New Evidence for the Benefit of Prostate-specific Antigen Screening: Data From 400,887 Kaiser Permanente Patients

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OBJECTIVE To investigate whether prostate cancer screening with prostate-specific antigen (PSA) is beneficial in reducing prostate cancer mortality, and to determine optimal screening intervals and age groups to be screened.

METHODS This is a retrospective cohort study of 400,887 men under age 80, with no history of prostate cancer, who had PSA testing at Kaiser Permanente Northern California in the 5 calendar years 1998-2002, and were followed up for 12-16 years. Subjects were stratified into 6 groups based on the screening interval, and into 7 groups based on age. Prostate cancer mortality rates for each of the 42 subgroups were calculated and compared.

RESULTS The data show that yearly PSA screening is beneficial, reducing prostate cancer deaths by 64% for men aged 55-75 years (95% confidence interval 50-78%, $P < .001$), and all-cause mortality by 24% (95% confidence interval 15%-34%, $P < .001$). This is the first study to evaluate various screening intervals and age groups, showing that yearly screening is the interval of choice. No benefit was found for screening at any interval for men under age 55.

CONCLUSION Yearly PSA screening is highly effective in reducing both prostate cancer mortality and all-cause mortality in men with prostate cancer, and when combined with active surveillance to prevent overtreatment, lends support for PSA screening for men in good health aged 55-75. UROLOGY 118: 119–126, 2018. © 2018 The Author. Published by Elsevier Inc.

Prostate cancer is the most common malignancy in men in the United States, with over 167,000 new cases and almost 27,000 cancer deaths per year.[1] When prostate-specific antigen (PSA) testing became available in 1986, it was hoped that through early detection, death from prostate cancer could be substantially reduced. But after 30 years, evidence for its usefulness has been questioned. In May 2012, the United States Preventive Services Task Force (USPSTF) downgraded their recommendation to Grade D, now advising against PSA screening in healthy men, concluding that PSA screening causes overtreatment and that the modest benefits of screening are outweighed by the harms.[2]

There have been 2 large randomized prospective studies of PSA screening. The first was the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial published in 2009.[3] Subjects were 76,693 men at 10 US centers, randomized either to annual PSA screening for 6 years or to "usual care." At 13 years follow-up, the difference between the 2 groups was not significant.[4] However, the control group ("usual care") in this study was highly contaminated, with more than 50% of the subjects having had PSA screening, making the lack of findings difficult to interpret.[5,6]

The second was the European Randomized Study of Screening for Prostate Cancer (ERSPC) that published their 11- and 13-year follow-ups in 2012,[7] and 2014.[8] Subjects were 182,162 men aged 50-74, from 7 European countries, randomized either to PSA screening every 4 years or to control. They found a 21% reduction in prostate cancer deaths in the screened group as compared to the controls. However; using a 2-year screening interval rather than the 4-year interval, the Göteborg subset of the ERSPC

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indicated a 44% reduction in prostate cancer deaths.[9] This suggests that the choice of a shorter screening interval may have led to more powerful results.

The present study re-examines the value of prostate cancer screening, and seeks to determine both the optimal screening interval, and the appropriate age groups to be screened.

METHODS

Project Design

This study uses a retrospective cohort design. Although the nonrandomized nature of the design potentially produces complications in the data, various statistical methods were used to adjust for these complications. The benefit of the design is the ability to take advantage of the enormous databanks from large health plans like Kaiser Permanente, which care for large populations of patients over many years.

Subjects and Eligibility Criteria

Subjects consisted of all 400,887 men under 80 years of age, with no history of prostate cancer, who had PSA testing done at Kaiser Permanente Northern California in calendar years 1998-2002. Subject data were derived from the Kaiser Permanente Northern California electronic database, which includes information for all patients dating back to 1992. It contains demographic data, laboratory results, pathology results, and cancer treatment information. Mortality data were obtained from the Kaiser Permanente Division of Research mortality database that identifies death from in-system and out-of-system sources; the latter including Social Security death master file data and California State Department of Vital Statistics data. Data were collected on subjects through calendar year 2013.

The 5-year study period 1998-2002 was selected because there were prior PSA data going back to 1992, allowing for 6-11 years of prior data to examine screening intervals. This study period also provided 12-16 years of follow-up on patients diagnosed with prostate cancer, an amount of time deemed reasonable to calculate mortality rates. In addition, more than 400,000 subjects under age 80 had PSA testing in this period, providing a large study population.

