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Oncology: Prostate/Testis/Penis/Urethra

THE PROSTATE SPECIFIC ANTIGEN ERA IN THE UNITED STATES IS OVER FOR PROSTATE CANCER: WHAT HAPPENED IN THE LAST 20 YEARS?

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ABSTRACT

Purpose: We assessed how well preoperative serum prostate specific antigen (PSA) reflects the largest cancer in consecutive untreated radical prostatectomies during the last 20 years at Stanford University.

Materials and Methods: A total of 1,317 consecutive radical prostatectomies were divided into 4, 5-year periods between August 1983 and July 2003, and examined sequentially in 3 mm step sections by 1 pathologist. The largest cancer and 5 other histological variables in each prostate were measured. Preoperative clinical stages were tabulated for each 5-year period. Means, Pearson correlation coefficients, % change and multiple regression were used to compare selected variables.

Results: Most parameters decreased linearly during the 20 years, including palpable nodules on digital rectal examination from 91% to 17%, mean age from 64 to 59 years, mean serum PSA from 25 to 8 ng/ml, and index (largest) cancer volume from 5.3 to 2.4 cc. Percent Gleason grade 4/5 of the largest cancer averaged 27% to 35% and prostate weight 44 to 53 gm. Contrasting August 1983 to December 1988 with January 1999 to July 2003, 6 histological cancer parameters had statistically significant relationships to serum PSA in the first period. In the last 5 years serum PSA was related only to prostate size.

Conclusions: Serum PSA was related to prostate cancer 20 years ago. In the last 5 years serum PSA has only been related to benign prostatic hyperplasia. There is an urgent need for serum markers that reflect the size and grade of this ubiquitous cancer.

KEY WORDS: prostate-specific antigen, prostatic neoplasms, biological markers, prostatic hyperplasia

We reported in 1987 that serum prostate specific antigen (PSA) was proportional to increasing palpable stages of prostate cancer as measured by digital rectal examination (DRE).[1] We also showed that the excision of large nodules of benign prostatic hyperplasia decreased serum PSA dramatically.[1] In 1989 we confirmed that serum PSA was directly proportional to increasing clinical stages of prostate cancer.[2]

Unlike these earlier reports[1,2] we have shown in 2001 and 2002 that there are now serious limitations in the relationship of serum PSA to prostate cancer volume and Gleason grade 4/5 cancer[3,4]—the 2 primary determinants of failure to cure prostate cancer by radical prostatectomy.[5] This said, it is not surprising that a preoperative serum PSA between 2 and 10 ng/ml fails to predict postoperative cure rates,[3,4] an observation that is also true of PSA in large peripheral zone cancers 6 cc or larger in volume.[6] In fact positive prostate biopsy rates consistently increase with age at PSA levels between 4 and 10 ng/ml in men with normal digital rectal examinations.[7] In a recent contemporary biopsy series (1999 to 2000), positive biopsy rates for prostate cancer in men with serum PSA 2 to 4 ng/ml are nearly the same as in men with a serum PSA of 2 to 20 ng/ml.[8] Thus, current evidence from the last 10 years is convincing that the relationship between prostate cancer and serum PSA is tenuous at best, especially with serum PSA less than 10 ng/ml and perhaps even less than 22 ng/ml.[4] This time is not the first we have had second thoughts regarding the usefulness of serum PSA in preoperatively reflecting prostate cancer.[9] The question we address here is what happened in the last 20 years to make serum PSA in 2003 so misleading in the diagnosis of prostate cancer?

