

BRIEF COMMUNICATION

Cigarette Smoking and Prostate Cancer Recurrence After Prostatectomy

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Toward the establishment of evidence-based recommendations for the prevention of prostate cancer recurrence after treatment, we examined the association between smoking and prostate cancer recurrence in a retrospective cohort study of 1416 men who underwent radical prostatectomy. Surgeries were performed by a single surgeon at Johns Hopkins Hospital between January 1, 1993, and March 31, 2006. Smoking status at 5 years before and 1 year after surgery was assessed by survey. Prostate cancer recurrence was defined as confirmed re-elevation of prostate-specific antigen levels, local recurrence, metastasis, or prostate cancer death. The cumulative incidence of recurrence was 34.3% among current smokers, 14.8% among former smokers, and 12.1% among never smokers, with a mean follow-up time of 7.3 years. Men who were current smokers at 1 year after surgery were more likely than never smokers to have disease recurrence after adjusting for pathological characteristics, including stage and grade (hazard ratio for recurrence = 2.31, 95% confidence interval = 1.05 to 5.10). This result suggests an association between cigarette smoking and risk of prostate cancer recurrence.

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Within 10 years, prostate cancer recurs in approximately 20% of men who undergo prostatectomy to treat clinically localized prostate cancer (1). Evidence-based recommendations have not been established for the prevention of this recurrence after treatment, although lifestyle changes may provide opportunities to prevent recurrence and improve overall health.

Cigarette smoking is a leading preventable cause of death in the United States (2); yet, 20% of adult men smoke (3). Some studies have found an association between current or recent smoking and prostate cancer mortality but not with prostate cancer incidence [references in (4)]. Among men with prostate cancer, several studies have suggested that smokers have an elevated risk of advanced stage and high-grade disease, which are both indicators of poor prognosis (5). Despite these findings, few studies (6–10) have investigated the influence of cigarette smoking on prostate cancer recurrence after treatment for early stage disease, and only one of these

studies (10) was conducted in men who had prostatectomies.

Thus, in a retrospective cohort study in which we accounted for prognostic pathological factors, we investigated whether cigarette smoking, both before and after surgery, was associated with the risk of recurrence after prostatectomy for clinically localized prostate cancer. A total of 2209 men who underwent radical retropubic prostatectomy between January 1, 1993, and March 31, 2006, by a single surgeon at Johns Hopkins Hospital, who were not previously treated with hormone or radiation therapy, and who were known to be alive and residing in the United States as of November 2007 were mailed a survey to determine lifestyle factors. After excluding men with incorrect addresses ($n = 148$) and men who died ($n = 6$), the response rate was 77.2%. All other clinically relevant factors were abstracted from the medical records. All 1416 men with complete survey information were followed for recurrence through August 2009 (mean = 7.3 years).

The Institutional Review Boards at the Johns Hopkins School of Medicine and the Johns Hopkins Bloomberg School of Public Health approved this study.

We evaluated smoking status 5 years before and 1 year after surgery. Men were classified in two ways: 1) ever vs never smoker and 2) never, former, or current smoker. Ever smokers provided the ages at which they started and quit smoking (if applicable) and the number of cigarettes that they smoked daily during several age periods (<15 years of age, from 15 to 19 years of age, and during each subsequent decade of life). We calculated the mean number of cigarettes smoked daily while they were active smokers and the number of pack-years smoked (number of packs per day \times number of years).

The men were followed for recurrence, which was defined as a confirmed re-elevation of prostate-specific antigen (PSA) levels to 0.2 ng/mL or greater above a nadir of nondetectable, local recurrence, metastasis, or prostate cancer death. Patients underwent PSA tests and digital rectal examinations every 3 months for the first year after surgery, semiannually for the second year, and annually thereafter. The surgeon requested that the men's physicians send their most recent PSA test results annually; he repeated elevated tests. We obtained information on prostate cancer deaths through family reports or linkage to the National Death Index. A total of 106 out of 1416 men experienced recurrences of prostate cancer; of these, 10% had metastatic disease or died from prostate cancer.

We estimated age-adjusted characteristics by smoking status 5 years before surgery using regression modeling and tested coefficients using the Wald test. We estimated the cumulative incidence of recurrence using the life table approach. We used Cox proportional hazards regression to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) of recurrence according to smoking status at 5 years before and 1 year after surgery, the mean number of packs smoked per day, or the number of pack-years smoked. Time at risk was calculated starting from 1 year after surgery. We adjusted all analyses for age (continuous), race (white vs nonwhite),

CONTEXT AND CAVEATS

Prior knowledge

Few studies have examined the influence of cigarette smoking on risk of prostate cancer recurrence.

