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Review

Obesity and prostate cancer: Is there a link?

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SUMMARY

Background & aims: Obesity (BMI ≥30 kg/m^2) is associated with a number of chronic health problems such as diabetes, heart disease, hypertension and cancer. Epidemiological data has linked obesity with prostate cancer. The aim of this review is to provide an up to date account of the relationship between obesity and prostate cancer based on scientific research evidence.

Methods: A search of several databases using key words such as "prostate", "cancer", "obesity" and "overweight", identified a total of 2195 articles. From this, 47 were selected for review, based on the number of citations, impact factor and relevance to the field. Studies published in the past five years were favoured. Two on-going trials were also included for reference.

Results: Potential ways in which obesity may affect prostate cancer is via a detection bias, facilitating aggressive tumour growth, poor treatment outcomes and reduced survival rates. The most commonly studied mechanisms underlying obesity and prostate cancer include alterations in the levels of insulin, adipokines and androgen, as well as altered sensitivity and efficacy.

Conclusions: Evidence on the potential link between obesity and prostate cancer is conflicting. Many studies indicate the need for further research into the field. Specifically, there is a need for further large-scale multi-centre meta-analyses to triangulate factors affecting prostate cancer and obesity. A proxy measure for obesity that reliably accounts for adiposity is also needed. Overall, although most studies conclude that obesity has a negative impact on health, its effect on prostate cancer progression remains unclear.

1. Introduction

According to the World Health Organization (WHO) criteria, obesity is defined by a body mass index (BMI) of 30 kg/m^2 or greater [1]. A BMI above the healthy range of 18–25 kg/m^2 is common in Western cultures and has been linked to both consumption of a Western diet (i.e. high saturated fat, high calorie content), and sedentary lifestyles. Obesity is associated with a number of chronic health problems including heart disease, diabetes and certain cancer types.

Prostate Cancer (PCa) is the most common cancer diagnosis and the second most common cause of cancer-related deaths in men in the UK [2], although the underlying aetiology is still not fully understood. Many risk factors for PCa development have been suggested, including lifestyle and diet. Mouse models of PCa have shown that diet induced obesity escalated PCa progression, whilst a 30% calorie restriction reduced cancer progression [3]. Although such animal studies indicate a causal link between obesity and PCa, the data are more confounded in humans.

The incidence of PCa has increased since the late 1980s, and this has been attributed in part to implementation of widespread prostate-specific antigen (PSA) screening in some developed countries [4]. However, it has been suggested that screening may be less beneficial for overweight men as obesity appears to decrease the likelihood of tumour detection, which may allow time for tumour progression [5]. Although the treatment recommendation for PCa is based on many factors, such as age, disease grade, stage and overall health, some research has suggested that current

Non-standard abbreviations: BMI, body mass index; WHO, World Health Organization; PCa, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy; DRE, digital rectal examination; CT, computed tomography; BCR, biochemical recurrence; HIFU, high-intensity focused ultrasound; IGF, Insulin-like growth factor; IGFBP, IGF-binding protein; OS, oxidative stress; MRI, Magnetic resonance imaging; IGRT, Image-guided radiation therapy; LHRH, Luteinizing hormone releasing hormone; TRUS, Transrectal Ultrasound.

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treatment options are not suitable for obese men due to physical constraints and dosage issues [6]. Despite this, overall survival rates following treatment are increasing [2], which may mean that treatment and screening techniques are improving, even for obese patients.

Although the exact mechanisms driving both PCa development and recurrence are not known, some of the most frequently studied biological mechanisms are linked to the actions and levels of key cell signalling factors such as insulin, adipokines and androgens [7–9]. Insulin is a peptide hormone produced by the pancreas and is normally involved in regulating carbohydrate and fat metabolism. Its normal function is to allow cells to uptake glucose from the blood. However, high levels of serum insulin have been linked to an increased risk of prostate cancer, although the evidence is relatively limited [7]. Adipokines are proteins released by adipose (fat) tissue, thus obesity may affect their blood concentrations. However, the connection with PCa and its progression are still debated [8]. Androgens are sex hormones, which amongst other functions play a role in the development of the prostate gland, as well are regulating its function. However, during the early stages of prostate cancer development, tumour cells rely on androgens for their growth. Levels of the androgen testosterone are often higher in obese patients [9], and thus, this has been linked to prostate PCa development [10].

The aim of this review is to discuss recent and highly cited scientific research that extrapolates data linking obesity and PCa. The first part will present evidence linking obesity with the incidence of PCa, and its impact on cancer detection, treatment, progression and survival. The second part will present a cross-sample of research on some of the molecular mechanisms underlying obesity and PCa.

