Comparison of Prostate Specific Antigen Velocity in Screened Versus Referred Patients With Prostate Cancer

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Purpose: Despite the tremendous stage migration associated with prostate cancer screening to our knowledge it remains unproven whether prostate specific antigen based screening decreases prostate cancer specific mortality. Recent studies have shown that prostate specific antigen velocity more than 2 ng/ml per year in the year before diagnosis is associated with a significantly greater risk of prostate cancer specific mortality after treatment. This may serve as a surrogate marker for prostate cancer outcomes. We compared the prostate specific antigen velocity profile between patients with prostate cancer in whom the tumor was detected in a formal screening study and those who were referred for treatment.

Materials and Methods: We evaluated prostate specific antigen velocity in 1,101 men from a prostate cancer screening study and in 368 not enrolled in a screening study who were referred for treatment. All patients underwent radical prostatectomy for clinically localized disease and had multiple preoperative prostate specific antigen measurements to calculate prostate specific antigen velocity.

Results: Median prostate specific antigen velocity before diagnosis was significantly higher in referred vs screened men (1.35 vs 0.68 ng/ml per year, $p < 0.0001$). In addition, a significantly greater proportion of referred patients had prostate specific antigen velocity more than 2 ng/ml per year (38% vs 17%, $p < 0.0001$). On multivariate analysis using prostate specific antigen, clinical stage and biopsy Gleason score screened vs referred status was a significant independent predictor of prostate specific antigen velocity more than 2 ng/ml per year ($p < 0.0004$).

Conclusions: Prostate specific antigen velocity more than 2 ng/ml per year has been linked to a significantly greater risk of prostate cancer specific mortality. Patients who underwent serial screening had a more favorable prostate specific antigen velocity profile at diagnosis, suggesting that screen detected prostate cancer may be more likely to be cured with definitive therapy.

Key Words: prostate, prostatic neoplasms, prostate-specific antigen, mass screening, mortality

The primary goal of PCa screening is to identify the cancer at a stage when treatment with curative intent is possible. During the last decade PCa specific mortality has decreased by almost 33% in the United States, concurrent with the widespread use of PSA based screening.[1,2] Similar screening efforts and improved outcomes were reported in Tyrol, Austria, where there was a significant decrease in advanced stage PCa and the PCa specific mortality rate after organized PSA based screening and high quality treatment became available.[3] In addition, our research group has previously reported that men in whom cancer was diagnosed through longitudinal screening have more favorable pathological tumor features and a higher biochemical progression-free survival rate after radical prostatectomy than men referred for treatment by the same surgeon.[4]

Nevertheless, some groups have argued that aggressive PCa screening results in the over diagnosis of potentially insignificant tumors that may have remained clinically indolent during the patient lifetime. Furthermore, the morbidity associated with PCa treatment, such as incontinence and erectile dysfunction, are clearly documented, while the mortality benefits of PSA based screening have not been proved.[5] A statistical model developed by Draisma et al estimated an over diagnosis rate of PCa of almost 50% in men 55 to 74 years old and predicted a lead time of more than 11 years.[6] In sum this suggests that annual screening does not improve survival but simply results in an increased rate of PCa detection.

Data from randomized, controlled clinical trials, such as ERSPC and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, are not yet available to further elucidate the direct impact of screening on PCa specific mortality. Therefore, it is useful to look at surrogate markers for PCa specific mortality. One such parameter is the change in PSA with time before PCa diagnosis, referred to as PSAV. Although PSAV has been used as an aid to PCa detection since the early 1990s, more recent studies demon-

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For another article on a related topic see page 1593.

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TABLE 1. *Study population clinical characteristics*

	Screened		Referred		p Value
No. race (% white)	1,014	(92)	355	(96)	0.0001
Median age at diagnosis (range)	66	(43–89)	60	(41–76)	<0.0001
Median ng/ml PSA (range)	3.8	(0.1–36.2)	5.1	(0.6–35.0)	<0.0001
No. biopsy Gleason sum 7 or greater (%)	145	(14)	107	(29)	<0.0001
No. clinical stage greater than T1 (%)	229	(21)	94	(26)	0.09

strated that patients with PSAV greater than 2.0 ng/ml per year are at 10-fold greater risk of death from PCa after radical prostatectomy and at 12-fold greater risk after external beam radiation therapy.[7,8] In addition, Carter et al recently reported that PSAV greater than 0.35 ng/ml per year approximately 5 to 15 years before PCa diagnosis was significantly associated with a higher risk of PCa specific mortality more than a decade later.[9] Therefore, we compared the PSAV profile in men who were diagnosed with PCa in a longitudinal PCa screening study vs that in men diagnosed outside a formal screening program.