Design for Data Analysis

The 400,887 subjects were sorted into 42 subgroups: 6 groups based on PSA intervals (12-18 months, 18-24 months, 2-3 years, 3-4 years, 4-9 years, or no prior PSA) and 7 age groups (<50, 50-54, 55-59, 60-64, 65-69, 70-74, and 75-79). For each subgroup, a tally was made of the number of men tested for PSA, the number diagnosed with prostate cancer, the number who died of prostate cancer; and the number with prostate cancer who died of other causes. Differences between the groups were examined, and chi-square tests were used to assess significance. An alpha level of 0.01 was used for all statistical tests. Megastat was the statistical software utilized.

The number of men needed to be screened (NNS) to prevent 1 death from prostate cancer was calculated as the inverse of the absolute risk reduction. The number of men needed to be diagnosed (NND) to prevent 1 death from prostate cancer is NNS times the prostate cancer incidence in the screened group.

In addition to examining risk reduction for prostate cancer deaths, risk reduction was examined for all-cause mortality. As an inadvertent result of the retrospective design, subjects screened at yearly intervals had fewer nonprostate cancer deaths than unscreened subjects, suggesting a healthier population. In an attempt to compensate for this difference and equalize nonprostate cancer death rates for the 2 groups, the number of excess deaths from nonprostate causes in the unscreened group was subtracted from the all-cause deaths in that group. Although this mathematical adjustment excessively reduces the estimated difference in all-cause mortality between the screened and unscreened groups, it avoids the risk of overestimating the screening benefit. This is because healthier subjects who have not died of other causes are alive and, thus, still at risk for dying of prostate cancer. For the same reason, it should be noted that this health disparity also has the potential effect of underestimating the magnitude of the observed differences between screened and unscreened groups for prostate cancer-specific mortality.

Definition of Terms

Screening PSA: a PSA to test for prostate cancer in the absence of signs or symptoms.

PSA for cause: a PSA to test for prostate cancer when there are signs or symptoms of possible disease.

Marker PSA: the PSA test done during the 1998 through 2002 period. If there were more than 1 PSA in this period, and one of them led to a cancer diagnosis, that 1 was designated the Marker PSA. If there were multiple tests and no cancer diagnosis, the PSA in this period that provided the shortest PSA interval was chosen as the Marker PSA.

Prior PSA: the most recent PSA done 12 or more months before the Marker PSA. These were all treated as screening PSAs, and subjects were assigned to groups based on the PSA Interval (defined in the following).

PSA Interval: the time interval between the Marker PSA and the Prior PSA.

In text and tables, notation was simplified in reference to intervals.

12-18 months = 12 to <18 months
18-24 months = 18 to <24 months
2-3 years = 2 to <3 years
3-4 years = 3 to <4 years
4-9 years = 4 to <9 years

No Prior PSA Group: subjects who had no PSA done before the Marker PSA. This was considered to be the unscreened group.

Example

A 62-year-old male had a screening PSA in August 1998 which had not led to a diagnosis of prostate cancer. In October 1999, he had another screening PSA = 4.3. A

biopsy in December 1999 showed prostate cancer, Gleason 3 + 3.

Marker PSA: October 1999. This is the date of PSA leading to biopsy and diagnosis.

Prior PSA: August 1998. This is the most recent PSA >12 months before diagnosis.

PSA Interval: 14 months.

Determining Screening PSA vs PSA for Cause

A problem with the Kaiser database is the inability to distinguish between PSA tests done for screening vs those obtained for signs and symptoms. Although the problem potentially affects the results in 3 ways, it is possible to calculate the direction of the effect and to ascertain, as discussed in the following, that in each situation, the effect is to underestimate, rather than inflate, the differences between the PSA screened vs unscreened subjects.

Situation 1: Prior PSA

It was assumed that all of these had been done for screening, as they all had a screening interval of at least 12 months, suggesting benign findings at the time of the prior PSA.

Errors will be PSAs for cause mislabeled as "screening."

Effect: these PSAs for cause will increase the mortality statistic of the screened group, and decrease the potential mortality difference between screened and unscreened groups. The potential effect would be to understate the magnitude of the observed differences between screened and unscreened groups.

Situations 2 and 3: Marker PSAs

Screened groups: includes all subjects who had a prior PSA. For subjects in these groups**,** it was assumed that all PSAs were for screening.

