Chapter One

1.1 Introduction:

Prostate cancer is a form of cancer that develops in the prostate gland in the male reproductive system,most are slow growing (Samlister, 2009).

In 2011 prostate cancer is the second most frequently diagnosed cancer and the six leading cause of cancer death in worldwide (Jemal, 2011), in Sudan, university of Gezira registry reported that prostate cancer was the commonest cancer among male patient in Gezira state (Hamad and Abuidris, 2011).

The primary risk factors of prostate cancer are obesity,age and family history (Hankey,*et al*. 1999),other risk include genetic, dietary (e.g. higher meat consumption),infections or inflammation specially sexual infection (Dennis,*et al*. 2002),sexual factor such as many lifetime sexual partners or starting sexual activity early in life (Dennis,*et al*. 2002),increase level of testosterone (Gann,*et al*. 1996),high blood pressure (Martin,*et al.* 2010) and may lack of exercise (Friedenreich,*et al*. 2010).

For diagnosis of prostate cancer only test confirm the result is biopsy, however prior to biopsy less invasive testing can be conducted such that Digital rectal examination(DRE),prostate imaging such as ultrasound (US) (Bonekamp,*et al*. 2011), Gleason score which depend on evaluation of microscopic features of any cancer found (Figueiredo,*et al*. 2009) and tumor markers such as prostate specific antigen(PSA) to determine the origin of malignant cells that metastasized (Chuang,*et al*. 2007).

Treatment of prostate cancer is done by several ways according to stage such as radiation therapy, radical prostatectomy (Mouraviev,*et al.* 2006), chemotherapy, cryotherapy and hormonal therapy (Hong,*et al*. 2009).

Previous reports, which demonstrate the presence of acid mucin secretions to be more frequent in malignant versus benign prostate lesions (Mathur, *et al.*

2014),andallow differentiation of benign and malignant hyperplastic tissue (PinderandMcmahon. 1990).

Corpora amylacea are present in the benign acini of prostate glands; however their presence can't be used to exclude cancer (Christian, *et al*, 2005).

1.2 Objectives:

1.2.1 General objective:

This study aimed to detect corpora amylacea and acidicmucins in prostate tumor.

1.2.2 Specific objectives:

1-To correlate the corpora amylacea and acidicmucins with histological diagnosis of prostate tumors.

2-To determine the relation between patient's age and the incidence of the prostate tumors.

Chapter Two

2. Literature review:

2.1 Scientific background:

Histologically, the prostate is a compound tubulo-alveolar organ which presents as small to fairly large glandular spaces lined by epithelium. Characteristically the glands are lined by two layers of cells,a basal layer of low cuboidal epithelium covered by a second layer of columnar secretary cells. These glands have a distinct basement membrane and are separated by abundant fibro muscular stroma(Anchit Khanna, *et al*. 2014).

2.2Structure of the prostate:

The prostate gland is covered with a layer of connective tissue called the prostatic capsule. The prostate gland is made up of different types of cell, these cells are gland cells that produce the fluid portion of semen, muscle cells that control urine flow and ejaculation and fibrous cells that provide the supportive structure of the gland, the prostate gland is divided into 3 zones peripheral, transition and central zone.

The peripheral zone is the largest zone of prostate that found closely to the rectum during a digital rectal examination (DRE). The majority of prostate tumors (approximately 75%) are found in the peripheral zone, the transition zone is the middle area of the prostate, between the peripheral and central zones,and it surrounds the urethra as it passes through the prostate. This zone makes up about 20% of the prostate gland until the age of 40, and the central zone is in front of the transition zone,it is the part of the prostate that is farthest from the rectum,because of this, prostate tumors in this zone cannot be felt during a digital rectal examination (Martini, *et al*. 2012).

2.3Functionof the prostate:

The main function of the prostate is to produce the fluid portion of semen. The gland cells within the prostate produce a thin fluid rich in proteins and minerals that maintain and nourish sperm, this fluid is made continuously and excess passes from the body in the urine. When a man is sexually aroused, the prostate produces larger amounts of this fluid, it then mixes with sperm and is ejaculated as semen (Martini,*et al*. 2012).

