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Authors

Zapata, DF
Howard, LE
Aronson, WJ
[et al.](#)

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Original Article: Clinical Investigation**Smoking is a predictor of adverse pathological features at radical prostatectomy: Results from the Shared Equal Access Regional Cancer Hospital database**

Daniel F Zapata,¹ Lauren E Howard,^{1,2} William J Aronson,³ Christopher J Kane,⁴ Martha K Terris,⁵ Christopher L Amling,⁶ Matthew R Cooperberg⁷ and Stephen J Freedland^{1,2}

¹Duke University Medical Center, Durham, ²Durham Veterans Affairs Medical Center, Durham, North Carolina, ³University of California, Los Angeles School of Medicine, Los Angeles, ⁴University of California, San Diego, ⁷University of California San Francisco, San Francisco, California, USA, ⁵Medical College of Georgia, Georgia Regents University, Augusta, Georgia, and ⁶Oregon Health and Sciences University, Portland, Oregon, USA

Abbreviations & Acronyms

BMI = body mass index
ECE = extracapsular extension
PC = prostate cancer
PSA = prostate-specific antigen
Q1 = 25th percentile
Q3 = 75th percentile
RP = radical prostatectomy
SEARCH = Shared Equal Access Regional Cancer Hospital
SVI = seminal vesicle invasion
TV = tumor volume
VA = Veterans Affairs

Correspondence: Stephen J Freedland M.D., Cedars Sinai Medical Center, 8635 West 3rd Street, Suite 1070W, Los Angeles, CA 90048, USA. Email: stephen.freedland@cshs.org

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Objective: To test the relationship of smoking and aggressive prostate cancer in men undergoing radical prostatectomy.

Methods: A retrospective analysis of 2290 men who underwent radical prostatectomy from the Shared Equal Access Regional Cancer Hospital database from 2000 to 2013 was carried out. There were 1592 (70%) non-smokers and 698 (30%) smokers at radical prostatectomy. Logistic regression was used to examine whether smoking predicted Gleason score ($\geq 4+3$), margin status, extracapsular extension or seminal vesicle invasion. Linear regression was used to test the relationship between smoking and tumor volume.

Results: Smokers were younger, more likely to be black, had lower body mass index, higher pathological Gleason score, more positive margins and extracapsular extension (all $P < 0.05$) versus non-smokers. On crude analysis, smoking was associated with positive margins (odds ratio 1.32; $P = 0.003$) and extracapsular extension (odds ratio 1.26; $P = 0.036$). After adjusting for multiple clinical factors, smoking remained associated with a 19–35% increased risk of every adverse feature studied, though only the association with extracapsular extension reached significance. On multivariable analysis, a trend for smokers to have larger tumor volumes (geometric mean 5.8 vs 5.3 g; $P = 0.062$) was found.

Conclusions: In patients undergoing radical prostatectomy, there seems to be a trend for smokers to have worse pathological features compared with non-/former smokers. If confirmed in future studies, smoking should be considered a modifiable risk factor for aggressive prostate cancer.

Key words: pathology, prostatectomy, prostatic neoplasms, risk, smoking.

Introduction

PC is the second most frequently diagnosed cancer and the sixth leading cause of cancer deaths in men worldwide.¹ In the USA, PC accounts for almost 25% of all new diagnosed malignancies in men and for approximately 28 000 deaths per year.² Cigarette smoking is the leading cause of preventable morbidity and mortality, and the leading cause of cancer-related mortality in the USA.³ While traditionally, PC has not been thought of as a smoking-related cancer, newer research suggests that on a population level there might be a link between smoking and aggressive PC including worse prognosis and higher PC-specific mortality^{4–9} regardless of treatment type. To what degree this is attributable to treatment bias (i.e. smokers receiving less aggressive treatment because of concerns about comorbidities leading to undertreatment) versus biologically more aggressive disease is unclear. For example, when examining patients who are all treated equally with a single modality (i.e. radiation or surgery), some studies found smokers had worse outcomes,^{10–15} whereas other studies found no association.^{16–19} We previously examined the relationship between smoking and outcomes in a surgical cohort, and found smokers were at increased risk of metastatic disease.¹⁴ However, in our prior study, the number of men with metastases was small ($n = 26$), and median follow up was limited (6 years). Based on this, we hypothesize that smoking is inherently related to more aggressive PC. Herein, we sought to test this hypothesis using intermediate end-points that are known to correlate with aggressive PC including TV, grade and stage to overcome the limitations of our prior study, and to further support our

findings. Furthermore, as much has changed in PC diagnosis and treatment over the past ≥ 20 years, we focused on more recently-treated patients to better understand the contemporary association between smoking and disease aggressiveness.

