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Examining the Efficacy of Screening with Prostate-Specific Antigen Testing in

Reducing Prostate Cancer Mortality

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Abstract

Prostate cancer is a prevalent, worldwide problem among male adults. This literature review, “Examining the Efficacy of Screening with Prostate-Specific Antigen Testing in Reducing Prostate Cancer Mortality,” focuses on a safe and effective screening test for detecting prostate cancer in its early stages—prostate-specific antigen testing—and seeks to answer the clinical question, “Does screening with PSA testing for the early detection of prostate cancer in males ages 50-80 years significantly reduce prostate cancer mortality?” A literature search of peer-reviewed articles within the last fifteen years on databases such as CINAHL and Pub Med was conducted to find five articles that pertained to the clinical question. An analysis and synthesis of the research articles provided promising yet not conclusive evidence that prostate-specific antigen testing significantly reduces the absolute risk of prostate cancer mortality. Further research is needed to provide more substantial evidence to support the use of prostate-specific antigen testing in clinical practice.

Introduction

The efficacy of screening with prostate-specific antigen (PSA) testing for the early detection of prostate cancer is a topic of heated debate in the medical world. Articles have recently been published highlighting the harms and risks of PSA testing. One of the most recent, a systematic review released by the U.S. Preventive Services Task Force (USPSTF), reveals findings that confound the issue further. For example, the USPSTF found PSA testing detects a modest amount of prostate cancers; however, it may lead to overdiagnosis of prostate cancer and further risks such as pain secondary to prostate biopsy (2008, pp. 185-187). In addition to this evidence, the USPSTF found most prostate cancers detected with PSA testing will not be harmful to the patient during their lifetime (2008, p. 187). Due to recently published articles and the 2008 positional statement of the USPSTF, screening for prostate cancer has become a paradox. To address the current debate about PSA testing and its role in screening for prostate cancer, it is pertinent to ask the following: Does screening with PSA testing for the early detection of prostate cancer in males ages 50-80 years significantly reduce prostate cancer mortality?

Discussion of Prostate Cancer and Prostate Cancer Screening

The high prevalence of prostate cancer and the clinical importance of determining whether current screening methods are effective in reducing prostate cancer mortality is non-debatable. According to the World Health Organization (WHO), prostate cancer is among the top five types of cancer that cause the majority of cancer fatalities (WHO, 2012). In the United States, prostate cancer is the second-leading cancer type, and in 2007, was one of the leading causes of cancer death among all men, yielding 29,093

deaths related to prostate cancer (Centers for Disease Control and Prevention, 2011). As prostate cancer remains a prevalent problem, it is pertinent to critically examine the efficacy of the methods currently used to screen for prostate cancer.

Common methods used to screen for prostate cancer in the clinical setting include both PSA testing and digital rectal exam (DRE). Prostate-specific antigen is a protein produced by the prostate gland that is a biologic marker of prostate cancer as well as benign prostate conditions (National Cancer Institute, 2009). PSA testing does not distinguish between benign and cancerous prostate conditions; however, levels elevated above set thresholds are a red flag for clinicians to pursue further testing (National Cancer Institute, 2009). According to the American Urological Society (AUA), prostate-specific antigen testing remains the single best test to detect prostate cancer in its early stages (2009, p.14). Furthermore, in combination with digital rectal examination, PSA testing may detect prostate cancer in its early stages at even higher rates (AUA, 2009, p. 14). Why, then, is testing with PSA so controversial in practice? There are several medical uncertainties associated with it.

First, there is great variability with the sensitivity and specificity of PSA testing. At lower cutoff points for detecting prostate cancer, specificity is sacrificed for sensitivity, increasing the risk of overdiagnosis. In addition to variable sensitivity and specificity of PSA testing, clinical guidelines differ in their recommendations for screening intervals and interpretations of test results. With no clear clinical pathway to follow and the recent contradictory evidence of the benefits and risks of prostate cancer screening with PSA testing, many clinicians have simply chosen to refrain from prostate cancer screening, raising ethical concerns regarding a patient's right to be screened. One

must carefully review and critically appraise the current evidence of the efficacy of PSA testing to determine whether it significantly reduces prostate cancer mortality.