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MATERIALS AND METHODS

Since August 1983 radical prostatectomies performed by different urologists at Stanford, including several community physicians, have been examined with 3 mm step sections by 1 pathologist (JEM) in the Department of Urology. He has quantitated all histological aspects of the cancer including the index (largest) cancer volume and the % Gleason grade 4/5 in the largest cancer, as well as other less important variables. A quantitative map and data summary (fig. 1) are prepared from direct tracings of the histological slides.[10]

Our publications during these last 20 years are consistent the 2 primary determinants of failure to cure prostate cancer by radical prostatectomy are the size of the index (largest) cancer and the percent of that cancer composed of Gleason grades 4

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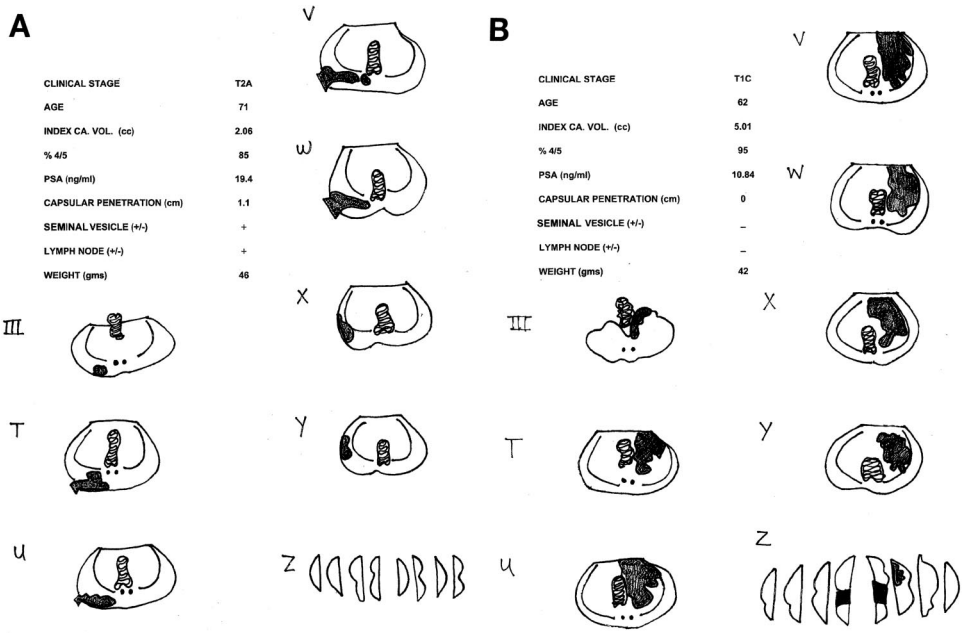

FIG. 1. Peripheral zone cancer (*A*) and transition zone cancer (*B*). Typical example of 3 mm transverse step sections performed on every radical prostatectomy in Department of Urology since 1983. Outer posterior-lateral peripheral zone is separated from inner transition zone containing vertically oriented urethra that gradually rises to anterior vesical neck in section III. Distal 6 mm of apex is cut in 3 mm vertical sections (*Z*) to obtain maximal exposure of capsule at prostate apex. As often occurs PZ cancer (*A*) shows extensive capsular penetration of cancer (1.1 cm in sections *T* through *W*) while TZ cancer (*B*) shows none. Ejaculatory ducts (2) are seen in TZ cancer from bladder neck (section III) to section *W*, and to section *U* in PZ cancer. Note that lymph nodes and seminal vesicles were positive in PZ cancer. Weight of prostate is recorded after removing seminal vesicles and before fixation of tissues. Cancer is seen in all 3 mm step sections for both cases except for section *Z* in peripheral zone cancer. Capsular penetration in PZ cancer is seen in sections *T* through *W*.

and 5 (the 2 undifferentiated grades in the Gleason classification).[5] This information, collected and catalogued since 1983, allows us to examine quantitatively all histological changes in serial radical prostatectomies at Stanford since August 24, 1983, and to relate these changes to the preoperative level of serum PSA during these 20 years.

Serum PSA was performed at the Department of Urology using the monoclonal Tosoh AIA assay (Tosoh Bioscience, South San Francisco, California). In the early years of this report we used a polyclonal PSA assay, the values of which were converted to monoclonal equivalents years ago. Approximately 80% of these men were diagnosed by local, nonuniversity urologists before referral to Stanford. We believe our information is characteristic of most radical prostatectomies performed in this country in men of similar ages.

