African Journal of Urology
1110-5704

Vol. 14, No. 1, 2008
15-22

Original Article

Correlation of Serum PSA and Gleason Score in Nigerian Men with Prostate Cancer

C.A. Okolo[1], O.M. Akinosun[2], O.B. Shittu[3], E.O. Olapade-Olaopa[3], L.I. Okeke[3], E.E.U. Akang[1] and J.O. Ogunbiyi[1]

[1]Departments of Pathology, [2]Chemical Pathology and [3]Surgery, University of Ibadan, University College Hospital, Ibadan, Nigeria

ABSTRACT

Objective: Prostate cancer is an important cause of morbidity and mortality worldwide. While the predisposing factors are not fully understood, African descent is an important risk factor, and prostate cancer has become the number-one cancer in Nigerian men. This was a retrospective study of the correlation between serum prostate specific antigen (PSA) and Gleason grade and score in patients of Nigerian descent.

Patients and Methods: The University College Hospital (UCH) Ibadan Cancer Registry was used to identify and quantify the incidence of prostate cancers occurring between 1998 and 2000. The histological slides of appropriate cases were reviewed to confirm the Gleason grade and score. The serum PSA values were retrieved from the patients' case notes and laboratory files. The data obtained were subjected to statistical analysis to look for associations and correlations.

Results: The study included 67 men with prostate adenocarcinoma and PSA measurements who were diagnosed and treated at the UCH Ibadan between January 1998 and December 2000. There was a positive correlation between serum PSA and Gleason grade, as well as between serum PSA and Gleason score in our cohort of Nigerian African men with prostate cancer. PSA levels were significantly lower in patients with stage B disease than in patients with stage D disease.

Conclusion: Serum PSA is significantly higher in metastatic than in localized disease. Further studies are necessary to determine biomarkers that complement serum PSA and the Gleason grading system in the prognostication of prostate cancer in African patients.

Keywords : Prostate cancer, prostate specific antigen (PSA), Gleason score, Nigeria

Corresponding Author: Dr. Olufemi J. Ogunbiyi, Department of Pathology, University College Hospital, Ibadan, Nigeria, Email: f_ogunbiyi@yahoo.com

Article Info: Date received : 7/9/2007 Date accepted (after revision): 29/1/2008

INTRODUCTION

According to the American Cancer Society the global burden of cancer in 2007 was estimated to be 12.3 million new cases with a total of 7.6 million cancer deaths[1]. As the average age of a population increases, the incidence of cancer rises and increasingly accounts for death. The most common cancers worldwide in both sexes (lung and bronchus, breast, prostate, cervix uteri, stomach, colon and rectum, liver) are related to age and environmental exposures such as tobacco, alcohol, diet, and hepatitis B virus. Breast cancer in women and prostate cancer in men are an increasing burden also in the developing world as life expectancy increases due to improvements in public health and socioeconomic indices[2].

Prostate cancer is the fifth most common cancer globally, and the second most common cancer in men. Worldwide, there are an estimated 782,647 new cases of prostate cancer and 253,906 deaths annually[1], an important cause of cancer morbidity and mortality. Therefore, prostate cancer detection and

Table 1: University College Hospital Ibadan Cancer Registry Data on most common cancers seen between 1991 and 2000.

CANCER TYPE	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
Male										
Hepatocellular	15	33	18	12	32	31	23	37	12	51
Prostate	**3**	**39**	**22**	**34**	**63**	**58**	**49**	**75**	**22**	**100**
Lymphoma	33	35	35	15	32	42	20	43	9	28
Lung	2	13	6	0	14	14	4	10	2	9
Sarcoma	1	4	3	0	1	5	2	0	1	2
Colon	1	13	9	4	7	8	6	8	0	13
Female										
Breast	105	190	240	73	214	170	165	199	71	257
Ovary	10	14	9	9	7	20	14	28	9	18
Endometrial	1	14	6	5	10	7	10	9	2	5
Cervix	19	146	151	68	168	143	145	172	22	170
Lymphoma	19	30	10	9	23	16	3	16	5	23
Lung	0	5	2	1	1	2	3	0	2	4
Sarcoma	0	1	1	0	0	2	1	1	0	0
Colon	1	5	3	3	6	6	4	5	1	5

treatment is under intense study in Europe and North America[3].