The prostate also plays a part in controlling the flow of urine. The urethra runs from the bladder, through the prostate, and out through the penis. The muscle fibers of the prostate are wrapped around the urethra and are under involuntary nervous system control, these fibers contract to slow and stop the flow of urine (Martini, *et al*. 2012).

2.4 Prostate abnormality:

2.4.1 Benign prostatic hyperplasia:

It is common condition in middle age and elderly males is almost certainly due to some disturbance in the balance of male hormone production. The condition caused by an overgrowth of various stromal elements of the prostate glands, smooth muscle and fibrous tissue, thereby producing glandular and stromal nodules which distort the prostatic urethra. It affect only the central and superior portions of the gland, and when excessive may produce a rounded nodule of prostate at the base of the bladder between the ureteric orifices. This cause obstructive uropathy. BPH may give a significantly raised serum level of prostate specific antigen (Levison,*et al*. 2008).

2.4.2Prostate cancer:

2.4.2.1Definition:

Prostate cancer happens when cells in the prostate begin to grow out of control, this growth usually is slow but sometimes grow quickly and invade niebouring

tissue, then spread to nearly lymph node, hence to other areas of the body (Carducci, 2001).

2.4.2.2Types of prostate cancer:

2.4.2.2.1 Small cell prostate cancer:

Small cell prostate cancer develops from cells in the prostate called neuroendocrine cells,it called a neuroendocrine prostate cancer. Neuroendocrine cells do not produce PSA, so a PSA test do not help in diagnosis of it. It may be aggressive andmay be treated with chemotherapy (Paner, *et al*. 2012).

2.4.2.2.2 Large cell prostate cancer:

Like small cell prostate cancer, it develops from neuroendocrine cells in the prostate. Large cell prostate cancer is very rare (Grignon, *et al*. 2004).

2.4.2.2.3 Ductal prostate cancer:

Ductal prostate cancer may grow close to the urethra. It can cause problems and blood in urine. And it might be more aggressive than typical prostate cancer (Orihuela, *et al*. 2008).

2.4.2.2.4 Mucinous prostate cancer:

Like typical prostate cancer, mucinous prostate cancer can cause the levels of PSA in the blood to rise. There is some studies suggest it is aggressive and does not respond well to treatments for typical prostate cancer. But more recent research shows it might not be as aggressive as once thought (Osunkoya, *et al*. 2008).

2.4.2.2.5 Signet ring cell prostate cancer:

Most signet ring cell cancers in the prostate are secondary cancers,they have developed in another part of the body such as the bladder or stomach and then spread to the prostate. For example, a signet ring cell cancer that started in the stomach is stomach cancer, even if it has spread to the prostate. But if the cancer started in the prostate, it’s prostate cancer (Warner, *et al*. 2010)

2.4.2.2.6 Basal cell prostate cancer:

This described as adenoid cystic prostate cancer. It may be diagnosed after a transurethral resection of the prostate (TURP). Basal cell prostate cancer is very rare. Some studies suggest it is not very aggressive. But other studies suggest it might be more aggressive (Begnami, *et al*. 2007).

2.4.2.2.7 Prostate sarcomas:

There are several types of prostate sarcomas. The most common in adults is calledleiomyosarcoma. There is another type called rhabdomyosarcoma, which may affect children and young men. This can be treated with chemotherapy and radiotherapy. Not all prostate sarcomas are aggressive (Mazzucchelli, *et al*. 2008).

Some men with prostate sarcoma will have another type of prostate cancer as well, such as a glandular cancer called a sarcomatoid carcinoma or a carcinosarcoma. These cancers may be aggressive (Hansel, *et al*. 2006).

