ng/mL, age ≥65	1,433 (4.8)	21 (0.5)	8 (1.0)	0 (0.0)	1,454 (4.3)
≤1 ng/mL, age ≥60	9,174 (30.9)	275 (6.5)	75 (9.2)	30 (13.8)	9,449 (27.9)
≤1 ng/mL, age ≥65	4,419 (14.9)	134 (3.2)	39 (4.8)	13 (6.0)	4,553 (13.4)

PSA 1.01–2.5 ng/mL

The ACS suggests that a 2-year screening interval may be appropriate for all men with PSA < 2.5 ng/mL. However, the cumulative incidences of prostate cancer and aggressive disease in our study are noticeably higher for men with PSA 1.01–2.5 ng/mL than for men with PSA ≤ 1 ng/mL (**Table 2**). The 36.7% of men with baseline PSA 1–2.5 ng/mL contributed 30.4% of prostate cancer–related deaths over 15 years. The 2- and 5-year cumulative incidences of prostate cancer were much higher than for PSA ≤ 1 ng/mL: 0.62% (95% CI, 0.48%–0.76%) and 3.1% (95% CI, 2.8%–3.4%), respectively (**Table 3**). The 5-year cumulative incidence of aggressive disease was 0.51% (95% CI, 0.38%–0.74%). There were significant differences between the incidence, aggressive disease, and mortality curves between men with baseline PSA ≤ 1 ng/mL and 1.01–2.5 ng/mL ($P < 0.0001$).

Racial/ethnic differences among men with baseline PSA ≤ 1 ng/mL

The cumulative incidences of prostate cancer, aggressive disease, and prostate cancer–related mortality by race/ethnicity are presented in **Table 4**. There were no significant differences by race/ethnicity in prostate cancer incidence or aggressive disease incidence at 5 years ($P = 0.85$ and $P = 0.48$, respectively). However, at 10 years there were significant differences in both cancer incidence and aggressive disease by race/ethnicity ($P = 0.007$ and $P = 0.005$, respectively). Black men had the highest 10-year risks: 4.1% (95% CI, 2.2%–5.9%) prostate

