HISTOMORPHOLOGICAL CHARACTERISTICS OF PROSTATE SPECIMENS ANALYZED AT A REFERRAL HOSPITAL IN KENYA.

Vincent Musungu[1] Willis Oyieko[1] Domnic Marera[1] Gideon Ng'wena Magak[1]
[1] Maseno University school of medicine, department of Human Anatomy
Corresponding Author: Dr. Vincent Musungu. Email: **vinn.musungu@gmail.com**
ORCID ID: https://orcid.org/0000-0002-9818-5175

ABSTRACT

Background: Global shift to high energy foods is important risk factor for new variants of prostate cancer. Some prostate tumors have an indolent course while others have an aggressive course; therefore, knowledge of tumor subtypes can help in clinical decision-making based on the patient profile. **Methods:** The main aim of the study was to determine the histomorphological characteristics of prostate specimens analyzed at regional referral hospital. The study was a cross-sectional retrospective study. The target specimens in this study consisted of prostate specimens that had prostate specific antigen level and were analyzed and reported between 2017 and 2022 at Jaramogi Odinga Oginga teaching and referral hospital, Kisumu Kenya. **Results:** Prostate color was not reported in eight reports. Of the 72 specimens observed, 50 (69.4%) were reported to be white, 12 (16.7%) were reported to be tan/white, 9 (12.5%) were tan brown, and 1 (1.4%) was tan grey. There was significant variation (p=0.001) in prostate specimen color. Of the 80 specimens, 47 (58.75%) had coarse surface, 16(20.00%) nodulated surfaces and 17 (21.25%) shrunken surfaces. There was variation in prostate surfaces ($p<0.00001$, $X^2=23.275$). Majority of specimens 55 (68.8%) measured between 0-29 mm, 12 (15%) measured 30-59 mm, 7 (8.8%) measured 60-89, 3 (3.8%) measured 90-119, 2 (2.5%) measured >150 mm and 1 (1.3%) measured 120-149 mm. There was no significant difference in the prostate biopsy sizes in comparison to the mean (p=0.984, t=0.020, 95% CI). The majority 20 (25%), of specimens had prostate cancer 15 (18.75%) had atypical findings, and 2 (2.5%) had high-grade proliferative intraepithelial neoplasia. The microscopic features of the groups did not differ significantly (F2, 34 = 1.469, p = 0.244). There is positive correlation between Gleason scores and Prostate specific antigen levels (p = 0.004, r = 0.474). **Conclusion:** There is variation of specimen color in prostate specimen with prostate cancer implying that advanced prostate disease causes changes in prostate color. Atypical prostate findings are common in age 50-59 which may suggest that targeted prevention and intervention should focus on this age group. Higher Gleason scores are likely to be observed in patients with higher PSA levels among patients being evaluated for prostate tumors.

Keywords: Adenocarcinoma; prostate cancer; histomorphology

INTRODUCTION

Prostate cancer is the second common cancer diagnosis made in men behind skin cancer. Globally, prostate cancer is the fifth leading cause of death and may be asymptomatic at the early stage with an indolent course (Rawla, 2019). Diagnosis of prostate malignancy is made on the underpinning of urinary tract symptoms and elevated PSA levels (>10ng/mL) which then prompts the need for biopsy to confirm the diagnosis. There has been global shift to genetically modified diet and generally people use high energy foods in form of fast foods which according to various researches can alter prostate molecules and be molecular determinants of prostate cancer variation. The molecular basis of carcinogenesis in the prostate cancer are

emerging due to the fact that alterations in molecules that regulate the cell cycle and apoptosis contribute to the pathogenesis of prostate cancer. While studies done in the western world have demonstrated that acinar adenocarcinoma is common, variations due to changing lifestyle, fast foods and genetics among African men cannot be ignored. There is scarce information on prostate biology and histological characteristics of prostate tumors among men in western part of Kenya who are all exposed to factors that can alter the biology of prostate gland thus predisposing to prostate cancer variants that may be different from the conventional adenocarcinoma. Such scarcity of information could lead to assumptions that all prostate tumors are adenocarcinoma. Such assumptions can cause delayed decision making in care. In addition, geographical and racial factors are documented by American society of urology as independent risk factors for prostate tumors. Men in western part of Kenya could have different prostate histological characteristics given different geography and race. Such knowledge will guide the aggressiveness in pursuit of treatment for patients whose prostate specimens are reported positive for cancer. The study sought to determine histomorphological characteristics of prostate specimens analyzed and processed at JOOTRH between 2017 and 2022.

