Preventive Medicine 85 (2016) 1–10

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Review

Cigarette smoking and testosterone in men and women: A systematic review and meta-analysis of observational studies

Jie Zhao [a], June Yue Yan Leung [a], Shi Lin Lin [a], C. Mary Schooling [a,b,*]

[a] School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[b] School of Urban Public Health, Hunter College, CUNY School of Public Health, New York, USA

ARTICLE INFO

Available online 4 January 2016

Keywords:
Smoking
Testosterone
E-cigarettes
Meta-analysis

ABSTRACT

Recently Health Canada and the Food and Drug Administration warned about the cardiovascular risk of testosterone, making environmental drivers of testosterone potential prevention targets. Cotinine, a tobacco metabolite, inhibits testosterone breakdown. We assessed the association of smoking with testosterone in a systematic review and meta-analysis, searching PubMed and Web of Science through March 2015 using ("testosterone" or "androgen" or "sex hormone") and ("smoking" or "cigarette"). Two reviewers independently searched, selected, assessed quality and abstracted with differences resolved by consensus or reference to a third reviewer. The initial search yielded 2881 studies; 28 met the selection criteria. In 22 studies of 13,317 men, mean age 18–61 years, smokers had higher mean testosterone than non-smokers (1.53 nmol/L, 95% confidence interval (CI) 1.11 to 1.96) using a random effects model with inverse variance weighting. In 6 studies of 6089 women, mean age 28–62 years, smoking was not clearly associated with testosterone (0.11 nmol/L, 95% CI −0.08 to 0.30). Fixed effects models provided similar results, but suggested a positive association in women. Whether products which raise cotinine, such as e-cigarettes or nicotine replacement, also raise testosterone, should be investigated, to inform any regulatory action for e-cigarettes, which emit nicotine into the surrounding air, with relevance for both active and passive smokers.

Contents

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality globally (Lozano et al., 2013), with men having higher age-specific mortality rates than women (Kalin and Zumoff, 1990). Observationally serum testosterone is associated with lower cardiovascular disease (CVD) morbidity/mortality (Ruige et al., 2011). However, observational studies providing associations concerning endogenous testosterone are open to reverse causality because serum testosterone falls with age and ill-health (Feldman et al., 2002; Shi et al., 2013). Meta-analyses of small randomized controlled trials (RCTs) have not confirmed benefits of testosterone therapy among men, but suggested effects in the other direction (Xu et al., 2013; Fernandez-Balsells et al., 2010). Endogenous and exogenous testosterone may have different roles. However,

* Corresponding author at: G/F Patrick Manson Building (North Wing), 7 Sassoon Road, Hong Kong. Fax: +852 35201945.
E-mail address: cms1@hku.hk (C. Mary Schooling).

http://dx.doi.org/10.1016/j.ypmed.2015.12.021
0091-7435/

Mendelian randomization studies, using genetically determined serum testosterone, have also shown no benefits of endogenous testosterone for CVD risk factors (Zhao et al., 2014; Haring et al., 2013). The Food and Drug Administration (FDA) in the US and Health Canada have recently highlighted the possible cardiovascular risk of testosterone as a cause of heart attack (Health Canada, 2015; FDA, 2015-a), stroke (Health Canada, 2015; FDA, 2015-a), blood clots (Health Canada, 2015; FDA, 2015-b) and venous thromboembolism (FDA, 2015-b). As such, environmental drivers of androgens could provide mechanistic insight and new prevention strategies for CVD.

Smoking is a well-established cause of CVD, although the mechanism by which smoking causes such a wide range of diseases has not been fully elucidated (Carter et al., 2015). Smoking would also be expected to increase testosterone because nicotine and/or its metabolites share a disposal pathway with androgens, and so could competitively inhibit androgen disposal (Schooling, 2015). Specifically, testosterone, cotinine and *trans*-3′-hydroxycotinine (3HC) are all inactivated by glucuronidation, i.e., conjugation by enzymes from the uridine 5′-diphospho (UDP)-glucuronosyltransferase (UGT) superfamily (Chen et al., 2010; Chouinard et al., 2008), with the same UGT enzyme used for glucuronidation of both nicotine metabolites and androgens: the UGT2B10 enzyme for nicotine and cotinine, the UGT2B17 enzyme for 3HC (Chen et al., 2010), and the UGT2B7, UGT2B15 and UGT2B17 enzymes for androgens (Chouinard et al., 2008). Consistent with this potential mechanism (Schooling, 2015), some studies have reported higher androgens in smokers (Field et al., 1994). Commonality also exists between some effects of smoking and of androgens. For example, smoking promotes thrombosis (Barua and Ambrose, 2013), lowers HDL-cholesterol (Chelland Campbell et al., 2008) and has pro-inflammatory effects (Barua and Ambrose, 2013). Similarly, androgens promote thromboxane (Ajayi et al., 1995), raise hematocrit, lower high-density lipoprotein (HDL)-cholesterol (Fernandez-Balsells et al., 2010) and may promote low-grade systemic inflammation, by suppressing the immune system (Grossman, 1985). Smoking is also associated with prostate cancer (Carter et al., 2015). This same mechanism would also be expected to raise testosterone in users of smokeless tobacco (Schooling, 2015), which is associated with prostate cancer (Lee and Hamling, 2009), nicotine replacement or e-cigarettes. Notably, e-cigarettes also emit low levels of nicotine into the atmosphere (Grana et al., 2014), potentially causing harm by the same mechanism to bystanders.

