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RESEARCH ARTICLE

Age-Dependent Occurrence of Prostate Cancer in an African-American Patient Population of Predominantly West Indian Origins

Shabnam Seydafkan[1], Hagar Atia[1], Bo Lin[2] and Matthew R. Pincus[1]*

[1]Department of Pathology, SUNY Downstate Medical Center, 450 Clarkson, Brooklyn, NY 11203.
[2]AdventHealth, Department of Pathology, 301 Memorial Medical Pkwy, Daytona Beach, FL 32117, USA.

*To whom reprint request should be addressed at mrpincus2010@gmail.com or matthew.pincus@downstate.edu

ABSTRACT

In a prior study of the occurrence of prostate cancer in a unique population of African American patients many of whom have West Indian ancestry, we found that seventy percent of patients screened for prostate were found to have this disease and that, of the seventy percent diagnosed with prostate cancer, 70 percent were found to have high-grade (Gleason score ≥ 7) disease. Overall, therefore, high-grade prostate cancer was found in over 50 percent of all cancers diagnosed, a rate of occurrence that was significantly higher than the corresponding ones for other demographic populations. Since the average age for screening was 65, the same as in other demographic groups, we conjectured that earlier screening of our patients might eliminate many of these high-grade tumors. To validate this hypothesis, we have now examined the rates of occurrence of high-grade prostate cancers in successive age groups, i.e., 40-<50, 50-<60, 60-<70, 70-<80 and >80. Surprisingly, we found that, already in the 50-<60 age group, the frequency of occurrence of high-grade cancers is >50%. (The number of patients in the 40-<50, i.e.,12 and >80, i.e., 6, were too small to be accurately evaluated.) Since the high rate of high-grade cancer occurs in the 50-<60-year group, we conclude that screening for prostate cancer should be performed on our patients at significantly earlier ages such as 40-<50. Also, in view of the expectation that high-grade tumors would increase with increasing age, a second unexpected finding was that the percentage of high-grade tumors was statistically the same at >50 percent in the 50-<60, 60-<70 and 70-<80 age groups. This result could be explained if there was a concurrent increase in low-grade tumors occurring in older patients suggesting that continued, persistent screening is necessary even in advanced age groups. We further found that the mean Gleason score of the 50-<60 and 60-<70 age groups is statistically the same, suggesting that the high-grade tumors are "stable". However, there is a statistically significant increase in Gleason scores between the 70-<80 age group and the two lower age groups which is associated with a large increase in Gleason 9 cancers in the 70-<80 age group and a concurrent, marked decrease in Gleason 7 cancers, suggesting significant recurrent progression of high-grade tumors in this age group.

INTRODUCTION

In a prior study of the occurrence of prostate cancer in a predominately African-American population, a majority of whom are of West Indian or West African origin, we found that about seventy percent of patients screened for prostate cancer bases on elevated serum prostate-specific antigen (PSA) levels were found to be positive for this disease on subsequent biopsy[1]. In addition to this incidence's being unusually high, we further found that seventy percent of these patients were found on biopsy to have high-grade prostate cancer, i.e., Gleason scores of 7 or higher. Thus, the overall rate of occurrence of high-grade prostate cancer at first biopsy in our patient population was 50 percent, significantly higher than in other studies with different patient demographics.[1] These findings were compatible with the results of other studies that suggested that West African ancestry was a major risk factor for the development of higher-grade prostate cancer [2-4].

Because both the high incidence of prostate cancer and the unusually high incidence of high-grade prostate cancer in these patients, we recommended screening for prostate cancer at earlier ages such as at 40 years. Unfortunately, the efficacy of lowering the screening age was not possible due to the fact that few patients were screened before age 50[1], and most of these patients were in the 50-80 age group. In fact, in our previous study[1], we found that the mean age for first screening was 65±7 years although the recommended age for first screening is 55 and 45 for patients who are positive for increased risk such as family and/or demographic history of prostate cancer, elevated serum levels of prostate specific antigen (PSA), positive digito-rectal examination, etc.[5-8] This discrepancy between the actual and recommended screening age together with the increased-risk demographic history has motivated attempts to lower the age for first screening in our patient population.

