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Smoking and risk of low- and high-grade prostate cancer: Results from the REDUCE study

Tammy Ho^{1,2}, Lauren E. Howard^{2,3}, Adriana C. Vidal^{2,3}, Leah Gerber^{2,3}, Daniel Moreira⁴,
Madeleine McKeever², Gerald Andriole^{5,6}, Ramiro Castro-Santamaria⁷, and Stephen J.
Freedland^{2,3,8}

¹Duke University School of Medicine, Durham, NC, USA

²Durham Veterans Affairs Medical Center, Durham, NC, USA

³Division of Urology, Department of Surgery, Duke Prostate Center, Duke University School of
Medicine, Durham, NC

⁴Arthur Smith Institute for Urology, North Shore-Long Island Jewish Health System, New Hyde
Park, NY, USA

⁵Division of Urologic Surgery, Department of Surgery, Washington University School of Medicine
in St. Louis, St. Louis, MO, USA

⁶Prostate Study Center, Barnes-Jewish Hospital, St. Louis, MO, USA, Urology Section,
Department of Surgery, Veterans Affairs Medical Center, Durham, NC

⁷GlaxoSmithKline Oncology R&D, Collegeville, PA

⁸Department of Pathology, Duke University Medical Center, Durham, NC

Abstract

Background—Though the relationship between smoking and prostate cancer risk is inconsistent, some studies show smoking is associated with prostate cancer mortality. Whether this reflects delayed diagnosis or direct smoking-related effects is unknown. REDUCE, which followed biopsy-negative men with protocol-dictated PSA-independent biopsies at 2- and 4-years, provides an opportunity to evaluate smoking and prostate cancer diagnosis with minimal confounding from screening biases.

Methods—Logistic regression was conducted to test the association between smoking and cancer on the first on-study biopsy (no cancer, low-grade Gleason 4–6, high-grade Gleason 7–10) in REDUCE.

Results—Of 6,240 men with complete data and 1 on-study biopsy, 2,937 (45.8%) never smoked, 929 (14.5%) were current smokers, and 2,554 (39.8%) were former smokers. Among men with negative first on-study biopsies, smokers were 36% less likely to receive a second on-study biopsy ($p < 0.001$). At first on-study biopsy, 941 (14.7%) men had cancer. Both current and

Reprint requests to Division of Urology, Box 2626 DUMC, Duke University School of Medicine, Durham, NC 27710, phone (919) 668-5946, fax (919) 668-7093, steve.freedland@duke.edu, (Dr Freedland).

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former smoking were not significantly associated with either total or low-grade prostate cancer (all $p > 0.36$). Current (OR=1.44, $p=0.028$) but not former smokers (OR=1.21, $p=0.12$) were at increased risk of high-grade disease. On secondary analysis, there was an interaction between smoking and BMI (p -interaction=0.017): current smokers with BMI ≥ 25 had increased risk of low- (OR=1.54, $p=0.043$) and high-grade disease (OR=2.45, $p=0.002$), with null associations for BMI < 25 .

Conclusion—Among men with elevated PSA and negative pre-study biopsy in REDUCE, in which biopsies were largely PSA-independent, smoking was unrelated to overall prostate cancer diagnosis but was associated with increased risk of high-grade prostate cancer.

Keywords

Prostate cancer; smoking; REDUCE

INTRODUCTION

In 2014, it was estimated there will be 233,000 men would be newly diagnosed with prostate cancer (1). However, most prostate cancer cases do not result in death, but instead include substantial variation in natural history. Thus, identification of factors affecting either prostate cancer risk or disease progression should be examined. Cigarette smoking is a known risk factor for developing multiple cancer types including lung and bladder; however, its relationship with prostate cancer is less clear (2).

Despite increased interest in the effect of smoking on prostate cancer risk, the literature remains inconsistent. Several large prospective studies in the United States found no association between cigarette smoking and prostate cancer incidence (3–5). A meta-analysis of 24 prospective cohort studies with over 21,579 overall prostate cancer cases also found no association with prostate cancer incidence on pooled analysis, although they observed a 13% increased prostate cancer risk among patients with highest compared to lowest exposure (6). The study also reported a 14% increased risk of fatal prostate cancer in current smokers versus nonsmokers, with the heaviest smokers experiencing a 24–30% greater risk of prostate cancer-related death. This is consistent with several studies in which smokers had up to twice the risk of prostate cancer-related mortality (7, 8). Furthermore, other studies of men with prostate cancer reported smoking was associated with more advanced disease (9, 10) and inferior outcomes following radiation therapy (11, 12).

