PREVALENCE OF BENIGN, PRECANCEROUS, AND MALIGNANT LESIONS OF THE PROSTATE IN MEN AGED TWENTY (20) YEARS AND ABOVE.

A DISSERTATION SUBMITTED IN PART-FULFILMENT FOR THE DEGREE OF MASTER OF MEDICINE IN PATHOLOGY IN THE UNIVERSITY OF NAIROBI.

(2007)

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DECLARATION

I certify that this work is original and has not, to the best of my knowledge been submitted for a degree in any other university.

Signed..... Date.....

This dissertation has been submitted for examination with the approval of my supervisor (s)

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Signed..... Date.....

DEDICATION

I dedicate this book to my loving wife, Mwende and my children Ndanu and Mbuuko.

ACKNOWLEDGEMENT

I am very grateful to all those who enabled me to successfully complete this project. My supervisors, Dr. W. Waweru and Prof. D. Gatei , of the Department of Human pathology, University of Nairobi, for their support, guidance and availability, Dr A. Gachie for looking at some of the histology slides as a quality control measure.

I am also very grateful to Prof. C. Kigondu for her guidance and encouragement throughout the study.

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LIST OF ABBREVIATIONS

AAH	Atypical Adenomatous Hyperplasia
BPH	Benign Prostatic Hypertrophy
CAM	Corpora amylacea
CM	City Mortuary
DRE	Digital Rectal Examination
H/E	Haematoxylin / Eosin
HGPIN	High Grade Intraepithelial Neoplasia
KNH	Kenyatta National Hospital
LGPIN	Low Grade Intraepithelial Neoplasia
PAP	Prostatic Acid Phosphatase
PBP	Prostate binding Protein
PIN	Prostatic Intraepithelial Neoplasia
PSA	Prostate Specific Antigen
SOPs	Standard Operating Procedures
UTI	Urinary Tract Infection
US	Ultrasound

DEFINITIONS

Atypical Adenomatous hyperplasia - localized proliferation of small acini within the prostate

Benign prostatic hyperplasia - hyperplasia of prostatic stromal and epithelial cells

Latent cancer – incidental microscopic cancer.

Occult cancer- cancer of the prostate that is not seen microscopically in the prostate

Precancer -lesions with malignant potential that precede cancer

Prostatic intraepithelial neoplasia – dysplasia of the epithelium lining prostate glands.

Corpora amylacea- round laminated bodies derived from proteinaceous secretions.

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1.0ABSTRACT

Introduction: The main diseases of the prostate are prostatitis, benign prostatic hypertrophy and prostate cancer. One in ten men will develop clinically significant prostate cancer in their lifetime. Men who are diagnosed in their 50s and 60s probably started to develop the disease in their 30s and 40s. Prostatic Intraepithelial Neoplasia has been associated with prostate cancer on epidemiologic, clinical, genetic, and molecular levels.

Objective: To determine the prevalence of carcinoma of the prostate, high grade prostatic intraepithelial neoplasia (HGPIN), low grade prostatic intraepithelial neoplasia (LGPIN),benign prostatic hyperplasia, atypical adenomatous hyperplasia, squamous metaplasia and prostatitis in autopsy prostate specimens and compare the findings with those from other geographical areas.

Design: Descriptive cross-sectional study conducted from November 2006 to October 2007.

Setting: The KNH mausoleum, the City Mortuary, Nairobi and the histopathology laboratory, University of Nairobi.

Subjects: One hundred and three prostates removed at autopsy from men aged twenty years and above who were not known to have prostate pathology. All the subjects were black Africans.

Methods: A total of 103 prostatic gland specimens were examined by standard histopathological methods. The glands were fixed in 10% formalin, weighed, sliced at 2-4mm intervals from the apex to the bladder base and then paraffin embedded.

The paraffin blocks were sectioned with a microtome to 5μm sections that were mounted on microscopic slides. The histological slides were stained with haematoxylin and eosin. They were then examined by the principal investigator and the diagnoses confirmed by the supervisor. Another pathologist counterchecked some of the slides.

Outcome measures: Age, prostate weights, benign prostatic hypertrophy, atypical adenomatous hyperplasia, squamous metaplasia, prostatitis, corpora amylacea, low grade prostatic intraepithelial neoplasia, high grade prostatic intraepithelial neoplasia, prostatic carcinoma.

***Results*:** All the 103 prostate gland specimens were processed and the histological results analyzed using the SSPS software. The average weight of all the specimens was 27.8 grammes. Four of the specimens were more than 40 grammes. Microscopy showed that 31.1% were essentially normal, 29.1% had chronic prostatitis, 27.2% microscopic hyperplasia, 23.3% LGPIN, 15.5%HGPIN, 10.7% atypical adenomatous hyperplasia, 1% prostate carcinoma in a 48 year old, 7.8% squamous metaplasia. Corpora amylacea was seen in 25.2% of the specimens. The mean prostate weights increased with age. Microscopic benign prostatic hyperplasia increased from 15.8% in the fourth decade to 80% in the seventh decade. Low grade prostatic intraepithelial neoplasia was 24% in the third decade, increasing to 28.6% in the fifth decade. High grade prostatic intraepithelial neoplasia was 4% in the third decade, increasing to 40% in the seventh decade.

Conclusion: Premalignant lesions of the prostate are common in black Africans. The prevalence of incidental carcinoma was very low in this study. Benign prostatic hyperplasia starts early and increases with age. Chronic prostatitis was common in all age groups and it did not follow a particular pattern. Corpora amylacea was seen in all age brackets.

Recommendations: Another study of the same nature that involves, as well other investigative modalitities like immunohistochemistry.
Setting up a national policy on the basis of that of cancer of the cervix.

2.0 INTRODUCTION

The prostate is a gland of the male reproductive system that wraps around the urethra and serves to add nutritional secretions to sperm. It is 30% muscle and the rest is glandular tissue. As a man gets older his prostate may increase in size. The common diseases of the prostate are: - Benign Prostatic Hypertrophy, Prostatitis, and prostate cancer. Prostate carcinomas arise from the peripheral zones of the prostate almost always from a posterior location. Prostatic intraepithelial neoplasia, a precursor for invasive prostate carcinoma usually involves an acinus or a cluster of acini but it can be more extensive.

