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Natural history of benign prostatic enlargement: long-term longitudinal population-based study of prostate volume doubling times

Michael M. Lieber, Thomas Rhodes^{*}, Debra J. Jacobson[†], Michaela E. McGree[†], Cynthia J. Girman^{*}, Steven J. Jacobsen[‡], and Jennifer L. St. Sauver[§]

Department of Urology, Mayo Clinic, Rochester, MN

[†]Divisions of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN

[§]Divisions of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN

^{*}Merck Research Laboratories, North Wales, PA

[‡]Southern California Permanente Medical Group, Pasadena, CA, USA

Abstract

Objectives—To measure prostate volume doubling times (PVDTs) for a large sample of community men followed serially by transrectal ultrasonography (TRUS), and to determine whether specific characteristics are associated with a rapid PVDT.

Subjects and Methods—A subsample of 446 subjects from a larger cohort of American white men aged 40–79 years were evaluated biennially for a median (range) follow-up of 10 (3–14) years. Mixed-effects regression models were used to estimate prostate growth rates and PVDT for subjects with three or more or with five or more serial biennial TRUS PV measurements.

Results—The median (25–75th percentile) PVDT was 32.6 (24.6–44.0) years. The average annual increase in PV was 2.2%. The PVDT distribution was constant in men of all age groups studied ($r < 0.001$, $P = 0.99$). The factor most strongly associated with PVDT was baseline transition zone volume ($r = -0.55$, $P < 0.001$). Baseline total prostate-specific antigen (PSA) level, free PSA and total PV were also significantly inversely associated with PVDT ($r = -0.30$, -0.44 and -0.32 , respectively, all $P < 0.001$). Age, baseline anthropomorphic measurements, hormone levels and specific lifestyle characteristics were not significantly correlated with PVDT.

Conclusion—These data indicate that PVDT might be a useful future measure of benign prostatic growth. They provide a basis to forecast PV at 10, 20, or 30 years later, after one baseline TRUS measurement of prostate volume, and can be presented in a simple nomogram.

Keywords

benign prostate enlargement; prostate growth rates

Correspondence: Jennifer L. St. Sauver, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. stsauver.jennifer@mayo.edu.

CONFLICT OF INTEREST

None declared.

Introduction

As long as there have been urologists, prostate size estimated by a DRE and cystoscopy have been used to determine the appropriate surgical technique to treat the symptoms and complications of benign prostatic enlargement (BPE). For the past decade, prostate volume (PV) estimated by DRE, PSA level, or TRUS has been used to identify those men who might benefit from medical therapy for BPE using finasteride or dutasteride. Despite the central importance of prostate size in treating symptomatic middle-aged and elderly men, knowledge of the natural dynamics of BPE is limited. Autopsy [1] and newer TRUS cross-sectional population-based studies of PV are now available from several continents [2–5]. These studies provide a general view of the average rate of prostate growth with age. Bosch *et al.* [2] used cross-sectional data to estimate a 2% annual increase in PV among men aged 55–74 years. From a short-term longitudinal study we previously reported a prostate growth rate of 1.6% per year among men residing in Olmsted County, MN, USA, after 5 years of follow-up [3]. However, it is still unclear which men are at increased risk of rapid prostate growth or which factors are associated with prostate growth.

As PV is a primary basis for many urological clinical decisions, we propose the measure of PV doubling time (PVDT) as a way of helping clinicians to determine whether individual patients have slowly or rapidly growing prostates, and to help clinicians convey quantitatively the future risk of prostatic enlargement to their patients. In the present study we update previous results with long-term data and define three distinct groups of men: those with rapidly growing prostates, those with slowly growing prostates, and those with intermediate prostate growth rates, and examine some factors that might be associated with rapid or slow prostate growth.

Subjects and Methods

Many of the details of the present study were reported previously [4,5]. Briefly, a randomly sampled, population-based group of white men aged 40–79 years and residing in Olmsted County, MN, USA in 1990 was identified through the Rochester Epidemiology Project [6]. These men have predominantly German, Norwegian, Irish and English ethnic backgrounds [6]. Men who had a history of prostate or bladder surgery, urethral surgery or stricture, or medical or other neurological condition that could affect normal urinary function were excluded. After excluding men with pre-existing conditions, 3874 men were asked to join the study and 2115 agreed to participate (55%). A comparison of medical records of participants and non-participants indicated few differences except for a history of urological diagnosis, with responders having a slightly greater prevalence of diagnosis of kidney stones, UTIs or BPH [7].