2.4.2.3 Epidemiology:

Prostate cancer develops primarily in men over fifty. It is the most common type of cancer in men in the United States, with 186,000 new cases in 2008 and 28,600 deaths (Jemal, *et al*. 2008). As of 2011, prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males worldwide (Jemal, *et al*. 2011). In Europe in 2012 it was the third most diagnosed cancer after breast and colorectal at 417,000 cases (Ferlay, *et al*. 2013). Reported that total prostate cancer incidence in Africa is lower than that among African Americans (Lisa, *et al*. 2011).

2.4.2.4 Risk factors of prostate cancer:

2.4.2.4.1Age:

In males under 45 years prostate cancer is unusual, as males get older, the prostate cancer incidence is progressively increasing,with a peak around 65-70years (Bardan, *etal*.2007).

2.4.2.4.2 Genetic factor:

A number of mutant genes, located on the chromosomes 1, 17 and X, were described in patients with prostate cancer. Hereditary prostate cancer gene (HPC1) and prostate cancer predisposing gene are located on chromosome 1, while human prostate cancer gene is located on chromosome X(Bardan,*et al*. 2007).

2.4.2.4.3 Diet:

Some evidence supports little role for dietary fruits and vegetables in prostate cancer occurrence (Key, 2011). Red meat and processed meat also appear to have little effect in human studies (Alexander, *et al*. 2010). Lower blood levels of vitamin D may increase the risk of developing prostate cancer (Wigle, *et al*. 2008).

2.4.2.4.4 Infections or inflammation:

Prostatitis may increase the chance for prostate cancer while another study shows infection may help prevent prostate cancer by increasing blood to the area. In particular, infection with the sexually transmitted infections chlamydia, gonorrhea, or syphilis seems to increase risk (Dennis, *et al*. 2002).

2.4.2.4.5Sexual factors:

Several case-control studies have shown that having many lifetime sexual partners or starting sexual activity early in life substantially increases the risk of prostate cancer (Sarma, *et al*. 2006).

2.4.2.4.6Body mass

A high average of body mass is also considered a risk factor in the pathogenesis of prostate cancer, the mechanism is probably dual, being influenced by the hormonal status and also by the increased intake of fats (Bardan, et al. 2007)

2.4.2.4.7Hormonal factors:

Males in populations with low 5-alpha-reductase excretion, prostate cancer incidence is very low. Testosterone (and its active metabolite, dihydrotestosterone) has a significant role in the etiopathogeny of prostate cancer and benign prostatic hyperplasia(Bardan,*et al*. 2007).

2.4.2.4.8Family history:

A history of prostate cancer in a first-degree relative increases risk of the disease by 120–150%. The risk for men with an affected father is increased by 112–140%, while those with an affected brother have a 187–230% risk increased, risk is also increased by 90–150% for men with an affected second-degree relative (Kicinski, *et al*. 2011). Men with a mother diagnosed with breast cancer have a 19–24% increased risk of prostate cancer according to studies conducted in the United States and Sweden (Chen, *et al*. 2008).

2.4.2.4.9 Insulin-like growth factor-1:

Men with the highest levels of insulin-like growth factor-1 (IGF-1) have a 38–83% increased risk of prostate cancer (Renehan, *et al.* 2004).

2.4.2.4.10 previous cancers:

Men with a previous renal cell cancer have an increased risk of prostate cancer, with a recent study showing a 69% increased risk (Liu, *et al*. 2011). A previous thyroid cancer has also been associated with an increased risk (Subramanian, *et al*. 2007).

2.4.2.4.11 Lack of exercise:

There is a small increased risk of prostate cancer associated with lack of exercise (Friedenreich, *et al*.2010).

2.4.2.5Diagnosis:

2.4.2.5.1 Digital rectalexamination:

These test done to determine any enlargement, lumps or other types of abnormal texture in prostate, by inserting a gloved, lubricated finger into the rectum, because

the prostate lies in front of the rectum this simple procedure is called a digital rectal examination (DRE) (Ries, 2004).

