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Pathologic Characteristics of Cancers Detected in the Prostate Cancer Prevention Trial: Implications for Prostate Cancer Detection and Chemoprevention

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Abstract The Prostate Cancer Prevention Trial (PCPT) showed a risk of prostate cancer at prostate-specific antigen (PSA) <4.0 ng/mL and that prostate cancer risk is reduced by finasteride. A major concern about early detection by PSA and prevention by finasteride is that they may involve biologically inconsequential tumors. We reviewed the pathologic characteristics of prostate biopsies from men in the placebo and finasteride groups of the PCPT. We examined tumor pathology characteristics stratified by level of PSA for men in the placebo group who underwent radical prostatectomy. Seventy-five percent of all cancers and 62% of Gleason score ≤6 cancers in the PCPT met the biopsy criteria for clinically significant tumors. Surrogate measures for tumor volume (number of cores positive, percent cores positive, linear extent, and bilaterality) and risk of perineural invasion were lower in men who received finasteride. The PSA-associated risks of insignificant cancer were 51.7% (PSA, 0-1.0 ng/mL), 33.7% (1.1-2.5 ng/mL), 17.8% (2.6-4.0 ng/mL), and 11.7% (4.1-10 ng/mL). Conversely, the risks of high-grade (Gleason score ≥7) tumors for the same PSA strata were 15.6%, 37.9%, 49.1%, and 52.4%, respectively. These data highlight the dilemma of PSA when used for screening: Lower cutoff levels increase detection of insignificant disease, but cure is more likely, whereas higher cutoff levels make detection of significant cancer more likely, but cure is less likely. Therefore, the effectiveness of finasteride in preventing prostate cancer, including Gleason score ≤6 cancer, with meaningful rates of significant disease in the PCPT suggests that cutoff values for PSA screening should be individualized and that men undergoing screening should be informed of the opportunity to reduce their risk of disease with finasteride.

The adoption of widespread prostate cancer screening with prostate-specific antigen (PSA) has dramatically increased the number of prostate cancers diagnosed in the United States (1). Although most cases of prostate cancer in the United States are detected by an elevated PSA, this marker is not cancer specific but also marks benign prostate conditions including nodular hyperplasia, inflammation, and trauma (2, 3). In the late 1980s, PSA began to be considered a dichotomous marker of disease, with the value 4.0 ng/mL as the threshold for a prostate biopsy recommendation. It was recognized in the late 1990s that men (especially at earlier ages) with PSA levels from 2.5 to 4.0 ng/mL had a similar prostate cancer risk to that of men with PSAs >4.0 ng/mL (4). In a 2004 analysis of 2,950 men of the placebo arm of the Prostate Cancer Prevention Trial (PCPT), who underwent prostate biopsies regardless of PSA and digital rectal examination (DRE) findings, we showed that any level of PSA denoted a risk of prostate cancer, even high-grade cancer, and that the risk was proportional to PSA level (5). These analyses clearly showed that dichotomous PSA thresholds represent a trade-off between cancer detection (PSA sensitivity) and differentiation of cancer from noncancerous conditions (PSA specificity; ref. 6).

A serious concern about detection with a lower PSA value is an increased likelihood of detecting indolent, clinically inconsequential tumors. The current lifetime risk of a prostate cancer diagnosis is 17%, whereas the risk of prostate cancer death is only 3% (7). Evidence suggests that tumor volume and grade are related to PSA levels and that clinically unimportant

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tumors are more commonly detected at lower levels of PSA (8), suggesting that the threshold value of PSA for prompting a prostate biopsy should not be lowered (9).

The most accepted pathologic definition of a clinically insignificant tumor (not requiring treatment) is an organ-confined, low-volume, and low-Gleason score tumor (10). Several studies have produced conflicting conclusions about tumor characteristics present in needle biopsy specimens that would identify insignificant disease (11, 12). The following characteristics proposed by Epstein may be the most commonly cited criteria for insignificant disease: a combination of clinical factors (stage T_{1c} and PSA density <0.15 ng/mL/g), grade of tumor on biopsy (Gleason score ≤6, no Gleason pattern 4 or 5), and extent of tumor on biopsy [<3 cores with tumor (no core with >50% tumor) or <3 mm cancer present in only 1 core; ref. 10]. The present study explored the relationship between PSA at diagnosis of prostate cancer and pathologic tumor features at biopsy and radical prostatectomy in relation to the Epstein criteria. We also comprehensively reassessed the effect of finasteride on prostate cancer risk in the PCPT.

