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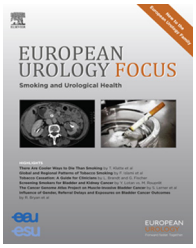

Review – Prostate Cancer

Smoking and Prostate Cancer: A Systematic Review

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Abstract

Context: Cigarette smoking is the leading cause of death from cancer, although the relationship between smoking and prostate cancer (PCa) is controversial.
Objective: To evaluate the available evidence of the role of cigarette smoking and PCa development and progression and to discuss possible clinical implications for PCa management.
Evidence acquisition: A PubMed search for relevant articles published between 2004 and September 2014 was performed by combining the following PICO (patient population, intervention, comparison, outcome) terms: *male, smoking, prostate, prostate cancer, prevention, diagnosis, treatment*, and *prognosis.* Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were followed.
Evidence synthesis: The association between cigarette smoking and PCa incidence is controversial, particularly in recent series. Current cigarette smoking is associated with an increased risk of PCa death, and the number of cigarettes smoked per day had a dose–response association with PCa mortality. Smokers present a higher risk of biochemical or distant failure after PCa treatment. Several biological mechanisms behind these associations have been proposed, although the molecular mechanisms remain unclear. Further research is required to better understand the role of smoking on PCa development and progression and, particularly, to evaluate the possible effect of smoking cessation on PCa management.
Conclusions: Data from the peer-reviewed literature suggested an association of smoking and aggressive PCa. Although the pathophysiology underlying this association remains unclear, smokers presented higher PCa mortality and worse outcome after treatment. Smoking-cessation counseling should be implemented for patients with PCa, although its effect on PCa progression should be investigated.
Patient summary: We looked at the association between smoking and prostate cancer (PCa). Smokers have a higher risk of PCa mortality and worse outcomes after treatment. Smoking cessation should be encouraged in men with or at risk of having PCa.

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1. Introduction

Prostate cancer (PCa) is the leading cause of nonskin cancer among men worldwide and, after lung, is the second most common cause of death from cancer in men in the United States [1,2]. PCa is considered a chronic disease with early initiation and slow progression; it develops through early and late precancerous histologic modifications [3]. The only

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established risk factors associated with PCa are age, race, and family history, although large geographic variations in PCa risk suggest that lifestyle and environmental factors may also contribute to its etiology [3]. It has been hypothesized that the increased prevalence of metabolic syndrome resulting from lifestyle changes associated with a Western lifestyle (including physical inactivity and higher intakes of refined carbohydrates and excess calories) may explain, in part, the fact that once Asians migrate to the United States, their risk of PCa approaches that of white Americans within one or two generations [4–6]. There is little evidence for any association between alcohol and prostate cancer [7]. Paradoxically, several studies have reported an inverse association between diabetes mellitus and prostate cancer risk [8,9].

Cigarette use is the leading cause of death from cancer, but the relationship between smoking and PCa remains controversial; some studies indicate no association, whereas others suggest an elevated risk among smokers [10]. A recent meta-analysis found a modest but statistically significant association between cigarette smoking and PCa death; a dose-response relationship was also found. Conversely, the association between cigarette smoking and PCa incidence was mixed [11]. Smoking may also have a significant effect on treatment outcome of cancers for which smoking is not related [12]. As such, there has been growing interest in the field as to whether patients with a history of smoking present with worse disease, have worse response to treatment, or have other confounding factors that could explain inferior outcomes [12].

The possibility of modifying environmental factors, including smoking, have been proposed as a new frontier in the prevention and management of several cancers including PCa [13]. In this review we evaluate contemporary evidence regarding smoking as a causative factor in PCa development and as a significant variable in disease outcome. We also discuss the potential clinical implications of this evidence and suggest directions for future research.

2. Evidence acquisition

A search of the National Center for Biotechnology Information PubMed database for relevant articles published between 2004 and September 2014 was performed by combining the following PICO (patient population, intervention, comparison, outcome) terms: *male, smoking, prostate, prostate cancer, prevention, diagnosis, treatment*, and *prognosis.* Only articles published in the English language were selected. In addition, sources in the reference sections of the identified publications were also added to the list. Evidence was not limited to human data; data from animal studies were also included in the review. Each article title and abstract was reviewed for relevance and appropriateness with regard to the relationship between cigarette smoking and PCa. Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were followed to ensure transparent and complete reporting of this systematic review (Fig. 1). Details of the selected references are summarized in Tables 1 and 2.

3. Evidence synthesis

3.1. The burden of smoking behavior

Native Americans were using tobacco products in the Americas prior to the arrival of Columbus, but widespread use of tobacco in cigarettes is more recent, occurring largely during the 20th century [47]. Concern among members of the scientific community that cigarette smoking caused disease grew with the publication of retrospective epidemiologic studies of lung cancer in the late 1940s and early 1950s. Currently, tobacco smoking is considered a major public health concern because it is responsible for high levels of mortality and morbidity worldwide. Smoking causes increased risk of mortality from lung cancer and aerodigestive, bladder, and several other cancers; it is also associated with an increased risk of cardiovascular disease, stroke, chronic respiratory disease, and a number of other medical conditions [48]. In the developed world, smoking was reported to be the risk factor with the largest attributable mortality and attributable disability-adjusted life years (DAYLS) by the World Health Organization: 12.2% of all DALYS were attributed to smoking. Most of the deaths attributable to smoking may be grouped into three broad categories: cancers, cardiovascular diseases, and respiratory diseases. Data from Canada showed that cancer accounted for 46.8% of smoking-attributable death, cardiovascular disease accounted for 27.6%, and respiratory diseases accounted for 22.3% [48].

Notwithstanding the related morbidity and mortality and all of the prevention campaigns and smoking-cessation counseling programs conducted in the last 50 yr, the number of daily smokers and total cigarettes consumed each year worldwide is increasing. There is a continuous increase in the number of men and women who smoke daily, increasing form 721 million (95% confidence interval [CI], 700 million–742 million) in 1980 to 967 million (95% CI, 944 million–989 million; $p = 0.001$) in 2012. Between 1980 and 2012, the number of cigarettes smoked worldwide increased from 4.96 trillion (95% CI, 4.78 trillion–5.16 trillion) to 6.25 trillion (95% CI, 6.07 trillion–6.44 trillion; $p = 0.001$). Estimated prevalence of daily smoking also varies according to different geographic area, from >50% in Western Europe and Asia (Russia, Armenia, Indonesia) to 27.5–34.7% in Central Europe (France, Spain, Germany); 16.5–19.7% in the United States, Canada, and Brazil; and <10% in sub-Saharan Africa (Niger, Nigeria, Ghana, Sudan) [49]. Possible differences in smoking behavior should be considered when comparing PCa data from different geographic areas.

3.2. Association between smoking and prostate cancer

3.2.1. Potential biological mechanisms

Some studies have shown possible mechanistic pathways linking smoking and PCa development and progression, but