One possible explanation for the more consistent association between smoking and prostate cancer mortality but weaker association with incidence is smokers may delay diagnosis and treatment, resulting in poorer survival. Another reason could be smoking may induce biologic changes leading to a more aggressive cancer phenotype and decreased survival. Alternatively, smoking may only influence aggressive disease and not indolent prostate cancer. However, most previous studies on smoking and prostate cancer were unable to distinguish whether the association between smoking and prostate cancer-mortality was due to delayed diagnosis and/or treatment or the direct effects of smoking. The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, wherein biopsy negative men were followed with protocol-directed biopsies independent of PSA, offered a unique opportunity

to evaluate cigarette smoking and prostate cancer incidence while reducing possible confounding due to differential screening.

MATERIALS AND METHODS

Study Population

REDUCE was a 4-year, multicenter, randomized, double-blind, placebo-controlled study (13). Eligible participants were 50–75 years old, had a serum PSA of 2.5–10.0 ng/ml if 50–60 years or 3.0–10.0 ng/ml if older than 60 years, and had a single, negative prostate biopsy (6–12 cores) within 6 months prior of enrollment independent of the study. Subjects were randomized to 0.5 mg dutasteride daily or placebo. Visits were scheduled every 6 months and total serum PSA was doubled (± 0.1 ng/ml) when reported to investigators for men receiving dutasteride to maintain the blinded nature of the study. All subjects underwent a “protocol-dependent” 10-core transrectal ultrasound-guided biopsy at 2 and 4 years regardless of PSA. “Protocol-independent” biopsies were performed as clinically indicated. If obtained during months 19–24 or 43–48 of the study, for-cause biopsies were considered as a protocol-dependent biopsy.

Among the 8,122 men included in the efficacy population, we identified 6,729 men (82.5%) who have had at least one on-study biopsy. The details of the men who had at least one on-study biopsy were previously published (14). From these men, we excluded men missing smoking status ($n=9$), PSA ($n=15$), prostate volume on transrectal ultrasound ($n=78$), BMI ($n=201$), and digital rectal examination ($n=6$) for a final study population of 6,420 men.

Statistical Analysis

Baseline characteristics, such as smoking history (including pack-years), alcohol use, medication use, and medical comorbidities, were obtained at study baseline. Patients were classified as: 1) never smokers, 2) ex-smokers, and 3) current smokers. Other forms of smoking, including cigars or pipes were not ascertained. Other sources of tobacco exposure, such as second-hand smoke or chewing tobacco were not evaluated.

Comparison between baseline characteristics among the three smoking categories was performed using chi-square and Kruskal-Wallis tests for categorical and continuous variables. Similarly, baseline characteristics between patients who received only one vs. more than one on-study biopsy, excluding patients who had cancer detected on the first biopsy, were compared using chi-square and Wilcoxon rank sum tests for categorical and continuous variables. Because of concerns with study compliance among smokers, we only used results from the first on-study biopsy to determine cancer outcome. To evaluate the association between smoking status and either prostate cancer diagnosis (based upon pathology review of the first on-study biopsy) or disease grade (no cancer, low-grade Gleason 4–6, high-grade Gleason 7–10), we used logistic regression or multinomial logistic regression, respectively. These results were compared with results that included all on-study biopsies to determine if the detection bias among less compliant smokers attenuated the relationship between smoking and prostate cancer risk. All multivariable analyses were adjusted for factors at baseline including age, race (black, white, other), geographic region

by continent (Europe, or Other vs. North America), PSA, prostate volume, digital rectal examination findings, BMI, and treatment arm (dutasteride vs. placebo). PSA, prostate volume, BMI, and pack-years (continuous variable) were logarithmically transformed due to their non-normal distributions.

Secondary analyses were conducted testing for interactions between smoking and BMI (< 25, 25.0–29.9, ≥ 30 kg/m²), age (median age 63 years, >63 years), treatment arm, and geographic region in predicting cancer and disease grade. Cross product terms of smoking X variable of interest were included in the multivariable models along with the main effects and likelihood ratio tests between the models with and without the interaction terms were used to determine if the interaction was significant. For the variables with significant p-interactions, models were stratified to detect differences in the effect of smoking between strata. All p values were two-sided and alpha was <0.05 for statistical significance. All analyses were performed using Stata 11.0 (Stata Corp, College Station, TX).

