Early effects and future implications of USPSTF's recommendation against prostate cancer screening

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Dedication

Dedicated to my parents, boyfriend, and best friend, for their endless encouragement and support these past 27 months

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Introduction

Prostate cancer is the most prevalent solid organ cancer of men and the second leading cause of death in males in the United States. This type of cancer alone is responsible for one-fourth of new cancer diagnoses in men (Siegel, Miller, & Jemal, 2015). Prostate cancer rarely produces early warning signs or symptoms and so detection of early prostate cancer in asymptomatic men is crucial for prompt and effective treatment (Ilic, Neuberger, Djulbegovic, & Dahm, 2013). Early detection of prostate cancer is also important in preventing morbidity associated with the disease including bleeding, urinary tract obstruction, and the development of painful bony metastases (Barry, 2001).

One method of detecting cancer early is by implementing screening tests. Screening tests aim to identify a disease at an earlier stage in order to expedite treatment of the disease and subsequently improve overall health outcomes by decreasing overall and disease specific mortality (Lin, Croswell, Koenig, Lam, & Maltz, 2011). The most prominent method of screening for prostate cancer in the United States is the measurement of prostate-specific antigen (PSA) in the serum. PSA is a protease produced by prostatic luminal epithelial cells. It is typically found in low concentrations in the serum but becomes elevated with prostatic disease including prostate cancer (Catalona et al., 1991). The elevation of PSA levels associated with cancer of the prostate is a result of increased production of PSA in addition to architectural changes of the prostate gland itself allowing PSA to have better access to the circulation (Barry, 2001)

Since the approval of the test in the 1990s by the FDA, the PSA test has been widely used in U.S. clinical practice for screening of prostate cancer (Ross, Berkowitz, & Ekwueme, 2008). Following the widespread utilization of the PSA test for prostate cancer screening, prostate cancer incidence rates have been steadily increasing. The rise in incidence is most prominent among local-regional prostate cancers and is associated with a reduction in the frequency of distant-stage prostate cancers. It is estimated that since the implementation of the PSA test, the incidence of distant-stage prostate cancer has dropped by more than 70%, from 22 per 100,000 to 6.5 per 100,000 (Ankerst, Tangen, & Thompson, 2009). Another notable trend since the induction of the PSA test in the 1990s is the substantial decline in prostate cancer mortality rates. It has been estimated that mortality associated with prostate cancer since its peak in 1992 has decreased by 35% with an average decrease in mortality of approximately 4.1% per year from 1995 to 2005 (Ries et al., 2008).

Despite these record trends in prostate cancer incidence and mortality, the true benefit of prostate cancer screening remains uncertain and the question of whether screening for prostate cancer is reducing deaths due to prostate cancer has remained up for debate. One of the major concerns regarding PSA testing is over diagnosis of prostate cancer (Schroder et al., 2009). Over diagnosis in this context refers to identifying prostate cancer in a man via PSA testing that otherwise would not have been found if the testing were not completed (Etzioni et al., 2002). PSA testing has been beneficial for diagnosing prostate cancer early and has changed the stage of presentation of prostate cancer with more men presenting with treatable, localized disease. However, a good proportion of the asymptomatic cancers detected by PSA

testing are associated with a low risk of mortality as the tumor will not progress or will progress at a pace where it would otherwise remain asymptomatic for the remainder of the man's lifetime. Thus, the increased incidence of prostate cancer in this context may result in more harm than good (Schroder et al., 2009).

Another concern regarding the utility of the PSA for prostate cancer screening is the high rate of false positive results associated with the test. A major challenge in the utilization of the PSA test for prostate cancer screening is discerning prostate cancer from other benign conditions. While PSA becomes elevated with prostate cancer, the level also rises with a number of benign conditions including prostatitis, benign prostatic hyperplasia, and urinary retention (Wein, Kavoussi, Partin, & Peters, 2016). The PSA test has a suboptimal specificity and it has been estimated approximately 75% of men who undergo a prostate biopsy due to an elevated PSA of 4.0 to 10.0 ng per millimeter have a false positive result and do not have any evidence of cancer (Barry, 2001). Additionally, men who have prostatic biopsies completed as a follow-up for an abnormal PSA test are subjected to harm related to the diagnostic procedure itself. The harms associated with prostate biopsies include bleeding, serious infections, and urinary retention and occur in approximately 1 in every 200 men receiving a prostate biopsy (Chou et al., 2011).

The advantages and shortcomings of PSA-based prostate cancer screening were investigated in detail by the U.S. Preventative Services Task Force (USPSTF) in 2011 (Lin et al., 2011). The USPSTF is a panel of experts that establishes evidence-based recommendations about clinical preventative services including screening tests. Each recommendation regarding clinical preventative services is based on findings from

a systematic review of the most up to date literature on the topic available (U.S. Preventive Services Task Force, 2016). Through extensive critique and analysis of results of two fair quality large randomized control trials to support their position, the USPSTF determined that the harms of PSA-based prostate cancer screening outweighed the benefits (Chou et al., 2011).

The first major study investigated by the USPSTF was the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial; a randomized control trial conducted from 1993 through 2001 at ten United States study centers. The focus of the study was to determine the effect of PSA testing on prostate cancer mortality. The study investigators randomly assigned men ages 55 to 74 years to annual screening (n=38,343) or to usual care (n=38,350). Study participants in the usual care group were the control group. The screening group was given annual PSA tests for 6 years and digital rectal examination (DRE) for 4 years. This trial concluded that after 7 years there was a statistically significant increase in prostate cancer incidence in the screening group (RR 1.22 [95% CI, 1.16-1.29]) but no difference in prostate cancer mortality (RR, 1.13 [95% CI, 0.75-1.70]) between the screening and control groups. Follow-up after 10 years concluded similar findings (RR 1.1 [95% CI, 0.92 to 1.0]) (Andriole et al., 2009).

The second major trial examined by the USPSTF was the European Randomized Study of Screening for Prostate Cancer (ERSPC); a randomized control trial conducted throughout seven European countries. The focus of this study was the same as the PLCO trial: to determine the effect of PSA testing on prostate cancer mortality. The study investigators identified 182,000 men between ages 50 and 74 years and assigned them to screening or no screening. After 9 years of follow-up, this trial concluded there

was no statistically significant difference in risk of prostate cancer deaths between the screening group and control group (RR, 0.85 [95% CI, 0.73-1.00]). A statistically significant absolute risk reduction in prostate cancer mortality in of 0.071% (RR 0.080 [95% CI, 0.65-0.98]) was found in a subgroup of men aged 55 to 69 years (n=162,243). The authors indicated that this 0.071% absolute risk reduction means that 1,410 men would need to be invited for screening and 48 men would need to be treated in order to prevent one prostate cancer death (Schroder et al., 2009).

The harms of PSA-based prostate cancer screening reported in these two randomized control trials were also evaluated by the USPSTF. The rate of false positive results was significant in both the ERSPC and PLCO trials. In the ERSPC trial, 75.9% of men that underwent prostate biopsy for an elevated PSA test had false positive results wherein the workup showed no evidence of histopathological diagnosis of prostate cancer (Schroder et al., 2009). In the PLCO trial, the investigators concluded that men had a 12.9% risk of having at least one false positive result after having four PSA tests (Andriole et al., 2009). Physical harms including bruising or fainting from venipuncture and infection, bleeding, and urinary difficulty from diagnostic procedures were also reported at substantial rates in the PLCO trial (Andriole et al., 2009). One study center of the ERSPC trial documented fever, urinary retention, hematuria, hematospermia, and hospitalization for urosepsis as harms associated with prostatic biopsy performed as a follow-up for an elevated PSA testing (Schroder et al., 2009).

In May 2012, the USPSTF finalized their grade D recommendation discouraging the use of PSA-based prostate cancer screening in men of all age groups on the basis of the findings from these two studies (Moyer & Force, 2012). A grade D

recommendation indicates the USPSTF found with moderate or high certainty that PSA-based prostate cancer screening has no net benefit or that the harms of utilizing PSA screening outweigh the benefits (U.S. Preventive Services Task Force, 2014). As a result of this Grade D recommendation, the USPSTF does not recommend routine PSA-based testing for prostate cancer screening for men of any age (Moyer & Force, 2012).

Controversy remains on whether this recommendation will reverse decades of improvement in prostate cancer incidence and mortality rates (Banerji et al., 2016). Modeling studies based on the natural history of prostate cancer have been completed to estimate population effects of the new PSA screening guidelines. These models aim to replicate surveillance data and in doing so evaluate the expected contribution of PSA screening on prostate cancer mortality trends (Ankerst et al., 2009). One simulation study utilizing two models created by the Cancer Intervention and Surveillance Modeling Network found that a substantial 75% of all prostate cancer diagnoses in 2010 were over diagnosed. This modeling study concluded that discontinuing screening altogether could terminate all over-diagnosed cases of prostate cancer. Unfortunately eliminating over diagnosed cases is associated with a large trade off, as this study estimated the number of metastatic prostate cancer cases at presentation would more than double in the absence of PSA testing. Additionally, the study found that prostate cancer mortality rates would be influenced substantially by the elimination of PSA screening. The investigators of this modeling study found that prostate cancer mortality rates would increase by 13% to 20% if prostate cancer screening were discontinued completely, accounting for between 13,000 to 22,000 individuals. The study investigators concluded that while continuing to use PSA tests for screening would over-diagnose approximately

710,000 to 1,120,000 men with prostate cancer by 2025, screening would also prevent a number of metastatic cancers and reduce prostate cancer mortality (Gulati et al., 2014).