Methods

Study population

After obtaining institutional review board approval, data from patients who underwent RP at six VA medical centers (West Los Angeles, Palo Alto and San Diego, CA; Augusta, GA; Asheville and Durham, NC) were collected to form the SEARCH database.²⁰ Of note, smoking data are not currently available for the San Diego VA Medical Center in SEARCH and thus, this center was excluded. Patients treated with neoadjuvant hormonal or radiation therapy were excluded. The database includes information on age at surgery, race, BMI, smoking status, clinical stage, biopsy Gleason score, preoperative PSA, surgical specimen pathology (specimen weight, Gleason score, ECE, surgical margin status, lymph node and SVI). We obtained data on cigarette smoking status at surgery (yes/no/former) from review of preoperative surgical and anesthesia notes. As the electronic medical records were sparse before 2000, we only examined men treated in the year 2000 or later. TV was calculated by multiplying specimen weight by percent of cancer in the RP specimen (data taken from the pathology reports – slides were not re-reviewed) and dividing by 100.

Of 2745 patients in SEARCH treated from 2000 onwards (not including the San Diego VA), we excluded patients who had missing information on smoking history ($n=243$), pathological features ($n=51$), pathological Gleason score ($n=8$), race (1), BMI ($n=67$), preoperative PSA ($n=4$), biopsy Gleason score ($n=14$) or clinical stage ($n=67$). This resulted in a study population of 2290 participants. A subset of 1317 patients had information available to calculate TV.

Statistical analysis

Among men who were not smokers at the time of RP, we found no difference in the risk for any pathological feature between never-smokers and former-smokers (data not shown). Therefore, we combined these two categories into one.

We compared demographic, clinical and pathological characteristics between smokers and non-/former smokers at the time of RP. Associations were tested using the *t*-test for continuous, normally distributed variables, the Wilcoxon rank-sum test for continuous, non-normally distributed variables and the χ^2 -test for categorical variables.

We then carried out crude and adjusted multivariable logistic regression analyses to test smoking as an independent predictor for each adverse pathological feature: pathological Gleason score (7–10 vs 2–6), positive margins, SVI and ECE. We could not examine lymph nodes as an outcome because of small numbers ($n=21$). Crude and adjusted linear regression was used to assess the relationship between smoking and TV (log-transformed) in the subset of men with available data. Predicted geometric mean of TV was calculated by exponentiating the predicted mean for each smoking status from crude and

adjusted models. Because of the non-linear nature of the TV data, we reported back transformed predicted geometric mean \pm standard error to represent the distribution of each group. All multivariable models were adjusted for age (continuous), year of surgery, race (white, black, other), center of surgery, BMI (continuous; log-transformed), clinical stage (T1 vs T2/T3), PSA (continuous; log-transformed) and biopsy Gleason score (2–6, 3+4, 4+3–10; not included in analysis of pathological Gleason score). We explored whether smoking pack years was associated with pathological Gleason score (7–10 vs 2–6), positive margins, SVI, ECE and TV using identical methods as aforementioned. Pack years was treated as a continuous variable, but modeled as per 10 pack years. Men who never smoked were considered to have 0 pack years and were included in all analyses using pack years.

To explore whether differences in race explained our results, we tested for an interaction between race (black vs non-black) and smoking for all outcomes examined by including a cross-product term in the multivariable model.

Statistical analyses were carried out using Stata 11.2 (StataCorp, College Station, TX, USA). *P*-values < 0.05 were considered statistically significant.

Results

Table 1 describes patient demographics, and clinical and pathological characteristics. Of 2290 men in our cohort, 698 (30%) reported smoking at the time of RP, whereas 1592 (70%) did not. Overall, smokers were younger (59.5 vs 61.9 years; $P < 0.01$), had greater median pack years (35 vs 25 years; $P < 0.01$), had lower BMI (26.9 vs 28.5 kg/m²; $P < 0.01$), were more likely to be black (49 vs 37%; $P < 0.01$), had less recent surgery (2006 vs 2007; $P < 0.01$), more positive margins (46 vs 39%, $P < 0.01$) and more ECE (22 vs 18%; $P = 0.04$) versus non-/former smokers. Although not statistically significant, a trend towards more SVI (10 vs 8%; $P = 0.07$) and higher PSA values (6.3 vs 6.1; $P = 0.07$) was noted among smokers.

