Follow up study of “atypical” prostate needle core biopsies; the Winnipeg Experience and Literature Review

By

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Abstract

High grade intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) are two pathological lesions associated with prostate adenocarcinoma. HGPIN is an architectural finding, while ASAP is a term used to describe a lesion that cannot confidently be diagnosed as prostate adenocarcinoma. The mean incidence rate for HGPIN is 7.7% with a median of 5.2% and range of 0-24.6% and the cancer detection rate mean is 18.1%. The mean incidence rate for ASAP is 5.0% with a median of 4.4% and a range of 0.7-23.4%. The mean cancer detection rate is 40.2%. Currently, the incidence and cancer detection rates for HGPIN and ASAP for Winnipeg, Manitoba, have not been published. A retrospective study was conducted on all prostate biopsies collected from the Manitoba Cancer Care Prostate Centre (MCCPC) from 2008 and 2009. Prostate biopsies with a diagnosis of isolated HGPIN and or ASAP and no previous history of cancer were included in this study. In Winnipeg, Manitoba, from 2008-2009, the mean HGPIN incidence rate was 5.0% and the mean cancer detection rate was 46.1%. The mean ASAP incidence rate was 4.6% and the mean cancer detection rate of 48.2%. As a control, the cancer detection rate following a benign diagnosis was also calculated at 33.3%. The mean incidence and cancer detection rates for HGPIN and ASAP for Winnipeg, Manitoba are slightly lower than literature, but still fall within the published range. In addition, the mean ASAP cancer detection rate is similar to the cancer detection rate following a benign diagnosis indicating that, in our study, both a benign finding and a diagnosis of ASAP hold the same predictive value for cancer on a subsequent re-biopsy.

List of Abbreviations

ASAP	Atypical small acinar proliferation
ASAPB	ASAP favours benign
ASAPM	ASAP favours malignancy with
ASAPH	ASAP highly suspicious for but not diagnostic of malignancy
BPH	Benign prostatic hyperplasia
DRE	Digital rectal exam
DSM	Diagnostic Services Manitoba
HE	Hematoxylin and Eosin
HGPIN	High-grade prostatic intraepithelial neoplasia
HSC	Health Sciences Centre
LGPIN	Low-grade prostatic intraepithelial neoplasia
LIS	Laboratory information system
MCCPC	Manitoba Cancer Care Prostate Centre
PIN	Prostatic intraepithelial neoplasia
PrCa	Prostate Cancer
PSA	Prostate-specific antigen
USPSTF	United States Preventative Services Task Force

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I. Introduction and Literature Review

Lung cancer remains the number one cause of death by cancer in Canada for the past two decades with 10800 mortalities in males in 2012 [10]. The second and third most common causes of death by cancer in males are colorectal and prostate cancer with 5000 and 4000 deaths in 2012 respectively [10]. Over the last two decades, the top three cancer killers still remain relatively the same. The number of incidence cases has changed dramatically, particularly for prostate cancer. In 1990, there were 10300 new cases of prostate cancer [10]. As of 2012, the number of new cases had more than doubled to 26500 [10].

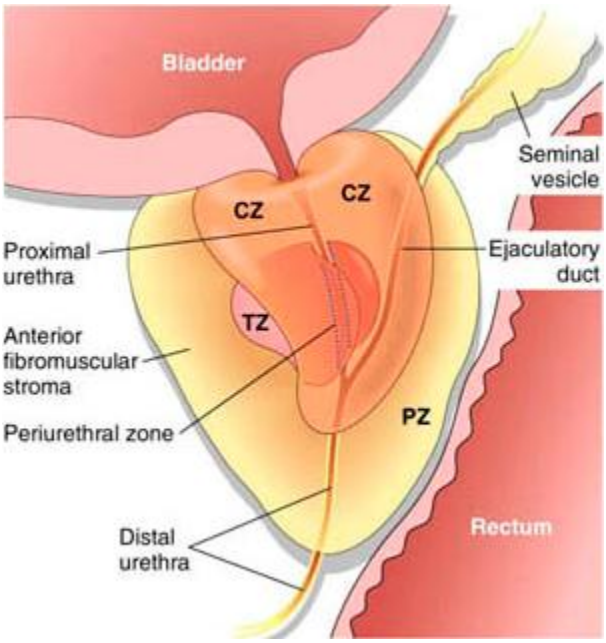
Alternatively, in the USA, while the number one cause of death by cancer in males is still lung, the second cause of death by cancer is prostate cancer, particularly among the Caucasian, African-American, native and Hispanic population [3, 47]. Among the male Asian population, prostate cancer is the top fourth cause of death [3, 47]. Furthermore, in comparison worldwide, prostate cancer is the number six cause of death by cancer with the highest incidence rates of prostate cancer occurring in developed countries among white males over the age of fifty in Australia, Western Europe and North America. The lowest incidence rates occur in Asian populations such as south-central and eastern Asia. The differences in incidence rates from around the world and among different races have been attributed to factors such as diet, genetics, viruses, education, and wealth [3, 10, 30, 47].

Prostate Adenocarcinoma

Adenocarcinoma of the prostate accounts for 90-95% of all prostate carcinomas [30, 47]. It is defined as the malignant proliferation of prostatic gland cells [30]. The prostate gland is divided

into four zones: transitional, central, peripheral and anterior fibromusclar zone. The prostate is also divided into four lobes: anterior left and right and posterior left and right (Figure 1) [30].

Figure 1 – Diagram of prostate gland: zones (TZ – transitional zone, CZ – central zone, PZ – peripheral zone)

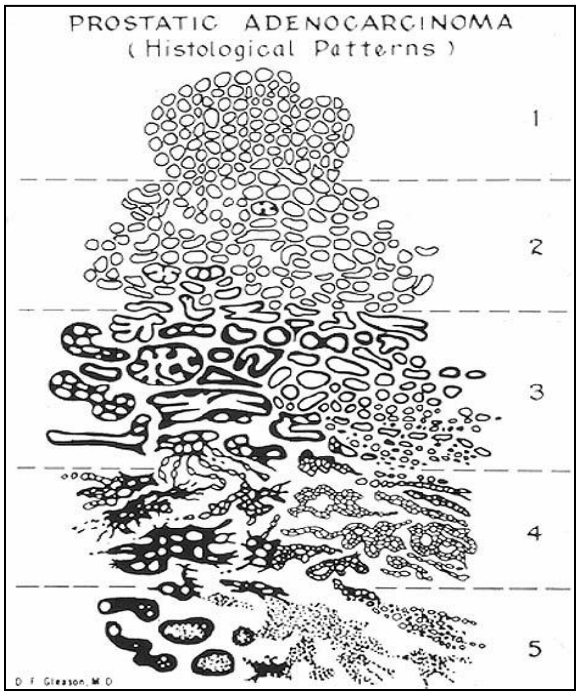


Adenocarcinoma most commonly arises in the posterior inferior aspect of the prostate within the peripheral zone but can arise in any zone [30, 47]. While prostate cancer is the second cancer killer amongst men in USA and third amongst men in Canada, prostatic adenocarcinoma is usually a slow growing lesion and asymptomatic [3, 10, 30]. In fact, the mortality rate following a diagnosis of adenocarcinoma is only 15% and males diagnosed with prostate adenocarcinoma most often succumb to other illnesses or disease processes [3, 10, 30].

Not every case of prostate adenocarcinoma will behave the same biologically and they can be graded through histological analysis. Each case is treated differently to a certain degree based on the grade of the lesion [12, 30, 47]. The grading of prostate adenocarcinoma is determined

using the Gleason Grading System [12]. The Gleason Grading System was first introduced in 1960 by Donald Gleason and was updated with modifications being made to each pattern in 2005 by the International Society of Urological Pathologists [12, 30]. The system classifies prostatic adenocarcinoma based upon the degree of differentiation of gland cells within the prostate at the microscopic level. There are five different patterns as initially described by Gleason in 1960 (Figure 2) [12].

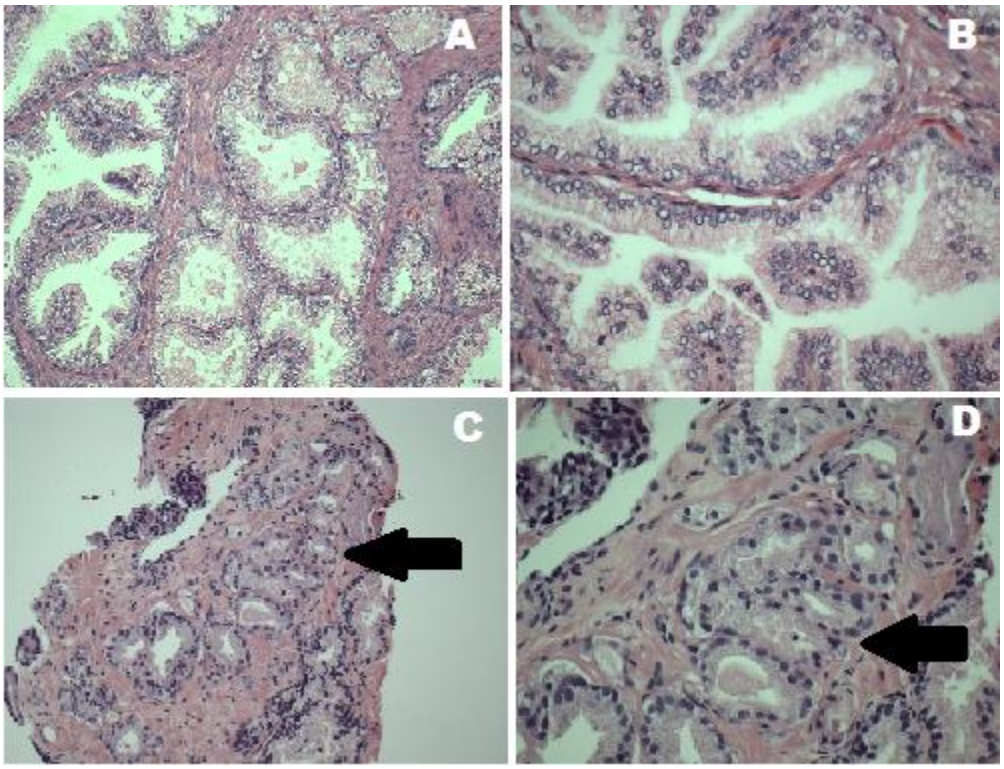
Figure 2 – Gleason Grading System



The patterns range from 1(small uniform glands) to 5(undifferentiated) [12]. At a ctyologic level, carcinomas demonstrate large nuclei and prominent nucleoli, as opposed to the small nuclei and inconspicuous nuclei of benign glands which can be visualized when stained with hematoxylin and eosin (HE). Additionally, benign glands are surrounded by an intact basal cell layer [12, 16].

