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Risk of prostate cancer death following a low prostate-specific antigen level in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening 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) aged 55–74yrs with a baseline PSA test in the intervention arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial (USA, 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 mortality for men with baseline PSA 0.5ng/ml (N=4,862), 1ng/ml (N=15,110) and 1.01–2.5ng/ml (N=12,422). 217 men died from prostate cancer through 15yrs, though no men with PSA 1ng/ml died from prostate cancer within 5yrs (95% 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 1ng/ml, and higher for men with baseline PSA 1.01–2.5ng/ml (0.51%, 95% CI: 0.38–0.74). No men aged 65yrs with PSA 0.5ng/ml died from prostate cancer within 15yrs (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 to white men, black men with PSA 1ng/ml had higher 10-year rates of aggressive disease (1.6% vs. 0.4%, $p < 0.01$). 5-year screening intervals may be appropriate for the 45% of men with PSA 1ng/ml. Men aged 65yrs with PSA 0.5ng/ml could consider stopping screening. Substantial risk disparities suggest appropriate screening intervals could depend on race/ethnicity.

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Keywords

PSA; prostate cancer; screening; PLCO; screening intervals; risk stratification; precision screening

Introduction

Death due to prostate cancer is the second leading cause of cancer death in US 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 aged 50–69 (with biopsy referral at 4ng/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 United States 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 towards 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 <2.5ng/ml,[8] while Memorial Sloan Kettering Cancer Center (MSKCC) recommended a 6–10 year interval for men with PSA<1ng/ml, and to stop screening men aged 60 years with PSA<1ng/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 deaths. We estimated risks of prostate cancer, aggressive prostate cancer (Gleason 8 and/or Stage III/IV), and prostate cancer death, among men with low baseline PSA levels, in the PSA screening arm of the PLCO. [19] Additionally, we consider for which men, based on PSA and age, stopping screening may be appropriate.

Methods

The PLCO was a large, multi-center, randomized controlled trial designed to assess the effectiveness of screening in reducing disease-specific mortality. We restrict our analyses to men aged 55–74 years randomized to the intervention arm (PSA testing at baseline and 5 further annual PSA screens, and a digital rectal exam (DRE) at baseline and 3 further annual DRE screens) between 1993–2001. 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 six months. From April 1995, men

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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 >4ng/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.

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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 12/31/2009 or 13 years of follow-up, whichever came first, and for mortality through 12/31/2012, 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 12/31/2009; 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, pathological cancer stage was used, otherwise clinical stage. Since 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 12/31/2012.

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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) 0.5ng/ml, (ii) 1ng/ml (including 0.5ng/ml) and (iii) 1.01–2.5ng/ml. These thresholds were chosen based on current screening guidelines, where 1ng/ml is a common cutoff for determining the screening interval (e.g. NCCN [7] and EAU-ESTRO-SIOG [6] guidelines), and a cutoff of 2.5ng/ml is currently used by the American Cancer Society.[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, Asian). These provide risk estimates for aggressive disease in the absence of non-aggressive disease, and of prostate cancer 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 when there were zero events were calculated using an exact binomial test.

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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.

Results

Of 38,340 men randomized to the intervention arm, 33,897 men with an adequate baseline PSA test were included in the current 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 mortality, there were 217 prostate cancer deaths in the analysis cohort (median time to death 11.4 years) (Table 2). PSA values increased with increasing age (Supplementary Table 1). The distributions of PSA levels were similar between races/ethnicities for men with PSA ≥ 2.5 ng/ml (Supplementary Table 2). 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 (Figure 1, Table 3). 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 mortality by age are presented in Supplementary Table 3. 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 ($p=0.004$) (Figure 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 mortality was 0.07% (95% CI: 0.01%–0.13%) (Table 3). Within 15 years, prostate cancer mortality in the 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 mortality was 0.08% (95% CI: 0.00%–0.16%). Within 15 years, prostate cancer 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 4 screening rounds) further PSA test exceed 4 ng/ml during the following 4 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. 11 of these men were diagnosed with cancer within 5 years of their baseline PSA, of whom 3 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 non-aggressive disease at diagnosis). Therefore at most 8 prostate cancer 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 3 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 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%) (8 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 3), a cumulative incidence of 0.10% (95% CI: 0.00%–0.20%).