Taking into account the modeling study by Gulati et al. as well as the conflicting results from the ERSPC and PLCO trials, it is unclear how the determent of health practitioners from screening for prostate cancer with PSA testing will change the picture of prostate cancer moving forward. Despite the inability to evaluate prostate cancer mortality rates since the release of the USPSTF's grade D recommendation against PSA-based prostate cancer screening in the present time, there is still much value in evaluating how this recommendation has changed the face of prostate cancer screening on a temporal basis in the time since the recommendation was released to the public. This literature review aims to identify the impact of this grade D recommendation on prostate cancer screening rates, prostate biopsy rates, and prostate cancer incidence since its release in 2012.

Problem Statement

Prostate cancer screening using PSA has remained controversial because of uncertainty surrounding its benefits and risks (Barry, 2009). Evidence from two randomized control trials led the USPSTF to issue a grade D recommendation against prostate cancer, indicating there was limited benefit and substantial potential risks associated with overdiagnosis and overtreatment (Moyer & Force, 2012). Controversy remains on whether this recommendation will reverse decades of improvement in prostate cancer detection and treatment (Banerji et al., 2016).

Purpose

This literature review will investigate the effects of the USPSTF's 2012 grade D recommendation against PSA-based prostate cancer screening. This review will also emphasize the future implications and consequences of this recommendation on prostate cancer incidence and mortality in the United States.

Research Question

What is the impact of the 2012 USPSTF grade D recommendation discouraging PSA-based prostate cancer screening on PSA screening rates, prostate biopsy rates, and prostate cancer incidence?

Definitions

PSA – Prostate specific antigen; A protein produced by the cells of the prostate gland that are often elevated in men with prostate cancer; A normal PSA level is less than 4 ng/mL

Gleason Classification System – The most common grading system for prostate cancer based on pathology from prostate biopsy; Gleason scores range from 1 to 10 and are divided into low-grade (less than 6), intermediate-grade (7), or high-grade (8 to 10) (American Cancer Society, 2016)

TNM staging system – Developed by the American Joint Committee on Cancer to describe how far cancer has spread; Includes five variables: T category (extent of primary tumor), N category (lymph nodes affected), M category (metastasis), PSA level at the time of diagnosis, and Gleason score (American Cancer Society, 2016)

T stage – Size of the tumor on rectal exam and/or ultrasound

D'Amico Risk Classification – Classification for risk assessment using PSA level, Gleason grade, and T stage; Groups men as low, intermediate, or high-risk (University of California San Francisco Department of Urology, 2016)

CAPRA score – Cancer of the Prostate Risk Assessment; Predicts an individual's likelihood of metastasis and prostate cancer mortality by weighing 5 variables: Age at diagnosis, PSA at diagnosis, Gleason score, clinical stage, and percent positive biopsy cores; CAPRA scores range from 0 to 10 where 0-2 indicates low risk, 3-5 indicates intermediate risk, and 6-10 indicates high risk (University of California San Francisco Department of Urology, 2016)

USPSTF – United States Preventative Services Task Force; An independent panel of experts that develops recommendations for clinical preventive services

Grade D recommendation – "The USPSTF recommends against this service. There is moderate or high certainty that the service has no net benefit or that harms outweigh the benefits" (U.S. Preventive Services Task Force, 2014).

DRE – Digital Rectal Exam

PSA density – Serum total PSA level divided by prostate volume

PSA kinetics – Includes PSA velocity and PSA doubling time

PSA velocity – Absolute PSA increase per time interval

PSA doubling time – Time interval for doubling of initial PSA level

Age-adjusted PSA levels – Adjustment of PSA level to account for increase in prostate size with age

PCA3 – Prostate cancer gene 3; a tumor marker for prostate cancer detected in urine

Methodology

A systematic literature review was completed in order to answer the question: What is the impact of the 2012 USPSTF grade D recommendation discouraging PSA-based prostate cancer screening on PSA screening rates, prostate biopsy rates, and prostate cancer incidence?

Search terms:

United States Preventative Services Task Force

USPSTF

Prostate cancer

Prostate cancer screening

Prostate-specific antigen

PSA testing patterns

Prostatic neoplasms

Databases:

PubMed

EBSCOhost

Inclusion and exclusion criteria for articles: No articles were excluded based on date of publication. Background information may be cited from any time due to the extensive use of PSA as a screening tool in the past 30 years. Research will be limited to the past 5 years with a focus on the past two years when substantial research on this topic has been published. Research articles included observational studies, case control studies, pre-post studies, and trend analyses. All articles must be originally printed in English and be published in the United States only as the focus is on the effect of the USPSTF

recommendation on the United States population. Articles published in journals outside of the United States will be included as long as the study was completed in the United States.

Literature Review

National Self-reported PSA-based PCa Screening Rates

Since the implementation of the grade D recommendation against prostate cancer screening, four studies have assessed the frequency of self-reported PSA-based prostate cancer screening rates in the United States and noted substantial decreases. Each of these studies utilized PSA-based prostate cancer screening data from the National Health Interview Survey (NHIS). The NHIS is an in-person household health survey collected via confidential interviews to obtain valuable health data on the civilian non-institutionalized population of the United States. It is one of the major data collection programs for a part of the Centers for Disease Control and Prevention (CDC) called the National Center for Health Statistics (NHC). As a result of multistage area probability sampling, the data obtained by the NHIS provides a representation of the United States population and can be extrapolated to analyze national health trends (Center for Disease Control and Prevention, 2015b).

The first study completed by Li and colleagues utilized NHIS data from 2005, 2008, 2010, and 2013 to assess self-reported PSA screening rates in men ages 40 and older with no history of prostate cancer that had a PSA test as part of a routine examination. Data from each year was combined and analyzed using linear contrasts. The study investigators found the overall percentage of PSA testing declined considerably from 2008 (31.8%) to 2013 (24.2%). This decline was appreciated in each age group: 40 to 49 years, 50 to 74 years, and 75 years and older. Men ages 75 years and greater faced the most significant reduction in percentage of PSA testing with a 14.0% decrease ($P<0.001$) from 2008 to 2013. The study investigators hypothesized

that the decline in PSA testing between 2010 and 2013 is a result of the 2012 USPSTF recommendation (Li, Berkowitz, & Hall, 2015).

Another study by Drazer and colleagues used NHIS data from 2005, 2010, and 2013 to assess the impact of the 2012 USPSTF recommendation on a population basis. The study investigators first examined the PSA-based prostate cancer screening rates in men 40 years and older with no history of prostate cancer who had a PSA test during a routine examination. Men who were unfamiliar with PSA testing or who did not see a physician within the last year were excluded from analysis. The cohort was divided by age into 5-year subgroups and the number of participants in each group who had a PSA test in the year before the 2005, 2010, and 2013 surveys was compared. This study found that self-reported PSA screening rates were substantially lower in all age groups except age 40 to 49 years from 2010 to 2013. The percentage of PSA tests performed on men age 50 to 59 decreased from 33.2% (95% CI, 30.1% to 36.3%) in 2010 to 24.8% (95% CI, 22.3% to 27.3%) in 2013 (OR, 0.66;P<0.01). The most heavily screened age group was that of men aged 60 to 74 years. This age group saw a substantial decline in PSA testing from 51.2% (95% CI, 48.1% to 54.2%) in 2010 to 43.6% (95% CI, 41.0% to 46.2%) in 2013 (OR, 0.74; P<0.01). Finally, in men 75 years and older, the percentage of PSA testing dropped from 43.9% (95% CI, 39.1% to 48.7%) in 2010 to 37.1% (95% CI, 33.2% to 41.0%) in 2013 (OR, 0.75; P=0.03). This study demonstrates a significant decline in prostate cancer screening among men who saw a physician following the USPSTF 2012 recommendation against PSA-based screening (Drazer, Huo, & Eggener, 2015).

Another study by Jemal and colleagues examined the rates of self-reported PSA testing among men 50 years and older through analysis of NHIS data from 2005, 2008, 2010, and 2013. Participants were divided according to age into two subgroups: 50 to 74 years and 75 years and older. The study analyzed 18,385 men 50 years and older who received PSA testing for screening as part of a routine examination and 19,014 men 50 years and older who received PSA testing for "any reason." Data was analyzed and adjusted using logistic regression models with predicted marginal probabilities. The study demonstrated reductions in PSA-based screening rates among men 50 years and older from 37.8% (99% CI, 35.3% to 40.2%) in 2010 to 30.8% (99% CI, 29.0% to 32.7%) in 2013. Screening rate ratios (SRR) were determined to detect relative changes between survey years among PSA screening rates. From 2010 to 2013, PSA-based screening rates in men 50 years and older underwent an absolute decrease of 7.0% and a relative decrease of 18% (SRR, 0.82; 99% CI, 0.75 to 0.89). Findings were similar between both age subgroups, although the change in PSA screening rates in men 75 years and older was not statistically significant. This study also demonstrates significant reductions in prostate cancer screening rates by PSA which parallel the 2012 USPSTF recommendation discouraging PSA based prostate cancer screening (Jemal et al., 2015).

