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CLINICAL TRIAL ENROLLMENT IN A MULTIDISCIPLINARY PROSTATE CANCER

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by

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A

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Publication No. _____

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Purpose: Clinical oncology trials are hampered by low accrual rates. Less than 5% of adult cancer patients are treated on a clinical trial. We aimed to evaluate clinical trial enrollment in our Multidisciplinary Prostate Cancer Clinic and to assess if a clinical trial initiative, introduced in 2006, increased our trial enrollment.

Methods: Prostate cancer patients with non-metastatic disease who were seen in the clinic from 2004 to 2008 were included in the analysis. Men were categorized by whether they were seen before or after the clinical trial enrollment initiative started in 2006. The initiative included posting trial details in the clinic, educating patients about appropriate clinical trial options during the treatment recommendation discussion, and providing patients with documentation of trials offered to them. Univariate and multivariate (MVA) logistic regression analysis evaluated the impact of patient characteristics and the clinical trial initiative on clinical trial enrollment.

Results: The majority of the 1,370 men were white (83%), and lived within the surrounding counties or state (69.4%). Median age was 64.2 years. Seventy-three point five percent enrolled in at least one trial and 28.5% enrolled in more than one trial. Sixty-seven percent enrolled in laboratory studies, 18% quality of life studies, 13% novel studies, and 3.7%

procedural studies. On MVA, men seen in later years ($p < 0.0001$) were more likely to enroll in trials. The proportion of men enrolling increased from 38.9% to 84.3% ($p<0.0001$) after the clinical trial initiative. On MVA, older men ($p < 0.0001$) were less likely to enroll in clinical trials. There was a trend toward men in the high-risk group being more likely to participate in clinical trials ($p = 0.056$). There was a second trend for men of Hispanic, Asian, Native American and Indian decent being less likely to participate in clinical trials ($p = 0.054$).

Conclusion: Clinical trial enrollment in the multidisciplinary clinic increased after introduction of a clinical trial initiative. Older men were less likely to enroll in trials. We speculate we achieved high enrollment rates because 1) specific trials are discussed at time of treatment recommendations, 2) we provide a letter documenting offered trials and 3) we introduce patients to the research team at the same clinic visit if they are interested in trial participation.

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Introduction

Prostate Cancer

Prostate Cancer (PCa) is a tumor of the prostate gland that occurs when normal glandular cells mutate into malignant cancer cells whose growth, function, and proliferation is no longer under the body's regulatory control. The majority of prostate cancers are adenocarcinomas, an epithelial cancer that originates within glands and/or glandular tissue (Crawford, 2009). However, a small percentage can develop from aberrant squamous cells, signet ring, transitional cells or even neuro-endocrine stem cells all normally found in the prostate (Bracarda, et al., 2005). PCa is more likely to be a quiescent localized disease with a protracted course but it can also manifest as a rapidly progressing tumor with high metastatic potential (Crawford, 2009). PCa tends to be a highly heterogeneous disease. This is partly due to the biology and morphology of the prostate gland.

The prostate gland itself is an integral part of the male genitourinary system, located in the pelvic cavity, nestled between the urinary bladder and the rectum. It is responsible for the production and storage of seminal fluid and is typically classified into 3 different zones: central, transition and the peripheral zone. Although the tumor may originate in one specific zone of the prostate, the majority of these tumors have multiple separate copies scattered throughout all three zones of the prostrate (Crawford, 2009). Because of this, prostate cancers are considered by convention to be multifocal/multi-centric tumors. Furthermore, these multicentric lesions can and often do have differing glandular patterns and degrees of tumor cell differentiation (Bracarda et al., 2005). Localized prostate tumors tend to spread first to the seminal vesicles, urinary bladder and the surrounding tissues (Bracarda et al.,

2005). Prostate tumors metastasize primarily to the bone, via the lymphatic system or direct hematogenous (Bracarda et al., 2005).

Prevalence and Incidence

One in 6 men over the age of 50 will be diagnosed with PCa in their lifetime; of these, 1 in 33 will die of the disease (Weissbach et al., 2009). Despite this seemingly moderate death rate, studies show that PCa is second only to lung caner in cancer-related mortality in men (Jemal et al., 2010). The American Cancer Society reported 217,730 newly diagnosed cases of PCa and 32,050 deaths in the US in 2010 alone (Rosenberg et al., 2010; Jemal et al., 2010). The incidence of PCa has been on the rise since 1975 starting at 195 cases per 100,000 and spiking in 1992 to nearly 250 per 100,000 (Jemal et al., 2010). This increase is mostly due to the advent of prostate-specific antigen (PSA) screening, which was implemented in the late 1980s (Bracarda et al., 2005). Its widespread use leveled off by the early 2000s, coinciding with the leveling off PCa incidence rates (Bracarda et al., 2005). As of 2010, the US incidence of PCa was 155.5 cases per 100,000 (Jemal et al., 2010). Screening and early detection have driven the mortality rates down. Currently, the 5-year survival rate for PCa approaches 100%, while the 10-year survival rate is 93% (Rosenberg et al., 2010). PCa is a significant problem in the population at large. One way to combat the problem is to learn more about the disease through education and research.

Screening and Diagnosis

Prostate-specific antigen (PSA) is a glycoprotein produced by the epithelial cells of the prostate gland, and is mainly concentrated within the prostate gland (Greene et al, 2009).

Serum PSA level is very low in an individual with normal prostate function, however aberrant changes in the functionality and integrity of the prostate often gives rise to leakage and elevated levels of PSA in the blood. Because of positive correlation between serum PSA level and prostate abnormalities, serum PSA screening has been implemented as a diagnostic and/or prognostic biomarker for prostate cancer. PSA screening guidelines vary across different medical organizations. As of 2009, the age at which the American Urological Association (AUA) recommends individuals obtain a baseline PSA has been lowered from 50 years to 40 years for those at an average risk (non-African-American, no family history) of prostate cancer development (Greene et al., 2009). Thereafter, individuals are recommended to return for regularly scheduled PSA tests (Greene et al, 2009).

PSA, while being specific to the prostate gland, is not necessarily sensitive only to PCa (Bracarda et al., 2005). Because elevated serum PSA is also highly characteristic of non-cancerous prostate abnormalities (ex. prostatitis, benign prostate hyperplasia, etc.), a digital rectal examine (DRE) is recommended in conjunction with a screening PSA test (Bracarda et al., 2005). In the presence of an abnormal DRE and/or an elevated PSA, a positive prostate biopsy is required for a differential diagnosis (Greene et al., 2009). A review of all possible contributing factors such as PSA density and velocity, prostate size, patient age and ethnicity, co-morbidities and previous prostate biopsy is also recommended (Horwich, et al., 2010).

Risk Group

The inherent heterogeneity of prostate tumors necessitates an unique scoring system. In addition to the standard TNM (Tumor, Node, Metastasis) staging for solid tumors,

prostate cancers are subjected to the disease-specific Gleason score. The Gleason scoring system is based specifically on the glandular pattern of the tumor and the degree of differentiation of the tumor cells themselves (Bracarda et al., 2005). Tumors are stratified into five different grades (1-5), with grade 5 having the worse prognosis (Bracarda et al., 2005). The two most prominent grades of disease are added together to give a single Gleason score which would then be used as a prognostic indicator. Unfortunately, Gleason scores are only useful in scoring adenocarcinomas of the prostate. This tends not to be an immediate concern since approximately 95% of prostate cancers are adenocarcinomas (Bracarda et al., 2005).

Based on PSA level, Gleason score, and T-stage clinically localized tumors are further categorized into prognostic recurrence risk groupings (Horwich et al., 2010). [See Table 1 for the NCCN (National Comprehensive Cancer Network) risk group criteria.] Risk group predicts the likely treatment outcome and guides the physician in making the appropriate treatment recommendations. Risk group is also a key factor in the majority of interventional clinical trials inclusion/exclusion criteria. Clinicians/Investigators also consider patient age and life expectancy, co-morbidities and general health status (Horwich et al., 2010).

Table 1. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer risk group criteria, Version 1. 2010.