RESULTS

Patient Demographics

Of the 6,240 subjects, 2,937 (45.8%) never smoked, 929 (14.5%) were current smokers, and 2,554 (39.8%) were ex-smokers (table 1). Current smokers were younger ($p=0.0001$), had lower BMI ($p=0.0001$), and had smaller prostatic volume ($p=0.004$). As smoking was related to age and age can be related to both prostate volume and BMI, we performed a linear regression analysis with BMI and prostate volume (log-transformed) as the outcomes and smoking categories as predictors adjusted for age. When this was done, the association between smoking and BMI remained significant (current smokers: $p=0.023$ and former smokers: $p<0.001$), but the association between smoking and prostate volume was only significant for current smokers (current smokers: $p=0.035$ and former smokers: $p=0.54$). Additionally, current smokers were more likely to be from Europe or other location ($p<0.001$) than from North America. During the entire study period, 1,447 (22.5%) men had a positive biopsy, with 1,008 (15.7%) and 439 (6.8%) men classified with low-grade and high-grade disease, respectively. On the first on-study biopsy ($n=5,479$), 941 (17.2%) men had a positive biopsy, of which 635 (11.6%) were low-grade and 306 (6%) were high-grade.

Study Subject Compliance

Of the full REDUCE cohort on crude analysis, current smokers were equally likely to receive at least one on-study biopsy versus never smokers (OR 0.89; $p=0.155$). However, after adjusting for demographic (BMI, age, race, geographic location, and treatment arm) and disease characteristics (PSA, digital rectal examination findings and prostate volume), current smoking was significantly associated with a decreased risk of receiving at least one on-study biopsy (OR 0.80; $p=0.013$). Of the patients who received a first biopsy with no cancer detected, current smokers were less likely to receive a second biopsy versus nonsmokers on crude analysis (OR 0.65; $p<0.001$), which remained significant after adjusting for demographic and disease characteristics (OR 0.64; $p<0.001$). There were no differences in compliance between former smokers and nonsmokers for the first or second biopsy (all $p>0.05$).

Subjects who received only one negative on-study biopsy were older than those who received more than one on-study biopsy at baseline ($p=0.020$; supplementary table 1). There was an association between race and receiving 1 vs. >1 on-study biopsy ($p=0.014$). All other baseline characteristics were similar between patients who received one biopsy vs. more than one biopsy.

Smoking and Prostate Cancer

Relative to never smokers, the risk of prostate cancer diagnosis on the first biopsy was not significantly different among smokers ($p=0.41$) or former smokers ($p=0.43$) on crude analysis (table 2). Additionally, both current ($p=0.66$) and former smoking ($p=0.96$) were unrelated to low-grade disease. However, current smoking was associated with a 44% increased risk of high-grade disease (OR 1.44, 95% CI 1.04–2.00, $p=0.028$) while former smoking was not related to high-grade disease (OR 1.21, $p=0.12$). Results were largely unchanged after adjusting for various clinical and demographic characteristics. Defining high-grade disease as Gleason 4+3 did not change the direction of the associations between current or former smoking and low- or high-grade disease diagnosis, though results for current smoking were no longer statistically significant based on only 89 men having Gleason 4+3 disease (data not shown). When using data from all on-study biopsies, accepting that current smokers were more likely to receive only one on-study biopsy, the association between smoking and high-grade was attenuated and there was no significant association between smoking and prostate cancer or disease grade (supplementary table 2).

Pack-years and Prostate Cancer

A total of 54 current and 165 former smokers did not have pack-year data. We also excluded the upper 5% who reported >55 pack-years from these analyses. On multivariable analysis among current and former smokers with pack-year data ($n=2,972$), more pack-years smoked was associated with decreased risk of diagnosis of low-grade prostate cancer (OR_{log pack-years} 0.83, 95% CI 0.73–0.95, $p=0.007$), but was unrelated to high-grade prostate cancer ($p=0.395$).

