Applying the Principles of Disease Screening to Prostate Cancer

Maria Paiva, BSP, PharmD, BCPS 1,2
Mary H. H. Ensom, B. Sc. (Pharm), PharmD, FASHP, FCCP, FCSHP, FCAHS1,3
1Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada
2Building for the Future Generation, Mampong, Ashanti, Ghana
3Children’s and Women’s Health Centre of BC, Vancouver, BC, Canada

Population screening has been incorporated into multiple disease management strategies. Despite prostate cancer screening programs being in place for almost two decades, their effectiveness in reducing mortality continues to be contentiously debated, resulting in polarized recommendations by various interest groups. Pharmacists are relied upon by multiple stakeholders to critically appraise various types of literature, including non-drug interventions such as disease screening programs. It is important to understand both the purpose and principles of screening to effectively apply the literature. A review was done on the purpose and eight core attributes of effective screening programs with prostate cancer as the model disease state. Based on a critical appraisal of the mortality data along with the remaining seven desired attributes of a screening program, it may be appropriate to follow recommendations to cease prostate cancer screening with currently available methods unless requested by patients informed of the benefits and harms of screening.

Introduction

Screening for disease is an important component of public health. It aids in the discovery of disease among those who are asymptomatic with the goal of preventing or reducing future disease burden (1). In most circumstances, it is irrational to screen everyone for every disease, thus requiring implementation of a targeted and evidence-based approach. The sentinel report published by Wilson and Junger in 1968, “The Principles and Practice of Screening for Disease”, discusses desirable attributes of screening programs and has provided guidance in the development, implementation, and evaluation of screening initiatives worldwide (1).

The effectiveness of prostate cancer screening programs has been under constant scrutiny by healthcare professionals and receives substantial media attention, especially during the month of November, prostate cancer awareness month. The need for governments, budget administrators, and health insurance companies to fund services that provide high health value and eliminate those that do not, as well as the focus of services impacting health outcomes, has led to implementation of tools and testing to evaluate these services, with pharmacists playing a key role (2). Appraising and applying literature on health services is a vital role of clinical pharmacy practice (3), and there is evidence demonstrating the ability of pharmacists to positively impact economic, clinical, and human health outcomes (2). The ongoing controversy surrounding prostate cancer screening provides the opportunity to review the fundamentals of disease screening and understanding these fundamentals will help in applying the evidence to patients.

Background

The primary methods of screening for prostate cancer include the digital rectal exam (DRE) and prostate specific antigen (PSA) laboratory test, used both separate and in combination (4). DRE involves a physician inserting a finger into the rectum and palpating the prostate gland for abnormalities through the rectal wall. PSA is a protein produced by cells of the prostate gland, not prostate cancer cells. Elevated PSA levels observed with prostate cancer are due to increased PSA production and disrupted tissue barriers between the prostate gland lumen and capillaries with subsequent leakage into the serum.

The Canadian Task Force on Preventative Health Care released a protocol on January 18, 2013 for development of prostate cancer screening guidelines, which included a summary of recommendations from national and international organizations (4). Ten different organizations have released guidelines ranging from cessation of prostate cancer screening with PSA and DRE altogether to age or PSA level-specific testing intervals, despite recommendations being derived from the same literature. The projected release date of the updated Canadian guidelines was September 2013; however, no document has been released yet. Much of the debate centers on the existence of a prostate cancer-specific or overall mortality benefit attributable to screening.
Derivation of a prostate cancer-specific or overall mortality benefit represents one of eight core attributes that should be examined when assessing the effectiveness of a cancer screening program, as discussed by Wilson and Junger (1,5). We will review these attributes as they pertain to prostate cancer screening.

**Discussion**

**Attribute 1: The Disease is a Major Health Problem**

With no defined parameters delineating major from minor health problems, we examine some quantifiable measures of disease burden. There has been an overall increase in the diagnosis of prostate cancer since 1980, which has been attributed to the aging population and implementation of population screening programs; however, the mortality rate has steadily decreased (6). Between 2001 and 2009, the age-standardized mortality rate declined from 26.7 to 19.5 deaths per 100,000 men and is estimated to be 17 deaths per 100,000 men in 2014 (6). Although it is the most commonly diagnosed cancer (excluding non-melanoma skin cancer) in Canadian men, the majority of cases (63%) are found in men 65 years of age or older and more men die annually from lung cancer, cardiovascular disease, stroke, and colorectal cancer (7). On autopsy, prostate cancer is detected in 33% of men < 80 years of age and in 66% of men ≥ 80 years, suggesting that the majority die of other causes and the prostate cancer did not lead to clinically important consequences (8).