Undifferentiated glands demonstrate a lack of a basal cell layer, and crowded cells with prominent nuclei and nucleoli when stained with hematoxylin and eosin (Figure 3) [12, 16].

Figure 3 – Hematoxylin and eosin (HE) stained prostate glands. A and B: Benign glands, C and D: Malignant glands – arrow indicates malignant glands (A and C x100 original magnification; B and D x400 original magnification)



For each case of prostatic adenocarcinoma, multiple patterns are visible; however, each Gleason Score is the sum of the primary and secondary pattern, as given by the pathologist [12, 16]. Therefore, there will always be a minimum score of 2 and maximum score of 10 [12, 16]. Prostate cancers with a lower score have a tendency to be less aggressive than those with a higher score [12, 15, 16]. In the clinical setting, the lowest score given by a pathologist is 6 (3+3). Additional scores can include 7 (3+4 or 4+3) and 8+ [12, 15, 16]. In current practice, patients diagnosed with prostate adenocarcinoma on a prostate biopsy with a Gleason score of 6, are placed on active surveillance [12, 15, 16]. On occasion, patients diagnosed with prostate

adenocarcinoma with a score of 7 (3+4) can also be placed on active surveillance [12, 15, 16]. Patients placed on active surveillance will undergo repeat biopsies on a scheduled basis in addition to prostate specific antigen (PSA) monitoring and a digital rectal exam (DRE).

In general, patients with scores of 7 or more are recommended to undergo treatment [12, 15, 16]. There are four current practices of treatment for prostatic cancer which can be used in combination with one another. Treatments include: radical prostatectomy, external beam radiotherapy, brachytherapy and hormonal therapy [34]. Radical prostatectomy involves removal of the entire prostate and is suitable for patients who are at low operative risk [34]. External-beam radiotherapy involves external beams of radiation directed at the prostate to destroy cancer cells while brachytherapy involves insertion of radioactive needles, which decay over time, into the prostate [34]. Hormonal therapies involve androgen deprivation therapy either through an orchiectomy or drugs [34]. In addition patients who are not suitable candidates for surgery (elderly, patients with metastasis) can undergo procedures such as transurethral resection of the prostate, hormonal therapy, or radiotherapy to relieve symptoms or treat metastases to the bones [34].

Precursors of Prostate Cancer

Adenocarcinoma of the prostate was thought to be preceded by atypical adenomatous hyperplasia or adenosis and proliferative inflammatory atrophy [13]. If fact, there are still some pathologists who believe that adenosis is still a precursor of prostate adenocarcinoma [13]. Numerous studies have demonstrated that there is no increased risk in developing adenocarcinoma upon diagnosis of either pathological finding [13]. In addition, benign prostatic

hyperplasia (BPH) can also present as an enlarged prostate with increased PSA levels [30, 47]. However, BPH is not a precursor of prostate cancer nor does it increase the chance of developing prostate cancer [30, 47].

Within the past decade, numerous studies have demonstrated that two pathological diagnoses have been associated prostate adenocarcinoma: high-grade prostatic intraepithelial neoplasia (HGPIN), and atypical small cell acinar proliferation (ASAP) [4, 6, 8-9, 13-16, 22-28, 35, 37, 40-41, 48]. HGPIN and ASAP are seen often on pathology reports following a prostate transrectal ultrasound guided biopsy. Over the last two decades, the incidence of HGPIN has remained constant and the cancer detection rate following a diagnosis of HGPIN has decreased [15]. The incidence of ASAP has decreased while the cancer detection rate has remained the same [15]. This has changed the standard of practice with regards to re-biopsying patients diagnosed with either finding, particularly with regards to HGPIN. In a review article published in 2006 in the Journal of Urology by Epstein and Herawi, a thorough evaluation of HGPIN and ASAP was conducted by reviewing the past two decades of critical research articles related to HGPIN and ASAP.

Benign prostatic hyperplasia

Urologists can easily mistake BPH for prostate cancer on a digital rectal exam without further tests as BPH does increase the size of the prostate gland and as well as PSA levels [30, 47]. However, BPH is a completely benign process, with no malignant potential [30, 47]. BPH does not alter the morphology of the cells, but simply increases the number of cells present [30, 47]. BPH can cause various complications, particularly frequent and/or painful urination as the urethra becomes constricted as the prostate gland enlarges [30].

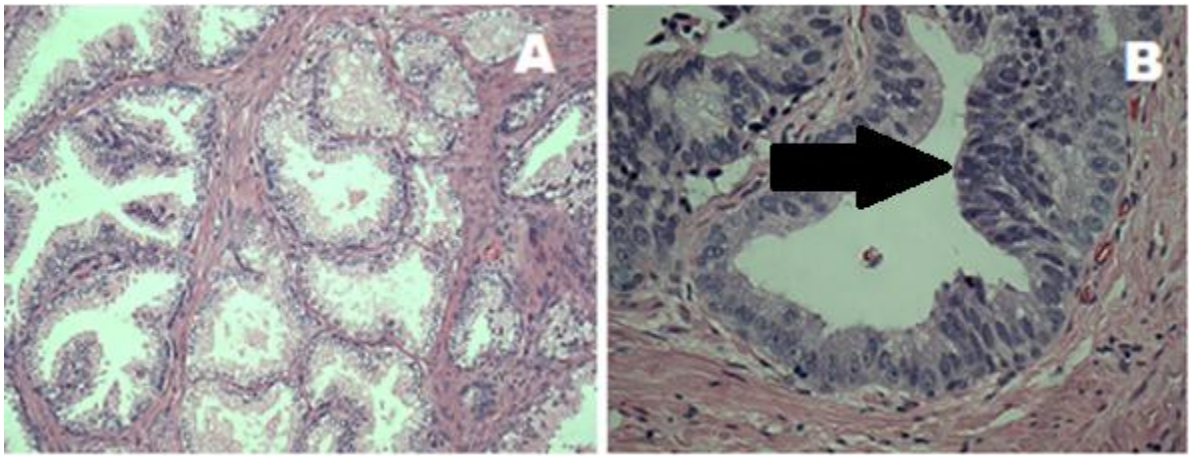
High-grade prostatic intraepithelial neoplasia (HGPIN)

Prostatic intraepithelial neoplasia (PIN) was first described in the 1960s and was referred to as intraductal dysplasia [32]. PIN is an asymptomatic pathological process that is detected microscopically on prostate tissue samples. It is characterized by prostatic acini that are architecturally benign [30, 47]. These acini are lined by cytologically atypical cells that demonstrate nuclear crowding, enlargement, as well as hyperchromasia [6, 8, 30, 47]. However, it remains architecturally benign and retains a basal cell layer (Figure 4) [6, 8, 30, 47]. Initially classified as PIN grade 1, 2 or 3, today, PIN is separated into either low grade PIN (LGPIN) which encompasses PIN grade 1, or high grade PIN (HGPIN) which includes PIN grade 2 and 3 [12, 16]. The main difference between LGPIN and HGPIN is the presence of prominent nucleoli upon HE staining. With regards to adenocarcinoma, there is no association with LGPIN [12, 16]. Alternatively, HGPIN has been found in 85-100% of radical prostatectomies removed for prostate cancer and can usually be found in conjunction with prostatic adenocarcinoma on needle core biopsies [6, 8, 30, 47]. In addition, both HGPIN and adenocarcinoma share similar genetic abnormalities and both become multi-focal overtime [6, 8, 30, 47]. Intraductal carcinoma can also be confused with HGPIN as they both share similar morphological characteristics[6, 8, 14, 30, 47].

According to Epstein's review of HGPIN and ASAP, the mean incidence rate of HGPIN is 7.7% with a median of 5.2% and a range of 0-24.6% [15]. Epstein determined that 43% of studies published post 2000 and 55% of studies published in the 1990s demonstrated a HGPIN incidence rate that fell below the current median of 5.2% [15]. Thus, there is no apparent trend in the incidence rate of HGPIN despite the type of practice setting publishing the data (ie.

Community hospital, academic institution, private lab). Based on Epstein's review, multiple variables can contribute to the wide range of published HGPIN incidences.

Figure 4 – HE stained prostate glands. A: Benign prostatic glands – x100 original magnification; B: prostate glands diagnosed as HGPIN (arrow indicates nuclear crowding) - x400 original magnification



One variable includes inter-observer reproducibility, particularly between genitourinary pathologists and generalist pathologists [15]. In a study conducted by Epstein *et al.,* 25 cases of PIN were selected to include classic examples of HGPIN and difficult cases as well. These 25 cases were sent to seven urological pathologists. Each case was separated into 1-benign/LGPIN, 2-HGPIN and HGPIN/cannot rule out cancer, 3- HGPIN with carcinoma. Among the seven urological pathologists, a kappa statistic was utilized to quantify the level of agreement between pathologists. A kappa statistic of 0.61 was generated indicating that a significant level of disagreement in the diagnosis existed [14]. Areas of disagreement included cribiform glands and glands with necrosis. At times, it was difficult distinguish HGPIN from carcinoma or HGPIN mimicking carcinoma due to poor histology or tangential [14]. Allam *et al*., also looked at the inter-observer variability in diagnosing HGPIN. In his study, 321 biopsies were reviewed by 8

pathologists who were of different backgrounds and only 2 were considered to have special expertise in prostate pathology. Diagnoses were divided into negative, HGPIN, suspicious for HGPIN, carcinoma and suspicious for carcinoma. More than one diagnosis was permitted with the exception of negative. High levels of agreement existed between all eight pathologists regarding cases of carcinoma with a kappa coefficient of 0.81-1.0 [1]. With regards to HGPIN, a kappa coefficient of 0.41-0.6 was returned indicating moderate disagreement [1].

Epstein also described technical factors as having an effect on the incidence rate of HGPIN [15]. Studies with incidence rates on the upper end of the literature range reported fixing prostate biopsy specimens in non standard fixatives which enhanced nuclear detail and nuclear prominence [15]. Alternatively, variations in microtomy skills can result in non uniform thickness which results in the increased uptake of dyes and can obscure nuclear detail [42, 43].