In addition, a concomitant problem in this patient group is the occurrence of the high percentage (>50%) of high-grade tumors. This raises the question as to when these high-grade tumors develop, i.e., do they occur spontaneously or do they develop from low-grade tumors. If the latter possibility occurs, treatment of low-grade tumors would prevent high-grade tumor development. This question has not been resolved although several studies have suggested that a significant, although not a high, percentage of low-grade prostate cancers convert to high-grade .[9,10] In one study, 18.7 percent of low-grade cancers converted to high-grade, over half of which did so within a two year period.[9] In another study[10], 17.3 percent of patients diagnosed with prostatic atypical small acinar proliferation (ASAP) were found on further biopsy to have Gleason scores >7.

On the other hand, several studies suggest that progression from low-grade to high-grade tumors is uncommon.[11,12] In one large scale retrospective study on prostatectomy specimens,[11] over a prolonged time period that encompassed years during which early detection methods (e.g., PSA) were not available and subsequent years when these methods were available, it was found that, while tumor stage was significantly reduced (i.e., T1/T2, T3, T4/N1/ M1) as a result of early detection, the re-assessed Gleason scores for the specimens changed only mildly. This result suggested that increasing Gleason score for prostate cancers was "not a major feature of prostate cancer." [11]

Other studies have focused on genetic similarities and differences between low-grade, high-grade and metastatic prostate cancers. In one study[12] laser capture microdissection (LMD) of prostate cancers of four patients with foci of low-grade (Gleason score of 6) and high-grade (Gleason scores of 8 and 9) prostate cancers was performed. In two of the high-grade tumors, lymph node metastases were found and likewise subjected to LMD. All of these samples were then subjected to exomic sequencing. Seventy of 79 (87%) high-confidence somatic mutations were found to be unique to low-grade tumor foci while only seven of 80 (9%) high confidence somatic mutations of high-grade foci were shared with those of low-grade foci. In contrast, 65 of the 80 (82%) high confidence somatic mutations of the high-grade foci were shared with those of the metastatic foci.[12] Importantly, uniquely in the high-grade and metastatic foci, mutations were found involving known cancer-associated genes and genes involved in p53-dependent pathways. These results suggest that there is early divergence between low-grade and high-grade prostate cancer foci.[12]

Screening our patient population at younger ages, e.g. 40-50 years, can shed light on answering the question of whether low-grade tumors progress to high-grade ones. If the percentage of low-grade tumors in this age group were found to be higher than that for high-grade tumors, the possibility of tumor progression from low to high-grade would be enhanced because in the 50-80 age group, the ratio of high-grade to low-grade tumors is >1.

Given the above considerations, we attempt to answer the following questions regarding our patient population: Do the high-grade tumors occur at relatively younger ages, e.g., 40-50 or 50-60, or at older ages? If they develop at younger ages, does the percent of high-grade tumors increase with increasing age? If so, does the mean Gleason score increase in the high-grade tumors with increasing age?

To answer these questions, we have investigated the distribution of low- and high-grade cancers in successive age groups, i.e., 50-<60, 60-<70 and 70-<80 and the percentages in each age group of high-grade tumor Gleason scores from 7-10. The approach is to determine if there are patterns of low-and high-grade cancer occurrence among these age groups. If a pattern can be established, it may be possible to predict the high and low-grade tumor percentages in patients of ages < 50 from which we can predict whether screening our patient population in the 40-<50 age range would lower the rate of high-grade cancer. This approach can also reveal how screening in each age group affects the frequency of occurrence of high- and low-grade cancers in successive age groups.

METHODS

Procedure: We re-analyzed our original data[1] concerning our prostate study that involved 378 patients who were diagnosed with r/o prostate cancer from elevated serum PSA and/or digitorectal examination and who were found upon biopsy to have prostate cancer within one-month post-procedure. We divided the patient results into five age groups: 40-≤50, 50-≤60,60-≤70,70-≤80, and >80. We then determined the numbers of biopsy results that yielded low Gleason scores (≤6) (low-grade tumors) and high Gleason scores (>6) (high-grade tumors) within each age group. In addition, for each age group, we computed the means and standard deviations for the Gleason scores of the high-grade tumors in each age group to determine if these increased as age increased, and we computed the distribution of Gleason scores in age group to detect if there were increases in high Gleason scores at increasing age.

Statistical Analysis: We used the two-tailed T-test to determine the significance of the differences of means for Gleason scores of patients in each age group and to determine whether there were significant differences between the mean ages of patients with high-grade prostate cancers and low-grade prostate cancers.

