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The Causal Role of Cigarette Smoking in Bladder Cancer Initiation and Progression, and the Role of Urologists in Smoking Cessation

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Purpose: Cigarette smoking is a well established risk factor for bladder cancer. We characterize the changing impact of this exposure throughout the course of bladder cancer from incidence through progression. We also discuss how understanding the risk of bladder cancer attributable to smoking can help urologists effectively communicate with their patients and influence smoking cessation in their patients.

Materials and Methods: A review using the MEDLINE® database from 1975 through 2007 was performed to search for studies from the epidemiological and medical literature on cigarette smoking and bladder cancer.

Results: Cigarette smoking accounts for up to 50% of all incident bladder cancer cases, an attributable fraction that may be increasing. The general public is not informed of the association between cigarette smoking and bladder cancer, and physicians do a poor job of counseling patients regarding this risk. Smoking cessation has proven beneficial in decreasing the risk of many smoking related illnesses, including bladder cancer. Simple physician interventions can be effective in triggering patient attempts at quitting smoking.

Conclusions: Bladder cancer is causally related to cigarette smoking but this knowledge may not be well disseminated to patients. Furthermore, cigarette smoking cessation decreases bladder cancer risk and may decrease the recurrence of superficial bladder cancer. Urologists have a vital role in influencing patient knowledge of their smoking risk and in encouraging smoking cessation.

Key Words: bladder, bladder neoplasms, smoking, epidemiology, physician-patient relations

Cigarette smoking is causally related to the development of bladder cancer. In urology this simple statement is widely accepted. However, the epidemiological principles underlying this statement are not well-known by physicians[1] and the amount of bladder cancer attributable to cigarette smoking is not understood by patients.[2] Because 67,160 new cases of bladder cancer were expected in the United States in 2007,[3] bladder cancer imposes a significant burden on patients and the health care system. Furthermore, bladder cancer is among the most costly cancers to treat in the United States.[4]

We examined the epidemiological and medical evidence linking cigarette smoking with bladder cancer. We established how the risk of bladder cancer from smoking is calculated, explored the evidence that smoking cessation can affect bladder cancer recurrence and determined the public knowledge of bladder cancer risk. Finally, the role and efficacy of the urologist in cigarette smoking cessation counseling was examined.

ATTRIBUTABLE RISK OF SMOKING ON BLADDER CANCER

Before patients can be counseled effectively on the risk factors that influence their health their physicians must fully understand the impact of those risk factors. Unfortunately the amount of bladder cancer risk that can be attributed to cigarette smoking varies. In urology texts and general reviews of bladder cancer smoking is stated to account for a third to a half of bladder cancers.[5,6] To determine why such ranges exist in these estimates it is necessary to discuss how the allocation of risk to a single possible cause of cancer is calculated.

When a putative risk factor is determined to cause a disease, a determination of the amount of disease caused by the risk factor is necessary. To this end the term attributable risk was introduced in 1976 by Walter.[7] While attributable risk has been used for various epidemiological measurements in the past,[8] current terminology uses the term attributable fraction for causal risk factors. Two common methods of expressing this attributable fraction are used. The fraction of disease due to an exposure in the total population, for example smokers and nonsmokers, is considered the attributable fraction. The proportion of disease in the total exposed population, for example only smokers, is considered the attributable fraction in the exposed.[8] Thus, the definitions of attributable fraction differ in the population at risk for the disease. For bladder cancer the attributable fraction would be the amount of disease due to smoking in

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the whole population with the total population in the denominator of the equation. Attributable fraction in the exposed would use only the number of smokers as the denominator. For population studies attributable fraction in the whole population is the important statistic and it is commonly referred to as PAR. PAR is important in public health work because it represents the proportion of cases that could be theoretically eliminated from the population if the exposure was removed.[9]

Mathematically the attributable fraction in the exposed can be expressed as the estimated risk ratio minus 1 divided by the estimated risk ratio. The attributable fraction is the proportion of new cases exposed multiplied by the attributable fraction in the exposed. To clarify we can look at a simple example. Envision a prospective cohort study with 100 patients examined during 5 years. There are 50 smokers and 50 fifty nonsmokers. Bladder cancer develops in 30 smokers and 10 nonsmokers. The risk ratio for a smoker to have bladder cancer is (30/50)/(10/50) = 3. Therefore, the attributable fraction in the exposed is (3 − 1)/3 = 66%. The attributable fraction is (30/40)(0.66) = 0.495. The PAR of bladder cancer in this population is approximately 50%.