MATERIALS AND METHODS

Study area
The study was conducted at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) which is a level five hospital located in Kisumu Kenya and has a well-established pathology laboratory with adequate staffing and necessary equipment to analyze histology specimens.

Study design
The current study was a descriptive cross sectional retrospective study design that utilized prostate specimen histology reported in a pathology laboratory as reported between 2018 and 2022. Random sampling was used to get the specimen as reported. A sampling frame consisted of pathology register of the histopathological reports of the prostate specimens analyzed in the laboratory. Each name in the register was assigned serial numbers. All the numbers were fed in a computer program (randomizer application) to randomly sample (determined by Yamane Taro formula) 80 names out of those so that each had an equal chance of getting selected.

Sampling methods
Systematic random sampling was used. A sampling frame consisted of pathology register of the histopathological reports of the prostate specimens analyzed at JOOTRH. Each name in the register was assigned serial numbers. All the numbers were fed in a computer program (randomizer application) to randomly sample 80 names out of those so that each had an equal chance of getting selected. Only samples reported with PSA levels were included in the study.

Data collection
The researcher collected the data from hospital pathology laboratory with the help of two research assistants who were laboratory technicians working in the pathology laboratory and conversant with retrieving soft copy data from the storage site. The data from each prostate pathology report was then transferred into each data extraction form for each patient profile: the age, clinical notes including PSA levels, microscopic and macroscopic examination, and conclusion was extracted and recorded in the research data extraction form. Photographs of slides mounted on a

microscope were also taken for prostate tissues with prostate cancer and with benign prostatic hypertrophy.

Data analysis

Descriptive and inferential statistics were done with SPSS version 29 for Windows. One sample chi-square was used to test the hypothesis that there is no variation in specimen colour and surface. One sample t test was used to assess if the specimen size differed significantly from the mean. ANOVA was used to check whether microscopic features differed significantly. A post hoc analysis based on the Levine statistic was achieved by Dunnett's 3 analysis to check

which group contributed to differences. A p value of <0.05 was considered statistically significant at 95% CI.

Ethical approval

This study was licensed by National commission of science, technology and innovation (NACOSTI) vide license number NACOSTI/P/23/22845. The study was approved by JOOTRH ethics committee vide letter reference number ISERC/JOOTRH/659/22. The data collection was allowed by the JOOTRH hospital CEO vide letter reference number GEN/21A. No patient identifiers were collected during the study.

RESULTS

Gross morphology of prostate specimens
Specimen color

A total of 80 prostate histology reports for prostate specimens were retrieved. The prostate specimen colors reported were categorized as white, tan/white, tan/brown, and tan/grey. Prostate color was not reported in eight reports. Of the 72 specimens observed, 50 (69.4%) were reported to be white, 12 (16.7%) were reported to be tan/white, 9 (12.5%) were tan brown, and 1 (1.4%) was tan grey (Table 1).

Table 1: Prostate tissue color

	Frequency	Percent
White	50	62.5
Tan/white	12	15.0
Tan/Brown	9	11.3
Tan/grey	1	1.3
No colour reported	8	10.0
Total	**80**	**100.0**

One sample chi-square was used to test the hypothesis that the categories of prostate specimen color occur with equal chances. One sample Chi-square statistic was used to examine this hypothesis. There was statistically significant variation (X^2=79.444,

p=0.001) in prostate specimen color as reported in prostate histology.

Specimen surface

The surface of prostate specimens was described in clinical categories: coarse, shrunken, or nodular (Figure 2). Of the 80 specimens, (47; 58.75%) had prostate biopsy surfaces that were coarse, followed by nodulated surfaces (16; 20.00%) and shrunken surfaces (17; 21.25%); Figure 2. The study sought to establish whether the texture reported was due to chance.