Materials and Methods

In the PCPT, subjects with PSA levels of ≤3 ng/mL and normal DRE were randomized to receive either 5 mg/d of finasteride or placebo (13). All men were followed with annual DRE and PSA measurement. If DRE was abnormal or if PSA exceeded 4.0 ng/mL in the placebo group, biopsy was recommended. In the finasteride group, biopsy was recommended if DRE was abnormal or if annual PSA exceeded a threshold value set to prompt a similar number of biopsy recommendations as those in the placebo group. Biopsies for abnormal DRE or PSA were referred to as a "for cause" biopsy. To minimize potential bias from this adjustment, an end-of-study biopsy after 7 years of participation was recommended for all cancer-free subjects. All biopsies were recommended to have a minimum of six biopsy cores. Prostate volume at biopsy was measured by transrectal ultrasound.

Prostate cancer diagnosis was established by agreement between pathologists at the PCPT Core Laboratory and the participant's study site. Disagreements between these two pathologists were resolved by a consensus diagnosis involving an arbiter pathologist. Tumor grade was provided by the Core Pathology Laboratory pathologist (M.S.L.) who was blinded to the participant's study group.

The Core Pathology Laboratory reviewed 94.3% of all PCPT cancer biopsies. The final biopsy Gleason score included the biopsy core with the highest tumor grade. Prognostic features associated with tumor extent and aggressiveness were recorded by the Core Pathology Laboratory for needle biopsies and included the total number of biopsy cores, number and percent of cores positive for cancer, greatest linear extent of cancer (in millimeters) for each core (measured by an optical reticule), aggregate linear extent (in millimeters) of cancer within all cores, percent of core involvement, bilateral involvement (if known), and perineural invasion.

Treatment for prostate cancer diagnosed in the PCPT was not specified in the study protocol. In known cases of radical prostatectomy, pathologic materials were requested, regardless of grade, and every prostatectomy received by the Core Pathology Laboratory was analyzed by one pathologist (M.S.L.) blinded to treatment assignment. Tumor Gleason score in these specimens was based on the predominant and secondary tumor pattern. Tumors were staged according to the 1997 American Joint Committee on Cancer guidelines and were considered margin positive if tumor was present at surface ink (14).

To determine the risk of potential diagnosis of an indolent tumor, biopsies were categorized as "potentially insignificant" if they met all of the following criteria (criteria 1): (*a*) stage T_{1c}, (*b*) PSA density calculated at ultrasound of <0.15 ng/mL/g, (*c*) no evidence of Gleason pattern 4 or 5 tumor (Gleason score ≤6), and (*d*) tumor limited to <3 cores with no more than 50% involvement of any core (10, 15). For subjects on finasteride, PSA used for calculating PSA density used the adjusted value: observed PSA multiplied by 1.0 (if not currently on active study drug), by 2.0 (years 1 through 3), or by 2.3 (year 4 onward). An alternative set of criteria (criteria 2) were also applied to take into account the millimeter extent of tumor as suggested by some reports (10, 12). Using criteria 2, biopsies were considered potentially insignificant if they met conditions (*a*) to (*c*) of criteria set 1 and tumor was limited to <3 mm involving 1 core (10, 12). Adverse features at prostatectomy were defined as Gleason score ≥7, positive surgical margin, or non–organ-confined disease. To examine the relationship of risk of indolent disease and likelihood of cure and their relationship with PSA at diagnosis, we examined categories of PSA values in ranges of 0 to 1.0, 1.1 to 2.5, 2.6 to 4.0, 4.1 to 10.0, and >10.0 ng/mL.

Comparisons between the finasteride and placebo groups used the following tests: χ^2 tests for comparing the pathologic features of prostatic carcinomas and patient characteristics at prostatectomy, and Kruskal-Wallis test and χ^2 tests (as appropriate) for comparing the biopsy characteristics of tumors.