Errors would be any PSAs done "for cause" that were mislabeled as for "screening."

Effect: overestimate the mortality statistic of the screened group.

No Prior group: for subjects in this group, it was assumed all PSAs were "for cause."

Errors would be any PSAs done for "screening" and mislabeled as "for cause."

Effect: underestimate the mortality statistic for No Prior (unscreened) group.

Net Effect: in each of the above 2 situations, the errors would potentially decrease the calculated difference in mortality between the screened and unscreened groups.

RESULTS

Treatment Modalities

Of the 400,887 men studied, 8542 had a biopsy-proven prostate cancer diagnosis during the 5-year period selected for study. Table 1 shows the initial treatment modality for the diagnosed subjects. During the 12-16 years of follow-up, 770 died of prostate cancer, 2512 died of other causes, and 5260 patients remained alive.

Assessment of Data Completeness

Of the 8542 subjects diagnosed with prostate cancer, 76.4% were Kaiser Permanente members at their death or at 12-16 years of follow-up. This 76.4% included 7.7% dead of prostate cancer, 23.5% dead of other causes, and 45.3% alive at 16 years. Another 8.5% of subjects were reported dead after leaving Kaiser, resulting in complete outcome data for 85% of subjects. The remaining 15% were no longer Kaiser members at 16 years of follow-up, had not been reported dead in any databases, and were assumed to be alive. Given the possibility of unreported deaths in this last group of 15%, it is important to assess its potential impact. If deaths in the non-Kaiser group were to occur in the same proportion as in subjects who remained Kaiser members, 9.6% (rather than 8.5%) of nonmember subjects would be expected to be dead, and 14% (rather than 15%) would be expected to be alive at 16 years of follow-up. This suggests that approximately 1% of our data might be missing due to unreported deaths for subjects dying after leaving Kaiser.

Effect of Screening by Age Groups

Table 2 shows all of the data stratified by PSA test interval and age group. For ease of comparison, Table 3 details the fourth column of Table 2, and shows the prostate cancer mortality rates per 100,000 subjects tested by PSA interval and by age group. The last column shows combined data for subjects aged 55-74 years. Of note is the finding that of the 400,887 men tested during this period, 154,125 or 38% were 54 or younger, equally divided between those under 50, and those 50-54, and there is no demonstrable benefit to screening men less than 55 years of age.

For the <50-year-old group, χ^2 (5, N = 77,157) = 3.51, P = .62.

For the 50- to 54-year-old group, χ^2 (5, N = 76,968) = 4.04, P = .54.

Table 1. Initial treatment modality for cancer patients

Primary Treatment	Number of Subjects	Died of CaP (n)	Percent Died of CaP (%)	Median PSA at Diagnosis	Mean Gleason at Diagnosis	Mean Age at Diagnosis
Surgery	2269	121	5.3%	6.2	6.3	62.7
Radiation	3745	257	6.9%	7.5	6.4	67.1
Palliation only	1149	282	24.5%	15.4	6.9	69.3
No treatment	1379	110	8.0%	6.9	6.1	67.2
Total group	8542	770	9.0%	7.4	6.4	66.3

CaP, prostate cancer.