Very Low Risk	Low Risk	Intermediate Risk	High Risk	Very High Risk	Metastatic
T1a Gleason ≤6 PSA <10 ng/mL < 3 + biopsy cores w/ ≤50% cancer PSA density <0.15 ng/mL	T1 – T2a Gleason 2-6 PSA <10 ng/mL	T2b - T2c **or** Gleason 7 **or** PSA 10-20 ng/mL	T3a **or** Gleason 8 – 10 **Or** PSA >20 ng/mL	(locally Advanced disease) T3b – T4	(locally advanced disease) Any T, N1 Any T, Any N, M1

Treatment Options and Side Effects

Active surveillance consists of identification of prostate cancer patients with low or very low risk disease who are then put on a periodic disease monitoring/re-staging schedule until such time as a PSA test, DRE or other clinical indicator of progression crosses the risk threshold, indicating the need for active treatment (Large et al., 2009). The main drawback associated with the active surveillance approach is increased patient anxiety caused by the psychosocial burden of living with an untreated cancer that may or may not have the potential to progress and become life threatening (Andrew et al., 2010).

Radical prostatectomy (RP) is the surgical removal of the prostate gland (Andrew et al., 2010). Along with the normal post-operative complications (i.e. pain, bleeding) RP carries with it the threat of stress or total urinary incontinence, and erectile dysfunction (possibly long-term) (Andrew et al., 2010).

Brachytherapy is the insertion of radioactive isotopes seeds into the prostate gland, which would deliver a steady dose of therapeutic radiation to the tumor site and surrounding tissues over time. Brachytherapy can be done with either temporary implants or permanent ones (Horwich et al., 2010). The risk group generally determines whether the patient will receive temporary or permanent implants. External beam radiotherapy is radiation therapy that originates from a source outside the body. External beam radiotherapy uses a rotating machine (gantry) to aim the radiation at the site of the patient's cancer, in this case, the prostate gland. Radiation treatment(s), whether it is external beam therapy or internal seed implants, all carry the similar side effect profile: bladder, urethra or rectal irritation, frequent

urination, burning urination and stronger urges to urinate, rectal soreness or bleeding, and frequent bowel movements (Andrew et al., 2010).

Hormone therapy in the context of prostate cancer treatment consists of Androgen Deprivation Therapy (ADT). ADT is generally a drug given to patients that reduces the production and/or effects of androgenic hormones (i.e. testosterone) by preventing the cancer cells from interacting with testosterone. This results in tumor shrinkage because many prostate cancers require testosterone for growth and proliferation. LHRH (luteinizing hormone-releasing hormone) agonists are drugs that work indirectly by inducing the pituitary gland to release LHRH which cause the testicles to halt the production of testosterone. Orchiectomy is the surgical removal of the testicles, which in turn guarantees a substantial and permanent halt to testosterone production. The timing for giving hormone therapy may vary (adjuvant, neo-adjuvant, post-relapse, post-metastasis) (Horwich et al., 2010). All hormone therapies cause the same general side effects: impotence, weakness and loss of muscle mass, osteoporosis, shrunken testicles (absent testicles in the case of orchiectomy), and depression, low self-esteem, loss of aggressiveness/alertness, weight gain/obesity and diabetes (Andrew et al., 2010). In recent years, there is some indication that hormone therapy in men with prostate cancer can increase the risk of cardiovascular disease and cardiovascular events (i.e. myocardial infarction) (Schwandt et al., 2009)

Two emerging therapy options for PCa that have been in the spotlight in recent years are cryotherapy and HIFU. Both are focal therapies and still under interventional investigation. Focal therapy is loosely defined as any form of incomplete prostate ablation therapy (i.e. hemi-ablation, three quarter's ablation) (Eggener et al., 2010). The overall

Table 2: NCCN Practice Guidelines in Oncology, PCa Initial Treatment Recommendations, version 1. 2010.

Risk Group	Life Expectancy	Initial Therapy Recommendation	Adjuvant Therapy Recommendations
Note: *The NCCN believes that the best management for any cancer patient is in a clinical trial. Therefore, participation in clinical trials is highly encouraged.*			
Very Low Risk	< 20yrs	AS PSA every 6 months DRE every 12 months	
Low Risk	<10	AS PSA every 6 months DRE every 12 months	
	≥10	AS PSA every 6 months DRE every 12 months Biopsy every 12 months	
		RT	
		RP ± PLND	Observation **or** RT
			If + lymph nodes: Observation or ADT
Intermediate Risk	<10 yrs	AS PSA every 6 months DRE every 12 months	
		RT ± short term ADT ±Brachytherapy	
		RP ± PLND	Observe **or** RT
			If + lymph nodes: Observe or ADT
	≥10yrs	RP ± PLND	Observation **or** RT
			If + lymph nodes: Observation **or** ADT
		RT ± short term ADT ± Brachytherapy	
High Risk		RT + long term ADT	
		RP + PLND	Observation **or** RT
			If + Lymph nodes: Observation **or** ADT
Very High Risk / Locally Advanced		RT + long term ADT	
		RP + PLND	Observe **or** RT
			If + Lymph nodes: Observation **or** ADT
		ADT	
Metastatic Any T, N1		ADT Or RT + short term ADT	
Metastatic Any T, Any N, M1		ADT	

AS = Active surveillance, **ADT** = Androgen deprivation therapy, **DRE** = Digital rectal exam, **RT** = Radiation therapy, **RP** = Radical prostatectomy, **PLND** = Pelvic lymph node dissection.

objectives of focal therapy are to a) selectively ablate tumor cells/tissue, b) preserve organ function, and c) minimize treatment morbidity (Karavitakis et al., 2010).

Cryotherapy, more colorfully known as "the male lumpectomy", is the localized destruction of tissue using alternating cycles of extreme freezing and thawing (Lindner et al., 2010, Lecornet et al., 2010). Cryotherapy is already known to have many advantages. It is a one-time (often outpatient) treatment, which can be repeated as both a focal and a whole gland treatment if necessary (Singh et al., 2010). However, it does carry with it the worrisome risk of erectile dysfunction (Singh et al., 2010). Other known side effects of the treatment are urethral fistula, urethral sloughing and incontinence, although the rates of these effects are relatively low (Singh et al., 2010).

HIFU (High intensity focused ultrasound) therapy is the use of a tightly focused ultrasound frequency (between 0.8 and 3.5 MHz) to generate high energy density which when aimed at a specific point in the prostate gland causes heating, protein denaturation, coagulative necrosis and ultimately tissue death/damage (Lecornet et al., 2010; Eggener et al., 2010). Its use is associated with varying rates of the following side effects: urethral strictures, urethro-rectal fistulas, urinary incontinence and impotence (Eggener et al., 2010). Further observations and interventional studies of focal therapies need to be completed to report on the full potential and/or limitations of both HIFU and cryotherapy. However, low accrual rates on clinical trials have slowed efforts to refine these emerging therapies.

Risk Factors and Etiology

To date, no direct cause of PCa has been clearly identified. Studies have suggested a plethora of possible contributing factors (previous diagnosis of benign prostatic hyperplasia, history of vasectomy, level of sexual activity, weight and diet, smoking, deficiency in vitamin E or D, alcohol consumption etc.) but none of these have stood firm against rigorous scientific investigation (Bracarda et al., 2005). However, there is consistent, corroborative evidence to support several recognized risk factors that contribute to the development of PCa: age, race, a positive family history, and a hereditary pre-disposition.

Studies and statistics show that the risk of prostate cancer increases with increasing age. According to statistical analysis run on cancer-free US males from 2004 to 2006, from birth to age 39, the probability of being diagnosed with PCa is only 1 in 9,422 (Jemal et al, 2010). For ages 40 to 50, the probability increases to 1 in 41, for ages 60 to 69 the probability is 1 in 16, and for males 70 or older the probability of developing prostate cancer peaks at 1 in 8 (Jemal et al, 2010). Additionally, the American Cancer Society states that 63% of PCa cases diagnosed in the US occurred in patients 65 years or over (Mordukhovish et. al., 2010)

Tumor cells, whether they originate from prostate tissue or another neoplastic source, develop as a result of certain genetic alterations (mutations) in key genes or transcription factors involved in regulatory pathways controlling cell growth, proliferation, and function. With each round of a cell's replicative lifespan, dividing cells accumulate or are at risk of accumulating gain-of-function or loss-of-function mutations which can damage or alter the cell cycle in such a way that promotes neoplastic transformation. Cancerous cells are

unlikely to develop as a result of any one mutation. Even mutations in proto-oncogenes (gene whose mutation or increased expression has a high potential to cause cancer) often require some corroborating mutation, infection, or environmental factor to express its full neoplastic potential. However, with increasing age, the cells undergo countless rounds of replication, each of which has the potential for mutations and transcriptional errors to occur. Increasing age ensures, that given enough time, the 'lethal' combination of aberrant cells or a key mutation in a proto-oncogene will cause a neoplastic transformation.