On crude analyses, smoking was significantly associated with positive margins (OR 1.32; $P = 0.003$) and ECE (OR 1.26; $P = 0.036$; Table 2). After adjusting for multiple clinical demographic characteristics, while smoking remained positively associated with higher pathological Gleason (OR 1.25; $P = 0.061$), positive margins (OR 1.19; $P = 0.09$), ECE (OR 1.33; $P = 0.024$) and SVI (OR 1.35; $P = 0.093$), only the association between smoking and ECE was significant.

Overall, 1880 (82%) patients had data on the number of pack years smoked. On crude analysis, pack years smoked was associated with increased odds of all adverse pathological features, though only the associations with positive margins (OR 1.05; $P = 0.014$) and ECE (OR 1.05; $P = 0.023$) were significant. On adjusted analysis, more pack years smoked remained associated with increased odds of all adverse features, but only the associations with pathological Gleason (OR 1.07; $P = 0.01$) and positive margins (OR 1.08; $P = 0.001$) were significant (Table 3).

Tumor volume

TV data were available for 1317 patients (58%). Men with and without TV data available overall had similar demographic,

Table 1 Demographic, clinical and pathological characteristics of patients by smoking status at RP

	Non-smokers/ former smokers (n = 1592) 70%	Smokers (n = 698) 30%	P-value
Mean age (years)	61.9 ± 5.9	59.5 ± 5.8	<0.01*
Median pack-years (Q1–Q3)†	25 (12–40)	35 (20–50)	<0.01**
Median BMI (Q1–Q3)	28.5 (26.0–31.9)	26.9 (23.7–29.6)	<0.01**
Race, n (%)			
White	899 (57)	331 (48)	<0.01
Black	595 (37)	344 (49)	
Other	98 (6)	26 (3)	
Median PSA (Q1–Q3)	6.1 (4.6–8.7)	6.3 (4.7–9.7)	0.07**
Median year of surgery (Q1–Q3)	2007 (2004–2010)	2006 (2003–2009)	<0.01**
Clinical stage, n (%)			
T1	1068 (71)	460 (70)	0.58***
T2/T3	524 (29)	238 (30)	
Biopsy Gleason, n (%)			
2–6	745 (47)	336 (48)	
3 + 4	434 (27)	198 (28)	0.46***
≥4 + 3	413 (26)	164 (24)	
Pathological Gleason, n (%)			
2–6	506 (32)	202 (29)	
3 + 4	588 (37)	298 (43)	0.03***
≥4 + 3	498 (31)	198 (28)	
Positive margins, n (%)	620 (39)	319 (46)	<0.01***
Seminal vesicle invasion, n (%)	129 (8)	73 (10)	0.07***
Extracapsular extension, n (%)	289 (18)	153 (22)	0.04***
Positive lymph nodes, n (%)	31 (2)	15 (2)	0.84***

P-values calculated by *t-test, **Wilcoxon rank-sum test, or *** χ^2 -test. †For patients with data available.

Table 2 Crude and adjusted odds ratios for smoking predicting pathological features

	OR	95% CI	P-value
Pathological Gleason			
Crude	1.14	0.94–1.39	0.175
Adjusted†	1.24	0.99–1.55	0.061
Positive margins			
Crude	1.32	1.10–1.58	0.003
Adjusted‡	1.19	0.97–1.45	0.090
Extracapsular extension			
Crude	1.26	1.02–1.58	0.036
Adjusted‡	1.33	1.04–1.72	0.024
Seminal vesicle invasion			
Crude	1.32	0.98–1.79	0.068
Adjusted‡	1.35	0.95–1.90	0.093

†Adjusted for age, year, race, surgical center, BMI, clinical stage and PSA. ‡Adjusted for age, year, race, surgical center, BMI, clinical stage, PSA and biopsy Gleason score.

Table 3 Crude and adjusted odds ratios for smoking pack years predicting pathological features

	OR§	95% CI	P-value
Pathological Gleason			
Crude	1.02	0.98–1.06	0.270
Adjusted†	1.07	1.02–1.13	0.008
Positive margins			
Crude	1.05	1.01–1.08	0.014
Adjusted‡	1.08	1.03–1.13	0.001
Extracapsular extension			
Crude	1.05	1.01–1.10	0.023
Adjusted‡	1.03	0.97–1.08	0.335
Seminal vesicle invasion			
Crude	1.06	0.99–1.12	0.055
Adjusted‡	1.06	0.99–1.14	0.092

†Adjusted for age, year, race, surgical center, BMI, clinical stage and PSA. ‡Adjusted for age, year, race, surgical center, BMI, clinical stage, PSA and biopsy Gleason score. §Odds ratios are for every 10 pack years.

clinical and pathological characteristics. However, men with TV were older and more likely to have more recent surgery (both $P < 0.01$). Consistent with a more contemporary cohort, men with TV data were more likely to have Gleason 3 + 4 disease, more Gleason 4 + 3 – 10 disease and were more likely to have not had a lymph node dissection carried out, though these differences were slight (Table S1; all $P < 0.05$).

