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A Review of the Impact of Obesity on Prostate Cancer Progression and Epigenetic Regulation

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A REVIEW OF THE IMPACT OF OBESITY ON PROSTATE CANCER PROGRESSION AND EPIGENETIC REGULATION

by

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A Review of the Impact of Obesity on Prostate Cancer Progression and Epigenetic Regulation

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Abstract

Background: Prostate cancer and obesity are both serious conditions that affect millions of men. While studies regarding associations between the two conditions have had conflicting conclusions, investigation into etiologic mechanisms may shed a more specific light on any existing link. Epigenetics is an emerging field which finds environmental factors influencing genetic transcription factors, without modifying the DNA. Epigenetics may hold promise both in finding a link between prostate cancer and obesity, and also in developing more specific screening tests for prostate cancer in all men. Search criteria: A literature search was performed of PubMed using MeSH terms "Prostate Neoplasm," "Obesity," and "Epigenetics." Articles were selected based on detail of analysis, novelty, and clinical applicability. Findings: While studies have had conflicting conclusions about whether obesity is or is not associated with overall prostate cancer risk, there is a clearer association between obesity and high grade tumors. Research is also conflicting about whether obesity affects morbidity or mortality prognosis after diagnosis of prostate cancer. Considering the poor specificity in screening men with prostate-specific antigen, research into genetic and epigenetic mechanisms may lead to better screening tests for prostate cancer in obese men and all men as a whole. (198 words)

Keywords: Prostate Cancer, Obesity, Epigenetics

Introduction

Prostate cancer is currently the most commonly diagnosed cancer in men and causes the second highest number of cancer deaths in men (American Cancer Society, 2013). Research into prostate cancer progresses on several fronts, particularly pathogenesis, diagnosis and appropriate screening tests, risk stratification, and treatment. Prostate-specific antigen (PSA) has been commonly used in the last decade to screen for prostate cancer, but recent guideline changes have altered screening strategies in by acknowledging inadequacy of using PSA for screening (Moyer, 2012). Incorporating PSA into screening and treatment strategies can lead to false-positive screening and performing unnecessary surgeries that reduce quality of life when removing benign lesions or non-life threatening cancers (Moyer, 2012).

It is important to identify people through routine and targeted screening who are at increased risk of disease. Labels of 'overweight' and 'obese' have been developed by health agencies to identify those who are at increased risk of disease because of their weight. A simple and accessible way of identifying overweight and obese people is by calculating their body mass index from their height and weight. The Centers for Disease Control and Prevention (CDC) defines "overweight" as a BMI of 25.0 to 29.9 kg/m^2 and "obese" as greater than 30.0 kg/m^2 (CDC, 2012). They acknowledge however, that this calculation is an estimate of a person's body fat and disease risk, and that it may not be accurate for all, particularly people with large muscle mass, like athletes. Other methods of estimating body fat exists, and range from simple tests like posterior arm skin fat fold caliper measurement, or waist circumference, to technical and costly measurements by ultrasound, computed tomography or magnetic resonance imaging (CDC, 2012).

The role of obesity in prostate cancer risk is debated in the medical community. Rates of obesity are climbing in the United States and its presence and severity is linked with many adverse health conditions (Bray, 2004; Sturm, 2007). If obesity is linked with prostate cancer, it will be important to take obesity status into consideration when developing guidelines for screening and treatment of prostate cancer. It will also be important to understand mechanisms of a link between obesity and prostate cancer, if one exists.

Both inheritable genetic changes and environmental factors can impact risk of cancer development. Besides the direct impact on the DNA by environmental factors, these factors can also affect the epigenome, or biochemical factors that alter expression levels of a gene without directly affecting the DNA sequence. Epigenetic changes are particularly sensitive to lifestyle and environmental conditions (Zhang et al., 2011). Epigenetic changes may include hypomethylation which can induce gene transcription of oncogenes, or hypermethylation which can silence tumor suppressor genes (Ellinger et al, 2010; Kargul & Laurent, 2009; Nelson, De Marzo, & Yegnasubramanian, 2009). Research is ongoing into the association between obesity and methylation status in prostate cancer biopsy samples.

The purpose of this review of the literature is to describe existing knowledge about association between obesity and prostate cancer, in its screening, diagnosis, severity, and prognosis. Attention will also be given to possibilities of an epigenetic link between the two conditions.

Search Strategy

In this literature review, the researcher searched PubMed, via the University of North Dakota Harley French Health Science Library, for MeSH major topic terms and keywords of

"Prostatic Neoplasms" AND "Obesity" and "Prostatic Neoplasms" AND "Epigenetics". The researcher selected original research to include based on the detail of analysis, mechanistic support of data, novelty, and potential clinical usefulness of the findings.