3.0 LITERATURE REVIEW

One in ten men will develop clinically significant cancer in their lifetime. One of the misconceptions about prostate cancer is that it is "an old man's disease. '' The truth is that prostate cancer runs prevalent in men in their forties and fifties. Prostate cancer can be also present for many years without causing any symptoms and is not often detected until it is at an advanced stage. Men who are diagnosed in their 50s and 60s probably started to develop the disease in their 30s and 40s.[1]

Prostatic Intraepithelial Neoplasia has been associated with prostate cancer on epidemiologic, clinical, genetic, and molecular levels. The frequency of PIN in prostates with cancer has been shown to be significantly increased compared with that in prostates not harboring carcinoma (82% versus 43%). Increasing frequency of PIN with advancing age and its association with cancer has been reported. [2, 3]

Prostate cancer is slow growing, taking many years to replicate and double enough to cause symptoms. It is one of the one of the "better" cancers to get since it is curable if detected early. However it is still a major cause of cancer deaths. In South Africa, it is ranked third, causing 10.7% of all male cancer deaths .[4]

Autopsy studies in Hungary, of men above twenty years have shown a 38.8% prevalence of latent cancer and HGPIN. Both were detected in the third decade and the incidence was seen to increase with age. In the age group 81 to 95 years 86.6% and 60% of men had prostate cancer and HGPIN respectively .[5] An Indian study showed a 7.02% prevalence of latent cancer in men aged above fifty years .[6] In the USA, the incidence of latent prostate cancer has been to increase from 20% in men in their fifties to 70% in men between 70 and 80 years .[7]

In Nigeria, an autopsy prostate study, where the median age of necropsy cases was 50.0 years showed a prevalence of 6.7%.[8]

In Greenland, a study of 67 autopsy prostates showed only one case of latent carcinoma .[9] A Spanish study that involved examination of 162 consecutive autopsy prostates of men aged 20-80 years showed a 3.58%, 8.82%, 14.28%, 23.80%, 31.7 %and 33.33% prevalence of latent cancer the 3rd, 4th, 5th, 6th, 7th, and 8th decade respectively. That of HGPIN was 7.14%, 11.75%, 35.71%, 38.06%, 45.40% and 48.15% respectively [10]. In a 10 year (1979-1988) retrospective Italian study of 3942 prostates, an increase of both PIN and incidental prostate cancer was noted.[11] This tallied with a Scandinavian study.[12]

A USA study of one hundred autopsy prostates of men aged twenty to forty years found atypical hyperplasia (mild to moderate) in 10% of the 20-29 age group and 24% in the 30-40 age group.[13] The results of prostate autopsy of 100 men aged above 50 in Germany suggested that dysplasia of the prostate may represent a potential precancerous lesion.[14] In the USA it has been shown that African-American men with clinically localized prostate cancer tend to have more

advanced stage at the time of radical prostatectomy compared with Caucasian men. Black males are at a higher risk of dying from cancer of the prostate than white males; the disease is more common, starts earlier, and is more aggressive.[15]
In Michigan two hundred and forty nine prostates from men aged 20-69 years were evaluated for the presence of PIN and carcinoma. The histologic diagnoses of all positive cases were as follows: seventy seven percent of the prostates with HGPIN harbored adenocarcinoma, whereas the frequency of cancer in the prostates without HGPIN was 24%. High Grade Intraepithelial Neoplasia was encountered in 0, 5, 10, 41 and 63% of men in the third, fourth, fifth, sixth and seventh decades respectively. The corresponding figures for invasive carcinoma were 2, 29, 32, 55 and 64% respectively.[16]

Results of a Japanese autopsy prostate study of men aged over 90 years showed latent carcinoma in 17 cases (58.6%), all in the peripheral region. The majority of these latent carcinomas were considered to correspond to stage A1 tumors.[17] In another Japanese study of autopsy prostates a positive relationship was shown between HGPIN and latent prostate cancer.[18]

Prostate cancer incidence and magnitude in black African has been misunderstood and underestimated in the past. It is perhaps the most common urological malignancy affecting black Africans.[19]

Atypical adenomatous hyperplasia has been identified in men under the age of 30.[20] Brawn PN et al documented the presence of atypical hyperplasia in prostates of men aged twenty to forty years in a study that involved microscopic examination of necropsy autopsy prostates.[21]

In a study by Stamatiou K et al, microscopic benign prostatic hypertrophy was seen in 65.5% of 212 consecutive autopsy prostates in men aged between 30 and 98 years. In that study atypical adenomatous hyperplasia and latent prostate carcinoma accounted for 15.5% (33 cases) and 18.8% (40 cases respectively).[22]

4.0 RATIONALE

At KNH, Magoha noted in 1995 that patients with prostate cancer presented late with symptoms of prostatic obstruction. In 2000, Magoha confirmed the same.[19] Incidence of prostate cancer is likely to increase with changing lifestyles and increased life expectancy. Studies done elsewhere on the frequency of precancer and cancer of the prostate have shown, surprisingly, the appearance of precancer as early as the third decade of life.

The findings of this study would determine the frequency of latent prostate cancer, premalignant lesions and other benign lesions of the prostate in KNH mausoleum and the City mortuary, Nairobi. This could provide a basis for a screening programme to be set up, like that of cancer of the cervix.

4.1 Justification

(i) Studies of the prevalence of prostate cancer and precancer as well as other prostate pathology have been done in several countries.

(ii) No local studies have been conducted.

(iii) This study would provide that data.

4.2 Broad objective

To carry out a histological study to determine the prevalence of benign, premalignant and malignant lesions in autopsy prostate specimens in men aged twenty years and above.

4.3 Specific objectives

(i) To determine the proportion of men with benign prostatic hyperplasia, LGPIN, HGPIN, latent prostate cancer, and any other prostate pathology.

(ii) To correlate the various pathologies with age at autopsy.

(iii) To compare and contrast the findings of this study with those from other countries.

(iv) To use the findings as a basis for recommendations on establishment of a screening programme to be set up.

4.4 Hypothesis

The prevalence of benign, precancerous and malignant lesions of the prostate is not different from that in other countries.

5.0 STUDY DESIGN

This was a descriptive cross-sectional study that involved the histological examination of one hundred and three consecutive series of autopsy prostate glands of men aged above twenty (20) years.

Study area

The area of study was the KNH Mausoleum and City Mortuary, Nairobi. The KNH mausoleum is where bodies of patients who die in the KNH wards are taken awaiting collection by relatives. In the year 2004 one hundred and seventeen autopsies were done, out of those forty-five were of men aged above twenty years. In the year 2005, one hundred autopsies were done and fifty-two were of men aged above twenty years

The CM handles the bulk of bodies from Nairobi and its environs as well as bodies that have been referred for postmortem from various districts. An average of ten postmortems is done in a day.

Study population

The study population involved men aged twenty years and above who had died and their bodies taken to the KNH mausoleum or the CM, Nairobi for an autopsy to be performed. The commonest cause of death was trauma.

Inclusion criteria were: -

(i) Age at death twenty years and above. The age was obtained from clinical records, police records, from relatives, or from identification cards.

(ii) Death from homicide, accident, sudden death at home or death from other medical or surgical conditions, unrelated to the prostate.

Exclusion criteria were: -

(i) Known history of prostate disease. Information from the file records and history where possible.

(ii) Previous urological surgery. Information was obtained from clinical notes or the presence of scar seen at post mortem.

(iii) If the body was already decomposed/decomposing.

(iv) Where relatives did not consent.

Sample size determination

Using the formula $n = \frac{Z^2(p-1)p}{d^2}$

where:-
n = sample size,
Z = Z statistic for a level of confidence (for level of confidence of 95% Z is 1.96)
P = expected prevalence (prevalence of incidental cancer in a Nigerian autopsy study, 6.7% P= 0.067) [8]
d = precision
(In proportion of one; if 5%, d = 0.05).

$$\frac{1.96 \times 1.96(1-0.067)0.067}{0.05 \times 0.05} = 96$$

Ninety six autopsy prostates were required for the study.