From this conceptual framework we can examine the PAR of cigarette smoking for bladder cancer cases. Early case-control studies showed a difference in the PAR for smoking in men and women. For example, Howe et al determined that the PAR in men was 61% and in women it was 26%.[10] Thus, if smoking was eliminated from the population, there would be 61% fewer bladder cancer cases in men and 26% fewer in women. Other studies that collected data in the 1980s showed similar results. Hartge et al noted in a population based case-control study that the PAR for cigarette smoking was 50% in men and 33% in women.[11] In a Norwegian case-control study nested in a prospective cohort study of 120,852 adult participants Zeegers et al determined that the estimated PAR for cigarette smoking in men was 50%, whereas in women it was 23%.[12]

From these results we might conclude that eliminating cigarette smoking would have different effects on the rates of bladder cancer in men and women. However, this interpretation of the PAR would not be fully correct. The incidence of bladder cancer is 3 times higher in men than in women.[3] This higher rate of cancer could be an intrinsic genetic factor associated with being male or the higher incidence rate could be a result of differential exposure between men and women. In the case of bladder cancer women in the studies with data from the 1980s had different cigarette smoking histories than men.[12,13] Thus, an important interplay is established between an individual risk of disease, population rates of disease and the prevalence of a risk factor in a population.

Risk is conceptualized as the probability of disease developing in an individual and rates are population based measures of disease.[14] Rates can measure incidence (the number of new cases of a disease) or prevalence (the total number of cases in a population).[14] When discussing risk factors, the prevalence of the risk factor in the population is important. Since the prevalence of cigarette smoking in women is lower than in men, the risk and the rate of bladder cancer are lower in women. Because fewer women than men smoke, women in whom bladder cancer develops are less likely to have a smoking history. If risk in women is examined based on cigarette smoking status, ie attributable fraction in the exposed, the risk of bladder cancer in women with a cigarette smoking history is equal or greater than that in men with the same degree of cigarette smoking.[13,15] Thus, the lower PAR of cigarette smoking in women than in men in current studies is a reflection of a lower frequency of smoking in women and not a lower risk of smoking in women.

The influence of cigarette smoking on bladder cancer risk is not static. Zeegers et al noted in a meta-analysis of studies of smoking and bladder cancer from the 1960s to the 1990s that the PAR for cigarette smoking in Europe was 34.7% in females and 50% in males.[16] This PAR was based on an average prevalence of smoking of 28% in women and 43% in men across the studies examined. Since the prevalence of cigarette smoking in women in Europe is estimated to range from 5% in Belarus to 32% in Norway and in men from 25% in Iceland to 60% in Albania,[17] the PAR estimated in the Zeegers et al meta-analysis[16] will change in the future.

Another subtlety of the PAR is reflected in the meta-analysis of the risks of cigarette smoking on bladder cancer in men by Brennan et al.[18] In this study 11 case-control studies with data collected in the 1980s and 1990s were combined. The PAR for ever smoking in males was 66% and the PAR for current smoking in males was 32%. At first glance these results do not appear to be correct. If smoking is a cause of bladder cancer, should not current smokers be at highest risk? Indeed, at the individual level former smokers had lower odds of bladder cancer than current smokers. The higher PAR for a history of smoking than for continued smoking reflects the much larger pool of former smokers than current smokers in the populations studied. Therefore, more bladder cancer cases represent former smokers than continuing smokers, although continuing smokers may be at individually higher risk for bladder cancer than former smokers. Interestingly Brennan et al found that in men younger than 60 years the PAR for ever smoking was 73%, raising the possibility that group effects by age are present. Thus, in the meta-analysis by Brennan et al smoking appears to be increasing in importance as a risk factor for bladder cancer in more recent patient cohorts. Brennan et al speculated that decreasing industrial exposure could have been replaced by increasing exposure to cigarette smoking in more recent cohorts.