Results

Gleason score and measures of extent of tumor on biopsy were compared between finasteride (671) and placebo (955) participants (1,626 total participants; Table 1). Table 1 does not include 391 participants (152 finasteride, 239 placebo) for whom detailed pathologic data were not available. Grade was stratified into three tiers: Gleason score ≤6, Gleason score 7, and Gleason score ≥8. In all three tiers, mean values for the number and percent of positive cores and greatest and aggregate linear tumor extent were greater in the placebo than in the finasteride group. Mean number of cores positive was significantly greater in the placebo group (versus finasteride) for the Gleason score ≤6 stratum (1.55 versus 1.40, $P = 0.024$); mean percent of cores positive was greater in the placebo group for tumors of Gleason score 7 (36.7% versus 31.2%, $P = 0.009$). Tumors were also more often bilateral in the placebo group than in the finasteride group for tumors of all Gleason scores, but this achieved significance only among tumors of Gleason score ≥8 (44.6% placebo versus 28.6% finasteride, $P = 0.047$). Perineural invasion was more common in the placebo group for all Gleason scores but this was not significant. Median prostate volume was significantly lower in the finasteride than in the placebo group across all tumor grades ($P < 0.001$). Within each treatment group, median PSA density (ng/mL/g; calculated by ultrasound volume) increased with higher grade [placebo: 0.06 Gleason ≤6 versus 0.09 Gleason 7 versus 0.12 Gleason ≥8 (nonparametric Pearson correlation, 0.26; $P < 0.001$); finasteride: 0.07 Gleason ≤6 versus 0.13 Gleason 7 versus 0.19 Gleason ≥8 (nonparametric Pearson correlation, 0.34; $P < 0.001$)]. Median PSA density was higher in the finasteride group compared with the placebo group across all tumor grades ($P < 0.001$, Gleason ≤6 and 7; $P = 0.002$, Gleason ≥8). The number and percent of tumors within each grade tier that could be considered insignificant were determined based on two sets of criteria. For criteria set 1 (T_{1c}, PSA density <0.15 ng/mL/g, Gleason score ≤6,

Table 1. Pathologic and clinical characteristics of tumors diagnosed in the PCPT stratified by grade and treatment group

Characteristic	Gleason ≤6				Gleason 7				Gleason ≥8			
	Finasteride (*n* = 389)		Placebo (*n* = 711)		Finasteride (*n* = 191)		Placebo (*n* = 187)		Finasteride (*n* = 91)		Placebo (*n* = 57)	
	Mean (SD)	Med (10-90%)	Mean (SD)	Med (10-90%)	Mean (SD)	Med (10-90%)	Mean (SD)	Med (10-90%)	Mean (SD)	Med (10-90%)	Mean (SD)	Med (10-90%)
No. cores positive*	1.40 (0.71)	1 (1-2)	1.55 (0.93)	1 (1-3)	1.99 (1.03)	2 (1-3)	2.36 (1.53)	2 (1-4)	2.59 (1.77)	2 (1-4.5)	2.98 (1.91)	3 (1-5)
Percent cores positive†	22.1 (11.3)	16.7 (12.5-37.5)	23.9 (13.7)	16.7 (12.5-41.4)	31.2 (16.4)	33.3 (14.3-50.0)	36.7 (20.3)	33.3 (16.7-66.7)	38.4 (20.5)	33.3 (16.7-61.1)	43.3 (23.8)	45.0 (16.7-80.0)
Greatest linear extent (mm)	1.76 (1.53)	1.30 (0.50-3.50)	1.95 (1.75)	1.30 (0.50-4.40)	4.13 (3.04)	3.20 (1.00-8.40)	4.56 (3.16)	4.00 (1.30-9.00)	4.97 (2.95)	4.50 (1.50-9.00)	5.45 (3.62)	4.50 (1.50-10.10)
Aggregate linear extent (mm)	2.31 (2.68)	1.40 (0.50-5.00)	2.72 (3.20)	1.60 (0.50-6.40)	6.66 (6.16)	4.50 (1.00-14.90)	8.18 (8.07)	5.50 (1.50-18.50)	9.61 (10.88)	6.20 (1.50-21.00)	12.37 (13.52)	7.25 (2.00-36.00)
Bilateral (%)‡	11.1		14.2		20.0		26.3		28.6		44.6	
Perineural invasion (%)	4.4		5.3		16.3		21.0		9.9		17.9	
Median prostate volume (cm^3)§	23.8		32.7		25.1		33.5		23.8		38.8	
Median adjusted PSA (ng/mL)	1.80		2.00		3.40		3.70		4.80		4.60	
Median PSA density (ng/mL/g)‖	0.07		0.06		0.13		0.09		0.19		0.12	
Median total biopsy cores	6		6		6		6		6		6	
Insignificant cancer (%; criteria 1)¶	36.0		38.4		0		0		0		0	
Insignificant cancer (%; criteria 2)**	38.5		42.2		0		0		0		0	