We have divided the 20 years since August 1983 into 4 nearly equal 5-year intervals of August 24, 1983 to December 31, 1988; January 1, 1989 to December 31, 1993; January 1, 1994 to December 31, 1998 and January 1, 1999 to July 1, 2003. Our technique of quantitating all histological aspects of these 1,317 previously untreated radical prostatectomies, recently summarized by McNeal and Haillot,[10] allows us to separate 222 transition zone cancers (those that arise in the anterior portion of the prostate in the area of benign prostatic hyperplasia) from the more common and much more malignant, posteriorly located peripheral zone cancers (in 1,095, fig. 1). Although there are no acceptable preoperative methods currently to clinically separate transition zone (TZ) from peripheral zone (PZ) cancers, they are readily distinguishable on histological examination of the whole prostate. Because of the substantially better prognosis in TZ cancers even when matched by cancer grade and volume with peripheral zone cancers,[11] we present our PSA data for TZ cancers separately from the much more common PZ cancers. However, we have combined PZ and TZ cancers in our analysis as if they were 1 type of prostate cancer, a presentation that may be more clinically relevant, although less accurate biologically.

Means, Pearson correlation coefficients, and percent change were calculated for all variables and intervals. We have also used multiple regression analysis for peripheral zone variables comparing them to log PSA from the first 5-year period to the most recent 5-year period.

RESULTS

Substantial changes in clinical stage as determined by digital rectal examination across the 20 years are shown in figure 2. We present in table 1 for all 4 5-year time periods the supporting clinical and histological data for 1,095 radical prostatectomies in which the largest cancer was located in the PZ. Table 2 shows the same information for 222 cancers located in the TZ. Table 3 combines the PZ and TZ groups (into 1,317 men) because we cannot distinguish between the 2 groups preoperatively. These 3 tables document the clinical and histological findings at radical prostatectomy with percent change during the 4, 5-year intervals from August 1983

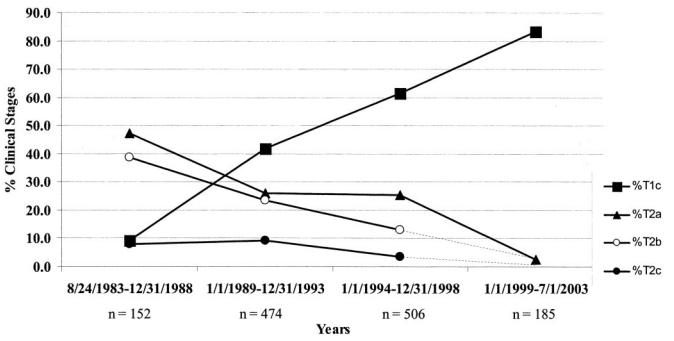

FIG. 2. Change in clinical stages from August 24, 1983 to July 1, 2003 in 1,317 radical prostatectomies for peripheral and transition zone cancers. T1c, no palpable cancer on DRE. T2a, palpable nodule on DRE occupying less than half of 1 lobe. T2b, palpable nodule occupying more than half of 1 lobe. T2c, bilaterally palpable cancer.

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TABLE 1. *Changes in cancer morphology during 20 years in 4 periods for 1,095 peripheral zone cancers*