There is also a well-established hierarchy of risk for prostate cancer seen among the different ethnicity groups (see figure 1). In the US, the observed incidence of prostate cancer is markedly lower in Asian/Pacific Islanders and Native Americans/Alaska Natives at approximately 83 cases per 100,000 as compared to Caucasians males at 146.3 cases per 100,000 (Jemal, 2010). The PCa incidence among Hispanic/Latino Americans (131.4 cases per 100,000) is lower in comparison to Caucasian males but higher in the hierarchy than Asian/Pacific Islanders and Native Americans/Alaska Natives (Jemal et al., 2010). Meanwhile, African-American men have the highest incidence of PCa at 231.9 cases per 100,000 (Jemal et al., 2010). A similar risk hierarchy is observed in PCa death rates among the different racial/ethnic groups (see figure 2).

Ironically, racial and ethnic minorities are under-represented among clinical trials participant populations, particularly African-Americans and Hispanics/Latinos (Pinsky et al., 2008). Few comparisons have been compiled in which the data includes the Hispanic/Latino, Asian/Pacific Islander, or American Indian/Alaska Native groups in numbers significant enough to generalize. Because of this accrual/enrollment disparity, the discussion below will focus mainly on the Caucasian--African-American dichotomy.

Overall, African-Americans are approximately 1.4 times more likely to develop PCa than Caucasian men, the next highest ethnic group (Chornokur et al., 2010). SEER (the Surveillance, Epidemiology, and End Results Program) found similar racial disparities in PCa incidence rates for African-American and Caucasian males (Mordukhovich et al., 2010). Not surprisingly these disparities are carried over into the prognosis, treatment and

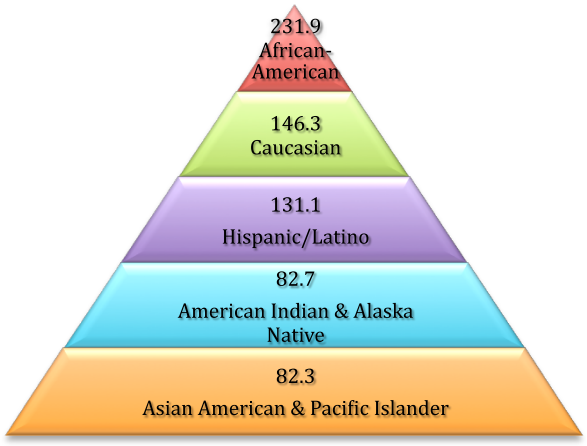

Figure 1: Age-adjusted prostate cancer incidence rates per 100,000 population, stratified by race/ethnicity, United States, 2002 – 2006.

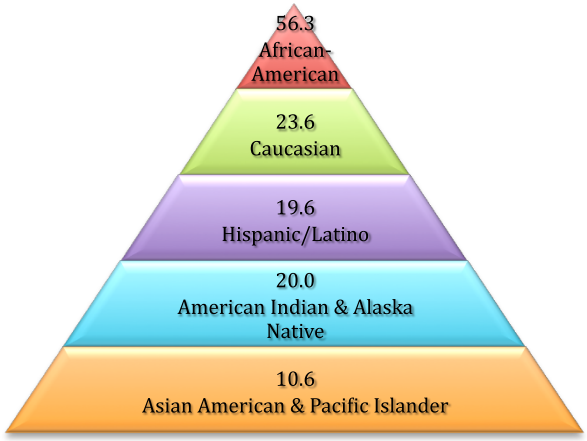

Figure 2: Age-adjusted prostate cancer mortality rates per 100,000 population, stratified by race/ethnicity, United States, 2002 – 2006

PCa specific mortality rates. A greater percentage of African-American males are diagnosed at later stages as compared to Caucasians males; Six percent of African-Americans have distant metastasis at initial diagnosis vs. only 4% of Caucasians (Mordukhovich et al., 2010). CDC (Centers for Disease Control and Prevention) indicates that African-American males have an earlier onset of disease, on average being diagnosed with PCa 3 years earlier than Caucasian males (Chornokur et al., 2010). Furthermore, a cohort study performed on 37 African-American PCa patients and 35 demographically matched Caucasian patients, each receiving radical prostatectomy, showed that the percentage of African-American males whose Gleason score was pathologically up-staged post-surgery was nearly double that of Caucasian patients (49% vs. 26% respectively) (Chornokur et al., 2010). The study also observed that African-American patients tended to have greater tumor volume, and 2.8 times more tumor per ng/ml of serum PSA than their Caucasian counterparts (Chornokur et al., 2010).

The basis for these disparities is largely unknown, however, several viable hypotheses have been purposed and explored by researchers. Some suggest that the disparity between African Americans and Caucasians is due to lapses in the patterns and quality of care (Barocas, et al., 2010). In studies looking at racial disparities in PCa and the possible causes, it is observed that African-Americans are less likely to received radial prostatectomy (a definitive, curative therapy) and more likely to receive radiotherapy or watchful waiting (a delay of active treatment until such time as tumor progression is detected) (Chornokur et al., 2010). These treatment decisions are possibly due to different values and concerns among African-American men regarding the effects of invasive therapy such as urinary dysfunction and long-lasting sexual impairment. Some studies suggest that

the reason for these patterns, particularly those observed in African-Americans vs. Caucasians are more a reflection of socio-economic disparities such as income, education, health insurance and employment status (Barocas et al., 2010). There are a larger percentage of African-American men that are unemployed (15.5% vs. 8.8% of Caucasians), below the poverty line (24% vs. 8.6% of Caucasians), and without health insurance (19.5% vs 10.4% of Caucasians) (Barocas et al., 2010).

A second theory points instead to hereditary pre-disposition or ethnicity-specific biologic differences to explain racial disparities (Chornokur et al., 2010). GWAS studies, which have been undertaken to search for causal or risk-baring genomic locations which confer a hereditary pre-disposition to PCa development, have shown that certain SNPs (single nucleotide polymorphisms) associated with PCa risk vary by race (Liu et al., 2011). (Of note: of the 71 subgroups examined in the study, only 2 were of Asian descent and 4 of African American descent.) (Liu et al., 2011). Results showed that some risk SNPs are only significantly associated with PCa in European populations, likewise others are only significant among Asians populations or African-American populations (Liu et al., 2011). This suggests that the racial hierarchy observed in PCa incidence, prognosis and survival has a basis in genetics and other biologic factors. It could be that certain; as yet unidentified, ethnicity-specific biologic factor(s) are what drive some tumors to develop more aggressively than others. Conversely, it has also been observed that PCa incidence rates in Japanese men who immigrated to the United States were noticeably elevated in comparison to Japanese men still residing in their native country (Crawford, 2009). This would seem to suggest an environmental risk factor were at heart of racial disparities seen in PCa. There is

also the possibility that several interlocking social, economic, and/or biologic factors would best explain the racial hierarchy as opposed to a singular cause.

In addition to age and race, having a positive family history of PCa is a consistently observed risk factor for PCa development. Case control studies done on African-American populations in Jamaica and Caucasian populations in Canada both reveal significant results among first-degree relatives. In the Jamaican study, pedigrees and family history information were obtained from histologically proven cases and their demographically similar controls (Glover et al., 1998). Individuals with a first degree relative with a history of PCa were twice as likely to develop prostate cancer as individuals without a positive family history (Glover et al., 1998). Among 263 cases, 30 patients had a father, son or brother who also had PCa compared to only 15 of 263 controls (Glover et al., 1998). A threefold difference was observed when examining more distant relatives. Nine cases had a grandfather, grandson or uncle with PCa compared with only 3 controls with an affected second-degree relative (Glover et al., 1998). In the Canadian study there were 640 PCa cases and 639 demographically similar controls (Ghadirian et al., 1997). Fifteen percent (94) of cases self-reported one or more relatives (father or brother or both) with a history of PCa while only 5% (32) of controls revealed first degree relatives with a history of PCa (Ghadirian et al., 1997). Again, a threefold difference is observed, suggesting that PCa does indeed 'run in the family'.