Table 2: Chi-square test of fitness output
Test Statistics

	Surface texture
Chi-Square	23.275[a]
df	2
Asymp. Sig.	.000

One sample chi-square test of fitness was used to test the hypothesis that prostate surfaces as reported occurred by chance. The researcher could not demonstrate that the prostate specimen surfaces occur with equal changes (p<0.05, X^2=23.275, df=2, 95% CI) (Table 2). Hence H1 was supported.

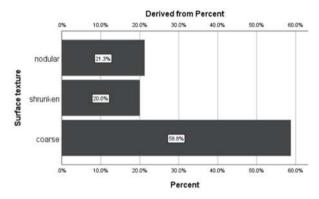Figure 1: Photograph of nodulated prostate gland (arrow indicate specific nodules)

Figure 2: Frequency distribution of Prostate surface texture

Specimen size
Majority of the biopsy specimens 55 (68.8%) measured between 0-29 mm, 12 (15%) measured 30-59 mm, 7 (8.8%) measured 60-89, 3 (3.8%) measured 90-119, 2 (2.5%) measured >150 mm and 1 (1.3%) measured 120-149 mm (Figure 3).
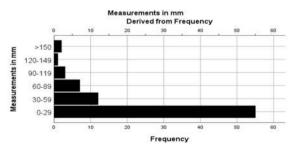

Figure 3: Prostate specimen measurements

One sample t test was run to assess if the specimen sizes differed significantly in comparison to the mean prostate biopsy size. The descriptive statistics showed that prostate biopsy size had a mean of 1.61, with a standard deviation of 1.142. The results reveal that there is no statistically significant difference in the prostate biopsy sizes in comparison to the mean (p=0.984, t=0.020, 95% CI) (Table 3).

Table 3: One sample t test on specimen measurement in mm

One-Sample Test					
			Test Value = 1.61		
				95% Confidence Interval of the Difference	
	t	df	Sig. (2-tailed)	Mean Difference	Lower	Upper
Measurements in mm	.020	79	.984	.002	-.25	.26

Microscopic morphology
The study sought to establish the microscopic features of prostate specimens as reported. Majority 43 (54%) of the specimens had BPH/no cancer. The microscopic features of 37 (46%) prostates specimens were reported as either having atypical findings, high grade prostatic intraepithelial neoplasia (HGPIN), or prostate cancer. The majority of specimens analyzed were labelled as having prostate cancer in 20 (25%), followed by those labelled as atypical in 15 (18.75%), and high-grade PIN in at least 2 (2.5%) (Figure 4).

Gleason scores
The specimens were further characterized in terms of Gleason or group scores. (Table 4).

Table 4: Gleason scores, PSA crosstabulation

		PSA (ng/ml)					Total
		0-4	5-10	11-49	50-99	>100	
Gleason Scores	Gleason<6/Group 1	0	2	3	2	1	8
		0.0%	66.7%	60.0%	33.3%	4.8%	22.2%
	Gleason 7/Group 2	1	0	1	1	6	9
		100.0%	0.0%	20.0%	16.7%	28.6%	25.0%
	Gleason 7/Group 3	0	1	1	1	5	8
		0.0%	33.3%	20.0%	16.7%	23.8%	22.2%
	Gleason 8/Group 4	0	0	0	2	4	6
		0.0%	0.0%	0.0%	33.3%	19.0%	16.7%
	Gleason 9or10/Group 5	0	0	0	0	5	5
		0.0%	0.0%	0.0%	0.0%	23.8%	13.9%
Total		1	3	5	6	21	36
		100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Prostate microscopic features and age
The hypothesis tested if the microscopic features differed across different age groups. Prostate histology reports were divided into

four groups based on the age of the patient (Group 1: 40–49 years, Group 2: 50–59 years, Group 3: 60–79 years, and Group 4: above 80 years) (Figure 4). The ANOVA results suggest that the microscopic features of the groups did not differ significantly ($F_{2,34} = 1.469$, p = 0.244, 95% CI). Since Levine's statistic for the mean is significant (p=0.001), an equal variance was not assumed.
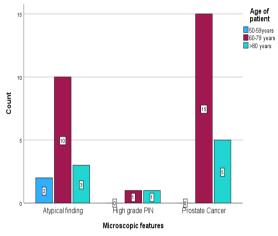

Figure 4: Microscopic features

To check for individual differences between groups, post-hoc comparisons were assessed using Dunnett's T3. The test indicated that the mean microscopic features for ages 50–59 years (M = 1.00, SD = 0.000) were significantly different from those for ages 60–79 years (M = 2.19, SD = 0.981). The mean differences were significant at the 0.05 level. However, no significant differences were detected between the other groups.