	8/24/1983–12/31/1988	1/1/1989–12/31/1993	1/1/1994–12/31/1998	1/1/1999–7/1/2003	% Change
No. cases	138	407	399	151	
Age ±1 SD	64.14 ± 7.67	63.40 ± 6.84	62.01 ± 6.70	59.54 ± 6.93	−7.2
% Palpable Ca on DRE	92.75	60.69	43.36	17.22	−81.4
Mean serum PSA (ng/ml) ±1 SD	24.41 ± 39.47	16.81 ± 15.35	9.23 ± 7.88	7.32 ± 6.65	−70.0
Mean index Ca vol (cc) ±1 SD	5.15 ± 6.59	4.17 ± 4.47	3.13 ± 3.21	2.10 ± 2.62	−59.2
% Grade 4/5 Ca ±1 SD	31.77 ± 30.03	25.92 ± 27.31	29.17 ± 30.33	34.21 ± 30.86	7.7
Mean prostate wt (gm) ±1 SD	44.83 ± 24.72	53.17 ± 24.76	52.84 ± 19.69	43.76 ± 21.45	−2.3
% With seminal vesicle invasion	24.64	7.13	5.01	6.62	−73.1
% Pos lymph nodes	13.77	7.13	4.51	0.00	
Mean capsular penetration (cm) ±1 SD	1.66 ± 2.88	1.02 ± 2.24	0.62 ± 2.26	0.23 ± 0.81	−86.4

TABLE 2. *Changes in cancer morphology during 20 years in 4 periods for 222 transition zone cancers*

	8/24/1983–12/31/1988	1/1/1989–12/31/1993	1/1/1994–12/31/1998	1/1/1999–7/1/2003	% Change
No. cases	14	67	107	34	
Age ±1 SD	65.21 ± 8.69	64.82 ± 6.33	62.81 ± 6.20	57.59 ± 7.50	−11.7
% Palpable Ca on DRE	71.43	41.79	20.56	14.71	−79.4
Mean serum PSA (ng/ml) ±1 SD	28.08 ± 20.19	39.44 ± 38.10	13.92 ± 11.82	11.77 ± 17.50	−58.1
Mean index Ca vol (cc) ±1 SD	7.02 ± 7.52	9.52 ± 8.73	6.12 ± 6.72	3.96 ± 4.18	−43.6
% Grade 4/5 Ca ±1 SD	22.21 ± 32.81	32.34 ± 32.39	23.65 ± 27.54	38.68 ± 32.78	74.1
Mean prostate wt (gm) ±1 SD	63.14 ± 25.87	53.76 ± 17.90	53.27 ± 20.89	42.50 ± 13.92	−32.7
Mean capsular penetration (cm) ±1 SD	0.39 ± 0.62	1.00 ± 2.71	0.39 ± 2.09	0.18 ± 0.76	−54.2

We excluded 2 transition zone cancers with index cancer volumes of 96 and 48 cc associated with preoperative serum PSA levels of 456 and 490 ng/ml. Seminal vesicle invasion and positive lymph nodes almost never occur in pure transition zone cancers unless the TZ cancer has invaded posteriorly into the PZ, which is a rare occurrence.

TABLE 3. *Changes in cancer morphology during 20 years in 4 periods for 1,317 peripheral zone and transition zone cancers combined*

	8/24/1983–12/31/1988	1/1/1989–12/31/1993	1/1/1994–12/31/1998	1/1/1999–7/1/2003	% Change
No. cases	152	474	506	185	
Age ±1 SD	64.24 ± 7.74	63.60 ± 6.78	62.18 ± 6.60	59.18 ± 7.06	−7.9
% Palpable Ca on DRE	90.79	58.02	38.54	16.76	−81.5
Mean serum PSA (ng/ml) ±1 SD	24.74 ± 38.08	20.01 ± 21.61	10.22 ± 9.05	8.14 ± 9.70	−67.1
Mean index Ca vol (cc) ±1 SD	5.33 ± 6.68	4.93 ± 5.59	3.76 ± 4.37	2.44 ± 3.04	−54.1
Mean % Gleason grade 4/5 Ca ±1 SD	30.89 ± 30.30	26.82 ± 28.14	28.00 ± 29.82	35.03 ± 31.18	13.4
Mean prostate wt (gm) ±1 SD	46.52 ± 25.30	53.26 ± 23.89	52.93 ± 19.93	43.53 ± 20.25	−6.4
% With seminal vesicle invasion	23.03	6.96	4.74	5.41	−76.5
% Pos lymph nodes	12.50	7.17	4.55	0.00	
Mean capsular penetration (cm) ±1 SD	1.54 ± 2.78	1.02 ± 2.31	0.57 ± 2.22	0.22 ± 0.80	−85.9

