The Effects of Population-based Prostate-specific Antigen Screening Beginning at Age 40

Christopher J. Weight, Vikram M. Narayan, Daniel Smith, Simon P. Kim, and R. Jeffrey Karnes

OBJECTIVE To evaluate population-based prostate cancer (CaP) testing of men in their 40s, given the paucity of prospective data evaluating the consequences of prostate-specific antigen (PSA) testing in younger men for CaP.

MATERIALS AND METHODS A total of 1052 men in their 40s were followed longitudinally for prostate outcomes, from 1990 to 2010. A random subset of 268 men was selected to undergo biennial CaP testing including PSA testing, transrectal ultrasound, and a digital rectal examination. A representative population of 609 men with a subset of 159 men who also began CaP testing in their 50s was also evaluated as a comparison group. Risk of prostate biopsy (PBx), CaP, or death from CaP was compared between CaP-tested and the routine-care population cohort.

RESULTS Median follow-up was 17.2 years. Men aged 40-49, who underwent CaP testing were 2.4 times more likely to undergo a PBx (hazard ratio [HR] 2.4 95% confidence interval [CI] 1.8-3.3) and 2.2 times more likely to be diagnosed with low-risk CaP (HR 2.2, 95% CI 1.12-4.0). Those initiating CaP testing a decade earlier were 2.2 times and 1.7 times more likely to be biopsied and be diagnosed with CaP for any given age (HR 2.2 95% CI 1.4-3.5 and 1.7 95% CI 1.1-2.7, respectively).

CONCLUSION CaP testing in men beginning at age 40 resulted in a significant increase in the risk of PBx and diagnosis of low-risk CaP, without a measurable reduction in risk of CaP-death in this low-risk population. However, given the natural history of CaP, a longer follow-up is needed to confirm this finding. UROLOGY 110: 127–133, 2017. © 2017 Elsevier Inc.

Prostate-specific antigen (PSA) screening for the early detection of prostate cancer (CaP) remains controversial. Guidelines from professional societies have ranged from recommending a discussion of screening in asymptomatic men beginning at age 40 by the European Association of Urology,[1] or recommending screening beginning at age 45 by the National Comprehensive Cancer Network[2] on the more conservative end. The American Urological Association recommends screening beginning at age 55,[3] and the 2012 US Preventative Services Task Force recommended against PSA screening altogether.[4] There is little evidence evaluating the screening of men under age 50, despite retrospective data from banked serum samples that suggest that younger men with an elevated baseline PSA are more likely to have adverse long-term CaP outcomes.[5-7]

Since the institution of PSA screening in the United States, the overall death rate from CaP has dropped dramatically. There remains a debate over how much of this drop is attributable to screening itself.[8] The absolute number of deaths from CaP in the United States has changed relatively little in the past 30 years since the introduction of PSA. There were 27,262 deaths from CaP in 1986 (pre-PSA era)[9] and 26,120 in 2016[10]; adjusted for population growth, the number needed to treat to prevent 1 CaP-specific death by PSA screening remains high.[11] PSA screening, when applied prospectively and compared to a population with little screening, confers a cancer-specific survival advantage; to prevent 1 death from CaP, the number needed to screen and to treat is 1055 and 37, respectively.[12,13] This reduction in death from CaP does not translate into a reduction of death from any cause, however, and overall survival is equal between the groups during follow-up. Furthermore, a recent Cochrane review failed to find a significant reduction in CaP mortality and noted significant harms in a meta-analysis.[14]

Financial Disclosure: *The authors have no relevant financial relationships to the article to disclose.*

Funding Support: *This project was supported by research grants from the Public Health Service, Rochester Epidemiology Project, National Institutes of Health (DK58859, AG034676, and 1UL1 RR024150-01), and Merck Research Laboratories.*

From the Department of Urology, University of Minnesota, Minneapolis, MN; the Department of Urology, Case Western Reserve University, Cleveland, OH; and the Department of Urology, Mayo Clinic, Rochester, MN

Address correspondence to: Christopher J. Weight, M.D., M.S., MMC 394, 420 Delaware Street SE, Minneapolis, MN 55455. E-mail: cjweight@umn.edu

Submitted: April 24, 2017, accepted (with revisions): August 7, 2017

Harms of CaP screening include unnecessary biopsies, biopsy-related complications, patient anxiety, and adverse events related to the diagnosis and treatment of a potentially biologically inert "cancer."[15] In fact, it is estimated that as many as 1 million men in the past 20 years may have been overdiagnosed with nonlethal cancers.[11] Yet CaP continues to be a primary cause of cancer-specific death, with more than 300,000 men dying from CaP worldwide each year.[16]

Several retrospective cohort studies have found that men with a higher baseline PSA in their 40s are at significantly higher risk of subsequent development of CaP 20-30 years later.[5,6,17-19] Analysis of these studies has led to the conclusion that perhaps patients could be risk stratified with an early baseline PSA, with subsequent screening appropriately tailored. This stratified screening process could maintain the benefits of screening while minimizing harms. However, because these studies are largely based on banked serum, it remains unclear how patients and physicians might act on prospectively analyzed PSA, digital rectal examination (DRE), and ultrasound findings.