Secondary Analysis

On secondary analysis, we tested the interactions between smoking and age, treatment arm, geography, and BMI in predicting prostate cancer diagnosis and grade. None of the interactions between smoking and age, treatment arm, or geography were statistically significant (all $p>0.10$). However, there was an indication of an interaction between smoking and obesity. Thus, we stratified patients by BMI category, wherein there were 1,690 (27.2%) men with BMI $<25\text{kg/m}^2$, 3,267 (52.7%) men with BMI 25.0–29.9 kg/m^2 , and 1,244 (20.1%) men with BMI $\geq 30\text{kg/m}^2$. As the associations between smoking and prostate cancer diagnosis and grade were similar in men with a BMI 25.0–29.9 kg/m^2 and BMI $\geq 30\text{kg/m}^2$, we dichotomized BMI as <25 vs. $\geq 25\text{kg/m}^2$. When this was done, there were significant interactions between smoking and BMI for predicting overall prostate cancer ($p=0.003$) and grade ($p=0.002$). Specifically, there were no associations between current or former smoking and low- ($p>0.08$) or high-grade ($p>0.60$) disease among men with BMI ≥ 25 (table 3). However, among men with BMI $<25\text{kg/m}^2$, current smokers had an increased risk of low-grade (OR 1.54, $p=0.043$) and high-grade disease (OR 2.45, $p=0.002$) versus never smokers.

Former smokers with BMI ≥ 25 had increased risk of diagnosis of high-grade (OR 1.81, $p=0.022$), but not low-grade disease ($p=0.24$).

DISCUSSION

In this cohort of over 6,000 men all with a negative prostate biopsy at baseline who were enrolled in a clinical trial and expected to receive protocol-dictated biopsies at 2 and 4 years of follow-up regardless of PSA, we found smokers were 36% less likely to receive a second on-study biopsy. On the first on-study biopsy, current smokers were significantly more likely to be diagnosed with high-grade disease than never smokers. However, smoking was not related to low-grade or total prostate cancer risk. Interestingly, the association between smoking and prostate cancer differed as a function of BMI. Specifically, smoking was only related to high-grade disease in men with a BMI $<25\text{kg/m}^2$ and not in men with higher BMI values. These findings suggest current smoking is related to increased risk of aggressive prostate cancer diagnosis in lean men in REDUCE. Whether smoking influences prostate cancer progression cannot be tested in this study and requires further investigation.

Although smoking prevalence has historically decreased in the last 40 years, it remains a common habit practiced by 21.5% of men in the United States in 2011 (18). It is a leading cause of cancer including bladder, lung, and kidney, yet its relationship with prostate cancer is inconsistent. Although several studies found a positive association between smoking and prostate cancer risk (6, 16, 17), other large studies with extensive follow-up found no association between cigarette smoking and prostate cancer incidence (3–5). Meanwhile, the literature on smoking and mortality has been more consistent. Several studies reported increased prostate cancer-specific mortality with smoking (4, 6, 7, 17–19), even though one observed no association with incidence (4).

A potential explanation for the more consistent mortality data versus incidence data is smokers may be less likely to seek healthcare, leading to delayed diagnosis and/or delayed treatment and increased mortality. Our current findings support this given smokers were less compliant to follow-up and less likely to receive a second on-study biopsy versus never smokers. These findings are consistent with accumulating evidence suggesting smokers in general have lower compliance with cancer screening tests (20). However another possibility is smoking may induce cancers to develop an aggressive phenotype. Indeed, our results support this possibility too in that on first biopsy, smokers were more likely to be diagnosed with high-grade disease. Thus, our findings suggest that more aggressive disease among smokers may result from both delayed diagnosis and smoking being associated with aggressive disease. Indeed, smoking has been biologically linked with carcinogenesis. For example, polycyclic aromatic hydrocarbons (PAHs), products of incomplete combustion present in cigarettes, has prostate-specific carcinogenicity (21). Indeed, one study found smokers are more likely to be diagnosed with late stage or high grade cancer (22). However, it is difficult to distinguish whether delayed diagnosis leading to more advanced disease or the direct effects of smoking are responsible for the increase in prostate cancer-mortality observed in several studies, though our findings suggest that perhaps both factors (delayed diagnosis and fundamentally more aggressive disease) are contributory.

