Association of Smoking Status With Recurrence, Metastasis, and Mortality Among Patients With Localized Prostate Cancer Undergoing Prostatectomy or Radiotherapy
A Systematic Review and Meta-analysis

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IMPORTANCE Studies investigating the association of cigarette smoking with prostate cancer incidence and outcomes have revealed controversial results.

OBJECTIVE To systematically review and analyze the association of smoking status with biochemical recurrence, metastasis, and cancer-specific mortality among patients with localized prostate cancer undergoing primary radical prostatectomy or radiotherapy.

DATA SOURCES A systematic search of original articles published between January 2000 and March 2017 was performed using PubMed, MEDLINE, Embase, and Cochrane Library databases in March 2017.

STUDY SELECTION Observational studies reporting Cox proportional hazards regression or logistic regression analyses were independently screened.

DATA EXTRACTION AND SYNTHESIS This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the Cochrane Handbook for Systematic Reviews of Interventions. Available multivariable hazard ratios (HRs) and corresponding 95% CIs were included in quantitative analysis. A risk-of-bias assessment was completed for nonrandomized studies.

MAIN OUTCOMES AND MEASURES Prespecified outcomes of interest were biochemical recurrence, metastasis, and cancer-specific mortality.

RESULTS A total of 5157 reports were identified, of which 16 articles were selected for qualitative analysis and 11 articles were selected for quantitative analysis. All included studies were observational and nonrandomized and comprised a total of 22 549 patients. Overall, 4202 patients (18.6%) were current smokers. The overall median follow-up was 72 months. Current smokers had a statistically significantly higher risk of biochemical recurrence (HR, 1.40; 95% CI, 1.18-1.66; P < .001 [10 studies]), as did former smokers (HR, 1.19; 95% CI, 1.09-1.30; P < .001 [7 studies]). Current smokers were also at a higher risk of metastasis (HR, 2.51; 95% CI, 1.80-3.51; P < .001 [3 studies]) and cancer-specific mortality (HR, 1.89; 95% CI, 1.37-2.60; P < .001 [5 studies]), whereas former smokers were not (metastasis: HR, 1.61; 95% CI, 0.65-3.97; P = .31 [2 studies]; cancer-specific mortality: HR, 1.05; 95% CI, 0.81-1.37; P = .70 [4 studies]).

CONCLUSIONS AND RELEVANCE Current smokers at the time of primary curative treatment for localized prostate cancer are at higher risk of experiencing biochemical recurrence, metastasis, and cancer-specific mortality.
Burning tobacco products and its additives produces thousands of chemicals, including more than 70 well-known carcinogens.1,2 Tobacco smoking is known as a preventable risk factor for the development and mortality of several genitourinary cancers such as bladder cancer,3,4 upper tract urothelial carcinoma,5 and renal cell carcinoma.6,10 In contrast, the effect of tobacco consumption on the incidence of prostate cancer is still a matter of debate.7,8 Nevertheless, the association between cigarette smoking and prostate cancer mortality seems to be robust. Two meta-analyses that evaluated the association of smoking with prostate cancer outcomes confirmed a higher risk of death among current smokers than among nonsmokers.7,9 These apparently discordant findings could be explained by the presence of higher-grade or higher-stage disease at the time of diagnosis, the adverse effects of tobacco use on oncologic outcomes after primary treatment, or both. Some studies revealed a correlation between smoking status and higher tumor volumes, more expansive high-grade tumor volumes, and extracapsular extension during radical prostatectomy (RP).9,10

The aim of this systematic review and meta-analysis was to investigate the association of smoking status, number of cumulative pack-years, and smoking cessation with biochemical recurrence (BCR), metastasis, and cancer-specific mortality (CSM) among patients with prostate cancer who are undergoing primary RP or radiotherapy (RT). Our hypothesis was that current smokers have a higher risk of BCR, metastasis, and CSM compared with former smokers or never smokers.

Methods

Literature Search

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook for Systematic Reviews of Interventions.11,12 We systematically searched PubMed, MEDLINE, Embase, and the Cochrane Library to identify studies published between January 2000 and March 2017 that examined the association of smoking status with the prognosis of patients undergoing primary curative treatment (RP or RT) for localized prostate cancer. The bibliographic search was performed by B.F. and C.P. in March 2017. The following search terms were used: (“Cigarette” OR “Smoking” OR “Tobacco”) AND (“Prostate cancer”) AND (“Biochemical recurrence” OR “Recurrence” OR “Progression” OR “Survival” OR “Mortality” OR “Metastasis” OR “Prognosis”). No language restrictions were applied. All original articles found on the topic were observational cohort or case-control studies because the habit of smoking is not a factor that can be randomized. Biochemical recurrence, metastasis, and CSM were the primary end points of interest.