Few studies have also raised the issue that race has a tendency to increase or decrease incidence rates of HGPIN. Fowler *et al.*, demonstrated that HGPIN was present in 13.4% of black Americans while only present in 5.9% of Caucasian Americans [18]. According to Epstein, race is not a significant enough factor to account for such a wide range reported in the literature [15].

The cancer detection rate following a diagnosis of HGPIN was initially reported to be as high as 50% [15]. According to Epstien's review, over the past two decades, the cancer detection rate of HGPIN has decreased, almost to the point that the risk of detecting cancer on a repeat biopsy following a diagnosis of HGPIN is no different than detecting cancer following a benign diagnosis which has a cancer detection rate of 23.0% [15]. That does not mean that HGPIN should not be considered a precursor to prostatic adenocarcinoma, but rather other factors regarding

HPGIN affect its cancer detection rate on subsequent re-biopsy. A limited core sampling (6 or less cores) has a lesser chance of detecting prostatic adenocarcinoma on initial biopsy, thus earlier reported cancer detection rates at re-biopsy were high [15]. With the shift in standard protocol to take 12 or more cores, finding prostate adenocarcinoma is more common on initial biopsy resulting in a decreased cancer detection rate at re-biopsy [15]. In the study conducted by Moore *et al*., 1 out of 33 patients diagnosed with HGPIN on the initial biopsy involving a good sampling (12 or more cores), ended up with cancer on a repeat biopsy [36]. As a result, the cancer detection rate of HGPIN was significantly lower than previous data [36]. Moore concluded if a 12 core biopsy does not pick up cancer on the initial biopsy, but other clinical factors such as DRE and elevated PSA serum levels should dictate the frequency of re-biopsying [36].

However, incidence rates and cancer detection rates essentially have no use or meaning if they do not have an impact on clinical practice. A decade ago, with the cancer detection rate following an initial diagnosis of HGPIN being reported as high as 50%, the decision by the urologist to re-biopsy the patient was also high, with re-biopsy rates as aggressive as every 3-6 months for 2 years followed by yearly biopsies indefinitely [15]. As more reports regarding HGPIN were published, with multiple factors affecting the incidence rate of HGPIN and the cancer detection rate, it has led urologists to re-evaluate follow up treatment [15]. The use of other predictors, particularly PSA levels should play a more important role in deciding when and if a repeat biopsy should be carried out following an initial diagnosis of HGPIN with no previous history of prostatic adenocarcinoma [15]. Koca *et al.*, and Ploussard *et al.,* suggested that following the diagnosis of HGPIN, re-biopsy is not necessary and that clinical factors such as

serum PSA levels and DREs are much more useful and should be taken into consideration prior to re-biopsy [26, 40].

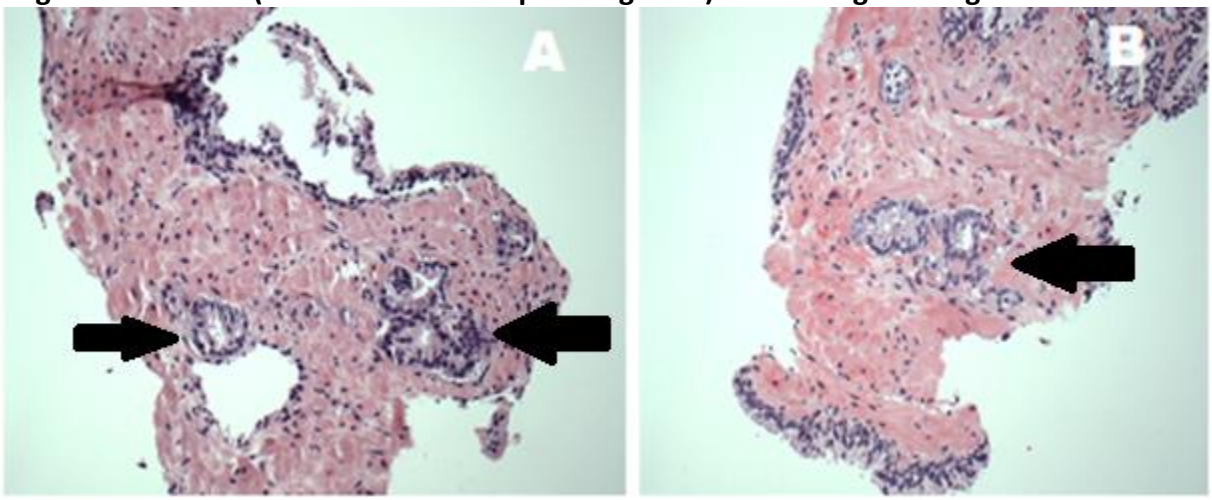
Additionally, the number of cores with HGPIN on initial biopsy plays an important role [28, 34, 37, 45]. Epstein described one positive core on initial biopsy to represent isolated HGPIN, while two or more positive cores increased the risk of detecting cancer on a repeat biopsy [15]. Schoenfield *et al.,* demonstrated that the greater the number of cores positive for HGPIN, the greater the risk of developing a malignancy on subsequent re-biopsy [45]. Similarly, Kronz *et al.,* found that the increasing number of positive cores correlated with an increased cancer detection rate with 1-2 positive cores having a 30% chance of developing cancer on repeat biopsy [28]. Three cores had a 40% chance and more than 3 cores had a 75% chance of malignancy on re-biopsy [28]. Netto *et al*., demonstrated that males with widespread HGPIN (4 positive cores or more) on an initial biopsy of 12 or more cores were at a 39% risk of finding prostate cancer on a repeat biopsy and therefore require a repeat biopsy [37]. Merriment *et al*., also concluded in her study that patients who underwent an extended sampling of the prostate with results that came back with multifocal PIN were more at risk of finding cancer on a repeat biopsy over males with unifocal pin [34].

Atypical small acinar proliferation (ASAP)

Unlike HGPIN which is an architectural finding, ASAP is a diagnosis based on a lack of definitive malignant pathologic criteria [15, 30, 47]. The diagnosis of prostate adenocarcinoma is based on several cytologic and histologic features, usually divided into major and minor features. Cytologic features include nuclear enlargement (nucleomegaly), nucleolar

enlargement (nucleolomegaly) and lack of a basal cell layer [12,13,16,30]. Furthermore the cytoplasm tends to be amphophillic [12,13,16,30]. Cancer glands also tend to be irregular with an infiltrative growth pattern. In general, a diagnosis of adenocarcinoma requires a minimum of 4-6 glands [12,13,16,30]. A diagnosis of ASAP is made when a focus of 2-5 glands measuring less than 1mm in size is suspicious for adenocarcinoma but cannot be diagnosed with confidence [48]. Despite the fact that the focus demonstrates many features of prostate adenocarcinoma, the number of glands makes a definitive diagnosis difficult.

Figure 5 – HE stained prostate glands. A and B: Glands suspicious for adenocarcinoma, diagnosed as ASAP (arrow indicates suspicious glands) – x100 original magnification



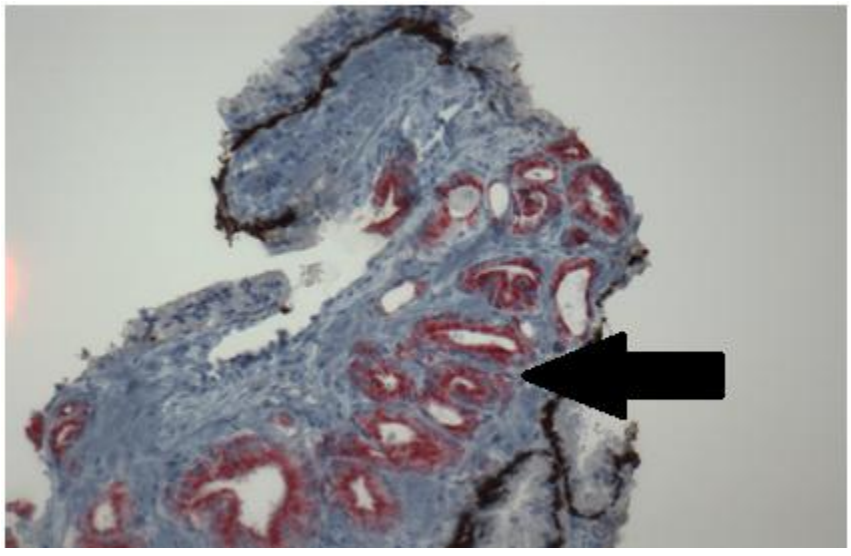
ASAP has a mean incidence rate of 5.0% with a median of 4.4% and a range of 0.7-23.4% [15]. Epstein reports that the incident rate for ASAP shows a decreasing trend over time [15]. The decrease in the ASAP incidence rate could be due to multiple factors. Similar to HGPIN, an important variable is the inter-observer reproducibility rate. Experts believe that ASAP is most commonly a marginally sampled cancer and a diagnosis of ASAP is made if a suspicious focus cannot be comfortably called malignant [15]. Poor inter-observer reproducibility stems from the fact that some pathologists are more confident than others leading to more conservative or

aggressive diagnosis of prostate adenocarcinoma [15]. As pathologists become more confident diagnosing and recognizing small cancers, the incidence rate of ASAP decreases [15]. Van der Kwast *et al*., investigated the inter-observer reproducibility by having 5 expert pathologists and 7 reference pathologists from the European Random Screening study of Prostate Cancer f 20 prostate biopsies with small atypical foci (less than 1mm) via digitalized slides. The kappa value generated among expert pathologists was 0.39 and the kappa value generated among the reference pathologists was 0.21 [48]. Expert pathologists also diagnosed adenocarcinoma significantly more than reference pathologists [48]. In addition, Van der Kwast *et al.,* determined that disagreement focused around atypical foci with 2-5 glands [48]. His study recommended inter-collegial consultation with an expert or specialized pathologist prior to making a final diagnosis of ASAP [48]. Epstein found that consultation with a specialized pathologist leads to a more definitive diagnosis [15]. Iczkowski *et al*., also investigated the inter-observer reproducibility in diagnosing ASAP by stratifying the degree of suspicion. The study retrospectively looked at 295 patients diagnosed with ASAP, with no previous history of prostate cancer, from the year 1991 to 1995 from UroCor. Each case was reviewed by two pathologists from UroCor initially and subsequently by two pathologists from the MayoClinic in Rochester, Minnesota. For each case, the diagnosis was categorized into either ASAP-favours benign (ASAPB), ASAP-favours malignant suspicious for but not diagnostic of malignancy (ASAPS), or ASAP-highly suspicious for but not diagnostic of malignancy (ASAPH). All ASAP categories had similar cancer detection rates on re-biopsy. At the present time, there has been no study on the effect of multiple positive cores with ASAP on the cancer detection rate [15].