Review of the Literature

This review of the literature will cover the following topics: the link between obesity and prostate cancer noted in the clinical practice and epidemiological studies, the impact of obesity on screening for prostate cancer, and epigenetic regulation in prostate cancer.

Obesity and prostate cancer incidence, severity and prognosis

Several articles have come to various conclusions about whether greater obesity raises or lowers overall risk of prostate cancer. In a single center retrospective cohort study, among 787 men referred for prostate biopsy, higher body mass index (BMI) was associated with a greater chance of the biopsy revealing prostate cancer (Freedland, Terris, Platz, & Presti, 2005). In a population case control study, 753 men age 40 to 64 with diagnosed prostate cancer were compared with 703 age matched controls. A weak ($p=0.04$) inverse relationship between BMI and prostate cancer was noted, but only if the researchers used non-standard cut-offs for BMI stratification (Porter & Stanford, 2005). In a large prospective randomized study, where all patients were definitively diagnosed with or without prostate cancer with biopsy, the overall prostate cancer risk was not affected by presence of obesity (Gong et al., 2006).

To investigate this association more clearly, some researchers have used novel methods to look at the relationship between obesity and prostate cancer. Computed tomography was used to evaluate the role in either visceral fat or subcutaneous fat in prostate cancer risk. A significantly higher risk of prostate cancer was found for participants with higher visceral fat, or

visceral to subcutaneous ratio (von Hafe, Pina, Perez, Tavares, & Barros, 2004). In a randomized prospective study, a genetic single nucleotide polymorphism (SNP) that is associated with obesity was tested against development of prostate cancer over five years. The abnormal allele that is associated with obesity was, in this study, associated with a lower incidence of prostate cancer overall, but a higher risk of more severe prostate cancer. The authors of this study felt as though using the SNP as an indicator of obesity would lead to fewer confounding factors. However, they acknowledged that the actual biologic mechanism of the genetic variation at this site is unknown (Lewis et al., 2010).

Studies have also looked at whether obesity is associated with grade of cancer at diagnosis. Several retrospective cohort studies of patients who underwent radical prostatectomy had their BMI evaluated in relation to their cancer's pathologic characteristics. In these five studies with large sample sizes, there was no significant relationship between BMI or other measures of obesity or adiposity and any pathologic variables including Gleason score, extra-capsular extension, cancer volume, seminal vesicle invasion, lymph node invasion, and positive surgical margins (Gallina et al., 2007; Isbarn et al., 2009; Pruthi, Swords, Schultz, Carson, & Wallen, 2009; Zilli et al., 2011). However, other studies have found a clearer association between BMI and poor pathologic characteristics. Three retrospective cohort studies, similar to those above, have noted associations with BMI and higher tumor grade, greater tumor size and percentage of prostate occupied by tumor, positive surgical margins, and Gleason score (Amling et al., 2001; Freedland et al., 2008; Freedland, Bañez, Sun, Fitzsimons, & Moul, 2009). In addition, a large, prospective randomized study, where every subject and control received a definitive diagnosis through biopsy, concluded that, compared with men of normal BMI, obese

men had a decreased risk of low grade prostate cancer and an increased risk of high-grade cancer (Gong et al., 2006).

Finally, several studies have investigated the role of obesity in prognosis of prostate cancer after diagnosis. A prospective follow up study of 1302 radical prostatectomy patients had no significant difference in biochemical recurrence related to BMI (van Roermund et al., 2009). A retrospective study came to the same conclusion (Banez et al., 2009). Another study following external beam radiation therapy investigated differences between obese and normal weight men, and found no significant difference in PSA relapse, deaths from prostate cancer, or deaths from any cause (Geinitz et al., 2011).

On the other hand, a prospective cohort study of higher stage prostate cancer patients found that overweight and obese patients were approximately 1.8 times more likely to die of their prostate cancer or the prostate cancer treatment than patients with normal weight (Efstathiou et al., 2007). A large multicenter retrospective cohort study found that obesity was significantly associated with biochemical recurrence, and that BMI was associated with recurrence in T1 stage cancers, but not in stage 2 or 3 prostate cancers. Interestingly, the same study also found that obese men diagnosed with prostate cancer by digital rectal exam, but not by PSA, have same long-term outcomes as normal BMI men. These authors hypothesized that although digital rectal exam is more technically difficult in obese men, its lower sensitivity may have compensated for some of the false positivity inherent in PSA screening (Freedland et al., 2008).

