TODAY MEN WITH PROSTATE CANCER HAVE 
LARGER PROSTATES

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ABSTRACT

Objectives. To examine the relationship between prostate size and the method of cancer detection in men with organ-confined prostate cancer, and compare prostate size in men with and without cancer.

Methods. Prostate volume was evaluated in 720 men who had undergone radical prostatectomy for Stage T1c or Stage T2 cancer. Men with Stage T2 cancer were divided into those treated before 1989 (when widespread prostate-specific antigen [PSA] testing began), or not. Gland volume was also examined in 265 men participating in the Baltimore Longitudinal Study of Aging who had no clinical evidence of cancer. Volumes were compared using linear regression to allow for age.

Results. Prostate volume in men with Stage T1c cancer was statistically significantly larger than in men with Stage T2 cancer diagnosed in the pre-PSA era after adjusting for age ($P = 0.0001$), and statistically significantly larger than in men without cancer above age 47 years based on 95% confidence intervals. Prostate volumes in men with Stage T2 cancer diagnosed in the pre-PSA era and in men without cancer were not statistically significantly different.

Conclusions. Prostate volume in men with PSA-detected, organ-confined cancer is larger than in men with palpable organ-confined cancer diagnosed in either the pre-PSA era or PSA era. These discrepancies may reflect a diagnostic bias due to the effect of benign prostatic hyperplasia on serum PSA that results in the selection of men with larger prostates for biopsy.

used for early detection), or not (from 1989 onwards). These groups are referred to henceforth as “pre-PSA era” and “PSA era” T2 cancers respectively. Of the 305 men with Stage T2 cancer, 95 were from the pre-PSA era and 210 from the PSA era.

**NONCANCER POPULATION**

Prostate volume in men without prostate cancer was evaluated in men from the Baltimore Longitudinal Study of Aging. This ongoing, long-term, prospective study of aging, conducted by the National Institute on Aging (Bethesda, Md), has been described previously. Since its inception in 1958, a total of 1645 men and 992 women have participated for varying lengths of time. Within the protocol, 433 men have undergone 797 pelvic magnetic resonance imaging (MRI) scans. Planimetric analysis of contoured measurements from axial T2-weighted surface coil MRI scans has been completed in 413 of these 797 scans. The present study evaluated only the first analyzed scan for each individual. After excluding men diagnosed with prostate cancer or abnormal digital rectal examination, the study group consisted of 266 men. Among these 266 men, only 2 individuals had PSA levels greater than 10.0 ng/mL. Of these 2 men, 1 had not undergone biopsy and was therefore excluded from the study group; the other had biopsy negative for cancer and was included in the analysis. The study population therefore consisted of 265 men.

**DEMOGRAPHIC DESCRIPTION OF CANCER AND NONCANCER STUDY GROUPS**

Study group age is described in Table I. Median age was compared between study groups using the Wilcoxon rank sum test. In men with Stage T1c cancer, age was greater compared with men without cancer (P = 0.05) and men with Stage T2 cancer in the PSA era (P = 0.03) but not significantly different from men with Stage T2 cancer in the pre-PSA era. Among men with Stage T2 cancer, there was no difference in age comparing those in the pre-PSA era with those in the PSA era. In men without cancer, age was not significantly different from men with Stage T2 cancer in either era.

**PROSTATE WEIGHT DETERMINATION**

In the noncancer cohort, prostatic weight (in grams) was taken to be equivalent to MRI volume (in milliliters), as established previously. In the cancer population, the recorded weight of radical prostatectomy specimens was adjusted for the contribution of the seminal vesicles. Mean weight of the seminal vesicles was determined in a previous study to be 8.7 mL (4 to 20 mL) and this amount was subtracted from the whole specimen weight.

**STATISTICAL METHODS**

Prostate gland size was examined in each study group. Linear regression was used to examine the trend of prostate volume with age within each group. Multiple regression analysis was performed to compare groups, examining the effect of grouping, age, and interaction between grouping and age. The interaction between grouping and age was removed from the regression model when it was not statistically significant.

**RESULTS**

Prostate volumes in each study group are described in Table II. Linear regression showed that prostate volume increased with age in each group (Fig. 1 and Table III). Allowing for age, prostate volume was 18.7 mL (95% CI 13.5 to 24.0 mL) greater in men with Stage T1c disease compared to men with Stage T2 cancer detected in the pre-PSA era (P = 0.0001). The effect of age on this difference was not statistically significant (Fig. 1).

Comparing men with Stage T1c prostate cancer and men without cancer, a statistically significant difference in the relation between prostate volume
and age was observed (P = 0.0002) (shown in Fig. 1): men with Stage T1c prostate cancer had a statistically significantly greater increase in prostate volume with age. The difference in prostate volume between the two groups increased by 0.75 mL per year of age and became statistically significant above age 47 years based on 95% confidence intervals constructed about the regression lines for each group (Fig. 2).