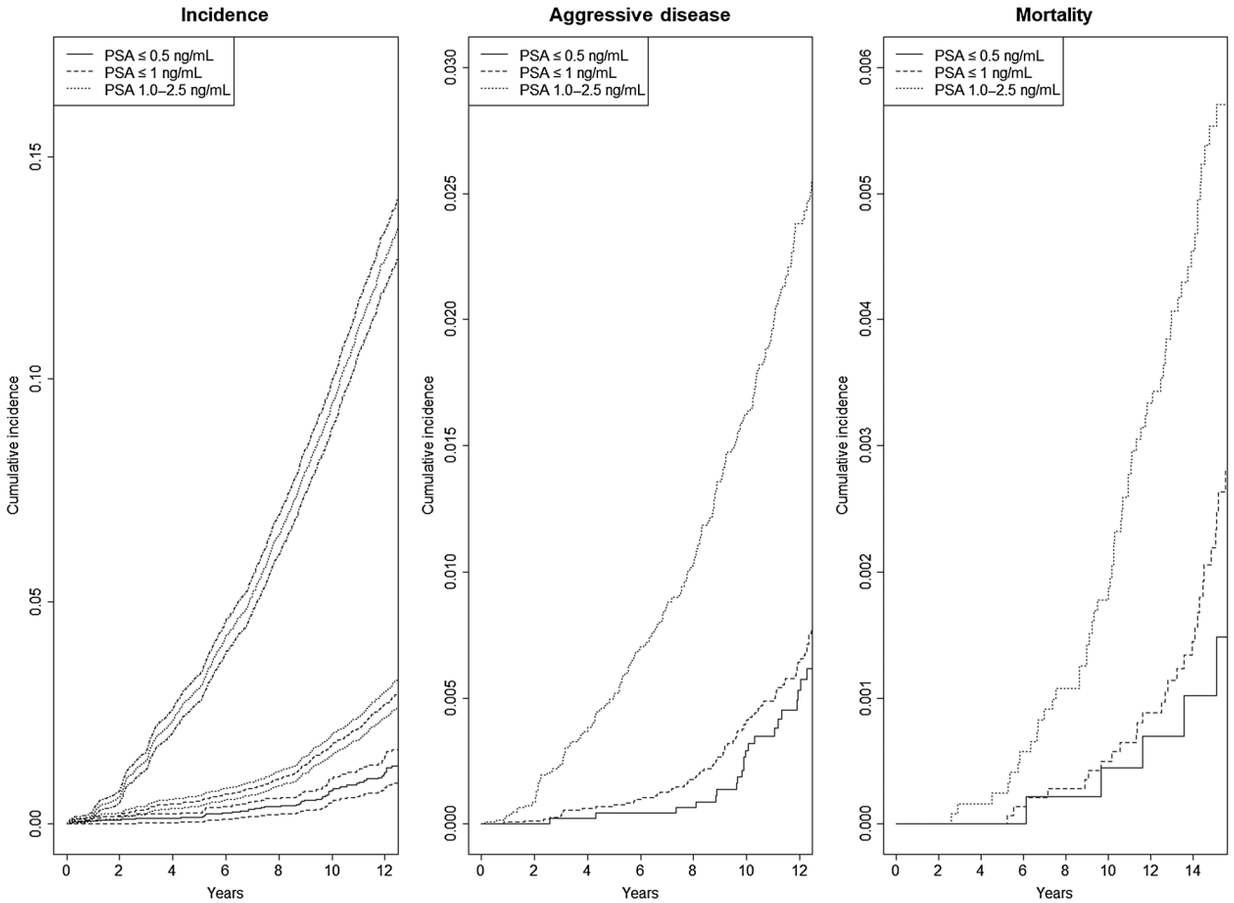

Figure 1.
Cumulative incidence of prostate cancer incidence, aggressive disease, and prostate cancer–related mortality by baseline PSA level.

cancer incidence and 1.6% (95% CI, 0.40%–2.9%) aggressive disease incidence (**Fig. 2**; **Table 4**). Asian-American men had the lowest 10-year risks: 1.1% (0.22%–1.9%) for incidence and 0% (0%–0.69%) for aggressive disease (**Table 4**). The 15-year cumulative incidence of prostate cancer–related mortality was 0.20% (95% CI, 0.11%–0.28%) for white men, 0.71% (95% CI, 0.00%–1.71%) for black men, and 1.86% (95% CI, 0.00%–4.39%) for Hispanic men. No Asian-American men died of prostate cancer during follow-up.

Discussion

A 5-year screening interval for men with PSA ≤ 1 ng/mL would reduce invasive procedures and harms versus annual screening, but more data on its safety, in particular, risk of prostate cancer–related death, are needed before it could be recommended. Over 15 years of follow-up, the PLCO has now accrued over 200 prostate cancer–related deaths. In PLCO, none of the 15,110 men with baseline PSA ≤ 1 ng/mL died from prostate cancer within 5 years. Their 0.08% 5-year cumulative incidence of aggressive prostate cancer was extremely low, demonstrating that returning earlier than 5 years identified little aggressive disease. Eight prostate cancers cases which did not result in death from prostate cancer were diagnosed as a result of screening almost 15,000 men annually instead of at a 5-year screening interval. The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, with less frequent screening than the annual screening in the PLCO, showed no mortality benefit until year 8 (23), so no cancer-related deaths are likely preventable in the first 5 years particularly given the long natural history of prostate cancer.

Stopping screening requires very low long-term risk of prostate cancer–related mortality. None of the 1,454 (11.7%) men aged ≥65 years who had PSA ≤ 0.5 ng/mL died from prostate cancer over 15 years, and their 0.25% 10-year risk of aggressive disease was low. They may have sufficiently low risk to consider immediately discontinuing screening, since in 10 years they would all attain ages where guidelines recommend ending screening.