Critical Analysis of the Evidence Related to the Clinical Question

Purpose

The studies by Andriole et al. (2009), Hugosson et al. (2010), Labrie et al. (1999a), and Schröder et al. (2009) share a common purpose of determining the impact of screening with prostate-specific antigen testing on prostate cancer mortality rates. The study by Sandblom, Varenhorst, Lofman, Rosell, & Carlsson (2004) is an exception because its purpose is to “to characterize prostate cancer detected in a population-based screening program” (p. 718) as well as to evaluate the efficacy of screening with PSA at three-year intervals. If the reader examines the primary outcomes measured in Sandblom et al.’s (2004) study, the efficacy of PSA screening is measured in overall and cancer-specific survival rates, an outcome similar to the aforementioned studies. The purpose of these studies reflects the purpose of the clinical question posed in this literature review.

Research design

The five research studies utilized one type of experimental design- randomized controlled trials (RCT)-with varying strengths. The study designs were primarily cluster-randomized controlled trials, where pre-existing males from specific populations were selected to be in either an intervention or control group. Of the randomized controlled trials, Schröder et al. (2009) and Hugosson et al. (2010) had the strongest designs, with large sample sizes, (power above .80), blinding to patient cause of death, and randomization before consent, increasing the generalizability of the study findings. In addition to these strengths, Schröder et al. (2009) utilized a central data center to ensure

quality data was obtained for the duration of the study. Sandblom et al. (2004) also had strengths, including randomization of participants prior to obtaining consent and control for the extraneous variable of treatment received by participants with a positive prostate cancer diagnosis. Strengths of Andriole et al.'s (2009) study included a large sample size and control for the extraneous variable of prostate cancer screening in the control group. A shared strength of all five studies was group equivalence, increasing the validity of the studies. Despite the strengths of these studies, limitations existed, with Labrie et al. (1999a), Andriole et al. (2009), and Sandblom et al. (2004) lacking a power analysis and blinding in their studies. Design limitations of all five studies included an absence of inter-rater reliability and instrumental validity scores as well as decreased generalizability of study findings due to the increased control associated with the study designs.

Sampling

In all five of the research studies, older male adults without a previous or current prostate cancer diagnosis represented the populations studied. Purposive, stratified sampling was used to select the participants in each study. The population demographics among the studies were fairly consistent, with high group equivalence due to randomization of the study groups. All five studies had a male population, with ages ranging from 50-69 (except Andriole et al. (2009) and Schröder et al. (2009), with upper age limits in the mid to high 70s). Ethnicity was not included in the population demographics for any of the five studies, consequently decreasing the external validity of these studies' findings. Attrition was addressed in some of the studies, with Schröder et al. (2009), Hugosson et al. (2010), and Sandblom et al. (2004) appropriately discussing the loss of their patients, which was largely due to immigration or death. The size of the

study samples varied according to study designs and limitations, and only Schröder et al. (2009) and Hugosson et al. (2010) justified their population size by a power analysis. Despite the lack of detailed demographic description in the studies, the following clinical and demographic characteristics of the studies, including lack of a previous or current prostate cancer diagnosis, all male subjects, and an age range of 50-80 years are a sufficient match for this literature review.

Variables

Prostate-specific antigen testing was the primary screening intervention utilized in all of the studies with the exception of Sandblom et al. (2004), who chose to utilize the combination of PSA testing and DRE. Schröder et al. (2009) and Labrie et al. (1999a) also utilized digital rectal exam for prostate cancer screening, however only for initial screening, and then only PSA testing after that. Andriole et al. (2009) screened with PSA and DRE separately, utilizing PSA testing for the first 6 years, then DRE for the last 4 years of their studies. Although the screening method was consistent in most of the studies, the screening interval and PSA cutoff to signal further testing for prostate cancer varied. Labrie et al. (1999a) and Andriole et al. (2009) both utilized an annual PSA screening interval, with a PSA cutoff of >4.0 ng/ml in Andriole et al.'s study (2009), and a PSA cutoff of >3.0 ng/ml in Labrie et al.'s (1999a) study. Conversely, Schröder et al. (2009) conducted PSA testing every 4 years, with a PSA cutoff interval of $>3.0-4.0$ ng/ml. Hugosson et al. (2010) screened for prostate cancer with a free/total PSA test every 2 years, utilizing a PSA cutoff of $>2.5-3.4$ ng/ml for further diagnostic testing. Sandblom et al. (2004) utilized a screening interval of 3 years, with a PSA cutoff of >4.0 ng/ml. The control used in all five studies was refraining from prostate cancer screening,

which was theoretically achieved by the control group not receiving invitations to screen. For the majority of the studies, the potential benefits of screening for prostate cancer were worth the risks.

