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Does Obesity have a role in developing prostate cancer?

Gaurav Kansal * and Naveen Goyal

MBBS, Department of Surgery and Medicine, Government Medical College Patiala, Patiala, Punjab, India.

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Abstract

Obesity has emerged as a significant public health concern globally, with growing evidence linking it to the development and progression of various malignancies, including prostate cancer. This abstract explores the role of obesity in the etiology and pathogenesis of prostate cancer, highlighting potential biological mechanisms and clinical implications. Epidemiological studies suggest that obese men may have an increased risk of developing aggressive and advanced prostate cancer, although the association with overall prostate cancer incidence remains controversial. Several mechanisms may underlie this relationship, including hormonal imbalances, chronic inflammation, insulin resistance, and alterations in adipokine levels. Obesity is associated with reduced levels of testosterone and increased estrogen, which may contribute to carcinogenesis in prostate tissue. Additionally, chronic low-grade inflammation in obese individuals promotes a tumor-friendly microenvironment by producing cytokines and inflammatory mediators. Insulin resistance and elevated levels of insulin-like growth factors (IGFs) also play a key role in promoting cellular proliferation and inhibiting apoptosis, thus facilitating tumor growth and progression.

Obesity may further complicate prostate cancer diagnosis and management. Increased body mass index (BMI) is often associated with lower prostate-specific antigen (PSA) levels, potentially leading to delayed detection and underdiagnosis. Moreover, obese patients tend to have poorer treatment outcomes and higher rates of recurrence following interventions such as surgery or radiation therapy.

Understanding the link between obesity and prostate cancer is crucial for developing targeted prevention strategies and improving patient outcomes. Weight management, lifestyle modifications, and early screening protocols may be particularly important in high-risk obese populations. Future research is warranted to clarify the biological pathways involved and to determine whether interventions targeting obesity can reduce prostate cancer incidence and mortality. In conclusion, obesity appears to play a significant role in the development and progression of prostate cancer, making it an important modifiable risk factor in disease prevention and control.

Keywords: Obesity; BMI; Prostate Cancer; Population

1 Introduction

The prevalence of obesity is higher among people with cancer compared to the general population, with over 30 % of cancer-related deaths attributed to obesity. Obesity is also a risk factor for the development of 13 different types of cancer and is likely to surpass tobacco as the leading preventable risk factor [1]. With improvements in diagnosis and treatments, people with cancer are living longer, however, the acute and long-term side effects may significantly impair quality of life. Consequently, obesity is becoming an increasingly important consideration throughout the cancer trajectory and is shown to impact the effectiveness of treatment, cancer progression, comorbidity development, and survival, particularly in people with colorectal, breast, and prostate cancer [2]

* Corresponding author: Gaurav Kansal

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For people with prostate cancer, obesity is associated with increased risk of recurrence following curative intent treatment, progression to advanced cancer, and prostate cancer-related mortality [3] While undergoing active treatment, obese men with prostate cancer are at increased risk of experiencing more severe, and a greater number of, acute and long-term adverse effects, and shorter time to develop castrate resistant prostate cancer relative to non-obese counterparts [3]. Obesity can also lead to the development of comorbidities such as cardiovascular disease (CVD) and diabetes mellitus, and impact mobility, social life, psychological status, and quality of life. [4] Following a prostate cancer diagnosis, non-obese men are vulnerable to becoming obese as a consequence of stress-related changes to eating habits due to heightened anxiety, decreased physical activity resulting from treatment side effects, and from androgen deprivation therapy (ADT), a common prostate cancer treatment which

reduces androgen concentrations to suppress tumor growth [5]. Although clinicians treating overweight or obese men with prostate cancer often address weight loss, it is commonly discussed in relation to the patient's general health and well-being, rather than as a potential adjuvant therapy. The advice given is often generic, encouraging patients to increase physical

activity and eat a healthy balanced diet. While prescribed exercise and nutrition interventions have been demonstrated to be safe for men with prostate cancer [6]. their impact on weight loss and prostate cancer-related outcomes, is largely unknown, particularly as it pertains to obese patients.