Table 2. Data for all subjects by PSA test interval and by age group

Interval to Prior PSA	Subjects With PSA Testing Done in 1998-2002	Subjects Dying of CaP	CaP Deaths per 100,000 Subjects	Subjects Diagnosed with CaP	CaPs per 100,000 Subjects
Subjects aged <50					
12-18 mo	5331	0	0	23	421
18-24 mo	3640	0	0	9	247
2-3 y	3165	1	32	8	253
3-4 y	1881	0	0	8	425
4-9 y	1885	1	53	7	371
No Prior	61,255	14	23	112	183
Total	77,157	16	21	167	219
Subjects aged 50-54					
12-18 mo	13,567	5	37	94	688
18-24 mo	7748	3	38	50	641
2-3 y	6425	2	31	52	803
3-4 y	3389	1	29	26	761
4-9 y	3458	0	0	22	632
No Prior	41,851	25	59	286	679
Total	76,968	36	47	530	689
Subjects aged 55-59					
12-18 mo	18,293	8	44	229	1252
18-24 mo	8762	7	80	150	1712
2-3 y	6536	3	46	124	1897
3-4 y	3574	3	84	59	1651
4-9 y	4815	4	83	93	1931
No Prior	25,296	41	162	462	1826
Total	67,276	66	98	1117	1660
Subjects aged 60-64					
12-18 mo	20,446	23	112	434	2123
18-24 mo	7825	12	179	254	3246
2-3 y	5413	10	185	192	3547
3-4 y	2792	4	143	99	3546
4-9 y	3931	8	204	130	3307
No Prior	17,068	58	340	573	3357
Total	57,475	117	204	1682	2926
Subjects aged 65-69					
12-18 mo	20,960	28	134	666	3177
18-24 mo	6856	14	204	347	5061
2-3 y	4355	9	207	214	4914
3-4 y	2177	11	505	120	5512
4-9 y	3289	13	395	144	4378
No Prior	13,375	85	636	646	4830
Total	51,012	160	314	2137	4189
Subjects aged 70-74					
12-18 mo	18,105	54	298	622	3436
18-24 mo	5173	18	348	283	5471
2-3 y	3181	21	660	194	6099
3-4 y	1699	18	1059	112	6592
4-9 y	2829	17	601	120	4242
No Prior	8738	78	893	466	5333
Total	39,725	206	519	1797	4524
Subjects aged 75-79					
12-18 mo	13,698	51	372	400	2920
18-24 mo	4022	15	373	163	4053
2-3 y	2602	16	615	110	4228
3-4 y	1452	8	551	57	3926
4-9 y	2603	26	999	111	4264
No Prior	6897	53	768	271	3929
Total	31,274	169	540	1112	3556
Total of all subjects	400,887	770	192	8542	2131

PSA, prostate-specific antigen.

For the 5 groups of 55 and over, the rate ratio (RR) of prostate cancer mortality between 12-18 months screening and no prior screening was highly significant by chi-square. The 95% confidence intervals (CIs) are also shown.

55-59 years old, RR 0.27 (95% CI −0.09 to 0.63, P <.001), or a 73% relative risk reduction.

60-64 years old, RR 0.33 (95% CI 0.04-0.62, P <.001), or a 67% relative risk reduction.

Table 3. Prostate cancer deaths rates per 100,000 subjects tested, stratified by interval to prior PSA and by age group

Death Rates per 100,000 Subjects Tested								
Age Groups	<50	50-54	55-59	60-64	65-69	70-74	75-79	55-74
Interval to prior PSA								
12-18 mo	0	37	44	112	134	298	372	145
18-24 mo	0	38	80	179	204	348	373	185
2-3 y	32	31	46	185	207	660	615	221
3-4 y	0	29	84	143	505	1059	551	351
4-9 y	53	0	83	204	395	601	999	283
No Prior	23	59	162	340	636	893	768	406
Total	21	47	98	204	314	519	540	255
Comparison of 12-18 mo Interval vs. No Prior								
12-18 mo	0	37	44	112	134	298	372	145
No Prior	23	59	162	340	636	893	768	406
% Change	–100%	–38%	–73%*	–67%*	–79%*	–67%*	–52%*	–64%*
P value	.27	.32	<.001	<.001	<.001	<.001	<.001	<.001
Comparison of 18-24 mo Interval vs. No Prior								
18-24 mo	0	38	80	179	204	348	373	185
No Prior	23	59	162	340	636	893	768	406
% Change	–100%	–35%	–51%	–47%	–68%*	–61%*	–51%	–54%*
P value	.36	.47	.08	.03	<.001	<.001	.11	<.001
Comparison of 2-3 year Interval vs. No Prior								
2-3 y	32	31	46	185	207	660	615	221
No Prior	23	59	162	340	636	893	768	406
% Change	0%	–48%	–72%	–46%	–67%*	–26%	–20%	–46%
P value	.40	.37	.26	.07	<.001	.22	.43	.35
Comparison of 3-4 year Interval vs. No Prior								
3-4 y	0	29	84	143	505	1059	551	351
No Prior	23	59	162	340	636	893	768	406
% Change	–100%	–51%	–48%	–58%	–20%	0%	–28%	–14%
P value	.51	.48	.26	.08	.47	.51	.38	.09
Comparison of 4-9 year Interval vs. No Prior								
4-9 y	53	0	83	204	395	601	999	283
No Prior	23	59	162	340	636	893	768	406
% Change	0%	–100%	–49%	–40%	–38%	–33%	0%	–30%
P value	.40	.15	.19	.17	.47	.51	.27	.30

* Reached statistical significance of $P \leq .01$.