(One hundred and three prostates were used in this study)

6.0. METHODOLOGY

(a) Identification

Identification of bodies where a postmortem had been requested and that fitted the inclusion criteria with the help of the staff at the KNH Mausoleum or the CM. Consent was from wife, next of kin, or other relatives where applicable. Either the research assistant(s) or the principle investigator got the consent the relative at the venue of the post mortem. (Appendix I).

(b) Removal of the prostate

The whole prostate gland was removed during the postmortem. The principle investigator participated fully in all the postmortems where the prostate glands were removed.

(c) Transport

Each prostate gland specimen was put in a plastic container containing 10% formalin and taken to the KNH pathology laboratory. The specimens were fixed for about two weeks before processing.

(d) Weighing the prostate.

The prostate gland's weight was recorded in grammes using the Avery® balance at the KNH histology laboratory.

d) Processing the prostate (Blocking and histological slide preparation)

The prostate specimens were processed using the Ackerman's surgical Pathology method for Radical Prostatectomy. (Appendix II- blocking and sectioning). Slicing was done at 2-4 mm from the prostatic apex to the base of the bladder. Microtome sections of 5μm were made and mounted on slides. Depending on the size of the prostate a minimum of six histological slides was achieved for the smallest prostate. The highest number of slides per prostate was thirteen.

(e) Examination of histological slides

The histological sections were examined by the principal investigator and confirmed by the supervisor for prostatitis, BPH, PIN, AAH, squamous metaplasia and prostate cancer which was graded using the Gleason grading. (Appendix iii)

(f) Quality control

(i) Specimens were fixed in formalin as soon as they were removed from the body to avoid autolysis.

(ii) The histological slides were prepared with strict adherence to the standard operating procedures (SOPs) as outlined in appendix II.

(iii) The supervisor confirmed the histological diagnosis.

(iv) A second opinion was obtained from another pathologist who examined some of the slides to confirm the diagnoses.

(g) Data analysis

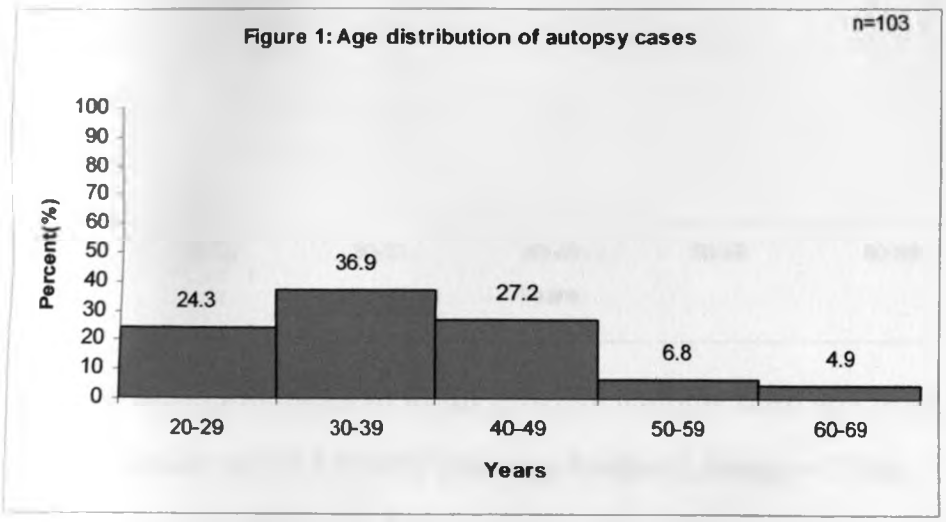
The data collected from this descriptive cross-sectional study was coded and analyzed using computer statistical software-SPSS 15.0®. The variables analyzed were: - age, benign prostatic hyperplasia, low grade prostatic intraepithelial neoplasia, high grade prostatic intraepithelial neoplasia, corpora amylacea and prostatitis. Some of the data was subjected to the chi- square test. The statistics was presented in graphs, tables, and percentages as discussed.

7.0 ETHICAL CONSIDERATIONS

- Authority to carry out the study was sought from the KNH Ethical and Research committee.
- Once approved by the Ethical Research Committee, a letter was written to the Director of the National Health laboratories explaining the nature of the study and the importance of using the City Mortuary in the study since it lies in the Director's docket. Permission to use the city mortuary was granted.
- Confidentiality was observed in the study.
- The relative(s) would be provided with the histological results of their decedent if they requested.

8.0 RESULTS

One hundred and three prostate gland specimens were removed at autopsy from bodies that met the inclusion criteria and where consent was given. The distribution of autopsy cases was 25(third decade), 38 (fourth decade), 28(fifth decade), 7(sixth decade) and 5 in the seventh decade. All the prostate glands were used in the study, although some showed features of partial autolysis. Age distribution is as shown in figure 1.



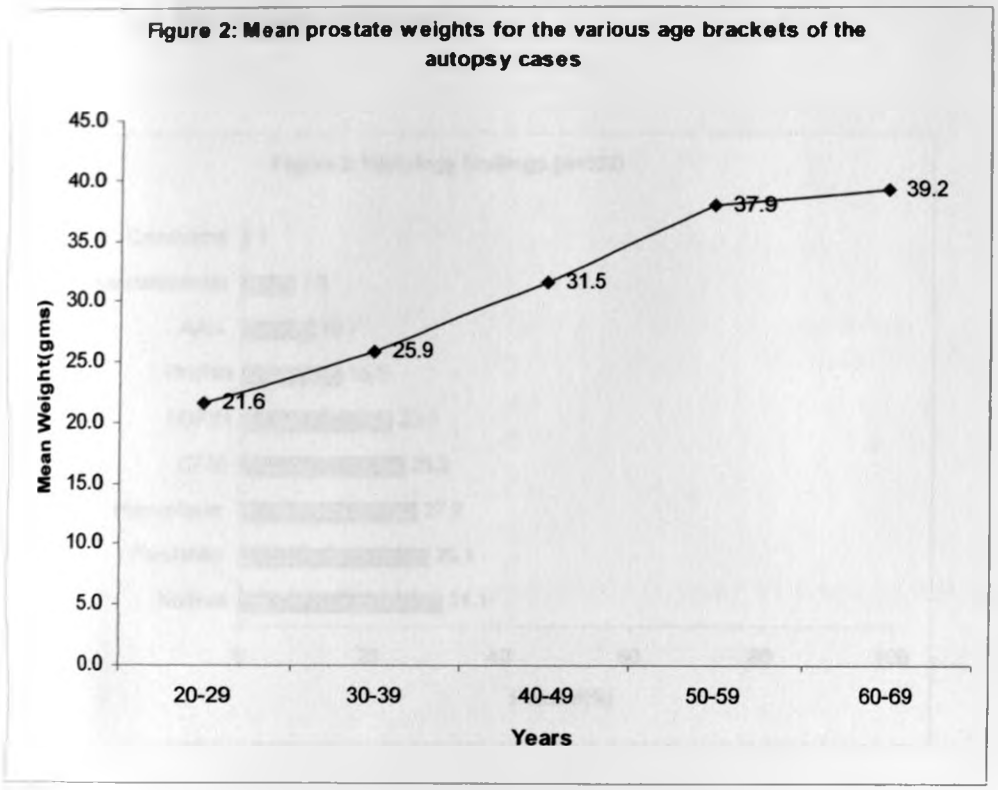
Age: 21 years- 69 years (range- 48 years)

Mean -37.6 years (SD=10.2 years)

Median- 37 years

The mean age was 37.6 years (range 21-69 years). Standard deviation 10.2 years. The median age was 37 years. The majority were in the 30-39 year age bracket (36.9%). The 60-69 year old bracket had the least number (4.9%).