Although there were no significant racial/ethnic differences among men with baseline PSA ≤ 1 ng/mL for 5-year risk, this

Table 3. Cumulative incidence of prostate cancer and aggressive disease at 2, 5, and 10 years, and prostate cancer–related mortality at 2, 5, 10, and 15-years, by baseline PSA.

	Incidence			Aggressive disease			Mortality		
	N events	Cumulative incidence (95% CI)		*N* events	Cumulative incidence (95% CI)		*N* events	Cumulative incidence (95% CI)	
Baseline PSA					**At 2 years**				
≤0.5 ng/mL	4	0.08%	(0.00–0.16)	0	0.00%	(0.00–0.08)	0	0.00%	(0.00–0.08)
≤1 ng/mL	27	0.18%	(0.11–0.25)	2	0.01%	(0.00–0.03)	0	0.00%	(0.00–0.03)
1.0–2.5 ng/mL	78	0.62%	(0.48–0.76)	11	0.09%	(0.04–0.14)	0	0.00%	(0.00–0.03)
≤0.5 ng/mL, age ≥60	3	0.10%	(0.00–0.21)	0	0.00%	(0.00–0.12)	0	0.00%	(0.00–0.12)
≤0.5 ng/mL, age ≥65	2	0.14%	(0.00–0.33)	0	0.00%	(0.00–0.26)	0	0.00%	(0.00–0.26)
≤1 ng/mL, age ≥60	17	0.18%	(0.09–0.27)	2	0.02%	(0.00–0.05)	0	0.00%	(0.00–0.04)
≤1 ng/mL, age ≥65	12	0.26%	(0.11–0.41)	0	0.00%	(0.00–0.08)	0	0.00%	(0.00–0.08)
Baseline PSA					**At 5 years**				
≤0.5 ng/mL	7	0.15%	(0.04–0.25)	2	0.04%	(0.00–0.10)	0	0.00%	(0.00–0.08)
≤1 ng/mL	77	0.51%	(0.39–0.62)	11	0.08%	(0.03–0.12)	0	0.00%	(0.00–0.03)
1.0–2.5 ng/mL	376	3.06%	(2.75–3.36)	62	0.51%	(0.38–0.74)	3	0.02%	(0.00–0.05)
≤0.5 ng/mL, age ≥60	5	0.17%	(0.00–0.31)	1	0.03%	(0.00–0.10)	0	0.00%	(0.00–0.13)
≤0.5 ng/mL, age ≥65	4	0.28%	(0.01–0.56)	1	0.07%	(0.00–0.21)	0	0.00%	(0.00–0.27)
≤1 ng/mL, age ≥60	55	0.60%	(0.44–0.76)	9	0.10%	(0.03–0.16)	0	0.00%	(0.00–0.04)
≤1 ng/mL, age ≥65	32	0.73%	(0.48–0.98)	4	0.09%	(0.00–0.18)	0	0.00%	(0.00–0.09)
Baseline PSA					**At 10 years**				
≤0.5 ng/mL	33	0.76%	(0.50–1.02)	12	0.29%	(0.13–0.46)	2	0.04%	(0.00–0.11)
≤1 ng/mL	245	1.70%	(1.48–1.92)	55	0.38%	(0.28–0.49)	7	0.05%	(0.01–0.09)
1.0–2.5 ng/mL	1094	9.42%	(8.88–9.95)	181	1.62%	(1.39–1.86)	22	0.19%	(0.11–0.26)
≤0.5 ng/mL, age ≥60	23	0.87%	(0.51–1.22)	8	0.32%	(0.10–0.54)	1	0.04%	(0.00–0.11)
≤0.5 ng/mL, age ≥65	14	1.12%	(0.53–1.71)	3	0.25%	(0.00–0.53)	0	0.00%	(0.00–0.32)
≤1 ng/mL, age ≥60	175	2.08%	(1.77–2.38)	39	0.48%	(0.33–0.62)	6	0.07%	(0.01–0.13)
≤1 ng/mL, age ≥65	91	2.30%	(1.83–2.77)	20	0.53%	(0.30–0.76)	3	0.08%	(0.00–0.16)
Baseline PSA					**At 15 years**				
≤0.5 ng/mL	[a]	[a]	[a]	[a]	[a]	[a]	4	0.10%	(0.00–0.20)
≤1 ng/mL	[a]	[a]	[a]	[a]	[a]	[a]	24	0.21%	(0.12–0.30)
1.0–2.5 ng/mL	[a]	[a]	[a]	[a]	[a]	[a]	56	0.55%	(0.41–0.70)
≤0.5 ng/mL, age ≥60	[a]	[a]	[a]	[a]	[a]	[a]	3	0.13%	(0.00–0.28)
≤0.5 ng/mL, age ≥65	[a]	[a]	[a]	[a]	[a]	[a]	0	0.00%	(0.00–0.59)
≤1 ng/mL, age ≥60	[a]	[a]	[a]	[a]	[a]	[a]	21	0.31%	(0.18–0.45)
≤1 ng/mL, age ≥65	[a]	[a]	[a]	[a]	[a]	[a]	9	0.29%	(0.10–0.48)

