



## Original article

# Smoking history, intensity, and duration and risk of prostate cancer recurrence among men with prostate cancer who received definitive treatment



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## ABSTRACT

**Purpose:** To examine the association of smoking history and multiple measures of smoking intensity and duration with risk of biochemical recurrence in men treated for prostate cancer.

**Methods:** We conducted a prospective cohort study of 1641 men (773 ever-smokers) treated with radical prostatectomy or radiation between 2003 and 2010. The association between ever-smoking and risk of biochemical recurrence was examined using Cox Proportional Hazards models with adjustment for confounders. Among ever-smokers, we further assessed the association between multiple measures of smoking duration and intensity and risk of biochemical recurrence.

**Results:** In the full cohort, we observed no association between ever-smoking and risk of biochemical recurrence. However, among ever-smokers, a smoking duration of greater than or equal to 10 years was significantly associated with biochemical recurrence (hazard ratio: 2.32, 95% confidence interval: 1.01, 5.33). Our results also suggested that greater than or equal to 10 pack-years of smoking may be associated with an increased risk of biochemical recurrence (hazard ratio: 1.75, 95% confidence interval: 0.97, 3.15). No association was observed between packs smoked per day or years since smoking cessation (among former smokers) and risk of biochemical recurrence.

**Conclusion:** Smoking duration is a significant predictor of biochemical recurrence among men with prostate cancer who are current or former smokers.

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## Introduction

Prostate cancer is the most common incident cancer among men in the United States [1]. In 2018, an estimated 164,690 men were diagnosed with prostate cancer [1]. Twenty to thirty percent of these men will experience biochemical recurrence, an important indicator of prostate cancer progression, within 10 years of treatment [2–4]. However, the strongest established predictors for biochemical recurrence are nonmodifiable risk factors such prostate-specific antigen (PSA) levels, Gleason score, surgical margins, seminal vesicle invasion, and extracapsular disease after definitive treatment [5–7]. More recent evidence has suggested that smoking, a potentially

modifiable factor, is a risk factor for both prostate cancer incidence and mortality [8–10]. Smoking can potentially promote adverse prostate cancer outcomes through multiple mechanisms, including inflammation, exposure to carcinogens, hormonal changes, increased tumor angiogenesis, and genetic mutations [8,11].

However, the evidence regarding the association of smoking status and biochemical recurrence is inconclusive, with some studies suggesting that smoking is positively associated with biochemical recurrence [12–17]; and others reporting no evidence of an association [18–21]. Nonetheless, a 2018 meta-analysis found that both current smoking (pooled hazard ratio [HR]: 1.40, 95% confidence interval [CI]: 1.18, 1.66) and former smoking (pooled HR: 1.19, 95% CI: 1.09, 1.30) were significantly associated with biochemical recurrence [22]. However, there was significant heterogeneity in the included studies of current smokers, with five of ten included studies not reporting a statistically significant association between current smoking and biochemical recurrence. While among the included studies of former smokers, five of the seven studies did not report a

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statistically significant association [22]. These findings suggest that individual studies may not have a large enough sample size or be adequately powered to detect a significant difference. Other studies have also suggested that the association of smoking with biochemical recurrence is stronger in obese men with a weaker or lack of association observed in normal weight men [18,19,23].

Few of these studies have examined detailed smoking exposure histories with measures of smoking duration, smoking intensity, pack-years smoked, or years since smoking cessation [12–15,17]. These studies have been similarly inconclusive, with most of these studies reporting no association between smoking duration, smoking intensity, or pack-years smoked [12,14,15]. However, two studies have suggested that greater pack-years of smoking exposure is associated with an increased risk of biochemical recurrence [13,17]. In addition, there is some limited evidence that smoking cessation before or at prostate cancer diagnosis may reduce the risk of biochemical recurrence [12,17].

In our study, we examined smoking exposure as a risk factor for biochemical recurrence among a cohort of men that received definitive treatment for prostate cancer. We examine smoking as a risk factor in the overall cohort as well as multiple measures of smoking intensity and duration specifically among former and current smokers. Because we evaluate multiple measures of smoking including duration (years smoked), packs smoked per day, pack-years smoked, and years since smoking cessation (among former smokers), we were able to assess which measure of smoking exposure is most predictive of adverse prostate cancer outcomes. This study adds to the limited and conflicting evidence on smoking history, duration, and intensity and risk of biochemical recurrence.