MATERIALS AND METHODS

From 1991 to 2001 approximately 26,000 men participated in a longitudinal PCa screening study. As previously described, the study protocol involved DRE or PSA testing at 6 or 12-month intervals.[10] Biopsy was recommended for PSA greater than 4.0 ng/ml until May 1995 or greater than 2.5 ng/ml after May 1995, or findings on DRE suggestive of cancer.

From this study we identified 1,101 men who were diagnosed with PCa and underwent radical prostatectomy, as performed by a single surgeon (WJC). These men formed the screened cohort. As a comparison group, we identified 368 men in whom PCa was diagnosed by other physicians and who were referred for radical prostatectomy performed by the same surgeon. The indication for biopsy in these men was not standardized and it may have included increased PSA, suspicious DRE or evaluation for other urological problems. PSAV was calculated using linear regression of all PSA values obtained in the year before diagnosis. PSAV calculation included 2 PSA values in 752 (68%) screened and 265 (72%) referred men vs 3 or more values in 349 (32%) screened and 103 (28%) referred men ($p = 0.18$).

The chi-square and Wilcoxon rank sum tests were used to compare PSAV as well as other clinical and pathological features between the groups. Logistic regression was used for multivariate analysis. In these models the adjusted OR represents the increased risk of PSAV greater than 2.0 ng/ml per year, controlling for other predictors that were significant on univariate analysis ($p < 0.05$). All statistical analyses were performed using SAS®, version 8.2 and SPSS® 10.0 for Windows®.

TABLE 3. *Multivariate analysis of prediction of PSAV greater than 2 ng/ml per year*

	OR	95% CI	p Value
Age (continuous)	1.00	0.98–1.01	0.6
Race	0.91	0.49–1.71	0.8
Referred (vs screened)	1.87	1.34–2.62	0.0003
Biopsy Gleason 7 or greater	1.27	0.89–1.81	0.1
Clinical stage (T2/3 vs T1)	0.76	0.52–1.10	0.1
PSA	1.41	1.32–1.50	<0.0001

RESULTS

Clinical Characteristics

Table 1 shows the clinical characteristics of the study population. Most men in the screened and referred cohorts were white, although there were more nonwhite men in the screened cohort. Screened men were also significantly older than those in the referred cohort ($p < 0.0001$). Men were followed in the longitudinal screening study for a median of 41 months before PCa diagnosis and they had significantly lower PSA at diagnosis than the referred cohort (3.8 vs 5.8 ng/ml, $p < 0.0001$). The screened cohort also had a significantly lower percent of men with a biopsy Gleason score of 7 or greater and they tended to have a lower proportion of clinical stage T2 or greater disease.

PSAV

Median PSAV before diagnosis was significantly lower in screened men ($p < 0.0001$), while referred men were significantly more likely to have PSAV greater than 0.75 ng/ml per year (table 2). With regard to prognostication 71% of men in the referred cohort had PSAV greater than 0.35 ng/ml per year compared to 62% of screened men ($p = 0.003$). Furthermore, more than twice as many men in the referred cohort had PSAV greater than 2.0 ng/ml per year in the year before diagnosis (38% vs 17%, $p < 0.0001$).

Multivariate Analysis

Due to the significant correlation between PSA velocity and total PSA[11] multivariate analysis was performed to determine whether referred men had higher PSAV merely because they had higher total PSA or other unfavorable clinical characteristics (table 3). However, in the multivariate model referral status was a stronger predictor of PSAV greater than 2.0 ng/ml per year than age, race, Gleason score, clinical stage or preoperative PSA.

DISCUSSION

Screening for PCa remains controversial and to our knowledge there is no conclusive evidence as yet proving an improvement in disease specific mortality. Epidemiological studies from the Surveillance, Epidemiology and End Results database have demonstrated a 17.9% decrease in PCa

TABLE 2. *PSAV profiles in screened and referred men*

	Screened		Referred		p Value
Median preop ng/ml/yr PSAV (range)	0.68	(−10.01–72.91)	1.35	(−52.14–37.27)	<0.0001
No. PSAV greater than 0.75 ng/ml/yr (%)	515	(47)	239	(65)	<0.0001
No. PSAV greater than 0.35 ng/ml/yr (%)	686	(62)	261	(71)	<0.003
No. PSAV greater than 2.0 ng/ml/yr (%)	189	(17)	141	(38)	<0.0001