Eligibility Criteria

As proposed by the PRISMA guidelines, we used the population, intervention, comparator, outcome, and study design approach to specify the inclusion criteria. Reports were considered relevant when they included patients who received a diagnosis of prostate cancer (population), recorded smoking status (comparator), and the patients underwent primary curative treatment (intervention) to independently determine the association of smoking status with BCR, metastasis, and CSM (outcome) using Cox proportional hazards regression or logistic regression analyses (study design). We were primarily focused on comparing the risk of current, former, and never smoking.

Second, we aimed to investigate cumulative risk groups (pack-years) and different durations of smoking cessation. The main focus regarding primary curative treatment was on RP, RT, or both. Studies with mixed treatment populations had to consist of at least 80% of these 2 modalities and had to be adjusted for primary therapy. Only studies with smoking status examined in multivariable Cox proportional hazards regression analyses were considered for meta-analysis. If more than 1 report of the same study population existed, we selected the most recent regarding a specific survival outcome. Review articles, editorials, comments, and meeting abstracts were excluded. Search results were independently screened by B.F. and C.P. The references of the included articles were scanned for additional studies of interest. Disagreements were resolved by consulting the senior author (S.F.S.).

Data Extraction

After evaluation of full-text articles, data were independently extracted by B.F. and C.P. for further assessment of qualitative and quantitative analyses. All extracted variables were cross-checked to ensure their reliability. Discrepancies were generally resolved by consensus or finally decided by the senior author (S.F.S.).

We recorded the overall and risk-specific (smoking status) number of included participants with the corresponding frequency of BCR, the occurrence of metastasis and disease-specific mortality, and the median or mean duration of follow-up. Subsequently, the hazard ratio (HR) and 95% CI associated with the respective smoking status and outcome were retrieved. Furthermore, we searched for baseline characteristics, methods, and important confounders to establish comparability.
Statistical Analysis
Owing to the observational nature of the included studies, we extracted adjusted HRs and 95% CIs for the cumulative effect size calculation. Studies with univariable Cox proportional hazards regression or general logistic regression analyses were not considered for meta-analysis but were included in the systematic review. Effect summary estimation methods were not used in these cases because a high level of additional selection bias would have been introduced. If multivariable testing was performed but the results were not shown, we took univariable data into account. Statistical pooling of effect measures was based on the level of heterogeneity among studies, which was assessed with the Cochrane Q test and the $I^2$ statistic. Significant heterogeneity was indicated by $P < .05$ in Cochrane Q tests and a ratio greater than 50% in $I^2$ statistics, which led to the use of random-effects models according to the DerSimonian and Laird method.13-15 When these tests were negative for heterogeneity, fixed-effects models were chosen for calculation of pooled HRs through the inverse-variance method. Publication bias that included a small-study effect was evaluated by visual inspection of funnel plots for all assessed comparisons.16 Statistical analyses were performed using STATA/MP, version 14.2 (StataCorp). $P < .05$ was considered significant.

Risk of Bias
The risk-of-bias evaluation of the included studies was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions for including nonrandomized studies.17,18 Because the included studies were nonrandomized, risk of bias was determined using the pragmatic approach by examining the risk of preassigned confounders. The main confounding factors were identified as the most important prognostic factors at the time of primary prostate cancer treatment. We therefore reviewed the articles, adjusting for the effects of age, prostate-specific antigen level, clinical or pathologic stage, Gleason score, positive surgical margins, and the use of neoadjuvant androgen deprivation therapy within their Cox proportional hazards regression models. The presence of confounders was determined by consensus between two of us (B.F. and C.P.). The risk-of-bias summary and graph were built using the Cochrane Review Manager, version 5.3.19