2.4.2.5.2 PSA blood test:

The prostate-specific antigen (PSA) blood testis used mainly to try to find prostatecancer early in men without symptoms. But it is also one of the first testsdone in men who have symptoms that might be caused by prostate cancer.The PSA test can also be useful if prostate cancer has already been found.It can be used along with physical exam results and tumor grade to help decide if other tests (such as CT scans or bone scans) areneeded.It can help tell if cancer is still confined to the prostate gland. This may affect the treatment options (Barry, 2001).

2.4.2.5.3 Prostate imaging:

Ultrasound (US) and magnetic resonance imaging (MRI) are the two main imaging methods used for prostate cancer detection.Prostate MRI has better soft tissue resolution than ultrasound (Bonekamp, *et al*. 2011).

2.4.2.5.4 Prostate biopsy:

If cancer is suspected, a biopsy is offered expediently. During a biopsy, urologist or radiologist obtains tissue samples from the prostate via the rectum. A biopsy gun inserts and removes special hollow-core needles (usually three to six on each side of the prostate) in less than a second. Prostate biopsies are routinely done on an outpatient basis and rarely require hospitalization. Fifty-five percent of men report discomfort during prostate biopsy (Essink-Bot, *et al*. 1998).

2.4.2.5.5 Gleason score:

The tissue samples are then examined under a microscope to determine whether cancer cells are present, and to evaluate the microscopic features (or Gleason score) of any cancer found. Prostate specific membrane antigen is a transmembranecarboxypeptidase and exhibits folate hydrolase activity, this protein

is overexpressed in prostate cancer tissues and is associated with a higher Gleason score(Figueiredo, *et al.* 2009).

2.4.2.5.6Tumor markers:

Tissue samples can be stained for the presence of PSA and other tumor markers in order to determine the origin of malignant cells that have metastasized (Chuang, *et al.* 2007).The oncoprotein BCL-2, has been associated with the development of androgen-independent prostate cancer due to its high levels of expression in androgen-independent tumors in advanced stages of the pathology (Catz and Johnson, 2003).

The expression of Ki-67 by immunohistochemistry may be a significant predictor of patient outcome for men with prostate cancer (Srikumar, *et al.* 2009).

2.4.2.6Treatment of prostate cancer:

Management strategies for prostate cancer should be guided by the severity of the disease. Many low-risk tumors can be safely followed with active surveillance. Curative treatment generally involves surgery, various forms of radiation therapy, or, less commonly, cryosurgery; hormonal therapy and chemotherapy are generally reserved for cases of advanced disease (although hormonal therapy may be given with radiation in some cases) (Dimitropoulou, *et al.* 2009).Treatment discussions often focus on balancing the goals of therapy with the risks of lifestyle alterations. A combination of the treatment options is often recommended for managing prostate cancer (Picard, *et al.* 2009).

2.5 Acidic mucins and its relation with prostate cancer:

Acidic mucinshave been referred to as mucopolysaccharides, glycosaminoglycan, mucosubstances and mucins. Usually consisting of hexuronic acid alternating with hexose amine, and the latter group being polypeptide structures with branching carbohydrate side chains, often having either sialic acid or sulfate radicals occupying a terminal position, and bound covalently to varying amount of protein.

The synthesis of mucinis initiated in the rough endoplasmic reticulum of the producing cell, and is completed in the Golgi apparatus. Sulfation of the hexoseamines molecule occur also in the Golgi region. Acidic reactive groups are present in this type of mucin, most surfacesare coated with mucin having an obvious lubricatory function (Bancroft and Marilyn, 2002).

2.5.1 Acidic mucins types:

2.5.1.1 Strongly sulfated:

Which include connective tissue mucins (proteoglycan), and epithelial mucins, and their sub-types (Bancroft and Marilyn, 2002).

2.5.1.2 Weakly sulfated epithelial mucins:

It epithelial in type, and consist of polysaccharide sulfate esters. It differ from strongly type in reacting at slightly higher pH level with cationic dye (Bancroft and Marilyn, 2002).

2.5.1.3 Carboxylatedsialomucins:

This type include N-acetyl form which are digested by the enzyme sialidase so called enzyme-labile, and N-acetyl-O-acetyl form which are not digested by the enzyme sialidaseso called enzyme resistance(Bancroft and Marilyn, 2002).