Immunohistochemical staining can be helpful in the diagnosis of small foci of prostate adenocarcinoma, as immunostaining can help to offset the difference in pathologist confidence and expertise levels. In a study conducted by Ng *et al.,* the use of a "triple cocktail": two basal cell antibody markers and A-racemase(a prostate cancer marker), proved to be more effective than using either antibody alone [38]. The negative staining of the two basal cell markers, indicates the lack of a basal cell layer (which would stain brown if present), while the racemase stains the cytoplasm of malignant prostatic glands, as indicated by the presence of a red color (Figure 6) [38].

As reported by Renshaw, important histological techniques can decrease a diagnosis of ASAP. At least 3 levels should be prepared from a paraffin block with unstained sections in between each level to be used for immunohistochemistry as required [43]. Additionally, only a single prostate core should be embedded in a single paraffin block as this allows for a more complete assessment of the biopsy [42].

Figure 6 – Immunohistochemical stain of malignant prostate glands (indicated by arrow) – x100 original magnification



The risk of finding cancer following a diagnosis of ASAP on an initial biopsy is 40.2% with a median of 38.5% and a range of 17-70% [15]. Studies have demonstrated a correlation with cancer and rising PSA levels following a diagnosis of ASAP [11, 23]. In Iczkowski's study, PSA levels were elevated in patients diagnosed with prostate cancer after ASAP but remained statistically insignificant [23]. Similarly, in a study by Cheville *et al.*, it was found that in 15 of 25 patients diagnosed with cancer following ASAP had serum PSA levels greater than those who had no cancer [11]. Alternatively, other studies have determined that PSA levels are not reliable following a diagnosis of ASAP [39]. Ouyang *et al.*, compared the incidence of cancer following ASAP diagnosis compared to incidences of cancer diagnosed solely on clinical factors including age, multiple serum PSA levels, and time intervals between benign biopsies. Cancer was detected in 53% of cases following a diagnosis of ASAP compared to a cancer detection rate of 20% following a benign biopsy [39]. In addition, clinical factors such as DRE, serum PSA and age did not carry any significant predictive value for cancer after an initial diagnosis of ASAP [39].

With a shift from a 6 core biopsy to a standard protocol of 12 cores, the decrease in the cancer detection rate following a diagnosis of HGPIN has made the need for re-biopsy questionable [15,16]. However, the evidence for re-biopsy following a diagnosis of ASAP is strong and thus the suggested time frame of re-biopsy is within less than 6 months following an initial diagnosis [15,16]. In addition, once ASAP has been diagnosed, repeat biopsies should be saturated random samples [39, 45]. Ouyang *et al*., looked at biopsies performed by side and established that the majority of cancers were identified on the same side as the ASAP but 27% ended up with cancer on the contra lateral side [39]. He also demonstrated that sextant biopsies showed 53% of cancer being found in the same location as the ASAP focus [39].

ASAP with HGPIN

In practice, there is also the possibility that HGPIN and ASAP occur simultaneously [2, 15, 29]. Epstein described two possible situations in which both HGPIN and ASAP occurs together. The first situation involves the presence of both pathological processes separated from one another [15]. In this scenario, the patient should be treated as if the diagnosis was isolated ASAP [15]. The second scenario includes the presence of HGPIN associated as a single focus with ASAP. Even with the use of stains, typical HGPIN can be difficult to separate from ASAP as some HGPIN have discontinuous staining with basal cell markers similar to the negative basal staining of carcinoma [15]. Thus, patients with HGPIN in association with ASAP should be followed up on as if they were diagnosed with isolated ASAP [15]. Few studies have investigated the risk of cancer following a diagnosis of HGPIN with ASAP. Kronz *et al* reviewed 71 cases in which a cancer detection rate of 46% was generated following a diagnosis of HGPIN with ASAP [29]. Alsikafi *et al* also investigated the same scenario and reported a cancer detection rate of 75% [2].

Prostate Cancer Screening

The incidence rate of prostate adenocarcinoma in North America has increased substantially. There has also been an associated decrease in prostate adenocarcinoma mortality [3, 10, 30, 47]. The increase in prostate cancer incidence can be attributed to the increased use of prostate specific antigen (PSA) screening [30, 33]. The majority of prostate cancer is asymptomatic and its probability of occurrence increases with age. PSA screening can detect prostate cancer at an early stage when treatment is still curative. Unfortunately, prostate adenocarcinoma detected by PSA screening is often indolent and asymptomatic [30, 33, 46]. PSA testing is usually

performed in conjunction with a digital rectal exam (DRE). Following an abnormal DRE or PSA, a prostate biopsy usually follows [16, 30, 33].

Digital rectal exam (DRE)

DREs are usually performed on a regular basis without prior indications for prostate cancer, and can also be performed based on PSA level findings as well. While prostate cancer can present as an indurated lump, other pathologies, particularly benign prostatic hyperplasia can also present with an enlarged prostate. Thus, DRE findings are not a strong indicator of prostate cancer but may provoke further PSA testing or biopsy [16, 30, 33].

Prostate specific antigen (PSA)

Prostate specific antigen is a glycoprotein enzyme found in male ejaculate that is required for sperm to swim freely and to dissolve cervical mucus within females [30, 33]. The base level of PSA within males differs; however, it has been shown that increased PSA levels can occur in conjunction with prostate cancer [15]. The increase in PSA levels can also be a consequence of prostatic inflammation, benign prostatic hyperplasia, and irritation of the prostate from activities such as running [15, 30, 33]. Males can naturally possess a high level of PSA which could potentially mask an increased PSA level if base levels are not taken initially [15, 30, 33]. High PSA levels are not cancer specific nor do low values represent the absence of cancer. Thus, PSA levels can give false positives and negatives and should not be solely relied upon as an indicator of prostate cancer [15, 30, 33].

Prostate Biopsy

A prostate biopsy involves the insertion of a cutting needle into a prostate gland, using ultra sound guidance, with the submission of tissue for examination by a pathologist [5, 41]. In the early 1990's, the development of a biopsy gun called the BIOPTY gun (Figure 7) changed the way prostate biopsying was conducted [5, 51].

With the biopsy gun, a prostate biopsy has become an outpatient procedure with local anaesthetic only [15, 41]. It is a spring loaded biopsy gun attached to a transrectal probe with an 18g needle [5]. The cutting needle is fired into various sections of the prostate, with a focus on the posterior peripheral zone, and the tissue is submitted for histological anaylsis.

Figure 7 – BIOPTY gun

The current standard of practice requires a minimum of 12 needle cores, with a focus on the posterior prostate, to be submitted for pathological analysis [15]. Prior, 6 or less needle core samples of the prostate were taken but studies have demonstrated that increasing the

sampling of the prostate increases the chances of detecting small cancers [11, 15, 28, 39]. Generally, a prostate biopsy is recommended following a finding of a palpable masses on a DRE and/or and increased PSA levels. If PSA levels continue to rise and biopsies have no pathological finding, a saturated TRUS biopsy can be performed with more extensive sampling of the prostate (48+). Additionally, biopsies can be taken trans-perineally using a template to access all lobes of the prostate, not just the posterior [16, 33].

Over Diagnosis of Prostate Cancer

As prostate adenocarcinoma has a mortality rate of 15%, most men often die with, not of, their prostate cancer [3, 10, 30]. This has led to controversy of the value of PSA screening and the diagnosis of asymptomatic cancer in general [46]. The treatment of prostate cancer has a variety of complications which vary depending on treatment. A radical prostatectomy can result in incontinence or impotence [33]. In general practice, this occurs in 60% of patients post surgery. Incontinence is less common but still a serious concern to the patient [33]. Radiotherapy can also cause impotence, with the additional complication of radiation injury to the bladder or rectum [33]. Furthermore, complications from prostate biopsies can arise, such as bacterial infection and bleeding from the urethra or rectum [33].

Over-diagnosis can be defined as the correct diagnosis of prostate adenocarcinoma which would have been slow-growing and asymptomatic during the patient's life time. Given the number of complications that can arise from treatment, concerns have risen over the over-diagnosis and over-treatment of prostate cancer [46]. In 2012 the United States Preventative Services Task Force (USPSTF) began advocating that urologists stop the practice of PSA

screening [46]. The action taken by USPSTF is based on the limited effectiveness that PSA screening has had on decreasing prostate adenocarcinoma mortality [46]. The number of men put at risk injured through treatment of asymptomatic prostate cancer based on a PSA test may not be worth it [46]. The USPTF does not believe a PSA test to be an effective screening method. This view is not universal. Some experts have noted that the studies used to support USPTF's view are flawed by short follow up [46].

Significance of HGPIN and ASAP on Biopsy

Cancer detection rates for both HGPIN and ASAP influence follow up plans for the patient. In regards to HGPIN, with a cancer detection rate falling to a level similar to that following a benign diagnosis, the concern for re-biopsy has decreased and results from a PSA test have began to dictate if and when a re-biopsy should occur [15]. In addition, the number of positive cores also influence whether a re-biopsy is recommended [28, 34, 37, 45]. In regards to ASAP, while the incidence rate has decreased, there has been little change in the cancer detection rate following a diagnosis. Thus, it is strongly recommended that a patient undergo a re-biopsy within the first year following a diagnosis of ASAP [15].

It is important that various institutions study and publish their HGPIN and ASAP incidence and cancer detection rates. Knowledge of the data will help an institution to determine whether they are over-diagnosing or under-diagnosing either lesion. In addition, as a result of such information, the clinicians will have a better understanding and interpretation of pathology reports which will lead to the best possible treatment and outcome for the patient. The purpose of this study is to perform a retrospective review of all prostate biopsy reports

conducted for the Manitoba Cancer Care Prostate Centre (MCCPC) from 2008 and 2009. The HGPIN and ASAP incidence and cancer detection rates will be determined as well as the re-biopsy rate following a diagnosis of either HGPIN or ASAP.