One of the most important risk factors for prostate cancer in the United States is African-American descent and, while screening for prostate cancer is recommended for Caucasian, Asian and Hispanic men at age 50, for African-Americans it is recommended at age 40.[4,5] The increased risk amongst men of African-American descent is believed to be a result of increased frequencies of predisposing genes, adverse environmental factors and poor access to healthcare, but delineating the exact roles of these factors has proven difficult[6].

Prostate cancer is clinically staged using the American Joint Commission on Cancer and the Whitmore-Jewett clinical staging systems. The Gleason histological grading system is widely used for prostatic adenocarcinoma and is believed to be an important factor for prognosis. Based on the primary and secondary patterns, the Gleason score has been widely validated as a useful prognosticator. In Europe and North America, patients are currently stratified for different therapeutic modalities based on the Gleason score[7]. The measurement of serum PSA is also a general prognostic factor for prostatic carcinoma and correlates fairly well with tumor volume in most populations[8].

The Gleason system is based on the degree of glandular differentiation and the growth pattern of the tumor in relation to the stroma, as evaluated on low-power microscopic examination. The Gleason score does not take cytological characteristics into consideration, and five distinct patterns of growth and glandular differentiation are separated based on arbitrary, although easily definable, cut-off points.

PSA is a 34-kilodalton glycoprotein secreted by prostatic epithelial cells, unless they are extremely poorly differentiated. Serum determination of PSA is useful in the

Table 2: Clinical stage distribution of patients.

Clinical stage	Number	Percentage
A	0	0
B	41	61.1%
C	7	10.5%
D	19	28.4%
Total	67	100%

diagnosis of prostate cancer. The test has a high sensitivity, but rather low specificity, it is rapid and inexpensive and is minimally invasive[9]. Clinical testing for serum PSA was introduced in the late 1980s and has had a major impact for screening, early diagnosis of prostate cancer, monitoring of established disease, and as a general prognostic factor[10].

A standard PSA immunoassay measures the total amount of PSA bound to antichymotrypsin along with free PSA; the PSA bound to α-macroglobulin is not measured by this technique.

Elevated serum PSA levels may result from prostatic disease processes in which there is increased production of PSA and/or when there are architectural abnormalities that allow easier access of PSA to the circulation[11].Prostatic carcinoma is characteristically associated with a markedly elevated PSA, except for poorly differentiated cancers.

The incidence of prostate cancer in Nigerians is believed to be increasing, and it has become the number-one cancer in Nigerian men, moving ahead of hepatocellular carcinoma in incidence and mortality[12]. A study in Ibadan carried out in 2000 demonstrated that the normal value for PSA in men with benign prostatic hypertrophy (BPH) was in the range of 0-4 μg\l.[12] A PSA value of greater than 10 μg/l is considered frankly elevated while a value in the 4-10 μg/l range is borderline elevated in this population[13,14].

Although several studies correlating Gleason grades and PSA for prostate cancer have been reported in the English literature, none has been reported for our center, despite the increasing importance of this cancer among our male population. The present study was undertaken in order to investigate the correlation between histological grading of prostatic carcinoma and serum PSA levels in an indigenous African population.

PATIENTS AND METHODS

The University College Hospital (UCH) Ibadan, established in 1952 as an affiliate of the University College Hospital in London, UK, uses a cancer registry that was created in 1960 by the British Empire Cancer Campaign and is maintained by the Department of Pathology and the College of Medicine, University of Ibadan, Nigeria, established as independent units in 1962. The UCH Ibadan is a 900-bed facility and serves as a regional cancer center for South-Western Nigeria where about 50 million of the estimated total population of 140 million Nigerians live.

The clinical laboratory at the UCH has published an analysis of the range of PSA values in a population of normal men and men with BPH[13].

The present report includes all cases of prostate cancer diagnosed from 1998 to 2000. Our study was favored by the following factors: the data set used for this study was from a well-run hospital-based cancer registry, the catchment area for this registry is large with

Fig. 1: Age distribution of 67 patients with prostatic adenocarcinoma.