65-69 years old, RR 0.21 (95% CI −0.02 to 0.44, $P < .001$), or a 79% relative risk reduction.

70-74 years old, RR 0.33 (95% CI 0.10-0.57, $P < .001$), or a 67% relative risk reduction.

75-79 years old, RR 0.48 (95% CI 0.19-0.78, $P < .001$), or a 52% relative risk reduction.

And for the combined groups:

55-74 years old, RR 0.36 (95% CI 0.22-0.50, $P < .001$), or a 64% relative risk reduction.

Number Needed to be Screened or Diagnosed

The NNS to prevent 1 death from prostate cancer over an average of 14 years of follow-up is easily calculated from data in Table 3. For the 65- to 69-year-old group, there are 636 deaths per 100,000 screened in the No Prior group, and 134 deaths per 100,000 screened at 12-18 months. The absolute reduction is 502 deaths (636 − 134) per 100,000 screened. To save 1 life, (100,000 screened)/(502 deaths prevented) = 199 men screened for each life saved (95% CI 155-228, $P < .001$).

The NND to prevent 1 death from prostate cancer is similarly calculated from data in Tables 2 and 3. In the example earlier, 3177 cancers will be detected among the 100,000 men, aged 65-69, screened at 12-18 months intervals, while preventing 502 deaths. NND = (3177 cancers diagnosed)/(502 lives saved) = 6.3 cancers diagnosed for each life saved (95% CI 4.9-8.8, $P < .001$).

Effect of Screening Intervals on Prostate Cancer Mortality

To determine the most effective screening interval, each of the intervals was compared to no prior testing. The lower portion of Table 3 shows that the efficacy of screening drops off rapidly for intervals greater than 12-18 months. In addition, it can be seen that statistically significant values (highlighted by asterisks) only occur for subjects aged 55-79 for the 12-18 group, for subjects aged 65-74 for the 18-24 months interval group, and for subjects aged 65-69, only for the 2-3 years interval group. For the combined groups aged 55-74, there was a 64% reduction in cancer mortality with 12-18 months screening. This dropped to 54% with 18-24 months screening, and to 46% with 2-3 years screening, although this latter value did not achieve statistical significance.

Effect of Screening on All-cause Mortality

Risk reduction for all-cause mortality was examined in subjects aged 55-74, comparing 12-18 months screening and

no prior screening. As discussed in the methods section, the 12-18 months group appeared much healthier, with 671 nonprostate cancer deaths per 100,000 men screened, compared to 1008 deaths in the No Prior group. If there were 217 fewer nonprostate cancer deaths in the No Prior group, the 2 groups would have equal nonprostate cancer death rates (see Table 4). If 217 deaths are subtracted from the all-cause deaths in the No Prior group, it is possible to get a corrected estimate of the all-cause death rate reduction. As seen in Table 4, there is a 24% reduction in all-cause deaths at 12-16 years of follow-up—from 1078 per 100,000 screened for the No Prior group to 816 for the 12-18 months group (95% CI 15-34%, P <.001).

DISCUSSION

These data strongly support the hypothesis that PSA screening is beneficial, reducing prostate cancer deaths by 64% and all-cause mortality by 24% for men aged 55-74 years. They also strongly support the second hypothesis that the screening interval is critical and show that yearly screening is the interval of choice.

The third hypothesis was that age would be a critical variable in determining the value of PSA screening. The data show a maximal benefit to men aged 55-74, with no benefit of screening for men under age 55.

The magnitude of these results is compatible with other independent findings. The Göteborg subset of the ERSPC indicated a 44% reduction in prostate cancer deaths with 2-year screening.[9] This is consistent with our data for 18-24 months and 2-3 years screening, which showed decreases of 54% and 46%, respectively in prostate cancer mortality when compared to no prior screening for men aged 55-74 (see Table 3). Data from the National Cancer Institute (NCI) showed that from 1993 to 2014, there was a 51% decrease in the prostate cancer death rate in the United States (from 39.3 to 19.1 deaths per 100,000).[1] This is the same period in which widespread PSA screening was done. Although this does not prove a causal relationship, it is highly suggestive, and the improvements in radiation therapy and chemotherapy in this time period cannot account for the magnitude of this change. Since considerably fewer than 100% of eligible American men were regularly screened, to achieve a 51% reduction in mortality rates, the efficacy of PSA screening would have to be significantly greater than 51%, which is compatible with the findings of the present study.