Study design

A cohort of 1416 men who were given radical prostatectomies by a single surgeon were followed for a mean of 7.3 years for recurrence of prostate cancer, which occurred in 106 of the men. Smoking status was retrospectively evaluated at 5 years before and 1 year after surgery.

Contribution

Ever smoking and smoking at 5 years before surgery were not statistically significantly associated with risk of prostate cancer recurrence. Men who had quit smoking by 1 year after surgery did not have higher risk than never smokers. However, current smokers at 1 year after surgery had roughly twice as much risk of prostate cancer recurrence compared with former smokers.

Implications

Quitting smoking after prostate cancer surgery may be associated with a lower risk of cancer recurrence.

Limitations

A relatively small population was studied, from a single location. After imputation of missing data for current smoking status, the increased risk for current smokers was not statistically significant.

From the Editors

Table 1. Age-adjusted demographic and pathological tumor characteristics of 1416 patients undergoing radical prostatectomy by smoking status 5 years before surgery*

Characteristic	Smoking status			P†
	Never (n = 750)	Former (n = 571)	Current (n = 95)	
Mean age, y (SD)	56.2 (6.7)	57.4 (6.3)	54.3 (5.8)	≤.001
Race, %				.52
White	94.0	96.1	93.8	
Black	2.2	1.5	3.0	
Other or missing	3.7	2.4	3.2	
Family history of prostate cancer, %				.09
No	65.7	68.4	72.0	
Yes	28.2	25.4	17.0	
Missing	6.1	6.2	10.9	
Mean preoperative PSA (SE)	6.41 (0.16)	6.69 (0.19)	6.94 (0.46)	.35
Mean surgery year (SE)	1999.3 (.13)	1999.2 (.15)	1998.6 (.38)	.17
Mean pathological Gleason sum (SE)	6.28 (0.02)	6.28 (0.03)	6.30 (0.06)	.91
Pathological stage, %				.05
Organ-confined	76.2	74.0	63.6	
Focal or established capsular penetration	21.1	21.9	27.7	
Seminal vesicle or lymph node positive	2.7	4.0	7.6	
Positive surgical margins, % 5 y before prostatectomy	4.7	7.2	11.0	.02
Mean packs smoked per day (SE)†	NA	0.5 (0.02)	0.6 (0.05)	.09
Mean pack-years (SE)‡	NA	12.8 (0.60)	25.3 (1.74)	<.001
Mean body mass index, kg/m ² (SE)	25.7 (0.11)	26.3 (0.13)	26.4 (0.31)	<.01
1 y after prostatectomy				
Smoking status, %				.03
Never	100	0	0	
Former	0	100	46.3	
Current	0	0	53.7	
Mean packs smoked per day (SE)‡	NA	0.5 (0.02)	0.6 (0.08)	.28
Mean pack-years (SE)‡	NA	14.0 (0.62)	27.5 (3.16)	<.001
Mean body mass index, kg/m ² (SE)	25.7 (0.11)	26.3 (0.12)	26.7 (0.30)	<.001

* PSA = prostate-specific antigen.

† Estimated from regression modeling. P values are from two-sided Wald tests.

‡ Analysis in subset of 1318 men with complete information on smoking amount and duration.

family history of prostate cancer (yes, no, or missing), year of prostatectomy (continuous), preoperative PSA concentration (continuous), pathological stage and grade (extraprostatic extension and Gleason 4+3 or greater, no extraprostatic extension and Gleason 4+3 or greater, extraprostatic extension and Gleason 3+4 or less, and no extraprostatic extension and Gleason 3+4 or less), surgical margins (positive vs negative), and body mass index (continuous). We confirmed the proportional hazards assumption for all models by including an interaction term between the main effect and follow-up time in the model and testing the coefficient using the Wald test. All models were compatible with the proportional hazards assumption. To address the possibility of selection bias in this

retrospective cohort study, we used multiple imputation to impute missing current smoking status for men who did not respond to the questionnaire but were otherwise eligible for this analysis. All P values are from two-sided tests, and a P less than .05 was considered to be statistically significant.

At 5 years before prostatectomy, approximately 40% of men were former smokers and 7% were current smokers. Compared with never smokers, current smokers were younger and more likely to have positive surgical margins (Table 1). Current smokers had a higher body mass index at 5 years before and 1 year after

surgery. Approximately, 46% of current smokers at 5 years before surgery had quit smoking by 1 year after surgery.