II. Hypothesis

As cited in the current literature, the mean incidence rate of HGPIN is 7.7% with a median of 5.2% and a range of 0-24.6% and a cancer detection rate of 18.1%. The mean incidence rate for ASAP is 5% with a median of 4.4% and a range of 0.7-23.4% and a cancer detection rate of 40.2%. These numbers have been reported by various institutions from around the world including Canada, USA and Turkey. Currently, the incidence and cancer detection rates for Winnipeg have not been studied or reported. This study aims to determine the incidence and cancer detection rates through a retrospective study of all prostate biopsies collected from 2008-2009 for the MCCPC. It is hypothesised that the incidence and cancer detections rates reported in this study will fall within the ranges as cited in the literature.

III. Materials and Methods

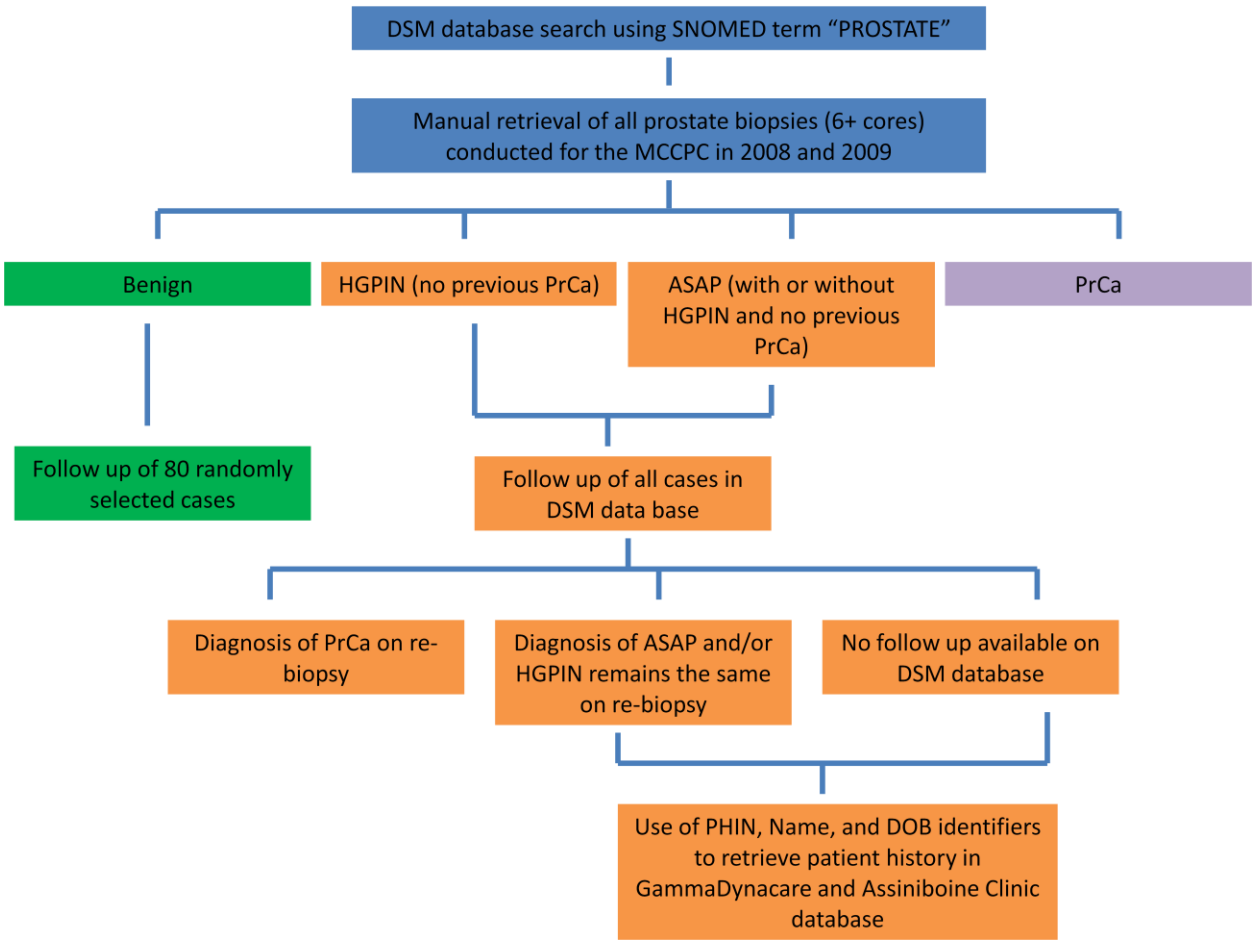
Initial Search

An initial search was carried out using the M-CCMB-PROSTATE database without patient name fields. Only cases containing "prostate" under the SNOMED code from January 1 2007 to January 31 2012 were returned (Appendix 1, Figure 11). From the 8261 files returned, only those from 2008 and 2009 were examined using the surgical pathology number. Cases that were conducted for the HSC-CCMB Prostate Centre, and consisted of 6 or more TRUS biopsies were collected for this study. Reports for radical prostatectomies, TURP specimens, TRUS biopsies not conducted by the HSC-CCMB prostate centre or less than 6 core biopsies were excluded. A final total of 1515 cases were collected for 2008 and 2009. The following patient information was collected: name, PHIN number, LIS number, DOB, age, PSA (if applicable), issuing physician, reporting pathologist and diagnosis.

Follow-up

Cases from 2008 and 2009 with a diagnosis of isolated HGPIN, ASAP or ASAP with HGPIN were followed up using either patient name or PHIN number to search for subsequent biopsies or previous biopsies. Cases with a previous history of cancer were removed from the study. Initial follow up was conducted using the Diagnostics Services Manitoba (DSM) database until patients had a confirmation of adenocarcinoma on re-biopsy (up until 2012). Patients who still maintained a diagnosis of HGPIN and/or ASAP or had no follow-up history in the DSM data base were further investigated using the Assiniboine clinic database using patient name or DOB or PHIN as well as the GammaDynacare system using the same parameters (Figure 8).

Figure 8 – Experimental Design Flow Chart



Incidence Rate

The incidence rate was calculated by dividing the number of isolated HGPIN or ASAP by the total number of prostate biopsies for both 2008 and 2009. For this study, the term ASAP includes both isolated ASAP and ASAP with HGPIN.

Re-biopsy Rate

The re-biopsy rate for HGPIN and ASAP was calculated by dividing the number of HGPIN or ASAP that underwent a repeat biopsy by the total number of cases of HGPIN or ASAP.

Cancer Detection Rate

The cancer detection rate was calculated by dividing the total number of HGPIN or ASAP that developed adenocarcinoma on subsequent biopsy by the total number of HGPIN or ASAP that underwent a repeat biopsy. In addition, 80 cases in total from 2008 and 2009 with a benign diagnosis and no previous history of prostate adenocarcinoma were collected. Subsequent biopsies were followed and the cancer detection rate was also calculated using the same methods described above.

P-value calculation

P-values were calculated using a 2x2 contingency table and using a Fischer's exact test to generate a two-tailed p-value to determine statistical significance of data

IV. Results

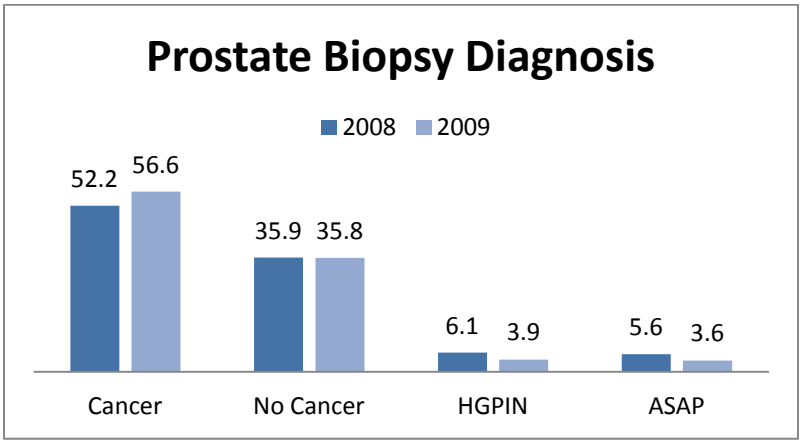
A. Population Sample Statistics

The mean age for patients in 2008 and 2009 was 65. Each prostate biopsy collected in this study was divided into one of four categories: prostate cancer (PrCa), benign, isolated HGPIN and isolated ASAP (with or without HGPIN). The breakdown for each category per year can be seen in Table 1 and Figure 9.

Table 1 : Population Sample Breakdown

Category	2008	2009
Benign	265	280
HGPIN	45	30
ASAP (with or without HGPIN	42	28
PrCa	385	440
Total	737	778

Figure 9: Prostate Biopsy Diagnosis for 2008 and 2009 (in percent)



B. Incidence Rates

The incidence rate of HGPIN was 6.1% and 3.8% in 2008 and 2009 respectively (Appendix 2). ASAP had an incidence rate of 5.7% and 3.5% in 2008 and 2009 respectively (table 2). Furthermore, in 2008, adenocarcinoma was diagnosed in 52.2% of prostate biopsies with an average Gleason score of 6.8. Similarly, in 2009, adenocarcinoma was diagnosed in 56.6% of prostate biopsies with an average Gleason score of 6.9. The Gleason score distribution per year can be seen in figure 10. The Gleason scores were categorized as follows: Gleason score 6 (3+3), Gleason score 7 (3+4 or 4+3), Gleason score of 8, 9 and 10.