Results
Study Population
Overall, we identified 16 studies for qualitative analysis (eTable 1 in the Supplement) and 11 studies for quantitative analysis (Figure 1). The number of included participants from each selected study for meta-analysis ranged from 416 to 6538 participants (median, 1416 participants; mean, 2050 participants). Overall, the meta-analysis comprised 22 549 patients; 4202 (18.6%) were current smokers at the time of primary curative treatment, and 18 347 (81.4%) were nonsmokers (former and never smokers combined). Not all studies differentiated between former smoking and never smoking. The overall median follow-up period was 72 months for the entire cohort, which represented North America, Europe, and East Asia. All available data covered by the systematic review on BCR, metastasis, and CSM are summarized in eTables 1 to 6 in the Supplement. The risk-of-bias assessment revealed a moderate to high level of bias across studies (eFigure 1 in the Supplement) owing to the type of studies included (observational and nonrandomized) and confounding.

Biochemical Recurrence
Among studies that investigated BCR, 4656 of the included 21 797 participants (21.4%) experienced BCR during a median follow-up of 61 months.

Current Smoking
The association of current smoking status with BCR was investigated in 13 of the included articles. Ten of these articles provided multivariable HRs for inclusion into meta-analysis.20-31 The corresponding forest plot (Figure 2A) revealed that current smokers had a significantly higher risk of experiencing BCR compared with non-smokers whether they had undergone RP or RT (HR, 1.40; 95% CI, 1.18-1.66; $P < .001$). The Cochrane Q test and the $I^2$ statistic showed heterogeneity; therefore, a random-effects analysis was performed. However, we included 2 studies20,25 that
compared current smoking vs nonsmoking. Both showed no significant association with BCR. When comparing current smokers with neversmokers only, the association was higher (HR, 1.59; 95% CI, 1.40-1.80; \( P < .001 \)). Inspection of the funnel plot did not demonstrate publication bias (eFigure 2A in the Supplement).

Former Smoking

Former smoking as a risk factor for BCR after primary treatment was assessed in 8 studies,21-23,27-31 7 of which were integrated into the meta-analysis.21-23,27,29-31 Among the included patients, former smoking was independently associated (Figure 2B32-34) with BCR (HR, 1.19; 95% CI, 1.09-1.30; \( P < .001 \)). The data were homogeneous according to the \( I^2 \) statistic and the Cochrane Q test; therefore, a fixed-effects model was used for cumulative analysis. Inspection of the corresponding funnel plot did not show evidence of publication bias (eFigure 2B in the Supplement).

Cumulative Pack-years

Data about cumulative smoking exposure in pack-years were too heterogeneous to analyze. Moreover, the results were

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**Figure 2. Forest Plots of Studies Investigating the Association of Current and Former Smoking With Biochemical Recurrence (BCR)**

A, Current smokers. Weights are from random-effects analysis. B, Former smokers. Weights are from fixed-effects analysis. The reference status “nonsmokers” contains never smokers and former smokers. BCR definitions include American Society for Therapeutic Radiology and Oncology (ASTRO) (3 consecutive increases greater than the nadir [1997])32; Houston (a PSA increase of \( \geq 2 \) ng/mL above the nadir, defined as the last nonrising PSA [2002])33; and Phoenix (an increase of \( \geq 2 \) ng/mL above the absolute nadir [2006]).34 EU indicates Europe; HR, hazard ratio; PSA, prostate-specific antigen. The dashed line indicates the overall pooled effect size (HR).
inconsistent. Joshu et al\textsuperscript{21} compared patients with a history of 10 pack-years or more vs never smokers during RP and found no significant association with BCR (HR, 0.87; 95% CI, 0.51-1.47). Rieken et al\textsuperscript{29} investigated patients with a history of more than 20 vs less than 20 pack-years and found no significant difference (HR, 0.92; 95% CI, 0.72-1.12; \(P = .50\)). In contrast, Ngo et al\textsuperscript{10} found a slightly higher risk (HR, 1.27; 95% CI, 1.03-1.54; \(P = .02\)) among patients with more than 20 pack-years of cumulative smoking exposure. Kenfield et al\textsuperscript{22} compared patients with a history of 39 pack-years or less and those with 40 pack-years or more vs never smokers in a mixed cohort (RP and RT). They reported contradictory results, with an elevated risk among patients with 39 pack-years or less (HR, 2.13; 95% CI, 1.24-3.64). Patients with a history of 40 pack-years or more did not have such an association (HR, 1.48; 95% CI, 0.88-2.48).