The final study by Sammon and colleagues utilized NHIS data from 2000, 2005, 2010, and 2013 to examine the prevalence of prostate cancer screening among men 50 years and older (n=20,757) by survey year. The association between survey year and odds of screening before and after the USPSTF recommendation was examined using adjusted complex-sample logistic regression models. This study demonstrated an

overall decrease in prevalence of PSA screening from 36% (95% CI, 34% to 37%) in 2010 to 31% (95% CI, 30% to 33%) in 2013. Pooled analysis concluded the odds of PSA screening in 2013 was lower than the odds of PSA screening in 2010 (odds ratio [OR], 0.79 [95% CI, 0.71 to 0.88]). The decrease in PSA screening prevalence was only found in men younger than 75 years (OR, 0.78 [95% CI, 0.70 to 0.88]). Men ages 50 to 54 years faced a significant reduction in PSA screening from 23% (95% CI, 20 to 26%) in 2010 to 18% (95% CI, 15% to 21%) in 2013. Similarly, men ages 60 to 64 years were found to have a substantial decrease in PSA screening from 45% (95% CI, 41% to 49%) in 2010 to 35% (95% CI, 32% to 39%) in 2013. This study is further evidence that the prevalence of PSA screening has declined among men younger than 75 years of age since the release of the 2012 recommendations (Sammon et al., 2015).

It is clear that the USPSTF recommendation has made a national impact on self-reported PSA screening rates as demonstrated by the findings of several recent studies (Drazer et al., 2015; Jemal et al., 2015; Li et al., 2015; Sammon et al., 2015). Furthermore, as the NHIS data can be extrapolated to make statements regarding health trends for the nation, these study findings provide solid evidence that PSA testing has declined in accordance with the 2012 USPSTF recommendation. However, the utilization of NHIS data does not come without drawbacks. Limitations of using interview-based reporting for data interpretation include the possibility of recall bias due to self-reported information (Jemal et al., 2015). Another limitation of using NHIS for data is the most recent survey available was from 2013 only a year following the May 2012 official release of the USPSTF recommendation against prostate cancer screening. This provided only a short period of time for the recommendation to be

distributed into screening practices. Thus, the conclusions inferred from this data are limited and only provide a snapshot of screening practices for the year following this recommendation (Drazer et al., 2015). Lastly, another limitation of using NHIS data for interpretation of prostate cancer screening practices is the possibility of selection bias related to response rates as data about survey non-respondents was not available for analysis (Drazer et al., 2015; Li et al., 2015).

Regional Trends in PSA-based PCa Screening Rates

Upon review of the literature, two studies were identified that assessed the effects of the 2012 USPSTF recommendation against prostate cancer on a regional basis in the United States. Both studies sought to determine the impact of the recommendation on PSA screening practices at their large institutions. These studies provide insight on how clinical practices are changing at institutions in different areas of the country, but the findings of these studies are of limited utility as they are not nationally representative.

Aslani and colleagues evaluated the impact of the USPSTF 2012 recommendation on prostate cancer screening in their regional health system of northeastern Ohio. The study investigators assessed the total number of PSA tests ordered over time to detect trends in PSA screening rates since the USPSTF recommendation by location, patient age, and provider type. All PSA testing data was obtained from the institution's central laboratory and de-identified. Only PSA tests coded for screening were included. PSA tests for diagnostic or monitoring purposes were excluded (Aslani et al., 2014).

The investigators divided the 5-year period into 3 distinct sections: January 2008 to February 2009, March 2009 to April 2012, and May 2012 to December 2012, in order to compare trends prior to the release of the ERSPC and PLCO studies, after the release of the ERSPC and PLCO studies in March 2009, and after the release of the May 2012 USPSTF recommendation against PSA-based prostate cancer screening. A ratio of the number of PSA tests to cholesterol tests at each hospital per month was used to adjust for patient volume and population changes in their large health system.

The slope of each time segment was determined and linear and segmented regression models were applied to assess trends in PSA testing (Aslani et al., 2014).

The results of this study demonstrated an increase in adjusted overall PSA screening tests performed from the beginning of the study period in January 2008 until the release of the ERSPC and PLCO trials in March 2009 ($\beta=0.0002$, $p<0.001$). Following the release of the ERSPC and PLCO trials in March 2009, there was a decrease in PSA screening tests until May 2012 ($\beta=-0.001$, $p<0.001$), corresponding with the release of the 2012 USPSTF recommendation. From May 2012 until the end of the study period in December 2012, a continued trend downward in adjusted PSA tests performed was noted although was not statistically significant (Aslani et al., 2014).

Interestingly, Aslani and colleagues also studied changes in adjusted PSA use by physician specialty following the 2012 USPSTF recommendation and found that urologists exhibited the greatest reduction in adjusted PSA test use ($\beta=-0.0014$, $p<0.05$). Internal Medicine and Family Medicine physicians also demonstrated declines in adjusted PSA test use, although this was not statistically significant. This suggests that the USPSTF recommendation has been applied to clinical practice more rapidly in this specialty, possibly due to prostate cancer being a topic of great concern and frequent referrals for urologists (Aslani et al., 2014).

Rezaee and colleagues conducted a retrospective cohort study to assess PSA utilization in Southeastern Michigan following the USPSTF 2012 recommendation against PSA-based prostate cancer screening. The study investigators identified all male patients 50 years and older insured by a health insurance plan entitled the Beaumont Employee Health Plan (BEHP) and used billing data to compare the rates of

PSA tests ordered by any physician prior to the USPSTF recommendation from January 1, 2010 to December 31, 2011 and after the USPSTF recommendation from January 1, 2013 to December 31, 2014. Data from 2012 was excluded from this analysis to account for the release of the recommendation in May 2012 and subsequent dissemination of the new practice guidelines among health care providers. A linear model was utilized to assess the rate of PSA screening before and after the 2012 USPSTF recommendation (Rezaee, Ward, Odom, & Pollock, 2016).

This study analyzed average PSA utilization rates and noted an increase in men over the age of 50 receiving annual PSA screening following the USPSTF recommendation. Prior the recommendation, 72.1% of 3647 identified men received PSA-based prostate cancer screening as opposed to 79.3% of 3618 identified men following the release of the USPSTF recommendation ($p=0.48$). This demonstrable increase exemplifies that annual PSA testing is still being utilized in this region of the United States at a rate of nearly 80%. This implies that the USPSTF recommendation has not been implemented or accepted as readily in this region of the United States (Rezaee et al., 2016).

The studies by Aslani and colleagues and Rezaee and colleagues exhibit contradicting findings in regards to PSA testing practices in their respective regions. This demonstrates that significant regional variation in PSA utilization practices likely exists across the United States. Both studies have several limitations. First and foremost, the results of either study cannot be generalized on a national level as the data used is from specific regional institutions and is not nationally representative. The findings of Rezaee et al are also limited as their patient sample consisted only of

employees and spouses of a single health care system with private health insurance. This creates the argument that their results are not applicable to those without insurance or with limited health care access (Rezaee et al., 2016). Aslani et al used a PSA-to-cholesterol ratio to adjust for their patient volume. This ratio was used because cholesterol tests are readily performed at patient visits for screening, although the utilization of this ratio for adjustment is not reflective of actual population changes and is therefore a limitation of this study (Aslani et al., 2014). All in all, the findings of these studies provide evidence that the USPSTF recommendation has had varying regional effects on PSA testing practices following its release in May of 2012.

National PSA Screening Rates Among Primary Care Providers

It has been previously recognized that the PSA recommendations provided by the USPSTF are the strongest influence on primary care physicians screening practices (Tasian et al., 2012). Additionally, primary care physicians order more screening PSA tests than any other specialty aside from urology as a part of preventative measures (Cohn et al., 2014). With this concept in mind, several research investigators worked to analyze changes in rates of prostate cancer screening by primary-care physicians following the 2012 USPSTF recommendation discouraging prostate cancer screening.

Two studies used information collected from the National Ambulatory Medical Care Survey (NAMCS) to analyze trends in PSA screening data. The NAMCS is a national survey completed annually by the Centers for Disease Control and Prevention (CDC) that reports several components of ambulatory care in the United States including patient demographics, patient diagnoses, diagnostic test orders, and medication orders. The survey is designed to be nationally representative by utilizing a multistage estimation method. The data collected by the survey is used by several entities to analyze changes in medical practice (Center for Disease Control and Prevention, 2015a).

The first study by Zavaski and colleagues compared the frequency of PSA-based prostate cancer testing for preventative care by specialty among men 50 to 74 years of age before and after the release of the USPSTF 2012 recommendation. Data was collected from the 2010 and 2012 NAMCS surveys conducted from December 28, 2009 to December 26, 2010 and from December 28, 2011 to December 26, 2012, respectively. Exclusion criteria included men with a history of prostate cancer, prior

elevated PSA level, benign prostatic hyperplasia, or prostatitis. The specialties of interest for this study were primary care providers, which included both family medicine and internal medicine, and urologists. The NAMCS data from each year was analyzed and compared taking into account the complex survey design (Zavaski et al., 2016).

The study concluded that PSA testing by primary care providers declined from 36.5% in 2010, prior to the USPSTF recommendation, to 16.4% in 2012, following the USPSTF recommendation (OR 0.45; 95% CI, 0.23 to 0.81; P=0.009). The rates of PSA testing by urologists also declined but on a smaller scale from 38.7% in 2010, prior to the USPSTF recommendation, to 34.5% in 2012, following the USPSTF recommendation (OR 0.34; 95% CI, 0.10 to 1.20; P=0.09). The difference between testing practices by primary care providers and urologists during the years studied was found to be statistically significant ($P < 0.001$). This study demonstrates that there was a significant decrease in PSA testing by both primary care providers and urologists from 2010 to 2012 paralleling the release of the 2012 USPSTF recommendation against prostate cancer screening (Zavaski et al., 2016).