## Methods

### *Study population and data collection*

The study population consisted of men who enrolled in the Washington University Prostate Cancer Prospective Cohort (PCPC) study. The study enrolled men who were diagnosed with biopsy-confirmed prostate cancer at the Washington University in St. Louis School of Medicine between 2003 and 2010. Recruitment occurred at time of diagnosis and before treatment. Clinical characteristics of the prostate cancer, treatment, and follow-up visits were determined by medical records. Medical record abstraction occurred biannually. If men received follow-up care from outside Washington University, they were contacted by phone, and medical records were obtained from the current provider. Medical record follow-up was 98% complete by the end of the study on December 31st, 2012. On enrollment, participants also completed a mail-in survey. The survey collected information on sociodemographic characteristics, smoking history, and general health. Informed consent was obtained at time of study enrollment, and the study was approved by the institutional review board at the Washington University School of Medicine.

The PCPC enrolled 1938 participants (51.3% were former or current smokers). To be eligible for the current analyses, participants had to receive definitive prostate cancer treatment (radical prostatectomy or radiation) and identify as non-Hispanic ( $n = 1884$ ). We excluded Hispanic men as there were only five Hispanic men enrolled in the PCPC cohort. In addition, we excluded participants with missing exposure or covariate information, so that our final analytic cohort consisted of 1641 men ( $n = 868$  nonsmokers; 598 former smokers; 175 current smokers).

### *Smoking exposure, covariates, and outcome*

In the full analytic cohort, smoking exposure was assessed as ever-smoking versus never-smoking cigarettes. Ever-smoking was

a combined category consisting of former and current cigarette smokers. Due to the small number of current smokers, we were unable to examine former and current smokers in separate categories. In this study, all smoking exposure measures were measures of cigarette smoking.

Among the subcohort of ever-smokers, we examined multiple measures of smoking intensity and duration including smoking duration in years, packs smoked per day, and pack-years smoked. Among former smokers, smoking duration was calculated by subtracting the year the patient stopped smoking from the year the patient initiated smoking. Among current smokers, smoking duration was calculated by subtracting the year of primary prostate cancer treatment from the year the patient initiated smoking. We chose the primary treatment year as the endpoint for smoking duration as patients are at risk for biochemical recurrence after primary treatment (i.e. the risk period for biochemical recurrence begins after treatment). Packs smoked per day was based on the average number of packs per day a patient smoked or currently smokes. Pack-years of smoking was determined by multiplying smoking duration (in years) by packs smoked per day. Years since smoking cessation, among former smokers, was determined by subtracting the year patient quit smoking from the year the patient initiated smoking. To maximize power, measures of smoking exposure were dichotomized in all analyses: smoking duration ( $\geq 10$  years vs.  $< 10$  years), packs smoked per day ( $\geq 1$  pack/day vs.  $< 1$  pack/day), pack-years ( $\geq 10$  pack-years,  $< 10$  pack-years), and years since smoking cessation ( $\geq 10$  years vs.  $< 10$  years) [24–27].

Confounders were selected based on prior literature and known risk factors for biochemical recurrence. Age at diagnosis was analyzed as a continuous variable. Race was self-reported, and participants were characterized as “white” or “other.” Most of the “other” category consisted of African American men (96%). Self-reported weight and height were used to determine a participant's body mass index (BMI). Based on World Health Organization cut points, men were classified as obese (BMI  $\geq 30$ ) or nonobese (BMI  $< 30$ ) [28]. Clinical characteristics including Gleason score ( $\leq 7$  vs.  $> 7$ ), clinical stage (T1 vs. T2/T3), and treatment type (radical prostatectomy vs. radiation) were determined using medical records and analyzed as dichotomous variables.

Our primary outcome of interest was biochemical recurrence. Biochemical recurrence was defined as a PSA of 0.2 ng per mL or higher for two consecutive assays among participants treated with radical prostatectomy [29]. For participants treated with radiation, biochemical recurrence was defined as a PSA rise of 2 ng per mL or more above the nadir achieved after radiation [30]. Secondary treatments, for any rise in PSA, were classified as biochemical recurrence. However, adjuvant therapies without a rise in PSA were not considered biochemical recurrence.

