Prostate-Specific Antigen and Prostate Cancer Mortality
A Systematic Review
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Context: Although findings from recently published clinical trials and a review from the U.S. Preventive Services Task Force suggest that there is limited to no prostate cancer mortality benefit associated with prostate-specific antigen (PSA) screening, confusion remains as to whether the use of PSA as a screening tool for prostate cancer is warranted.

Evidence acquisition: A systematic literature review was done in 2012 to identify case–control studies from the past 20 years that focused on evaluating the association between screening for prostate cancer and prostate cancer mortality. Emphasis was put on synthesizing the results of these studies, evaluating their limitations, and identifying remaining questions and issues that should be addressed in future studies.

Evidence synthesis: A total of seven studies were identified in this time period, with the majority suggesting that a reduction in prostate cancer mortality is associated with PSA screening. However, the findings may be limited by various biases inherent to case–control studies of screening tests, such as selection biases resulting from both case and control subject selection, exposure measurement issues, lead and length biases, and issues specific to prostate cancer screening such as the influence of digital rectal examinations.

Conclusions: Findings from existing case–control studies of PSA and prostate cancer mortality suggest that there is a mortality benefit from PSA screening. However, these studies may be limited by bias and must therefore be interpreted with caution. As uncertainty regarding PSA screening remains, future studies to evaluate the association between PSA and prostate cancer mortality should address these potential biases directly.


Background
Prostate cancer mortality rates have steadily decreased in the U.S. over the past 20 years. This decrease began around the same time that prostate-specific antigen (PSA) screening was adopted in the U.S. However, it remains arguable whether the decrease is due to the implementation of screening or to non-screening related factors such as improved treatment options.

Currently, PSA remains the most commonly used screening test for prostate cancer, even among elderly men. An estimated 43% of men aged ≥75 years received an annual test in 2010. Controversy surrounds the use of PSA as a screening tool for prostate cancer, as findings from two recent RCTs suggest that there is limited to no prostate cancer mortality benefit associated with PSA screening. Further, the potential harms associated with PSA screening include the overdiagnosis and subsequent treatment of indolent prostate cancers. Recently, the U.S. Preventive Services Task Force reviewed the existing evidence and recommended against PSA screening. However, their assessment of the evidence was limited to the results from systematic reviews, meta-analyses, and the two clinical RCTs that produced conflicting results. As a result, the debate remains about whether the use of PSA screening is still warranted in certain patient populations.

In light of the discussion surrounding PSA screening, it is prudent to also consider the results from existing observational studies to further inform this debate. The majority of the observational studies to date that evaluated the association between PSA and prostate...
cancer mortality employed a case–control design. Although they are cost effective and more efficient, case–control studies of screening tests are particularly prone to bias; therefore, their results should be interpreted with caution. These biases can include selection biases introduced in the selection of both case and control subjects, lead and length biases, and the misclassification of screening versus diagnostic tests arising from the influence of digital rectal examinations and lower urinary tract symptoms. Thus, the findings from these studies are often discounted. However, it remains unclear whether the biases present have a sufficiently strong impact to outweigh the relevance of the results.

Because the variability in the findings of the existing case–control studies of PSA screening and prostate cancer mortality are as confusing as the RCT results, the goal of the current study is to comprehensively evaluate the findings from these case–control studies in light of their methodologic limitations and potential biases. Findings from this study can then further inform the debate surrounding PSA screening and prostate cancer mortality and guide the development of future observational research in this area.

Evidence Acquisition
A comprehensive, structured literature search was used to identify studies of PSA screening and prostate cancer mortality. The goal of the search was to identify studies evaluating whether screening for prostate cancer (PSA testing with or without digital rectal exam [DRE]) leads to reduced mortality in a screened versus unscreened population of men. Search criteria were developed and a comprehensive literature review was performed by Doctor Evidence, LLC (a specialty software platform and services company) based on the IOM’s standards for developing and initiating a systematic review.10

Inclusion criteria included limiting the search to studies that evaluated PSA with and without DRE and had at least a one-time measurement of screening (Figure 1). Further, studies were excluded if they did not include men aged ≥50 years and/or African-American men aged ≥40 years, or men with a family history of prostate cancer aged ≥40 years who are free of prostate cancer symptoms. Studies that were included also had to involve unscreened comparison groups and include a minimum of 1-year follow-up for outcomes. In addition, only studies published in English during the past 20 years were eligible.