In this study, we evaluate how CaP testing initiated in men in their 40s would affect the subsequent risks of undergoing a prostate biopsy, receiving a CaP diagnosis, and tumor characteristics when followed prospectively compared with a representative population cohort undergoing routine care. We also compare these risks with men who commence CaP testing starting at age 50.

MATERIALS AND METHODS

The principal study population consisted of men (n = 1052) ages 40-49, living in Olmsted County, Minnesota, enrolled in a prospective cohort study entitled "Natural History of Prostatism: The Olmsted County Study" (DK058859). The study, in part, was designed to prospectively assess the natural history of benign prostatic hyperplasia and to understand how surrogate measures of prostate growth, such as PSA, changed over time. A random sample of these men was chosen for clinic evaluation as described later (n = 268). An additional random sample (n = 161) of men was selected to undergo CaP testing, ages 50-59, and were chosen from a population cohort (n = 609) undergoing routine care. This "older" cohort was followed and compared with the men entering the study in their 40s. The entire cohort has been described previously.[20] Beginning in 1990, 3874 men living in Olmsted County, between the ages of 40 and 79, were invited to participate; 2115 (55%) of eligible subjects enrolled at baseline and completed biennial questionnaires about overall health status, urinary symptoms, and sexual function. Men in the first few years of the study who died or were lost to follow-up were replaced during rounds 2 and 3 (in 1992 and 1994), resulting in a total of 2447 study participants, of which 1052 were ages 40-49, and 609 were ages 50-59 at study entry. A random sample, including 268 and 161 men between ages 40 and 49 and 50 and 59, respectively, was selected as a "clinic cohort," with 87% participating in a biennial CaP testing. This included a DRE, PSA screening, and a transrectal ultrasound of the prostate. Patients with abnormal DRE results, elevated PSA (>4.0 ng/mL), or suspicious lesions on transrectal ultrasound were further evaluated with a prostate biopsy. Two men, ages 50-59 at baseline, had a previous biopsy and were excluded from subsequent analysis, leaving a cohort of 159. Men not included in the CaP testing cohort completed questionnaires only and were free to undergo CaP testing at the discretion of their primary care physicians. The study population was then maintained as a closed cohort and followed biennially. This study received institutional review board approval from the Mayo Clinic and Olmsted Medical Center.

The community medical records of all study participants were abstracted to obtain information on CaP diagnosis, prostate biopsy, death, and cause of death, if applicable.

If a PSA above the age-specific norm was identified during the course of the study (>2.5 ng/mL for 40-49, >3.5 ng/mL for 50-59, >4.5 ng/mL for 60-69, and >5.5 ng/mL for 70-79),[20] or if an abnormality in texture (nodule or asymmetry) was noted on DRE, a letter to the patient advised them to seek medical attention.

Differences between men randomly selected to CaP testing were analyzed by chi-square, Fisher exact test, or Wilcoxon log rank as appropriate. These comparisons were also made according to which decade of life PSA screening commenced. Risk of subsequent biopsy or cancer diagnosis was calculated using Kaplan-Meier curves (graphing failure instead of survival), log-rank test, and proportional hazard ratios (HR). To account for the differential risk of cancer between men in their 50s vs 40s at study entry, Kaplan-Meier curves used age on the *x*-axis. Proportional hazards assumptions were not met for CaP diagnosis in patients after 18 years of follow-up; therefore, follow-up was censored in these patients at 18 years for these analyses. Incidence was calculated by dividing the incident cases during a specified time period by years of at risk follow-up during that time period, and standardized against US incidence rates from 1992 to 2008. Estimates of new cases were calculated using 2011 US census data and Olmsted County incidence rates. All analyses were performed using JMP 9.0.1 (SAS Institute, Cary, NC). All tests of statistical significance were 2-sided with an alpha of 0.05.

RESULTS

A comparison of baseline statistics can be found in Tables 1 and 2, stratified according to whether subjects were randomly selected to participate in the screening cohort or whether they began protocol screening in the fourth or fifth decade of life. There were only small, clinically insignificant differences in baseline risk.

Comparison of Screened Cohort vs Routine Care Beginning Ages 40-49

The risks of undergoing a biopsy, developing CaP, and death from any cause are presented in Supplemental Table S1. Notably, men who began CaP screening at age 40 had a more than 2-fold higher risk of undergoing prostate biopsy than age-matched population controls (HR 2.4, 95% confidence interval [CI] 1.7-3.3). The screened men were also twice as likely to be diagnosed with low-risk CaP (HR 2.2, 95% CI 1.12-4.0). Negative biopsy rates were high in both cohorts (Supplemental Table S1) although they were 2.6-fold higher in the screened cohort. Similar findings were noted on survival curves depicting risk of subsequent prostate biopsy or CaP (Fig. 1). In the 40- to 49-year-old-screened cohort, no man (n = 0 of 268) went on to develop high-risk CaP (Gleason Score >7) and only 1 man in the nonscreened cohort did (n = 1 of 759).