**Smoking Cessation**

Owing to heterogeneous data on smoking cessation, a meta-analysis could not be performed. Overall, 3 studies explored smoking cessation, whereas 2 studies investigated a time frame of smoking cessation greater than 10 years. In both reports, smoking cessation for more than 10 years was a protective factor for BCR (HR, 0.6; 95% CI, 0.4-0.9 [compared with current smokers]); HR, 0.96; 95% CI, 0.68-1.37 [compared with never smokers]), but smoking cessation for less than 10 years was not protective (eTable 3 in the Supplement).\textsuperscript{22,29} Furthermore, Joshu et al\textsuperscript{21} investigated a 5-year time frame of smoking cessation that did not show a benefit.

**Metastasis**

In 2 of 3 included reports that provided data on metastasis, 90 of 2086 patients (4.3%) developed metastases.\textsuperscript{27,31} The median follow-up was 75 months.

**Current Smoking**

Current smoking as a risk factor for developing metastasis was reported in 3 studies.\textsuperscript{25,27,31} Meta-analysis of available HRs (Figure 3A) revealed that current smoking was associated with metastasis (HR, 2.51; 95% CI, 1.80-3.51; \(P < .001\)). No heterogeneity was observed, and the funnel plot did not show evidence of publication bias (eFigure 2C in the Supplement).

**Former Smoking**

The association of former smoking status with metastasis was reported in 2 studies\textsuperscript{27,31} and revealed contradictory results (Figure 3B). Both studies comprised patients undergoing RT only. Pooling of HRs showed no association with developing metastasis (HR, 1.61; 95% CI, 0.65-3.97; \(P = .31\)). Owing to heterogeneity between the studies, a random-effects model was used. The funnel plot was negative for publication bias (eFigure 2D in the Supplement).

**Cancer-Specific Mortality**

Among all included 7924 participants, 654 (8.3%) died of prostate cancer within a median follow-up of 95 months.

**Current Smoking**

Current smoking status as a risk factor for CSM was reported in 8 studies.\textsuperscript{22,25,27,28,31,35-37} 5 of which provided multivariable HRs for inclusion in meta-analysis.\textsuperscript{22,25,27,31,35} Data were homogeneous according to the Cochrane Q test and the \(I^2\) statistic and could therefore be analyzed with a fixed-effects analysis. The cumulative pooling of available HRs across both treatment modalities (Figure 4A) demonstrated that being an active smoker during primary therapy was significantly associated with the risk of CSM by approximately a factor of 2 (HR, 1.89; 95% CI, 1.37-2.60; \(P < .001\)). Visual inspection of the appro-
A total of 4 studies investigated the association of former smoking status with CSM.22,27,31,35 All 4 studies were selected for cumulative analysis. Pooling of available HRs within RT and mixed cohorts (Figure 4B) revealed that patients who had a history of smoking were not at higher risk of CSM (HR, 1.05; 95% CI, 0.81-1.37; \( P = .70 \)). Data were homogeneous in the Cochrane \( Q \) test and the \( I^2 \) statistic, and the corresponding funnel plot revealed no publication bias (eFigure 2F in the Supplement).

Cumulative Pack-years

Overall, 2 studies examined the association of cumulative exposure and smoking cessation with CSM.22,35 Data were too heterogeneous to analyze. Gong et al35 reported that a summarized dosage of 15 pack-years or more was significantly associated with CSM (HR, 5.82; 95% CI, 1.96-17.30; \( P < .001 \)). In addition, a dosage between 1 and 9 pack-years was correlated with CSM (HR, 2.70; 95% CI, 1.10-6.64). Kenfield et al22 found no significant correlation between a cumulative dose of 40 pack-years or more and CSM (HR, 1.75; 95% CI, 0.73-4.19).

Smoking Cessation

In contrast, 2 studies showed that patients who had stopped smoking for 10 years or more were not at higher risk to die of prostate cancer (eTable 6 in the Supplement). Gong et al35 reported an HR of 0.45 (95% CI, 0.19-1.05) for patients who quit smoking more than 10 years ago compared with never smokers. Kenfield et al22 revealed a protective effect for patients who stopped smoking 10 years or more ago (HR, 0.6; 95% CI, 0.4-0.9) in comparison with current smokers.