[a]Incidence data was only available up to 13 years of follow-up.

was not true for 10-year risks. Black men had 1.6% 10-year risk of aggressive disease, white men had 0.4% risk, and no Asian-American men had aggressive disease, suggesting the potential for considering racial/ethnic differences in screening intervals or tailoring guideline implementation strategies for specific racial/ethnic groups.

The ACS recommends a 2-year screening interval for all men with PSA < 2.5 ng/mL. However, PSA thresholds within this range provided further risk stratification, with substantially lower risks for men with PSA ≤ 0.5 ng/mL and ≤1 ng/mL than PSA 1.0–2.5 ng/mL. This suggests a need for separate guidelines for PSA ≤ 1 ng/mL versus PSA 1.0–2.5 ng/mL. Caution should be exercised when recommending biopsy, especially considering that recent studies in the United States have shown the risk of infection following biopsy to be as high as 3.5% and rising (24), and the risk of sepsis to be 1.5% (25). The use of prebiopsy multi-parametric MRI has the potential to avoid immediate biopsies for a subset of men, and enhance detection of clinically significant disease (26).

Risk prediction models have been proposed to determine screening intervals and management (13, 16, 27, 28). There are over 100 unique prostate cancer risk prediction models which include PSA, although many have not been validated (29). However no prostate cancer screening guidelines yet recommend the use of any risk calculator. Our data support efforts to further stratify men beyond the use of PSA to determine appropriate screening intervals; the increasing number of strata which predict risk (e.g., age, race, and PSA level) suggest use of a validated risk calculator would be appropriate.

A key component of most prostate cancer screening guidelines is shared decision-making between men considering screening and their physician. These discussions should include information on what screening involves, and the potential benefits and harms of screening, as well as providing men with information on their risk of prostate cancer. Information on risk of aggressive disease and prostate cancer–related mortality may improve shared decision-making discussions, as these outcomes are more clinically relevant. The risk information provided in this study may also help men decide when to stop screening.

Previous studies supporting longer screening intervals for men with low PSA levels include the ERSPC (30), as well as