The second study by Shoag and colleagues also utilized NAMCS data from 2002 to 2012 to study trends in PSA testing rates among men 40 years and older by primary care providers for preventative care purposes following the 2012 USPSTF recommendation. The NAMCS data was analyzed accounting for the complex survey design and a chi-square test was performed to assess screening rates before and after the USPSTF recommendation. A total of 146 million (2,756 unweighted) visits from 2002 to October 2011 and 22 million (1,279 unweighted) visits from October 2011 to December 2012 were studied (Shoag et al., 2016).

The study investigators concluded that following the USPSTF recommendation, the proportion of visits where a PSA test was performed declined from 27.3% (95% CI, 24.5 to 30.3) to 16.7% (95% CI, 12.9 to 21.2; P<0.001). This accounts for a relative 39% decline in PSA testing following the USPSTF recommendation against PSA-based prostate cancer screening. A subset analysis of men 55 to 69 years of age was performed and demonstrated a decreased rate of PSA testing from 32.6% (95% CI, 28.2 to 37.4) prior to the recommendation to 19.9% (95% CI, 15.3 to 25.5; P<0.001) following the recommendation. The results of this study also demonstrate that primary care providers have modified their practice in accordance to the recommendation provided by the USPSTF and are ordering less PSA tests (Shoag et al., 2016).

Both Zavarski and colleagues and Shoag and colleagues exhibited concordance in their study findings using NAMCS data. These studies found there was a decrease in PSA test utilization by primary care providers following the 2012 USPSTF recommendation. It is important to acknowledge that utilizing NAMCS data comes with a few limitations. First, it uses small patient samples to estimate national practice patterns using multi-stage probability. Additionally, in the survey year of 2012, there was a decreased response rate compared to previous survey years. Both limitations could result in potential inaccuracies regarding national PSA testing patterns. Finally, NAMCS data was only available through 2012, providing only a short window of time to analyze changes in PSA testing patterns by primary care providers since the release of the final recommendation in May of 2012 (Shoag et al., 2016; Zavaski et al., 2016).

Regional PSA Screening by Primary Care Providers

The decline in PSA-based prostate cancer screening by primary care providers in nationally representative studies has also been demonstrated by two studies utilizing regional health care data.

Werntz and colleagues from Oregon Health and Science University in Portland, Oregon used data from their institution's electronic data warehouse to evaluate PSA testing by primary care providers at their institution before and after the May 2012 USPSTF recommendation discouraging PSA-based prostate cancer screening in all men. The study investigators identified 12,345 men over the age of 40 who were seen as new patients by family practice or internal medicine clinics affiliated with their institution between January 2008 and December 2013. The men were divided by age according to decades (40-49 years, 50-59 years, 60-69 years, and 70 years and older). Men with a history of prostate cancer were excluded from the study. The frequency of PSA testing among men in each age group before the USPSTF recommendation in May of 2012 was compared with the frequency of PSA testing among men in each age group seen after the USPSTF recommendation. The PSA testing frequency differences were tested for significance using the Pearson chi-square test (Werntz R, 2015).

The study investigators identified 1241 men who received a PSA test prior to May 2012 and 223 who received a PSA test following this time. The results of this study demonstrated significant decreases in PSA testing frequency among men ages 50-59 years. Prior to the USPSTF recommendation, men in this age group received a PSA test 19.2% of the time as opposed to 8.5% of the time following the USPSTF recommendation ($p<0.0001$). A substantial decrease in PSA testing frequency was also

seen among men ages 60-69 years. The frequency of PSA testing in this age group was 19.3% prior to the recommendation and 7.7% following the recommendation ($p<0.0001$). Combining these age groups together to represent men ages 50-70 years, PSA testing frequency dropped substantially from 19.3% before the USPSTF recommendation to 8.2% after the USPSTF recommendation ($p<0.0001$). The findings of this study demonstrate a substantial decline in PSA testing by primary care physicians in a large academic institution following the release of the USPSTF recommendation against PSA-based prostate cancer screening (Werntz R, 2015).

Cohn and colleagues also used the electronic data warehouse at their institution to evaluate trends in PSA screening frequency by primary care providers before and after the May 2012 USPSTF recommendation against prostate cancer screening. The study investigators identified men 40 to 79 years of age who were seen by an Internal Medicine or Family Medicine physician in the 6 months before (June to November 2011) and 6 months after (June to November 2012) the USPSTF recommendation. Men with a history of prostate cancer or past visit to an urologist were excluded from analysis. The proportion of men who received a PSA screening test among all eligible men during each 6-month period were compared. Proportion of PSA screening was determined by dividing the number of men receiving a PSA test divided by the total number of men who visited a primary care physician at least once within that time period. The proportion of PSA screening in the time frame prior to the recommendation and the time frame after the recommendation were analyzed using bivariate and multivariate logistic regression. Additional analysis was conducted to assess changes in screening among age groups (Cohn et al., 2014).

The study investigators identified 21,034 men who were seen by a primary care physician in the 6 months before the USPSTF recommendation and 26,338 men who were seen by a primary care physician in the 6 months after the USPSTF recommendation. The results demonstrated a decline in the proportion of men who had a PSA test conducted after the USPSTF recommendation. In the 6-month period prior to the USPSTF recommendation, 8.6% of men had a PSA test drawn compared to 7.6% of men who had a PSA test drawn in the 6-month period following the USPSTF recommendation ($p<0.0001$). Subset analysis demonstrated a downward trend in screening among all age groups. The decline in PSA-screening following the USPSTF recommendation was most prominent in men aged 40 to 49 years and in men aged 70 to 79 years, whom saw a relative 18.1% decrease ($p=0.004$) and a relative 21.8% decrease ($p=0.01$) in PSA screening, respectively. In accordance with the study by Werntz and colleagues, this study displays further evidence of decreases in PSA-based prostate cancer screening by primary care physicians in a large health system (Cohn et al., 2014).

Both Werntz and colleagues and Cohn and colleagues concluded that PSA screening by primary care providers at their respective institutions has decreased following the USPSTF recommendation. Limitations of these studies include an inability to extrapolate findings on a national level due to the utilization of solely regional institutional data for analysis. Other limitations of these studies include a lack of data past 2012 and 2013 for the studies by Cohn et al and Werntz et al, respectively. This limits the ability to assess if these changes in PSA testing by primary care providers will continue long-term (Cohn et al., 2014; Werntz R, 2015).

Prostate Biopsy Rates and Trends in Tertiary Center Referrals

The effects of the USPSTF recommendation can be assessed by analyzing changes in the frequency of prostate biopsies and referrals to urology following an elevated PSA level. It can be hypothesized that with the elimination of PSA testing as advised by the USPSTF, there would consequently be fewer biopsies performed and fewer referrals to urologists and other tertiary centers as a result of fewer elevated PSA tests being detected.

Studies Utilizing An Interrupted Time Series Design

McGinley et al performed a study using an interrupted time series design to assess changes in the number of prostate biopsies performed, number evaluations for elevated PSA levels completed, and number of patient visits in their large urology practice following the USPSTF draft recommendation in October 2011 against PSA-based prostate cancer screening. The urology practice studied consists of 32 physicians and services approximately 1.7 million people within a 2500 square mile area. The study period was divided for analysis with October 2010 to September 2011 representing the baseline period prior to the recommendation and two periods: October 2011 to September 2012 and October 2012 to September 2013 representing two time increments following the USPSTF draft recommendation. October 2011 was used as the interruption point in the study and represented the release of the USPSTF draft recommendation (McGinley, McMahon, & Brown, 2015).

In regards to patient volume, the urology practice documented 103,600 patient encounters from October 2010 to September 2011, during the baseline period. This number increased to 114,163 encounters, representing by a +10.2% increase, from

October 2011 to September 2012, and further amplified to 128,531 encounters, representing a +12.6% increase, from October 2012 to September 2013. Thus, compared to the baseline period, this urology practice saw an increase in practice volume of 24.1% following the release of the USPSTF recommendation (McGinley et al., 2015).

In regards to evaluations for elevated PSA levels, an overall downward trend was exhibited throughout the study period. The urology practice saw 28,698 patients from October 2010 to September 2011. This number decreased to 25,065 evaluations from October 2011 to September 2012 and further decreased to 24,002 evaluations from October 2012 to September 2013, representing a -12.7% and -4.2% annual percent change in each study period, respectively. Compared to the baseline period, a 16.4% decrease in total evaluations for elevated PSA levels was seen by this urology practice in the 2 years following the USPSTF draft recommendation. This is illustrated by a decrease of 317 visits per month for elevated PSA levels (95% CI, -573 to -61; P=0.017). The sharpest decline in evaluations for elevated PSA levels was seen in November 2011, one month following the USPSTF draft recommendation (McGinley et al., 2015).

An overall downward trend in monthly prostate biopsy rates was also demonstrated throughout the study period. During the baseline period, the practice performed 2465 prostate biopsies. This number decreased in both subsequent post-USPSTF recommendation periods to 1988 biopsies performed in October 2011 to September 2012 and 1929 biopsies performed in October 2012 to September 2013. This represents a -19.4% and -3.0% annual percent change in prostate biopsies

performed in each study period, respectively. This is illustrated by an overall decrease of 42 prostate biopsies per month (95% CI, -64 to -19; P=0.001) from October 2011 to September 2013, the period following the USPSTF draft recommendation (McGinley et al., 2015).