Databases that were searched for eligible studies included PubMed and EMBASE. A variety of medical subject headings (MeSH) that are related to prostate cancer screening were used. Of the 79 eligible studies identified based on these criteria, which included a variety of designs including cohort studies and RCTs, eight employed a case–control design. One additional study was excluded because it focused solely on DRE screening, leaving a total of seven case–control studies eligible for the current review. In 2012, the studies were critically appraised to evaluate the quality of the study populations, exposure, and outcome definitions and potential sources of bias. The results from the studies were compiled and summarized; emphasis was placed on evaluating common sources of bias across studies.

Evidence Synthesis

Study Populations
Of the seven case–control studies evaluated, three of the studies used health care organizations as their source population, two11,12 of which were HMOs and one13 used data from ten Department of Veteran’s Affairs (VA) medical centers. The remaining four studies were community-based, two of which took place in established cohorts that focus on urologic disease (Olmsted County MN and King County WA)14,15, one in Ontario, Canada16; and one among married men residing in New Jersey.17 A total of 5558 men were included in these studies. Of these men, 2472 were identified as prostate cancer mortality case subjects, and 3086 were matched control subjects. The studies incorporated prostate cancer deaths occurring from the early 1990s through 2007. The racial composition of the populations differed across studies.

Definition of Case Subjects
Although the majority of studies (six) defined case subjects based on date of prostate cancer death, Kopeck et al.16 used metastatic prostate cancer to define case subjects. Concato and colleagues13 further defined case subjects as men whose deaths were due specifically to metastatic prostate cancer. Overall mortality was assessed as an outcome in one study,13 and Agalli et al.15 assessed other-cause mortality as an outcome in addition to prostate cancer mortality. Case subjects were identified from various source populations including cancer registries,11,12,15 state vital statistics,11 pathology reports (VA system),13 and physician recruitment (where case subjects were men with metastatic disease).12 Studies by both Weinmann and colleagues11,12 and Bergstralh et al.14 reviewed medical records and death certificates, when available, to confirm that the case subjects died of prostate cancer.