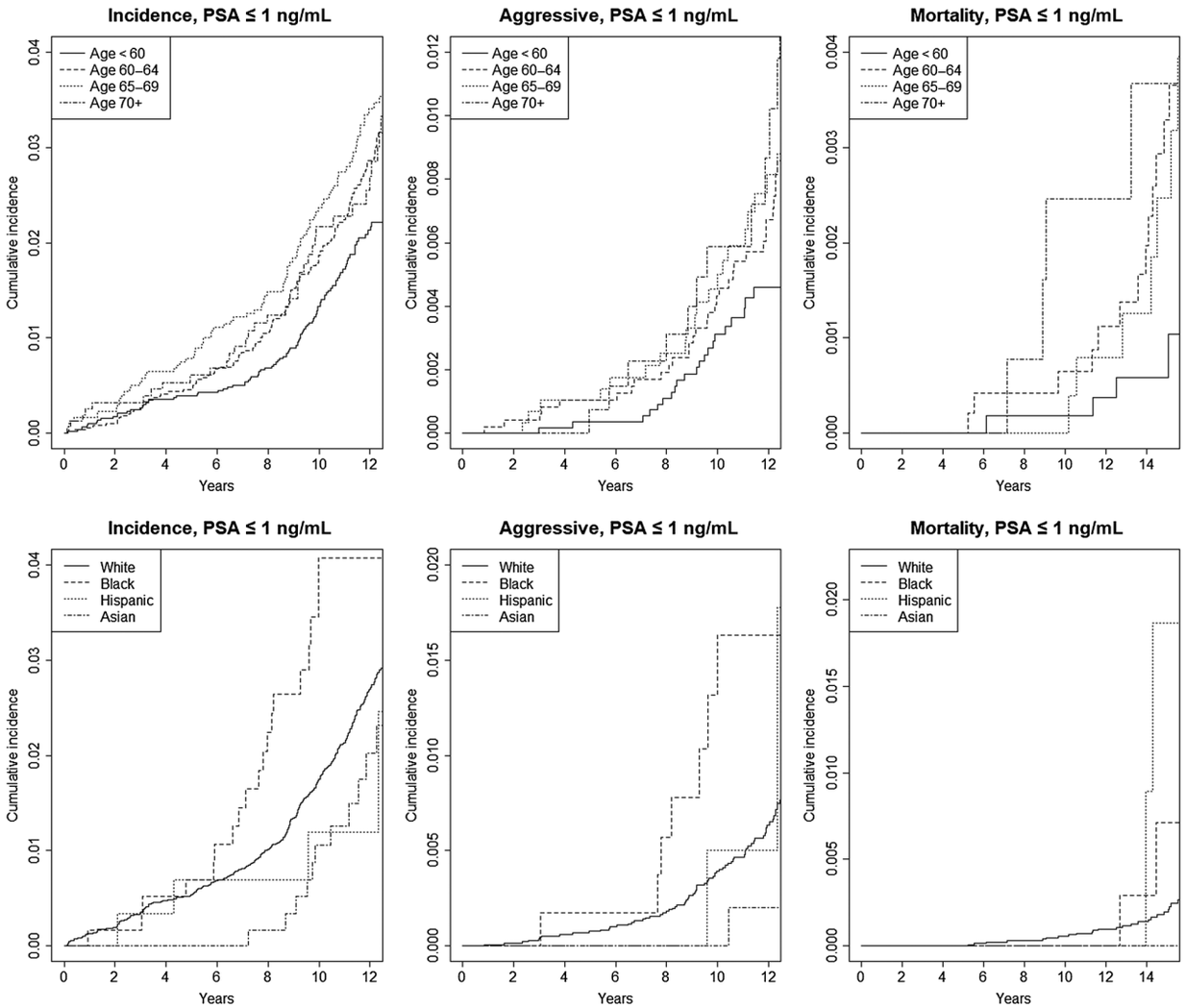

Figure 2.

Cumulative incidence of prostate cancer incidence, aggressive disease, and prostate cancer–related mortality for men with baseline PSA ≤ 1 ng/mL, by age and race/ethnicity.

observational (17, 31, 32) and simulation studies (4). Midlife PSA has been shown to be predictive of prostate cancer and lethal prostate cancer for up to 25–30 years (17, 32–34). A recent study showed that black men in the Southern Community Cohort Study with a PSA of 1–3 ng/mL at age 40–64 years were also at higher risk of total and aggressive prostate cancer after a median of 4.4 years follow-up, compared with men with PSA < 1 ng/mL (31). Our study provides empirical confirmation of the safety of a longer interval using data collected in a prospective randomized control trial. Cost-effectiveness analyses have also supported longer-than-annual screening intervals (35) and varying screening intervals by PSA result (36).