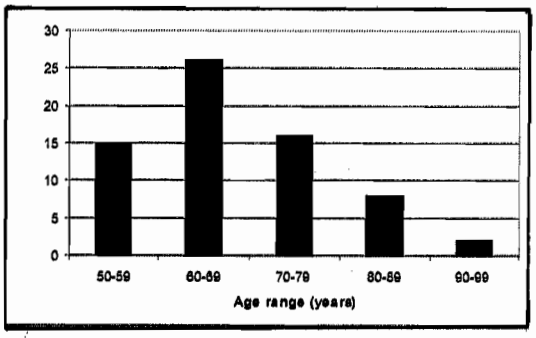
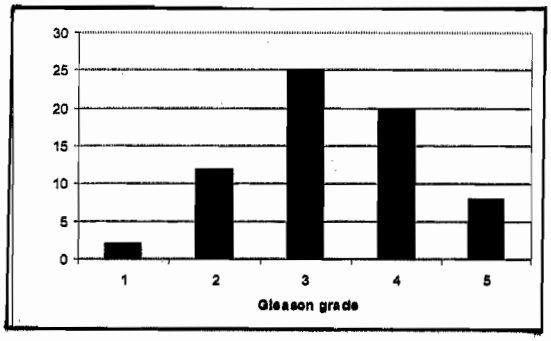


Fig. 2: Distribution of Gleason grades.



a population base of about 50 million people, multi-disciplinary care optimizes the quality of the data yielded in our cancer centre and the histological grading is reliable because one of the pathologists was involved in a previous international correlation study of Gleason grading of prostatic adenocarcinoma[15].

The cases were selected based on the following criteria:

1. histologically confirmed prostatic adenocarcinoma,
2. a pre-treatment PSA value,
3. treatment at the UCH Ibadan and available records, and
4. specimens suitable for histopathological review using the Gleason histological grading[15].

For the analysis we used the Whitmore-Jewett staging system[17]. The patients' medical records were reviewed blinded to the results of the PSA and histopathological grading subsequently conducted. File reviews were conducted by the first author, medical records officers, and two residents in training in pathology. The first author verified the consistency of all the data which were then entered into a database.

The surgical specimens were fixed in formalin and routinely processed into paraffin blocks, from which slides stained with hematoxylin and eosin were prepared and reviewed by three pathologists.

Histopathological diagnosis was made using the classification adopted by the Veterans Administration Cooperative Urological Research Group[18]. Over 98% of prostate cancer types in the UCH Ibadan Cancer Registry are adenocarcinomas. This study reports on a subset of these adenocarcinomas. The Gleason grade and score were used to classify the samples[19].

Each pathologist reviewed the slides using the Gleason grading system, assigning a first and second grade pattern, thereafter summing up the grades to obtain the Gleason score. Discrepancies were resolved at a consensus review. Scores were assigned for needle biopsies by doubling the value of the highest grade, while those for prostatectomies were a sum of the two most dominant grade patterns.

The data obtained were subjected to statistical analysis using Microsoft Office Excel 2003 and the SPSS 11 statistical package. Frequencies of variables were determined and cross-tabulations of the variables were generated. Continuous variables were summarized using means ± standard deviations. Student's t-test was employed to compare means to determine statistical significance. Spearman's correlation coefficient was employed to test the relationships between serum PSA, clinical stage, Gleason grade and Gleason score.

Fig. 3: Distribution of Gleason scores.

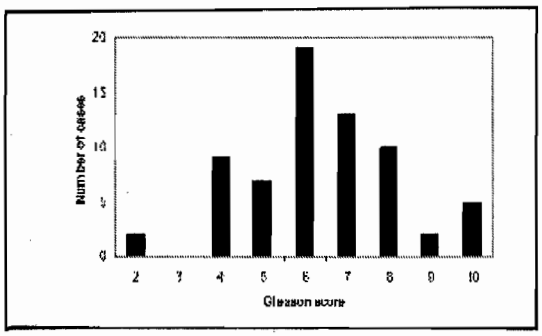
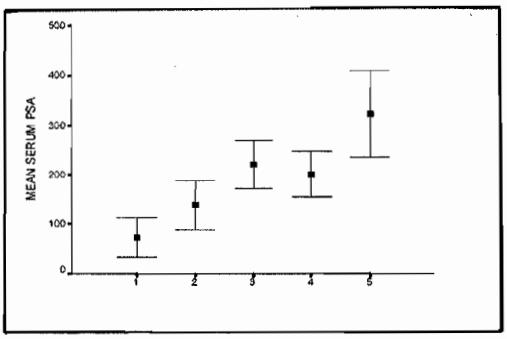


Fig. 4: Correlation of mean (± SEM) serum PSA and Gleason grade.