Such speculation has empirical support. Since the bladder cancer incidence increases with increasing age,[3] current bladder cancer incidence rates reflect the influence of cigarette smoking prevalence from the 1950s and 1960s. The prevalence of smoking peaked at 42% of all adults in the United States in 1965[19] and it is currently 20%.[20] Due to the long latency period from cigarette smoking exposure to the development of bladder cancer the population at risk for bladder cancer remains large. As the cohorts with a lower past prevalence of smoking age, the overall rate of bladder cancer should decrease. However, the PAR due to smoking may increase, remain stable or decrease depending on the distribution of other risk factors for bladder cancer in the population.

Overall cigarette smoking is strongly associated with an increased risk of bladder cancer. Tables 1 and 2 show the link between the prevalence of smoking and the bladder cancer incidence. Likely this link is increasing in more recent cohorts since the full effect of the smoking epidemic becomes apparent in bladder cancer incidence rates.[21] The current low PAR in women is likely related to the lower rates

TABLE 1. *Fast facts about smoking and bladder cancer*

	% Pts
Bladder Ca due to cigarette smoking:[16]	
Men	50
Women	34.7
Current cigarette smoking in new pts with bladder Ca in 1996[38]	40
Cigarette smoking in United States in 2005:[39]	
Men	23.9
Women	18.1

of female cigarette consumption compared to men in the past. As the smoking histories of women catch up to their male peers, the PAR for bladder cancer related to cigarette smoking in women will likely increase.[21]

SECONDHAND SMOKING AND BLADDER CANCER RISK

In addition to the individual choice to smoke cigarettes, many individuals have been exposed indirectly to the carcinogens in cigarette smoke through secondhand smoking. This passive tobacco exposure or environmental tobacco smoking could be an important risk factor for bladder cancer in those classified as nonsmokers in older studies. The results of examining this factor in prospective studies have been inconsistent. In a large prospective cohort study no measures of secondhand smoking were significantly associated with an increased bladder cancer risk.[12] In a second large cohort study exposure to secondhand smoke as a child was significantly associated with an increased risk of bladder cancer but adult exposure to secondhand smoke was not.[22] This is in contrast to lung cancer results, for which exposure to secondhand tobacco smoke in childhood was inconsistently associated with the development of disease and adult exposure was significantly related to the risk of the disease.[23] In a smaller prospective cohort study a group with a followup that started in 1963 showed a 2.3-time increase in the risk of bladder cancer in nonsmoking women exposed to secondhand smoke compared to that in nonsmoking women not so exposed.[24] In that study a group followed since 1975 showed no association between secondhand smoke and bladder cancer. The most recent study on this subject by Jiang et al indicated a dose response effect for the amount of secondhand smoke exposure that a woman experienced in her life and the development of bladder cancer.[25] Also, childhood exposure to more than 1 smoker significantly increased the odds of bladder cancer. Jiang et al determined from these results that 74% of bladder cancer in female nonsmokers may be attributable to environmental tobacco smoke exposure.

Overall the results of studies of environmental tobacco smoke and bladder cancer show that exposures in childhood and in women exposed to spousal and workplace smoking might be a risk factor for bladder cancer but consistent results have not been found. Multiple issues with misclassification may be present in these studies. Although these studies were prospective, they asked adults about their exposures to smoking as children. Furthermore, environmental tobacco smoke exposure was measured differently in these studies,[12,22,24,25] so that comparisons across the studies might not be valid. Also, the duration and frequency of exposure were not consistently measured, so that additional sources of misclassification may exist. For example, an individual with a spouse who was a smoker would be classified as exposed even if the spouse never smoked in the presence of the subject.