Given the known harms of smoking, RCTs examining the effect of smoking on androgens are not available. Observational studies have reported various associations of smoking with androgens (Wang et al., 2013; Brand et al., 2011; Shaarawy and Mahmoud, 1982; Soldin et al., 2011). To our knowledge, no systematic review or meta-analysis has synthesized the association of smoking with serum androgens. To test the hypothesis that smoking raises androgens (Schooling, 2015), we carried out a systematic review and meta-analysis of observational studies, among men and women, to examine the association of cigarette smoking with two different biomarkers of serum androgens (testosterone and androstanediol glucuronide (AAG)).

Methods

We implemented this meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, and a published protocol (Zhao et al., 2015). Two reviewers searched independently and compared their selections at the end of the search process. The differences were resolved by consensus or by reference to a third reviewer. The reviewers also extracted information from the selected studies, with the guidance from a third reviewer and a statistician.

Data source and searches

We searched PubMed for observational studies concerning cigarette smoking and serum androgens until March 2015, using ("testosterone" or "androgen" or "sex hormone") and ("smoking" or "cigarette") in any field, with the selection limited to studies in humans and in English, because preliminary analysis suggested that most studies were in English. We also searched Web of Science using a similar strategy. We first discarded any studies that were irrelevant based on title or abstract and read the remaining to select observational studies where the association of smoking with androgens was reported. Then we did a bibliographic search of the selected studies and relevant reviews to identify additional studies.

Study selection

We included any observational study which assessed the association of active smoking with serum androgens (testosterone and AAG). We selected testosterone as a measure of gonadal production, which is commonly used. We selected AAG as a correlate of the final breakdown product of androgen production by the gonads, adrenals and locally (Labrie et al., 2009; Vandenput et al., 2007). Observationally, AAG is poorly correlated with serum testosterone (Schooling, 2013a), and has associations with cardiovascular related factors more similar to those observed with experimental administration of exogenous testosterone than does serum testosterone (Schooling, 2013a). We did not assess serum dihydrotestosterone or free testosterone, because they are strongly correlated with testosterone (Vandenput et al., 2007) and less often reported. We did not exclude studies based on the number of participants, in order to make full use of all the evidence available. We did not exclude studies based on date of publication, because there is no reason to think that the association of smoking with androgens has changed over the years. We excluded studies which focused on passive smoking or smoking cessation. We also excluded studies in groups with a condition possibly caused by smoking or androgens, such as hypogonadism, erectile dysfunction and polycystic ovary syndrome (PCOS), because such selection into the study could generate a biased association (Flanders et al., 2014). We also excluded participants with atypical hormone status, such as pregnant women.

Data extraction

Two reviewers extracted information from the selected studies and double checked with each other. The extracted information included publication details (author, year of publication, title and journal), characteristics of the study population, including age, sex, setting, study design (cross-sectional, case–control or cohort studies), years of follow-up and loss to follow up, if available, classification of smoking status, the number of participants by smoking status, mean and standard deviation (SD) of androgen levels by smoking status, the adjusted regression coefficient (β) with 95% confidence intervals (CIs) when a regression of serum androgens on smoking status was performed, androgen measurement method, funding source and confounders included in the assessment. We did not include the studies with incomplete information (sample size, mean and SD of androgen levels by smoking status). Age is a well-established confounder of the relation between smoking and androgens; androgens fall with age (Schooling, 2013b), and smoking decreases with age (Neaton and Wentworth, 1992). In meta-analysis we cannot control for age without individual level data, so in study selection we only included studies which controlled for age. For studies showing beta-coefficients rather than mean androgen levels by smoking status, we contacted the authors by email (twice) to ask for age-adjusted means and SDs of androgen levels by smoking status. For studies using geometric means and SDs, we converted to arithmetic means and SDs with well-established formulas (Higgins et al., 2008).

Quality assessment for individual studies

The reviewers used a well-established tool, the Newcastle–Ottawa quality scale, to evaluate the quality of each study (Wells et al., n.d.). Notably, the quality assessment included the appropriateness of covariate adjustment in the section on comparability, where age is considered to be the most well-established covariate relevant to the comparability of smokers and non-smokers. The reviewers also assessed and gave higher score (by one) to the individual studies controlling for other potential confounders, such as alcohol consumption, ethnicity and co-morbidities, but not controlling for factors possibly on the causal pathway (i.e., mediators, such as body weight). The reviewers assessed independently, double checked with each other, and resolved any difference by consensus. We did a sensitivity analysis excluding the low quality studies.