The level of statistical significance was set at $p \leq 0.05$.

RESULTS

Table 1 illustrates the frequency of the most common male and female cancers recorded in the Ibadan Cancer Registry from 1991 to 2000. During this decade, a dramatic increase in the frequency of prostate cancer was noted relative to other cancers in men, and it is the third most prevalent cancer overall after breast and cervical cancer in females, and the leading cancer in Nigerian men at Ibadan.

In total, 67 men had PSA performed at diagnosis and prior to therapy between January 1998 and December 2000. None of the patients was taking finasteride at the time of diagnosis that could interfere with serum PSA levels.[20] All patients were Nigerian African males resident in South-Western Nigeria. The patients' age ranged from 50-99 years, with a mean (± standard deviation) of 67.4 ± 10.8 years. Most patients in this series were in their seventh decade of life (Fig. 1). Forty-one (61%) patients presented with clinical stage B, 7 (10%) with stage C and 19 (28%) with stage D tumors (Table 2).

Twenty-nine patients had needle biopsy and 38 had either retropubic prostatectomy or transurethral resection of the prostate.

Twenty-five (37.3%) patients presented with Gleason grade 3. Only 14 (20.9%) patients had a well-differentiated (grades 1 and 2) prostatic adenocarcinoma (Fig. 2). The modal Gleason score was 6, while only 18 patients (26.9%) had a Gleason score < 5 (Fig. 3).

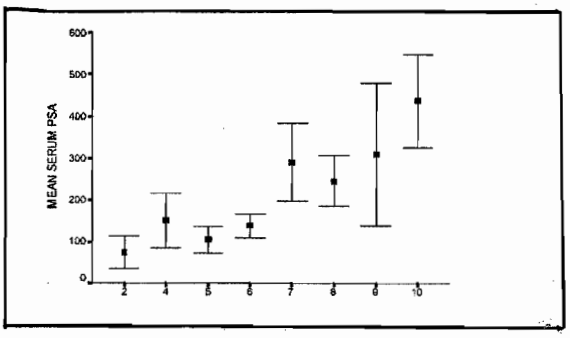
The predominant Gleason grade was 3 as demonstrated in Fig. 2. The mean was 3 and the median was 3.3 showing that the distribution was skewed to higher grades. Similarly, Fig. 3 shows the distribution of Gleason scores with a mean of 6.4 (median 6), and the distribution was skewed towards higher scores.

The mean serum PSA was 207.9 ± 221.3 µg/l (range 10-940.5 µg/l). Fifty-five percent of our patients had PSA values >100 µg/l.

As shown in Figure 4, there was a trend of increasing serum PSA levels with increasing histological grade (Spearman's correlation coefficient = 0.233, p = 0.058). The mean serum PSA level for cases with grade-1 adenocarcinomas (73.0 ± 57.2 µg/l) was significantly lower than that for grade-5 adenocarcinomas (322.3 ± 246.8 µg/l) (p = 0.03).

There was a statistically significant positive correlation between increasing mean serum PSA levels and Gleason score (Spearman's correlation coefficient = 0.40, p = 0.001) (Fig. 5). The mean serum PSA levels for patients with a Gleason score of <6 (124.2 ± 147.3 µg/l) was significantly lower than that of patients with a Gleason score of ≥

Fig. 5: Correlation of mean (± SEM) serum PSA and Gleason score.



6 (238.6 ± 236.8 μg/l) (p = 0.003). There was no significant correlation between patient age and clinical stage. However, PSA levels were significantly lower in patients with stage B disease (110.6 ± 122.6 μg/l) than in patients with stage D (394.3 ± 260.7 μg/l (p < 0.001).

DISCUSSION

A recent census in Nigeria will facilitate the institution of a country-wide cancer registry; an effort already under way with the generous support of the World Health Organization and the Exxon Mobil Foundation.

Cancer of the prostate is currently the most frequent malignancy of the adult Nigerian male as documented by the UCH Ibadan cancer registry. The new registries will facilitate the evaluation of prospective trials for the screening of prostate cancer and the use of innovative and cost-effective treatment strategies best suited to our limited resources.