RESULTS

Table 1 summarizes the results for the occurrences of low- and high-grade prostate cancers. As can be seen in this table, significant screening occurred beginning at age 50 and continued up to age 80. Below age 50, there was only a low level of screening resulting in only 12 cases of prostate cancer, eight of which (67%) were low-grade cancers and four of which (33 percent) were high-grade cancers. For patients at ages of 80 or more, little screening occurred resulting in only six cases of prostate cancer, five of which (83 percent) were high-grade. This table also shows that the highest number of patients screened occurred in the 60-<70 years age group explaining the high average age of 65±7 years for screening.

Table 1. Prostate Cancer Grade per Age Group in the 378 Patient Study

Age	<50	50-<60	60-<70	70-<80	≥ 80
Total in Each Group	12	98	178	102	6
Low-grade	8 (67)*	46 (46.9)	87 (48.9)	48 (47.1)	1(17)
High-grade	4 (33)	52 (53.1)	91 (51.1)	54 (52.9)	5(83)

***Numbers in parentheses are percentages of the total in each group.**

Unique Features of Prostate Cancers in the Patient Population. Several unique features are present in this table. First, in the initial group for which significant numbers of results were available, i.e., the 50-<60 years group, the rate of high-grade cancers was >50 percent. If the reasonable assumption is made that high-grade cancers are most often preceded by low-grade cancers, this finding alone strongly implies that screening patients in our population must occur at ages < 50, i.e., in the 40-<50 age group, when presumably most of these high-grade tumors were low-grade ones and could be diagnosed at an early stage and treated. We have found that the average age for development of low-grade prostate cancer was 61 while for high-grade prostate cancer it was 66 (p=0.01) suggesting that the time for progression of low to high-grade cancer occurs in approximately 5 years in this population.

Second, the percentage of high-grade cancers remained slightly greater than 50 percent of all of the tumors diagnosed *in each of the three age ranges, 50-<60, 60-<70 and 70-<80.*

Third, of the high-grade cancers in each of the three major groups, the average Gleason scores for the high-grade tumors increased only by a small amount as summarized in Table 2. In fact, the mean average Gleason scores for the 50-<60 and 60-<70 age groups were not statistically significantly different as shown in Table 2. However, there was a statistically significant increase in the mean Gleason value for the 70-<80 age group compared with those for the other two age groups with p values of 0.02 (Table 2).

Table 2. Mean Gleason Scores for Age Groups with High-grade Prostate Cancers

	<50*	**50-<60**	**60-<70**	**70-<80**	**>=80***
Mean ± Standard Deviation	7 ± 0	7.30 ± 0.62	7.39 ±0.76	7.73 ±0.94	8.17 ±0.98
P value 50-<60 group vs:	-	-	0.5**	0.02***	-
P value 60-<70 group vs:	-	-	-	0.02***	-

These groups were composed of a statistically insignificant number of patients.
****Not significantly different from the 60-<70 group with an alpha cutoff value of 0.05.***
*****Significant difference from comparison group with an alpha cutoff of 0.05.***

Distribution of Gleason Scores in the High-grade Prostate Cancers as a Function of Age. In order to hone in a bit more on the course of progression of high-grade tumors in our patient population, we have analyzed the frequency of individual Gleason scores for the high-grade tumors in each age group represented as bar graphs as shown in Figure 1. Although we have included the <50 and > 80 age groups, because of their very small sample sizes (8 in the <50 age group and 6 in the ≥80 age group), the results for these two groups have no statistical significance. There are two important trends in this figure. Gleason 7 cancers (blue in Figure 1) decreased markedly from 80 percent of the 50-<60 year group (100 percent in the <40 year old group) to 56.4 percent in the 70-<80 year old group (33.3 percent in the ≥80 group), an almost 30 percent drop. In contrast, Gleason 9 scores (gray in Figure 1) were at 7.5-7.6 percent for the 50-<60 and 60-<70 groups but underwent a more than threefold increase to 23.6 percent for the 70-<80 group. Gleason 8 scores (orange in Figure 1) increased moderately from 12.5 (50-<60 group) to 16.4 (70-<80 group). Gleason 10 scores (yellow in Figure 1) were low at 0 for the 50-<60 group and underwent a small increase to 3.6 percent in the 70-<80 group. Thus, as age progresses for these cancer patients, Gleason 7 scores decrease while Gleason 9 scores increase suggesting further that patients in the lower age groups such as 50-<60 should be actively screened for this disease.

DISCUSSION

Prostate Cancer Screening Should be Carried Out at Significantly Lower Ages. Our findings shown in Table 1, that more than half of all prostate cancers screened in our patient population in the 50-<60 year age range were high-grade ones, strongly suggest that screening for prostate cancer in this population should begin at substantially lower ages than 50, e.g., 40-<50. From Table 1, it may be noted that the highest number of patients screened were in the 60-<70 years of age group. Given the above findings, the preponderance of screening should be centered on the 40-<50 and 50-<60 year old patients.