*Comparison of number of cores positive significant for Gleason ≤6 ($P = 0.024$, Kruskal-Wallis test).

†Comparison of percent cores positive significant for Gleason 7 ($P = 0.009$, Kruskal-Wallis test).

‡Comparison of percent bilateral significant for Gleason 8-10 ($P = 0.047$, χ^2 test).

§Comparison of median prostate volume significant in all subgroups ($P < 0.001$ for all three, Kruskal-Wallis test).

‖Comparison of median PSA density significant in all subgroups [$P < 0.001$ (Gleason 6), $P < 0.001$ (Gleason 7), and $P = 0.002$ (Gleason 8-10), Kruskal-Wallis test].

¶Stage T_{1c} + PSA density <0.15 ng/mL/g + Gleason score ≤6 (no pattern 4 or 5) + tumor limited to <3 cores + no core with >50% involvement.

**Stage T_{1c} + PSA density <0.15 ng/mL/g + Gleason score ≤6 (no pattern 4 or 5) + tumor limited to <3 mm on 1 core.

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Table 2. Relationship between PSA at diagnosis and features related to tumor significance in biopsy specimens (placebo group only)

	PSA (ng/mL)				
	0-1.0	1.1-2.5	2.6-4.0	4.1-10.0	>10
No. subjects	161	352	192	238	12
Gleason score	5.98 (0.54)	6.08 (0.61)	6.43 (0.95)	6.55 (0.94)	6.92 (1.16)
	6	6	6	6	7
No. cores positive	1.32 (0.63)	1.61 (0.90)	2.02 (1.44)	2.17 (1.56)	2.00 (1.13)
	1	1	2	2	2
Percent cores positive	20.0 (10.0)	25.7 (14.7)	31.2 (19.2)	32.1 (20.0)	32.5 (19.0)
	16.7	16.7	25.0	27.3	26.7
Greatest linear extent (mm)	1.63 (1.48)	2.24 (2.04)	3.09 (2.64)	3.55 (3.23)	3.91 (3.32)
	1.10	1.60	2.25	2.60	3.70
Aggregate linear extent (mm)	2.06 (2.39)	3.29 (3.97)	5.37 (7.39)	6.54 (8.71)	6.25 (7.32)
	1.15	1.80	3.00	3.40	5.05
Bilateral (%)	8.7	15.6	21.5	26.0	33.3
Perineural invasion (%)	1.2	8.3	13.4	12.5	0.0
Median prostate volume (cm^3)	27.2	31.9	36.1	40.0	31.9
Median PSA density (ng/mL/g)	0.03	0.05	0.09	0.12	0.48
Insignificant cancer (%; criteria 1)*	51.7	33.7	17.8	11.7	0.0
Insignificant cancer (%; criteria 2)†	55.4	38.8	17.2	13.5	0.0

NOTE: Numbers represent mean, (SD), and median from top to bottom unless otherwise noted.

*Stage T_{1c} + PSA density <0.15 ng/mL/g + Gleason score ≤6 (no pattern 4 or 5) + tumor limited to <3 cores + no core with >50% involvement.