SMOKING AND GENETIC PREDISPOSITION TO BLADDER CANCER

Although exposure to cigarette smoke increases the risk of bladder cancer, bladder cancer does not develop in all smokers. Significant gene environment interactions must exist that make the risk of smoking substantially greater in susceptible individuals. Indeed, a family history of bladder cancer alone did not increase the bladder cancer risk but a family history combined with smoking significantly increased the odds of bladder cancer.[26] Multiple studies have explored the association between genetic polymorphisms and bladder cancer risk with inconsistent results. [27–31] The polymorphism most closely tied to an increase in bladder cancer risk has been the NAT2 slow acetylator phenotype.[32]

While exploring genetic factors in the initiation and progression of bladder cancer is vital to developing new diagnostic and therapeutic modalities, the usefulness of genetic factors in disease prevention is less clear. The desire to find personalized risk factors has been tied to the idea of personal prevention.[33] However, since genetic factors are not modifiable, interventions occur on environmental factors, such as cigarette smoking, that interact with genetic factors to cause disease. While a genetic predisposition to cancer development might spur patients to quit smoking, the small ORs found in epidemiological studies make it difficult to classify individuals into specific risk categories.[34] Furthermore, in patients who have already successfully quit smoking identifying a genetic predisposition to cancer development may help with early disease detection and screening but not prevent the development of disease. Thus, even more in individuals with a genetic predisposition toward an increased bladder cancer incidence with smoking, eliminating smoking behaviors is the key to preventing the development of bladder cancer.

SMOKING CESSATION AND REDUCTION OF BLADDER CANCER RISK

Smoking cessation decreases the future risk of bladder cancer. The risk of bladder cancer in former smokers decreases at a significant rate of up to 40% in the first 4 years after cessation.[18] The risk reduction may be progressive with increasing years since smoking cessation.[12] Alternatively a

TABLE 2. *Cigarette smoking prevalence by age and gender in United States in 2005*[39]

Age	% pts
Men:	
18–24	28
25–44	26.8
45–64	25.2
65 or Older	8.9
Women:	
18–24	20.7
25–44	21.4
45–64	18.8
65 or Older	8.3

plateau in the risk reduction may occur.[18,22] Although some damage due to smoking may be irreversible, in many individuals eliminating smoking will decrease the individual risk of bladder cancer.

While decreasing the incidence of bladder cancer through eliminating cigarette smoking would be an important public health activity, interventions to decrease recurrent bladder cancer might also be warranted. Can smoking cessation prevent or decrease bladder cancer recurrence? A retrospective review from Memorial-Sloan Kettering Cancer Center addressed this issue in patients with superficial disease.[35] Continued smokers had more rapid recurrence than nonsmokers and ex-smokers, and on multivariate analysis continued smoking was associated with a significantly increased relative risk of cancer recurrence.[35] These data were reanalyzed as part of a systematic literature review of bladder cancer recurrence and smoking. The HR for recurrence when smoking was stopped at diagnosis vs continued smoking was 0.71 (95% CI 0.48 to 1.05).[36] The evidence from available studies favors a decreased recurrence risk with quitting but lacked sufficient statistical power to persuasively claim a benefit for any individual patient.[36] Chen et al provided further evidence for a beneficial effect of smoking cessation on bladder cancer recurrence.[37] Continued smokers were found to have a 2.2-time increased risk of bladder cancer recurrence compared to individuals who quit smoking within 1 year before and 3 months after diagnosis. Although smoking cessation is not likely to affect mortality, it may decrease superficial bladder cancer recurrences as well as the burden of the disease.