### *Statistical analysis*

Kaplan–Meier plots were used to compare biochemical-free survival by ever-smoking status in the full cohort and by smoking duration, packs smoked per day, pack-years smoked, and years since smoking cessation in the subcohort of ever-smokers. In the full cohort, Cox Proportional Hazard models were used to assess the association between ever-smoking and biochemical recurrence. Similarly, among ever-smokers, Cox Proportional Hazards models were used to assess the association between each smoking measure and biochemical recurrence. Each smoking exposure (i.e. smoking duration, packs smoked per day, pack-years smoked, and years since smoking cessation) was examined in a separate model. In all analyses, primary models were adjusted for age at diagnosis, race, and obesity, whereas secondary models were additionally adjusted for clinical characteristics including Gleason score and stage.

**Table 1**  
Demographic and clinical characteristics of men in the Washington University Prostate Cancer Prospective Cohort, by smoking and recurrence status

Characteristic	Nonsmokers		P-value*	Ever-smokers (current + former)		P-value*
	All participants (n = 1641) N (%)	Participants with recurrence (n = 99) N (%)		Participants without recurrence (n = 769) N (%)	Participants with recurrence (n = 94) N (%)	
Age at diagnosis (mean, SD)	60.2 (7.3)	59.9 (7.2)	.52	61.0 (6.7)	61.2 (7.2)	.72
Race			.66			.63
White	1457 (88.8)	90 (90.9)		84 (89.4)	595 (87.6)	
Other	184 (11.2)	9 (9.1)		10 (10.6)	84 (12.4)	
Clinical Gleason score			<.01			<.01
≤7	996 (60.7)	24 (24.2)		22 (23.4)	415 (61.1)	
>7	645 (39.3)	75 (75.8)		72 (76.6)	264 (38.9)	
Clinical stage			<.01			<.01
T1	1318 (80.3)	71 (71.7)		62 (66.0)	543 (80.0)	
T2/T3	323 (19.7)	28 (28.3)		32 (34.0)	136 (20.0)	
Obesity			.10			.28
Obese	602 (36.7)	44 (44.4)		39 (41.5)	243 (35.8)	
Not obese	1039 (63.3)	55 (55.6)		55 (58.5)	436 (64.2)	
Treatment type			.41			.11
Radical prostatectomy	1503 (91.6)	94 (95.0)		89 (94.7)	607 (89.4)	
Radiation	138 (8.4)	5 (5.1)		5 (5.3)	72 (10.6)	

\* P-value determined using the chi-square test for all continuous variables. The P-value for age was determined using a *t* test.

For each categorical variable, we assessed the proportional hazard assumption by examining Kaplan–Meier plots and (log [–log survival probability]) plots. If the plots suggested that there may be a potential violation of the proportional hazards assumption, we subsequently examined whether the interaction between the variable of interest and time to biochemical recurrence was statistically significant using an *a priori* alpha = 0.05. Any significant interactions were retained in all models. Schoenfeld residuals were used for assessing the proportional hazard assumption for continuous variables.

We conducted several sensitivity analyses. First, we examined smoking durations of greater than 10 years. We examined both ≥15 years (vs. <15 years) and ≥20 years (vs. <20 years) in separate models. Second, because results observed in ever-smokers may be driven by current smokers, we conducted a sensitivity analysis in which current smokers were excluded. Finally, because our study consisted of men treated both with radical prostatectomy and radiation, we conducted a sensitivity analysis limiting our study to only men treated with radical prostatectomy, the primary treatment type in our study population.

All analyses were conducted using SAS 9.4 (Cary, NC).

## Results

### Characteristics of study population

Full cohort (Table 1): The mean age at diagnosis was 60.2 years. Most of the participants were white (88.8%), had a Gleason score less than or equal to 7 (80.3%), were diagnosed with clinical stage T1 (60.7%), were not obese (63.3%), and were treated with radical prostatectomy (91.6%). In the overall cohort, 11.8% of men experienced a recurrence, and the average follow-up time was 4.5 years (median: 4.1 years).