†Stage T_{1c} + PSA density <0.15 ng/mL/g + Gleason score ≤6 (no pattern 4 or 5) + tumor limited to <3 mm on 1 core.

cancer on <3 cores with no more than 50% involvement of any core), 37.5% of Gleason score ≤6 tumors met these criteria (38.4% placebo, 36.0% finasteride). Overall, 24.5% of tumors in Table 1 (27.7% placebo, 19.9% finasteride) met the criteria for potentially insignificant using criteria set 1. For criteria set 2 (T_{1c}, PSA density <0.15 ng/mL/g, Gleason score ≤6, cancer <3 mm on 1 core), 40.9% of Gleason score ≤6 tumors (42.2% placebo, 38.5% finasteride) and 26.7% of tumors overall (30.5% placebo, 21.4% finasteride) could be considered potentially insignificant. If tumors in which significance could not be assessed were uniformly classified as insignificant, the rates of insignificant tumors using criteria 1 and 2 would be 29.9% and 31.6%, respectively.

We compared the pathologic features of tumors at biopsy, prostate volume, and PSA density with serum PSA level at the time of biopsy within the placebo group tumors (Tables 2 and 3). Percent cores positive, greatest and aggregate linear extent of tumor on biopsy, and bilaterality were proportional to serum PSA level at the time of diagnosis in accordance with the relationship between these features and tumor volume. To assess this relationship, nonparametric Pearson product-moment correlations were calculated by assigning ranks to values for linear variables (Table 3); ties were broken arbitrarily. True dichotomous variables [bilaterality, perineural invasion, and insignificant tumor (both criteria)] were left unranked, but their correlations were calculated with the ranked PSA values. Nonparametric correlations were chosen over the standard Pearson product-moment correlations due to the skewness and discreteness of the data. Although highly statistically significant, most correlations were relatively weak. Median PSA density also increased with increasing serum PSA. Median prostate volume also increased with increasing PSA for PSA values up to 10 ng/mL, suggesting that prostatic hyperplasia contributes in part to serum PSA levels at relatively low PSA levels. In contrast, tumor cell–derived PSA seemed to contribute more to serum PSA at serum PSA levels >10 ng/mL. No tumors met the criteria for insignificance at serum PSA levels >10 ng/mL. Proportionally, more tumors met the criteria for potentially insignificant at lower PSA values, with 51.7% (criteria 1) to 55.4% (criteria 2) of tumors meeting these criteria at PSA levels of ≤1.0 ng/mL.

The relationship between serum PSA at diagnosis and pathologic features at prostatectomy was compared for 275 participants from the placebo group for whom complete pathologic data were available from radical prostatectomy specimens (Table 4). Adverse pathologic features at prostatectomy were defined as tumors having one or more of the following: Gleason score ≥7, extraprostatic extension, seminal vesicle invasion, positive surgical margin, or lymph node metastasis. In men who presented with PSA values ≤1.0 ng/mL, 15.6% had adverse pathology at prostatectomy; Gleason score of ≥7 accounted for all of these cases. No participants who presented with PSA ≤1.0 ng/mL had extraprostatic extension, seminal vesicle invasion, metastasis, or positive margins at surgery. In men with PSA values between 1.1 and 2.5 ng/mL, 37.9% (39 of 103) had one or more adverse pathology features at prostatectomy. This increased to

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49.1% (26 of 53) in men with PSAs between 2.6 and 4.0 ng/mL, 52.4% (44 of 84) in men with PSAs between 4.1 and 10.0 ng/mL, and 66.7% (2 of 3) in men with PSAs >10.0 ng/mL. In men with PSA values of 1.1 to 2.5 ng/mL, 13.6% had extraprostatic extension, and the prevalence of extraprostatic extension increased with increasing PSA. The prevalence of adverse pathology was similar in men with PSA values of 2.6 to 4.0 ng/mL and those with PSA values between 4.1 and 10.0 ng/mL. Relatively few events of seminal vesicle invasion and lymph node metastasis were found in this population. Examining only stage-related adverse features (presence of disease beyond the confines the prostate or positive margins), for men with PSAs >1.0 ng/mL, there was a stepwise increase in risk with increasing levels of PSA.