2 Epidemiology

Global patterns of change in incidence rates over time show the impact of PSA screening on prostate cancer epidemiology. During the past 40 years , age-adjusted incidence rates have generally increased across the world. Notably, this increasing trend has paralleled the uptake of PSA screening in certain regions, such as the United States, Europe, and Australia. In the United States, for example, a large peak in prostate cancer incidence is observed in the early 1990s when PSA screening is first introduced at the population level. The emergence of PSA screening has also led to a shift in the stage at diagnosis, with a higher proportion of men diagnosed with localized disease. Moreover, because of the lead time associated with prostate cancer, estimated to be 3 to 10 years, men are being diagnosed at an earlier age. A further consequence of PSA screening has been an increasing incidence of cancers considered to be overdiagnosis (i.e., cancers that would not have come to light clinically nor led to mortality in the absence of screening) . However, incidence rates have also increased in regions where PSA testing has not yet been widely used, such as in Japan and some other Asian and Eastern European countries. The trend in these regions suggests that environmental or lifestyle factors, as discussed later in this chapter, may also influence prostate cancer incidence.

3 Risk factors

Epidemiologic studies of prostate cancer have revealed numerous ways in which individual biology and lifestyle factors influence risk of developing prostate cancer and survival from this disease [7]. Although many questions remain about the etiology of this common disease, our current understanding of risk factors points to ways to identify individuals at high risk and use behavior change to reduce the burden of disease. As discussed in the previous section, prostate cancer is a clinically heterogeneous disease. Whereas some men have an aggressive form of prostate cancer, most others have a slow-growing or indolent form of disease. This clinical heterogeneity is reflected also in the underlying etiology of this disease. As detailed in the sections below, several risk factors show different associations for indolent as compared with lethal disease. Thus, it is imperative in prostate cancer epidemiology to differentiate between risk factors for total prostate cancer and for advanced or fatal disease.[7]

Established risk factors for total prostate cancer incidence are limited to older age, African-American race, and positive family history of prostate cancer. More recently, genome-wide association studies (GWAS) have provided additional evidence of genetic predisposition to prostate cancer. In populations with ethnically diverse ancestry, more than 180 genetic risk loci have been confirmed. Additionally, there is probable evidence that taller height increases risk of total prostate cancer. Although these factors are not modifiable, they are illustrative of the possible mechanisms involved in prostate carcinogenesis and could be used to identify individuals at increased risk of developing this disease (risk stratification).

Age is strongly associated with risk of total prostate cancer. Prostate cancer is rare among men younger than 40 years of age. The incidence rate of prostate cancer increases dramatically after 55 years of age, following a similar trend as other epithelial cancers. This trend is evident in global prostate cancer rates, as well as in both low and highly developed regions. It is noteworthy that 10% of U.S. men diagnosed with prostate cancer in 2012 were less than 55 years of age,

and early-onset prostate cancer may have a distinct etiology and clinical phenotype [8] The practice of PSA screening results in a lead time of ~10 years because of detection of prostate cancer before symptom onset. Following the implementation of PSA screening in the United States, the average age at prostate cancer diagnosis shifted earlier and is currently 66 years of age.