2. Methods of literature review

The following sources were searched for peer-reviewed articles published between January 2000 to October 2013: PubMed, The Cochrane Library, GoogleScholar, Scopus, and MEDLINE. The BMJ and Clinical Nutrition journals were also hand-searched for relevant articles. Data was ranked based on citation numbers, journal impact factor and year of publication, with the most highly cited and recent studies being favoured. Seminal papers published at any time were found using citation searches on Web of Science and Google Scholar. NCBI email updates on new research in the field were received weekly. Google.com and ClinicalTrials.gov were also used to find relevant data, including clinical trials. Details on the keywords used and search strategy are detailed in Supplementary Information 1.

3. Results of the literature search

The results of the literature search are summarised in Fig. 1. Detailed information on the characteristics of the studies included in the review can be found in Supplementary Information II.

4. Obesity

According to the WHO, a BMI (weight-for-height measurement) of $\geq$25 kg/m^2 is classed as being overweight, whilst $\geq$30 kg/m^2 is classed as obese [1]. The proportion of people worldwide who are overweight has increased dramatically, with the prevalence almost doubling between 1980 and 2008. Furthermore, the situation is becoming more common in previously unreported low income countries [1]. A BMI above the healthy range is most common in Western cultures and has been linked to both consumption of a high energy diet and other lifestyle factors. Obesity contributes to a number of global health burdens, and it has been estimated that between 7% and 41% of certain cancers are attributable to being overweight or obese [1].

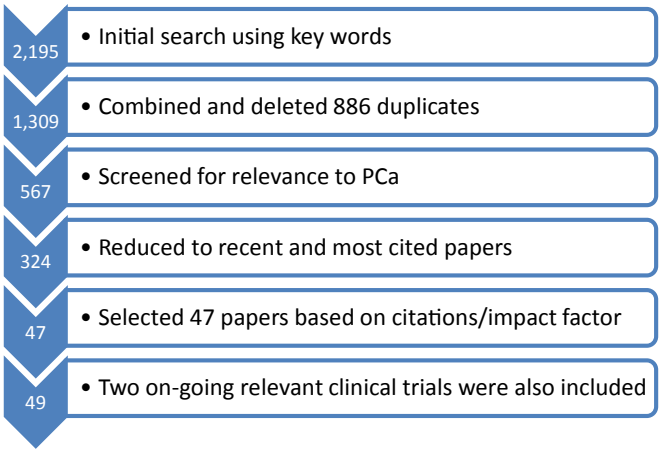

Fig. 1. Results of the Literature Search. The initial literature search from January 2000 to October 2013 identified 2195 papers using key words related to obesity and prostate cancer. Duplicate removal left 1309 papers. Screening for relevance resulted in 567 papers, which was reduced to 324 of the most cited or recent papers. Of these, 47 were selected based on how recent they were published, impact factor and number of times cited. Two on-going clinical trials were found and included for reference.

5. The prostate and cancer

The prostate is a walnut sized gland located at the base of the urinary bladder where it surrounds the urethra. The functions of the prostate gland include production of prostatic fluid which liquefies the ejaculate and provides nutrients and optimal conditions for survival of sperm in the female reproductive tract. Normal development and function of the prostate gland relies on the presence of androgens [11]. The majority of prostate cancers (PCa) develop in the outer peripheral zone of the prostate gland and are commonly classed as adenocarcinomas. However, during disease progression the tumour may become locally advanced extending beyond the prostatic capsule and may eventually metastasize to distant sites, most commonly the axial skeleton, leading to morbidity and mortality [12]. PCa is the most common cancer diagnosis (25.6% of diagnoses in 2011), and the second most common cause of cancer related deaths in men in the UK [2], as well as other developed countries. There are many suggested risk factors for PCa development and progression including age, ethnicity, family history, diet, lifestyle and hormonal factors [1,5,9,10]. This review will focus on the potential links between obesity and prostate cancer, with an emphasis on the risk of cancer development and progression.

The detection and diagnosis of PCa is most commonly performed by a triad of serum PSA measurements, digital rectal examination (DRE), and Transrectal Ultrasound (TRUS) guided biopsies of the prostate which are examined under the microscope [13]. PCa may progress through a variety of grades and stages, eventually leading to overt metastatic disease.

Currently, the management of patients with PCa is dependent upon a number of factors including tumour Gleason score, stage of disease, risk of progression (high, low or intermediate risk), and patient age. Treatment options include active surveillance, radical prostatectomy, brachytherapy, external beam radiotherapy and hormonal therapy [13]. During hormonal therapy, the production of testosterone and other androgens may be blocked either using drugs such as Luteinizing hormone releasing hormone (LHRH) agonists (e.g. Goserelin), or surgically