Discussion

The PCPT showed that finasteride reduced the risk of a prostate cancer diagnosis by ~25% (versus placebo) when given over a period of 7 years in men ≥55 years old (13). The reduced risk involved low-Gleason score (≤6) cancers, but an increase in high-grade (Gleason score ≥7) tumor diagnoses in the finasteride arm also occurred. We recently showed that the increased high-grade disease was due in large part to increased detection of small high-grade foci caused by the effects of finasteride on PSA performance and prostate volume likely combined with a relatively selective activity of finasteride for low-grade cancer (16–18). Our present comprehensive analysis of the pathologic and clinical features at the time of biopsy in the PCPT extends our earlier study (18) by defining the nature (significance) of prevented disease in the PCPT (primarily Gleason score ≤6 cancer) and by assessing potential aggressivity of high-grade disease as stratified by Gleason score 7 or ≥8 (versus combined Gleason score 7-10 in the earlier analysis) in men of the finasteride versus the placebo group.

As shown in Table 1, the features of tumors diagnosed by biopsy (number and percent of positive cores, extent of tumor, bilaterality, and perineural invasion) suggest that finasteride-treated men had smaller, less aggressive tumors (versus placebo). This difference achieved statistical significance for number of cores positive in Gleason score ≤6 tumors, percent of positive cores for Gleason score 7 tumors, and percent of bilateral tumors in Gleason score ≥8 tumors. These significant differences occurred despite our finding of a significantly smaller prostate volume in finasteride-treated men, which should have *increased* the number of positive cores and linear tumor extent because both measures are a function of the ratio of tumor volume to prostate volume. These observations on the finasteride group could be due to the effects of the agent in delaying tumor development, slowing tumor growth rates, or having a direct cytotoxic effect on the tumor. It is noteworthy that the difference in prostate volume between treatment groups was greatest in participants diagnosed with Gleason score ≥8 tumors, suggesting that finasteride could

Table 3. Correlations of biopsy features with PSA value, placebo group only

Variable	Nonparametric Pearson's correlation*	
	Correlation	*P*
Gleason score	0.28	<0.001
No. cores positive	0.25	<0.001
Percent cores positive	0.26	<0.001
Greatest linear extent of tumor	0.28	<0.001
Aggregate linear extent of tumor	0.29	<0.001
Bilateral	0.16	<0.001
Perineural invasion	0.15	<0.001
Prostate volume	0.31	<0.001
Insignificant tumor (criteria 1)†	−0.32	<0.001
Insignificant tumor (criteria 2)‡	−0.34	<0.001

*Ranks assigned to PSA values and all linear values; ties broken arbitrarily. Pearson product-moment correlations were calculated on the ranked variables. True dichotomous variables [bilateral, Perineural invasion, and insignificant tumor (both criteria)] were not ranked; their correlations were calculated with ranked PSA values.

†Stage T_{1c} + PSA density <0.15 ng/mL/g + Gleason score ≤6 (no pattern 4 or 5) + tumor limited to <3 cores + no core with >50% involvement.

‡Stage T_{1c} + PSA density <0.15 ng/mL/g + Gleason score ≤6 (no pattern 4 or 5) + tumor limited to <3 mm on 1 core.

Table 4. Relationship between PSA at diagnosis and features related to outcomes after prostatectomy (placebo group only)

Prostatectomy feature	PSA (ng/mL)				
	<1.0 (*n* = 32)	1.1-2.5 (*n* = 103)	2.6-4.0 (*n* = 53)	4.1-10.0 (*n* = 84)	>10 (*n* = 3)
	n (%)				
Gleason score					
≤6	27 (84.4)	69 (67.0)	30 (56.6)	43 (51.2)	1 (33.3)
≥7	5 (15.6)	34 (33.0)	23 (43.4)	41 (48.8)	2 (66.7)
Extraprostatic extension					
Yes	0 (0)	14 (13.6)	10 (18.9)	22 (26.2)	1 (33.3)
Seminal vesicle invasion					
Yes	0 (0)	3 (2.9)	0 (0)	3 (3.6)	1 (33.3)
Margins					
Positive	0 (0)	20 (19.4)	16 (30.2)	21 (25.0)	2 (66.7)
Lymph node metastasis					
Yes	0 (0)	0 (0)	1 (1.9)	0 (0)	0 (0)
All adverse features negative	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Any one adverse feature	5 (15.6)	39 (37.9)	26 (49.1)	44 (52.4)	2 (66.7)
pT_3 or N_1 disease	0 (0)	14 (13.6)	10 (18.9)	22 (26.2)	1 (33.3)

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have biased in favor of detecting these high-Gleason score tumors, which reinforces our previous observations in participants diagnosed with Gleason score ≥7 tumors (18). Median PSA density was significantly higher in the finasteride group compared with placebo at all tumor grades (likely reflecting the combined effects of finasteride in reducing prostate volume and increasing the specificity of PSA for cancer, as we have previously shown; refs. 16, 18). This finding explains why there was slightly less clinically insignificant cancer of Gleason score ≤6 in the finasteride than in the placebo group. Calculating PSA density in the finasteride group required adjusted PSA values, and this approach has yet to be validated.