In our current study, all men received protocol-directed biopsies at specific time points. In a setting where potential confounding from delayed diagnosis of prostate cancer in smokers was minimized, we found no association between smoking and diagnosis of overall or low-grade prostate cancer. This is consistent with two large prospective cohort studies which reported that smoking was unrelated to prostate cancer incidence (3, 5). Though both prior studies noted increased rates of prostate cancer-related mortality, neither study could account for possible bias through delayed diagnosis in smokers. However, the Health Professionals Follow-up Study, which also showed no relationship between smoking and prostate cancer incidence, conducted a sub-analysis among men with a negative digital rectal examination in order to reduce potential bias from any difference in screening behavior between smokers and nonsmokers (4). Among these men, there was an even stronger association between smoking and distant metastatic and fatal prostate cancer. If screening biases contributed to the association between smoking and prostate cancer, then attenuation, rather than accentuation, would have been expected in this subgroup. In line with the idea that smoking may preferentially influence aggressive prostate cancer unrelated to screening detection issues, we found in men who all underwent a biopsy that smokers were more likely to have high-grade prostate cancer. These findings suggest that worse prostate cancer mortality among smokers cannot be explained solely by screening differences resulting in a bias in delayed diagnosis but rather reflect a true underlying association between smoking and aggressive prostate cancer. However, it would have been advantageous to evaluate prostate cancer-related mortality or overall mortality in our study to more fully assess these effects, though these data are unavailable.

We also observed that smokers had lower average BMI versus never smokers, consistent with previous studies (16, 23). Recent studies suggested smokers with a higher BMI may be at a reduced risk of several cancers (24, 25). Thus, we stratified subjects by BMI on secondary analysis. Interesting, we found a significant interaction between smoking and BMI for predicting overall prostate cancer ($p=0.003$) and grade ($p=0.002$). Among men with BMI $<25\text{kg/m}^2$, current smokers had an increased risk of low-grade ($p=0.043$) and high-grade prostate cancer diagnosis ($p=0.002$), versus never smokers. However, among men with a higher BMI, both current and former smoking were unrelated to prostate cancer diagnosis or grade. The reason for this observation is unclear. It is possible that in men with lower BMI, who have lower plasma volume (26), carcinogens in cigarettes are present in a higher concentration in the serum. However, this is purely speculative. Of note, a case-only study of men undergoing radical prostatectomy with a mean BMI of 25.7 kg/m^2 in never smokers (versus 27.1 kg/m^2 in the current study) found current but not past smoking was associated with prostate cancer progression (27). This is somewhat consistent with our results of more aggressive disease among normal-weight smokers. Moreover, a recent study in head and neck cancers also found an interaction between BMI and smoking for predicting cancer risk, adding plausibility to our findings (25). However, as this was a secondary analysis, this modification by BMI requires future study to validate and if correct, to understand its biological basis.

Although our follow-up was 4 years, various studies suggested only recent tobacco use influences prostate cancer risk and progression. For example, in a large study of male health professionals in the United States, increased risk of fatal prostate cancer existed only in men

who had smoked in the preceding 10 years (4). Within 10 years after quitting, the excess risk of smokers was eliminated. In two recent studies of men undergoing surgical treatment, former smokers had similar risks of PSA recurrence after surgical treatment compared to nonsmokers, while current smokers experienced increased risk of extraprostatic disease and recurrence (9, 27). Likewise, we found no altered risk of prostate cancer diagnosis in former smokers except for high-grade disease in lean men, though the association was less strong than for current smokers. It is possible that with increased follow-up, baseline surveys assessing smoking status become less accurate due a greater proportion of subjects in the “exposed” group who have ceased smoking as the cohort aged, which would underestimate the effect of smoking (28). Indeed, a large investigation of nearly 250,000 veterans with a 26-year follow-up found an attenuation of prostate cancer-related death risk in smokers from over 200% increased risk at 2.5 years to just an 18% increased risk at 26 years of follow-up (29). This may also explain why pack-years which reflects lifetime smoking were unrelated to high-grade prostate cancer diagnosis in our study. Unfortunately, for former smokers time since quitting was unavailable preventing us from addressing how time since quitting relates to prostate cancer diagnosis. Thus, although smoking status in our study was only assessed at study entry, our relatively short follow-up in combination with protocol-dictated biopsies allowed us to more accurately assess the effect of current smoking on risk of prostate cancer diagnosis while minimizing confounding from smoking cessation.

Our study population was biopsy-negative men, which prevented us from testing the association between smoking and first prostate biopsy. While we did look at cumulative pack-years smoked, data regarding the amount smoked per day, the duration smoked, and the patient age during exposure were unavailable. Additionally, data on other types of tobacco exposure, including cigars, pipes, chewing tobacco, or second-hand smoking, were unavailable. Given the short follow-up, it is likely nearly all prostate cancers detected were prevalent at study initiation. Studies are needed to assess the association between smoking and future prostate cancer risk. Finally, our study only examined the relationship between smoking and prostate cancer diagnosis and did not evaluate other clinically relevant end-points such as metastasis or mortality. These limitations are balanced by the strength of our study’s protocol-dictated biopsies, which allowed us to examine the relationship between smoking and prostate cancer risk while minimizing potential confounding from diagnosis delay.

