Prostate-Specific Antigen Screening and Mortality from Prostate Cancer

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BACKGROUND: There is no available evidence from randomized trials that early detection of prostate cancer improves health outcomes, but the prostate-specific antigen (PSA) test is commonly used to screen men for prostate cancer.

OBJECTIVE: The objective of the study is to see if screening with PSA decreases mortality from prostate cancer.

DESIGN, SETTING, AND PARTICIPANTS: This is a case-control study using one-to-one matching on race, age, and time of availability of exposure to PSA screening. Decedents, 380, from New Jersey Vital Statistics 1997 to 2000 inclusive, 55–79 years of age at diagnosis were matched to living controls without metastatic prostate cancer. Medical records were obtained from all providers, and we abstracted information about PSA tests from 1989 to the time of diagnosis in each index case.

MEASUREMENTS: Measurements consist of a comparison of screening (yes, no) between cases and controls. Measure of association was the odds ratio.

RESULTS: Eligible cases were diagnosed each year from 1989 to 1999 with the median year being 1993. PSA screening was evident in 23.2–29.2% of cases and 21.8–26.1% of controls depending on the screening criteria. The unadjusted, matched odds ratio for dying of prostate cancer if ever screened was 1.09 (95% CI 0.76 to 1.60) for the most restrictive criteria and 1.19 (95% CI, 0.85 to 1.66) for the least restrictive. Adjustment for comorbidity and education level made no significant differences in these values. There were no significant interactions by age or race.

CONCLUSIONS: PSA screening using an ever/never tabulation for tests from 1989 until 2000 did not protect New Jersey men from prostate cancer mortality.

KEY WORDS: prostate cancer; screening; prostate specific antigen.

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BACKGROUND

Prostate cancer is the second leading cause of cancer death among U.S. men and is particularly common among the elderly. Although there is no evidence from randomized trials that early detection of prostate cancer improves health outcomes, the determination of prostate-specific antigen (PSA) to screen men for prostate cancer is now routine. Approximately 77% of the U.S. male population ages 55–79 has been tested at least once with the PSA test¹.

Screening for prostate cancer with the PSA test is a contentious issue. Various organizations differ on whether there is enough justification for population screening^{2–4}. Findings support the test's ability to detect early-stage prostate cancer, but high-grade disease is missed with traditional PSA cut-points^[5–8]. For a screening test to benefit a population, it must detect cancer at a stage when it is more curable. There is some evidence that radical prostatectomy can decrease cancer-specific mortality in clinically detected, early cases^{9,10}, but this has not been demonstrated for cases detected by screening. Two case-control studies have reported conflicting results: one, based on 501 all-cause deaths, including 136 prostate cancer deaths, found no benefit¹¹ and the other, based on 236 cases of metastatic cases, reported a modest benefit but only after an unusual statistical adjustment¹². A third study showed a possible benefit from the digital rectal examination but was unable to estimate the separate influence of PSA testing¹³.

Our investigation used a statewide cancer registry to identify cases and recruited community-based controls. We hypothesized that men dying of prostate cancer were less likely than matched controls to have had a screening PSA test before diagnosis of prostate cancer.

DESIGN AND METHODS

Overall Approach

Our study paired men who died from prostate cancer in New Jersey with age- and race-matched controls from the community. Information on PSA testing was obtained from medical

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records of cases from 1989 to the time of first suspicion of prostate cancer and from the records of the matched control for the identical time period. We obtained access to medical records through the wife of the deceased, if a case, and through the subject himself if a control. We made an exhaustive attempt to obtain every record from every provider of care. Retrieval of records was assisted by a New Jersey statute that requires health care providers to release medical information about their patients to entities performing state-assisted studies with public health significance¹⁴. We obtained signed authorizations by the spouse of the case or the control subject. This study was approved by Institutional Review Boards from the UMDNJ-Robert Wood Johnson Medical School and the New Jersey Department of Health and Senior Services.