PSA screening for prostate cancer has become a widespread practice in the United States. Among men of ages >50 years, 75% report having had a PSA test and ~50% regularly undergo PSA testing (19, 20). Screening advocates point out that a diagnosis shift toward lower-stage disease and fewer men with advanced disease and a declining prostate cancer mortality rate have occurred since screening became widespread (21). There are concerns, however, over the widespread screening effects of overdetection of clinically inconsequential tumors and a relatively high rate of tumor recurrence with subsequent treatments after initial therapy (22, 23). Although PSA historically has been a dichotomous marker of disease risk (threshold values of 2.5 or 4.0 ng/mL, depending on patient age and practice patterns), our previous analysis of PCPT subjects showed that prostate cancer can be present in men with all ranges of PSA and that the risks of prostate cancer and high-grade disease at biopsy increase with increasing PSA (5). We extend these findings in the current study of the risk of an insignificant tumor at biopsy and of the prevalence of adverse tumor pathology at prostatectomy across a range of PSA values. A unique feature of the PCPT was its requested end-of-study biopsy from all participants regardless of DRE and PSA results. As a result of this feature, 48.4% of the men diagnosed with cancer had PSA values ≤4.0 ng/mL and normal DRE, leading to the reasonable concern that their tumors may be clinically insignificant (13).

Various sets of clinical and pathologic features of tumors at biopsy have been used in attempting to predict clinical insignificance at prostatectomy (10–12, 25–28). The most common set of defining features for an "insignificant" prostate tumor at biopsy includes confinement to the prostate, a volume of <0.5 cm^3, and Gleason score ≤6 (no pattern 4 or 5; ref. 24). The Epstein criteria (described in the introduction) constitute perhaps the best studied model for this purpose (10, 15). These criteria constituted our criteria set 1, by which only 24.5% of the tumors diagnosed in the PCPT could be classified as potentially insignificant. A second model used by some investigators was our criteria set 2, which consisted of criteria (*a*) to (*c*) of criteria set 1 and the criterion of tumor of <3 mm in only 1 core (10, 12). According to the second model, 26.7% of the tumors diagnosed in the PCPT could be classified as potentially insignificant, only a slightly higher rate than in the first model. Therefore, despite the large number of cancers diagnosed in men with "normal" PSA and DRE findings, the rate of potentially insignificant tumors was within the range of rates up to 31% for insignificant disease in men undergoing radical prostatectomy in previously published studies (11, 26). Among Gleason score ≤6 prostate cancers on biopsy in the PCPT, which were the cancers shown to be prevented by finasteride, ~62% met the Epstein criteria for significant disease, indicating that finasteride does prevent significant prostate cancer. Although it is intuitive that limiting the analysis to tumors of Gleason score ≤6 would increase the percentage of potentially insignificant tumors (38% versus overall 24.5% or 26.7%), this is the first report we know of to present such data.

A truly biologically insignificant cancer must be sufficiently indolent to cause no health problem for the lifetime of the patient. Therefore, any *treated* cancer is clinically significant by definition, regardless of its biological potential. This definition underscores the need to consider tumor factors (e.g., grade and size) and patient factors (e.g., age, general health, and comfort level with active surveillance) in the calculus of clinical significance. Unfortunately, most studies that have defined insignificant cancer have not taken patient factors into account. Furthermore, the needle biopsy criteria we used in the current analysis have had sensitivities ranging from 35% to 83% and specificities ranging from 68% to 98% in previous studies highlighting their imperfection (12). In a recent study using these criteria to select patients for expectant management, 31.5% of patients had clinical disease progression within 2 years (26). A report of a follow-up analysis of the Epstein criteria concluded that, although developed to identify candidates for expectant therapy, "these criteria also could be used to identify men for whom definitive therapy, with its excellent cure rate, would be appropriate" (27). This shift in attitude and the widespread use of brachytherapy for treating low-risk disease demand reexamination of the concept of clinical insignificance and suggest that even preventing biologically indolent prostate cancer has substantial clinical benefit.