A U.S. study evaluated a cohort of 15,924 veteran twin pairs (31,848 individuals); one thousand nine cases of PCa were identified within the cohort (Page et al., 1997). Researchers found that 15.7% of monozygotic twins (MZ) showed pairwise concordance (of PCa) in comparison to only 3.7% of dizygotic twins (DZ) (Page et al., 1997). Probandwise

comparison revealed a 27.1% concordance rate for PCa in MZ twins over the 7.1% seen in DZ twins (Page et al., 1997). This means a MZ twin whose brother was diagnosed with PCa would have a fourfold higher likelihood of having PCa than a DZ twin whose brother had been diagnosed with PCa (Page et al., 1997). Not surprisingly, the heritability (the component of the total variation that is due to genetic factors) of PCa was approximately 57% (Page et al., 1997). Environmental factors are thought to account for the remaining 43%.

These and other studies done on the etiology and genetic epidemiology of PCa have led scientists to classify prostate cancer into three distinctive types: sporadic, familial, and hereditary PCa (Sacco et al., 2005). Sporadic PCa is defined as occurring randomly within any given population, while familial PCa is defined as the observation of unpredictable clustering of PCa among relatives. Hereditary PCa is defined generally as having an earlier onset (an average of 6-7 years earlier) and very strong clustering pattern in families (Sacco et al., 2005). The evidence remains conflicting as to what specific pattern of inheritance is responsible for hereditary PCa. However, studies have consistently shown that family history is an important risk factor in both familial and hereditary PC. Further research is needed to identify and/or clarify the exact hereditary mechanisms and components that are integral to predicting the risk, inheritance and development of PCa.

Significance and Specific Aims

Despite the significant impact of prostate cancer on the population at large, very little research have been dedicated to identifying factors influencing participation in prostate cancer-specific clinical trials critical to the development and implementation of new and/or

improved diagnostic and therapeutic interventions. Also, unfortunately, clinical oncology trials aimed towards developing new interventions have been hampered by historically low accrual rates. Poor accrual and retention threaten the validity of and power supporting the study outcomes. Studies looking at clinical trials accrual patterns in oncology consistently show that clinical trial enrollment for adult cancer patients is dismally low at just 2 – 4% of all diagnosed patients (Movsas et al., 2007; Mills et al., 2006; Lara et al., 2001). However, much of the literature reporting accrual statistics on clinical trials participation is not specific to prostate cancer. The majority is either generalized to include multiple neoplastic sites or narrowed to investigate the accrual patterns and difficulties of an individual study or a limited demographic cohort.

Gross et al (2005) looks at the effects of sociodemographics, the protocol factors and the recruitment center have on enrollment of older patients onto (breast, lung, colorectal and prostate) oncology protocols. Pinsky et al (2008) conducts a similar study, looking at the enrollment of racial and ethnic minorities in a prostate, lung, colorectal, and ovarian cancer screening trial. Hoyo et al (2003) focused specifically on barriers and strategies for improving enrollment on to prostate cancer protocols, however, the cohort is restricted to African-Americans.

On the broad end of the spectrum, Movsas et al (2007) examines clinical trial enrollment patterns in oncology trials as a whole. Steinhauser et al. (2006) takes it a step further and reports on the difficulties of recruiting and retaining patient participation on longitudinal research aimed toward a large-body of serious illnesses including: late-stage cancers, advanced congestive heart failure, and advanced chronic obstructive pulmonary disease. Craig et al. (2010) and multiple studies conducted by Gross et al (2004, 2005)

examine the effect of managed healthcare and new reimbursement policies on all clinical oncology trial enrollment.

Other studies take a narrow approach. Many look at the successes and difficulties of recruitment and accrual on specific, individual oncology trials. For example, Wallace et al. (2006) reports on the accrual outcomes of a surgical prostatectomy vs. radiation intervention, while, Heiney et al (2010) details the successful recruitment methods used to accrue patients onto a PCa behavioral intervention trial. Only two studies were found to focus specifically on factors influencing enrollment in prostate cancer clinical trials. A Canadian survey study reported on the most influential factors that patients believe drive their decision to participate in prostate cancer protocols (Davison et al., 2008). A second family-oriented study analyzed the difficulties of enrollment and retention of PCa patients and their significant others, but only on one specific prostate cancer longitudinal randomized study (Northouse et al., 2006).

Because prostate cancer often has a more indolent course and thus a lower risk of death especially among older men (>75 years of age) there may be unique factors driving patient enrollment in prostate cancer clinical trials. The aim of this study is to evaluate clinical trial enrollment in the Multidisciplinary Prostate Cancer Clinic at UT MD Anderson Cancer Center and to assess if a clinical trial initiative, introduced in 2006, increased our trial enrollment. The secondary aim is to evaluate what factors, if any, contributed to the increased accrual. We hypothesize that increased clinical trial enrollment will be achieved after the onset of a prostate cancer specific clinical trial enrollment initiative in the Multidisciplinary Prostate Cancer Clinic at UT MD Anderson Cancer Center.

Methods and Materials

Study Cohort

Between the years 2004-2008, 1,370 men with localized prostate cancer were seen in the University of Texas MD Anderson Cancer Center Multidisciplinary Prostate Cancer Clinic (MPCC) and subsequently received treatment at MD Anderson Cancer Center. Prostate cancer patients seen in MPCC were self or physician referred, newly diagnosed (within 6 months) with localized disease and had not received definitive treatment. Each MPCC was composed of at least two physicians, an urologist and a radiation oncologist. Patients specifically interested in trials also had the option of having a medical oncologist present at the MPCC visit. In 2006, the clinical trial enrollment initiative was begun. The enrollment initiative employed active recruitment of MPCC patients on to open protocols. Information about specific protocols and their premise were posted in the clinic area. Based on eligibility criteria and appropriateness, clinicians presented the various clinical trial options to patients during the normal MPCC discussion of treatment options. Patients were then handed a letter at the end of the visit that outlined treatment options that were discussed with the patient, including a list of the trials that were offered to them.

Primary Outcome

The primary outcome was enrollment in a prostate cancer clinical trial. The selection of prostate cancer clinical trials open to accrual was divided into four categories: a) laboratory studies, b) quality of life (QOL) studies, c) procedure studies, d) novel studies. Two physicians (KEH, DAK) and a nurse practitioner (LM) categorized the trials. All three

agreed on the final characterization for all trials. The type of clinical trial and quantity of clinical trials that each patient chose to participant in was recorded in the electronic medical record.

Table 3: Four Categories of Clinical Trial Types

Category	Trial Types Included
Laboratory	Blood draws and tissue banking trials
Quality of Life (QOL)	Questionnaire and survey trials
Procedure	Trials involving new radiation and surgical techniques
Novel	Trials involving investigational treatments & systemic agents

Explanatory Variables

The explanatory variables evaluated for association with enrollment in a prostate cancer clinical trial included: age, year of visit, self-reported race, residence and prostate cancer risk group. Age was reported as a continuous variable, and then dichotomized on the median age of the study population (younger = younger than 64.2 years, older = older than 64.2 years). In this way proportional enrollment was report based on age. Visit year was evaluated as both a continuous and a categorical variable. Prostate cancer patients were categorized as either having visited the MPCC before the clinical trial enrollment initiative began in 2006 or after. Race was evaluated as a categorized variable: Caucasian, African-American, or Other. Residence was categorized as either within the Houston ten-county metropolitan statistical area or outside of the metropolitan area. The Houston-Sugar Land-Baytown Metropolitan Statistical Area consists of Austin, Brazoria, Chambers, Fort Bend, Galveston, Harris, Liberty, Montgomery, San Jacinto and Waller counties. Prostate cancer

risk group was evaluated as a categorical variable: a) low-risk, stage T1a-T2a and Gleason score ≤ 6 and PSA ≤ 10ng/ml; b) high-risk, stage T3-4 or Gleason score ≥ 8 or PSA > 20 ng/mL; c) intermediate-risk, all others.

Statistical Analysis

The SAS (v 9.2) statistical software was used to analyze the outcome data. Descriptive statistics were generated to characterize the study cohort. Characteristics included: visit year, age, ethnicity, risk group, patient residence, and clinical trial type. Proportional clinical trial enrollment was reported (figure 3) as well as proportional increase in trial enrollment (figure 6). In addition, total clinical trial enrollment was stratified by visit year (figure 7), trial type (figure 4), and patient characteristics (figure 5) and by age (figure 8). The outcome variable was clinical trial enrollment. There were multiple explanatory variables:

- Year (as both continuous and dichotomized as 2004-2005 vs. 2006-2008)
- Age
- Ethnicity
- Risk group
- Residence

For univariate analysis, logistic regression analysis was used to evaluate the association between clinical trial enrollment and each of the possible explanatory variables on a one to one basis. Pearson's chi square statistic was used to evaluate the significance of characteristics of patients who enrolled on clinical trials, to report on clinical trial enrollment by age group, to compare age vs. patient residence. Pearson's chi square statistic was also

used to evaluate the proportional enrollment increase broken down by trial type (see figure 6).