This study demonstrates the effects of the USPSTF recommendation against prostate cancer screening in a large urology practice. The study concluded that there was a significant decrease in evaluations for elevated PSA levels and prostate biopsies performed despite an overall increase in total practice volume in the two years following the USPSTF recommendation. The decline in evaluations for elevated PSA levels and prostate biopsies seen in this practice indicate that primary care providers in the surrounding area of this urology practice have taken into consideration the USPSTF recommendation and are performing fewer screening PSA tests. The decrease in PSA testing by primary care providers has also been demonstrated by Drazer et al, Cohn et al, and Werntz et al and are consistent with the findings of this study (McGinley et al., 2015).

Bhindi et al also performed a time series analysis to evaluate the change in prostate biopsy rates and prostate cancer detection rates following the USPSTF recommendation within a large Canadian health network in Toronto, accounting for approximately 5.58 million people. The investigators identified all transrectal ultrasound guided prostate biopsies within their institutional Genitourinary BioBank Project from October 1, 2008 to June 30, 2013. Change in biopsies performed and cancers detected per month were estimated using interventional ARIMA models with step functions. June

of 2012 was used as the interruption point in the study to account for the release of the USPSTF final recommendation statement on May 22, 2012 (Bhindi et al., 2015).

This study found that the median number of overall prostate biopsies performed decreased substantially in the year prior to the USPSTF recommendation to the year after the USPSTF recommendation, from 58 per month (IQR 54.5 to 63.0) to 35.5 per month (IQR 27.0 to 41.0), respectively (P=0.003). Similarly the median number of first-time biopsies also decreased significantly from 42.5 per month (IQR 37.5 to 57.5) to 24.0 per month (IQR 19.0 to 32.5) in the year before and after the USPSTF recommendation, respectively (p=0.025) (Bhindi et al., 2015).

This study demonstrates that the USPSTF recommendation is being implemented into clinical practice as less PSA-based prostate cancer screening means fewer elevated PSA levels and less prostate biopsies performed as a part of the work-up. As there was a reduction in overall and first-time biopsies noted in this Canadian health system but not complete cessation, this suggests that PSA testing has reduced but has not been eliminated in clinical practice. The findings of this study are also consistent with studies published previously exhibiting decreased PSA screening practices among primary care providers following the USPSTF recommendation (Bhindi et al., 2015).

The study findings of Bhindi et al and McGinley et al both demonstrated a significant decrease in prostate biopsy rates at each of their respective institutions. It is important to recognize that because both studies utilized data from a single institution for analysis, the results may not be generalizable to the American population. Furthermore, McGinley et al were unable to decipher between initial and repeat biopsies

for analysis, which could have led to an overall underestimate in the decrease of biopsy rates in their health system. Finally, Bhindi et al used data from a network of academic hospitals in Toronto, Canada. While the conclusions of this study were in concordance with previous studies completed by investigators in the United States, their findings cannot truly be representative of the American population and are unable to be used to draw conclusions on biopsy trends in the United States (Bhindi et al., 2015; McGinley et al., 2015).

Gershman et al also studied the changes in the rates of prostate biopsy following the 2012 USPSTF recommendation against prostate cancer screening using an interrupted time series analysis. The study investigators performed retrospective analysis of claims from the Optum Labs Data Warehouse. This data warehouse contains information on more than 100 million commercially insured Americans, of which 5,279,315 men aged 40 years or greater in the United States from January 1, 2005 to September 30, 2014 were identified and eligible for inclusion in this study. Of these men, 104,584 of them underwent a prostate biopsy during this time period and were included in the study for analysis. Men with a history of prostate cancer were excluded from the study (Gershman et al., 2016).

The findings of this study demonstrated a 33% decrease in adjusted rates of prostate biopsy among men 40 years and greater from the beginning of the study period in January of 2005 to the end of the study period in September of 2014, from 64.1 to 42.8 per 100,000 person-months. Of note, an abrupt decrease in prostate biopsy rates of -13.8 biopsies per 100,000 person-months (95% CI, -21.0 to -6.7; $P<0.001$) was appreciated following the release of the final USPSTF recommendation in May of 2012.

This study confirms previously appreciated decreases in prostate biopsy rates seen by McGinley et al and Bhindi et al following the USPSTF 2012 recommendation against prostate cancer screening. A limitation of this study is the reliance on administrative claims for data retrieval, which is subject to inaccuracies (Gershman et al., 2016).

Studies Utilizing a Retrospective Cohort Design

Rezaee and colleagues conducted a retrospective study to evaluate changes in transrectal ultrasound and prostate biopsy rates in a cohort of men 50 years and older in Southeastern Michigan before and after the USPSTF 2012 recommendation against prostate cancer screening. The study investigators identified all male patients 50 years and older insured by a health insurance plan entitled the Beaumont Employee Health Plan (BEHP) and used billing data to compare the rates of transrectal ultrasound and prostate biopsies ordered by any physician prior to the USPSTF recommendation, from January 1, 2010 to December 31, 2011, and after the USPSTF recommendation, from January 1, 2013 to December 31, 2014. Data from 2012 was excluded from this analysis to account for the release of the recommendation in May 2012 and subsequent distribution of the new practice guidelines among health care providers. A linear model with Poisson distribution and log link was utilized to assess the rate of PSA screening before and after the 2012 USPSTF recommendation (Rezaee et al., 2016).

The study investigators identified a total of 3,547 men in the pre-recommendation period from January 1, 2010 to December 3, 2011 and 3,618 men in the post-recommendation period from January 1, 2013 to December 31, 2014 to include in data analysis. In regards to average utilization of prostatic biopsies, the percentage of men receiving a prostate biopsy decreased from 12.6% in the pre-recommendation cohort to

8.1% of men receiving a prostate biopsy in the post-recommendation cohort (P<0.001). Similarly, a decrease in average utilization of transrectal ultrasounds was noted, demonstrated by a decrease from 4.0% to 3.3% in the pre-recommendation and post-recommendation cohorts, respectively (p=0.15) (Rezaee et al., 2016).

Data analysis showed no significant change in prostate biopsy rates in the post-recommendation cohort, although the rate of transrectal ultrasounds were stable in the pre-recommendation cohort (β=0.16; 95% CI, -0.03 to 0.35) and significantly decreased in the post-recommendation cohort (β = -0.27; 95% CI, -0.50 to -0.04). The study investigators correlate the stable rate of in prostate biopsies performed in the post-recommendation period to a similarly stable rate of PSA-testing performed in this region during this period. As mentioned in an earlier section, this study also found PSA testing is still being frequently used in this region of Michigan, which explains why no change in the rate of prostate biopsies was appreciated in this study (Rezaee et al., 2016).

Banerji and colleagues also conducted a retrospective cohort study with a historical control group to analyze changes in prostate biopsy patterns following the 2012 USPSTF recommendation against PSA screening for prostate cancer in all men. Data was retrieved from a prospective database of patients and identified men who had undergone a transrectal ultrasound guided prostate needle biopsy (PNB) at Virginia Mason between September 10, 2004 and November 10, 2014. Information retrieved from the database included patient demographics and biopsy characteristics. PSA level, stage, Gleason score, D'Amico risk score, and CAPRA score were used to compare patients seen prior to and after the USPSTF recommendation. Patients who had a history of prostate cancer or no prior PSA test were excluded. Cases were also

excluded if the PNB was performed between October 8, 2011 and May 24, 2012 to account for the USPSTF comment period. PNB with fewer than 10 core specimens were also excluded. Patients seen before the USPSTF recommendation (September 10, 2004 to October 7, 2011) and after the USPSTF recommendation (May 25, 2012 to November 10, 2014) were compared using analysis with Welch's t-test and chi-square tests with general linear regression (Banerji et al., 2016).

The study investigators identified 1,726 men who met the inclusion criteria: 1,416 patients who underwent a PNB in the 86 months prior to the USPSTF draft recommendation and 310 patients who underwent a PNB in the 30 months following the USPSTF draft recommendation. Data analysis revealed that the cohort patients who underwent PNB in the 30 months following the USPSTF recommendation were more likely to have PSA levels of 6.1 to 10 ng/mL (p=0.019) or 10.1 to 20 ng/mL (p=0.002). Additionally, these patients had a greater likelihood of Gleason 8-10 prostate cancer but this only became statistically significant after adjustment (p=0.088). The post-USPSTF recommendation group also had a greater likelihood of being diagnosed with clinical stage 2b (p=0.001) or stage 2c to 3a prostate cancer (p=0.027). Finally, this cohort of patients was also more likely to have be diagnosed with a D'Amico high risk prostate cancer (p=0.036) (Banerji et al., 2016).

Banerji and colleagues also compared a subset of patients who received a PNB in the 30 months prior to the USPSTF recommendation to the cohort of patients who received a PNB in the 30 months following the USPSTF recommendation. The cohort of patients who received a PNB in the 30 months following the USPSTF recommendation were also more likely to have a PSA level of 10.1 to 20 ng/mL (p=0.006). These patients

had a greater likelihood of being diagnosed with clinical stage 2b (p=0.012) or stage 2c to 3a prostate cancer (p=0.017) than the cohort that was seen in the 30 months prior to the USPSTF recommendation. The patients who were received a PNB in the 30 months following the USPSTF recommendation had a higher likelihood of being diagnosed with a D'Amico high risk prostate cancer (p=0.027) and were much less likely to be diagnosed with a D'Amico intermediate risk prostate cancer (p=0.042) (Banerji et al., 2016).