Our analysis of pathologic features at biopsy and prostatectomy over a wide range of PSA values revealed significant trade-offs for PSA-threshold prompts for prostate biopsy (Table 2). Men with lower PSA levels had a greater risk of small, unilateral, lower-grade tumors that will not manifest perineural invasion, a feature associated with the risk of extraprostatic disease. Indeed, 51.7% (criteria set 1) or 55.4% (criteria set 2) of tumors in men with PSAs ≤1.0 ng/mL met the criteria for potentially insignificant disease. In contrast, only 17.2% (set 2) or 17.8% (set 1) of men with PSAs of 2.6 to 4.0 ng/mL and 11.7% (set 1) or 13.5% (set 2) of men with PSAs of 4.1 to 10.0 ng/mL met insignificance criteria.

Because more than 90% of men diagnosed with prostate cancer in the United States opt for treatment, insignificant tumors carry the substantial risk of side effects of treatment that has little potential benefit to the patient. Our present analysis shows that PSA thresholds for prompting a biopsy pose a serious dilemma. Although cancers in men with PSA values of 0.0 to 1.0 ng/mL have the greatest risk of insignificant disease, they also have the greatest chance of cure (lowest risk of pathologic features associated with a risk of cancer recurrence). Conversely, men with PSAs of 4.0 to 10.0 ng/mL have a significantly lower risk of insignificant disease and a significantly lower chance of cure. The substantial differences between these two important outcomes suggest that there can be no clear-cut PSA threshold to prompt a cancer-confirming biopsy. Willet Whitmore, considered by many to be the father of American urologic oncology, eloquently summarized this paradox in 1988: "If cure is possible, is it necessary, and if cure is necessary, is it possible?" (29). Low values increase the potential for cure but also assuredly result in overtreating men

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with indolent disease. High values lead to disease recurrence after surgery or radiation: 33% at 4.0 to 10.0 ng/mL and 87% at 10.0 to 20.0 ng/mL (30). In an era of increasing attention to individualized medicine, patients and physicians must understand and discuss the trade-offs with different decisions based on prostate cancer screening.

This analysis also speaks to the meaning of the PCPT. Skeptics have argued that, largely because of the end-of-study biopsy, finasteride in the PCPT reduced the risk of mostly insignificant cancers since about half of the detected cancers were associated with a PSA <4.0 ng/mL and a normal DRE (9, 31). Our present study suggests that ~25% of detected tumors met the criteria for potential insignificance, a rate similar to those of the contemporary series of men who undergo treatment for their disease (25). Adding to the growing evidence supporting prostate cancer chemoprevention, this analysis suggests that men who developed prostate cancer on the finasteride arm had a lower tumor volume and other potential aggressive features across all tumor grades compared with the placebo arm.

Selecting a threshold value of PSA to prompt a prostate biopsy entails consideration of the inherent trade-off between the risk of diagnosing insignificant disease (a low threshold value) and the risk of diagnosing disease that cannot be cured (a high threshold value). Our data suggest that threshold diagnostic values should be individualized to patient preferences. About two thirds of all detected tumors and half of Gleason score ≤6 tumors, which finasteride is known to prevent, in the PCPT met the definition for clinical significance, and tumors among men treated with finasteride were smaller and had less extensive characteristics. These data confirm that men should be informed of the opportunity to reduce their risk of prostate cancer with finasteride.

Disclosure of Potential Conflicts of Interest

M.S. Lucia: commercial research grant, consultant, GlaxoSmithKline; P.J. Goodman: consultant, GlaxoSmithKline; C.A. Coltman: consultant, Seno Medical; I. Thompson: consultant, Veridex. The other authors disclosed no potential conflicts of interest.

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Pathologic Characteristics of Cancers Detected in the Prostate Cancer Prevention Trial: Implications for Prostate Cancer Detection and Chemoprevention

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