Multivariate logistic regression analysis was used to evaluate each variable's association with clinical trial enrollment while controlling for the influence of the other covariates. To accomplish this, logistic regression modeling was used to evaluate which characteristic(s) co-vary with trial enrollment. Logistic regression models were generated using clinical trial enrollment as the outcome variable. Visit year was first run a continuous variable, then rerun including visit year as a dichotomized variable (before and after the implementation of a clinical trial initiative). For both univariate and multivariate logistic regression analysis, the likelihood ratio chi-square was used to test for significance. The test for significant difference was determined using a p-value. P-values less than .05 were considered to represent a significant difference from zero…and thus a significant association. Trends were defined in terms of p-value. P-values between 0.1 - .05 were considered trends.

For both univariate and multivariate analysis odds ratio (OR) and adjusted Odds ratios (AOR) with corresponding 95% confidence intervals were generated for each covariate. The confidence interval is constructed at the 95% level in order to ensure the reliability of the study data gathered from this investigation. If this study were repeated 100 hundred times and 100 confidence intervals were constructed, then we would expect 95 of the hundred confidence intervals would contain the true, unknown, population parameters that we are trying to estimate with this study.

Results

Overview

A total of 1,370 prostate cancer patients were seen in the MD Anderson Cancer Center MPCC between the years of 2004 and 2008 and subsequently received treatment at MD Anderson Cancer Center. The median age at the time of visit was 64.2 years (interquartile range = 57.6yrs – 69.5yrs). The vast majority of the men were Caucasian (82.6%). African-American men represented 10.7% while other races made up the remaining 6.7% of the study population. The study population consisted of 442 (32%) low risk patients, 674 (49%) intermediate risk patients, and 254 (19%) high-risk patients. Approximately 70% of men were permanent residents of the Houston Metropolitan area. Thirty percent of the men resided outside the Houston Metropolitan area or outside the state of Texas. Of the 1,370 patients, 326 (24%) men were seen in MPCC before the 2006 enrollment initiative began, and 1,044 (76%) were seen after the 2006 enrollment initiated was implemented.

Of the total study population, 1,007 (73.5%) enrolled in at least one clinical trial, while 390 (28.5%) enrolled in 2 or more clinical trials (figure 3). Sixty-seven percent enrolled in laboratory studies, 18% enrolled in QOL studies, 3.7% enrolled in procedural studies, and 13% enrolled in novel treatment studies. Total patient enrollment increased from 38.9% before the clinical trial initiative to 84.3 % after the clinical trial initiative. Patient enrollment increased from 25% to 80% in laboratory studies, from 9% to 21% in procedural studies, from 6% to 15% in novel studies, and decreased from 8% to 2% in QOL studies. Eighty-three percent of Caucasian patient were enrolled on clinical trials as

compared to only 11% of African-American patients, and 6% of other race patients. Sixty-six percent of patients who resided in Houston Metropolitan were enrolled on clinical trials, while only 34% of non-Houston residences were enrolled on clinical trials. Forty-nine percent of patients of intermediate risk patients were enrolled on clinical trials, 32% of low risk patients and 19% of high risk patients were enrolled on clinical trials. Seventy-nine percent of younger age patients (younger than 64.2 years) were enrolled on clinical trials vs. 68% of older age patients (older than 64.2 years). Sixty-five percent of patients residing in Houston were younger patients, 35% of non-Houston residents were younger patients. Seventy-four percent of Houston residence patients were older patients while 26% of non-Houston residents were older patients.

Table 4: Characteristics of 1,370 men evaluated in a multidisciplinary prostate cancer clinic

Study Population	n	Median
Total	1,370	
Age (continuous)		64.2
Race/Ethnicity	**n**	**%**
Caucasian	1,132	82.6
African-American	146	10.7
Other	92	6.7
Risk Group		
Low risk	442	32.3
Intermediate risk	674	49.2
High risk	254	18.5
Residence		
Within Houston Metro	951	69.4
Outside Houston Metro	419	30.6
Visit Year		
Before Initiative 2004-2005	326	23.8
After Initiative 2006-2008	1,044	76.2

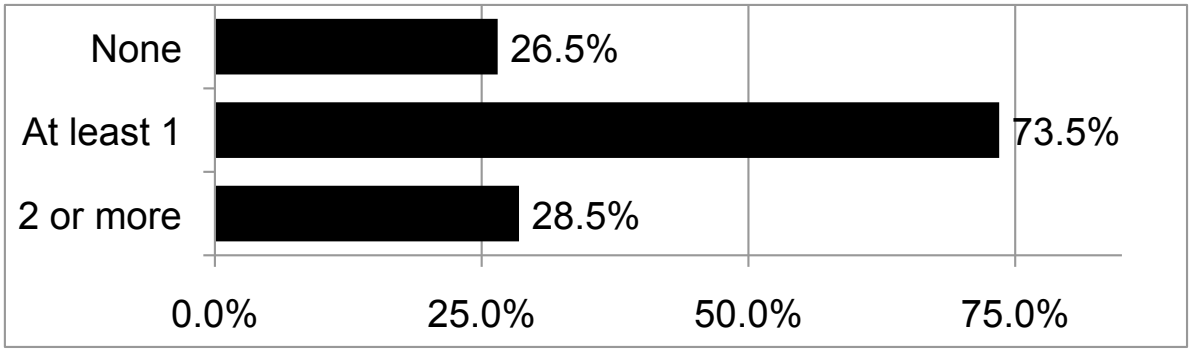

Figure 3: Total overall patient enrollment by number of trials

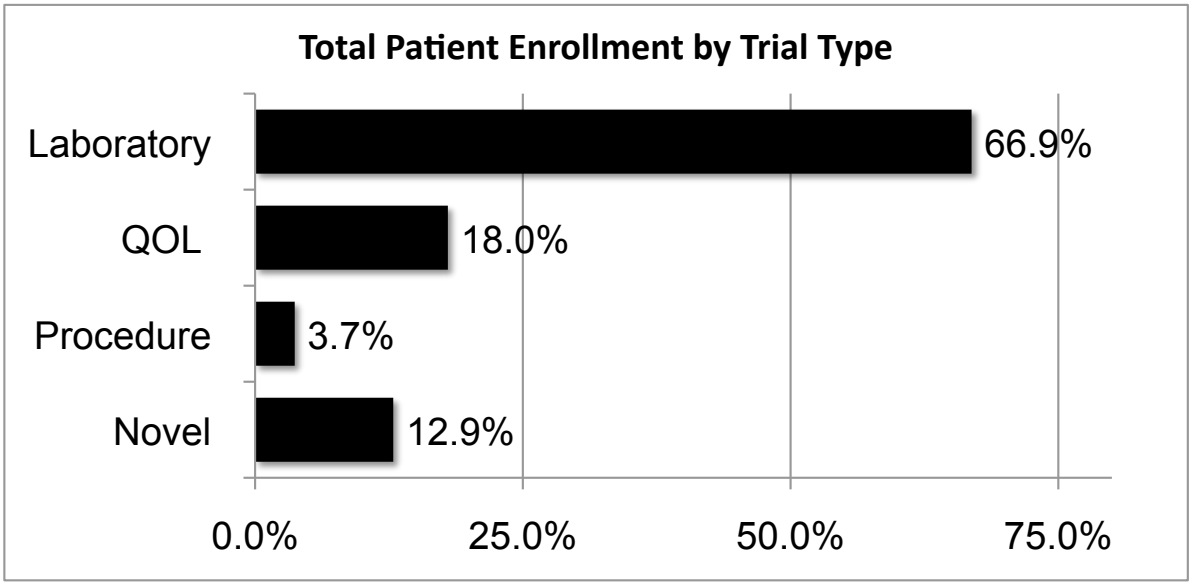

Figure 4: Total patient enrollment by trial type.