Study Subjects

We identified potential cases from New Jersey Vital Records. Married men who died from prostate cancer between 1997 and 2000 at age 55–79 years were eligible. There were 1,767 men in this age range who had prostate cancer listed as the cause of death. We required cases to be married at the time of death to increase the probability that there would be a knowledgeable, surviving informant to assist in identifying medical care providers. Eliminating those who were not married, or after review of the death certificate, did not have prostate cancer as the underlying cause of death, left 1,023 men in the sample. Of these, we were able to contact 718 spouses for a contact rate of 70%. A total of 553 responded affirmatively, and we excluded 166 for ineligibility after reviewing medical records or if a spouse could not provide sufficient information leaving us with 387 cases. Specifically, we excluded men whose medical records did not document symptomatic, metastatic prostate cancer at or near the time of death.

For each case, we matched one control subject by age (same 5-year age group) and race (white or black). Potential controls living in New Jersey and 55–64 years of age were identified by Northeast Research and The Watsroom, Inc. by previously described random digit dialing methods¹⁵. Potential controls aged 65–79 were identified by Westat, Inc. from New Jersey Medicare tapes. In the event of multiple controls, we selected the one that was closest in age. If a potential control did not respond, or proved ineligible, we selected the next closest in age. All controls were married. As the basis of protection from screening is in early detection, any control with early prostate cancer was included as they may have benefited from screening, and it would be a bias against screening to exclude them. Controls with metastatic prostate cancer were excluded as they were unlikely to have benefited from any screening.

Interviews

We invited widows of cases and also invited control men, to participate. Controls were offered a \$20 incentive at first contact. Because it was deemed insensitive to offer money to the widows of cases at the time of recruitment, we sent \$20 after completion of the study with a “thank you” letter. We obtained basic demographic information and secured written permission for release of medical records.

Review of Medical Records

We linked each case to a New Jersey Cancer Registry record and requested copies of all pertinent medical records from providers identified on the death certificate, in the registry, or from the interview. For controls, we followed up all sources of care identified in the interview. When other providers were identified in medical records not previously described, we sought records from these sources as well. In addition to PSA testing, we abstracted cancer grade and stage, comorbidities, and long-term medications from medical records and the cancer registry. Comorbidity was tabulated as a simple count of the number of chronic diseases. Controls with non-metastatic prostate cancer were not excluded if diagnosed after the case.

Period of Observation for PSA Tests

For each case-control pair, we tabulated PSA tests during the identical time period. This period started January 1, 1989, the first year that PSA testing came into significant clinical use in New Jersey and ended with the date of clinical suspicion of prostate cancer in the case. We defined this “date of suspicion” as the time of the first clinical finding leading to a biopsy (even if negative) or to frequent (more than once per year) follow-up examinations and PSA tests. A PSA test cannot be classified as screening during this period of suspicion.

Classification of PSA Tests

Based on medical records review, we classified reasons for PSA testing as follows: (1) screening, (2) lower urinary tract symptoms, (3) physical exam consistent with benign prostatic hypertrophy (BPH), (4) physical signs consistent with possible tumor such as a nodule, (5) previous history of an abnormality in either the digital rectal examination or PSA, and (6) other symptom or sign(s) possibly related to metastatic disease such as undefined back or bone pain. These categories were coded independently of one another as they may not be mutually exclusive.

In addition to the above classification that was applied to all PSA tests, we periodically convened a panel of three investigators (SWM, GGR, JLC) to review each PSA done within 6 months of the date of clinical suspicion of diagnosis without knowledge of the case-control status of the subject. This was done as an added precaution to ensure that those tests done close to a suspicion of diagnosis were in fact, true screens. We classified each PSA as “screening” or done for possible symptoms or a physical abnormality consistent with prostate cancer. PSA screening was defined in the context of a yearly examination, routine laboratory tests, “annual”, or specifically designated as a “screen”. When there was a difference in classification between these blinded judgments and the earlier categorization, the blinded judgments were used. In the initial chart review, it was not possible to blind the abstracter to case/control status. Changes from the initial classification were uncommon (less than 5% of the PSA tests within this 6-month interval). In addition, we randomly repeated the blinded review for the same PSA test for about 10% of the tests; the panel returned the same classification >98% of the time.