This study also found that following the USPSTF recommendation, the absolute number of prostate needle biopsies performed decreased from 448 in the 30 months prior to the USPSTF recommendation to 310 in the 30 months following the USPSTF recommendation, which illustrates an overall decrease of 31%. A reduction in the number of biopsies demonstrating high-risk disease (Gleason 8-10, D'Amico high risk, and CAPRA scores 6-10) was not evident following the USPSTF recommendation, although there was a reduction in the number of unnecessary biopsies performed. "Unnecessary" in this context refers to a prostate needle biopsy that was performed on a patient without evidence of prostate cancer, a Gleason score of 6, a D'Amico low risk score, or a CAPRA score of 0-2. Additionally, a significant reduction in PNBs revealing intermediate-risk tumors (Gleason 4+3, D'Amico intermediate risk, and CAPRA score of 3-5) was evident in the post-USPSTF period (Banerji et al., 2016).

This study concluded that patients who had a PNB performed in the 30 months following the USPSTF recommendation had an adjusted absolute risk difference and adjusted relative risk of 9.30% (95% CI, 0.64 to 17.98) and 1.25 (95% CI, 1.01 to 1.52), respectively, for D'Amico high-risk prostate cancer in comparison to patients who had a

PNB performed in the 86 months prior to the USPSTF recommendation. Thus, patients who had a prostate needle biopsy performed following the USPSTF recommendation had a 25% higher relative risk of being diagnosed with high-risk prostate cancer. Similarly, an adjusted relative risk difference and adjusted relative risk of 11.55 (95% CI, 1.35 to 21.75) and 1.33 (95% CI, 1.03 to 1.72), respectively, for D'Amico high-risk prostate cancer was demonstrated for patients who had a PNB performed in the 30 months following the USPSTF recommendation in comparison to patients who had a PNB performed in the 30 months prior to the USPSTF recommendation. This demonstrates a 33% higher relative risk of being diagnosed with high-risk prostate cancer following the USPSTF recommendation (Banerji et al., 2016).

Banerji and colleagues' study draws many conclusions about the trends of prostate needle biopsies in light of the USPSTF recommendation. They concluded that there was an overall decrease in prostate needle biopsies performed at their institution, mostly occurring in the number of PNBs diagnosing intermediate-risk disease. Additionally, they found that patients seen at Virginia Mason were more likely to be diagnosed with D'Amico high-risk prostate cancer and less likely to be diagnosed with D'Amico intermediate risk cancer. This is further illustrated by a significant 33% relative risk of being diagnosed with high-risk prostate cancer in the 30 months following the USPSTF recommendation compared to the 30 months prior to the USPSTF recommendation. This emphasizes the concern that eliminating prostate cancer screening may lead to delayed diagnoses as more patients are being diagnosed with higher-risk disease and less patients are being diagnosed with intermediate-risk, potentially treatable, disease (Banerji et al., 2016).

Perez and colleagues also performed a retrospective study to evaluate the effect of the 2012 USPSTF recommendation against prostate cancer screening on referrals from primary care providers and subsequent prostate cancer workup by urologists. The study investigators identified all men who were newly referred to their institution's urology department with an elevated PSA level 12 months before (June 12, 2011 to June 11, 2012) and 12 months after (June 12, 2012 to June 11, 2013) the USPSTF recommendation. Patients with a history of prostate cancer or chronically elevated PSA levels were excluded from data analysis. Patient demographics, PSA level, and biopsy characteristics including stage, Gleason score, D'Amico risk score, were compared using descriptive statistics for patients referred before and after the USPSTF recommendation (Perez et al., 2015).

The study investigators identified a total of 413 men who met inclusion criteria for the study: 201 men were referred to the institution during the pre-USPSTF period and 212 men were referred to the institution during the post-USPSTF period. This study demonstrated a slight increase of 5.2% in overall referrals for elevated PSA at their institution following the USPSTF recommendation. There was no change demonstrated in the percentage of patients who received a prostate biopsy following a urology referral during the pre-USPSTF and post-USPSTF time periods. In the year prior to the USPSTF recommendation, 44.3% of patients underwent a prostate biopsy, compared to 45.5% of patients who underwent a prostate biopsy in the year following the USPSTF recommendation ($p=0.8$). No difference in the percentage of positive biopsies was demonstrated. In the pre-USPSTF cohort, 53.4% had a positive prostate biopsy compared to 54.7% in the post-USPSTF cohort ($p=0.87$). Furthermore, no significant

difference was demonstrated in the distribution of D'Amico risk score (p=0.92) or Gleason grade (p=0.88) among positive prostate biopsies between the pre-USPSTF and post-USPSTF cohorts (Perez et al., 2015).

The findings of this study demonstrate that the 2012 USPSTF recommendation against prostate cancer screening has not significantly altered practices by urologists or primary care providers in this area as demonstrated by a slight increase in referrals for elevated PSA levels, stable prostate biopsy rates, and no change in prostate biopsy characteristics between the pre-USPSTF cohort and the post-USPSTF cohort. The absence of a decrease in referrals, which would be expected with adoption of the USPSTF recommendation, indicates primary care providers in this area are still screening men with PSA tests despite USPSTF recommendation against this practice. This study differs from findings by previous studies demonstrating declines in biopsy rates following the USPSTF recommendation against prostate cancer screening (Perez et al., 2015).

These three retrospective studies all face the limitation of not being able to generalize their findings to the American population as they utilize data from a single center. Furthermore, Banerji et al comment on the collaboration between the urologists and primary care providers in their network. Thus, their results may underestimate the true effects of the USPSTF recommendation on prostate biopsy rates at their institution due to negative influence on primary care providers by urologists regarding the recommendation (Banerji et al., 2016). The findings of Rezaee et al face further limitation as their cohort sample consisted only of employees and spouses of

employees in a single private health care system. Thus, their results are not generalizable to those with limited access to healthcare (Rezaee et al., 2016).

Prostate Cancer Incidence Trends

As the purpose of implementing screening tests is to detect and diagnose a disease early at a treatable stage it can be assumed that incidence rates are directly affected by changes in screening practice recommendations. Thus, another method of assessing the effects of the USPSTF recommendation against PSA-based prostate cancer screening is by analyzing prostate cancer incidence trends before and after the release of this recommendation.

Two study investigators examined trends in prostate cancer incidence following the USPSTF recommendation using data collected by the Surveillance, Epidemiology, and End Results (SEER) program. The SEER Program of the National Cancer Institute (NCI) publishes information about cancer incidence and survival including the stage of cancer at the time of diagnosis. The program uses several population-based cancer registries to comprehensively collect and publish this information. It is estimated that SEER data covers approximately 30 percent of the United States population (National Cancer Institute, 2016a).

Herget et al sought to define monthly prostate cancer incidence population trends by age, Gleason score, and stage at diagnosis using 349,517 prostate cancer cases diagnosed in 18 SEER registries from January 2007 to December 2012. JoinPoint software was utilized to analyze changes in the rate of annual percent change (APC) in overall prostate cancer incidence during the study period. Analysis was also done to reveal changes in the rate of APC in prostate cancer incidence by age, grade, and stage at diagnosis as well as ethnicity. Age at diagnosis was separated into four subgroups for analysis: 45-54 years, 55 to 64 years, 65 to 74 years, and 75 years and

older. Grade at diagnosis was separated for analysis according to Gleason score: Low grade (Gleason score ≤ 6), intermediate grade (Gleason score = 7), and high grade (Gleason score = 8, 9, or 10). Stage at diagnosis was separated for analysis according to TNM classification into Stage I/II, III, IV, and unknown. Stages I and II were combined as a result of a low number of cases diagnosed at Stage I. Cases without a documented age at diagnosis or month of diagnosis were excluded from data analysis (Herget, Patel, Hanson, Sweeney, & Lowrance, 2016).

Analysis of the SEER data demonstrated an overall decline in prostate cancer incidence following the implementation of the USPSTF screening recommendation. The steepest decline in overall prostate cancer incidence rate began in May of 2011 and continued through the end of the study period in December of 2012. This is demonstrated by a calculated -19.6% annual percent change (APC) (95% CI, -26.3 to -12.9; $P<0.05$) in May of 2011. The investigators of this study correlated the timing of this decrease in prostate cancer incidence with the publication of the ERSPC and PLCO trials, prior to the release of the USPSTF draft recommendation in October of 2011 and subsequent final screening recommendation by the USPSTF in May of 2012 (Herget et al., 2016).

The reduction in prostate cancer incidence was most pronounced for low-grade tumors (Gleason ≥ 6) and Stage I and II prostate cancers. This was exhibited by a drop in the incidence rate by -29.1% APC (95% CI, -36.2 to -21.9; $P<0.05$) in May of 2011 and a decrease in the incidence rate by -24.2% APC (95% CI, -30.1 to -18.2; $P<0.05$) in March of 2011 for low-grade tumors and Stage I and II prostate cancers, respectively (Herget et al., 2016). The study also found a significant reduction in prostate cancer

incidence for high-grade tumors (Gleason 8, 9, or 10) and Stage III prostate cancers, although less pronounced than for low-grade tumors and Stage I and II prostate cancers. This was demonstrated by a -10.8% APC (95% CI, -20.7 to -0.8; P<0.05) in prostate cancer incidence of high-grade tumors in August 2011 and a -16.7 APC (95% CI, -23.8 to -9.4; P<0.05) in prostate cancer incidence of Stage III prostate cancers in March 2011 (Herget et al., 2016).