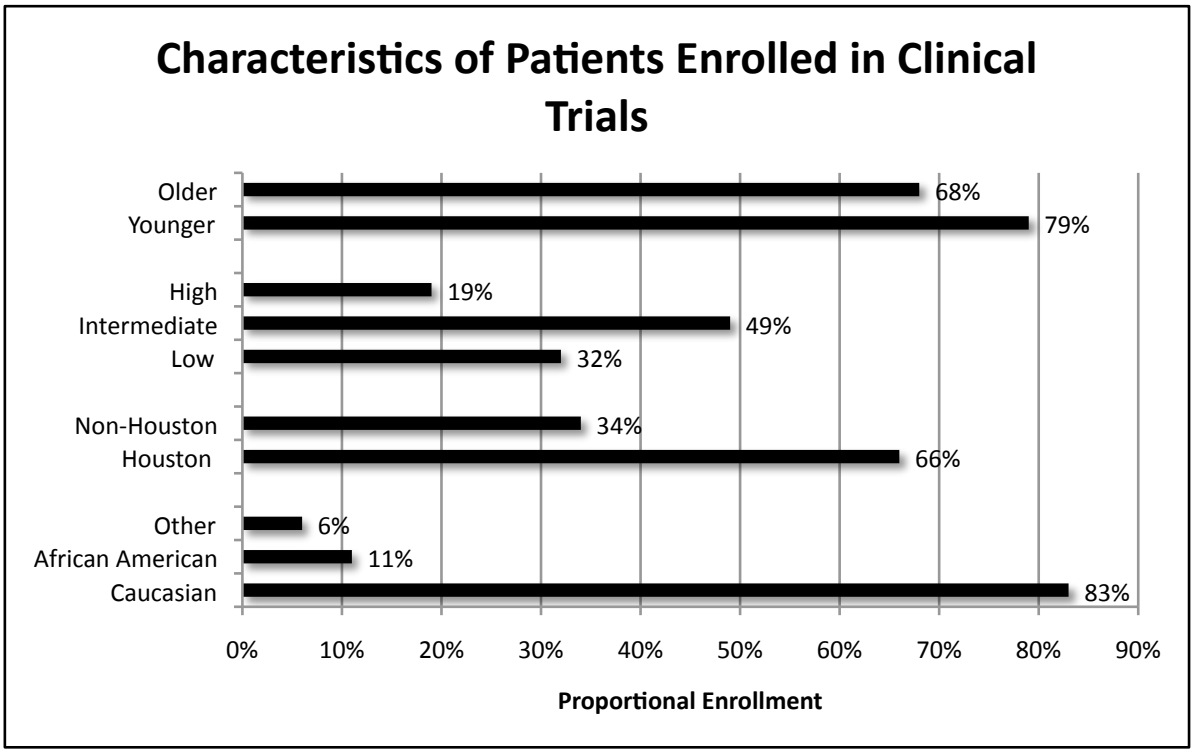

Figure 5: Characteristics of patients enrolled in clinical trials.

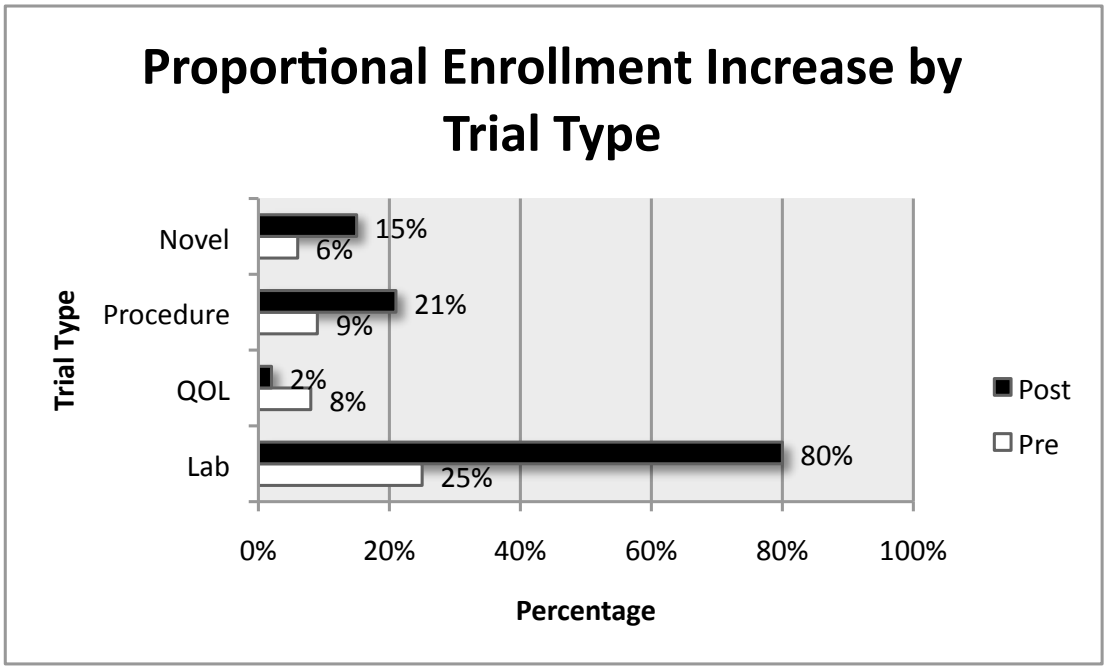

Figure 6: Pre/post proportional patient enrollment by trial type

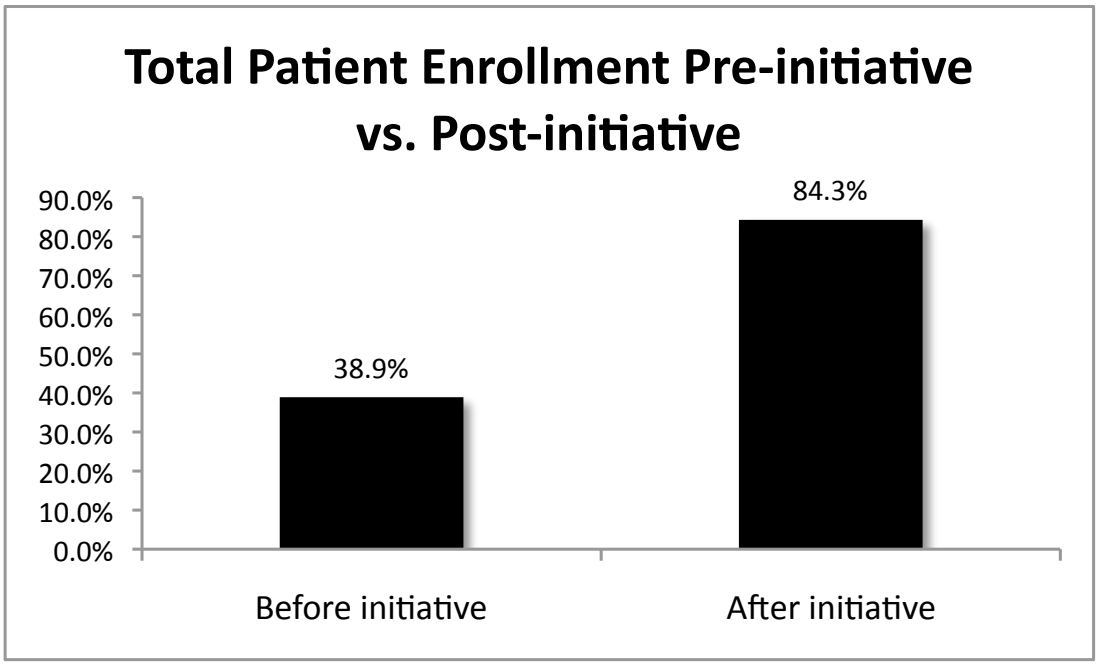

Figure 7: Total patient enrollment pre-initiative vs. post-initiative.