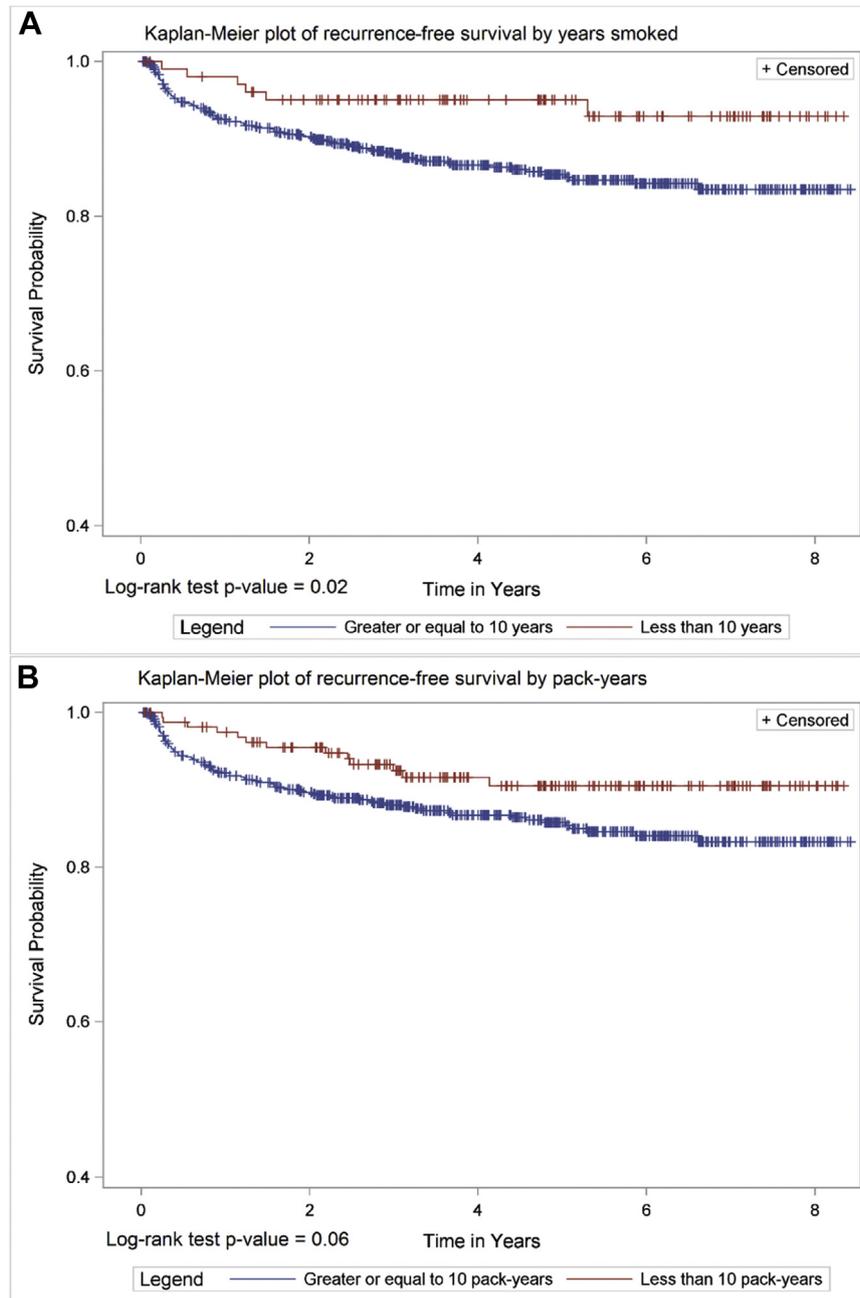
The incidence of recurrence was similar among never-smokers (11.4%) and ever-smokers (12.1%). Among never-smokers, age at diagnosis, race, and treatment type were similarly distributed among both men who did and did not experience a recurrence. However, never-smokers with a recurrence were more likely to have a Gleason score greater than 7, to be diagnosed with clinical stage T2/T3, and be obese. Among ever-smokers, age at diagnosis, race, obesity status, and treatment type were similarly distributed among both men who did and did not experience a recurrence, whereas men with a recurrence were more likely to have clinically advanced disease at diagnosis.

**Table 2**  
Smoking characteristics of ever-smokers in the Washington University Prostate Cancer Prospective Cohort, by recurrence status

Characteristic	All participants (n = 773) N (%)	Participants with recurrence (n = 94) N (%)	Participants without recurrence (n = 679) N (%)	P-value†
Smoking status				.74
Current smoker	175 (22.6)	20 (21.3)	155 (22.8)	
Former smoker	598 (77.4)	74 (78.7)	524 (77.2)	
Smoking duration				.03
≥ 10 y	669 (86.6)	88 (93.6)	581 (85.6)	
< 10 y	104 (13.5)	6 (6.4)	98 (14.4)	
Packs smoked per day				.65
≥ 1 pack/d	586 (75.8)	73 (77.7)	513 (75.6)	
< 1 pack/d	187 (24.2)	21 (22.3)	166 (24.5)	
Pack-years				.08
≥ 10 Pack-y	613 (79.3)	81 (86.2)	532 (78.4)	
< 10 Pack-y	160 (20.7)	13 (13.8)	147 (21.7)	
Years since smoking cessation among former smokers*				.79
≥ 10 y	475 (79.6)	58 (78.4)	417 (79.7)	
<10 y	122 (20.4)	16 (21.6)	106 (20.3)	

\* Years since smoking cessation unknown for one participant.