Analysis

We compared cases and controls using chi-square analysis for categorical variables and Student's *t* test for continuous variables. Conditional logistic regression was employed to model the outcome (case/control) status as a function of the independent variables¹⁶. We considered a priori that the key predictor, screening with one or more PSAs (yes or no), socioeconomic status as measured by education level, and a categorical number of comorbidities to be the independent variables.

We performed three analyses using different criteria for PSA screening: (1) least restrictive: either lower urinary tract symptoms or BPH could be present, (2) moderately restrictive: BPH on physical exam or by history but no evidence of lower urinary tract symptoms, and (3), most restrictive: no evidence of lower urinary tract symptoms or BPH. We used SAS software 9.1 (SAS Institute, Inc., Cary, NC) for all analyses.

We confirmed that controls were representative of the source population with respect to the frequency of PSA testing by comparing their PSA frequencies to those obtained from the New Jersey Behavioral Risk Factor Surveillance System (BRFSS) sponsored by the Centers for Disease Control and Prevention¹. For this comparison, we re-tabulated our control rates to include all PSA tests done from 1989 through 2000, not just the PSAs done during the time interval ending at the date of clinical suspicion of the matching case.

RESULTS

Response Rates and Control Screening Rates

The overall response rate for cases was 77% (*N*=553) with 387 eligible after the interview and medical record review. The control response rate was 57% (*N*=610) with 442 eligible after review. We were able to match 380 cases with controls. The extent of PSA testing for our controls was very similar to that of the age-comparable population of New Jersey male residents surveyed in the BRFSS¹. Table 1 shows the percentages of men ever tested with the PSA test by age range.

Table 1. Frequency of "Ever Been Tested" with a PSA test: Comparison of Study Controls with Those from the NJ Behavior Risk Factor Surveillance System*

Age range	Controls	NJBRFSS
	<i>n</i> / <i>N</i> (%)	<i>n</i> / <i>N</i> (%) [†]
55–59	14/21 (67)	94/139 (68)
60–64	24/33 (73)	93/118 (83)
65–69	57/76 (75)	100/131 (76)
70–74	92/117 (79)	88/110 (77)
75–79	106/133 (80)	76/91 (85)
55–79	293/380 (77)	451/589 (77)

N Number in each strata, *n* number in each strata who were screened at least once

*Survey of PSA tests as of 2001

[†]BRFSS percentages calculated with weights to correct for the sampling design to more accurately represent the general population of the state

Table 2. Comparison of Cases and Controls

Characteristic	Cases		Controls		P value
	(N=380)		(N=380)		
	n	(%)	N	(%)	
Race					.91
Black	39	(10)	40	(11)	
White	341	(90)	340	(89)	
Education					<.001*
<High school	82	(22)	50	(13)	
High school grad	195	(51)	193	(51)	
College grad	57	(15)	65	(17)	
Grad or pro school	41	(11)	70	(18)	
Comorbidity number					.05*
0	82	(21.6)	112	(29.5)	
1–2	109	(28.7)	103	(27.1)	
3–5	100	(26.3)	84	(22.1)	
6–10	63	(16.6)	59	(15.5)	
>10	26	(6.8)	22	(5.8)	
Age at time of diagnosis [mean (SD)]	67.2	(5.7)	66.5	(5.9)	

**P* for trend

Comparison of Cases and Controls

A comparison of demographic variables and comorbidity between cases and controls is shown in Table 2. Ten percent of cases and 11% of controls were black due to one case-control pair mismatch for race leaving 379 cases and 379 controls available for analysis. The mean age of the two groups was within 1 year. Cases were less likely to have graduated from high school, and controls were more likely to have attended graduate or professional school. Cases and controls were similar to one another with respect to the number of comorbidities in years before the case diagnosis of prostate cancer.