The mean weight of the prostate gland specimens were as shown in figure 2.



There was an increase in mean prostate weights with age from 21.6g (20-29 year age bracket) to 39.2 (60-69 year age bracket), range – 17.6g

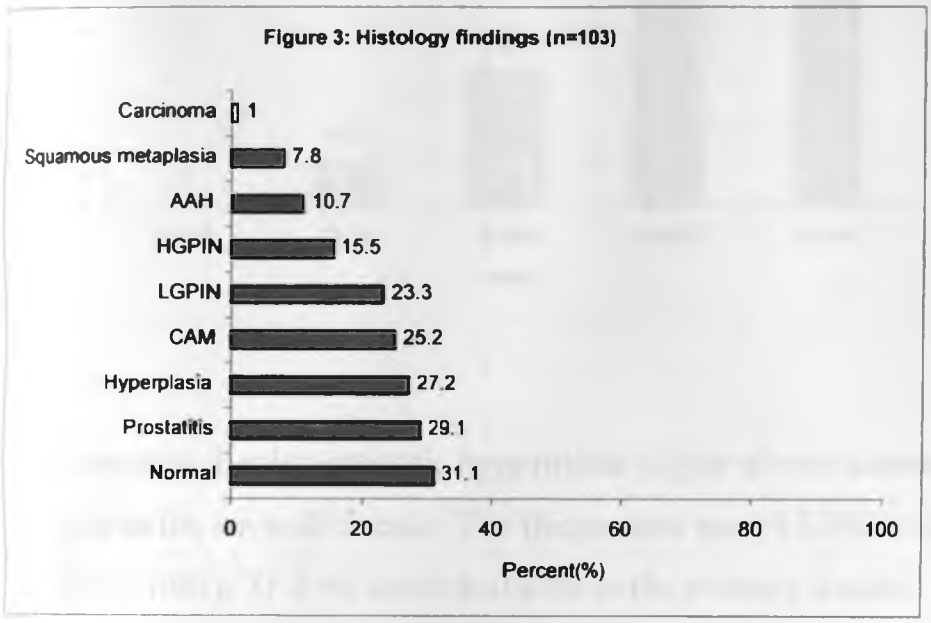
Minimum weight- 15g, Maximum weight- 55g

Median-27g, Mean-27.8g,

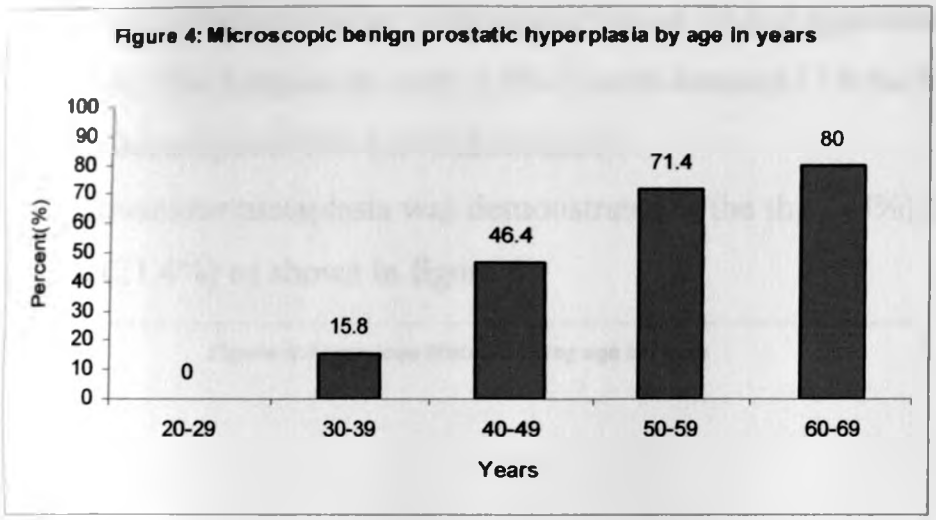
Std deviation-7.7.

Four of the prostate gland specimens weighed more than forty grammes.

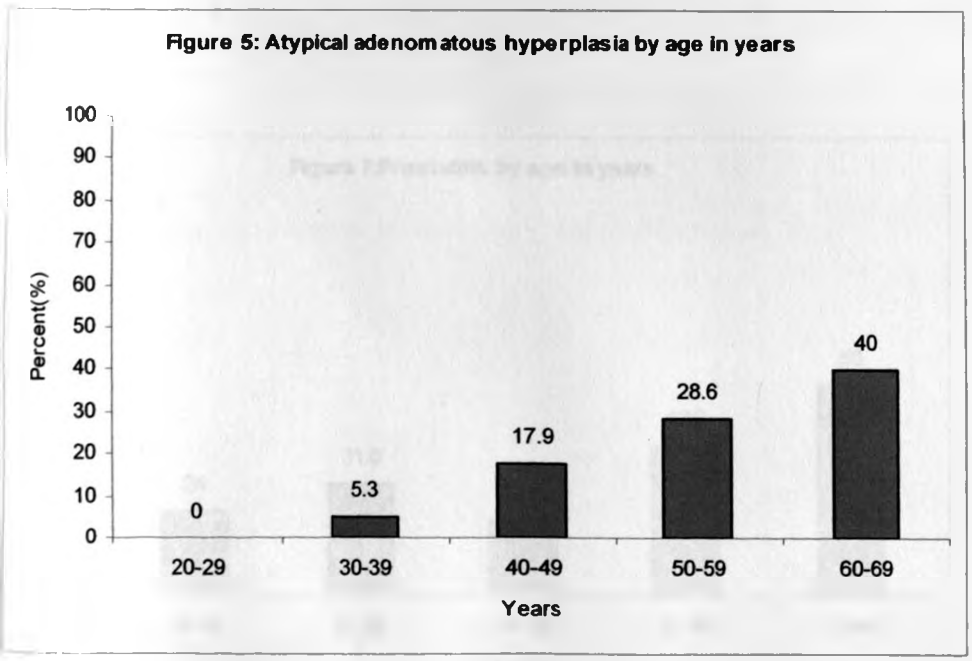
The number of blocks processed ranged from seven to thirteen. Microscopy findings are shown in figure 3.



Microscopy showed that 31.1% were essentially normal, 29.1% had chronic prostatitis, 27.2% microscopic benign prostatic hyperplasia, 23.3% LGPIN, 15.5%HGPIN, 10.7% adenomatous hyperplasia, 1% prostate carcinoma, 7.8% squamous metaplasia. Corpora amylacea was seen in 25.2% of the specimens.