Within this subset, and analogous to the whole cohort, smokers were younger, more likely to be black, had a lower BMI and had a less recent year of surgery (all $P < 0.01$; Table S2). Similarly, smokers had more Gleason 3 + 4 disease (49 vs 42%; $P = 0.03$) and more positive margins (47 vs 38%; $P < 0.01$) than non-/former smokers. On crude analysis, we found no difference in TV between smokers and non-/former smokers (mean 5.3 vs 5.6 g, respectively; $P = 0.43$; Table 4). However, after adjusting for clinical and demographic differences, there was a trend for smokers to have greater TV than non-/former smokers (geometric mean 5.8 vs 5.3 g; $P = 0.062$). There was a significant association between pack years smoked and TV on crude analysis ($P = 0.002$), but after adjusting for patient characteristics the association was no longer significant ($P = 0.397$; data not shown).

Finally, because smokers were more likely to be black, and given the well-established association between black race and more aggressive disease,²¹ we were concerned that the present results could have been influenced by this. Though we

Table 4 Crude and adjusted geometric mean TV by smoking status

Mean TV (g)	Non-smokers (n = 919)	Smokers (n = 398)	P-value*
Crude	5.6 (4.6–6.6)	5.3 (4.3–6.4)	0.43
Adjusted†	5.3 (4.3–6.3)	5.8 (4.8–6.9)	0.06

*P-value from linear regression model of smoking predicting log-TV. †Predicted TV from linear regression model adjusted for age, year, surgical center, BMI, clinical stage, PSA and biopsy Gleason score.

controlled for race in all analyses, as an exploratory analysis, we stratified our patients by race into black and non-black, and tested whether our results differed by race. Importantly, we found no statistically significant interaction between race and smoking for predicting any pathological feature or TV (all P -interactions >0.25 ; data not shown).

Discussion

Cigarette smoking has been traditionally implicated with an increased incidence of several cancers (lung, kidney, bladder etc.), but the association with PC remains controversial. Lotufo *et al.* showed no increased risk for PC incidence or mortality among smokers.²² On the contrary, new research on a population level suggests an association between smoking and an increased risk for aggressive disease and PC-specific mortality.^{4,5,9} It is unclear whether this is as a result of less aggressive treatment from concerns about patient comorbidities or from inherently more aggressive disease. For instance, among men treated equally with a single primary therapy (either radiation or surgery), some studies suggest smokers have worse outcomes,^{10–15} whereas other studies found no link between smoking and outcomes.^{16–19} We previously addressed this issue in a surgical cohort and found that smokers were at increased risk for metastatic disease versus non-smokers; however, the number of men with metastases was small and follow up was short.¹⁴ To address this controversy and to support our previous study by overcoming some of its limitations, we sought to analyze the association between smoking and adverse pathological features as an alternative measure for aggressive disease in patients undergoing RP. Also, we used a more contemporary cohort, as diagnostic and therapeutic strategies in PC have evolved over time.

In our cohort, we found the overall prevalence of active smokers to be approximately one-third, compared to the near one-quarter in the general population.²³ This is likely explained by the higher prevalence of smoking among veterans.²⁴ We also found that smokers were younger than non-smokers, which is supported by previous population-based studies that showed that the prevalence of smoking is indirectly related to age.²⁵ Furthermore, smokers had lower BMI at surgery. This is also consistent with population-level data that shows that smokers have lower BMI.^{25,26} Collectively, the present findings suggest that though we studied men in the VA system, smokers in our study had similar characteristics to smokers in the general population.

We found smoking was positively correlated with some adverse pathological findings at the time of surgery on univariable analysis. For example, smokers were significantly more likely to have ECE and more positive margins. Also, while not significant, the direction of the association was between smoking and increased odds of the other adverse features studied (Gleason score and SVI). Furthermore, although after adjustment for multiple clinical features smoking was only significantly related to ECE, smoking remained suggestively linked with every adverse finding studied. Specifically, even after adjustment, smokers were 19–35% more likely to have adverse pathology. The fact that all adverse features were suggestively linked with smoking argues against the possibility of a chance finding.