The PSA levels in men with prostatic adenocarcinoma in this study ranged from 10 μg/L to 940 μg/L with a mean of 208 μg/L. There was positive correlation between serum PSA and Gleason grade as well as Gleason score in our cohort of Nigerian African men with prostate cancer. Our findings are in agreement with results from studies carried out by other researchers in Nigeria and North America[21].

It should be noted that several conditions other than prostatic adenocarcinoma may account for an elevation of serum PSA. These include BPH, clinical prostatitis, urinary tract infection, urethral instrumentation, transurethral resection of the prostate, prostatic needle biopsy, and the transitory elevation following ejaculation[9,22]. While we are reasonably certain that none of the patients had undergone any procedures (including instrumentation), none had recently taken finasteride[20], and none had symptomatic prostatitis, subclinical prostatitis could not be entirely ruled out. It is well known that the volume of the tumor correlates with the serum PSA levels in patients with prostatic cancer[23], but such measurements were not done in this cohort of patients because of the lack of appropriate ultrasound probes.

In the present study, 61% of the patients had localized prostate cancer, while 39% were stages C or D. Fifty percent of our patients had PSA values >100μg/l. In a study of serum PSA levels in 703 American men with localised prostate cancer, the PSA values obtained in 99% of the patients were below 50 μg\l and only 1% had a PSA value > 50μg/l[21]. In a study done by Amayo and Obara, evaluating PSA in East African men with prostate cancer, the PSA values ranged from 1.78 μg/l to 4339 μg/l[24]. Other studies from Nigeria also corroborate the differences in PSA values between African men on one hand and American and African-American men on the other[25]. These studies suggest that higher PSA values in African men with prostate cancer are probably due to higher tumor stages in African than in American patients.

However, a few weaknesses of this study are acknowledged: 1) the retrospective nature of the study, which is subject to retrieval bias; 2) the small sample size of the study and 3) the lack of a national health system with resources for tracking follow-up.

Three large screening trials in the United States, Canada, and Europe will be completed in a few years[26,27]. An analysis from Efstathiou

et al. suggests that screening for prostate cancer increases the detection of early-stage cancers, lowers mortality and substantially lowers morbidity[28]. Furthermore, follow-up strategies using PSA can predict which patients are most likely to have recurrence and thereby suggest who may need further therapy to prolong survival[29]. At least two large databases in the United States are conducting randomized trials of therapy for early and late-stage prostate cancer[28]. Similar multi-center collaborative studies among Nigerian populations should increase the understanding of the natural history of prostate cancer in our environment and help us to further understand the best use of resources for our setting. Further studies are also required to determine ancillary markers that will complement serum PSA and Gleason grading in the diagnosis and prognosis of prostate cancer in African patients.