2.5.1.4 Sulfated sialomucins:

Which are the mixture of a sulfomucins and a sialomucins, it has been reported in prostatic carcinoma (Bancroft and Marilyn, 2002).

The histochemistry for the mucins of the prostate has proved to be greatly helpful, especially in demonstration of somewhat cancer specific acidmucin (Kufe, 2009).Previous reports, which demonstrate the presence of acid mucin secretions to be more frequent in malignant versus benign prostate lesions (Mathur, *et al*. 2014). However, the secretory capacity of synthesizing acid mucin is lost subsequently by malignant cells with higher grade i.e. with higher degree of an aplasia.

2.6 Corpora amylacea and its relation with prostate cancer:

Also known as prostatic concretions, are small hyaline masses of unknown significance found in the prostate gland, neuroglia and pulmonary alveoli. They are derived from degenerate cells or thickened secretions and occur more frequently with advancing age.In the prostate, they usually appear in benign glands; however, their presence cannot used to exclude cancer (Christian, *et al*, 2005).

Ultra are composed of bundles of fibrils and occasional interspersed electron dense areas (Drachenberg, *et al*, 1996). Corpora amylacea may vary in size and shape, but at most frequently round. Their color ranges from pink-purple to orange and the presence of concentric laminations is variable.

Chapter Three

3. Materials and Method:

3.1 Materials:

Archival tissue blocks of prostate tumors were used in this study.

3.2 Method

3.2.1 Study design:

This is a hospital based retrospective descriptive case study aimed to detect the corpora amylacea and acidicmucin in prostate tumor using histochemical method.

3.2.2 Study population:

Thirty nine prostate tumors blocks from samples previously diagnosed with haematoxylin and eosin stain as prostate tumors, ten are benign and twenty nine are malignant, At Omdurman military and Al-Amal National hospitals were used in this study. Patient identification data and other informations(age and diagnosis)were obtained from patient's file.

3.2.3 Sample processing:

Two sections of 5 µm in thickness were obtained from each formalin fixed paraffin wax embedded tissue using rotary microtome.

3.2.3.1 Alcian blue staining method for acid mucins:

Sections of 5µm were dewaxed in hot plate oven and cleared in two changes of xylene for two minutes, then hydrated through descending concentrations of ethanol (100%, 90%, 70%, 50%),and to water two minutes for each, then were treated with alcian blue solution for 5 minutes, then bloted and dried,thenstained by neutral red for 2 minutes and washed in water, then rinsed in alcohol, then cleared in xylene and mount in DPX mounting media (Bancroft and Marilyn, 2002).

3.2.3.2 Haematoxylin and Eosin Staining method for corpora amylacea:

Sections of 5µmweredewaxedin hot plate oven and cleared in two changes of xylene for two minutes, then hydrated through descending concentrations of ethanol (100%, 90%, 70%, 50%), and to water two minutes for each, then werestained with Mayer's haematoxylin solution for seven minutes, then washed in water and blued with ammoniated water for 16 second, then washed in water, then stained with eosin stain solution for two minutes, then washed in water, blotedand dried, then cleared in xylene and mount in DPX mounting media (Bancroft and Marilyn, 2002).

3.2.4 Result interpretation:

Results obtained from two sections were detected by researcher and confirmed by experienced histopathologist. Negative and positive controls were used.

3.2.5 Statistical analysis:

All information about the study population was entered a computer as well as obtained results. The data was analyzed using SPSS computer program. Frequencies, means, chi-square tests were calculated.

3.2.6 Ethical consideration:

All samples ethically taken after leader permission according to ethics from OMH and Al-AmalNational hospital.

Chapter Four

4. Results:

The study involves 39 samples, 29 of them (74.4) were malignant and 10 samples (25.6%) were benign prostatic hyperplasia as indicated in table (4.1).

The age of the study population ranged between 50 and 86, with mean age 69 ± 9 indicated in table (4.2). Most patients were aggregating in the age more than 65 years representing 71.8%, and the rest were less than 65 years representing 28.2%.