CONCLUSIONS

Among men with an elevated PSA and negative pre-study biopsy in REDUCE, in which men were instructed to receive biopsies independent of PSA levels, cigarette smoking was related to poor study biopsy compliance. At first on-study biopsy, smoking was unrelated to overall prostate cancer diagnosis or low grade disease. However, current smoking was associated with increased risk of high grade prostate cancer diagnosis in lean men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin.* 2014; 64:9–29. [PubMed: 24399786]
2. Zu K, Giovannucci E. Smoking and aggressive prostate cancer: a review of the epidemiologic evidence. *Cancer Causes & Control.* 2009; 20:1799–1810. [PubMed: 19562492]
3. Rohrmann S, Genkinger JM, Burke A, Helzlsouer KJ, Comstock GW, Alberg AJ, et al. Smoking and risk of fatal prostate cancer in a prospective U.S. study. *Urology.* 2007; 69:721–725. [PubMed: 17445658]
4. Giovannucci E, Rimm EB, Ascherio A, Colditz GA, Spiegelman D, Stampfer MJ, et al. Smoking and risk of total and fatal prostate cancer in United States health professionals. *Cancer Epidemiol Biomarkers Prev.* 1999; 8:277–282. [PubMed: 10207628]
5. Lotufo PA, Lee IM, Ajani UA, Hennekens CH, Manson JE. Cigarette smoking and risk of prostate cancer in the physicians' health study (United States). *International Journal of Cancer.* 2000; 87:141–144.
6. Huncharek M, Haddock KS, Reid R, Kupelnick B. Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. *American Journal of Public Health.* 2010; 100:693–701. [PubMed: 19608952]
7. Gong Z, Agalliu I, Lin DW, Stanford JL, Kristal AR. Cigarette smoking and prostate cancer-specific mortality following diagnosis in middle-aged men. *Cancer Causes & Control.* 2008; 19:25–31. [PubMed: 17906959]
8. Rohrmann S, Linseisen J, Allen N, Bueno-de-Mesquita HB, Johnsen NF, Tjonneland A, et al. Smoking and the risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *British Journal of Cancer.* 2013; 108:708–714. [PubMed: 23169298]
9. Moreira DM, Antonelli JA, Presti JC Jr, Aronson WJ, Terris MK, Kane CJ, et al. Association of cigarette smoking with interval to biochemical recurrence after radical prostatectomy: results from the SEARCH database. *Urology.* 2010; 76:1218–1223. [PubMed: 20381838]
10. Roberts WW, Platz EA, Walsh PC. Association of cigarette smoking with extraprostatic prostate cancer in young men. *J Urol.* 2003; 169:512–516. [PubMed: 12544299]
11. Pantarotto J, Malone S, Dahrouge S, Gallant V, Eapen L. Smoking is associated with worse outcomes in patients with prostate cancer treated by radical radiotherapy. *BJU International.* 2007; 99:564–569. [PubMed: 17166241]
12. Pickles T, Liu M, Berthelet E, Kim-Sing C, Kwan W, Tyldesley S. The effect of smoking on outcome following external radiation for localized prostate cancer. *The Journal of Urology.* 2004; 171:1543–1546. [PubMed: 15017216]
13. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med.* 2010; 362:1192–1202. [PubMed: 20357281]
14. Freedland SJ, Hamilton RJ, Gerber L, Banez LL, Moreira DM, Andriole GL, et al. Statin use and risk of prostate cancer and high-grade prostate cancer: results from the REDUCE study. *Prostate Cancer Prostatic Dis.* 2013; 16:254–259. [PubMed: 23567655]
15. Keating NL, Liu PH, O'Malley AJ, Freedland SJ, Smith MR. Androgen-deprivation Therapy and Diabetes Control Among Diabetic Men with Prostate Cancer. *Eur Urol.* 2014; 65:816–824. [PubMed: 23453420]
16. Cerhan JR, Torner JC, Lynch CF, Rubenstein LM, Lemke JH, Cohen MB, et al. Association of smoking, body mass, and physical activity with risk of prostate cancer in the Iowa 65+ Rural Health Study (United States). *Cancer Causes & Control.* 1997; 8:229–238. [PubMed: 9134247]