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 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 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 cancer incidence and 1.6% (95% CI: 0.40%–2.9%) aggressive disease incidence (Figure 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 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 1ng/ml would reduce invasive procedures and harms versus annual screening, but more data on its safety, in particular, risk of prostate cancer death, are needed before it could be recommended. Over 15 years of follow-up, the PLCO has now accrued over 200 prostate cancer deaths. In PLCO, none of the 15,110 men with baseline PSA 1ng/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 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 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 mortality. None of the 1454 (11.7%) men aged 65 years who had PSA 0.5ng/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 1ng/ml for 5-year risk, this 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<2.5ng/ml. However, PSA thresholds within this range provided further risk stratification, with substantially lower risks for men with PSA 0.5ng/ml and 1ng/ml than PSA 1.0–2.5ng/ml. This suggests a need for separate guidelines for PSA 1ng/ml, vs. PSA 1.0–2.5ng/ml. Caution should be exercised when recommending biopsy, especially considering that recent studies in the US 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 pre-biopsy 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, 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 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 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 1–3ng/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 to men with PSA <1ng/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 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 1ng/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, though a maximum of 8 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 1ng/ml, continued frequent PSA testing may contribute to screening harms with a low chance of finding aggressive or fatal cancers. Our findings confirm that men with PSA levels 1ng/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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

DRE	Digital rectal examination
ERSPC	European Randomized Study of Screening for Prostate Cancer
PSA	prostate specific antigen
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening trial

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

Figure 2:
Cumulative incidence of prostate cancer incidence, aggressive disease and prostate cancer mortality for men with baseline PSA $\leq$ 1 ng/ml, by age and race/ethnicity

Table 1:

Prostate cancer screening guidelines

Organization	Year of recommendations	Age range	Screening recommendations
American Urological Association [¹]	2018	shared decision making for men aged 55–69 years at “average risk”	“a routine screening interval of two years or more may be preferred over annual screening”
National Comprehensive Cancer Network [²]	2018	shared decision making for men aged 45–75 years	PSA<1ng/ml (DRE normal, if done): 2–4 year interval PSA 1–3ng/ml (DRE normal, if done): 1–2 year interval
United States Preventive Services Task Force [³]	2018	men aged 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 [⁴]	2018	n/a	“The AAFP does not recommend routine prostate-specific antigen (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.”
European Association of Urology (EAU) - European Society for Radiotherapy & Oncology (ESTRO) - International Society of Geriatric Oncology (SIOG) [⁵]	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>1ng/ml at age 40 years: 2-year interval. PSA>2ng/ml at age 60 years: 2-year interval. Otherwise 8-year interval
American College of Physicians [⁶]	2013	shared decision making for men aged 50–69 years at “average risk” with a life expectancy of more than 10–15 years	“longer [than annual] intervals may be indicated”
American Cancer Society [⁷]	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

[1] American Urological Association. Early Detection of Prostate Cancer 2018. Available from: [https://www.auanet.org/guidelines/prostate-cancer-early-detection-\(2013-reviewed-for-currency-2018\)](https://www.auanet.org/guidelines/prostate-cancer-early-detection-(2013-reviewed-for-currency-2018)).

[2] NCCN Guidelines Version 2.2018 Prostate Cancer Early Detection, April 5th 2018

[3] U.S. Preventive Services Task Force. Final Recommendation Statement. Prostate Cancer: Screening. 2018.

[4] AAFP Clinical Preventive Service Recommendation: Prostate Cancer. Available from: <https://www.aafp.org/patient-care/clinical-recommendations/all/prostate-cancer.html>

[5] Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *European urology* 2017;71(4):618–29.

[6] Qaseem A, Barry MJ, Denberg TD, et al. Screening for prostate cancer: a guidance statement from the Clinical Guidelines Committee of the American College of Physicians. *Annals of internal medicine* 2013;158(10):761–769

[7] Wolf, A.M., Wender, R.C., Etzioni, R.B., Thompson, I.M., D’Amico, A.V., Volk, R.J., Brooks, D.D., Dash, C., Guessous, I., Andrews, K. and DeSantis, C., 2010. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA: a cancer journal for clinicians*, 60(2), pp.70–98.