Definition of Control Subjects
Control subjects were identified via various sources, including health records,11–14 random-digit dialing,15,17 and tax
Table 1. Summary of the case-control study characteristics and findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population, control selection, and matching</th>
<th>n cases/controls</th>
<th>% screened (cases, controls)</th>
<th>Screening time period</th>
<th>Screening definition details</th>
<th>Outcome(s)</th>
<th>Case definition time period</th>
<th>Results</th>
<th>Approach to limiting biases</th>
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</thead>
<tbody>
<tr>
<td>Weinmann (2004)</td>
<td>MCO; ages 45–84 years; matched controls on age and membership length</td>
<td>171/342</td>
<td>69, 75</td>
<td>10 years prior</td>
<td>PSA and/or DRE any time up to case diagnosis date</td>
<td>Prostate cancer mortality</td>
<td>1992–1999</td>
<td>MOR=0.70 (0.46, 1.1)</td>
<td>Defined source population; chart review confirmed cause of death; took into account urinary symptom or previous elevated tests when defining screening tests; evaluated impact of DRE</td>
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<tr>
<td>Kopec (2005)</td>
<td>Population-based, Canada; controls randomly sampled from municipal tax records and matched on age and residence</td>
<td>236/462</td>
<td>24.6, 27.2</td>
<td>Up until diagnosis date or date of suspicion; unclear time period</td>
<td>PSA and/or DRE up to diagnosis date, or date of suspicion by indication in chart of symptoms, or use of imaging for diagnostic purposes; excluded those with LUTS</td>
<td>Metastatic prostate cancer</td>
<td>1999–2002</td>
<td>OR=0.65 (0.45, 0.93)</td>
<td>Population-based sample; took into account urinary symptom, previous elevated tests and abnormal DREs when defining screening tests</td>
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<td>Weinmann (2005)</td>
<td>Four MCOs; matched controls on health plan, age, race, and membership history</td>
<td>769/929</td>
<td>Definite: 62, 69 in whites; 59, 61 in blacks; those with no DRE: 5, 7 whites; 11, 4 blacks</td>
<td>10 years prior to and up to date of diagnosis</td>
<td>PSA and/or DRE up to or at time of diagnosis; excluded those with symptoms, and any indication in chart test was diagnostic. &quot;Definitely screened&quot;: test performed at a visit without any symptoms, BPH history or elevated PSA or abnormal DRE; &quot;probably screening&quot;: no elevated tests or abnormal DREs, stable symptoms not due to prostate cancer or BPH</td>
<td>Prostate cancer mortality</td>
<td>1997–2001</td>
<td>OR=0.73 (0.55, 0.97)</td>
<td>Defined source population; chart review confirmed cause of death; race-stratified analyses; evaluated impact of DRE</td>
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<tr>
<td>Concato (2006)</td>
<td>Ten VA centers; aged ≥50 years; matched controls on age and VA facility</td>
<td>136/136</td>
<td>Definite: 14, 13 overall; 20, 17 including BPH</td>
<td>5 years prior to diagnosis</td>
<td>PSA and/or DRE screening identified via chart review up until diagnosis date; screening tests were classified as definite, probable, done for differential diagnosis (nonscreening) and unknown</td>
<td>Prostate cancer mortality from metastatic prostate cancer and overall mortality</td>
<td>1991–1999</td>
<td>Overall mortality: OR=1.08 (0.71, 1.64); prostate cancer mortality: OR=1.13 (0.63, 2.06)</td>
<td>Defined source population; used classification scheme to differentiate between screening and diagnostic tests; included controls diagnosed with PCA, if control with PCA later died</td>
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<td>Bergstrath (2007)</td>
<td>Population-based, Olmsted County MN; matched controls on age and clinic registration date (±5 years)</td>
<td>74/192</td>
<td>PSA: 24.3, 39.6; DRE: 56.8, 78.7; PSA or DRE: 60.8, 81.3</td>
<td>5 years before diagnosis date to symptomatic date or 1 year before diagnosis</td>
<td>PSA and/or DRE screening up to 1 year before diagnosis; screening defined on the basis of absence of concurrent, obstructive symptoms or prostate cancer-related symptoms; symptom reference date also used based on bone, perineal or hematuria</td>
<td>Prostate cancer mortality</td>
<td>1992–2005</td>
<td>OR=0.40 (0.2, 0.7); Prior to symptomatic date: OR=0.8 (0.1, 1.7)</td>
<td>Population-based sample; included controls diagnosed with PCA only after case diagnosis date; defined screening test as those performed in absence of obstructive urinary or prostate cancer symptoms</td>
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<td>Agalliu (2007)</td>
<td>Population-based, King County WA; ages 50–64 years; matched controls on age and identified them through random-digit dialing</td>
<td>706/645</td>
<td>65.9, 82.5</td>
<td>5-year period prior to diagnosis</td>
<td>Self-reported PSA and/or DRE screening during routine checkup in 5-year period prior to diagnosis; patients were asked about reason for test</td>
<td>Prostate cancer and other-cause mortality</td>
<td>1993–2007</td>
<td>Prostate cancer mortality: OR=0.38 (0.19, 0.77); other-cause mortality: OR=1.02 (0.51, 2.02)</td>
<td>Population-based sample; collected social and behavioral characteristics through self-report</td>
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<td>Marcella (2008)</td>
<td>Married men aged 50–79 years at death; community</td>
<td>380/380</td>
<td>23, 21</td>
<td>10 years prior to diagnosis</td>
<td>Any PSA screening (ever yes/no), categorized as tests done for screening, LUTS,</td>
<td>Prostate cancer mortality</td>
<td>1997–2000</td>
<td>MOR=1.05 (0.71, 1.55)</td>
<td>Population-based sample; included only screening tests prior to date</td>
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All of the studies randomly selected the control populations and matched on age. Other matching factors used across studies included length or type of membership (for HMO-based studies); clinic facility (for VA and for Olmsted County); race; and area of residence (for population-based Canadian study). A control-to-case matching ratio of 1:1 was employed in three studies, with the remaining four using at least a 2:1 matching ratio.