17. Coughlin SS, Neaton JD, Sengupta A. Cigarette smoking as a predictor of death from prostate cancer in 348,874 men screened for the Multiple Risk Factor Intervention Trial. *American Journal of Epidemiology*. 1996; 143:1002–1006. [PubMed: 8629606]
18. Moreira DM, Aronson WJ, Terris MK, Kane CJ, Amling CL, Cooperberg MR, et al. Cigarette smoking is associated with an increased risk of biochemical disease recurrence, metastasis, castration-resistant prostate cancer, and mortality after radical prostatectomy: results from the SEARCH database. *Cancer*. 2014; 120:197–204. [PubMed: 24127391]
19. Moreira DM, Antonelli JA, Presti JC Jr, Aronson WJ, Terris MK, Kane CJ, et al. Association of Cigarette Smoking With Interval to Biochemical Recurrence After Radical Prostatectomy: Results from the SEARCH Database. *Urology*. 2010; 76:1218–1223. [PubMed: 20381838]
20. Byrne MM, Davila EP, Zhao W, Parker D, Hooper MW, Caban-Martinez A, et al. Cancer screening behaviors among smokers and non-smokers. *Cancer Epidemiology*. 2010; 34:611–617. [PubMed: 20655820]
21. Chen TT, Heidelberger C. Quantitative studies on the malignant transformation of mouse prostate cells by carcinogenic hydrocarbons in vitro. *International Journal of Cancer*. 1969; 4:166–178.
22. Daniell HW. A worse prognosis for smokers with prostate cancer. *The Journal of Urology*. 1995; 154:153–157. [PubMed: 7776411]
23. Albanes D, Jones DY, Micozzi MS, Mattson ME. Associations between smoking and body weight in the US population: analysis of NHANES II. *American Journal of Public Health*. 1987; 77:439–444. [PubMed: 3493709]
24. Smith L, Brinton LA, Spitz MR, Lam TK, Park Y, Hollenbeck AR, et al. Body mass index and risk of lung cancer among never, former, and current smokers. *J Natl Cancer Inst*. 2012; 104:778–789. [PubMed: 22457475]
25. Petrick JL, Gaudet MM, Weissler MC, Funkhouser WK, Olshan AF. Body mass index and risk of head and neck cancer by race: the Carolina Head and Neck Cancer Epidemiology Study. *Ann Epidemiol*. 2014; 24:160–164. [PubMed: 24342030]
26. Banez LL, Hamilton RJ, Partin AW, Vollmer RT, Sun L, Rodriguez C, et al. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. *JAMA*. 2007; 298:2275–2280. [PubMed: 18029831]
27. Joshi CE, Mondul AM, Meinhold CL, Humphreys EB, Han M, Walsh PC, et al. Cigarette smoking and prostate cancer recurrence after prostatectomy. *Journal of the National Cancer Institute*. 2011; 103:835–838. [PubMed: 21498781]
28. Hymowitz N, Cummings KM, Hyland A, Lynn WR, Pechacek TF, Hartwell TD. Predictors of smoking cessation in a cohort of adult smokers followed for five years. *Tobacco control*. 1997; 6(Suppl 2):S57–S62. [PubMed: 9583654]
29. Hsing AW, McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF Jr. Tobacco use and prostate cancer: 26-year follow-up of US veterans. *American Journal of Epidemiology*. 1991; 133:437–441. [PubMed: 2000853]

TRANSLATIONAL RELEVANCE

These data suggest that smokers may be less likely to follow-up regarding recommendations for prostate cancer screening. However, when these are accounted for and all men undergo biopsy, we found that smoking was not a risk factor for future diagnosis of prostate cancer however it was related to diagnosis of high-grade disease. These data support the conclusion that smoking may be related to more aggressive prostate cancer, but this may in part be obscured by less screening among smokers.