The primary outcome measure of all of the studies was prostate cancer mortality (except Sandblom et al. (2004), the outcome of which was cancer-specific survival, an indirect measure of mortality). In addition to the measure of prostate cancer mortality rates, Hugosson et al. (2010) and Sandblom et al. (2004), examined the secondary outcome of cumulative prostate cancer incidence, Schröder et al. (2009) determined the number of people needed to screen and treat to prevent one prostate cancer-related death, Labrie et al. (1999a) measured life-years gained by the diagnosis and treatment of prostate cancer, and Andriole et al. (2009) determined the cost of prostate cancer diagnosis as well as prostate cancer incidence, staging, and survival from prostate cancer. Length of follow-up for measuring outcomes in the five studies varied, including 14 years for Hugosson et al. (2010), 9 years for Labrie et al. (1999a) and Schröder et al. (2009), 15 years for Sandblom et al. (2004), and an interval of 7-14 years for Andriole et al. (2009).

Extraneous variables, whether known or detected, were present in all five studies. A known extraneous variable for Andriole et al. (2009) and Labrie et al. (1999a) was participation of the control group in prostate cancer screening, which was controlled for in statistical analyses. Another known extraneous variable that was considered in the 2009 study design of Andriole et al. was the impact of different laboratory equipment on the consistency of PSA results, therefore Andriole et al. (2009) processed all PSA results through the same laboratory. Other known extraneous variables included bias related to prostate cancer treatment (Sandblom et al., 2004; Schröder et al., 2009) and the impact of

PSA testing as an established screening test on participant's intention to screen (Labrie et al., 1999a), which were considered in the study designs. Extraneous variables that existed, but were not included in the studies included the impact of race on prostate cancer risk (except in Andriole et al. (2009)) and the effect of varying personnel administering digital rectal exams on the detection rate of prostate cancer. The failure to address these extraneous variables decreases the internal validity of the studies.

Study measures

As mentioned in the previous section, the main outcome variable of the studies was prostate cancer mortality. It was determined by utilizing death registries, cancer registries, and mailed questionnaires. All five studies maintained a definition of prostate cancer mortality as death directly caused by prostate cancer, or death as a result of diagnostic procedures or treatments associated with prostate cancer. Cause of death was determined by committee review of medical records (Hugosson et al., 2010; Sandblom et al., 2004; Schröder et al., 2009), autopsy and pathology reports (Hugosson et al., 2010), and death certificates (Andriole et al., 2009). All of the methods used to determine prostate cancer mortality were established. Sandblom et al. (2004), however, were the only authors that discussed the validity of the cancer register utilized to determine mortality. With the exception of Sandblom et al. (2004), the other studies failed to discuss the reliability and validity of the methods utilized to determine prostate cancer mortality and survival rates as well as cause of death, weakening the internal validity of their studies.

Statistical Analysis

The statistical analyses used in the studies all differed from one another, yet each researcher utilized descriptive and inferential statistics appropriately. A strength of all the studies was their statistical significance levels were appropriately set at $p \leq .05$. Andriole et al. (2009) and Sandblom et al. (2004), however, did not always designate p values for each finding, making their external validity questionable. The statistical analysis methods utilized in the studies include the following: Poisson regression analysis (Andriole et al., 2009; Hugosson et al., 2010; Schröder et al., 2009), Cox regression models (Hugosson et al., 2010), the Nelsen-Aalen method (Hugosson et al., 2010; Schröder et al., 2009), a Kaplan Meir estimator (Hugosson et al., 2010; Sandblom et al., 2004), two-sided Fisher's exact and Barnard's tests (Labrie et al., 1999b), and log-rank tests (Sandblom et al., 2004). All statistical tests utilized were appropriate for medical survival analysis as well as detecting significant differences between the intervention and control groups. Despite the appropriateness of these statistical analyses, their statistical conclusion validity is low and their risk for type II error is high (except in Hugosson et al. (2010) and Schröder et al.'s (2009) studies) because no official analysis to verify appropriate population size was conducted (Andriole et al., 2009; Labrie et al., 1999a) or their p value was simply not strong enough (Sandblom et al., 2004). The use of a power analysis and appropriate statistical analysis methods makes Schröder et al. (2009) and Hugosson et al.'s (2010) findings the highest in statistical conclusion validity.

Findings

With the utilization of PSA testing at regular intervals, a significant reduction in the absolute risk for prostate cancer death after screening with PSA testing was found in Schröder et al. (2009) and Hugosson et al.'s (2010) studies. Similarly, Labrie et al.

(1999a) found regular PSA testing lead to a significant reduction in the incidence of prostate cancer deaths. Contrary to these findings, Sandblom et al. (2004) did not find a significant difference in prostate cancer-specific survival after screening with PSA testing and Andriole et al. (2009) did not find a significant difference between the screening and control groups in the reduction of prostate cancer mortality rates.