A decline in prostate cancer incidence trends by age was revealed for all of the age subgroups but was not found to be statistically significant. Finally, a statistically significant decrease in prostate cancer incidence was found for each ethnicity over time with the steepest declines in incidence exhibited between March and June of 2011. The most prominent decrease in prostate cancer incidence by ethnicity was found in non-Hispanic whites as revealed by a -23.8% APC (95% CI, -29.9 to -17.6; P <0.05). A sharp decline in prostate cancer incidence in black men and Hispanic men was also seen as exhibited by a -18.2% APC (95% CI, -28.2 to -8.1; P <0.05) and -17.6% APC (95% CI, -25.8 to -9.3; P <0.05), respectively, in June of 2011 (Herget et al., 2016).

The results from this study demonstrate that the publication of the ERSPC and PLCO studies as well as the draft and final recommendation by the USPSTF has made a considerable impact on prostate cancer incidence rates with fewer overall diagnoses of prostate cancer being made. The study provides evidence that less low-grade tumors and Stage I and II prostate cancers are being detected, thus the concern of over-diagnosis of prostate cancer in patients with indolent cancer will be slowly diminishing. Although, this study draws concern to the consequences of not screening men for prostate cancer – that fewer high-grade tumors are being detected. While the greatest

decline in incidence was noted in regards to low-grade tumors and Stage I and II cancers, the decline in incidence of high-grade tumors was still substantial at -10.8% APC. Detecting less low-grade prostate cancer in men may be beneficial, though there is much concern that potentially treatable high-grade prostate cancers will now go undetected as a result of the elimination of PSA testing in all men. Since the data for this study was limited and exhausted at 2012, additional studies with long-term data are needed to define the full consequence of eliminating prostate cancer screening on prostate cancer incidence rates down the road (Herget et al., 2016).

Jemal et al also sought to examine changes in prostate cancer incidence following the 2012 USPSTF recommendation. The study investigators used incidence data from 2005 to 2012 from 18 SEER registries and identified 446,009 cases of prostate cancer in men aged 50 years and older. Prostate cancer incidence and incidence ratios (IRs) by age and stage were calculated and compared for each consecutive year from 2005 to 2012. Age was separated into 3 sub-groups: ≥50 years, 50-74 years, and ≥75 years. Stage was divided into localized or regional and distant. According to SEER, Localized is defined as “confined to primary site,” regional is defined as “spread to regional lymph nodes,” and distant is defined as “cancer has metastasized” in this context (National Cancer Institute, 2016b). Incidence was corrected for delays in reporting and 99% confidence intervals were computed by age, race, stage, and SEER registry (Jemal et al., 2015).

This study also found a reduction in prostate cancer incidence corresponding to the USPSTF recommendation in 2012 against prostate cancer screening. This is demonstrated by a prominent decline in annual prostate cancer incidence in men 50

years and older from 498.3 cases per 100,000 (99% CI, 492.8 to 503.9) in 2011 to 416.2 cases per 100,000 (99% CI, 411.2 to 421.2) in 2012. From 2011 to 2012, there was an absolute decline of 82.1 cases per 100,000 men and a relative decline of 16% (IR, 0.84; 99% CI, 0.82 to 0.85) (Jemal et al., 2015).

Analysis of the data established that this decrease in prostate cancer incidence was limited to local and regional stage disease and consistent across all age groups and races. This is illustrated by a calculated decrease in incidence in men 50 years and older with local and regional stage disease from 447.2 cases per 100,000 (99% CI, 442.0 to 452.4) in 2011 to 367.3 cases per 100,000 (99% CI, 362.7 to 372.0) in 2012. From 2011 to 2012, there was an absolute decrease of 79.9 cases per 100,000 and a relative decrease of 18% (IR, 0.82; 99% CI, 0.81 to 0.84). There was no change in the incidence for distant-stage disease over the study period except in those 75 years and older. In this age group, the incidence rate increased from 57.7 cases per 100,000 (99% CI, 53.2 to 62.3) in 2011 to 65.0 cases per 100,000 (99% CI, 60.3 to 69.9) in 2012 (Jemal et al., 2015).

Jemal et al also performed subsequent analysis on changes in prostate cancer incidence by age using data from the 18 SEER registries of the National Cancer Institute in addition to the National Program of Cancer Registries from the Centers for Disease Control and Prevention (CDC). Combining the incidence data from these registries is estimated to account for approximately 99% of the US population. The results of this analysis were similar to the calculations from SEER registry data alone, though the incidence rates were slightly decreased. In men 50 years and older, the incidence of prostate cancer in men decreased from 468.7 cases per 100,000 (99% CI,

466.2 to 471.1) in 2011 to 381.2 cases per 100,000 (99% CI, 379.0 to 383.3) in 2012. Using the data from these combined registries, it was found that 33,519 fewer men were diagnosed with prostate cancer in 2012 compared to 2011 (Jemal et al., 2015).

Jemal et al also performed supplementary analysis on changes in prostate cancer incidence by age from 2005 to 2013 for a single registry of the SEER registry program as a result of a special request and subsequent availability of data through 2013. Analysis of the data from this single registry through 2013 demonstrated similar prostate cancer incidence patterns in men 50 years and older with a continued decrease in prostate cancer incidence through 2013. A decrease in incidence was noted from 2011 to 2012 and also from 2012 to 2013. In 2011, there were 519.0 cases per 100,000, which lowered to 436.5 cases per 100,000 in 2012. A further decrease in incidence was demonstrated in 2013 at an incidence rate of 408.3 cases per 100,000. A relative decrease of 6% (IR, 0.84; 99% CI, 0.80 to 0.88) was demonstrated from 2012 to 2013 (Jemal et al., 2015).

The findings of this study further demonstrate the significant decrease in prostate cancer incidence following the USPSTF recommendation. Similar to the study findings of Herget et al, Jemal and investigators also found a significant decrease in the number of cases of low-grade (localized and regional) prostate cancers being detected. While this demonstrates a reduction in over-diagnosis and decrease in subsequent harm from over-treatment, a concern of biologically important early lesions going undetected is once again raised. The 33,519 men who did not receive a prostate cancer diagnosis in 2012 as compared to 2011 further elucidate this concern. Furthermore, due to the slow progression of prostate cancer and long natural history of the disease, it will take further

time and long-term data to establish the true consequence associated with the elimination of PSA screening and subsequent decrease in prostate cancer diagnoses on prostate cancer mortality as a result of the 2012 USPSTF recommendation (Jemal et al., 2015).

Jemal et al recently released a subsequent publication in August of 2016 using the same methods as their previous study but incorporated SEER data from 2005 through 2013. The study investigators aimed to determine if the decrease in prostate cancer incidence in men 50 years and older demonstrated in their previous study continued from 2012 to 2013. The study found that the incidence of localized and regional prostate cancer continued to decline from 2012 to 2013 but at a slower rate than from 2011 to 2012. They concluded that the incidence of localized and regional prostate cancer in men 50 to 74 years old declined from 356.5 cases per 100,000 in 2012 to 335.4 cases per 100,000 in 2013 (IR, 0.94; 99% CI, 0.92 to 0.96). This decline was also found in men 75 years and older as illustrated by a decrease from 379.2 cases per 100,000 in 2012 to 353.6 cases per 100,000 in 2013 (IR, 0.93; 99% CI, 0.89 to 0.97). On the other hand, no change in incidence rates for distant-stage prostate cancer in men 50 to 74 years old and men 75 years and older were seen from 2012 to 2013. This additional publication further demonstrates the decrease in low-grade prostate cancer diagnoses following the USPSTF recommendation against PSA based prostate cancer screening in all men in 2012 (Jemal et al., 2016).

Barocas et al also sought to evaluate changes prostate cancer incidence by month following the USPSTF grade D draft recommendation in October 2011. The study investigators utilized the NCDB (National Cancer Database) to identify prostate

cancer diagnoses between January of 2010 and December of 2012 (Barocas et al., 2015). This is an oncology outcomes database and a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society that compiles newly diagnosed cases of cancer from 1,500 national cancer programs nationwide. It is estimated that this database captures approximately 70 percent of all newly diagnosed cancer cases (American College of Surgeons, 2016). Within NCDB, the study investigators identified 352,020 incident prostate cancer cases in patients 18 years and older between 2010 and 2012 for subsequent analysis. Data analysis with an interrupted time series and comparison series was computed to assess changes in the number of prostate diagnosis by month before and after the USPSTF guideline. Prostate cancer incident diagnoses were compared with those of colon cancer as there was no change in colon cancer screening recommendations during the study period (Barocas et al., 2015).

The study investigators found there were -1,373 fewer cases of incident prostate cancer diagnoses in October of 2011 following the release of the USPSTF draft recommendation. This reduction represents a -12.2% ($P<0.01$) decrease in incidence immediately following the release of the draft recommendations. Comparing change in monthly incident prostate cancer diagnoses prior to and after the draft recommendation, a relative decrease of -164 cases per month was demonstrated with an ongoing reduction in prostate cancer incidence rate of -1.8% per month ($P<0.01$). Within 1 year following the draft guideline, the number of new incident prostate diagnoses decreased by 27.9% when compared to the expected trend from the period prior to the draft recommendation (Barocas et al., 2015).