Screening at Older Ages May Also be Advisable. While earlier screening would be effective in reducing advanced prostate cancer in our patient population, another finding shown in Table 1 suggests further screening may be necessary. Our results show that the percentage of high-grade cancers in the three age groups for which screening rates were the highest, i.e., 50-<60, 60-<70, 70<80, were surprisingly constant at >50 percent. Normally, it would be expected that, as age progresses, tumor grade would also progress leading to an increase in the fraction of high-grade tumors in the higher age groups although this is hypothetical.[13] However, if patients screened in a particular age group include patients who were previously screened and found to be normal but, on re-screening, have converted to having low-grade prostate cancer, these patients would contribute a significant source of low-grade cancers. If this conclusion is valid, then

screening of patients must be continued to advanced ages since apparently new cancers develop in a significant number of these patients who were previously found to be prostate cancer-free. This conclusion is compatible with the results of a recent study[14] of the age-specific incidence rates (ASIR) of prostate cancer in a large cohort of Norwegian patients which found that there was a six-fold increase in ASIR for patients who were 75-79 as compared with those who were 55-59. The study recommended screening for older men.[14]

Figure 1. Seydafkan et al.

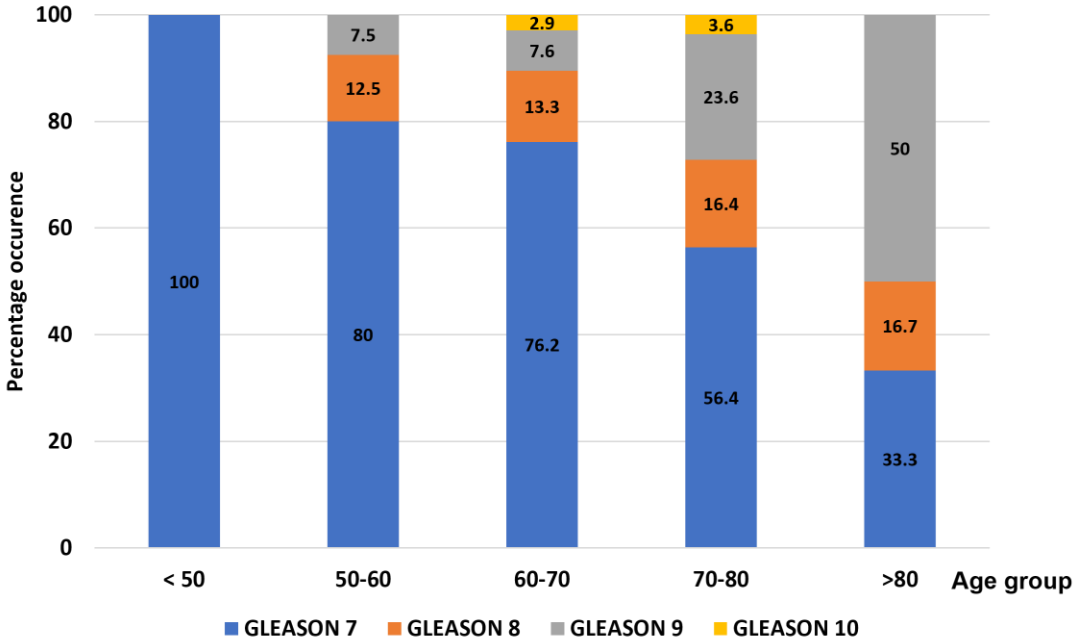

Figure 1: Bar graphs showing the distribution of Gleason scores (frequency of occurrence, Y-axis) for high-grade (Gleason scores ≥ 7) prostate cancers in each of the age groups (X-axis) of patients with this disease. The color codes representing each Gleason score from 7-10 are shown in the figure. The percentage of each tumor Gleason score is likewise shown in each bar graph.

Changes in Gleason Scores in High-grade Cancers between Age Groups. It would be expected that, as age increases, the average Gleason score would increase significantly because most patients screened in each age group are patients who have not undergone screening. In the more advanced age groups, previously unscreened patients who have prostate cancer and have been harboring it over more prolonged periods would be likely to have more advanced cancer. Interestingly, from Table 2, the mean Gleason scores for the 50-<60 and 60-<70 year age groups are not statistically significantly different. This finding suggests that, while high-grade cancer development may occur rapidly, the resulting high-grade tumors progress to higher grades at slower rates. However, the mean Gleason score increases significantly in the 70-<80 age group. The cause of this change is seen from Figure 2 to be due to a tripling of Gleason 9 tumors and a twenty percent drop in the percentage of Gleason 7 cancers. This finding further supports continuous screening for patients in the 60-<70 and the 70-<80 age groups.