TABLE 4. *Comparison of Pearson correlations of preoperative serum PSA with radical prostatectomy morphology in the first and last 5-year period*

	8/24/1983–12/31/1988	p Value	1/1/1999–7/1/2003	p Value
No. radical prostatectomy	152		185	
Vol largest Ca (cc)	0.659	p <0.0005	0.148	p <0.045
Capsular penetration (cm)	0.539	p <0.0005	0.033	p <0.653
Pos lymph nodes	0.493	p <0.0005	None	
% Seminal vesicle invasion	0.437	p <0.0005	0.059	p <0.428
% Gleason grade 4/5 of largest Ca	0.274	p <0.001	0.031	p <0.678
Prostate wt (gm)	0.238	p <0.003	0.246	p <0.001
Clinical stage	0.151	p <0.063	−0.001	p <0.987
Age	0.042	p <0.609	0.085	p <0.247

to July 2003. Table 4 shows the contrast in Pearson correlation coefficients between preoperative serum PSA (there are 2 outliers excluded in interval 2 of PSA 456 and 490 ng/ml) and 6 of the critical morphological cancer variables (plus clinical stage and age) in the first (August 1983 to January 1989) and last (January 1999 to July 2003) 5-year periods for 337 PZ and TZ cancers.

Figures 3 to 5 show the change during these last 20 years in Pearson correlation coefficients for serum PSA compared to the largest (index) cancer volume in 1,095 PZ cancers, 222 TZ cancers, and in 1,317 PZ and TZ cancers across the 5-year periods from August 1983 to July 2003. These figures also show the R^2 value for these relationships in each period which, if multiplied by 100, can be interpreted as the proportion of variance of the dependant variable (PSA) explained by the independent variable (index cancer volume). For example figure 3 indicates 44% of the 138 observations in time period 1 (1983 to 1988) showed a relationship between serum PSA and the largest cancer in the radical prostatectomies with a correlation coefficient that approaches 70%. However, that relationship since January 1, 1999 has decreased to only 2%, ie, there is now no clinical relationship between serum PSA and the largest cancer in the prostate.

It is particularly instructive to compare in table 4 the Pearson correlations of serum PSA before prostatectomy with postoperative prostate morphology in the first 5-year period (August 1983 thru December 1988) with the most recent 5-year period (January 1999 thru July 2003). Serum PSA correlates well with almost all the basic cancer morphology in the first 5-year period except for age and possibly clinical stage. All other cancer variables were significantly related to preoperative serum PSA. In sharp contrast the last 5-year period ending July 2003 shows no correlation of serum PSA with any morphological variable except prostate weight. This finding suggests that PSA today as a basis for diagnosing and treating prostate cancer is related only to the amount of benign prostatic hyperplasia in the prostate.

In multivariate regression, prostate weight (ie benign pros-

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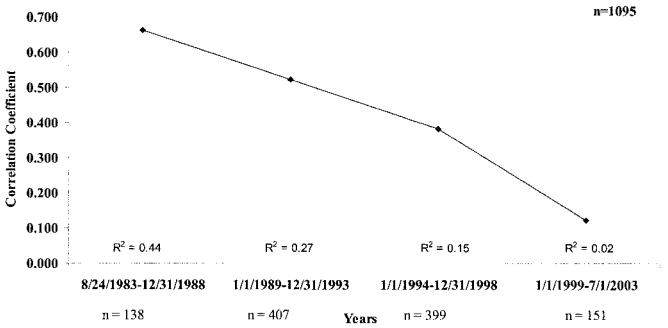

FIG. 3. Pearson correlation coefficients for serum PSA and index (largest) cancer volume in 1,095 radical prostatectomies for preoperative serum PSA and index cancer volume in PZ cancers at 4 consecutive 5-year intervals.