Tumor Characteristics and Survival Times

The year 1993 was the median year of diagnosis for cases. Stage at diagnosis and Gleason scores for the cases are shown in Table 3. We could not obtain Gleason scores for 7%. About 25% of cases had Gleason scores of 6 or less, 46% had scores of 7 or 8, and 23% had scores of 9 or greater. The time from suspicion to diagnostic confirmation was ≤1 month for 66.7 and 70% for those with distant and non-distant disease, respectively. The median length of survival from suspicion of cancer was 2.9 years for those with distant disease compared to 6.2 years for those with non-distant disease. Forty (10.5%) controls had a history of prostate cancer that was identified subsequent to the date of suspicion of the matched case. The Gleason score was 7 or 8 in 22.5% of these controls and 6 or less in the remainder.

Association of PSA Screening and Mortality from Prostate Cancer

We analyzed the association between PSA screening and death from prostate cancer using three definitions of PSA "screening". Using the most restrictive definition, we documented

Table 3. Gleason Scores and Clinical Stage of Cases

	N (%)
Gleason Score	
5 or less	46 (12.1)
6	48 (12.6)
7	91 (23.9)
8	83 (21.8)
9	75 (19.7)
10	12 (3.2)
Not specified	25 (6.6)
Clinical stage	
Localized (T1/2, node -)	144 (37.9)
Regional (T3/4 or node +)	61 (16.1)
Distant	153 (40.3)
Not assessed	22 (5.8)
Year of diagnosis	
1989	22 (5.8)
1990	24 (6.3)
1991	44 (11.6)
1992	60 (15.8)
1993	44 (11.6)
1994	45 (11.8)
1995	32 (8.4)
1996	41 (10.8)
1997	37 (9.7)
1998	14 (3.7)
1999	17 (4.5)

screens for 23.2% and 21.8% of cases and controls, respectively. The matched odds ratio estimate was 1.09 (95% CI, 0.76–1.58; Table 4). Using the moderately or least restrictive definitions for PSA screening modestly increased the number of tests in both groups, but yielded nearly identical matched odds ratios.

Controls were more educated than the cases as shown in Table 2, but educational level was not much related to the frequency of PSA screening (data not shown). We used conditional logistic regression to adjust for differences between cases and controls for the number of comorbidities and education level. These adjustments did not affect the results (Table 4). No statistically significant interactions were seen for age or race with PSA, but the point estimates for black men were 0.43 ($p=0.16$) and 0.56 ($p=0.24$) using the most restrictive and least restrictive definitions, respectively.

DISCUSSION

In this population-based study of 380 prostate cancer deaths and 380 matched controls, we found no evidence that PSA screening, as used clinically in the 1990s, reduced prostate cancer mortality. In view of the widespread use of PSA screening and the morbidity, expense, and worry experienced by patients needing biopsies and surgery related to screening, this result is disturbing. Case-control studies have successfully identified the benefits of fecal occult blood screening and colonoscopy for colon cancer^{17–19}, cytological screening for cervical cancer^{20,21}, and mammography for breast cancer²².

Our results are nearly identical to those found by Concato et al. using a similar population-based, case-control design¹¹. Both their study and this one use “ever screened” as the metric

of exposure, rather than tabulating screening in specific short intervals before diagnosis. This is important because screening can affect the date of diagnosis. In a patient with preclinical prostate cancer, the occurrence of screening has a high probability of leading to the diagnosis. Such patients will usually not have been screened in the years immediately before diagnosis because had they been tested earlier, the diagnosis would likely have been made then. Tabulating screening as ever/never largely avoids this problem.

Interpretation of a third case-control study of PSA screening is complicated by this issue. Kopec et al.¹² found no difference in the proportion of cases and controls that had ever been screened, in agreement with the negative findings cited above. However, these authors apparently counted PSA tests in controls during the period of clinical suspicion in the cases and also stratified their analysis of PSA tests by time period before diagnosis in a manner that likely overweighted the experience in prior years when a deficit of screening in the cases was to be expected. These procedures produced an adjusted result showing a benefit of screening that we believe may have been spurious.