A concern that both the NCI and the ERSPC data raise is the increased number of clinically insignificant prostate cancers discovered with screening, an increase of approximately 30% in the NCI data.[1] The unnecessary treatment of this group prompted the USPSTF to recommend against PSA screening in 2012. However, the overtreatment problem can be solved by utilizing active surveillance for appropriate low-grade, low-stage cancers. It is estimated that 36% of patients with a new diagnosis of prostate cancer are candidates for active surveillance, and that 30% of patients electing active surveillance will

Table 4. Data for subjects aged 55-74 by PSA test intervals 12-18 months and No Prior Corrected for Health differences to calculate all-cause mortality change

Interval to Prior PSA	Subjects with PSA Testing	Subjects Dying of CaP	CaP Deaths per 100,000 Subjects	Subjects With CaP Dying of All Causes	All-Cause Deaths per 100,000 Subjects Tested	Subjects With CaP Dying of Other Causes	Non-CaP Deaths per 100,000 Subjects Tested
12-18 mo	77,804	113	145	635	816	522	671
No Prior	64,477	262	406	912	1414	650	1008
No Prior Corrected for Health	64,477	262	406	(912 – 217) = 695	1078	(650 – 217) = 433	671
% Change			–64%		–24%		

ultimately have treatment for progression.[10] If the 36% of patients eligible for active surveillance elected this, and 70% never require treatment, then 25% of patients with a diagnosis of prostate cancer will never require treatment. This compensates for the approximately 30% increase in the rate of prostate cancer diagnoses and mitigates against the USPSTF's argument that screening causes too much unnecessary treatment and attendant morbidity.

CONCLUSION

These data show that yearly PSA screening is highly beneficial, reducing prostate cancer deaths by 64% for men aged 55-74 years, and reducing all-cause mortality in this group by 24%. Yearly screening is the interval of choice. No benefit was found for men under age 55. When combined with active surveillance to prevent overtreatment, these data lend support for yearly population-based PSA screening for prostate cancer for men aged 55-74 who are in good health.

References

1. Siegel R, Miller K, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7-30.
2. Moyer VA. Screening for prostate cancer: U.S. preventive services task force recommendation statement. *Ann Intern Med*. 2012;157:120-134.
3. Andriole GL, Crawford ED, Grubb RL, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*. 2009;360:1310-1319.
4. Andriole GL, Crawford ED, Grubb RL, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, And Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst*. 2012;104:1-8.
5. Pinsky PF, Blacka A, Kramer BS, Miller A, Prorok PC, Berg C. Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. *Clin Trials*. 2010;7:303-311.
6. Shoag JE, Mittal S, Hu JC. Reevaluating PSA testing rates in the PLCO Trial. *N Engl J Med*. 2016;374:1795-1796.
7. Schröder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med*. 2012;366:981-990.
8. Schröder FH, Hugosson J, Roobol MJ, et al. The European randomized study of screening for prostate cancer—prostate cancer mortality at 13 years of follow-up. *Lancet*. 2014;384:2027-2035.
9. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol*. 2010;11:725-732.
10. Dall'Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate cancer: a systematic review of the literature. *Eur Urol*. 2012;62:976-983.

APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urology.2018.02.049.

EDITORIAL COMMENT

Prostate cancer (PCa) is the most common non-skin cancer and the second leading cause of cancer death for men in the United States.[1] Strategies for managing PCa are mainly aimed at early detection because 68% of PCa mortality takes place under the age of 75 (the average life expectancy for men in the US). This is substantiated by scientific literature that demonstrates that early detection can play a vital role in the survival of individuals affected by cancer.[2] Despite the evidence surrounding early detection, differences of opinion abound on the screening recommendations for PCa because of the high false positive rate and the over-detection of indolent disease.[3]

Dr. Alpert conducted a large-scale investigation of patients receiving screening and concluded that a 12-18 month time interval between screens was the most optimal screening strategy.[4] This recommendation reverts to an older approach that did not consider patient risk. Of note, great variation in the risk and frequency for PCa exists particularly among African Americans (AA). Compared with Caucasians, AA men are more likely to develop PCa, and are nearly 2.5 times as likely to die from the disease, largely due to late diagnosis.[5]