Figure 10: Gleason Score Distribution 2008 and 2009

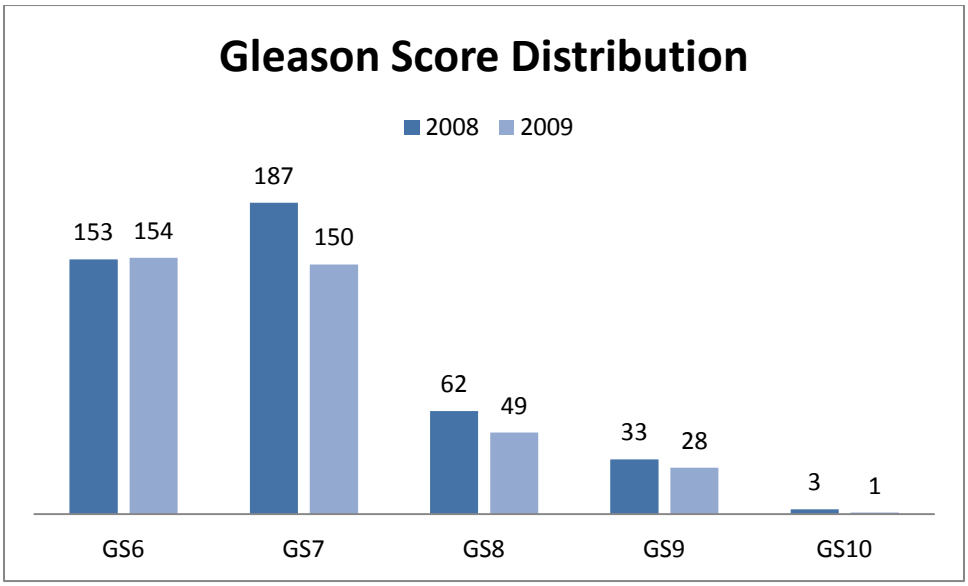


Table 2: HGPIN and ASAP incidence rates for 2008 and 2009

YEAR	2008	2009	2008 and 2009 combined
HGPIN	6.1% (45)	3.8% (30)	5.0% (75)
ASAP	5.7% (42; 30 ASAP, 12 ASAP with HGPIN)	3.5% (28; 15 ASAP, 13 ASAP with HGPIN)	4.6% (70)
Total Cases	737	778	1515

C. Follow-up

The total number of subsequent biopsies as well as the average time taken in between each biopsy is summarized in Table 3.

Overall, 26/75 (34.6%) of patients diagnosed with HGPIN underwent at least one re-biopsy within an average of 17.3 months following the initial diagnosis. In 2008, 16 out of 45 cases of HGPIN underwent at least one re-biopsy by the end of 2012, and of those 16, 2 had a third follow up biopsy. In 2009, 10/30 cases of HGPIN underwent at least one re-biopsy and of those 10, 3 underwent a third follow-up biopsy and 1 underwent a fourth follow-up biopsy.

With regards to ASAP overall, 39/70 (55.7%) of patients underwent at least one re-biopsy within an average of 18.3 months following the initial diagnosis. In 2008, 21 of 42 underwent at least one re-biopsy and out of the 21, 3 had a third follow-up biopsy and 1 had a fourth follow-up biopsy. In 2009, 18 of 28 had at least one re-biopsy and out of those 18, 3 had a third follow-up biopsy, and 1 had a fourth follow-up biopsy.

Table 3: Number of Subsequent Biopsies Following a Diagnosis of HGPIN and/or ASAP, 2008/2009

Year	Number of patients with at least one re-biopsy	Average Time (in months) since previous biopsy
2008	HGPIN – 35.0%(16/45)	15.8
	ASAP – 50.0%(21/42)	17.2
2009	HGPIN – 33.3%(10/30)	18.8
	ASAP – 64.2%(18/28)	19.3

D. Cancer Detection Rate

The cancer detection rate was calculated for HGPIN and ASAP, as well as following a diagnosis that was benign (Table 4).

D1. HGPIN

HGPIN had a cancer detection rate of 50% and 40% in 2008 and 2009 respectively (Table 4). In both 2008 and 2009, the average number of HGPIN positive cores with a subsequent diagnosis of adenocarcinoma was 2 with the majority of the detected adenocarcinoma having a Gleason score of 3+3 or 4+3. In 2008, out of the 16 cases with HGPIN that underwent a 2nd re-biopsy, 6 had confirmed adenocarcinoma. Both of the two cases with HGPIN that underwent a 3rd follow-up biopsy came back positive for adenocarcinoma. Alternatively, in 2009, only 2 out of the 10 cases diagnosed with HGPIN came back positive for adenocarcinoma after the 2nd re-biopsy and 1 out of 3 that underwent a third follow-up biopsy and 1 out of 1 that had a fourth follow-up biopsy had confirmed adenocarcinoma.

D2. ASAP

ASAP had a cancer detection rate of 33.3% and 22.2% in 2008 and 2009 respectively (Table 4). For both 2008 and 2009, the average number of positive ASAP cores with a subsequent diagnosis of adenocarcinoma was 1 core having an average Gleason score of 3+3. In 2008, 7 out of 21 cases with ASAP resulted in adenocarcinoma on the second follow-up, 0 out of 3 cases had adenocarcinoma after a third follow-up biopsy and 0 out 1 had adenocarcinoma after a fourth follow-up biopsy. Similarly, in 2009, 2 out of 18 cases had adenocarcinoma following a second follow-up, 1 out of 3 had adenocarcinoma following a third follow-up biopsy and 1 out of 1 had cancer following a fourth follow-up biopsy.

D3. Benign (Control)

From the 80 randomly selected cases with a benign diagnosis, only 24 underwent at least one re-biopsy. Out of those 24, only 8 developed adenocarcinoma on a repeat biopsy (Table 4).

Table 4: Post HGPIN and Post ASAP Cancer Detection Rates, 2008 and 2009

YEAR	2008	2009	2008 and 2009 combined
HGPIN	50.0%(8/16)	40.0%(4/10)	46.1%(12/26)
ASAP	33.3%(7/21)	22.2%(4/18)	28.2%(11/39)
BENIGN (total of 80)			33.3%(8/24)

E. Statistical Analysis

A sample contingency table can be found in Appendix 2.

E1. Incidence Rates of HGPIN and ASAP

A P-value of 0.73 was returned when the average incidence rates of HGPIN and ASAP from 2008 and 2009 were compared against one another. When the incidence rate of HGPIN in 2008 was compared against the incidence rate of HGPIN in 2009 a P-value of 0.045 was given. The p-value returned when comparing the 2008 ASAP incidence rate against the 2009 incidence rate was 0.065.

E2. Re-biopsy Rates

The average re-biopsy rates of HGPIN versus ASAP were compared and a p-value of 0.0126 was returned. When the re-biopsy rates of HGPIN in 2008 and 2009 were compared a p-value of 0.1981 was returned. When the re-biopsy rate for ASAP in 2008 and 2009 were compared a p-value of 0.3267 was returned.

E3. Cancer Detection Rates

The average cancer detection rate of HGPIN from 2008 and 2009 was compared against the benign cancer detection rate from 2008 and 2009 and returned a p-value of 0.3991. Similarly, the average ASAP cancer detection rate was also compared against the benign cancer detection rate and returned a p-value of 0.7792.

The average cancer detection rate of HGPIN for 2008 and 2009 was compared against the average cancer detection rate of ASAP and returned a p-value of 0.1871.

V. Discussion

This study's main goals were to determine the incidence and post-biopsy cancer detection rates of high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP). In addition, the study aimed to investigate the re-biopsy rate following a diagnosis of either pathological lesion in comparison to that established in the literature.

High-grade prostatic intraepithelial neoplasia (HGPIN)

The mean incidence rate for HGPIN in the literature is 7.7% with a median of 5.2% and range of 0-24.6% [15].In this study, the incidence rate of HGPIN from 2008/2009 was 5.0%. The incidence rate falls below the published average but closely matches the median, and falls within the published range. When looking at each study year individually, the incidence rate in 2008 was 6.1% and in 2009 it was 3.8%. The difference is statistically significant with a p-value of 0.045. This difference in incidence rates from one year to the next could be a result of pathologists gaining more confidence in what they interpret as HGPIN. Also, it is possible that with the decrease in significance of isolated HGPIN (1 core), pathologists are becoming more restrictive in their definition and diagnosis of HGPIN [28, 34, 37, 45]. However, a slide review was not conducted in this study, nor was data regarding the number of positive cores collected. Thus the true reason for the change in incidence rates between 2008 and 2009 cannot be determined.

The literature's post HGPIN cancer detection rate has a mean of 18.1% with a range of 2.3-79.2% [15]. The cancer detection rate in our study is 46.1% which is substantially above the literature mean but again falls within the published range.

Atypical small acinar proliferation (ASAP)

The mean incidence rate for ASAP in the literature is 5.0% with a median of 4.4% and a range of 0.7-23.4% [15]. In this study, the incidence rate of ASAP in 2008/2009 was 4.6% which closely approaches both the literature mean and median rate. The literature mean post ASAP cancer detection rate was 40.2%. The cancer detection rate in this study was less than half at 28.2%.

The data shows that our post-ASAP cancer detection rate is less than the literature mean. This does not necessarily suggest that local pathologists are under diagnosing ASAP as incidence rates fall within the literature range. Rather, it suggests one of two scenarios. Local pathologists could be aggressive and be calling small suspicious malignant foci adenocarcinoma over ASAP. Alternatively, local pathologists may be diagnosing benign foci as ASAP. Thus, in either case the incidence rate is maintained while the cancer detection rate falls.

Benign Prostate Biopsy

One major flaw in many studies regarding HGPIN and ASAP is the lack of comparison between a post ASAP or HGPIN cancer detection rate and post benign biopsy cancer detection rate. According to Epstein, the post benign biopsy cancer detection rate is approximately 23% [15]. The calculation of a post benign biopsy cancer detection rate is crucial in determining the

relative risk of cancer following an atypical diagnosis. In this study, the post benign biopsy cancer detection rate of the sample population was determined to be 33.3% (8/24). In comparison to the HGPIN cancer detection rate of 46.1%, there is higher risk of finding cancer following a diagnosis of HGPIN on an initial biopsy. However, after comparing both rates, a p-value of 0.3991 was returned which indicates no clinical significance. Additionally, the post ASAP cancer detection rate of 28.2% is only 4.8% lower than the post benign biopsy cancer detection rate of 33.0%. However, when compared against one another, a p-value of 0.7992 was returned indicating no statistical significance. Therefore, the data suggests that there is no increased risk of finding cancer following a diagnosis of ASAP beyond the usual indicators, such as a DRE or PSA test, that would result in a re-biopsy in a given patient. In comparison to Epstein's review article, the results in this study appear to contradict the literature [15]. The HGPIN cancer detection rate should be similar to that of benign cancer detection rate while ASAP should have a higher cancer detection rate in comparison to a benign cancer detection rate [15].