Participants completed a previously validated baseline questionnaire that assessed LUTS severity from questions similar to the AUA Symptom Index (AUASI), comorbidities and biosocial risk factors. All participants also voided into a portable uroflowmeter to measure maximum urinary flow rates (Q_{max}). A 25% random subsample was invited to participate in a detailed clinical urological examination, including TRUS imaging to determine PV, and a measurement of serum PSA level. In all, 475 of 537 (88%) men agreed to participate in this more intensive examination.

The cohort was actively followed biennially for 14 years using a similar protocol to the initial examination. Anthropometric and androgen measures were added during the third and seventh visits, respectively. During the second and third round of visits, men who did not participate in the follow-up were replaced by men randomly selected from the community, after being screened for the exclusion criteria used at baseline (332 men). Of the replacement men, 158 were added to the clinic subset; since then the study has been maintained as a closed cohort.

Treatment for symptoms associated with BPH or diagnosis of prostate cancer was evaluated during the follow-up. Measurements (of 115 men) made after the date of initiation of treatment for a diagnosis of BPH or prostate cancer were excluded from the analyses. The study was reviewed and approved by the Institutional Review Boards of Mayo Clinic and Olmsted Medical Center.

The methods for measuring each factor were reported previously. Briefly, prostate size was measured by TRUS (type 8551, Bruel & Kjaer, Denmark; 7.0 MHz endosonic multiplane transducer) [3,8]. LUTS were measured by a previously validated questionnaire with questions similar to the AUASI [9,10]. Serum PSA levels were determined with the Tandem-R PSA assay (Hybritech Inc, San Diego, CA, USA). The serum samples were obtained before any prostatic manipulations, including the DRE or TRUS [11]. $Q_{\max}$ was measured electronically using a urometer (Dantec 1000, Dantec Medical, Santa Clara, CA, USA) [12]. Methods to quantify serum hormone levels and anthropomorphic measures were described previously [13].

A linear mixed-effects regression model was used to estimate longitudinal changes in PV with time [3]. Because PV values follow a log-normal distribution, regression analyses were based on log-transformed measurements. The modelled estimates of annual percentage change in PV were transformed to PVDTs, calculated as $(\text{natural log}(2)/\% \text{ change/year}) \times 100$. 'Spaghetti' plots and histograms were used to describe the distributions of the raw data, model estimates and PVDT. A nomogram depicting the predicted distribution of PVs at 10, 20 and 30 years after the initial study visit was developed, based on the mixed model results, highlighting the median, 25th and 75th percentiles of the distribution. Men were classified as having slowly growing (upper 20th), intermediate growing (middle), and rapidly growing (lower 20th) prostates, based on percentiles of the PVDT distribution. Baseline characteristics were compared across the level of PVDT using the Kruskal–Wallis and Mantel–Haenszel tests for continuous and categorical variables, respectively. To account for multiple comparisons, a $P < 0.005$ was considered to indicate statistical significance.

Results

At least three serial biennial TRUS measures of PV were available for 446 (72%) of the men who were clinically examined. The results of individual serial PV measurements are depicted graphically in Fig. 1A, while the individual modelled smoothed slopes are shown in Fig. 1C. The median (25th and 75th percentile) PVDT for this group of randomly selected white men was 32.6 (24.6, 44.0) years. The overall distribution of PVDTs is shown in Fig. 2; the results were virtually identical when 291 men with at least five serial biennial TRUS measures of PV were analysed (Fig. 1B,D). The average annual rate of PV increase was 2.2% (Fig. 3). We defined men with the most rapidly growing prostates as having the lowest 20th percentile PVDT (red, Fig. 1A–D), and men with the highest 20th percentile PVDT as having the slowest growing prostates (blue, Fig. 1A–D). Men with the most rapidly growing prostates had a median (25th and 75th percentile) PVDT of 19.3 (16.8, 20.9), while those with the slowest growing prostates had a median PVDT of 73.8 (57.7, 135.0) years.

PVDT was not associated with participant age (Figs 3,4A), but it was associated with baseline total PV ($r = -0.32$, $P < 0.001$; Fig. 4B), baseline PSA level ($r = -0.30$, $P < 0.001$), baseline free PSA level ($r = -0.44$, $P < 0.001$), and baseline transition zone volume (TZV, $r = -0.55$, $P < 0.001$). We examined other characteristics of men with slow-, intermediate- and rapidly-growing prostates to determine if specific baseline characteristics were associated with a rapid PVDT, and again found that higher baseline PVs, PSA levels, free PSA levels, and TZVs were significantly associated with a rapid PVDT (Table 1). Specifically, men with the fastest PVDT had the highest baseline PSA and free PSA levels, and the largest baseline TZVs (Table 1).