The most significant potential limitation of all the observational studies is in determining what constitutes a “screen”. Some PSAs identified in medical records with little documentation may be interpreted as a screen when, in fact, they may have been ordered for suspicion of cancer or for urinary symptoms related to early cancer. However, three investigators blinded to case/control status reviewed all PSAs done within 6 months of the index case’s date of clinical suspicion (or the comparable time for the control). We obtained very similar results using different thresholds for classifying a PSA as a screen, and the PSA frequencies of our controls were similar to those reported in the New Jersey BRFSS. However, it is still possible we missed some PSAs. If more PSAs were missed in controls than in cases, the study results would be biased against the efficacy of screening. This seems unlikely as we directly interviewed controls about providers who might have ordered a PSA, whereas for cases, we relied on other medical records and the spouse to identify providers. We only counted

Table 4. Results of Conditional Logistic Regression: Odds Ratios for Prostate Cancer Mortality and PSA Screening in 379 Cases and 379 Controls*

Model	Most Restrictive	Moderately Restrictive	Least Restrictive
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Unadjusted, PSA ever screened	1.09 (0.76, 1.58)	1.07 (0.75, 1.51)	1.19 (0.85, 1.66)
Adjusted, PSA ever screened†	1.05 (0.71, 1.55)	1.03 (0.71, 1.49)	1.17 (0.82, 1.67)

Most restrictive No evidence of lower urinary tract symptoms or BPH, moderate restrictive BPH but no evidence of lower urinary tract symptoms, least restrictive either lower urinary tract symptoms or BPH could be present

*One case-control pair was mismatched for race and was not included in this analysis.

†Adjusted for education and number of comorbid conditions in the year before prostate cancer diagnosis

documented PSAs. The impact of excluding non-married subjects on ascertainment of PSA screens is unknown.

The confidence intervals are wide, and although a lower 95% bound of 0.76 includes a possible protective effect of 24%, we believe that the consistency of the point estimates around unity makes a protective effect less likely. We chose prostate cancer-specific mortality as our outcome. Overall mortality is also a relevant outcome in a population of men with prevalent comorbidity and the possibility of misclassification of the cause of death and the increased potential for treatment side-effects. However, using all-cause mortality as an outcome may make it difficult to show an effect of screening because the majority of these men will die of comorbidity rather than prostate cancer.

Evidence supporting the efficacy of PSA screening has been limited to date. Although the benefit of prostatectomy has been demonstrated for early prostate cancer, the studies thus far have depended on traditional, clinical detection of prostate cancer^{9,10}. One would expect that most of the cases in the randomized trial of surgery vs watchful waiting⁹ would have been detected by a PSA screen (had it been commonly used in the source population), but such screening would also have detected many slowly progressive cases. Many cases would not be expected to benefit from surgery thus diluting the overall benefit. Indeed, a competing risk analysis of watchful waiting for men diagnosed with prostate cancer in the pre-PSA era has demonstrated that for low and moderate grade tumors (Gleason ≤ 6), the risk of dying from the disease within 15 years is small²³.

Two randomized studies on PSA screening are still a few years away from completion^{24,25}. However, the results of the case-control studies suggest that any benefit of PSA screening identified in these trials is likely to be modest. Pending results from the trials, a conservative stance on PSA screening seems justified^{26,27}. Even if PSA testing is shown to have a modest, protective effect on mortality from prostate cancer, it will still be incumbent on the clinician to help the patient understand the trade-offs of this imperfect test. The high rates of prostate cancer incidence and mortality in black men and the protective odds ratio found for these men in the current study (albeit not statistically significant), may argue for more liberal use of testing in that group, but this needs further study with a larger sample size. We, along with others, await better methods for detecting prognostically ominous forms of this ubiquitous cancer.

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