Re-biopsy Rates

Previously, the recommendation following a diagnosis of HGPIN is to re-biopsy within 3-6 months [15, 16]. Recently, post HGPIN cancer detection rates have dropped to the point that some researchers have demonstrated no greater cancer risk than that following a benign diagnosis. Thus, the recommendation for rapid re-biopsy has been dropped and follow up post diagnosis of HGPIN has been individualised [15, 16]. While there is no firm consensus on which specific features of HGPIN would merit a rapid re-biopsy, recent data suggests following a

diagnosis of widespread or multi-focal HGPIN (2 or more positive cores) a rapid re-biopsy is recommended with cancer detection rates as high as 40% [15, 16, 28, 34, 37, 45]. In our population, 34.6% of patients underwent at least one re-biopsy by the end of 2012 within an average of 17.3 months following a diagnosis of HGPIN. This suggests that most patients in our population are not being re-biopsied, as recommended in the literature.

Following a diagnosis of ASAP on initial biopsy, rapid re-biopsy is recommended within less than 6 months of the initial biopsy as experts believe that ASAP is often marginally sampled cancer [15, 16]. In our population, 55.7% were re-biopsied with an average time of 18.25 months following a diagnosis of ASAP. While the re-biopsy percentage following a diagnosis of ASAP is higher than HGPIN (34.6%), when compared, a p-value of 0.0126 was returned indicating significance. Despite a higher re-biopsy rate, 45% of patients diagnosed with ASAP are not being re-biopsied which contradicts what is recommended in the literature [15].

Clinical Significance

The data suggests that local urologists are concerned with re-biopsying patients diagnosed with ASAP more so than patients diagnosed with HGPIN. The lack of re-biopsying patients with HGPIN mirrors the recommendations as reported in the literature [15]. Local urologists are then relying on other clinical indicators such as DREs and PSA levels, PSA velocities and PSA density tests to determine if and when a re-biopsy should occur which is what is recommended [15, 16, 28, 39]. With regards to ASAP, local urologists are re-biopsying more aggressively. ASAP re-biopsy rates are significantly higher than HGPIN re-biopsy rates with a p-value of 0.0126. While more patients are being re-biopsied post ASAP, half are still not being

re-biopsied. Furthermore, those that are being re-biopsied are being biopsied within a time frame that is three times greater than that recommended in the literature. Thus, urologists are failing to re-biopsy all patients with an ASAP diagnosis and are re-biopsying them late.

The most important finding in our study is that a diagnosis of ASAP has no significance in predicting cancer over a benign prostatic biopsy. In addition, HGPIN demonstrates a higher predictive value for cancer on re-biopsy but this difference is not significant according to our analysis. This may be a function of a small sample size. This data suggests that a need for re-biopsy following a diagnosis of ASAP is not as important as suggested in the literature.

Study Weaknesses

The major weakness in this study is the low frequency of relevant events. Out of 1515 cases collected from 2008 to 2009, only 75 diagnoses of HGPIN and 70 diagnoses of ASAP were returned. In addition when analysing cancer detection rates at re-biopsy, only 26/75 HGPIN and 29/70 ASAP were re-biopsied during the study. These low numbers made it difficult to accurately interpret statistical analysis.

An additional and unavoidable weakness was the lack of slide review. Such a review would not be ethical without committing to revised reports and patient notification if diagnoses were altered. Thus, reasons for higher than average HGPIN cancer detection rates or lower than average ASAP cancer detection rates cannot be clearly determined.

VI. Conclusion

This study demonstrates a HGPIN incidence rate of 5.0% and a post HGPIN cancer detection rate of 46.1%. The ASAP incidence rate is 4.6% and cancer detection rate 28.2%. This data falls within the acceptable literature range. These numbers indicate that local pathologists are not under-diagnosing HGPIN or ASAP. In addition, the cancer detection rate following a benign diagnosis is not significantly different than the cancer detection rate following a diagnosis of HGPIN or ASAP. However, the numbers collected for this study are small. Additionally, according to our data, local urologists are re-biopsying ASAP less aggressively than what is recommended in the literature. When biopsies are performed, they are performed beyond the recommended 6 month window.

VII. Future Actions

Improved LIS

The majority of the data accrued for this study was manually retrieved due to the lack of a good LIS. The initial data search involved using the SNOMED code term "prostate" resulted in over thousands of reports, each which had to be manually retrieved and reviewed for specific criteria regarding HGPIN, and ASAP. In the future, an improved LIS could be developed in which searching for specific criteria in reports such as final diagnosis, type of procedure or number of previous biopsies could be more efficient and less time consuming.

Investigation between expert and non expert pathologists

This study only observed the incidence and cancer detection rates by local pathologists as a whole. A future study could be conducted in which expert local pathologists could be separated out from non expert local pathologists to observe if there is any significant difference in the incidence and cancer detection rates among either group. Van der Kwast *et al.,* indicated that expert pathologists diagnose ASAP less frequently and tend to make a more definitive diagnosis, such as benign or adenocarcinoma [15, 48]. In addition, as ASAP is not a true pathologic diagnosis but an expression of uncertainty it was also recommended by Van der Kwast *et al.*, that inter-collegial consultation occurs before a final diagnosis of ASAP is made[48]. During the review of all pathologist reports for this study, there were very few comments indicating consultation with other colleagues nor were there were any comments made indicating that previous pathology reports were reviewed.

Multi-focal HGPIN

The significance of multi-focal and uni-focal HGPIN and ASAP could be addressed in detail, as well as the cancer detection rate of ASAP with HGPIN versus either entity alone. According to Epstein, few studies looked at this issue. A future study could include a slide review of cases diagnosed with ASAP and HGPIN followed by a correlation with the incidence and cancer detection rates.

VIII. References

1. Allam, C., Bostwick, D., Hayes, J., Upton, M., Wade, G., Domanowski, G., Klein, M., Boling, E., and Stilmant, M. *Interobserver Variability in the Diagnosis of High-grade Prostatic Intrapithelial Neoplasia and Adenocarcinoma.* Mod Pathol. 1996; 9(7):742-751
2. Alsikafi, N., Brendler, CB., Gerber, GS., and Yang, X. *High-grade Prostatic Intraepithelial Neoplasia with Adjacent Atypia is Associated with a Higher Incidence of Cancer on Subsequent Needle Biopsy than High-grade Prostatic Intraepithelial Noeplasia alone.* Urology. 2001; 57:296-300
3. American Cancer Society, Statistics. 1990, 2012. http://www.cancer.org/research/cancerfactsstatistics/
4. Amin, M., Jeyaganth, S., Fahmy, N., Begin, L., Aronson, S., Jacobson, S., Tanguay, S., and Aprikian, A. *Subsequent prostate cancer detection in patients with prostatic intraepithelial neoplasia or atypical small acinar proliferation.* CUAJ. 2007; 1(3):245-249
5. BARD Biopsy Systems. BIOPTY Gun. Accessed September 2013. http://www.bardbiopsy.com/products/biopty-cut.php
6. Bostwick, DG. *Prostatic Intraepithelial Neoplasia*. Current Urology Reports. 2000; 1:65-70
7. Bostwick, DG and Ma, J. *Over-diagnosis of High Grade Intraepithelial Neoplasia: A Prospective Study of 251 Cases.* BJU International. 2007; 100:1036-1039
8. Bostwick, DG., and Meiers, I. *Atypical Small Acinar Proliferation in the Prostate: Clinical Significance in 2006.* Arch Pathol Lab Med. 2006; 130:952-957
9. Bostwick, DG., Qian, J., and Frankel, K. *The Incidence of High Grade Prostatic Intraepithelial Neoplasia in Needle Biopsies*. Journal of Urology. 1995; 154:1791-1794
10. Canadian Cancer Soceity, Statistics. 1990, 2012. http://www.cancer.ca/en/cancer-information/cancer-101/canadian-cancer-statistics-publication/?region=on
11. Cheville, J., Reznicek, M., and Bostwick, DG. *The Focus of "Atypical Glands, Suspicious for Malignancy" in Prostatic Needle Biopsy Specimens Incidence, Histologic Features, and Clinical Follow-up Cases Diagnosed in a Community Practice.* Am J Clin Pathol. 1997; 108:633-640
12. Epstein, J. *The Gleason Grading System: A Complete Guide for Pathologists and Clinicians.* Lippincott, Williams and Wilkins. USA. 2012.
13. Epstein, JI. *Precursor Lesions to Prostatic Adenocarcinoma*. Virchows Arch. 2009; 454:1-16
14. Epstein, J., Grignon, D., Humphrey, P., McNeal, J., Sesterhenn, I., Troncoso, P., and Wheeler, T. *Interobserver Reproducibility in the Diagnosis of Prostatic Intraepithelial Neoplasia*. Am J Surg Pathol. 1995; 19(8):873-886
15. Epstein, JI., and Herawi, M. *Prostate Needle Biopsies Containing Prostatic Intraepithelial Neoplasia or Atypical Foci Suspicious for Carcinoma: Implications for Patient Care.* Journal of Urology. 2006; 175:820-834
16. Epstein, JI., and Netto, G. *Biopsy Interpretation of the Prostate Fourth Ed*. 2013.