Table 1

Baseline Characteristics

Variable	Never Smokers	Former Smokers	Current Smokers	P value*
Total patients (%)	2937 (46)	2554 (40)	929 (14)	
Age at study entry				0.0001
Mean (SD)	62.7 (6.0)	63.2 (6.1)	61.7 (5.8)	
Median (IQR)	63 (58–67)	63 (59–68)	62 (57–66)	
Ethnic group (%)				0.599 [†]
White	2690 (92)	2351 (92)	846 (91)	
Black	60 (2)	39 (2)	20 (2)	
Other	187 (6)	164 (6)	63 (7)	
Geographic region (%)				<0.001
US/Canada	675 (23)	698 (27)	180 (19)	
Europe	1772 (60)	1376 (54)	575 (62)	
Other	490 (17)	480 (19)	174 (19)	
Body mass index				0.0001
Mean (SD)	27.1 (3.6)	27.8 (3.8)	26.9 (3.9)	
Median (IQR)	26.4 (24.7–29.1)	27.3 (25.1–29.8)	26.4 (24.4–28.8)	
Suspicious DRE (%)	110 (4)	91 (4)	40 (4)	0.594 [†]
Prostate volume, median (IQR)	43.7 (33.1–56.0)	43.8 (33.9–56.9)	41.3 (31.7–56.2)	0.0041
Median PSA (IQR)	5.7 (4.4–7.3)	5.7 (4.4–7.3)	5.7 (4.3–7.4)	0.937
Biopsy Gleason score (%)				0.453 [†]
2–6	473 (71)	405 (69)	130 (66)	
3+4	141 (21)	120 (21)	51 (30)	
4+3	54 (8)	57 (10)	16 (8)	
Pack-Years, median (IQR)	0	18 (8–30)	25 (13–40)	0.0001
Treatment Arm (%)				0.612
Placebo	1475 (50)	1310 (51)	481 (52)	
Dutasteride	1462 (50)	1244 (49)	448 (48)	

Abbreviations: PSA (prostate specific antigen), SD (standard deviation), IQR (interquartile range)

* P value by Kruskal-Wallis, except where noted.

[†] P value by χ^2

Table 2
Association between smoking and prostate cancer risk or disease grade vs. non-smokers on first on-study biopsy

Variable	Never Smokers		Former Smokers		Current Smokers	
	OR	95% CI	OR	P-value	OR	P-value
Overall prostate cancer risk						
No. with cancer/total	417/2,937	382/2,554			142/929	
Univariable	Referent	1.06 0.91–1.24	1.06	0.43	1.09 0.89–1.34	0.41
Multivariable*	Referent	1.06 0.91–1.23	1.06	0.46	1.10 0.89–1.36	0.36
Disease grade, low grade						
No. with cancer/total**	295/2,815	253/2,425			87/874	
Univariable	Referent	1.00 0.83–1.19	1.00	0.96	0.94 0.73–1.22	0.66
Multivariable*	Referent	1.00 0.83–1.19	1.00	0.99	0.96 0.74–1.24	0.75
Disease grade, high grade						
No. with cancer/total***	122/2,642	129/2,301			55/842	
Univariable	Referent	1.23 0.95–1.58	1.23	0.12	1.44 1.04–2.00	0.028
Multivariable*	Referent	1.21 0.94–1.57	1.21	0.14	1.45 1.04–2.04	0.028

OR, odds ratio
CI, confidence interval

* Adjusted for age, race, geographic region, prostate specific antigen levels, prostate volume, digital rectal examination findings, body mass index, and treatment arm.

** Numbers reflect men included in the analysis: those with low-grade disease and those without cancer

*** Numbers reflect men included in the analysis: those with high-grade disease and those without cancer

Table 3
Smoking and disease grade as stratified by BMI category on first on-study biopsy

	Never Smokers			Former Smokers			Current Smokers			
	No. cancer/total**	OR	No. cancer/total**	OR*	95% CI	P-value	No. cancer/total**	OR*	95% CI	P-value
BMI										
<25.0	77/800	Referent	67/562	1.23	0.87–1.76	0.24	39/284	1.54	1.01–2.34	0.043
High Grade	29/752	Referent	37/532	1.81	1.09–3.01	0.022	25/270	2.45	1.39–4.32	0.002
25	169/1,507	Referent	186/1,863	0.91	0.74–1.12	0.39	48/590	0.75	0.54–1.04	0.085
High Grade	66/1,404	Referent	92/1,769	1.06	0.79–1.43	0.69	30/572	1.12	0.73–1.73	0.60

* Adjusted for age, race, treatment arm, PSA, prostate volume, DRE findings, and geographic region.

** Numbers reflect men included in the analysis: for the low-grade analysis this includes men with low-grade disease and those without cancer while for the high-grade analysis this includes men with high-grade disease and those without cancer

P-interaction<0.03 for current smoking and p-interaction<0.13 for former smoking