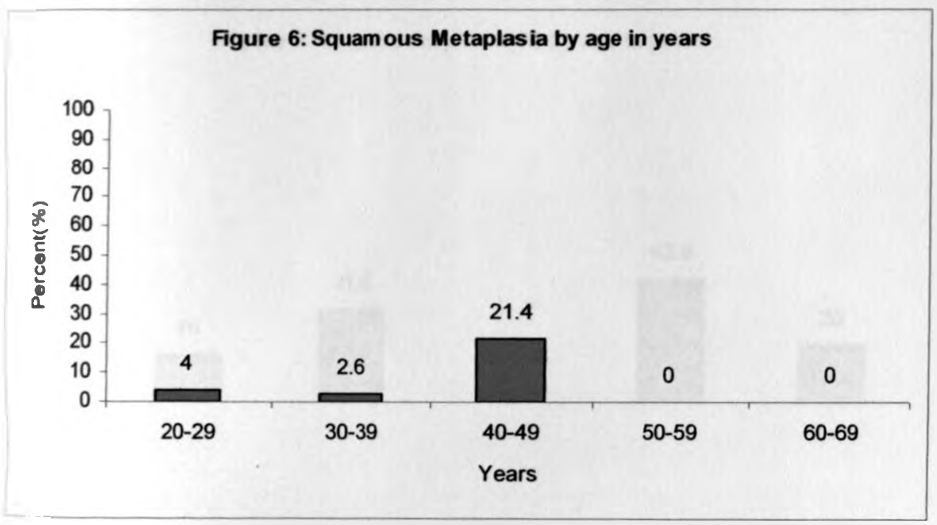


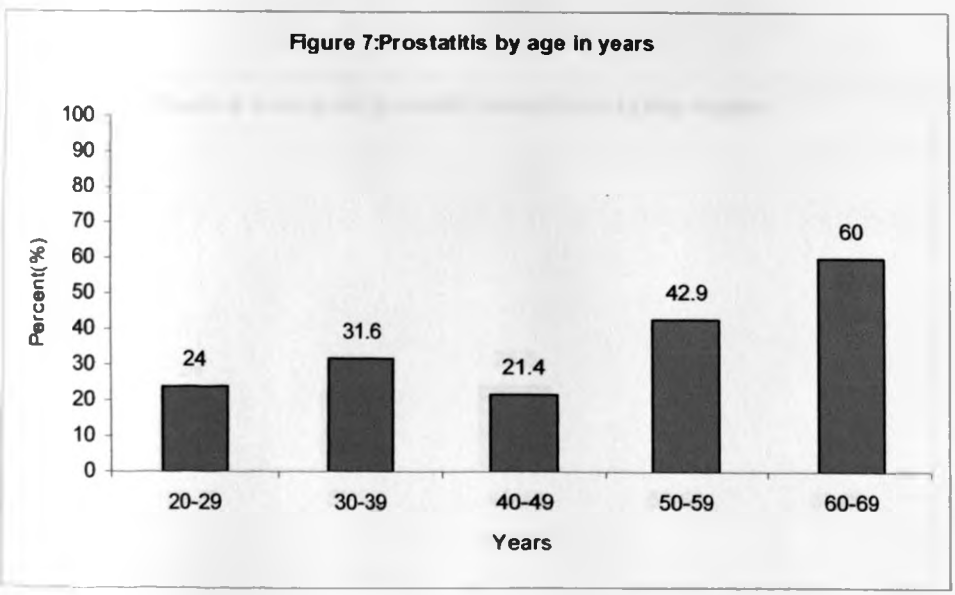
Microscopic benign prostatic hyperplasia (figure 4) was demonstrated from the fourth to the seventh decade. The frequencies were 15.8% in the fourth decade, 46.4 %(fifth), 71.4 %(sixth) and 80% in the seventh decade.



Atypical adenomatous hyperplasia (figure 5) was appreciated from the fourth decade. The frequencies were 5.3% (fourth decade) 17.9 %(fifth decade), 28.6 %(sixth decade) and 40% (seventh decade).

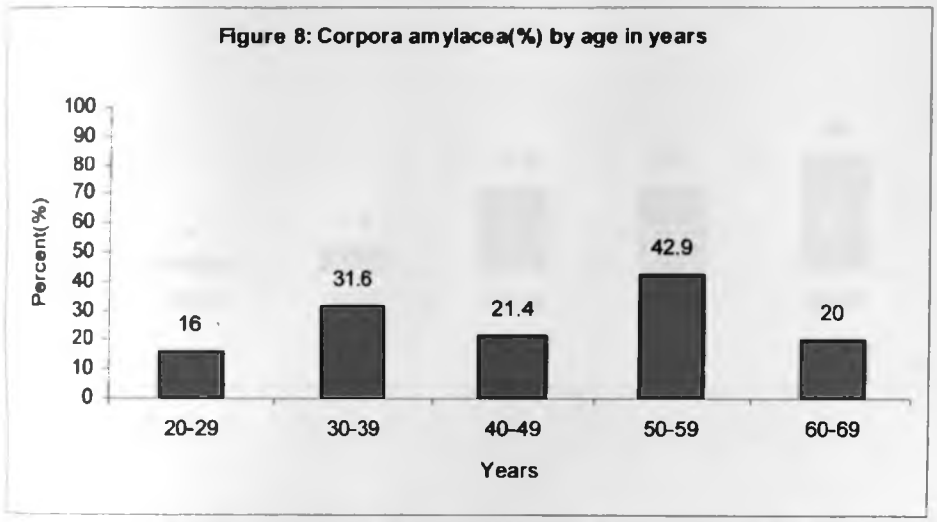
Squamous metaplasia was demonstrated in the third (4%), fourth (2.6%) and the fifth (21.4%) as shown in figure 6.



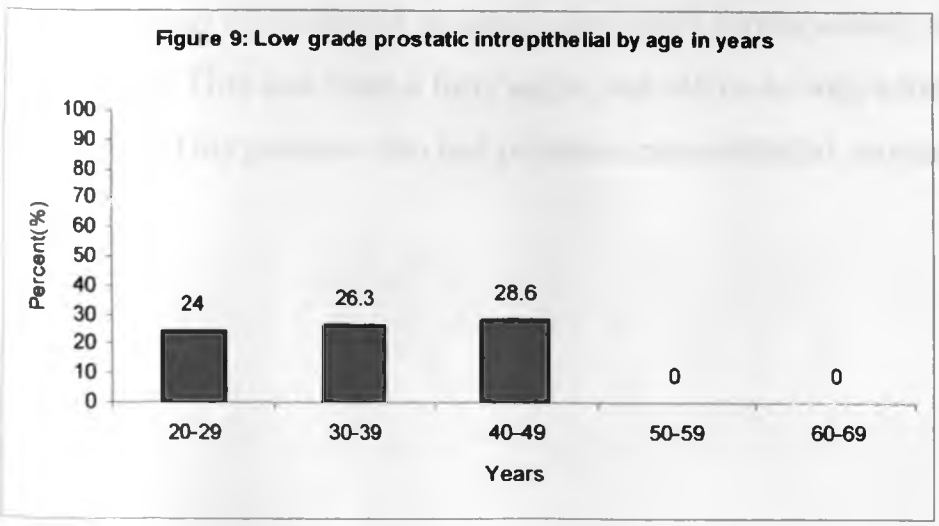


Prostatitis was demonstrated in all the age brackets and no particular trend was appreciated in its frequency. The lowest prevalence was seen in the fifth decade (21.4%) and the highest in the seventh decade (60%) as shown in figure 7.