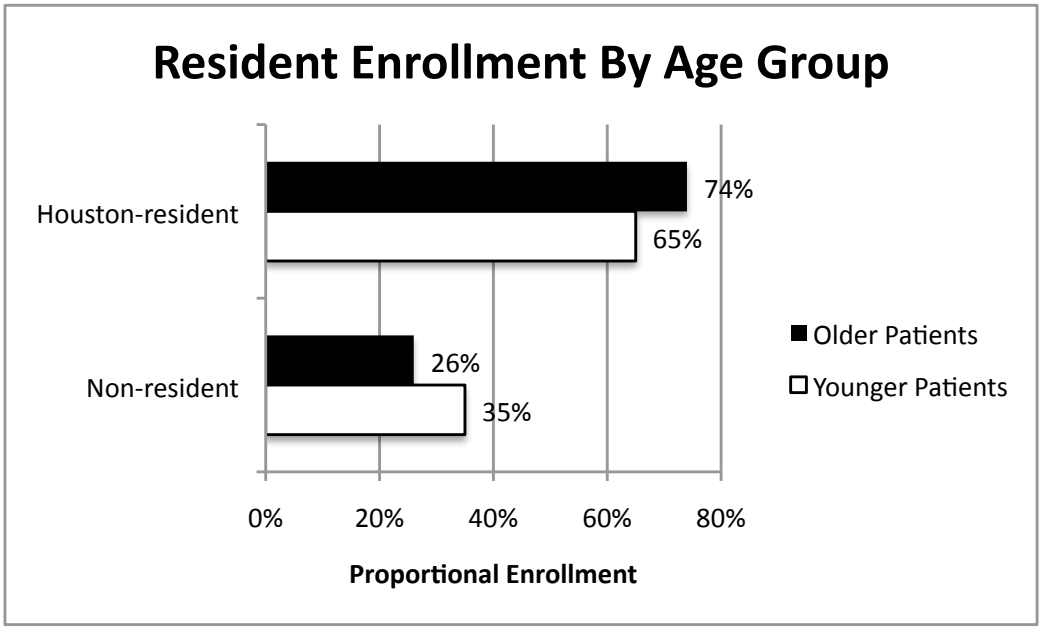

Figure 8: Resident enrollment by age group

Univariate analysis of factors associated with enrolling in a clinical trial

The year of MPCC visit was evaluated as both a continuous and a dichotomized variable. When visit year was evaluated as a continuous variable, patients seen in later years were more likely to enroll in a clinical trial (OR 2.33, 95% CI 2.09 – 2.63, $p < 0.0001$ per year increase). Similarly, when year of visit was evaluated as a dichotomized variable, patients seen after the 2006 enrollment initiative were more likely to enroll in clinical trials that patient seen prior to the clinical trials initiative (OR 8.41, 95% CI 6.37 – 11.10 $p < 0.0001$). The overall proportion of patients enrolling in clinical trials increased from 38.9% before the enrollment initiative to 84.3% after ($\frac{127}{326}$ vs. $\frac{880}{1044}$ participants, respectively). Residence and patient age at time of MPCC visit were also found to be associated with clinical trial enrollment. Older men (OR 0.97, 95% CI 0.95 – 0.98, $p < 0.0001$ per year increase) and men living outside the Houston Metropolitan area (OR 0.54, 95% CI 0.40 – 0.71, $p <.0001$) were less likely to participate in clinical trials than their younger age, locally residing counterparts. Race and risk group were not shown to be associated with clinical trial enrollment.

Table 5: Factors associated with clinical trial enrollment on univariate analysis

	Odds Ratio (95% CI)	p-Value
Age		
Continuous	0.97 (0.95, 0.98)	<.0001
Visit Year		
Per year increase	2.35 (2.09, 2.63)	<.0001
Categorical year		
Pre-initiative	Reference group	Reference group
Post-initiative	8.41 (6.37, 11.10)	<.0001
Race/Ethnicity		
Caucasian	Reference group	Reference group
African-American	1.12 (0.75, 1.68)	0.572
Other	0.66 (0.424, 1.04)	0.074
Residence		
Houston metro area	Reference group	Reference group
Non-Houston metro area	0.54 (0.40, 0.71)	<.0001
Risk Group		
Low	Reference group	Reference group
Intermediate	0.98 (0.75, 1.29)	0.887
High	1.05 (0.74, 1.49)	0.799

Multivariate analysis of factors associated with enrolling in a clinical trial

On multivariate analysis that adjusted for age, race, residence and prostate cancer risk group, patients seen in the MPCC clinic in later years were more likely to enroll in clinical trials (AOR 2.33, 95% CI 2.07 – 2.62, $p < 0.0001$ per year increase.) The year of the patient's clinic visit was analyzed as a dichotomized variable, before 2006 (before enrollment initiative) and after 2006 (after enrollment initiative). Men seen in clinic after implementation of the clinical trials enrollment initiative were more likely to enroll in a clinical trial than men seen before implementation of the trial enrollment initiative (AOR 8.22, 95% CI 6.16 – 10.96, $p < 0.0001$). Patient age at the time of MPCC was also found to be independently associated with clinical trial enrollment. Older patients were less likely to

enroll in clinical trials than their younger counterparts (AOR 0.97, 95% CI 0.95 – 0.98, p < 0.0001 per year increase). Multivariate analysis indentified a trend for patients in the highest prostate cancer risk group to be more likely to participate in clinical trials (AOR 1.43, 95% CI 0.96 – 2.13, p = 0.083) than low-risk patients. Multivariate analysis also revealed that patients of 'other' races (namely, Hispanics, Asians, Indians and Native Americans) were less likely to participate in clinical trials than Caucasians patients (AOR 0.56, 95% CI 0.34 – 0.94, p = 0.027).

Looking at visit year as continuous variable saw similar results except for race/ethnicity. Although a trend was identified as for patients of 'other' races to be less likely to participate in clinical trials than Caucasians patients (AOR 0.60, 95% CI 0.36, p = 0.054) it was not a statistically significant finding.

Table 6: Factors associated with clinical trial enrollment on multivariate analysis

Visit Year (Dichotomized)		
	Odds Ratio (95% CI)	**p-Value**
Age	0.97 (0.95, 0.98)	<.0001
Visit Year	8.22 (6.16, 10.96)	<.0001
Race/Ethnicity		
Caucasian	Reference group	Reference group
African-American	0.94 (0.59, 1.48)	0.779
Other	0.56 (0.34, 0.94)	0.027
Residence		
Houston metro area	Reference group	Reference group
Non-Houston metro area	0.80 (0.58, 1.10)	0.176
Risk Group		
Low	Reference group	Reference group
Intermediate	1.16 (0.85, 1.58)	0.346
High	1.43 (0.96, 2.13)	0.083

Discussion

Primary Finding

Our primary finding was that newly-diagnosed prostate cancer patients seen in the MPCC after the onset of the 2006 clinical trial enrollment initiative were more likely to enroll in prostate cancer clinical trials. This result is important because of the possible implications it may have on enrollment patterns of patients onto prostate cancer clinical trials. Identifying factors influencing participation in prostate cancer-specific clinical trials is critical to the development and implementation of new strategies for bolstering enrollment onto procedural and novel treatment investigations aimed toward improved diagnostic and therapeutic interventions for prostate cancer.

Wallace et al. (2006) looked at the accrual outcomes of a single phase III randomized trial comparing surgical prostatectomy vs. radiation intervention (SPIRIT) after the development and implementation of a multidisciplinary education session. Similar to our study, an enrollment initiative was developed both to education patients more thoroughly on their treatment options and to facilitate increased study accrual. Their enrollment initiative included an informative video about clinical trial participation following by a consultation with both an urologist and a radiology that explained the rationale of the study. Before the development of the multidisciplinary education session, 0 of 27 eligible patients who were presented with the option of participating in the SPIRIT trial consented to enroll. After implementation of the multidisciplinary education session, 47 sessions presented to 263 eligible patients yielded 34 participants. It has been showed with the SPIRIT study and this study as well that enhanced patient understanding of available clinical trials, treatment

options and the rationale for each, increases accrual. Active recruitment techniques such as patient education, multidisciplinary counseling, and study advertisement tailored specifically to enhance accrual of clinical trials in prostate cancer is important to the future of prostate cancer research. These enrollment initiatives can only be developed effectively with specific knowledge of what factors influence trial participation.

Secondary Finding

Our secondary finding suggests that age plays an important role in clinical trial enrollment patterns of prostate cancer patients. It was revealed that older patients were less likely to enroll in clinical trials than their younger counterparts. There are several probable explanations for this finding. Possibly, younger patients are generally healthier than older patients with more co-morbidities. Older patients are less able to meet the often-restrictive eligibility criteria defined by some clinical trials. Physicians may, consciously or unconsciously, adopt a more aggressive course of treatment with younger patients.