Comparisons with Other Studies. Our patient population consisting predominantly of African-American men, many of whom have West Indian ancestry, presents with unique features of prostate cancer. Most strikingly, the high level (>50 percent) of high-grade prostate cancer that we observed for all 378 patients in our prior study[1] occurs immediately in the lowest age group (50-<60) for which significant screening was performed. This high level of high-grade cancer is maintained over the entire 30 year age group (50-80). We have been unable to find systematic studies with which to compare these results directly although there are studies on limited age groups whose findings differ from one another and from our results.

In one such study[15] that was limited to the 70-80 age group, 61percent of patients with

diagnosed prostate cancer were found to have high-grade cancer in contrast to our value of 52.9 percent for this age group. This difference may be due to our additional finding that the fraction of prostate cancers that are high-grade in each age group over the 30 year period remained constant at around 50 percent in contrast to studies on other patient populations.

For example, in two large studies of prostate cancers in Norwegian men[13,14], it was found that high-grade cancers increased percentage-wise with age. In one of these studies[13] of patients in the 50-70 age range, in which the Gleason 7 score was divided into Gleason 4+3 and 3+4, the risk of being diagnosed with a Gleason 3+4 score increased yearly by 11 percent while the risk for being diagnosed with a Gleason 4+3 score increased by 8.5 percent yearly. Most of this increased risk seemed to occur after age 60.

In the other study[14], involving 20,356 men, the percent of these patients with high-grade disease was studied in the age groups 55-59, 65-69, 75-79 and 85-89. However, in this study, high-grade disease was defined as Gleason scores of 8-10 even though the score of 7 is also indicative of high-grade disease. In our prior study[1], we found that prostate cancers with Gleason scores of 7 and above had metastatic potential unlike cancers of grade 6 or lower, none of which metastasized.

Our Gleason 8-10 cancers in our 50-<60 (20%),60-<70 (23.7%) and 70-<80 (43.6%) age groups correlate with the ones in the 55-59 (16.5%),65-69 (23.4%) and 75-79 (37.2%) groups. However, the number of Gleason 7 tumors in each age group in our study but omitted in the comparison study, caused the percent of high-grade tumors to remain constant in the 50% range across the age groups. Since the percentage of Gleason 7 cases were not reported in ref. 14, we were unable to compare our results with the Gleason 7 cases.

In another large study in China, the occurrence of high-grade prostate cancers was studied in three age groups: ≤ 55, 56-75 and >75. The median Gleason scores in the three groups were 8,7 and 8, respectively.[16] The authors concluded that men aged ≤55 years or >75 years have higher levels of clinically significant prostate cancer compared with patients between the ages of 55 and 75 years and recommended screening in the youngest and oldest groups. If the ≤55 group can be compared with our 50-<60 age group (our median Gleason score was 8 as in the comparison study), then these results correlate with our findings that at least 50 percent of prostate cancers in the 50-<60 age range are high-grade cancers. However, this percentage persists in our study whereas it declines in the 56-75 age range in the comparison study. Furthermore, our median Gleason scores for the 60-<70 and 70-<80 age groups that more or less correlate with the 56-75 and >75were both 8.5, higher than7 and 8 in the comparison study.

Our patient population therefore appears to be unique in that high rates (over 50 percent) of high-grade cancer occurs at age 50-60, and this rate, unlike in prostate cancer studies of other ethnic and demographic groups, remains constant over the 50-80 year period. During this period, there appears to be the development of new low-grade cancers that seem to maintain the 50 percent prevalence of the high-grade cancers. The high-grade cancers seem to remain at their initial Gleason scores at least over the 50-70 age period after which time, there is a shift the in Gleason scores to higher values as can be seen in Figure 1.

CONCLUSION

Our results suggest that screening for prostate cancer should begin at age 40 in our unique patient population. This screening would greatly lower the percent of high-grade tumors found in the 50-<60 age group irrespective of whether the high-grade tumors derive from low-grade ones or whether they develop independently. Because of the apparent later development of low-grade cancers in this patient population, and because significant increases in higher grade Gleason tumors occur in the 70-<80 age group, continued screening should be performed.

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