**Attribute 2: The Disease is More Treatable if Detected Early**

Tumors restricted to the prostate gland have a high probability of being cured compared to tumors that have penetrated beyond the prostate capsule. The five-year relative survival among men with local or regional disease approaches 100% compared to approximately 30% among men diagnosed with distant metastases (7). The majority of diagnosed cases are early stage (9); however, most of these are indolent and may never become clinically significant. The challenge lies in differentiating between early-stage tumors that will remain indolent and those that can cause clinically important disease, which neither the DRE nor PSA can do. Furthermore, prostate cancer detection does not always warrant treatment, which is contrary to other malignancies.

**Attribute 3: The Test Should be Acceptable to Those Eligible**

Literature describing the acceptability of DRE and PSA blood test as a screening method is limited. An observational study from 1990 reported a 78% acceptance rate to undergo DRE. (10). Acceptance rate was defined as the number of (male) patients who underwent testing divided by the number of patients invited for testing (1163/1494). Forty-three percent of patients stated anxiousness or scepticism about the program as reasons for declining the intervention. A second observational study (n=269) from 2008 captured (male) patients’ expectations about DRE prior to undergoing the exam. Fifty-four percent of patients imagined that the DRE would be painful, humiliating, or bothersome and 46% imagined the test to be “normal”. After the exam, 51% of patients maintained their answer, while 49% modified their answer to a positive impression of the exam. Ninety-eight percent of men said they would repeat the exam annually as a method of screening for prostate cancer (11).

Serum PSA samples are obtained via venipuncture. About 10% of the population has a fear of needles (12). Trypanophobia is more common in women, younger patients, those with lower education level, and those who experienced previous adverse events with other injections. Compared to other types of needle-related procedures, venipuncture is likely the least distressing (12). Given that the eligible population consists of middle-aged males, trypanophobia is unlikely to be an issue.

**Attributes 4 and 5: The Test Should Have High Sensitivity and Specificity**

The DRE has an estimated sensitivity (the proportion of patients with the disease that test positive) of 59% (meaning that if 100 patients with prostate cancer had a DRE, 59 out of 100 would have abnormal findings) and a specificity (the proportion of patients without the disease that test negative) of 94% (meaning that if 100 patients without prostate cancer had a DRE, 94 out of 100 would have normal exam findings) (8). Estimated positive predict value (PPV: the proportion of positive test results that are true positives) of an abnormal DRE for prostate cancer varies between 5 to 30% (8).

A pooled analysis by the American Cancer Society estimated sensitivity of a PSA cut-off of 4.0 ng/mL or higher was 21% for detecting any prostate cancer. The estimated specificity was 91%. The traditional cut-off for an elevated PSA level is 4.0 ng/mL or greater in the majority of trials. Based on these thresholds, a PPV of 30% and negative predictive value (NPV: the proportion of negative results that are true negatives) of 85% were estimated. For PSA levels between 4.0-10 ng/mL, and greater than 10 ng/mL, the PPV is estimated around 25% and in the range of 42-54%, respectively (8). When used in combination, DRE and PSA can increase the rate of cancer detection; however, randomized trials have not confirmed a benefit on prostate cancer outcomes (discussed below) (9,13).

Unfortunately, PSA levels can be altered by a number of variables. Medications including non-steroidal anti-inflammatory drugs (NSAIDs), statins, thiazide diuretics, and finasteride have been found to
lower PSA levels (14). Diseases such as benign prostatic hypertrophy (BPH), prostatitis, and urinary retention or urological manipulations can cause PSA level elevation (14). PSA levels also rise as men age.

Lastly, results can vary among commercial PSA assays and converting values between assays is unreliable and not recommended. Depending on which of the two reference standards is used to calibrate the assay, PSA levels can vary by approximately 20% (15).

**Attribute 6: The Test is Inexpensive**

The cost of a PSA test ranges from $20 to $30 in North America (16). In the United States, Medicare provides coverage for an annual PSA test for all men aged ≥50 years. In Canada, coverage varies by province when used as a screening test. It has been estimated the United States annually spends approximately $3 billion on PSA tests (both screening and diagnostic) (17). The financial burden of prostate cancer screening varies depending on payment structure.