Gleason score
Majority 6 (28.6%) of patients who presented with PSA levels greater than 100 ng/ml contributed most to group 2 Gleason score (25%) (Table 4). The study sought to establish the correlation between Gleason scores and PSA levels.

Table 5: Pearson PSA and Gleason scores correlation

Correlations

		PSA (ng/ml)	Gleason Scores
PSA (ng/ml)	Pearson Correlation	1	.474**
	Sig. (2-tailed)		.004
	N	80	36
Gleason Scores	Pearson Correlation	.474**	1
	Sig. (2-tailed)	.004	
	N	36	36

**. Correlation is significant at the 0.01 level (2-tailed).

Pearson correlation statistics was used to examine the correlation between Gleason's scores and PSA levels. There is a statistically significant positive correlation between Gleason scores and PSA levels (p = 0.004, r = 0.474) (Table 5). Therefore, the null hypothesis was not supported.
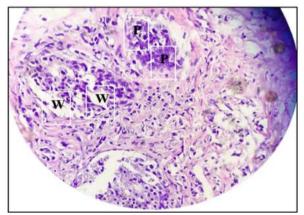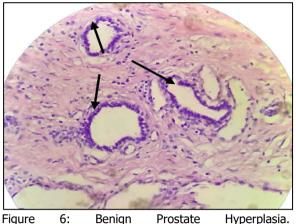

Figure 5: Prostate adenocarcinoma. Photomicrograph showing large nuclear, prominent nucleoli and collagenous micronodules infiltration. P: Prominent nucleoli, W: collagenous micronodules infiltration

Figure 5 prominent nucleoli and micronodule infiltration is notable which is tandem with prostate adenocarcinoma. Histological characteristics of prostate cancer requires any of the three: the presence of circumferential perineural infiltration, collagenous micronodules and glomerulation.

Figure 6: Benign Prostate Hyperplasia.

Photomicrograph showing solid nests. Arrow points to nested cells

In Figure 6 the arrow shows nested cells in two layers of epithelial cells which is characteristic of benign prostatic hyperplasia. Benign prostatic hyperplasia is characterized by infoldings, two layers of epithelial tissues giving it a nested cells appearance (arrows). It is also characterized by hyperplasia of smooth muscles of prostate, enlarged glands and enlarged fibrous tissue.

DISCUSSION

The results from the current study suggest that there is significant variation in prostate specimen color, with the majority being white (50%), tan/white (12%), tan/brown (9%) and tan gray (1%) (Table 1). It should be kept in mind that a normal prostate gland appears white on gross examination and therefore one possible interpretation of results shown in Table 1 is that color variation occurs due to pathologic changes or biopsy technique. Lindh et al. (2018), found that white, tan, yellow, and orange tumors made up the majority of those that could be definitively diagnosed as prostate tumor. In the current study, there was no documentation of color as yellow or orange, a major contradiction from findings by Lindh et al. (2018). This could be because of variation in pathologist coding of colors due to non-standardization of prostate color reporting. Another possible explanation could be that the biopsy technique or the stage of prostate disease, distort the gross prostate histologic features to induce gross changes in prostate appearance.

The current study revealed that there is no difference in the prostate biopsy sizes in comparison to the mean of 14 mm. (p = 0.984). The findings shown in Figure 3 are similar to that of Obek et al. (2012) who indicated that mean prostate core biopsy size is 12 mm and Fiset et al. (2013) who found biopsy size to be 13 mm. One possible interpretation of these results is that needle core length could be an important morphometric parameter of transrectal prostate biopsies that directly influences the biopsy size and thus the cancer detection rate. The results of the current study agree with other authors (Fiset et al., 2013; Öbek et al., 2012) and this could be explained by the fact that there could be guidelines on the standard prostate biopsy technique in which core biopsy needle is used. It could also be argued that perhaps core biopsies are the common technique of sample collection for prostate specimens.