Discussion

In this systematic review and meta-analysis, we investigated the oncologic outcomes of patients with a different smoking status at the time of primary RP or definitive RT for localized prostate cancer.
prostate cancer. We found that current smokers are at higher risk for BCR, metastasis, and CSM compared with nonsmokers. In addition, former smokers undergoing primary curative treatment were at a significantly higher risk of BCR, but not metastasis or CSM, compared with never smokers. Quantitative analyses on cumulative exposure and smoking cessation were not possible owing to the heterogeneity of data. However, after systematically reviewing all available studies, only 2 studies for each outcome reported on the association of smoking cessation using a cutoff point of 10 years or more; both studies found a clinically significant benefit of smoking cessation of 10 years or more regarding BCR. However, the association with CSM was not significant in 1 of the studies, probably owing to a low event rate.

These findings encourage physicians to use the diagnosis and treatment of localized prostate cancer as a teachable moment to counsel patients to stop smoking. Here, we identified a modifiable risk factor that may improve the outcome of patients with prostate cancer. In fact, smoking appears to affect all disease phases: recurrence, metastasis, and CSM. Regarding the association of smoking with the outcomes of different treatment modalities, the effect summaries for RP and RT do not look different. However, there are statistical limitations to draw this conclusion. The biological underpinning of the association between smoking and poorer oncologic outcomes is further bolstered by the finding of more adverse pathologic features during RP (tumor volume, high-grade volume, and ≥pT3) in smokers. For example, Silva et al found that Hispanic patients with a history of smoking had nearly twice the risk of their Gleason score increasing during active surveillance. Finally, Oefelein and Resnick found an independent association of cigarette smoking with time to castration resistance in a cohort with advanced prostate cancer undergoing androgen deprivation therapy. These reports are consistently building robust evidence. Nevertheless, further research in this field is needed to allow more decisive evidence for guideline recommendations and policymakers.

At the molecular level, several mechanisms can explain the association between smoking and progression of prostate cancer. Inflammatory processes within the prostate have been identified as a disease driver. Furthermore, nicotine is another candidate mechanism that may explain a higher risk of metastasis after diagnosis by increasing interleukin 8 levels. The association between smokeless tobacco and prostate cancer points toward a crucial role of nicotine in prostate cancer. However, another possible way in which smoking may affect prostate cancer outcomes is through CpG hypermethylation. Methylation analysis showed significant correlation between smoking and multigene hypermethylation.

**Limitations**

The methods of the studies included in the meta-analysis are suboptimal. Most of these reports had information about smoking status at the time of primary therapy only but not during follow-up. Some patients may have quit smoking after treatment, and the differential effect on oncologic outcomes of quitting at that time remains unknown. Westmaas et al reported that a cancer diagnosis, even in tumors that are not strongly related to smoking, is associated with a higher subsequent rate of smoking cessation. This outcome could also explain, in part, why former smoking was not associated with CSM as it was with BCR. Another explanation for this lack of association is the limited follow-up and the long natural history of prostate cancer. Furthermore, studies did not provide data on whether former smokers remained nonsmokers during follow-up or not.

Other limitations include the observational and nonrandomized design of the included studies introducing different biases, such as selection and recall biases. Studies’ populations and methods varied widely. Some articles did not differentiate between former smokers and never smokers, grouping them as nonsmokers. Overall, the extracted data were heterogeneous and could not always be compared. Nevertheless, we combined different treatment modalities for comparison owing to the paucity of reports and thereby possibly creating additional bias. Our conclusions are limited by the small numbers of eligible studies in each treatment group and outcome. Furthermore, some studies did not report all calculated results and numerical data, which were required to compare nonrandomized studies. The overall risk of bias was moderate to high. However, through inclusion of multivariable results only, adjusted for the effects of major confounders, we could lower the bias and establish a satisfactory level of comparability.

**Conclusions**

To our knowledge, this is the first systematic review and meta-analysis that investigated the association of smoking with oncologic outcomes after primary treatment for localized prostate cancer. We found that current smokers at the time of RP or RT were at a higher risk of experiencing BCR, metastasis, and CSM after local therapy. Results regarding former smoking and time to cessation were inconclusive because available data were sparse and heterogeneous. Our findings encourage radiation oncologists and urologists to counsel patients to stop smoking, using primary prostate cancer treatment as a teachable moment. Further studies with clear definitions of the study population and a precise assessment of the smoking exposure are needed to clarify the association of smoking cessation with long-term oncologic outcomes.
Author Contributions: Dr Foerster had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Foerster and Pozo are co-first authors.

