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.

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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.[1] An estimated 43% of men aged ≥75 years received an annual test in 2010.[2] 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.[3,4] 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.[5] 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.[6] As a result, the debate remains about whether the use of PSA screening is still warranted in certain patient populations.[7,8]

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

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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[9]; 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.

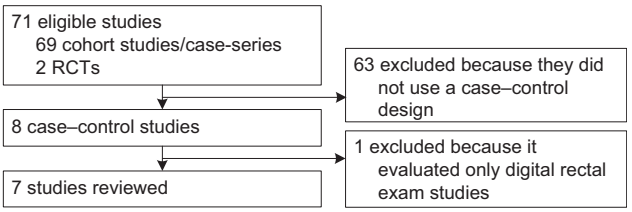

Figure 1. Flow diagram of inclusion/exclusion criteria for selecting studies for the review

Evidence Synthesis

Study Populations

Of the seven case–control studies evaluated, three of the studies used health care organizations as their source population, two[11,12] of which were HMOs and one[13] 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, Canada[16]; 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, Kopec et al.[16] used metastatic prostate cancer to define case subjects. Concato and colleagues[13] 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 Agalliu 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 colleagues[11,12] 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