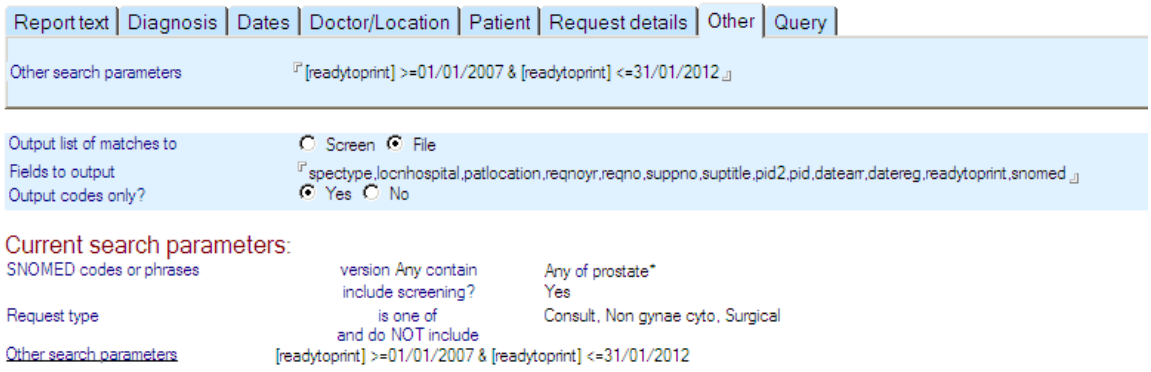
17. Fadare, O., Wang, S., and MAriappan, R. *Practice Patterns of CLinicans Following Isolated Diagnoses of Atypical Small Acinar Proliferation on Prostate Biopsy Specimens.* Arch Pathol Lab Med. 2004; 128:557-560
18. Fowler, J., Brigler, S., Lynch, C., Wilson, S., and Farabaugh, P. *Prospective Study of Correlation Between Biopsy Detected High-grade Prostatic Intraepithelial Neoplasia, Serum PSA and Race.* Cancer. 2001; 91:1291-1296
19. Girasole, CR., Cookson, MS., Putzi, MJ., Chang, SS., Smith, JA., Wells, N, Oppenheimer, JR., and Shappell, SB. *Significance of Aypical and Suspicious Small Acinar Proliferations and High Grade Prostatic Intraepithelial Neoplasia on Prostate Biopsy: Implications for Cancer Detection and Biopsy Strategy.* Journal of Urology. 2006; 175:929-933
20. Gupta, C., Ren, JZ., and Wojno, K. *Individual Submission and Embedding of Prostate Biopsies Decreases Rates of Equivocal Pathology Reports.* Urology, 2004: 63: 83-86
21. Herawi, M., Kahane, H., Cavallo, C., and Epstein, J. *Risk of Prostate Cancer on First Re-Biopsy Within 1 Year Following a Diagnosis of High Grade Prostatic Intraepithelial Neoplasia is Related to the Number of Cores Sampled.* Journal of Urology. 2006; 175:121-124
22. Hou, H., Li, X., Chen, X., Wang, C., Zhang, G., Wang, H., Gong, H., Deng, Y., Wang, M., and Zhang, X. *Prediction Value of High-Grade Prostatic Intraepithelial Neoplasia for Prostate Cancer on Repeat Biopsies.* Chinese-German Journal of Clinical Oncology. 2011; 10(7):410-414
23. Iczkowski, K., MacLennan, G., and Bostwick, DG. *Aytpical Small Acinar Proliferation Suspicious for Malignancy in Prostate Needle Biopsies; Clinical Significance in 33 Cases.* American Journal of Surgical Pathology. 1997; 21(12):1489-1495
24. Iczkowski, K., Bassler, T., Schwob, I., Bassler, I., Junnel, B., Orozco, R., and Bostwick, DG. *Diagnosis of "Suspicious for Malignancy" in Prostate Biopsies: Predictive Value for Cancer.* Urology. 1998; 51:749-758
25. Jian, Z., and Woda, B. *Diagnositc Utility of alpha-Methylacyl CoA Racemase (P504S) on Prostatic Needle Biopsy.* Adv Anat Pathol. 2004; 11(6):316-321
26. Koca, O., Caliskan, S., Ozturk, M., Gunes, M., and Karaman, I. *Significance of Atypical Small Acinar Proliferation and High-Grade Prostatic Intraepithelial Neoplasia in Prostate Biopsy*. Korean Journal of Urology. 2011; 52:736-740
27. Korkes, F., Mo, S., Koza de Jesus, C., and Castro, M. *Prostate Biopsies Containing Prostate Intraepithelial Neoplasia and Atypical Small Acinar Proliferation: What do to?* Einstein. 2009; 7(4 Pt 1):411-414
28. Kronz, J., Shaikh, A., and Epstein, J. *High-grade Prostatic Intraepithelial Neoplasia with Adjacent Small Atypical Glands on Prostate Biopsy.* Human Pathol. 2001; 32(389):389-395

29. Kronz, J., Allan, C., Shaikh, A., and Epstein, J. *Predicting Cancer Following a Diagnosis of High-Grade Prostatic Intraepithelial Neoplasia on Needle Biopsy.* Am J Surg Pathol. 2001; 25(8):1079-1085
30. Kumar Vinay, Abbas Abul K., Fausto Nelson., Aster Jon C. *Robbins and Cotran Pathologic Basis of Disease.* 8th Ed. Page 993-1002. Elsavier. Philadelphia, PA, USA, 2010
31. Lopez, J. *Prostate Adenocarcinoma Detected After High-Grade Prostatic Intraepithelial Neoplasia or Atypical Small Acinar Proliferation.* BJU. 2007; 100:1272-1276
32. McNeal, J., and Bostwick, DG. *Intraductal Dysplasia.* Human Pathology. 1986; 17(1):64-71
33. Medscape. Prostate Cancer: Diagnosis and Staging. http://emedicine.medscape.com/article/458011-overview Accessed September 2013
34. Merrimen, J., Jones, G., and Srigley, J. *Is High Grade Prostatic Intraepithelial Neoplasia Still a Risk Factor for Adenocarcinoma in the Era of Extended Biopsy Sampling.* Pathology. 2010; 42(4):325-329
35. Montironi, R., Vela Navarrete, R., Lopez- Beltran, A., Mazzucchelli., Mikuz, G., and Bono, A. *Histopathology Reporting of Prostate Needle Biopsies. 2005 Update.* Virchows, Arch. 2006; 449:1-13
36. Moore, C., Karikehalli, S., Nazeer, T., Fisher, H., Kaufman, R., and Mian, B. *Prognostic Significance of High-grade Intraepithelial Neoplasia and Atypical Small Acinar Proliferation in the Contemporary Era.* Journal of Urology. 2005; 173: 70-72
37. Netto, G., and Epstein, J. *Widespread High-Grade Prostatic Intraepithelial Neoplasia on Prostatic Needle Biopsy: A Significant Likelihood of Subsequently Diagnosed Adenocarcinoma.* Am J Surg Pathol. 2006; 30(9):1184-1188
38. Ng, V., Koh, M., Tim, S., and Tan, P. *Is Triple Immunostaining with 34BE12, p63, and Racemase in Prostate Cancer Advantageous?* Am J Clin Pathol. 2007; 127:248-253
39. Ouyang, RC., Kenwright., D., Nacey, J., and Delahunt, B. *The Presecence of Atypical Small Acinar Proliferation in Prostate Needle Biopsy is Predictive of Carcinoma on Subsequent Biopsy.* BJU International. 2001; 87:70-74
40. Ploussard, G., PLennevaux, G., Allory, Y., Salomon, L., Azoulay, S., Vordos, D., Hoznek, A., Abbou, C., and de la Taille, A. *High-grade Prostatic Intraepthelial Neoplasisa and Atypical Small Acinar Proliferation on Initial 21-Core Extended Biopsy Shceme: Incidence and Implications for Patient Care and Surveillance.* World J Urolo. 2009; 27:587-592
41. Ragde, H., Aldape, H., and Bagley, C. *Ultrasound Guided Prostate Biopsy. BIOPTY Gun Superior to Aspiration.* Urology. 1988; 32(6):503-506
42. Reyes, A., and Humphrey, P. *Diagnostic Effect of Complete Histologic Sampling of Prostate Needle Biopsy Specimens.* Am J Clin Pathol. 1998; 109:416-422
43. Renshaw, A. *Adequate Tissue Sampling of Prostate Core Needle Biopsies.* Am J Clin Pathol. 1997; 107:26-29
44. Robinson, B., Maqi-Galuzzi, C., and Zhou, M. *Intraductal Carcinoma of the Prostate*. Arch Pathol Lab Med. 2012; 136(4):418-425

45. Schoenfield, L., Jones, JS., Zippe, CD., Reuther, AM., Klein, E., Zhou, M., and Magi-Galluzzi, C. *The Inicidence of high-grade prostatic intraepithelial neoplasia and atypical glands suspicious for carcinoma on first-time saturation needle biopsy, and the subsequent risk of cancer.* BJU Int. 2007; 99(4):770-774
46. United States Preventative Task Force Services. Prostate Screening. http://www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm Accessed September 2013.
47. World Health Organization Classification of Tumours. "Tumours of the Urinary System and Male Genital Organs." 2004; pages 160-198
48. Van der Kwast, T., Evans, A., Lockwood, G., Tkachuk, D., Bostwick, D., Epstein, J., Humphrey, P., Montironi, R., Van Leenders, G., Pihl, C., Neetens, I., Kujala, P., Laruilla, M., Mazerolles, C., Bubendorf, L., Finelli A., Watson, K., and Srigly, J. *Variability in Diagnostic Opinion Among Pathologists for Single Small Atypical Foci in Prostate Biopsies.* Am J Surg Pathol. 2010; 34(2):169-177

IX. Appendix 1 – Search Parameters

Figure 11: Search Parameters using the M-CCMB-Prostate Database



X. Appendix 2 – Sample Calculations

The following calculations use the data collected for HGPIN in 2008 as indicated in Table 1

Table 1 – Population Sample Breakdown

Category	2008	2009
Benign	265	280
HGPIN	45	30
ASAP (with or without HGPIN	42	28
PrCa	385	440
Total	737	778

Sample Calculation 1 - HGPIN Incidence Rate

$$\frac{\text{Number of cases in 2008 with HGPIN}}{\text{Total Number of cases in 2008}} = \frac{45}{737} = 0.0061 = 6.1\%$$

Sample Calculation 2 - HGPIN Cancer Detection Rate

In 2008, 16 out of 45 patients diagnosed with HGPIN on the initial biopsy underwent at least one re-biopsy. Out of those 16 only 8 had a confirmation of adenocarcinoma on the re-biopsy:

$$\frac{\text{Number of cases with confirmed adenocarcinoma on re-biopsy}}{\text{Number of cases that underwent at least one re-biopsy}} = \frac{8}{16} = .5 = 50\%$$

Sample Calculation 3 – Sample calculation of p-value when comparing the overall HGPIN cancer detection rate versus the overall benign cancer detection rate

- In 2008 and 2009 a total of 12/26 cases had confirmed adenocarcinoma on a re-biopsy following an initial diagnosis of HGPIN. Therefore, 12 were "malignant" and 14 were "benign.
- In 2008 and 2009 a total of 80 benign cases were followed up on, with 24 having had follow up with at least one re-biopsy. Out of those 24, 8 had a confirmed diagnosis of adenocarcinoma on follow-up while 16 remained benign.

The numbers were input into a 2x2 contingency table to generate a p-value using a Fischer's exact test:

Analyze a 2x2 contingency table

	Benign	Malignant	Total
HGPIN	14	12	26
Benign	16	8	24
Total	30	20	50

Fisher's exact test

The two-tailed P value equals 0.3991
The association between rows (groups) and columns (outcomes) is considered to be not statistically significant.