Study concept and design: Foerster, Pozo, Abufaraj, Shariat.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Foerster, Pozo, Abufaraj, Shariat.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Foerster, Pozo, Mari, Kimura, Shariat.

Administrative, technical, or material support: Foerster, Abufaraj, Mari, D’Andrea, Shariat.

Study supervision: Foerster, Abufaraj, D’Andrea, Shariat.

Conflict of Interest Disclosures: Dr Shariat reported owning or co-owning the following patents: “Methods to determine prognosis after therapy for prostate cancer,” granted September 6, 2012; “Methods to determine prognosis after therapy for bladder cancer,” granted June 19, 2003; “Prognostic methods for patients with prostatic disease,” granted August 5, 2004; and “Soluble Fas: urinary marker for the detection of bladder transitional cell carcinoma,” granted July 20, 2010; serving as an advisory board member for Astellas, Cepheid, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanofi, and Wolff; and serving as a speaker for Astellas, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanomachen, Sanofi, and Wolff.

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**Invited Commentary**

**Smoking and Death From Prostate Cancer**

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The adverse effects of smoking are well established and include all of the above diseases. However, only recently has the association between smoking and prostate cancer become more clear. Part of the challenge is that the associations between smoking and many of those diseases are very strong compared with the association of smoking with prostate cancer, which tends to be weaker. Thus, while at first glance associations with prostate cancer may be null, with larger sample sizes, it is increasingly clear that smoking may be associated with prostate cancer. For example, a recent meta-analysis showed that smokers were 24% more likely than nonsmokers to die from prostate cancer.1 This link was suggested to account for more than 10,000 deaths per year from prostate cancer in Europe and North America alone.

In trying to understand the mechanism linking smoking and death from prostate cancer, the 2 major broad classes of mechanisms are nonbiological and biological. Regarding the former, a previous study showed that smokers were less likely to follow up with recommended biopsy schedules, even when they were enrolled in a phase 3 trial that mandated study-related biopsies.2 Even though smoking was unrelated to risk of prostate cancer or aggressive prostate cancer, when accounting for the fact that fewer smokers underwent biopsy, smoking was positively correlated with high-grade prostate cancer. This finding suggests that smokers may not seek early care soon enough, leading to delayed diagnosis and worse disease at diagnosis. This scenario alone could explain a higher risk of death from prostate cancer. Alternatively, as smoking is associated with death from many competing causes, perhaps smokers do not live long enough to die from prostate cancer. This scenario would predict a lower risk of death from prostate cancer among smokers. To what degree the 24% increased risk of death reflects these 2 opposing confounders as well as any true biological link between smoking and prostate cancer is unclear.

To help address these issues, in this issue of *JAMA Oncology* Foerster et al3 examined men undergoing radical prostatectomy and assessed the association between smoking and death from prostate cancer. By including only men undergoing radical prostatectomy, they took an important and necessary step to level the playing field, as they examined only men who underwent treatment and all of the patients received the same aggressive treatment. Moreover, the study selected for men who were healthy enough to undergo surgery and therefore minimized (but did not eliminate) concerns that smokers do not live long enough to die from prostate cancer. In so doing, the authors found that smokers were 89% more likely to die from prostate cancer and had a 15% increased risk of metastases and a 40% increased risk of biochemical recurrence.

The risk of death from prostate cancer was 89% higher among healthy smokers undergoing surgery vs only 24% higher among all men. This finding shows that when we treat patients equally and minimize deaths from other causes, there is a stronger link between smoking and death from prostate cancer. This finding supports the idea that many smokers will not live long enough to die from prostate cancer, given the overall slower-growing nature of prostate cancer and the effects of smoking on competing causes of death. More important, however, it argues that the higher rate of death from prostate cancer among smokers is “real,” that is, there is a biological cause.

The exact biological link between smoking and prostate cancer is not clear, although several hypotheses have been put forward.4 For example, carcinogens inhaled from smoke are excreted in the urine, which explains the link between smoking and kidney and bladder cancer. As the urine passes through the prostate, it is possible that the urine is exposed to the same carcinogens. Alternatively, smoking leads to systemic hypoxia,5 which may contribute to aggressive prostate cancer.6 Another possibility is increased...