A similar study conducted by Trimble et al (1994) looked at not just prostate cancer but also lung, colorectal, pancreatic and hematological cancers. Trimble found that the 65+ male population were underrepresented in cancer treatment trials. Of the total number of male cancer patients enrolled in NCI sponsored clinical cooperative group treatment trials in 1992, only 39% were over 65 years of age. Since then, not much progress has been made in accrual rates in older cancer patients. Fifteen years later, in 2007, Stewart et al. examined gender, race/ethnicity, and age-based disparities in enrollment patterns specifically for surgical oncology trials in breast, lung, colorectal, and prostate cancer patients collectively. The study found that cancer patients 65-74 years old were less likely to be enrolled than

those 20-44 years old, making the point that the lack of proper representation of older patients in clinical trials is not restricted to prostate cancer alone. It is a widespread problem, but it is particularly troublesome in PCa because 63% of the cases diagnosed in the US occur in patients 65 years or over (Mordukhovish et. al., 2010). Thus, it is of great importance that the segment of the population most commonly affected by prostate cancer are adequately represented in clinical research aimed toward increasing the knowledge base and developing new/improved diagnostic and treatment methods.

Tertiary Finding

Upon univariate analysis, it appeared as though patient residence was a contributing factor in clinical trial enrollment, however upon multivariate analysis this association dissipated. In univariate analysis, each patient characteristic was evaluated independently for association with clinical trial enrollment. However, this is not ideal since realistically, these characteristics can never truly exist separately. They exist collectively and often interact with each other. Each patient is a certain age, a certain race, and lives in a certain area, etc. All these things may play a roll in the patient's decision to either enroll in or not to enroll in a clinical trial. Often time correlation among co-variates can mask significance in multivariate analysis. This could explain why it appeared that non-Houston residents were less likely to enroll in clinical trails on univariate analysis. Upon multivariate analysis, this association was not seen to be significant. It might be that non-Houston residence younger age patients more willing to travel father for treatment. When patient residence was crossed with patient age group it was noted that 35% of the non-Houston residents who

enrolled in Clinical Trials were younger patient as compared to only 26% of the non-Houston residents were older patients. It should also be noted that part of the inclusion criteria for this study requires that patients be seen and treated in the UT MD Anderson Cancer Center's MPCC regardless of whether they chose to be treated on-study or off-study.

Trends

Analysis of the dataset showed two additional findings that did not meet the criteria for significance, nevertheless, they are worthy of note. There was a trend seen for high-risk PCa patients to be more likely to enroll in clinical trials than the low risk patients. This study also identified a trend for PCa patients of 'Other' races (namely, Hispanics, Asians, Indians and Native Americans) to be less likely to participate in clinical trials than Caucasian patients. There are several lines of reasoning which could explain these trends.

High-risk PCa patients were categorized as such because their PSA level, Gleason score, and T-stage suggests that these patients had an increased risk of tumor recurrence following treatment. A patient's risk group status often guides the physician in making the appropriate treatment recommendations. Clinical trials, because they are often testing unproven therapies, are generally considered more aggressive than the proven standard-of-care options. It might be that physicians recommend what they view as a more aggressive treatment option to high-risk PCa patients more often than to low risk patients because high risk patient are expected to have a worse prognosis. In turn, a high-risk patient might be more willing to be treated on a PCa clinical trial because they perceive it as a more aggressive approach to eradicating their cancer.

In the US, the observed incidence of prostate cancer is lower in all the other races (Hispanic, Native Americans, Asians and Indians) as compared to Caucasians (Jemal, 2010). PCa incidence is lower among Hispanic races and lower still in Native and Asian Americans Caucasians and African Americans, thus the pool of potential patients is smaller. Asian Americans and Native Americans have the lowest incidence of PCa among the ethnic groups. A smaller population base of PCa patients means fewer trial candidates and therefore fewer clinical trials enrollees. There has also been research suggesting that different social values and concerns (such as fear of loss of virility and sexual function, fears of exploitation, and the spiritual/religious implications of treatment) among certain ethnic groups compel some to delayed diagnosis and treatment, or opt to forgo diagnosis/treatment altogether which could contribute to their underrepresentation in clinical trials. Socio-economic disparities among different ethnic groups could also explain the lower participation of 'other' race PCa patients in clinical trials. Lack of income, education and adequate health insurance likely contributes to the lack of access to the full range of therapy options, including, unfortunately clinical trial enrollment (particularly trials that require costly out-of-pocket expenditures).

Strengths and Limitations

The results of our study, while viable, lack a certain degree of generalizability. This is in part because data collection was confined to one site, the UT MD Anderson Cancer Center MPCC. There is also an unbalanced racial/ethical distribution among the study cohort. The vast majority of the participants were Caucasian males. As is true of clinical

trials in general, minorities are not adequately represented. This is particularly concerning to our study, considering African-American minorities have a disproportionately increased risk and incidence of prostate cancer and yet they remain underrepresented in prostate cancer clinical trials research. Future studies looking at accrual patterns in PCa patients should seek to include multiple study sites in order to broaden the variety of patients and to possibly recruit a higher percentage of minorities. Specific strategies should be implemented to target increasing clinical trial enrollment among African-Americans and other minority patients. This research is needed because some factors associated with clinical trials enrollment may vary with ethnicity. In addition, socioeconomic factors, which could possibly play an important roll in clinical trial enrollment particularly in minority populations, were not explored in this study.

The way in which the study was designed captures the trial type and number of clinical trials each patient chose to participate in, but not the total number and type of trials each patient was initially offered. Additionally, the trial design included a large heterogeneity of clinical trials, (laboratory studies, QOL, procedural and novel studies). It might be interesting and possibly more informative to examine one specific trial type. Another consideration not taken into account by the experimental design is the continuity of trial offerings over time. It could be that more trials were available after the enrollment initiative began. If there were less trial offerings available for patients seen before the initiative began, then there was a slight handicap to trial enrollment inherent to the experimental design, which was not controlled for. This begs the question, did trial enrollment increased because of the enrollment initiative or because of increased trial availability after the initiative.

Another similar issue is the number of each trial type available over time. Were the pool of potential clinical trials saturated with a majority of one trial type (ex. lab studies) at certain points of time, while other trial types were in short supply (QOL)? The fact that QOL studies were the only trial type that decreased rather than increased in enrollment after the enrollment initiative could be explained by a lack of availability of QOL trials in those years rather than a conscience decision by patients against the trial type. Uncontrolled variables in the study design such as trail availability and trial continuity over time tend to weaken the confidence is the study's outcome.

The major strength of the study was that it captured prostate cancer patients seen in the MPCC over a span of several years. A second strength of the study is that by having all data collected at one site there is better completeness and continuity of data. Examining an enrollment initiative impact on clinical trial accrual patterns at pre and post time points and then running a statistical analysis of the study data is a very straightforward study design. The outcome and conclusions that are drawn from the data are likewise unambiguous and can be readily incorporated into future investigations.

Recommendations

In future studies, there is a need to include multiple study sites in the collection of data. A conscious effort should be made to target minority enrollment in clinical trials, perhaps even focus entirely on minority recruitment with a newly designed enrollment initiative directed specifically toward under-represented ethnic populations. Making these

two adjustment to future trials would help to increase the generalizeability of the study outcome(s).

Additional alterations should be made in the study design in order to control for clinical trial availability and trial type availability over time. It would strengthen the study's internal validity if the quantity of trails available were held constant throughout the study. Likewise, an equal quantity of each trial type should be available throughout the study so that any increase or decrease in trial enrollment observed could be more confidently attributed to the enrollment initiative and not muddied by uncontrolled competing variables.

It might be a worthwhile endeavor to take a more microscopic approach to the subject matter. It would be interesting to focus on one specific trial type or even one individual trial and design an enrollment initiative tailored to enhance accrual on to just that trial type or that one clinical trial. This design might be more time-consuming. A pilot period may be required, wherein the study is run specifically to gauge patient interest in and/or initial reaction to participation in the study. Based on patient reactions and /or recommendations (captured via a survey or questionnaire) a suitable enrollment initiative could then be tailored to meet the needs of the individual trial or trial type.

Conclusion

Clinical trial enrollment in our multidisciplinary clinic was substantially higher than seen nationally in adult cancer patients. Enrollment rates increased after introduction of a clinical trial initiative. We further conclude that age plays an important role in clinical trial enrollment patterns of prostate cancer patients. We speculate we achieved high enrollment

rates because 1) specific trials are discussed at time of treatment recommendations, 2) we provide a letter documenting offered trials and 3) we introduce patients to the research team at the same clinic visit if they are interested in trial participation.

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Vita

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