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European Association of Urology

Platinum Priority – Review – Prostate Cancer

Editorial by Lars Holmberg on pp. 821–822 of this issue

Obesity and Prostate Cancer: Weighing the Evidence

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Article info

Article history:
Accepted November 7, 2012
Published online ahead of print on November 15, 2012

Keywords:
Estrogen
Insulin
Obesity
Prostate cancer
Review
Testosterone
Weight change

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Abstract

Context: Obesity and prostate cancer (PCa) affect substantial proportions of Western society. Mounting evidence, both epidemiologic and mechanistic, for an association between the two is of public health interest. An improved understanding of the role of this modifiable risk factor in PCa etiology is imperative to optimize screening, treatment, and prevention.
Objective: To consolidate and evaluate the evidence for an epidemiologic link between obesity and PCa, in addition to examining the proposed underlying molecular mechanisms.
Evidence acquisition: A PubMed search for relevant articles published between 1991 and July 2012 was performed by combining the following terms: *obesity, BMI, body mass index and prostate cancer risk, prostate cancer incidence, prostate cancer mortality, radical prostatectomy, androgen-deprivation therapy, external-beam radiation, brachytherapy, prostate cancer and quality of life, prostate cancer and active surveillance*, in addition to *obesity, BMI, body mass index and prostate cancer and insulin, insulin-like growth factor, androgen, estradiol, leptin, adiponectin*, and *IL-6*. Articles were selected based on content, date of publication, and relevancy, and their references were also searched for relevant articles.
Evidence synthesis: Increasing evidence suggests obesity is associated with elevated incidence of aggressive PCa, increased risk of biochemical failure following radical prostatectomy and external-beam radiotherapy, higher frequency of complications following androgen-deprivation therapy, and increased PCa-specific mortality, although perhaps a lower overall PCa incidence. These results may in part relate to difficulties in detecting and treating obese men. However, multiple molecular mechanisms could explain these associations as well. Weight loss slows PCa in animal models but has yet to be fully tested in human trials.
Conclusions: Obesity appears to be linked with aggressive PCa. We suggest clinical tips to better diagnose and treat obese men with PCa. Whether reversing obesity slows PCa growth is currently unknown, although it is an active area of research.

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1. Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer and the sixth most common cause of cancer-related mortality among men worldwide [1]. In the last decade, multiple epidemiologic studies have suggested that obesity is associated with increased risk and death from numerous cancer types including PCa [2–4]. Like PCa, obesity affects many men, with two-thirds of the US classified as overweight (body mass index [BMI] $\geq$25 kg/m^2) and

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2012.11.013

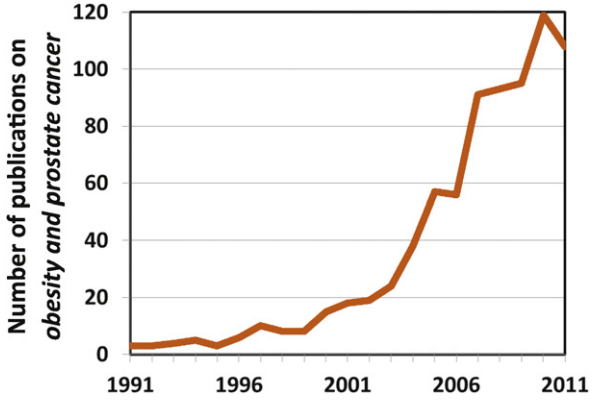

Fig. 1 – Using the search terms *obesity* and *prostate cancer*, the number of PubMed publications has increased in the past 20 yr.

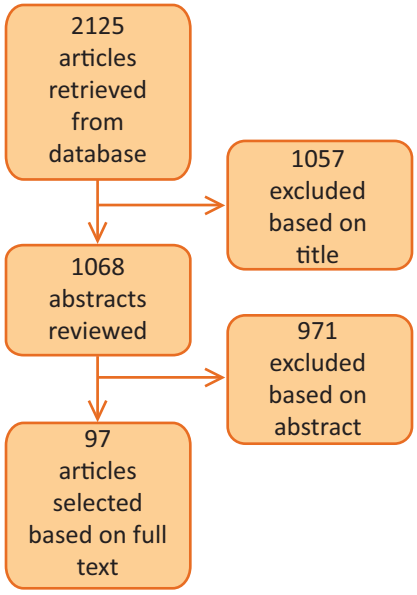

Fig. 2 – Flow diagram of search results.

one-third as obese (BMI $\geq$30 kg/m^2). These trends have stabilized in the past 10 yr [5], suggesting these levels are established as a permanent feature of US society. In Europe, the prevalence of overweight and obesity continues to rise, and current levels are comparable with those of the United States 15 yr ago [6].

Because obesity and PCa affect substantial proportions of the male population, the association between the two is of great public health significance. Existing epidemiologic data are somewhat conflicting, and the consolidation and review of findings to date is required. Attention is increasingly turning to the elucidation of underlying molecular mechanisms, a number of which are emerging. This review focuses on the epidemiologic association between obesity and PCa incidence, treatment, and mortality, in addition to proposed underlying molecular mechanisms. It concludes with clinical recommendations for our obese patients. The contribution of specific dietary components, clearly intertwined with obesity, is the focus of our companion review [7]. We previously reviewed the literature on this topic several years ago [8]. At that time, a PubMed search of obesity and PCa generated 237 articles. The same search in July 2012 generated 796 articles, a greater than three-fold increase in the past 5 yr (Fig. 1). Thus we decided an updated review was needed.

2. Evidence acquisition

Relevant literature published between January 1991 and July 2012 was identified by a search of the PubMed database using the following terms: *obesity, BMI, body mass index* combined with *prostate cancer risk, prostate cancer incidence, prostate cancer mortality, radical prostatectomy, androgen-deprivation therapy, external-beam radiation, brachytherapy, quality of life, active surveillance*, and *prostate cancer* combined with *obesity, BMI, body mass index, and insulin, IGF, sex hormones, adipokines, leptin, adiponectin*, and *IL-6* (Fig. 2). Relevant English-language articles were abstracted and reviewed using the reference list to identify additional potential articles for review. Studies were selected based on clinical relevance, and so studies were excluded when the study population and/or outcome measures lacked clinical significance or were not relevant to our review (eg, cancer cachexia). Wherever possible, randomized controlled trials, prospective population-based studies, systematic reviews, and meta-analyses were selected over case-control studies and reviews. If more than one article was published in the same study population, the study with the larger sample size was selected.

3. Evidence synthesis

3.1. Measuring obesity

BMI, calculated using an individual's height and weight (kilograms per square meter), is a straightforward and cost-effective method of measuring overall adiposity. Although BMI does not account for body mass composition or the distribution of adipose tissue, it has been repeatedly demonstrated as a reliable surrogate of obesity on a population level, with the advantage of being the most widely used measure, enabling interstudy comparisons. Thus, due to ease of use and near ubiquitous use in the literature, we focused nearly exclusively on BMI, accepting the inherent limitations of this approach.

3.2. Obesity and prostate cancer incidence

All three meta-analyses to date [4,9,10] reported a positive association between obesity and PCa incidence. The relative risks (RRs) in these studies were modest yet consistent, from 1.01 (95% confidence interval [CI], 1.0–1.02) per 1 kg/m^2 increase in BMI [10] to 1.05 (95% CI, 1.01–1.08) [9] and 1.03 (95% CI, 1.0–1.07) [4] per 5 kg/m^2 increment in BMI. However, the findings of the individual studies contributing to these meta-analyses differ dramatically, with some