Additional findings included the number of people that need to be screened (NNS) and treated (NNT) to prevent one prostate cancer-related death. Schröder et al. (2009) found the NNS and NNT were 1068 and 48 people and Hugosson et al. (2010) found the NNS and NNT were 293 and 12; numbers that appear significantly different, yet are quite similar with ratios applied (22:1 and 24:1). Additionally, Hugosson et al. (2010) found the control group had a significantly higher incidence of advanced prostate cancer than the screening group and Schröder et al. (2009) found screening with PSA testing significantly reduces the risk of diagnosis with metastatic prostate cancer. Sandblom et al.'s (2004) findings also demonstrated a significantly lower incidence of advanced tumor grades and metastases in the PSA testing intervention group than in the control group. Conversely, Andriole et al. (2009) determined there was no significant difference in the incidence of advanced (stage III of IV) prostate cancer in the screening and control groups.

Other important results were related to the efficacy of screening with DRE and the cost of PSA screening and diagnosis of prostate cancer. For example, Labrie et al. (1999a) found that "14 percent of cancers were discovered by DRE in men with normal PSA" levels, however, "5,000 DRE screenings are required to diagnose 1 case of prostate cancer at follow-up visits" (p. 88). Labrie et al. (1999a) found the cost of screening and

diagnosing prostate cancer is actually less expensive in comparison to the cost of screening and diagnosing cervical and breast cancer. With the exception of Andriole et al. (2009) and Sandblom et al.'s (2004) findings, the pattern of evidence in the studies supports the effectiveness of prostate specific antigen screening in significantly reducing prostate cancer mortality.

Synthesis “Answer” to the Clinical Question

An analytical review of the five research studies suggests that there is a moderate amount of evidence that screening for prostate cancer utilizing PSA testing significantly reduces the absolute risk of prostate cancer mortality. Although only three of the five studies found PSA testing reduces prostate cancer mortality, the weight of evidence comes from the clinical trials conducted by Schröder et al. (2009) and Hugosson et al. (2010), as they have the highest level of statistical conclusion validity. Schröder et al. (2009) found utilizing PSA testing every four years with a PSA cutoff value of 3-4 ng/ml over a period of 9 years significantly reduces prostate cancer mortality. Hugosson et al. (2010) determined screening for prostate cancer with PSA testing at 2 years intervals with a PSA cutoff 2.5-3.4 over a 14-year period significantly reduces prostate cancer mortality. Labrie et al.'s (1999a) study, although it lacks a power analysis, is another strong contributor to the evidence-base for PSA screening because it is an RCT, used valid measures, and had a large group size. Labrie et al. (1999a) discovered, in the initial screening visit, digital rectal examination detected 14% of prostate cancers in men with normal PSA levels, however the effectiveness of DRE declined in follow-up appointments. Limitations of Schröder et al. (2009) and Hugosson et al.'s (2010) studies' contribution to evidence-based practice is their lack of generalizability to the general

population of older male adults secondary to their tightly controlled study designs. Although the evidence provided by these studies is by no means conclusive, the statistically significant findings of Schröder et al. (2009) and Hugosson et al. (2010) demonstrate a need for replication or revision of these studies to provide further evidence to support the use of prostate-specific antigen testing in clinical practice.

Implications for Practice

Although the findings of Hugosson et al. (2010) and Schröder et al. (2009) carry a moderate weight of evidence supporting the use of PSA testing for prostate cancer screening, it is of critical importance that the clinical implications of their findings are carefully examined. It is crucial to consider how the findings of Hugosson et al. (2010) and Schröder et al. (2009) should be applied in practice when deciding what type of screening tests, screening intervals, and PSA cutoff points to utilize with prostate cancer screening. The findings of Hugosson et al. (2010) and Schröder et al. (2009) suggest that PSA testing used alone after the initial visit or throughout the course of testing is an effective screening test in reducing prostate cancer mortality. Although selecting PSA testing for prostate cancer screening is an initial step, the type of PSA test used in screening should also be considered as it could greatly impact the specificity of the test's results (American Urological Association, 2009, p. 21). The American Urological Society (AUA) has discovered the use of a free/total PSA ratio has been found to “reduce the number of biopsies in men with serum PSA levels between 4.0 and 10.0 ng/ml” (2009, p. 21). Theoretically, utilizing a free/total prostate ratio would then also reduce unnecessary mental and physical harm to the patient as well. It is also imperative to consider that the addition of DRE to PSA testing in the initial screening visit was found

by Labrie et al. (1999a) to increase the sensitivity of screening for detecting prostate cancer. Reflecting on these results, it would be appropriate to give patients the recommendation for initially screening with DRE and a free/total PSA ratio, and then solely using PSA testing to screen for prostate cancer thereafter.