Baseline anthropometric characteristics were not significantly associated with PVDT after adjusting for multiple comparisons; however, taller, heavier men were more likely to have faster PVDTs (Table 1). Finally, baseline hormone levels and baseline lifestyle characteristics were also not significantly associated with PVDT, although men who had three or four drinks per week were more likely to be in the slowest PVDT group than men who had fewer than three or four drinks/week (Table 1).

We developed a nomogram for predicting the PV at 10, 20 and 30 years after a baseline TRUS PV measurement for men in this population. The median (25th, 75th percentile) predicted PVs are shown in Fig. 5.

Discussion

The present population had a median PVDT of 32.6 years and an average annual PV change of 2.2%. We defined men in the upper 20th percentile of PVDTs as having slowly growing prostates, with a median PVDT of 73.8 years. If a man in this latter group started at age 40 years with a 20-mL prostate, it seems evident that subsequent treatment for BPE itself would be clinically unlikely during his current life-expectancy. Conversely, we defined men in the lower 20th percentile of PVDTs as having rapidly growing prostates, with a median PVDT of 19.3 years. We expect that men in this group will be of considerable interest to urologists, as they are the population substrate which yields patients with prostates of >60–100 g, requiring surgery for BPE symptoms and complications in future decades; men in this PVDT stratum certainly might benefit from prophylactic medical treatment for BPE.

Also, as shown previously for this population and confirmed in detail here [3], PVDT is not associated with age. Therefore, although age is associated with increasing PVs overall (Figs 3,4A), age does not appear to be associated with the specific *rate* at which PV increases. Using this information, along with the data suggesting that other variables are not strongly associated with PVDT, we developed a nomogram to forecast PV after 10, 20 and 30 years (Fig. 5). Based on these results, e.g. both a typical 50-year-old man and a typical 65-year-old man with 40-mL prostates could be expected to have PVs of ≈ 50 mL after 10 years and ≈ 60 mL after 20 years.

It is currently difficult to predict which younger men will be most likely to have rapidly growing prostates. In this study, we found that anthropometric characteristics, hormone levels and some lifestyle characteristics were not strongly associated with PVDT. Instead, the factors most strongly associated with rapid PVDTs (<20 years) were baseline PV, PSA level, free PSA level, and TZV, with baseline TZV being most strongly correlated with PVDT. These results are consistent with previous studies which have suggested that PSA levels are a useful surrogate for PV, and that TZV might be a more useful predictor of prostate growth than total PV [14]. We previously found that increases in TZV are not strongly correlated with increases in LUTS or decreased urinary flow rates [15]. However, the present study indicates that baseline TZV in particular might be a useful predictor of PVDT.

TRUS-estimated PVs have been measured recently for a large sample of Dutch men living in the municipality of Krimpen [2]. In this group of randomly selected community men, PVs were measured in 1410 men aged 55–74 years. The baseline distributions of PVs and the range (25th and 75th percentiles) for these Dutch men are quite similar to the baseline PVs measured in the present group from Olmsted County (white men with predominantly German, Norwegian, Irish and English ethnic backgrounds) [16]. This suggests that the PV measurements recorded here might be representative of a large group of community men living in northern Europe, or with ancestors from there. By contrast, the TRUS PVs measured for community-based men living in villages of Gujarat, India [17], in Arab men living in Kuwait and Oman [18] and

Japanese men living in the northern island of Hokkaido [14] are very different. On average these men have small and very slowly enlarging prostates. Their PVDTs, estimated from published TRUS baseline PVs, are similar to those seen for the 20% of men in the white Olmsted County group reported here, whose PVDTs are >50 years. Given the variability of prostate growth rate observed locally and globally, it is possible that distinct identifiable genetic [19,20] and/or environmental factors for both individuals and populations might play a role in the rate of development of BPE.

The present study has several potential limitations which might limit the utility of the results. First, the study comprised a homogeneous white population aged 40–79 years at baseline, which might limit the general applicability to other populations or age groups. Second, we have followed these men for <20 years; therefore, our projected increases in PV at 20 and 30 years might not be completely accurate if PVDTs suddenly tend to level off (or decline) in these later periods. However, >10 years of follow-up among men over a 40-year age range did not suggest that such a phenomenon is likely to occur. The strengths of our study include the long-term longitudinal measurements on a randomly selected population of men in Olmsted County using a standardized approach to TRUS over time.

Taken together, our results suggest that baseline PV, PSA and free PSA levels, and TZV are useful predictors of future prostate growth. Also, the nomogram presented here might be useful to clinicians when discussing the likelihood of future prostate growth and possible need for treatment with patients, and in designing future clinical research studies of BPE.