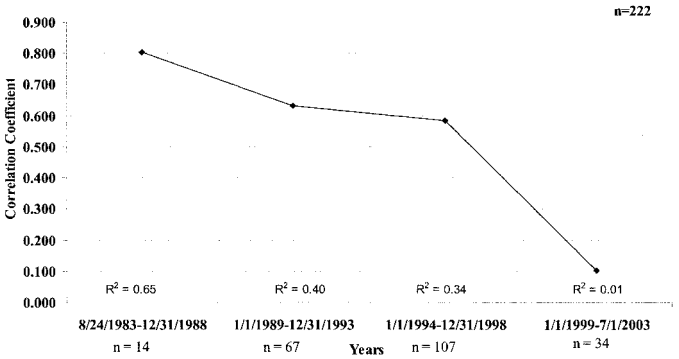

FIG. 4. Pearson correlation coefficients for serum PSA and index (largest) cancer volume in 1,095 radical prostatectomies for preoperative serum PSA and index cancer volume in 222 TZ cancers at 4 consecutive 5-year intervals.

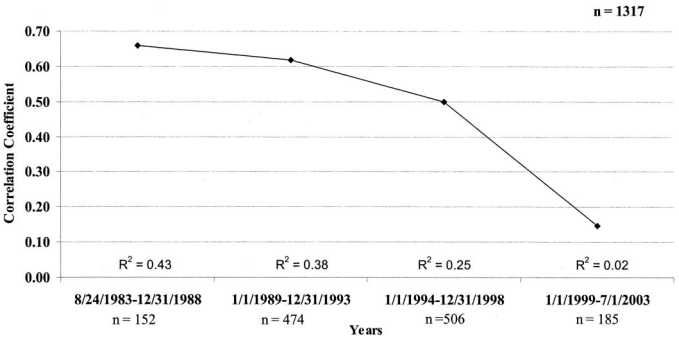

FIG. 5. Pearson correlation coefficients for serum PSA and index (largest) cancer volume in 1,095 radical prostatectomies for preoperative serum PSA and index cancer volume in peripheral and transition zone cancers at 4 consecutive 5-year intervals.

tatic hyperplasia) is the single most important variable in determining serum PSA in the first and last 5-year periods (table 5). The index cancer volume was also a strong determinant in the first 5 years but of less significance in the latest 5 years. Age, capsular penetration and seminal vesicle invasion were not important if the largest cancer, its percent Gleason grade 4/5 and prostate weight were measured.

DISCUSSION

The answer to what has happened with serum PSA in the last 20 years is that men in the United States between 50 and 80 years old have been so intensely screened with serum PSA of 2.5 to 10 ng/ml followed by ever increasing numbers of routine prostatic biopsies (from 6 to 10–12 to 23 per biopsy session)[12–14] that virtually all men with prostate cancer can now be detected. On the surface this would appear to be a great epidemiological accomplishment except for the disturbing fact that while prostate cancer is a ubiquitous tumor, it has an extraordinarily small death rate of 226 per 100,000 men older than 65 years.[15] Sakr et al deserve credit for the best and most recent demonstration of this ubiquity,[16] an omnipresence that Arnold Rice Rich, Chairman of the Department of Pathology at the Johns Hopkins Hospital, first inferred in 1935 when he observed that the autopsy routine of taking a single, random microscopic section from the prostate in men dying of other diseases demonstrated prostate cancer in a surprising 14% of men.[17] Sakr et al found that 8% of 525 men in their 20s, equally divided between white and black men killed accidentally on the streets of Detroit, had invasive prostate cancer when their prostates were examined by 2 to 3 mm whole mount step sections. Each increasing decade of life was accompanied by a linear increase in prostate cancer until 80% of both races in their 70s had invasive prostate cancer.[16] Collins et al recognized that men undergoing prostatic biopsies for a suspicious unilateral palpable nodule on rectal examination were just as likely to be biopsy positive only on the side opposite to the palpable nodule, leading them to suggest that the detection of prostate cancer was serendipitous.[18] We believe that table 4 and figure 5 represent solid evidence that in the first 10 years after PSA was introduced there was a reasonably good, although not great, correlation between serum PSA and prostate cancer volume. However, that relationship has now disappeared and only 2% of all radical prostatectomies have any relationship to the index (largest) cancer. As table 4 shows the relationship of serum PSA in the last 5 years rests exclusively with benign enlargement of the prostate.