Obesity and Prostate Cancer Screening

The fact that a traditional digital rectal exam as screening may offer improved prognosis over prostate cancers diagnosed by PSA screening highlights some of the issues that influenced the US Preventive Service Task Force to recently recommend against using PSA routinely for prostate cancer screening (Moyer, 2012). Particularly in obese men, the PSA may be falsely-negative. In addition, some scientists have theorized that having a greater body mass and plasma volume may dilute PSA and confuse prostate cancer diagnosis. Three single cohort analysis studies have found that with greater BMI among men without prostate cancer, the PSA trends lower (Beebe-Dimmer et al., 2008; Chia et al., 2009; Grubb et al., 2009). Grubb et al. also calculated whole-body mass of PSA, and found it to be consistent through BMI ranges. These authors suggested that if PSA is used for prostate cancer screening, that obese men may have a lower threshold for PSA before biopsy is recommended (Grubb et al., 2009).

Conflicting evidence regarding the relationships between obesity and prostate cancer, and between obesity and the use of PSA in screening, has prompted scientists to investigate alternate mechanisms in prostate cancer etiology and screening. These alternate mechanisms have included genetic and epigenetic mechanisms. As mentioned above, one obesity-associated SNP variation has been associated with a lower risk of prostate cancer overall, but with a higher risk of high-grade prostate cancer (Lewis et al., 2010).

Epigenetics and prostate cancer

Research over the last several decades has investigated changes in DNA mutations and deletions in relation to the development and progression of prostate cancer. More recently epigenetics has been identified as a useful specialty in prostate cancer research. While traditional genetics, related to actual changes in DNA, has long been implicated in cancer and

other human pathology, epigenetics deals with changes that occur without changing the actual DNA base pair sequence. Epigenetic changes may occur with methylation of DNA nucleotides, particularly at cytosine-phosphate-guanine (CpG) dinucleotide sequences in the DNA. These changes often are seen in promoter segments of DNA and may upregulate or downregulate gene expression (Dobosy, Roberts, Fu & Jarrod, 2007). Hypermethylation of the GSTP1 gene in particular is one of the more researched epigenetic change associated with prostate cancer (Yamanaka et al., 2003; Maruyama et al., 2002).

Another mechanism of epigenetic regulation is histone modification. Histones are bundles of protein which supply structural support to segments of DNA. Modification of histones, particularly acetylation and methylation may structurally cause the DNA to open or close, thus promoting or decreasing transcription of a particular gene (Jeronimo et al., 2011).

Compared to changes in DNA sequence, it is theorized that epigenetic changes in oncogenesis may be both more likely to be influenced by environmental or personal risk factors, and have become a new target for therapeutic interventions (Dobosy, Roberts, Fu & Jarrod, 2007). Dietary supplements of folate or methionine directly affect S-adenosylmethionine, the primary substrate for DNA methylation. Selenium supplements can also reduce hypomethylation (Dobosy, Roberts, Fu & Jarrod, 2007).

Several studies investigating the prevalence of a hypermethylation of GSTP1 transcriptional regulatory sequences have detected it in 90% of prostate cancer cases. This represents a greater proportion than any of the known genetic defects (Nelson, Marzo, & Yegnasubramanian, 2009). A recent meta-analysis concluded that GSTP-1 methylation testing offers good sensitivity in diagnosing prostate cancer. The study was strengthened by the fact that

the control group in this meta-analysis was rigorously chosen to be men who actually went in for prostate biopsy. These men were already those suspected to have prostate cancer, and compose an ideal control group against which to test the researchers' hypothesis (Wu, 2011). The use of GSTP-1 testing or a panel of prostate cancer associated gene promoter methylation sites may offer a good balance in sensitivity and specificity in screening for prostate cancer (Jeronimo, 2011).

There may potentially be a role of epigenetics in the link between obesity and prostate cancer. A case control study found that obesity can trigger methylation changes in DNA of peripheral leukocytes and may be linked to the relative immune compromise that obese people experience (Wang et al., 2010). However, to our knowledge, research has not been completed to evaluate the association between prostate cancer related epigenetic changes and obesity. In fact searches of PubMed to include Prostatic Neoplasm, Obesity, and Epigenetics returned no results when searched either by MeSH term or keyword.

Conclusion:

In summary, obesity appears to be associated with higher grade prostate tumors and poorer outcomes after prostatectomy. Improved diagnosis and prognosis may be attainable in obese men, with augmented understanding of the pathogenesis of prostate cancer through epigenetic changes. Screening for prostate cancer between PSA and epigenetic markers together may particularly benefit obese men, whose diagnosis by traditional PSA screening is more complicated by the aforementioned possible dilutional effect where PSA concentration goes down with greater BMI and plasma volume. An ideal test with perfect sensitivity and specificity is not currently possible, but through greater understanding, testing for prostate cancer can be

honed and result in screening that identifies life threatening cancers, and does not indicate risky procedures when they are unnecessary.

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