The current study found that prostate microscopic features of the groups differ significantly with age and that microscopic features for age 50–59 years were significantly different from 60–79 years, with the majority of the pathological changes (HGPIN and prostate cancer) observed more in the age bracket 60–79 years compared to atypical changes at 50–59 years. (Figure 4). The results are in agreement with other authors (Kopp et al., 2011; Liu et al., 2020), whose data suggest that patients aged 60–79 have an increased likelihood of developing BPH and prostate cancer. One possible explanation of the results could be that perhaps alterations in the prostate histological profile are pronounced at 60–79 years of age. The current study found that prostate atypical findings were mainly

observed in men aged 50–59, which agrees with Matti et al. (2022) and Miyai et al. (2014). The implications of this finding are that men aged 50–59 need screening for prostate diseases, possibly because they have an increased risk for prostate disease.

In the current study, 18.5% of patients whose samples were analyzed had atypical findings (Figure 4), compared to 30.6% and 25% in Yanez & So (2015) and Kopp et al. (2011), respectively. It should be noted however that the Yanez & So (2015) study was a 2-year prospective study carried out in the Philippines, which is a different geographical region, and thus racial differences could be an explanation of the variation, indicating that perhaps atypical prostate findings are more prevalent among men aged 50-59 in western countries compared to other parts of the world. Another possible interpretation is that most men present for prostate evaluation at ages 50-59 in sub-Saharan Africa.

The current study found that 5.4% of the samples analyzed had high-grade intraepithelial neoplasia, which is in contradiction to studies such as Kim et al.'s (2021) 70.4% and Pierorazio et al.'s (2007) 88.4%. The significant variation could suggest that either reporting for HGPIN is inadequately reported or perhaps the sample size in the current study was small compared to Pierorazio et al.'s (2007) study of 3460 subjects, which covered an 18-year period between 1988 and 2006. Another possible interpretation could be that, given that the studies by Fitet et al. (2013) and Pierorazio et al. (2007) were done in developed countries where an aging population forms a larger proportion of the population, it is more likely to have prostate pathologies reported compared to sub-Saharan Africa, where there are fewer aged men likely to present for evaluation of prostate disease. It is also possible that economic implications can make fewer men present for prostate evaluation in sub-Saharan hospitals.

Chi-square statistics were used to examine the association between Gleason's scores and PSA levels. The current study found a statistically significant correlation between Gleason scores and PSA levels ($p = 0.004$, $r = 0.474$) (Table 5). The current study results agree with Cihan et al.'s (2019) finding that Gleason score of patients was significantly and positively correlated with age and PSA levels. It should be noted, however, that although the findings agree, Cihan et al. (2019) carried out a prospective study, and their reporting would likely have been better compared to a retrospective study. Similarly, Gündodu et al. (2020) found that Gleason scores correlate positively with PSA levels in a prospective study of patients who underwent radical prostatectomy. The current findings, however, are in contradiction with Sanli et al. (2017). This could perhaps be due to the fact that Sanli et al. (2017) focused on patients who were on treatment follow-up, and therefore the relationship could have been confounded by treatment.

The histology reports analyzed were all from the hospital pathology laboratory computer data base, and this study did not establish whether there were any errors in data entry. More research on prostate histology among patients on treatment is required. Further research is needed to determine the changes in prostate histological features following treatment for prostate cancer.

CONCLUSION

These results suggest that there is significant variation in prostate biopsy specimen color in different men, but the majority of prostate specimens are white. Variations in colors such as tan and yellow could signify the effect of a disease process on the prostate that induces color alterations. The study found positive correlation between Gleason scores and PSA levels, implying that high Gleason scores are observed in patients with high PSA levels. Patients whose prostate specimens were reported to have HGPIN or

atypical findings need a repeat histology as soon as possible since these are premalignant findings or lesions that mimic prostate carcinoma. Based on these conclusions, the following recommendations are made: There is significant variation in histomorphology of prostate specimens in relation to color and surface. Therefore, pathologists need to correlate the specimen color with extend of disease using tools such as Gleason scores. Men aged 50-59 may have atypical findings on histology.

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