Ever smoking and smoking at 5 years before surgery, including current or former smoking, packs of cigarettes smoked per day, and number of pack-years smoked, were not statistically significantly associated with prostate cancer recurrence risk (Table 2). However, prostate cancer survivors who were current smokers at 1 year after surgery were more likely to experience a recurrence of prostate cancer than never and former smokers (cumulative incidence = 34.3% for current, 12.1% for never, and 14.8% for former smokers).

Table 2. Association between cigarette smoking and prostate cancer recurrence, 1416 men at Johns Hopkins Hospital, 1993–2006*

	No. of men who experienced recurrence/No. of men surgically treated for prostate cancer	Person-years	HR (95% CI)
Smoking status			
Never	48/750	5479	1.00 (referent)
Ever	58/666	4896	1.16 (0.78 to 1.74)
<0.5 pack/d†	19/264	1939	1.05 (0.61 to 1.83)
≥0.5 packs/d†	28/304	2220	1.12 (0.68 to 1.85)
Per 0.5 pack/d†	47/568	4159	1.00 (0.75 to 1.33)
<10 pack-years†	24/283	1942	1.41 (0.85 to 2.34)
≥10 pack-years†	23/285	2217	0.87 (0.51 to 1.47)
Per 10 pack-years†	44/537	3948	0.97 (0.82 to 1.14)
Former			
5 y before surgery	49/571	4151	1.19 (0.79 to 1.82)
1 y after surgery	50/615	4497	1.08 (0.71 to 1.64)
Per 0.5 pack/d†	43/547	3975	0.97 (0.72 to 1.30)
Per 10 pack-years†	43/547	3975	0.94 (0.80 to 1.12)
Current			
5 y before surgery	9/95	745	1.19 (0.55 to 2.57)
1 y after surgery	8/51	399	2.31 (1.05 to 5.10)
Per 0.5 pack/d†	4/21	184	2.10 (0.93 to 4.78)
Per 10 pack-years†	4/21	184	1.26 (0.85 to 1.89)

* Follow-up began 1 year after surgery. HR and 95% CI estimated from Cox proportional hazards regression adjusting for age, race, family history, year of prostatectomy, preoperative prostate-specific antigen levels, stage, grade, surgical margins, and body mass index from the same time period. CI = confidence interval; HR = hazard ratio.

† Analysis in subset of 1318 men with complete information on smoking amount and duration.

Current smokers had a statistically significant higher risk of prostate cancer recurrence than never smokers even after multivariable adjustment (HR for recurrence = 2.31, 95% CI = 1.05 to 5.10; Table 2). The risk of recurrence was not greater in men who had quit smoking by 1 year after surgery than that in never smokers. Compared with former smokers, current smokers had a higher risk of recurrence than men who quit (HR for recurrence = 2.14, 95% CI = 0.99 to 4.66). After imputing the missing current smoking status, the elevated risk of recurrence in current smokers vs never and former smokers was not statistically significant (HR for recurrence = 1.53, 95% CI = 0.75 to 3.32).

In this retrospective cohort study of men with clinically localized prostate cancer, current smoking 1 year after prostatectomy was associated with a more than twofold increased risk of recurrence. This finding was independent of the influence of smoking on pathological characteristics. Our study provides evidence that men who continue to smoke after prostate cancer diagnosis are more likely to recur, but that men who quit are not.

Our results are compatible with previous studies that found cigarette smoking

to be associated with a higher risk of prostate cancer death (11–13). Our findings are also consistent with studies on recurrence among men with prostate cancer treated by hormone deprivation therapy (7) and radiation therapy (6,8,9). However, our findings are inconsistent with the only other study on smoking and recurrence after prostatectomy, which found no association (10). This discrepancy might be partially explained by differences in study population and follow-up time; the prior study had a much higher proportion of black men and current smokers, and less than half of the follow-up time compared with our study.

We considered causal and noncausal explanations for our findings. The causal mechanism by which cigarette smoking may influence recurrence risk is uncertain, though a recent review by Zu and Giovannucci (5) suggested that the effects of smoking on mutagenesis, DNA methylation, angiogenesis, and hormone levels may be contributory. When we used imputation to address the possibility that participant nonresponse to the study survey may have influenced our results, current

smokers had a higher risk of recurrence than never or former smokers, but the difference in risk was not statistically significant.

In summary, we found a positive association between current smoking at 1 year after prostatectomy and prostate cancer recurrence. This result suggests that avoiding or quitting smoking may reduce the risk of recurrence among men who have undergone radical prostatectomy to treat clinically localized prostate cancer. Our work may contribute to the development of evidence-based recommendations for the prevention of prostate cancer recurrence after treatment for potentially curable prostate cancer.

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Notes

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