Recent suggestions to use "lower thresholds of PSA for recommending prostate biopsy"[19] ie from 4.1 to 2.6 ng/ml, are misguided because this is precisely the range of serum PSA for most men with benign prostatic hyperplasia, a common disease clinically and histologically. We emphasize that the most, and almost only, significant variable related to serum PSA in the radical prostatectomy specimens of the last 5 years (January 1999 to July 2003) is prostate weight (table 4), ie benign prostatic hyperplasia. We urgently need a serum marker that reflects prostate cancer in the current PSA range of 2 to 10 ng/ml.

In the meantime what are we to do in the face of such massive, unwarranted PSA screening? Our data strongly suggest that palpable cancers (fig. 2 and table 1), which were so common (93%) in the first 5 years of our radical prosta-

TABLE 5. *Multiple regression analysis of log PSA as a dependent variable compared to selected morphological variables for the first and last 5-year period*

Independent Variables	First 5 Yrs		Last 5 Yrs	
	Coefficient	p Value	Coefficient	p Value
Log Ca vol (cc)	0.36 ± 0.062	<0.001	0.07 ± 0.289	0.012
% Gleason grade 4/5	0.003 ± 0.001	0.009	0.002 ± 0.001	0.018
Log prostate wt (gm)	0.54 ± 0.156	<0.001	0.38 ± 0.143	0.008
Seminal vesicle invasion	0.13 ± 0.076	0.088	0.01 ± 0.01	0.323
Age	−0.002 ± 0.003	0.526	−0.001 ± 0.003	0.842
Log capsular penetration (cm)	0.01 ± 0.070	0.854	0.05 ± 0.090	0.609

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tectomy efforts almost always require some form of treatment. We should emphasize better training in careful palpation of the prostate, especially with the patient in the knee-chest position on the examining table as a far superior way to carefully palpate the prostate in all quadrants for the presence of cancer. Table 1 shows that palpable cancers were also common in the second and third 5-year intervals (61% and 43%).

What is urgently needed is a serum marker for prostate cancer that is truly proportional to the volume and grade of this ubiquitous cancer, and solid observations on who should and should not be treated which will surely require randomized trials once such a marker is available. Since there is no such marker for any other organ confined cancer, little is likely to change the current state of overdiagnosis (and overtreatment) of prostate cancer, a cancer we all get if we live long enough.[16] Finally, lowering the PSA cutoff indication for prostate biopsy from 4.0 to 2.5[19] simply compounds the tragedy by adding millions of men to the biopsy list.

CONCLUSIONS

Although the PSA era is probably over for prostate cancer in the United States it will remain an enduring marker for the amount of BPH and its rate of progression as the control arm of the PLESS trial has shown.[20] It will also continue to be useful as a marker of failure to cure the patient after radical prostatectomy and probably after irradiation of the prostate as well. It is important that the urological community accept Sakr et al's demonstration of the age related ubiquity of prostate cancer as he showed in 525 men dying of accidental causes on the streets of Detroit.[16] Prostate cancer began in men in their 20s and steadily increased with each passing decade until 80% had prostate cancer in their 70s. This means that any excuse to biopsy the prostate has an excellent, age dependent chance of being positive.

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