† P-value determined using the chi-square test for all continuous variables. The P-value for age was determined using a *t* test.



**Fig. 1.** Kaplan–Meier plot of recurrence-free survival by (A) years smoked ( $\geq 10$  years vs.  $< 10$  years) and (B) pack-years smoked ( $\geq 10$  pack-years vs.  $< 10$  pack-years).

Ever-smokers (Table 2): Most men had a smoking duration of greater than or equal to 10 years (86.6%), smoked greater than or equal to 1 pack per day (75.8%), and had greater than or equal to 10 pack-years of smoking exposure (79.3%). Among former smokers, the majority had quit smoking over 10 years ago (79.6%). The average follow-up time among ever-smokers was 4.1 years (median: 3.9 years).

A smoking duration of greater than or equal to 10 years was more prevalent in ever-smokers with recurrence than those without recurrence. Although greater than or equal to 10 pack-years of smoking was more prevalent in ever-smokers with recurrence than those without recurrence, there was no significant difference between the groups. Packs smoked per day and years since smoking cessation were similar across both groups.

#### Biochemical recurrence

The mean biochemical recurrence-free survival time was 5.94 years among the full cohort and 5.92 years among ever-smoker years based on the Kaplan–Meier estimator of the biochemical recurrence-free survival probability. The Kaplan–Meier plot for ever-smoking indicated that there was no difference in biochemical-free survival for ever-smokers versus nonsmokers (log-rank  $P$ -value: .62). Among ever-smokers, Kaplan–Meier plots for smoking duration and pack-years smoked can be seen in Figure 1. Kaplan–Meier survival estimates indicated that ever-smokers with greater than or equal to 10 years of smoking were significantly more likely to experience recurrence than men with less than 10 years of smoking (log-rank  $P$ -value: .02). Although

**Table 3**

Association of ever-smoking and prostate cancer recurrence, 193 recurrences, 6791.2 person-years, Washington University Prospective Cohort

Characteristic	Number of recurrences	Person-time in years	Adjusted HR* (95% CI)	Adjusted HR <sup>†</sup> (95% CI)
Overall	193	6791.2		
Ever-smoker				
Yes	99	3162.4	1.09 (0.82, 1.45)	0.94 (0.71, 1.26)
No	94	3628.8	Ref	Ref

\* Adjusted for age at diagnosis, race, and obesity.

<sup>†</sup> Adjusted for age at diagnosis, race, Gleason score, stage, and obesity.

our Kaplan–Meier plot suggests that greater than or equal to 10 pack-years of smoking may be associated with an increased risk of biochemical recurrence, there was no significant difference in survival estimates (log-rank *P*-value: .06). Kaplan–Meier survival estimates indicated no difference in biochemical recurrence-free survival time by packs smoked per day or years since smoking cessation among former smokers. No variables violated the proportional hazard assumption.

Results from Cox Proportional Hazards models were consistent with Kaplan–Meier estimates. In the full cohort, we observed no association between ever-smoking and risk of biochemical recurrence after adjustment for age at diagnosis, race, obesity (HR: 1.09, 95% CI: 0.82, 1.45) or with additional adjustment for clinical characteristics (HR: 0.94, 95% CI: 0.71, 1.26) (Table 3).

Among ever-smokers, a smoking duration of greater than or equal to 10 years (vs. <10 years) was significantly associated with biochemical recurrence after adjustment for age at diagnosis, race, obesity (HR: 2.48, 95% CI: 1.08, 5.69), and with additional adjustment for clinical characteristics (HR: 2.32, 95% CI: 1.01, 5.33) (Table 4). Moreover, our results suggested that greater than or equal to 10 pack-years of smoking (vs. < 10 pack-years) may be associated with an increased risk of biochemical recurrence in both models without (HR: 1.75, 95% CI: 0.98, 3.15) and with adjustment for clinical characteristics (HR: 1.75, 95% CI: 0.97, 3.15), although our findings were not statistically significant. No association was observed between packs smoked per day and biochemical recurrence. Among former smokers, we observed no association between years since smoking cessation and biochemical recurrence.