Our study has limitations. While 15 years may be too short to evaluate the full effect on mortality given the long natural history of prostate cancer (37), this is a screening study with one of the longest follow-ups available and one of the largest number of prostate cancer–related deaths. The number of deaths from prostate cancers is small in men with low PSA levels, resulting in wide confidence intervals. Because prostate cancer is often screen-detected prior to symptoms, men with higher PSA levels or positive DREs were more likely to have been invited for a biopsy and hence diagnosed. The 5-year cancer incidence risks may therefore overestimate those observed with a true 5-year interval, rather than annual screening for 5 years. However, the 0.08% 5-year cumulative incidence of aggressive prostate cancer among men with PSA ≤ 1 ng/mL was extremely low, even with annual screening. Vice versa, we may be underestimating mortality risks as treatment during follow-up may have prevented death from prostate cancer, although a maximum of eight deaths were prevented by annual screening. Finally, there were only small numbers of non-white racial/ethnic groups in PLCO, resulting in wide CIs.

In men with PSA levels ≤1 ng/mL, continued frequent PSA testing may contribute to screening harms with a low chance of

Table 4. Cumulative incidence of prostate cancer and aggressive disease at 2, 5, and 10 years, and prostate cancer–related mortality at 2, 5, 10, and 15-years, for men with baseline PSA ≤ 1 ng/mL, by race/ethnicity.

	Incidence			Aggressive disease			Mortality		
	N events	Cumulative incidence (95% CI)		*N* events	Cumulative incidence (95% CI)		*N* events	Cumulative incidence (95% CI)	
					At 2 years				
White	26	0.19%	(0.12–0.27)	2	0.01%	(0.00–0.04)	0	0.00%	(0.00–0.03)
Black	1	0.17%	(0.00–0.50)	0	0.00%	(0.00–0.63)	0	0.00%	(0.00–0.62)
Hispanic	0	0.00%	(0.00–1.26)	0	0.00%	(0.00–1.26)	0	0.00%	(0.00–1.24)
Asian	0	0.00%	(0.00–0.59)	0	0.00%	(0.00–0.59)	0	0.00%	(0.00–0.58)
					At 5 years				
White	71	0.54%	(0.41–0.66)	10	0.08%	(0.03–0.12)	0	0.00%	(0.00–0.03)
Black	4	0.70%	(0.01–1.38)	1	0.18%	(0.00–0.52)	0	0.00%	(0.00–0.65)
Hispanic	2	0.70%	(0.00–1.66)	0	0.00%	(0.00–1.35)	0	0.00%	(0.00–1.28)
Asian	0	0.00%	(0.00–0.61)	0	0.00%	(0.00–0.61)	0	0.00%	(0.00–0.60)
					At 10 years				
White	215	1.75%	(1.52–1.98)	47	0.39%	(0.28–0.51)	7	0.06%	(0.01–0.10)
Black	19	4.07%	(2.22–5.89)	7	1.63%	(0.40–2.85)	0	0.00%	(0.00–0.74)
Hispanic	3	1.20%	(0.00–2.56)	1	0.50%	(0.00–1.48)	0	0.00%	(0.00–1.42)
Asian	6	1.06%	(0.22–1.90)	0	0.00%	(0.00–0.69)	0	0.00%	(0.00–0.63)
					At 15 years				
White	[a]	[a]	[a]	[a]	[a]	[a]	20	0.20%	(0.11–0.28)
Black	[a]	[a]	[a]	[a]	[a]	[a]	2	0.71%	(0.00–1.71)
Hispanic	[a]	[a]	[a]	[a]	[a]	[a]	2	1.86%	(0.00–4.39)
Asian	[a]	[a]	[a]	[a]	[a]	[a]	0	0.00%	(0.00–1.02)

[a]Incidence data was only available up to 13 years of follow-up.

finding aggressive or fatal cancers. Our findings confirm that men with PSA levels ≤ 1 ng/mL could have 5-yearly screening, reducing the number of screens at minimal increased risk, and older men with low PSA levels might even stop screening.

Disclosure of Potential Conflicts of Interest

C.D. Berg reports receiving personal fees from GRAIL, Inc and personal fees from Medial Early Sign, LLC outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

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