Recent declines in screening following the USPSTF recommendation against routine PSA-based screening for PCa were associated with an increase in the incidence of more clinically aggressive PCa.[6] While, the previous recommendation against PSA screening was likely to be too restrictive, annual screening may result in over-screening and result in a similar debate about benefits and harms of screening. This increase in incidence of aggressive disease and mortality demonstrates the need for an evidence-based testing regime that is "patient specific"; i.e., a testing strategy that is based on the relatively new area of personalized medicine.[7]

Perhaps more important than PSA screening, is what happens after an elevated PSA. Should all men be biopsied or just some? Many factors can contribute to an elevated level, including prostate enlargement, infection, sexual activity, etc. What is important to find is cancer worth treating. First and foremost that depends on an assessment of the patient. Men with substantial co-morbidities or limited life-expectancy, like those enrolled on the PIVOT trial, are probably best not biopsied in the first place unless substantial elevations are seen in the PSA or significant abnormalities are found on the prostate exam.[8]

One way to separate "the good" and "the bad" is to use a multiparametric MRI (mpMRI). Shown in the PROMIS study, many men can forego a prostate biopsy if the mpMRI shows a favorable result.[9] Alternatively, older (free PSA or PCA3) or newer (PHI or 4K) non-invasive biomarkers have been suggested to risk-stratify men into higher and lower risk categories and determinations for or against biopsy can be made in a more rational manner.

After biopsies, it is important to risk stratify again. Much has been written about surveillance and treatment, and these issues do not need to be covered again here. Suffice it to state, we have continued to over-treat indolent disease and under-treat aggressive disease.

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References

1. Siegel R, Miller KD, Jemal A. Cancer statistics 2018. *CA Cancer J Clin*. 2018;68:7-30. doi:10.3322/caac.21442.
2. Wolf AMD, Wender RC, Etzioni RB, et al. American cancer society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin*. 2010;60:70-98. doi:10.3322/caac.20066.
3. Pinsky PF, Prorok PC, Kramer BS. Prostate cancer screening—a perspective on the current state of the evidence. *N Engl J Med*. 2017;376:1285-1289. doi:10.1056/NEJMsb1616281.
4. Alpert PF New evidence for the benefit of prostate-specific antigen screening: data from 400,887 Kaiser Permanente patients. Urology.
5. DeSantis C, Naishadham D, Jemal A. Cancer statistics for African Americans, 2013. *CA Cancer J Clin*. 2013;63:151-166. doi:10.3322/caac.21173.
6. Hu JC, Nguyen P, Mao J, et al. Increase in prostate cancer distant metastases at diagnosis in the United States. *JAMA Oncol*. 2017;3:705-707. doi:10.1001/jamaoncol.2016.5465.
7. Ablin RJ. The need for personalized therapy and companion diagnostics in prostate cancer. *Biomark Med*. 2011;5:281-283.
8. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. *N Engl J Med*. 2017;377:132-142. doi:10.1056/NEJMoa1615869.
9. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet*. 2017;389:815-822.

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AUTHOR REPLY

The commentator underscores several important points. First, since the United States Preventive Services Task Force recommendation to eliminate PSA screening, there has been an increased incidence of more clinically aggressive prostate cancers. Second, although the current data shows that with PSA screening at 12-18 months intervals, prostate cancer morbidity can be substantially reduced, it is critically important to mitigate the impact of unnecessary treatment by utilizing active surveillance, and various newer methods for risk stratification of patients with low-grade, low-stage disease.

In addition to underscoring these points, the commentator recommends the use of a personalized screening strategy for prostate cancer. A personalized screening strategy would be ideal, and should be built around baseline data for a patient with average risk. The current study provides these baseline data. For patients aged 55-74 with average levels of risk, the optimal screening interval is 12-18 months. With this as a baseline, one can modulate the intensity of screening up or down by changing the frequency of screening, and the ages to start or stop screening. These changes might be based on factors like ethnicity, family history, baseline PSA at an early age, substantial comorbidities, and life expectancy. Although in current clinical practice, I believe that most physicians do attempt to individualize in this way, the reality is that, at this point, we do not have the empirical data that would allow us to scientifically do this. For example, based on data showing a greater incidence and mortality risk of prostate cancer in African Americans, it is common to begin testing 5 years earlier in this population. However, at this point we can only guess that this is an appropriate modification. It is clear that more research is needed to move us from decisions that are based on hypotheses and logical guesses to those based on empirical evidence.

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