In men with Stage T2 cancer treated during the PSA era, prostate volume was 5.2 mL greater than in men with Stage T2 cancer treated during the pre-PSA era (95% CI 1.4 to 9.0 mL, P = 0.007), and 2.8 mL greater than in men without cancer (CI 0.01 to 5.51 mL, P = 0.05). Allowing for the effect of age, prostate volume in men with Stage T2 cancer diagnosed during the pre-PSA era was not significantly different from men without cancer (Fig. 1). There was no statistically significant difference in the effect of age on prostate volume between these groups.

When the data analysis included the 1 man excluded from the noncancer group (who had not had recommended biopsy for elevated PSA), the differences in prostate volume between the cancer and noncancer groups were not statistically significantly changed (data not shown).

COMMENT

These data demonstrate that men with organ-confined cancer detected by PSA (Stage T1c) have larger prostates than men with palpable tumors (Stage T2) in both the pre-PSA era and PSA era. We also observed that prostate volume in men with PSA-detected, organ-confined cancer (Stage T1c) was significantly greater than in men without prostate cancer. Taking age into account, the difference in gland volume between men with PSA-detected cancer and men without cancer increased with age and was significant in men over 47 years of age.

Prostates in men with Stage T2 cancer treated in the PSA era were larger, compared with prostates in men with Stage T2 cancer in the pre-PSA era and men without cancer. During the pre-PSA era, prostate volume in men with organ-confined Stage T2 cancer was similar to the prostate volume in men without cancer. The increase in volume in the PSA era was small relative to that demonstrated in men with PSA-detected cancer.

Our study suggests that there may be a diagnostic bias due to PSA testing that selects men with larger prostates for cancer detection. We showed that men with PSA-detected cancers (Stage T1c) have significantly larger prostates than men with T2 cancers detected before and after the introduction of PSA testing, as well as men without cancer. Furthermore, men with palpable tumors in the pre-PSA era did not have significantly larger prostates than a noncancer population.

Thus, the greater prostate volume in men with Stage T1c cancer appears to be due to PSA testing rather than an etiological relationship between prostate cancer and BPH. PSA is a method of assessing the risk of prostate cancer, and is also a surrogate for prostate size. Thus, the prostates of men who have cancer detected because of PSA elevation would be larger than those in whom prostate cancer was detected without PSA testing. We are unaware of any other published studies indicating that prostate volume has increased since the introduction of PSA testing.

McNaughton et al.6 have suggested that the detection of cancer is serendipitous when nonpalpable cancer has a volume less than 1.0 mL or when cancer is detected outside the palpable abnormality that prompted biopsy. Serendipitous detection of organ-confined cancer by PSA elevation due to BPH would be expected to result in a greater lead time in men with larger prostates. Consistent with this hypothesis, D’Amico et al.7 reported greater disease-free survival and more favorable pathologic features in men with prostates larger than 75 mL. If the detection of cancer is serendipitous in some men because of the effect of BPH on serum PSA, this could contribute to the increased lead time observed in their study.

Our study has the inherent limitations of a retrospective analysis. Assumptions made in volumetric analysis and use of corrected weight of surgical specimens for estimating gland volume have been shown previously to be valid.4,5 By evaluating men undergoing radical prostatectomy for biopsy-

FIGURE 2. Comparison of prostate volume in men with PSA-detected organ-confined cancer (Stage T1c) at radical prostatectomy and men without clinical evidence of prostate cancer, showing trends with age predicted by linear regression and 95% confidence intervals.
proved cancer and including only patients with organ-confined disease, bias of gland volume due to differences in tumor stage was eliminated. The possibility of bias due to local patterns of referral cannot be excluded; however, we believe there to have been no bias in the selection of patients for surgery based on prostate size. Because patients with prostate cancer are diagnosed before referral, our study cannot analyze the relationship between PSA, prostate volume, and biopsy rate in the screened population.

Our data indicate that the increase in prostate volume since the introduction of PSA testing occurred predominantly in men with PSA-detected cancer and was independent of the age-related increase in volume observed in men without cancer. We believe therefore that our data indicate that this is a diagnostic bias associated with PSA testing in men with BPH.

**CONCLUSIONS**

This study indicates that the volume of prostate glands removed for early stage cancer has increased substantially since the introduction of PSA testing. The study suggests that men with organ-confined prostate cancer detected by PSA have larger prostates than men with cancer diagnosed by digital rectal examination before PSA testing and men without prostate cancer. We postulate that this discrepancy reflects a diagnostic bias due to the effect of BPH on serum PSA that results in the selection of men with larger prostates for biopsy.

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**REFERENCES**