REFERENCES

1. http://www.cancer.org/downoads/STT/Global_Cancer_Facts_and_Figures_2007.pdf
2. Parkin DM, Bray F, Ferlay J,Pisani P. Global cancer statistics, 2002.CA Cancer.J.Clin.2005 Mar-Apr;55(2):74-108.
3. Lubeck DP, Litwin MS, Henning JM, Stier DM, Mazonson P, Fisk R, et al. The CaPSURE database: a methodology for clinical practice and research in prostate cancer. CaPSURE Research Panel. Cancer of the Prostate Strategic Urologic Research Endeavor. Urology.1996 Nov;48(5):773-7.
4. Sun L, Gancarczyk K, Paquette EL, McLeod DG, Kane C, Kusuda L, et al. Introduction to Department of Defense Center for Prostate Disease Research Multicenter National Prostate Cancer Database, and analysis of changes in the PSA-era.Urol.Oncol.2001;6(5):203-9.
5. Odedina FT, Ogunbiyi JO,Ukoli FA. Roots of prostate cancer in African-American men.J.Natl.Med.Assoc.2006 Apr;98(4):539-43.
6. Gardner WA,Jr, Coffey D, Karr JP, Chiarodo A, Epstein J, McNeal JE, et al. A uniform histopathologic grading system for prostate cancer. Subcommittee on Diagnostic Nomenclature, Prostate Cancer Working Group, Organ Systems Program.Hum.Pathol.1988 Jan;19(1):119-20.
7. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS,Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate.N.Engl.J.Med.1987 Oct 8;317(15):909-16.
8. Nadler RB, Humphrey PA, Smith DS, Catalona WJ,Ratliff TL. Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels.J.Urol.1995 Aug;154(2 Pt 1):407-13.
9. Polascik TJ, Oesterling JE,Partin AW. Prostate specific antigen: A decade of discovery--what we have learned and where we are going.J.Urol.1999 Aug;162(2):293-306.
10. Guinan P, Bush I, Ray V, Vieth R, Rao R,Bhatti R. The accuracy of the rectal examination in the diagnosis of prostate carcinoma.N.Engl.J.Med.1980 Aug 28;303(9):499-503.
11. Ogunbiyi JO,Shittu OB. Increased incidence of prostate cancer in Nigerians.J.Natl.Med.Assoc.1999 Mar;91(3):159-64.
12. Abbiyesuku FM, Shittu OB, Oduwole OO,Osotimehin BO. Prostate specific antigen in the Nigerian African. Afr.J.Med.Med.Sci.2000 Jun;29(2):97-100.
13. Kirby RS, Christmas TJ ,Brawer M. Tumors markers in prostate cancer.In:Kirby RS, Christmas TJ ,Brawer M, editors.Prostate cancer.1st ed.Italy:Mosby;1996. P.55-64.
14. Freeman VL, Coard KC, Wojcik E,Durazo Arvizu R. Use of the Gleason system in international comparisons of prostatic adenocarcinomas in blacks.Prostate.2004 Feb 1;58(2):169-73.
15. Gleason DF. Histological grading and clinical staging of prostatic carcinoma.In:Tannenbaum M, editor. Urologic pathology: The prostate.Philadelphia:Lea& Febiger;1977. P.171-98.
16. D'Amico AV, McGovern FT, Church PA ,Tempany CMC. The staging of prostate cancer.In:Kantoff PW, Wishnow KL ,Loughlin KR, editors.Prostate cancer: A multiisciplinary guide.1st ed.Massachusetts:Blackwell Scientific;1997. P.41-56.
17. Gleason DF,Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. 1974.J.Urol.2002 Feb;167(2 Pt 2):953-8; discussion 959.
18. Gleason DF. Histological grading of prostatic carcinoma. In:Bostwick DG, editor.Pathology of the prostate.New York:Churchill Livingstone;1990. P.83-93.
19. Thompson IM, Chi C, Ankerst DP, Goodman PJ, Tangen CM, Lippman SM, et al. Effect of finasteride on the sensitivity of PSA for detecting prostate cancer.J.Natl. Cancer Inst.2006 Aug 16;98(16):1128-33.
20. Partin AW, Yoo J, Carter HB, Pearson JD, Chan DW, Epstein JI, et al. The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer.J.Urol.1993 Jul;150(1):110-4.
21. Herschman JD, Smith DS,Catalona WJ. Effect of ejaculation on serum total and free prostate-specific antigen concentrations.Urology.1997 Aug;50(2):239-43.

22. Moul JW, Sesterhenn IA, Connelly RR, Douglas T, Srivastava S, Mostofi FK, et al. Prostate-specific antigen values at the time of prostate cancer diagnosis in African-American men.JAMA.1995 Oct 25;274(16):1277-81.

23. Amayo A,Obara W. Serum prostate specific antigen levels in men with benign prostatic hyperplasia and cancer of prostate.East Afr.Med.J.2004 Jan;81(1):22-6.

24. Iya D, Chanchani S, Belmonte J, Morris D, Glew RH, Van Der Jagt DJA. Prostate specific antigen in Africans: A study in Nigerian men. Nig J.Surg.Res.2003;5(3):114-9.

25. The European Randomized Study of Screening for Prostate Cancer(ERSPC). January 12, 2008;available at: http://www.erspc.org.

26. American Urological Association. Prostate cancer screening.2006. http://www.urologyhealth.org/adult/index.cfm

27. Efstathiou JA, Chen MH, Catalona WJ, McLeod DG, Carroll PR, Moul JW, et al. Prostate-specific antigen-based serial screening may decrease prostate cancer-specific mortality.Urology.2006 Aug;68(2):342-7.

28. Davidson P. and Gabbay J. . Should mass screening for prostate cancer be introduced at the national level? WHO Regional Office for Europe Health Evidence Network (HEN), May 2004.