Table 2:

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

Age	No Cancer (n=29,693)		Incidence (n=4,204)		Aggressive Disease (n=812)		Mortality (n=217)		Total (N=33,897)	
	%	N	%	N	%	N	%	N	%	N
<60	32.8%	9,737	22.8%	957	19.7%	160	12.4%	27	31.5%	10,694
60–64	31.4%	9,327	34.2%	1,436	35.1%	285	32.7%	71	31.8%	10,763
65–69	22.7%	6,742	28.6%	1,204	29.9%	243	30.0%	65	23.4%	7,946
70+	13.1%	3,887	14.4%	607	15.3%	124	24.9%	54	13.3%	4,494
Prior PSA										
Prior PSA	44.8%	13,293	49.2%	2,070	45.1%	366	44.7%	97	45.3%	15,363
No Prior PSA	46.2%	13,709	42.7%	1,795	47.4%	385	48.8%	106	45.7%	15,504
Unknown	9.1%	2,691	8.1%	339	7.5%	61	6.5%	14	8.9%	3,030
Race/Ethnicity										
White, Non-Hispanic	88.8%	26,368	89.7%	3,770	87.3%	709	87.1%	189	88.9%	30,138
Black, Non-Hispanic	4.0%	1,173	5.5%	232	6.7%	54	8.8%	19	4.1%	1,405
Asian	4.1%	1,229	2.6%	108	3.3%	27	1.4%	3	3.9%	1,337
Hispanic	2.1%	626	1.5%	63	1.5%	12	1.8%	4	2.0%	689
Other	0.8%	225	0.6%	27	1.1%	9	0.5%	1	0.7%	252
Unknown	0.2%	72	0.1%	4	0.1%	1	0.5%	1	0.2%	76
Family History										
Family History	7.0%	2,075	11.0%	463	10.7%	87	7.8%	17	7.5%	2,538
No Family History	90.4%	26,848	86.5%	3,637	86.8%	705	89.4%	194	89.9%	30,485
Unknown	2.6%	770	2.5%	104	2.5%	20	2.8%	6	2.6%	874
Year of Enrollment										
1993–1995	30.4%	9,020	39.4%	1,656	42.2%	343	50.7%	110	31.5%	10,676
1996–1998	45.9%	13,642	44.2%	1,860	43.5%	353	38.2%	83	45.7%	15,502
1999–2001	23.7%	7,031	16.4%	688	14.3%	116	11.1%	24	22.8%	7,719

Age	No Cancer (n=29,693)		Incidence (n=4,204)		Aggressive Disease (n=812)		Mortality (n=217)		Total (N=33,897)	
	%	N	%	N	%	N	%	N	%	N
Positive Baseline DRE										
DRE Positive	6.4%	1,889	13.3%	560	18.0%	146	24.4%	53	7.2%	2,449
DRE Negative	93.6%	27,804	86.7%	3,644	82.0%	666	75.6%	164	92.8%	31,448
Prior biopsy										
Prior biopsy	4.4%	1,304	7.6%	320	6.2%	50	6.5%	14	4.8%	1,624
No prior biopsy	95.4%	28,324	92.3%	3,881	93.8%	762	93.1%	202	95.0%	32,205
Unknown	0.2%	65	0.1%	3	0.0%	0	0.5%	1	0.2%	68
PSA Category										
0.5ng/ml	16.2%	4,809	1.3%	53	2.8%	23	2.8%	6	14.3%	4,862
1ng/ml	49.6%	14,730	9.0%	380	12.2%	99	15.7%	34	44.6%	15,110
1–2.5ng/ml	36.8%	10,922	35.7%	1,500	32.8%	266	30.4%	66	36.6%	12,422
2.5–4ng/ml	8.8%	2,625	25.0%	1,050	20.3%	165	18.9%	41	10.8%	3,675
>4ng/ml	4.8%	1,416	30.3%	1,274	34.7%	282	35.0%	76	7.9%	2,690
0.5ng/ml, age 60	10.1%	3,009	0.9%	39	2.1%	17	2.3%	5	9.0%	3,048
0.5ng/ml, age 65	4.8%	1,433	0.5%	21	1.0%	8	0.0%	0	4.3%	1,454
1ng/ml, age 60	30.9%	9,174	6.5%	275	9.2%	75	13.8%	30	27.9%	9,449
1ng/ml, age 65	14.9%	4,419	3.2%	134	4.8%	39	6.0%	13	13.4%	4,553