In addition to the use of PSA testing as a primary prostate cancer screening test, Hugosson et al. (2010) and Schröder et al. (2009) also suggest screening with PSA testing at intervals of 2-4 years significantly reduces prostate cancer mortality. This is a very broad range of screening intervals, and when applying these results to a patient, a clinician must also consider whether the patient has a previous history of abnormal PSA results, their personal and family history of prostate cancer, and their symptoms. While the suggested screening interval of every 2-4 years suggests clinicians may be more liberal with screening, clinicians should utilize a screening interval that is individualized for the patient.

Hugosson et al. (2010) and Schröder et al. (2009) provide an evidence base for an appropriate PSA threshold, an integral part of prostate cancer screening. The purpose of PSA threshold or cutoff values is they suggest an increased risk of prostate cancer and a need for further patient evaluation. Hugosson et al. (2010) and Schröder et al. (2009) imply that a PSA cutoff range of 2.5-4 ng/ml is clinically effective in detecting prostate cancer. This interval is fairly broad considering the difference of 1 ng/ml can dramatically change the sensitivity and specificity of PSA tests in detecting prostate cancer. The upper threshold of 4 ng/ml utilized by Schröder et al. (2009) has been found to have a sensitivity of 20% and a specificity of 60-70% (AUA, 2009, pp. 20-22). To increase the sensitivity and specificity of PSA tests, a lower PSA threshold for all men is

suggested (AUA, 2009, pp. 20-22), such as that used by Hugosson et al. (2010). To increase the specificity of PSA testing further, PSA thresholds can be age-adjusted, with lower PSA threshold levels utilized for younger men (AUA, 2009, p. 19). Considering the proven efficacy of the PSA thresholds utilized by Schröder et al. (2009) and Hugosson et al. (2010) and the evidence from the American Urological Association regarding the sensitivity and specificity of PSA thresholds, it would be advantageous for clinicians to use lower, age-adjusted PSA threshold levels for all men, such as the threshold of 2.5 ng/ml utilized by Hugosson et al. (2010).

Evidence regarding the length of follow-up for prostate cancer screening from Hugosson et al. (2010) and Schröder et al.'s (2009) studies also has important implications for clinical practice. Hugosson et al. (2010) and Schröder et al. (2009) found at 9 and 14 years of follow-up for prostate cancer screening, prostate cancer mortality is significantly reduced. These findings can be applied to clinical practice when clinicians are trying to determine when to commence or halt prostate cancer screening if the years of follow-up are viewed as male life expectancy. For example, if an elderly man has a life-expectancy of less than 9 years, it may be advantageous for the patient to stop PSA testing, because the benefits of refraining from testing may outweigh the risks.

The evaluation of current evidence with high statistical conclusion validity supports the use of prostate specific antigen testing in clinical practice to reduce prostate cancer mortality. While the particular formulas of PSA thresholds, screening intervals, and length of follow-up used by Schröder et al. (2009) and Hugosson et al. (2010) were both effective in reducing prostate cancer mortality, they varied quite a bit, meriting

consideration of further evidence such as recommendations from the American Urological Association (2009) prior to application of the results to clinical practice.

Prostate cancer screening must be tailored to the individual, as their personal risk factors, history, and treatment preferences may shape the course of screening. Finally, given the strength of the evidence above, clinicians should at the very least offer their patients the choice to be screened for prostate cancer with PSA testing, because PSA testing may reduce their risk of developing advanced or even metastatic prostate cancer.

Patient Education

After a patient is offered the choice to screen for prostate cancer, they should be presented with the current evidence regarding prostate cancer screening so they are well equipped to make an informed decision. If the patient chooses to undergo screening, they should be counseled that prostate cancer screening is tailored to the individual, with the clinician considering the patient's history, risk factors, life expectancy, and comfort level for testing. The patient should be educated about the PSA test, the sensitivity and specificity of PSA thresholds, screening intervals, and the next steps taken after a positive PSA result (additional PSA tests and referral for fine-needle biopsy). Lastly, the clinician should emphasize the patient is the key decision-maker for their plan of care, and regardless of where the patient is in the screening process, the patient has the right to halt or refuse screening and treatment.

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