Only one study excluded men with a history of prostate cancer from serving as control subjects. In the remaining studies, men with prostate cancer were eligible as control subjects, but different criteria for control eligibility were used. Concato et al. required control men to be alive on the case death date, and if they subsequently died, they were resampled as case subjects. Multiple studies required control men to be diagnosed with prostate cancer after the case’s diagnosis date. Two studies allowed control subjects to include men with nonmetastatic prostate cancer.

### Exposure/Screening Definition

All of the reviewed case–control studies evaluated PSA and/or DRE, and PSA screening was defined as having at least one PSA test during the study period. Only one study relied on self-reported screening. Various methods were used across studies to distinguish between screening and diagnostic tests. Most of the studies defined screening PSA tests as tests done up to suspicion date or symptomatic date, which was based on presence of symptoms that would indicate a need for the test or the use of services that would indicate that the testing was done for diagnostic purposes.

Concato and colleagues stratified by the likelihood that the test was done for screening purposes, categorizing tests into “definite, probable, differential diagnosis (non-screening) and unknown reasons.” Marcella et al. also reviewed any tests done within 6 months of diagnosis to confirm that the test was done for screening, and Bergstralh and colleagues did not include tests done 1 year prior to diagnosis. In addition to using a suspicion date, two studies also excluded tests done in the presence of symptoms that would indicate a need for the test or the use of services that would indicate that the testing was done for diagnostic purposes.

### Summary of Findings from the Studies

The majority of studies reviewed concluded that there was a reduction in prostate cancer mortality associated with PSA screening. Five studies found that PSA
screening was associated with a reduced risk of prostate cancer mortality. The reduction in risk ranged from 62% to 27% across studies (Table 1). However, two of 13,17 of the studies found no prostate cancer mortality benefit associated with PSA screening.

There was no clear trend in results based on study setting. The two MCO-based studies11,12 found a protective association, whereas the VA-based study13 found no association between PSA screening and prostate cancer mortality. Further, three of the population-based studies14–16 found a protective association, whereas only one found no association.17

Also, there was also no clear pattern of results that correlated with case definition. Of the five studies that found PSA screening was associated with a reduced risk in prostate cancer mortality, all except one16 defined case subjects based on prostate cancer mortality rather than metastatic disease. The two studies13,17 that found no association between PSA screening and prostate cancer mortality both defined case subjects as men who died from prostate cancer. Of note, Marcella et al.17 required case subjects to be married at the time of their death and only included those whose spouses agreed to participate. Five studies11–14,16 randomly selected control subjects from the same source population as the case subjects, and four11–14 used existing electronic medical files to identify them. Two employed random-digit-dialing to identify eligible control subjects, one17 that found no association and one15 that found a protective association, suggesting no clear trend in terms of control selection.

Whether or not screening tests were differentiated from diagnostic tests via chart review also did not seem to consistently affect the results of the studies reviewed. All but one15 of the studies that found a protective association employed chart review to determine the presence of symptoms to differentiate a diagnostic test from a screening test. Agaliu et al.15 relied on self-report of the reason for the PSA test to discriminate between diagnostic and screening tests. Both studies13,17 that found no association used a date of suspicion of prostate cancer (based on chart review) to differentiate diagnostic from screening PSA tests.

However, the proportion screened among cases and control subjects did seem to correlate with the results reported. Both studies13,17 that found no association between PSA screening and prostate cancer mortality reported a screening proportion of < 25% in the case and control subjects. Whereas all of the studies that found a protective association reported a > 60% screening proportion among cases and control subjects, with the exception of Kopec et al.,16 who reported that 24.6% and 27.2% of the cases and control subjects, respectively, had a screening PSA test.