The acidic mucins expression observed in 16 cases (41%) and not observed in 23 cases (59%), 16 cases were malignantas indicated in table (4.3) and (4.4).

The corpora amylacea expression observed in 8 cases (20.5%), and not observed in 31 cases (79.5%), 1 case of 8 was malignant and 7 cases were benign as indicated in table (4.5) and (4.6).

Table (4.1): Distribution of study samples by diagnosis

Sample	Frequency	Percent
Malignant	29	74.4
Benign	10	25.6
Total	39	100.0

Table (4.2): Distribution of age group among study subjects

Age group	Frequency	Percent
50-64	11	28.2
65-90	28	71.8
Total	39	100.0

Table (4.3):Frequency of acidic mucins expression among study samples

Acidic mucins	Frequency	Percent
Positive	16	41
Negative	23	59
Total	39	100.0

Table (4.4): Relation of the acidic mucinsexpressionwith the diagnosis

Diagnosis	Acidic mucins		Total
	Yes	No	
Malignant	16	13	29
Benign	0	10	10
Total	16	23	39

P value 0.002

Table (4.5): Frequency of corpora amylacea expression among study samples

Corpora amylacea	Frequency	Percent
Positive	8	20.5
Negative	31	79.5
Total	39	100.0

Table (4.6): Relation of corpora amylaceaexpression with the diagnosis

Diagnosis	Corpora amylacea		Total
	Yes	No	
Malignant	1	28	29
Benign	7	3	10
Total	8	31	39

P value 0.000

Chapter five

5.1 Discussion:

Prostate cancer tends to develop in men over the age of fifty (Siegel, 2011).Prostate cancer is most common in the developed world with increasing rates in the developing world. Globally it is the sixth leading cause of cancer-related death in men(Baade, *et al*. 2009) (it is now the first in the UK and second in the United States)(Siegel, 2011).

This study involve 39 prostatic samples, 29 of them (74.4%) were malignant and the rest 10 samples (25.6%) were benign for detection of acidic mucins and corpora amylacea.

The age of the study population ranged between 50 and 86, with mean age 69 ± 9. Most patients were aggregating in the age more than 65 years representing 71.8%, and the rest were less than 65 years representing 28.2%, this indicates that the risk of development of prostate tumors increases by increasing age, this result agree with Bardan, et al. (2007) who report that the prostate cancer incidence is progressively with a peak around 65-70 years.

Acidic mucins expression were observed in 16 cases of malignant tumor and not observed in13 cases of malignant tumor, and not observed in all cases (10) of benign tumor, with significant association with malignant condition (Pvalue 0.000), indicate the relation of acidic mucins with malignant cases rather than benign conditions this may related to the abnormal secretions of malignant glands of the prostate, this result agree with Mathur, *et al*. (2014) study who reported that the presence of acidic mucin secretions to be more frequent in malignant versus benign prostate lesions.

Corpora amylacea expression observed in one case of malignant tumor and not observed in 28 case of malignant tumor, and observed in 7 cases of benign tumor

and not observed in 3 cases of benign tumor with significant association with benign condition (Pvalue 0.002), indicate that the relation of corpora amylaceaappearance is strongly related to benign conditions than malignant forms, this result agree with Christian, et al.(2005), who reported that the corpora amylacea in the prostate usually appear in benign glands and their presence can't be used to exclude cancer.

5.2Conclusion:

From this study concluded that:

Acidicmucins expression associated with malignant prostate condition.

Corpora amylacea appearance is associated with benign conditionbut their presence not used to exclude malignancy.

5.3 Recommendations:

From this study we recommend that:

Expression of acidic mucins should be use for confirmation of malignant tumor, and can be detected using molecular technique.

Similar study should be conducted using large sample size witha different types and grades of the prostate cancer.

Haematoxylin and eosin stain give acceptable results for detection of corpora amylacea that can be use.