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

Table 3:

	Incidence		Aggressive Disease		Mortality	
	N events	Cumulative Incidence (95% CI)	N events	Cumulative Incidence (95% CI)	N events	Cumulative Incidence (95% CI)
at 2 yrs						
Baseline PSA						
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)
at 5 yrs						
0.5ng/ml, age 60	3	0.10% (0.00, 0.21)	0	0.00% (0.00, 0.12)	0	0.00% (0.00, 0.12)
0.5ng/ml, age 65	2	0.14% (0.00, 0.33)	0	0.00% (0.00, 0.26)	0	0.00% (0.00, 0.26)
1ng/ml, age 60	17	0.18% (0.09, 0.27)	2	0.02% (0.00, 0.05)	0	0.00% (0.00, 0.04)
1ng/ml, age 65	12	0.26% (0.11, 0.41)	0	0.00% (0.00, 0.08)	0	0.00% (0.00, 0.08)
at 5 yrs						
Baseline PSA						
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)
at 10 yrs						
0.5ng/ml, age 60	5	0.17% (0.00, 0.31)	1	0.03% (0.00, 0.10)	0	0.00% (0.00, 0.13)
0.5ng/ml, age 65	4	0.28% (0.01, 0.56)	1	0.07% (0.00, 0.21)	0	0.00% (0.00, 0.27)
1ng/ml, age 60	55	0.60% (0.44, 0.76)	9	0.10% (0.03, 0.16)	0	0.00% (0.00, 0.04)
1ng/ml, age 65	32	0.73% (0.48, 0.98)	4	0.09% (0.00, 0.18)	0	0.00% (0.00, 0.09)
at 10 yrs						
Baseline PSA						
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)
0.5ng/ml, age 60	23	0.87% (0.51, 1.22)	8	0.32% (0.10, 0.54)	1	0.04% (0.00, 0.11)
0.5ng/ml, age 65	14	1.12% (0.53, 1.71)	3	0.25% (0.00, 0.53)	0	0.00% (0.00, 0.32)

	Incidence			Aggressive Disease			Mortality	
	N events	Cumulative Incidence (95% CI)	N events	Cumulative Incidence (95% CI)	N events	Cumulative Incidence (95% CI)		
1ng/ml, age 60	175	2.08% (1.77, 2.38)	39	0.48% (0.33, 0.62)	6	0.07% (0.01, 0.13)		
1ng/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 yrs								
0.5 ng/ml	*	*	*	*	4	0.10% (0.00, 0.20)		
1 ng/ml	*	*	*	*	24	0.21% (0.12, 0.30)		
1.0–2.5 ng/ml	*	*	*	*	56	0.55% (0.41, 0.70)		
0.5ng/ml, age 60	*	*	*	*	3	0.13% (0.00, 0.28)		
0.5ng/ml, age 65	*	*	*	*	0	0.00% (0.00, 0.59)		
1ng/ml, age 60	*	*	*	*	21	0.31% (0.18, 0.45)		
1ng/ml, age 65	*	*	*	*	9	0.29% (0.10, 0.48)		

* Incidence data is only available up to 13 years of follow-up

Cumulative incidence of prostate cancer and aggressive disease at 2, 5, and 10 years, and prostate cancer mortality at 2, 5, 10 and 15-years, for men with baseline PSA 1 ng/ml, by race/ethnicity

Table 4:

	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	*	*	*	*	20	0.20% (0.11, 0.28)
Black	*	*	*	*	2	0.71% (0.00, 1.71)
Hispanic	*	*	*	*	2	1.86% (0.00, 4.39)
Asian	*	*	*	*	0	0.00% (0.00, 1.02)

* Incidence data is only available up to 13 years of follow-up