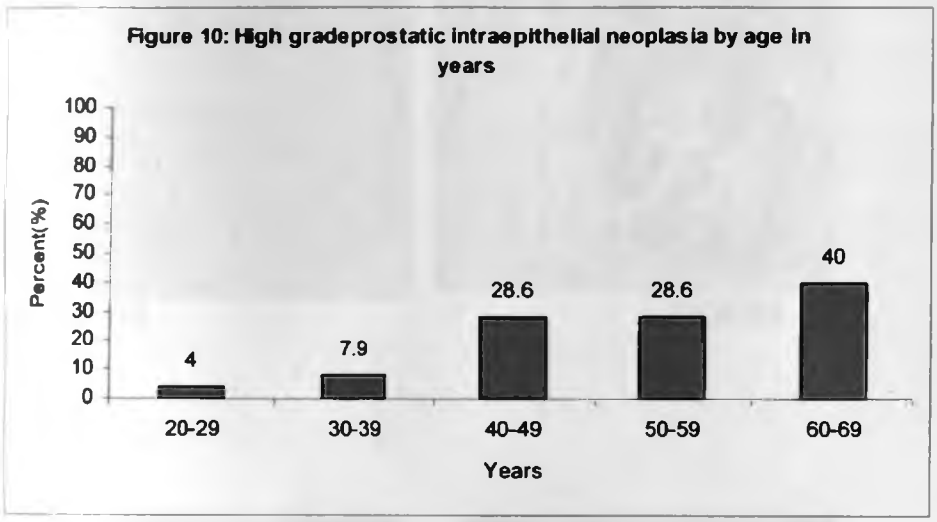
Corpora amylacea was appreciated in all the five age brackets as shown in figure 8.



No particular trend was observed in its frequency. The lowest was in the third decade (16%) and the highest in the sixth decade (42. 9%)



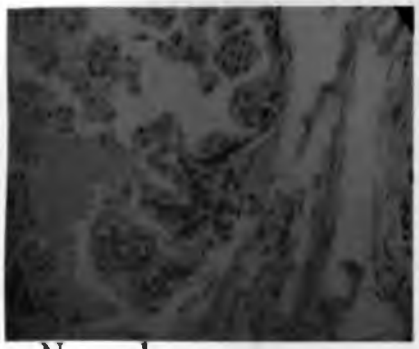
Low grade prostatic intraepithelial neoplasia (figure 9) was recorded in the third decade (24%), fourth decade (26.3%) and the fifth decade (28.6%).



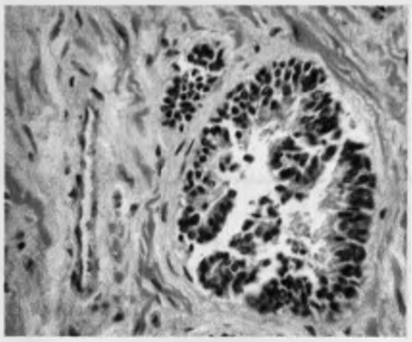
High grade prostatic intraepithelial neoplasia was recorded in all the five age brackets. The frequencies were observed to increase with age. The frequencies were 4% (third decade), 7.9 %(fourth decade), 28.6% (fifth decade), 28.6% (sixth decade) and 40% in the seventh decade (figure 10).

One case of incidental prostatic carcinoma corresponding to Gleason grade 2 was seen. This was from a forty eight year old male with a forty five gramme prostate. This prostate also had prostatic intraepithelial neoplasia.

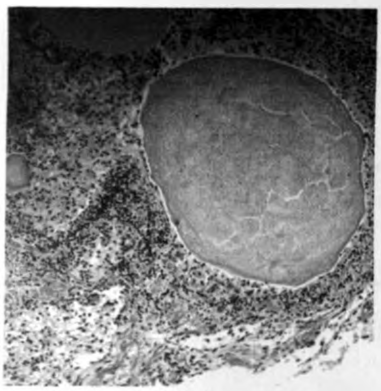
Plate 1: Some of the histological findings



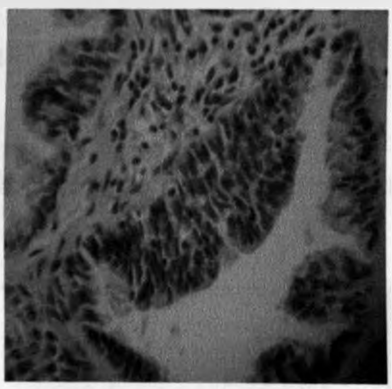
Normal



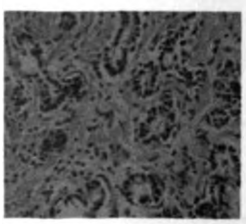
LGPIN

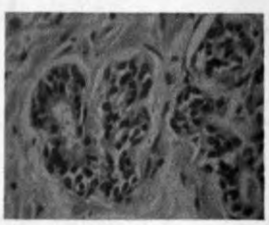


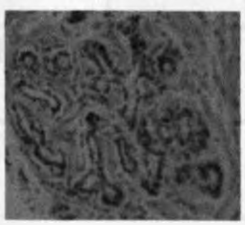
Corpora Amylacea



HGPIN







Foci of PCa

Table 1: Comparison of adenomatous hyperplasia and microscopic BPH

		AAH		TOTAL
Microscopic BPH		Yes (%)	No (%)	
	Yes	8 (72.7)	20(21.7)	28(27.2)
	No	3(27.3)	72(78.3)	75(72.8)
TOTAL		11(100)	92(100)	103 (100)

OR 9.6(2.3-39.6) P = 0.001

There was a statistically significant relationship between benign prostatic hyperplasia and adenomatous hyperplasia.

Table 2: Comparison of adenomatous hyperplasia and CAM

		CAM		TOTAL
HYPERPLASIA		Yes (%)	No (%)	
	Yes	5(19.2)	23(29.9)	28(27.2)
	No	21(80.8)	54(70.1)	75(72.8)
TOTAL		26(100)	77(100)	103 (100)

P = 0.445

The relationship between adenomatous hyperplasia and presence of corpora amylacea was not statistically significant.