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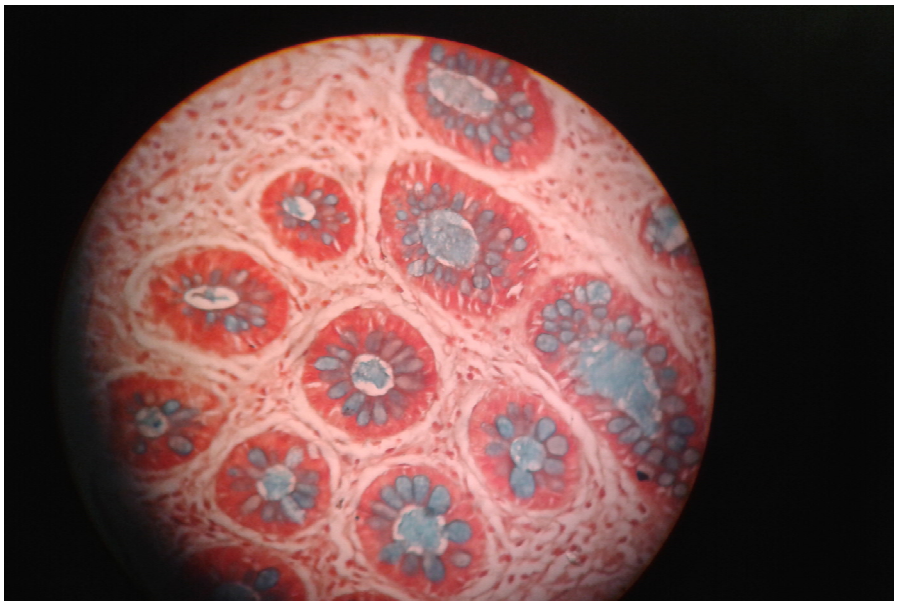
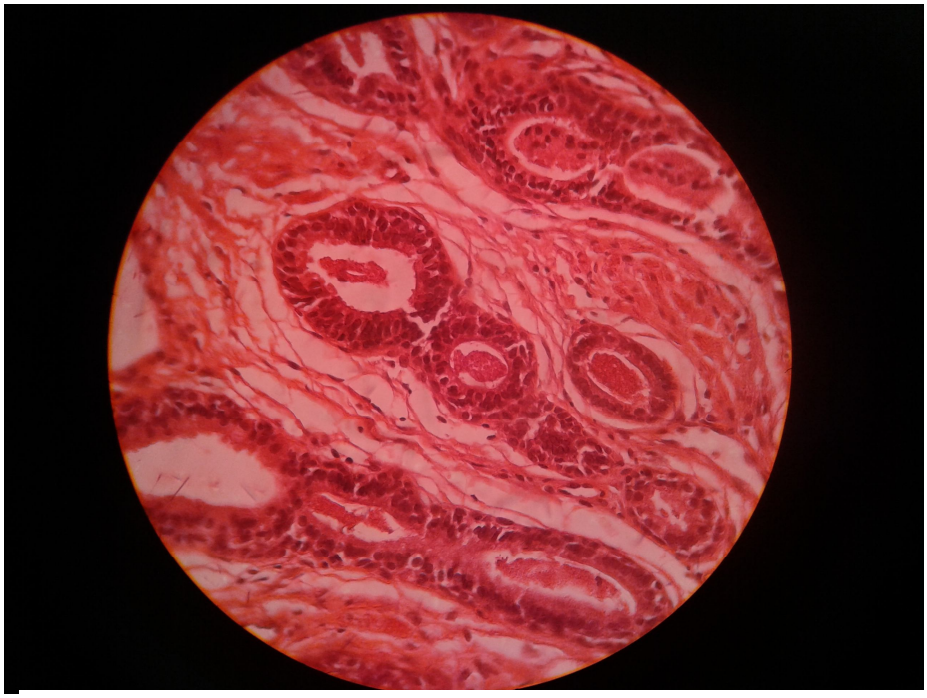
Appendex:



Acidic mucins in prostate cancer with alcian blue stain



Corpora amylacea in prostate tumor with H&E stain