**Discussion**

In reviewing the seven case–control studies of PSA screening and prostate cancer mortality that were done over the past 20 years, the majority of studies suggest that PSA screening is associated with a reduced risk of prostate cancer mortality. These findings are in line with the European Randomised Study of Screening for Prostate Cancer clinical trial that found PSA screening to be associated with a reduction in prostate cancer mortality, albeit limited.4 However, the results are in contrast to the findings from the screening trial performed in the U.S., the Prostate, Lung, Colorectal and Ovary Study,3 that found no significant difference between men who were randomized to screening compared to men who were not after 7–10 years of follow-up. In order to appropriately supplement the evidence from the existing clinical trial data, the results from the case–control studies must be interpreted in light of the potential biases inherent in case–control studies of screening tests.

**Diagnostic Versus Screening Tests**

A common limitation of case–control studies of screening tests is the difficulty in distinguishing between tests done for screening purposes and diagnostic tests.18 Misclassification of diagnostic tests as screening would most likely result in an underestimation of screening efficacy. All the studies reviewed attempted to discern diagnostic from screening tests. The majority of the studies relied on a date of suspicion that was defined by the onset of symptoms. However, using symptoms in the case of prostate disease is difficult because the presence of lower–urinary tract symptoms does not necessarily indicate the presence of cancer, but could be the result of benign prostatic conditions or infections.

A subset of studies attempted to more specifically identify diagnostic tests through chart review to determine the date of symptom onset.17 However, because there is no way to absolutely distinguish symptoms of prostate cancer from benign prostatic disease, as a result of their overlap, uncertainty remains regarding whether these tests were truly screening tests. Thus, the bias that results from the potential misclassification of diagnostic tests as screening cannot be fully ruled out in any of these studies. However, the resulting association between screening and prostate cancer mortality in these studies would be biased toward the null.

In the studies that found protective effects, this would result in an underestimation of the efficacy of screening that was directly related to the magnitude of this misclassification. In addition, one study14 relied on excluding tests done within 1 year before diagnosis. This method would actually lead to a decreased number of
case subjects being screened, and as a result, screening may look artificially beneficial in the presence of this bias.

**Case Subject Definition and Ascertainment**

The definition of case subjects in studies of prostate cancer screening is also critical, as they are subject to lead time and other biases. Studies that focus on prostate cancer screening efficacy should define case subjects based on the occurrence of prostate cancer death or another related adverse outcome, such as metastatic disease. If case subjects are defined instead by the date of initial prostate cancer diagnosis, this approach would underestimate the proportion of case subjects that would have undergone screening, thus leading to a falsely beneficial screening efficacy. This type of bias was avoided in the studies reviewed, as six of the seven studies defined case subjects based on prostate cancer death, and Kopec et al. defined case subjects based on the occurrence of metastatic disease, not initial prostate cancer diagnosis.

Lead-time bias, or ascertainment bias, arises when case subjects are defined based on time limits such as age or calendar time and screening or the preclinical phase occurs before this time period or age range. Therefore, the case eligibility period should be defined so that it is early enough that previous screening and preclinical disease risks are minimized. Otherwise, decreased mortality associated with screening will be due to the increased time period between early detection and mortality and not because of an actual beneficial effect of the screening program.

However, avoiding this bias is more difficult, as this must be balanced with the issue that the timing of diagnosis relative to the start of the screening program needs to be long enough so that case and control subjects have equal opportunity to screen. If this time period is too short, case subjects would be more likely to screen than control subjects, and the results of the study will be biased toward the null and potentially underestimate the benefit of screening. This is an issue as the majority of case–control studies reviewed assessed screening early in the PSA era and, therefore, case and control subjects would not yet have an equal opportunity to screen. As a result, a low prevalence of screening was reported in half of the studies, which also can lead to biased findings because case subjects would most likely be screened first.

**Length Bias**

Similar to lead bias, length bias can potentially lead to differential misclassification of the exposure early in the adoption of a screening program. When a screening test is first implemented, prevalent cancers make up the majority of cases identified. Thus, this over-represents indolent, slow-growing cancers and under-represents the more fulminant ones that are less likely to be detected through screening. This will lead to a relative decrease in number of deaths that occur in the nonscreening group early on. The resulting estimates of association will then be biased, making the screening program appear less beneficial.