**Attribute 7: Screening Will Have Been Shown to Reduce Mortality in Randomized Controlled Trials (RCTs)**

This is the most debated aspect of prostate cancer screening, despite similar findings in two large systematic reviews and meta-analyses. Djulbegovic et al (9) pooled data from six studies (n= 387,286, age 50-74 years) and found that screening increased the diagnosis of prostate cancer (RR 1.46, CI 1.21 to 1.77; p <0.001), but did not result in a statistically significant reduction in prostate cancer-specific (RR 0.88, CI 0.71 to1.09; p=0.25) or overall mortality (RR 0.99, CI 0.97 to 1.01; p=0.44). Ilic et al (13) pooled data from five studies (n= 341,351, age 50-74 years) and also found that screening increased the diagnosis of prostate cancer (RR 1.35, CI 1.06 to 1.72), but did not result in a statistically significant reduction in prostate cancer-specific (RR 0.95, CI 0.85 to 1.07) or overall mortality (RR 1.00, CI 0.98 to 1.02). They also analyzed age subgroups and found no reduction in prostate cancer-specific mortality. Secondary outcomes included quality of life and cost-effectiveness, but no results were reported. They also concluded that men with a life expectancy of less than ten years were unlikely to benefit from screening and for those with a longer life expectancy should be informed of risks and benefits when deciding to undertake screening for prostate cancer. Although there was low heterogeneity in effect size amongst trials in both meta-analyses, there were numerous differences between study designs, screening methodologies (DRE +/- PSA, different follow-up frequencies, and PSA thresholds), and statistical analyses. Due to slow growth rate and a long preclinical detectable phase, duration of follow up may have been insufficient in some studies to detect a difference in mortality. There were also issues with compliance in screening groups, contamination in control groups, and no data reported on quality of life, patient or practitioner preference, cost effectiveness, or impact of screening in high-risk populations (men with a positive family history or of African descent).

The two largest RCTs included in both meta-analyses were the European Randomized Study of Screening for Prostate Cancer (ERSPC, n= 182,000) (18) and the United States’ Prostate, Lung, Colorectal, and Ovarian (PLCO, n= 76,693) cancer screening trial (19). The ERSPC reported a 20% relative reduction in prostate specific-mortality in a predefined subset of men between the ages of 55 and 69 years and this benefit was sustained at 9 and 11 years of follow up (18,20). However, this benefit was lost when pooled with the entire study population of men ranging from 50-74 years of age. The absolute risk difference of 0.71 deaths per 1000 men (between 55-69 years old) results in a number needed to screen of 1410 to prevent one prostate cancer-related death. There was no difference in all-cause mortality for any age range (18). The PLCO group found no difference in prostate cancer-specific or all-cause mortality after 7, 10, and 13 years of follow up (19,21).

Harms of screening include those from the test and then subsequent diagnosis and treatment. Pain or bleeding (0.3 per 10,000 DRE), dizziness, bruising, hematoma, fainting (26.2 per 10,000 PSA tests) are the harms associated with the screening tests. Medical complications secondary to diagnostic procedures, namely biopsy include infection, bleeding, clot formation, urinary difficulties (68 per 10,000 evaluations) (18). Anxiety and physical discomfort are also associated with prostate biopsy (8). The false positive rate for men with an elevated PSA who underwent biopsy was approximately 75% and rate of over-diagnosis of prostate cancer was as high as 50% in the screening group (18). Over-diagnosis refers to the correct diagnosis of a disease, such as prostate cancer, but the disease has no clinical significance (such as causing symptoms or death) during a patient’s lifetime. It is challenging to compare rates of over-diagnosis between cancer screening programs as this outcome is not commonly reported in studies and is based on different models, but appears to occur more commonly with prostate as compared to breast cancer (10-30%) (22). Risks of treatment are variable. The mortality rate of radical prostatectomy is about 0.5% and increases to 1% in men over 75 years (8). More common complications include urinary incontinence, sexual dysfunction, and bowel problems. Radical prostatectomy adversely affects sexual function in 20 to 70% of men and leads to urinary problems in 15 to 50% of men. External beam radiation therapy can cause erectile dysfunction (20 to 45%), urinary incontinence (2 to 16%), and bowel dysfunction (6 to 25%) in men whom were previously healthy.
Attribute 8: Screening Will Have Been Shown to be a Cost-Effective Means of Controlling the Cancer

With effectiveness of screening in question, it is challenging to perform robust cost-effective analyses. Depending on perspective, screening protocol, and perceived benefits, results vary. It is argued that increasing costs surrounding prostate cancer is not due to treatment of the disease, but from widespread screening programs due to high false-positive, over-diagnosis, and over-treatment rates (23). Aggressive screening will lead to initiation of early treatment options that are more expensive than palliation of late disease. There is also the associated risk of technological advancement in treatment and its impact on survival, making it challenging to tease out a benefit solely attributable to screening.

Conclusion

Early detection of disease can be an important component of comprehensive cancer care and public health. However, its role in prostate cancer is unclear. Current screening practices do not appear to serve their purpose of identifying disease in asymptomatic men and reducing or preventing future disease burden. Perhaps prostate cancer is a more “common” rather than “major” health problem. It is more treatable if detected early, but does not always have to be treated when detected. Although the tests appear to have reasonable acceptability by the targeted population, sensitivity and specificity are less than desirable. There is no conclusive mortality benefit, but quantified harms of screening. PSA testing can be expensive with widespread use and no robust cost-effective analyses are available. Interpreting the mortality data along with the remaining seven desired attributes of a screening program, we believe it is appropriate to follow recommendations to cease prostate cancer screening with currently available methods (4). However, as patient-centered practitioners, it is important to consider each patient’s preferences and values to facilitate informed decision-making about the benefits and harms involved with screening and support our patients’ choices.

References

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