9.0 DISCUSSION

Several autopsy studies have been carried out to determine the frequencies of high grade prostatic intraepithelial neoplasia, incidental prostatic carcinomas as well as other prostate pathologies.[23]

Data from various autopsy studies have shown microscopic benign prostatic hyperplasia from as early as the third decade of life. In those studies similarities between age specific prevalences have been observed. Four autopsy studies from Japan have shown occurrence from the third and fourth decades. In these studies the prevalences have been noted to increase in a linear fashion .[23, 24, 25, 26]

Aso et al in a Chinese study showed microscopic benign hyperplasia from the third decade with an increase of prevalence of up to 100% in the eighth and ninth decade .[27] An average of autopsy BPH prevalences quoted in one study from England, Austria, Denmark, Norway and USA showed a similar trend.[28] A comparison of various autopsy studies and this study is shown below in table 3. Men diagnosed with BPH have been reported to be more likely (by as much as fivefold) to develop prostate cancer than are aged matched controls.[29]

Table 3: Comparison of microscopic BPH from autopsy studies

Study	Sample number perage bracket (% with microscopic BPH)						
	20-29	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-**
Karube , K et al Japan 1961)N=755	6 (0)	36(8.3%)	112(20.5%)	209(32.1%)	209(58.5%)	148(71.8%)	35(77.1
Botswick et al eview. Europe nd US(1991) N=1154	59(0)	67(1.5%)	83(21.7%)	216(42.1%)	307(67.4%)	309(82.8%)	113(85
Aso Y.et al. eview. China (1991) (N ot given	0	9%	35%	44%	65%	100%	100%
This study N=103	25(0)	38(15.8%)	28(46.4%)	7(71.4%)	5(80%)	_	_

In this study microscopic BPH was observed from the fourth decade. The prevalence was observed to increase with age. The local prevalences were observed to be higher when compared with those of corresponding ages from other studies. The sample in this study was however very small when compared with those other studies. The mean prostate weights were observed in this study to be higher than that of another autopsy study as reported by Berry et al. [30]. The table below shows that comparison.

Table 4: Comparison mean prostate weights for the various age brackets

Study	Mean prostate weights in grammes					
	20-29	30-39	40-49	50-59	60-69	70-79
Berry et al (N not given)	_	19.2	20.2	22.6	27.1	30.1
This study (N =103)	21.6	25.9	31.5	37.9	39.2	_

In this study, atypical adenomatous hyperplasia was seen from the fourth decade and prevalence was seen to increase with age. A relationship was observed between the atypical adenomatous hyperplasia and microscopic BPH ($p = 0.001$). A study by Brawn PN, Speights VO et al showed atypical hyperplasia of 20% in the third decade and 24% in the fourth decade. [31] Atypical hyperplasia may occur by itself or in association with prostatic carcinoma especially in older men .[32] It has been noted in some studies that it can be confused with prostate adenocarcinoma grade 1 or 2 and vise versa. [33] It has also been shown to arise in prostates with concomitant BPH and has been placed as an intermediate lesion between BPH and latent histological carcinoma of the prostate .[34] Other studies have indicated it to be premalignant or be in fact prostatic carcinomas [35], yet others have regarded it to be of undetermined oncological significance .[36] No significant relationship was observed between the presence of atypical adenomatous hyperplasia and the presence of corpora amylacea.

There have not been many studies where the prevalence of low grade prostatic intraepithelial neoplasia has been documented; indeed many pathologists do not report it. [37] In this study the prevalences were seen to increase with age from 24% in the third decade, 26.3% in the fourth decade and 28.6% in the fifth decade. Sakr

et al reported the same trend in 1993 in a United States population review of 9% in the third decade, 20% in the fourth decade and 34% in the fifth decade. [38] In this study the prevalence in the third decade was higher than that reported by Sakr; however the prevalences in the fourth and fifth decades were comparable.

Table 5: Comparison of LGPIN from autopsy studies

Study	Sample number per age bracket(% with LGPIN)						
	20-29	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-**
Sakr WA et al Michigan.1993 (N=140)	35(9%)	55(20%)	50(34%)	-	-	-	-
This study (N=103)	25(24%)	38(26.3%)	28(28.6%)	-	-	-	-

Several studies have been done to document the presence of high grade prostatic intraepithelial neoplasia at autopsy, in prostatectomy specimens and in prostate biopsies. In many of them the presence of HGPIN was appreciated from the third decade of life and its frequency was seen to increase with age. In this study the prevalences were 4% in the third decade, 7.5% in the fourth decade, 28.6% in both the fifth and sixth decades and 40% in the seventh decade .No two studies have been documented to produce exactly the same results. [39,40,41,42]

This is shown in table 6 below. Sakr et al has shown varying prevalences for two African American populations and the same for two Caucasian populations.

That study reported higher prevalences in the two African American populations compared to the two Caucasian populations. The African American prevalence was higher that of US average reported by Bostwick, DG et al in 2006. A Spanish study of autopsy prostates in Mediterranean Caucasians showed results that were different from the American Caucasians. [10]

Table 6: Comparison of HGPIN from various autopsy studies

Study	Sample number per age bracket(% with HGPIN)						
	20-29	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-**
Manuel S et al. Mediterranean caucasian. 2003 (N not given)	28(7.1%)	35(11.8%)	15(35.7%)	20(38.0%)	21(45.4%)	27(48.2%)	
US prevalence 2006Bostwick,DG . (N not given)	-	-	15.2%	24.0%	47.3%	58.4%	70.
Sakr et al. African American. 1995. N=152	8	18%	31%	69%	78%	86%	
Sakr et al. American Caucasian 1995. N=370	-	14%	21%	38%	50%	63%	
American study of 652 autopsies	7%	26%	46%	72%	75%	91%	
African Americans and Caucasians respectively. (2007)	8%	23%	29%	49%	53%	67%	
This study(N= 103)	25(4%)	38(7.5%)	28(28.6%)	7(28.6%)	5(40%)		

Note: The sample sizes and the number of cases in the various age brackets were note given in most of the studies.

In this study only one case of incidental prostate carcinoma was appreciated. This was seen in a 36g prostate from a 48 year old and it corresponded to Gleason grade 2. Other studies have shown varied results. A Greenland study of 61 autopsy prostates showed one case of incidental prostate carcinoma in a 73 year old, in a study where the minimum age was 18 years and the mean age was 58 years. [9] In Nigeria an autopsy prostate study where the median age at necropsy was 50 years showed a prevalence of 6.7%. Other autopsy studies have produced varied results.[8]

A Spanish study of 162 autopsy prostates, prevalences of 3.6, 8.8, 14.3, 23.8, 31.7 and 33.3% in the third, fourth, fifth, sixth, seventh and eighth decade respectively. [10]

In another study (September 2007) Magoha [19] reported a 2.1% prevalence of carcinoma of the prostate in Ugandan Africans from 2162 autopsies.

A summary of various studies is shown in table 7.

Table 7: Autopsy Prevalence Rates of Prostate Cancer worldwide

Age (Yrs)	%US White[43,44]	%US Black[43,44]	%Spain [45]	%Japan [46]	%Greece[47]	%Hungary[48]
21–30	8	8	4	0	0	0
31–40	31	31	9	20	0	27
41–50	37	43	14	13	2.6	20
51–60	44	46	24	22	5.2	28
61–70	65	70	32	35	13.8	44
71–80	83	81	33	41	30.9	58
81–90	0	0	0	48	40	73
Total	34.6	36.9	18.5	20.5	18.8	38

The prevalence of the various prostate lesion is different from he other studies quoted. The hypothesis is rejected.