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References

1. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol* 1984;132:474–9. [PubMed: 6206240]
2. Bosch JL, Hop WC, Niemer AQ, Bangma CH, Kirkels WJ, Schroder FH. Parameters of prostate volume and shape in a community based population of men 55–74 years old. *J Urol* 1994;152:1501–5. [PubMed: 7523706]
3. Rhodes T, Girman CJ, Jacobsen SJ, Roberts RO, Guess HA, Lieber MM. Longitudinal prostate growth rates during 5 years in randomly selected community men 40–79 years old. *J Urol* 1999;161:1174–9. [PubMed: 10081864]
4. Jacobsen SJ, Girman CJ, Guess HA, et al. Natural history of prostatism: factors associated with discordance between frequency and bother of urinary symptoms. *Urology* 1993;42:663–71. [PubMed: 7504848]
5. Jacobsen SJ, Girman CJ, Guess HA, et al. Do prostate size and urinary flow rates predict health care-seeking behavior for urinary symptoms in men? *Urology* 1995;45:64–9. [PubMed: 7529448]
6. Melton LJ. History of the Rochester Epidemiology Project. *Mayo Clin Proc* 1996;71:266–74. [PubMed: 8594285]
7. Panser LA, Chute CG, Guess HA, et al. The natural history of prostatism: the effects of non-response bias. *Int J Epidemiol* 1994;23:1198–205. [PubMed: 7536718]
8. Jacobsen SJ, Jacobson DJ, Girman CJ, et al. Natural history of prostatism: risk factors for acute urinary retention. *J Urol* 1997;158:481–7. [PubMed: 9224329]
9. Jacobsen SJ, Girman CJ, Guess HA, Oesterling JE, Lieber MM. New diagnostic and treatment guidelines for benign prostatic hyperplasia. Potential impact in the United States. *Arch Intern Med* 1995;155:477–81. [PubMed: 7532392]

10. Epstein RS, Deverka PA, Chute CG, et al. Validation of a new quality of life questionnaire for benign prostatic hyperplasia. *J Clin Epidemiol* 1992;45:1431–45. [PubMed: 1281223]
11. Roberts RO, Jacobson DJ, Girman CJ, et al. Insulin-like growth factor I, insulin-like growth factor binding protein 3, and urologic measures of benign prostatic hyperplasia. *Am J Epidemiol* 2003;157:784–91. [PubMed: 12727672]
12. Roberts RO, Jacobsen SJ, Jacobson DJ, Rhodes T, Girman CJ, Lieber MM. Longitudinal changes in peak urinary flow rates in a community based cohort. *J Urol* 2000;163:107–13. [PubMed: 10604326]
13. Burke JP, Rhodes T, Jacobson DJ, et al. Association of anthropometric measures with the presence and progression of benign prostatic hyperplasia. *Am J Epidemiol* 2006;164:41–6. [PubMed: 16611664]
14. Gupta A, Aragaki C, Gotoh M, et al. Relationship between prostate specific antigen and indexes of prostate volume in Japanese men. *J Urol* 2005;173:503–6. [PubMed: 15643229]
15. St Sauver JL, Jacobson DJ, Girman CJ, et al. Correlations between longitudinal changes in transitional zone volume and measures of benign prostatic hyperplasia in a population-based cohort. *Eur Urol* 2006;50:105–11. [PubMed: 16466847]
16. Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. *JAMA* 1993;270:860–4. [PubMed: 7688054]
17. Ganpule AP, Desai MR, Desai MM, Wani KD, Bapat SD. Natural history of lower urinary tract symptoms: preliminary report from a community-based Indian study. *BJU Int* 2004;94:332–4. [PubMed: 15291862]
18. Kehinde EO, Mojiminiyi OA, Sheikh M, et al. Age-specific reference levels of serum prostate-specific antigen and prostate volume in healthy Arab men. *BJU Int* 2005;96:308–12. [PubMed: 16042719]
19. Sutter NB, Bustamante CD, Chase K, et al. A single IGF1 allele is a major determinant of small size in dogs. *Science* 2007;316:112–5. [PubMed: 17412960]
20. McEvoy B, Richards M, Forster P, Bradley DG. The Longue Duree of genetic ancestry: multiple genetic marker systems and Celtic origins on the Atlantic facade of Europe. *Am J Hum Genet* 2004;75:693–702. [PubMed: 15309688]

Abbreviations

PV(DT)	prostate volume (doubling time)
TZV	transition zone volume
BPE	benign prostatic enlargement
AUASI	AUA Symptom Index
Q _{max}	peak urinary flow rate
IQR	interquartile range

Fig. 1.