Sensitivity analyses: First, we examined smoking durations of greater than or equal to 15 (vs. <15 years) and greater than or equal to 20 years (vs. <20 years). In fully adjusted models, we found that neither greater than or equal to 15 years of smoking (HR: 1.05, 95% CI: 0.65, 1.67) nor greater than or equal to 20 years of smoking (HR: 1.08, 95% CI: 0.70, 1.65) were associated with increased risk of prostate cancer recurrence. One possible explanation for these findings is that including men with up to 15 or 20 years of smoking exposure in the reference group results in a “diluted” reference group where men with increased risk are in the reference group instead of the “exposed group.” This would bias our results toward the null as observed. Second, we excluded current smokers from our analyses of smoking duration to examine whether our findings were driven by current smokers alone. Consistent with our previous findings, we observed that greater than or equal to 10 years (vs. <10 years) was significantly associated with biochemical recurrence (fully adjusted HR: 2.34, 95% CI: 1.01, 5.43), suggesting that our results were not driven by current smokers alone. Finally, we examined our findings in men treated by radical prostatectomy only. Our findings were consistent for smoking duration (fully adjusted HR: 2.70, 95% CI: 1.09, 6.67). Moreover, consistent with previous findings, we observed no association with ever-smoking, pack-years, packs per day, or years since smoking cessation and biochemical recurrence (data not shown).

**Table 4**

Association of smoking intensity, years since smoking cessation, and prostate cancer recurrence among ever-smokers, 94 recurrences, 3162.4 person-years, Washington University Prospective Cohort

Characteristic	Number of recurrences (n = 94)	Person-time in years	Adjusted HR* (95% CI)	Adjusted HR <sup>†</sup> (95% CI)
Overall	94	3162.4		
Smoking duration				
≥ 10 y	88	2680.2	2.48 (1.08, 5.69)	2.32 (1.01, 5.33)
< 10 y	6	482.2	Ref	Ref
Packs smoked per day				
≥ 1 pack/d	73	2411.5	1.11 (0.68, 1.81)	1.18 (0.72, 1.92)
< 1 pack/d	21	750.9	Ref	Ref
Pack-years				
≥ 10 pack-y	81	2455.5	1.75 (0.98, 3.15)	1.75 (0.97, 3.15)
< 10 pack-y	13	706.9	Ref	Ref
Years since smoking cessation among former smokers <sup>‡</sup>				
≥ 10 y	58	1956.0	0.94 (0.53, 1.66)	1.03 (0.59, 1.83)
<10 y	16	499.2	Ref	Ref

\* Adjusted for age at diagnosis, race, and obesity.

<sup>†</sup> Adjusted for age at diagnosis, race, Gleason score, stage, and obesity.

<sup>‡</sup> 74 recurrences among former smokers; years since smoking cessation is unknown for 1 former smoker.

## Discussion

In this study, we evaluated smoking as a risk factor for prostate cancer recurrence among men with incident prostate cancer treated with definitive therapy. In our overall cohort, we observed no association between smoking and biochemical recurrence. This is consistent with some previous findings [18–21]. However, other studies have suggested that smoking may increase risk of prostate cancer recurrence [12–17]. For this reason, we sought to further assess the subcohort of men in our study who were former or current smokers.

We found that a longer smoking duration and increased pack-years of smoking may be associated with an increased risk of biochemical recurrence among ever-smokers. Few studies have examined detailed smoking exposure histories with risk of biochemical recurrence [12–15,17]. To our knowledge, only one other study has examined smoking duration and risk of biochemical recurrence among men with prostate cancer. In contrast to our findings, Steinberger et al. reported no association between duration of smoking and biochemical recurrence [15]. However, this study was limited to men treated with radiation, and it was unclear how smoking duration was categorized [15]. Previous studies of pack-years smoked and risk of biochemical recurrence have been inconsistent [13–15,17]. Among the two studies that observed a positive association between pack-years and biochemical recurrence, the analyses were limited to a comparison group of non-smokers [13,17]. In our study, we were able to demonstrate that increased smoking duration and pack-years of smoking exposure may be important predictors of biochemical recurrence specifically among ever-smokers.