10.0 CONCLUSIONS

Low grade prostatic intraepithelial neoplasia and High grade prostatic intraepithelial neoplasia begin in the third decade. Both lesions become more frequent with increasing age. Microscopic BPH starts in the fourth decade and becomes more frequent with increasing age. Prevalence of histologic prostatic carcinoma is very low. The prevalences of microscopic BPH and HGPIN are higher than those observed in other studies. Atypical adenomatous hyperplasia is commoner when compared with other studies. Squamous metaplasia is also

common. Prostatitis and corpora amylacea are present in all age groups and none shows age preference.

11.0 LIMITATIONS

- Many cases were omitted due to unavailability of consent early enough when the body was still fresh.
- Many bodies were not included due to obvious features of decomposition.
- The age distribution was such that most of the postmortems were done on younger males, there were few postmortem cases involving the older age groups.
- Some histological slides showed partial autolysis hence some important histological findings may have been missed.

12.0 RECOMMENDATIONS

- Another study encompassing a larger geographical area and a larger sample size is recommended. There is need to use other modalities of picking out incidental carcinomas and prostatic intraepithelial neoplasia by use of immunohistochemical markers such as anti- keratin 34βE12 or p63. This study was carried out over a short period, the sample size was not large enough and most of the specimens were from the younger age groups.
- There is need to screen for premalignant lesions and other benign lesions like BPH from the fourth decade of life. It would be paramount to have a national policy as that of Cancer of the cervix. This study has shown these lesions in men not known to be symptomatic.

- There is need to sensitize the population on the possibilities of incidental prostatic cancer and other prostatic lesions and the importance of routine screening despite having no symptoms.

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14.0 APPENDICES

14.1 APPENDIX I

Consent form

Histological reports of autopsy prostates of men aged above thirty years from June 2006 to February 2007, a cross-sectional descriptive study

My name is Dr N. Mbuuko, I am carrying out a study to determine the prevalence of assymptomatic, undiagnosed prostate cancer, its precursor and any other prostate pathology.

The prostate is a golf ball sized gland that envelops the urethra of men just as it exits the urinary bladder. It plays a reproductive role. As men get older the prostate increases in size, sometimes as to cause urinary flow obstruction. This increase in size may be benign. In some cases the prostate may become cancerous, in which case the patient is assymptomatic early in the course of the disease.

The objective of this study is to determine the presence of hitherto unknown pathology in the prostate gland. My study involves the examinations of autopsy prostates.

The results of the study can be availed to you, if so required. Your approval to my removing and examination of your deceased relative's prostate is voluntary. This will not cause any structural change the appearance of the body.

I……..do consent for my relative's prostate to be included in the study.

Signature……Date……..

In case of any concerns you can contact

1. The ethical committee at KNH, tel…….
2. Dr W.Waweru, Department of Human Pathology, University of Nairobi.
3. Prof. D. Gatei, Department of Human Pathology, University of Nairobi

My contact is 0734 983432

Thank you for agreeing.

14.2 APPENDIX II

In the KNH laboratory the processing was as follows: -

(a) 2-5mm sections made

(b) Sections were fixed

The sections were fixed in 10% formalin for over one hour.

(c) Histological slides were processed from the fixed sections as follows: -

i. Dehydration in ascending concentrations of alcohol, 70% and 80% thirty minutes each.

ii. Clear in chloroform, two changes of one hour each.

iii. Impregnate in molten wax, two changes of one hour each to give internal support.

iv. Blocking using molten wax to give external support. Label the blocks.

v. Trimming of the blocks to remove excess wax with a microtome.

vi. Sectioning with a microtome at a thickness of 3-5 microns.

vii. Floating in water bath 2 degrees below point of melting wax(56 degrees)

viii. Fishing with a clean slide smeared with adhesive.

ix. Labeling the slide. Transfer all the information on the block to the slide.

x. Melting the wax in the oven at 60 degrees or at 100 degrees for 10 minutes.

xi. Dewaxing with xylene for a minimun of ten minutes

xii. Removing xylene with descending concentrations of alcohol, 805, then 70% then 505 and finally water.

xiii. Staining nucleus with Haematoxylin for five minutes

xiv. Differentiating with 1% acid alcohol to give contrast

xv. Bluing the nucleus with Scott's water.

xvi. Staining cytoplasm with eosin for 5 minutes.

xvii. Dehydrating with alcohol, clearing with xylene and mounting with DPX

14.3 APPENDIX III

The Gleason grading system of prostate cancer.

Grade 1: This grade consists of circumscribed masses of evenly placed uniform glands that closely resemble normal prostate glands. The cells have minimal nuclear changes.

Grade 2: The glands are similar to those in grade 1 but do not form circumscribed masses. There may be slight variation in size, shape, and spacing of glands. The glands can be seen infiltrating through the surrounding stroma

Grade 3: In this grade there is considerable variation in size, shape and spacing of glands. Irregular infiltration of the surrounding stroma may impart ragged appearance when seen at low power.

Grade 4: The glands are fused forming anastomosing network punctuated by glandular lumens. Glands are no longer recognized as individual units

Grade 5: The cancer cells form solid sheets and clusters or may infiltrate the prostate as individual cells. Necrosis may be present. There is no attempt at glandular formation.

14.4 APPENDIX IV

Questionnaire

Prevalence of latent prostate cancer and precancer at autopsy of me aged above twenty (20) years.

Admission number to mortuary....☐☐☐☐

Hospital number.....☐☐☐☐☐☐

Date of post mortem.....☐☐ ☐☐ ☐☐☐☐

Age in years.....☐☐

Actual (01) or estimate (02) age....☐☐

Where PM done, KNH(01), CM(02),☐☐

Study number.....☐☐☐

Weight of prostate in grams.....☐☐☐

Gross appearance,

describe.....

.....

.....

.....

.....

.....

Histology report

Normal=01, prostatitis=02, BPH=03, LGPIN=04, HGPIN=05, AAH=06,

Carcinoma=07, others =08 (describe below) ☐☐

.....

.....

.....

☐

Gleason grade for carcinoma..... (Appendix ii)

Investigator.....

signed.....Date.....Supervisor.....

15.0 ETHICAL COMMITTEE APPROVAL

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along, Ngong Rd.
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Fax: 725272
Telegrams: "MEDSUP", Nairobi.
Email: KNHplan@Ken.Healthnet.org

Ref: KNH-ERC/ 01/3831

Date: 13th October 2006

Dr. Ng'ali Mbuuko
Dept of Human Pathology
Faculty of Medicine
University of Nairobi

Dear Dr. Mbuuko,

RESEARCH PROPOSAL: "THE FREQUENCY OF LATENT PROSTATE CANCER AND PRECANCER AT AUTOPSY IN MEN AGED ABOVE TWENTY YEARS IN NAIROBI". (P126/6/2006)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** revised version of your above cited research proposal for the period 13th October 2006 – 12th October 2007.
You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely,

PROF A N GUANTAI
SECRETARY, KNH-ERC

c.c. Prof. K.M.Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
Dean, Faculty of Medicine, UON
Chairman, Dept of Human Pathology, UON
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