The majority of the studies reviewed here assessed screening early in the PSA era and found screening to be protective. Therefore, their findings are subject to this length bias that results in a biased estimate away from the null, making screening appear less beneficial. Not only do the results from these studies need to be interpreted in light of this bias, but the potential presence of this bias in the existing studies warrants future observational studies in which PSA screening is assessed after it was fully implemented in practice.

**Screening Measurement and Exposure Window**

 Appropriately defining PSA screening and the time period in which it occurs are two complex issues that persist in all of the case–control studies reviewed. The definition of PSA screening is particularly complex because it occurs in the presence of DREs, which can influence whether or not a man receives a PSA screening test. The inability to distinguish whether a man also had a DRE, uncertainty regarding how the results of the DRE influenced the use of the PSA test, and the limited number of men who received a PSA in the absence of a DRE limits the ability to determine what effect PSA alone has on prostate cancer mortality. None of the seven studies reviewed were able to accurately differentiate the effect of PSA from that of DRE on prostate cancer mortality. Separating the effect of PSA on prostate cancer mortality from that of DRE, and avoiding this type of bias, may not be possible as current clinical practice includes the use of both tests in conjunction with each other.

In addition to the influence of DREs on defining PSA screening, another potential problem arises when determining the appropriate length of the screening time period. The time period in which screening is considered should end when a case has a clinic visit that leads to diagnosis. If this time period continues past this point, the opportunity to screen is no longer equal between case and control subjects. In this instance, control subjects will have more opportunity to screen than case subjects. As a result, screening among control subjects will be inflated and lead to a biased estimate that makes screening appear more beneficial.

One critical issue that must be considered when determining the screening time period is how to best
define the length of the preclinical phase of prostate cancer. Screening for cancer should focus on targeting the detectable, preclinical phase. Therefore, assumptions must be made regarding the length of time prior to diagnosis that prostate cancer is detectable. The studies reviewed chose varying lengths of time, from 5 to 10 years prior to diagnosis. Screening that occurs before or after this phase has the potential to also bias the study’s results.22

Confounding Due to Self-Selection

Finally, an important bias to note that occurs often in case–control studies of screening tests is that which arises when those who choose to participate in screening differ from those who do not in that they may have differing prostate cancer incidence and mortality. Complicating this type of confounding is that the direction of the bias can go either way; those who screen may be at increased or decreased risk of mortality when compared to those who did not, and this may vary across study populations. Therefore, in order to mitigate this type of confounding, it is critical to collect information on potential confounders and established prostate cancer and prostate cancer mortality risk factors. If these factors are then found to be related to screening status, they should be accounted for in the analysis. Also, a priori identified known confounders should be matched to minimize the potential for bias. All of the studies reviewed matched in terms of age, and most matched for membership or utilization status, thus minimizing the potential differences in these characteristics among case and control subjects.

Future Directions

Interpreting the results from the existing case–control studies of PSA screening and prostate cancer mortality is difficult, as they are clouded by various types of bias. Given the limitations of these studies as well as the RCTs on this subject, uncertainty remains regarding the use of PSA as a screening tool for prostate cancer. Perhaps a different tactic should be taken that focuses on understanding the sources of the variability in these types of studies. For example, a study that empirically evaluates some of these biases by altering the methodologic definitions may help with the interpretation of existing and future observational research in this area.

In addition, questions remain regarding the best approach to designing future observational studies that evaluate the association between PSA and prostate cancer mortality. How long a preclinical phase of prostate cancer is necessary in order to accurately define the exposure/screening window? How far back in time should we assess screening as balancing the influence of ascertainment bias with allowing for equal opportunity to screen between case and control subjects is an issue? How do we limit self-selection biases and influence of confounding? How do we best assess and account for the influence of DRE and lower–urinary tract screening on this association? As a result, future studies should empirically evaluate the magnitude of these biases and attempt to address the remaining questions so that the results from existing studies of PSA and prostate cancer mortality can critically inform the discussion surrounding the use of PSA as a screening test for prostate cancer.

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References


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