Rather, this suggests that the present study might have been underpowered to detect the modest associations between smoking and aggressive PC. Furthermore, we found a trend for smokers to have greater TV (5.8 vs 5.3 g), though the difference in TV may not be clinically significant. Finally, we found that on multivariable analysis, more pack years smoked was significantly linked with pathological Gleason score 7–10 and positive margins, providing further support for the hypothesis that smoking is related to more aggressive PC.

A few studies analyzed the association between smoking and pathological outcomes after RP. Consistent with the present results, Ngo *et al.* using a smaller ($n = 630$) and less contemporary cohort (80% treated before 2000), showed that smokers had an increased risk for worse pathological outcomes versus non-smokers.¹³ Also, Roberts *et al.* in a cohort of 352 men aged younger than 55 years, found that smokers had more extraprostatic disease and higher Gleason scores at the time of surgery, though the prevalence of active smoking was just 5%.¹² On the contrary, Oh *et al.* found no association between smoking and adverse pathological findings at surgery, although among men with a BMI greater than 25, smoking was a predictor for biochemical recurrence-free survival and higher Gleason scores on multivariable analysis.¹⁹ In summary, though the associations did not always reach statistical significance, the preponderance of the data point to a link between smoking at the time of RP and higher risk of adverse pathological features. This is consistent with our previous results of increased risk for metastatic disease among smokers undergoing RP¹⁴ and together suggests smoking might be linked to more aggressive PC.

The mechanism for the link between smoking and aggressive PC is not yet understood, but there are biological, genetic and lifestyle factors that could explain why smokers could have worse outcomes when compared with non-smokers. Carcinogens, such as nitrosamines, acetaldehyde and heterocyclic amines, found in cigarettes might induce a higher cell turnover leading to a higher mutation rate in regulatory genes.²⁷ Also, smoking impacts body immune response, diminishing T-cell and natural killer cell activation,²⁸ which are key cells in the immune response against malignancy. Finally, an unhealthy lifestyle associated with smoking, such as increased alcohol consumption and a decreased exercise pattern, could help explain why smokers have more aggressive disease.²⁹

The present study had some limitations. Being a retrospective analysis from a veteran-only population with a greater incidence of smoking it is unclear whether our study is applicable to other types of populations. Other types of smoking, such as cigars or pipes, and other forms of tobacco exposure, such as second-hand smoking or tobacco chewing, were not evaluated, because these data were not available. Furthermore, data on the duration of smoking, cigarettes per day smoked or Brinkman index were not available for analysis. However, data on pack-years were available for over 80% of men, and we did find a suggestion of a dose response with more pack-years being associated with more adverse features. It is possible that smokers, because of their comorbidities, were screened less aggressively for early detection of PC. This would lead to delayed detection among smokers, which could account for the worse outcomes noted in the present study. Indeed, our smokers had higher

PSA values at the time of surgery. However, one could also argue that because of their more frequent contact with healthcare providers, smokers had a greater opportunity for screening. To support this, we found smokers were younger at the time of surgery and clinical stages were similar. To account for these possibilities, we controlled for PSA and stage at diagnosis, and though our results were slightly attenuated, smoking remained suggestively correlated with all adverse features including larger TV. As such, we conclude that any relationship between smoking and screening bias is unlikely to have influenced our results. Furthermore, all men in our cohort underwent RP as primary treatment. As such, there is a possibility that sicker smokers with low-risk disease received other treatment modalities, such as radiation therapy or active surveillance. Thus, this could limit the generalizability of the present results. Finally, as smoking pack year data were not available for all men, it is possible that this created a bias. However, the number of men missing pack year data was modest (18%) and the findings of this subanalysis were similar to the conclusions of the primary analysis (i.e. smoking was linked to adverse pathology and more smoking was worse than less smoking), lending credence to the conclusions of this subanalysis. Although further research is required to confirm our observations, if confirmed, smoking should be included into risk assessment models for aggressive PC.

In conclusion, among patients undergoing RP from the SEARCH database, we found a suggested association between smoking and worse pathological outcomes and greater TVs compared with non-/former smokers, though not all of these associations reached statistical significance. If future studies confirm a significant association between smoking and adverse pathology, smoking should be considered a modifiable risk factor for aggressive PC.

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Demographic, clinical, and pathological differences of men with and without TV data.

Table S2 Demographic, clinical, and pathological characteristics of patients with tumor volume by smoking status at RP.