A strength of our study is our ability to examine multiple smoking exposures within the same cohort. Our results indicated that smoking duration was the strongest predictor of biochemical recurrence. Indeed, we found that it was a stronger predictor than both packs smoked per day and pack-years smoked. This is an interesting finding, as one might expect pack-years of smoking to be the strongest predictor. Objectively, pack-years is the most comprehensive measure, incorporating both years smoked and number of cigarettes smoked per day. However, it is possible that smokers with prostate cancer are more accurately able to recall dates of smoking initiation and cessation than the average number of packs smoked per day. Previous research has indicated that

smokers are more reliably able to answer well-defined questions (e.g. when did you start smoking) than more salient questions about smoking history [31]. The average number of cigarettes smoked per day can change over years of smoking, and as such, could be harder for smokers to accurately recall. Moreover, given the variability of smoking intensity throughout years of smoking, it is possible that an average number of cigarettes smoked is not an accurate measure of smoking exposure, even if accurately recalled. Our findings suggest that determining smoking duration among men with prostate cancer could provide valuable clinical information regarding risk of biochemical recurrence.

Predicting which patients with prostate cancer will or will not experience biochemical recurrence at time of treatment is difficult. Numerous nomograms exist to predict risk of biochemical recurrence after radical prostatectomy or radiation [32,33]. However, the predictors included in these nomograms largely consist only of nonmodifiable clinical characteristics such as PSA, clinical stage, Gleason sum, seminal vesicle invasion, surgical margins, lymph node invasion, extracapsular extension, or number of positive cores [32,33]. Our study adds evidence that nonclinical factors, such as smoking intensity and duration, may also be valuable in predicting biochemical recurrence, especially among men with a history of smoking. Future predictive nomograms should consider incorporating smoking history into the predictive algorithm.

Beyond predicting the likelihood of recurrence at time of treatment, clinical detection of biochemical recurrence and timely administration of secondary treatment is largely dependent on patients receiving recommended follow-up care [34]. However, many prostate cancer survivors do not receive guideline-concordant follow-up care [35,36]. In a previous analysis among men in this cohort, we found that a quarter of men do not receive any follow-up visits in the 6 months after radical prostatectomy [35]. Our results suggest that men with many years of smoking exposure (i.e. a long duration) represent a high-risk group that could benefit from targeted interventions and clinical outreach to increase post-treatment screenings. Furthermore, we have previously shown that former or current smokers who have a history of weight gain are particularly at risk for biochemical recurrence [23]. Ensuring that high-risk men, such as those with a history of smoking or weight gain, receive adequate post-treatment care could help reduce the clinical consequences of biochemical recurrence. Importantly, unlike other clinical characteristics that are predictive of biochemical recurrence, smoking duration is potentially modifiable even among men with a history of smoking. Although we did not observe an association between years of smoking cessation and risk of biochemical recurrence, other studies have observed that smoking cessation may reduce biochemical risk [12,17].

Our study is limited to a single institution and relatively short follow-up time. Only 12% of the ever-smokers experienced a biochemical recurrence by the end of follow-up. Moreover, because our measures of smoking exposure were self-reported, men may have inaccurately recalled smoking history. If current or former smokers underreported smoking duration or intensity, our results could have been biased toward the null. Despite these limitations, we still observed a significant association between smoking duration and biochemical recurrence among ever-smokers. Our results also suggested that pack-years of smoking exposure might be associated with an increased risk of biochemical recurrence among ever-smokers. It is possible, with longer follow-up time or with a larger sample size, we may have observed a stronger association with pack-years or an association between years of smoking cessation and risk of biochemical recurrence. Key strengths of this study include its prospective design and utilization of multiple measures of smoking exposure within the same cohort. We

demonstrated that smoking duration is a stronger predictor of biochemical recurrence than either average number of packs smoked or pack-years of smoking exposure among ever-smokers with prostate cancer, and we are one of the first studies to report a strong positive association between smoking duration and biochemical recurrence. Our study adds to the limited and inconclusive literature on smoking history and risk of biochemical recurrence to date.

## Conclusion

A longer smoking duration is significantly associated with an increased risk of biochemical recurrence among ever-smokers with prostate cancer. Increased pack-years of smoking exposure may also be associated with biochemical recurrence. Smoking duration is a modifiable risk factor and could be used to identify the ever-smokers at highest risk for prostate cancer recurrence.

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