4 Obesity as a factor of developing prostate cancer

The prostate, situated in the lower pelvis just below the urinary bladder, is a composite organ composed of glandular and muscular elements. As an integral part of the male reproductive system, it functions as an accessory gland [9]. This gland is divided into different histologic zones: the peripheral, transition, and central zones. The peripheral zone is the region of origin of most prostate cancers, consisting of 70% tissue in normal cancers. The transition zone consists of about 5% of the prostate and is enlarged by benign prostatic hyperplasia (BPH), which is a common benign proliferation. Nevertheless, tumors that develop in the transition zone tend to stay in this area. The central zone, consisting of around 25%, is not a site of origin of any disease but still can be affected by cancer [10]. The growth and differentiation of the prostate is mainly under androgen control but is also dependent on other steroid and peptide hormones. Both genetic and environmental factors can lead to the development of cancer cells through various molecular mechanisms. Initiation of prostate carcinoma often involves the accumulation of cancerous cells, with changes in cell compartments. There are two possibilities for the cellular origin of PCA [11]. The first one is the transformation of final differentiated luminal cells, leading to partial dedifferentiation and immortality status. The other possibility consists of the oncogenic modification in prostate stem cells, believed to be located among basal cells [12]. These cells will originate proliferative cells with a luminal phenotype, consisting of the tumor [13]. In older individuals, BPH can occur due to prostate changes. BPH typical characteristics include basal layer expansion and hyperproliferation of the stromal. On the other hand, prostatic intraepithelial neoplasia (PIN) is an in-situ carcinoma, considered a precursor to invasive prostate carcinoma. The transition from PIN lesions to adenocarcinomas involves various histological changes in the invasive epithelial cells with a cytokeratin profile, such as excessive branching morphogenesis, basal cell layer lost, cytologic atypia with nuclei, and nucleoli expansion [14]. In early PCA stages, an important change occurring is the formation of proliferative inflammatory atrophy regions of epithelial cells that are related to inflammation in the stromal compartment. These regions present a higher cell proliferation and are proposed as a precursor to PIN [15]. Hence, the prostate is under androgen control and, thus, the Androgen Receptor (AR) presents an important physiological role in its normal function. More notably, AR is crucial for PCA development and proliferation. In normal tissue, the AR is responsible for maintaining the differentiation of endogenous stromal cells, inhibiting organ growth. As previously mentioned, the majority of PCA cases manifest as adenocarcinomas, stemming from the epithelial cells. The prostate epithelium comprises two key cell types—basal and luminal—which both express AR. For decades, the prevailing theory was that elevated testosterone levels could stimulate the proliferation of PCA. Consequently, various therapeutic approaches targeting PCA, including castration and Androgen-Deprivation Therapy (ADT), have been centered around the primary goal of reducing androgen levels [16]. Additionally, lower androgen levels have been associated with decreased PCA progression, but recent evidence suggests that the correlation between PCA and androgen levels is not as simple as initially thought. To begin with, there was no correlation between PCA proliferation and testosterone levels. Weitao and colleagues reported that physiological levels of testosterone could inhibit the proliferation of PCA cells in vitro, while suggesting that lower testosterone levels were essential for PCA initiation [18]. Meanwhile, supraphysiological testosterone levels were found to decrease the proliferation of PCA, as suggested by several authors [18-19]. Nowadays, the influence of testosterone on PCA development is recognized as having a dual nature. Lower testosterone levels are requisite for the initiation and progression of tumors, while supraphysiological levels hinder these processes. The impact of testosterone on PCA is intricately regulated by AR. The role of AR expression levels is pivotal in mediating the effects of testosterone on PCA. The therapeutic efficacy of supraphysiological testosterone levels in treating PCA can be attributed to the elevated AR expression observed in PCA cases. This upregulation of AR expression in PCA is suggested to be a compensatory mechanism aimed at counterbalancing the reduced levels of testosterone necessary for initiating tumor growth.

5 Conclusion

This review underscores the intricate link between obesity and prostate cancer, presenting robust evidence that excess body fat plays a critical role in disease development, progression, and clinical outcomes.[1] Despite ongoing debate, a number of research have consistently shown a high link between obesity and aggressive tumor features, increased recurrence risk, and mortality in prostate cancer.[1,2] The biological mechanisms underlying this relationship include hormonal imbalances, particularly decreased testosterone and increased estrogen levels, chronic inflammation, and insulin resistance—all of which contribute to a tumor-promoting microenvironment .[3,4] Additionally, obesity complicates disease detection due to lower PSA levels in obese individuals and contributes to poorer treatment

responses .[5] Given these findings, weight management and lifestyle interventions should be considered as essential components of prostate cancer prevention and management. This study provides a compelling rationale for integrating obesity control into public health strategies, offering societal benefits through improved cancer outcomes and guiding future research towards targeted therapies aimed at mitigating the obesity-related burden of prostate cancer.

Compliance with ethical standards

Disclosure of conflict of interest

All authors declare no conflict of interest of publishing this paper

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