Observed PVs: **A**, for 446 men with three or more serial biennial TRUS measurements of PV. Data from men with PVDTs in the fastest growing 20th percentile are shown in red, from the slowest growing 20th percentile in blue, and the intermediate growth rate prostates in black; **B**, for 291 men with five or more serial biennial TRUS measurements of PV. Modelled PVs for: **C**, 446 men with three or more measurements of PV; and **D**, 291 men with five or more measurements of PV.

Fig. 2. The distribution of PVDTs. (Twelve data points for men with PVDTs >300 years are not shown.)

Fig. 3. The annual percentage change in PV by baseline age

Fig. 4. PVDt by baseline: A, age, raw data; and B, by baseline PV, raw data

Fig. 5. A nomogram predicting PV in 10, 20 or 30 years by baseline PV

Table 1
Difference in variables among three groups of PVDT

Baseline characteristics	PVDT group			<i>P</i>
	Slow	Intermediate	Fast	
No. of men	89	268	89	
PVDT category, years	>48	23–48	<23	
Mean (SD) age, years	54.8 (10.7)	53.5 (10.0)	54.2 (9.9)	0.51
Median (25th, 75th percentile):				
Urological				
AUASI	5.0 (3.0, 8.0)	5.0 (2.0, 8.3)	6.0 (2.5, 8.0)	0.44
PSA, ng/mL	0.7 (0.4, 1.0)	0.9 (0.6, 1.4)	1.1 (0.8, 1.8)	<0.001
Free PSA, ng/mL	0.2 (0.1, 0.2)	0.3 (0.2, 0.4)	0.4 (0.3, 0.7)	<0.001
Q _{max} , mL/s	21.9 (16.1, 27.5)	20.6 (15.2, 26.5)	19.9 (14.8, 25.7)	0.43
Total PV, mL	22.5 (18.9, 28.0)	24.6 (20.0, 30.9)	31.0 (25.6, 40.0)	<0.001
TZV, mL	7.8 (5.7, 10.8)	11.0 (8.2, 14.9)	20.5 (13.4, 29.9)	<0.001
Anthropometric				
BMI, kg/m ²	27.4 (25.2, 29.7)	27.8 (25.6, 30.7)	28.9 (26.4, 31.3)	0.08
Height, cm	176.0 (172.0, 179.0)	177.0 (172.0, 181.0)	178.0 (174.0, 184.0)	0.05
Weight, kg	85.3 (76.8, 91.8)	87.6 (78.3, 98.0)	91.7 (79.9, 101.0)	0.01
Hips, cm	95.0 (89.0, 100.0)	96.5 (91.0, 103.5)	99.0 (91.0, 105.0)	0.06
Waist/hip ratio	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	0.63
Suprailiac, mm	21.0 (15.0, 26.0)	22.0 (17.0, 27.0)	24.0 (18.0, 30.0)	0.11
Subscapular, mm	22.0 (16.0, 29.0)	23.0 (17.0, 30.0)	25.0 (17.0, 32.0)	0.50
Tricep, mm	12.0 (9.0, 16.0)	12.0 (9.0, 16.0)	12.0 (9.0, 16.0)	0.83
Neck, cm	39.5 (37.5, 41.0)	39.5 (37.5, 41.5)	40.0 (38.0, 41.5)	0.36
Hormone levels				
Testosterone, ng/dL	375.0 (264.0, 475.0)	330.5 (266.0, 453.5)	359.0 (263.0, 491.0)	0.43
Bioavailable testosterone, ng/dL	52.1 (38.7, 71.0)	50.4 (38.7, 70.4)	49.6 (37.7, 75.6)	0.96
Oestradiol, pg/mL	21.7 (17.3, 27.8)	22.9 (18.0, 27.6)	22.5 (19.3, 29.7)	0.40
Lifestyle, <i>n</i> (%)				
Ever smoke	55 (61.8)	170 (63.4)	58 (65.2)	0.64
Regular activity	50 (56.2)	188 (70.1)	62 (69.7)	0.09
Alcohol intake ≥3–4 times/week	33 (37.1)	55 (20.5)	20 (22.5)	0.02
Alcohol intake 1–2 times/week	16 (18.0)	62 (23.1)	20 (22.5)	0.56
Diabetes	3 (3.4)	11 (4.1)	4 (4.5)	0.70
Hypertension	14 (15.7)	53 (19.8)	18 (20.2)	0.47