Changes in monthly incident prostate cancer diagnoses by D'Amico risk group were also calculated in this study. The D'Amico risk classification system divides men into low risk, intermediate risk, or high risk based on PSA level, Gleason grade, and T stage (University of California San Francisco Department of Urology, 2016). Following the October 2011 draft recommendation, a decrease in monthly incident prostate cancer diagnoses of -16.9%, -12.9%, and -10.1% for low risk, intermediate risk, and high risk, respectively, was found. Ongoing monthly changes in incident prostate cancer diagnoses from October 2011 onward were calculated at -2.7%, -1.9%, and -1.4% for low risk, intermediate risk, and high risk, respectively. Within 1 year following the draft guideline, the number of predicted low-risk prostate cancer diagnoses decreased by 37.9%. Similarly, the number of predicted intermediate-risk and high-risk prostate cancer diagnoses decreased by 28.1% and 23.1%, respectively (Barocas et al., 2015).

There was no significant change demonstrated in incident colon cancer diagnoses after October 2011 in comparison to incident prostate cancer diagnoses which supports that the study findings, illustrated by a decrease in prostate cancer diagnoses, are reflective of the USPSTF recommendation changes (Barocas et al., 2015).

This study found the number of low-risk cancers decreased significantly within 1 year following the USPSTF draft guideline. The low-risk strata of prostate cancer also demonstrated a more rapid decline than other disease risk strata by monthly incident diagnoses, which supports that the USPSTF recommendation is having its intended effect tackling the issue of over-diagnosis. On the other hand, similar to issues drawn up by Herget et al and Jemal et al, withdrawing screening does not come without

drawbacks. This study exhibited a significant reduction in diagnoses for intermediate-risk and high-risk cancers within 1 year following the USPSTF guideline. This exemplifies that eliminating screening is diminishing opportunities for diagnosing men with disease that could be treatable and thus putting eligible men into harm. Like the previous studies, the conclusions of this study also raise the concern that rates of advanced disease could rapidly progress in the years to come but further long-term data is needed to reveal the true consequences of the USPSTF recommendation on prostate cancer mortality (Barocas et al., 2015).

Discussion

The recommendation by the United States Preventative Services Task Force to eliminate PSA-based prostate cancer screening in men of all ages should be considered as such – a “recommendation.” This recommendation has dramatically transformed the face of prostate cancer in the United States with declines in PSA screening rates leading to decreased prostate biopsy rates and prostate cancer incidence rates as demonstrated in various studies referenced in this literature review. Unfortunately, it is too soon to observe the true ramifications of eliminating PSA-based prostate cancer screening but several deductions can be made thus far.

First and foremost, without screening it is likely that the incidence of advanced, metastatic prostate cancer will increase substantially. The utility of the PSA test in detecting early, treatable prostate cancer is important to recognize and should not be completely abandoned. While it harbors its own limitations in regards to lack of sensitivity and specificity, its non-invasive manner and ability to detect asymptomatic prostate cancer makes this test very advantageous. Instead of eliminating the use of PSA testing as a whole, PSA testing should be used judiciously taking into account several variables including a patient’s past medical history, risk factors, and current clinical presentation.

It is important to recognize that the United States Preventive Task Force is not the only group of national experts who provide recommendations on prostate cancer screening. In fact, the 2012 USPSTF panel that came to the conclusion to recommend against PSA-based prostate cancer screening in all men did not include any board-certified urologists (American Urological Association, 2013). This further discounts the

credibility of their recommendation statement, as urologists are the experts in diagnosing and treating prostate cancer and would be expected to be included in any decisions regarding prostate cancer screening recommendations.

Furthermore, the urology community is not in support of the USPSTF recommendation. They follow the American Urological Association (AUA) guidelines for prostate cancer screening, which are also strongly supported by the American Cancer Society and the American Society of Clinical Oncologists. The AUA released their guideline for early detection of prostate cancer in April of 2013 following a systematic review and meta-analysis of the literature regarding prostate cancer screening by an independent group of experts (American Urological Association, 2013).

The AUA concluded that there is no benefit of screening in men under age 40. For men ages 40 to 54 years, they stated screening should not be performed unless the individual is an increased risk of prostate cancer. The AUA recommends shared decision making between men ages 55 to 69 years and their clinician in order to justify the benefits and risks associated with screening and to make an informed decision on performing PSA testing based on this conversation. For men that decide to undergo screening, the AUA recommends a routine screening interval period of two years or more to reduce over-diagnosis and false positives. Finally, the AUA does not recommend screening in men greater than 70 years old or who have an expected life expectancy of 15 years or less. The AUA suggests that following these guidelines will increase the benefits of PSA screening, while eliminating harms such as over-diagnosis and overtreatment (American Urological Association, 2013).

Physician Assistants (PAs) should be familiar with the limitations of the USPSTF recommendation and the detrimental consequences that will result if PSA screening is eliminated completely. It is vital for Physician Assistants to be well informed of the benefits and consequences of PSA testing and be proponents of shared decision-making with their patients in regards to prostate cancer screening. PAs should be confident in their ability to discuss with their patients the benefits and risks of prostate cancer screening. Physician Assistants should be cognizant of the risk factors for prostate cancer including advancing age, African American race, and positive family history and inform their patients of the increased utility of PSA screening in patients with increased risk of prostate cancer.

PAs should also be familiar with patient decision aids (PDAs) that can be used to facilitate shared decision making with patients regarding PSA testing. PDAs are a valuable tool that can help to expedite the conversation of PSA testing while maintaining pertinent discussion points. These tools draw light on several elements of PSA testing including: Likelihood of false-positive and false-negative results, options following an elevated PSA test, mortality benefit of screening, and harms of screening (American Urological Association, 2013). Especially of utility in primary care when conversations with patients are brisk, PDAs can be given to patients in advance to help optimize discussion during the patient's visit and ultimately determine whether the patient will undergoing PSA screening for prostate cancer.

There are several areas for future research in prostate cancer screening. First, randomized control trials are necessary to establish long-term changes in prostate cancer mortality, especially following the 2012 USPSTF recommendation against PSA-

based prostate cancer screening. Second, further studies are warranted to determine if annual screening or testing at a different interval, such as every two or four years, is more beneficial. There is currently no evidence of the best screening interval for serial PSA tests to reduce prostate cancer specific death. Finally, further evidence on the utility of alternative prostate cancer screening tools is needed. This pertains to using DRE, PSA derivatives (PSA density, PSA kinetics, age adjusted PSA levels), PSA molecular forms (proPSA, freePSA, complexed PSA), urinary biomarkers (PCA3), or imaging as primary screening tests.

It is important to recognize there are several limitations of this literature review. This includes several studies with small sample sizes making it difficult to generalize conclusions to the U.S. population. Similarly, many of these studies are not nationally representative and are not able to be generalized to the population as a whole. Additionally, the studies referenced in this literature review are observational studies, thus direct causation between the USPSTF recommendation and PSA screening rates, prostate biopsy rates, and prostate cancer incidence rates cannot be definitively established. Confounding variables is also a significant as several factors influence a clinician or patient's decision to screen for prostate cancer with PSA. Finally, as the final USPSTF recommendation statement was released in 2012, majority of the studies had only a short follow-up time from the recommendation release date to the present time, thus conclusions regarding the effects of this recommendation are limited.

Conclusion

The United States Preventative Task Force 2012 recommendation against PSA-based prostate cancer screening in men of all ages has led to substantial changes in PSA screening practices, prostate biopsy rates, and prostate cancer incidence. Fewer clinicians are ordering and performing PSA tests. Prostate biopsy rates have also decreased. Overall prostate cancer incidence rates have also declined with fewer low-grade, intermediate-grade, and high-grade tumors being identified. Long-term follow-up is necessary to further ascertain the effects of eliminating PSA-based prostate screening on prostate cancer incidence and mortality rates.

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Abstract

Objective: Examine the literature to determine the impact of the 2012 USPSTF grade D recommendation discouraging PSA-based prostate cancer screening on PSA screening rates, prostate biopsy rates, and prostate cancer incidence.

Method: A literature review was conducted using PubMed and EBSCOhost with search terms including prostate cancer, United States Preventative Task Force, prostate cancer screening, and prostate specific antigen. Observational studies, case control studies, pre-post studies, and trend analyses were included. Publications within the last 5 years originally printed in English were included.

Results: Observational studies demonstrate a decrease in PSA screening rates on both a national and regional level following the release of the USPSTF recommendation against PSA-based prostate cancer screening in 2012. The decline in PSA screening rates was especially prominent among primary care providers. Subsequent declines in prostate cancer biopsy rates and prostate cancer incidence were also noted. The reduction in prostate cancer incidence was most pronounced for low-grade tumors. A significant reduction in incidence of intermediate-grade and high-grade prostate cancer was also demonstrated.

Conclusion: The literature exhibits declines in PSA screening rates, prostate biopsy rates, and prostate cancer incidence following the 2012 USPSTF recommendation. Further long-term studies are needed to determine the ramifications of this recommendation on prostate cancer mortality.

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Complete Title: Early Effects and Future Implications of USPSTF's Recommendation Against Prostate cancer screening

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