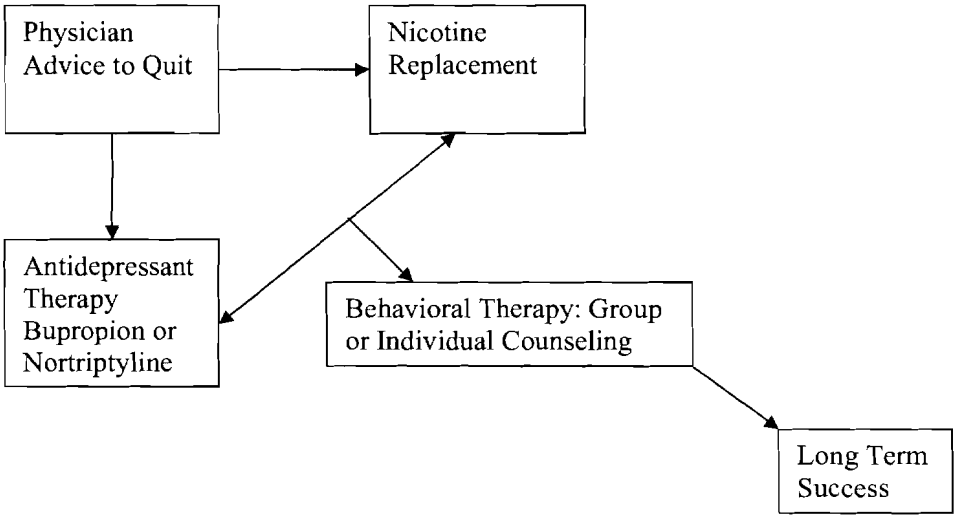
For smoking cessation to be successful as an intervention strategy to improve outcomes in patients with bladder cancer a significant percent of these patients must be current smokers. In a survey of patients from 1995 to 1996 at a single cancer center 40% of those newly diagnosed with bladder cancer were current smokers.[38] At such a high prevalence smoking cessation intervention would be warranted to try to help decrease disease recurrence. Unfortunately current data are lacking on the cigarette smoking prevalence in patients with bladder cancer. In the population 65 years or older most at risk for bladder cancer less than 9% are active smokers.[39] If this cigarette smoking prevalence matches the cigarette smoking frequency of patients in whom bladder cancer is currently developing, targeted interventions in smokers with bladder cancer would not decrease the risk of recurrent disease. Current population based data on the cigarette smoking prevalence in patients with incident bladder cancer is needed to fully assess the potential of smoking cessation as a health improvement strategy in this important population.

Beyond bladder cancer prevention and control the health benefits of smoking cessation are substantial. A recent commentary reviewed these benefits, as determined by a working group at the International Agency for Research on Cancer.[40] The Appendix lists these benefits of smoking cessation. Furthermore, a randomized clinical trial has shown a mortality benefit to smoking cessation intervention.[41]

PHYSICIAN ACTIVITY IN SMOKING CESSATION

Given the health benefits that accrue from smoking cessation, are physicians actively encouraging patients to quit smoking? General practitioners in England were shown to vary in their beliefs in the effectiveness of medical interventions for smoking and, thus, in their use of such interventions.[42] According to the 2000 National Health Interview Survey only 50% of daily smokers who visited a physician reported receiving advice to quit.[43] When assessing physician practice patterns from the National Medical Care Survey from 1991 to 1995, slightly more than 20% of visits by smokers included documented cessation counseling.[44] Additionally, smoking status was documented at only 67% of visits. Urologists as a specialty may do even worse with such counseling. Despite the well-known risks of smoking on bladder cancer, in a study from the United Kingdom only 7% of patients with bladder cancer reported being advised to quit by their urologist.[45]

A reason that physicians might not pursue smoking cessation counseling is the belief that their recommendations do not matter. In a systematic review Vogt et al found that 42% of primary care physicians believed that smoking cessation counseling was too time-consuming and 38% thought that it was not effective.[46] These beliefs of the lack of usefulness of smoking cessation counseling are not supported by



Smoking cessation overview

research into the effectiveness of physician advice for smoking cessation. In a study of a brief intervention by physicians and nurses during routine obstetrical followup visits 33% of smokers in the counseling group achieved abstinence compared to 8.3% who did not receive the targeted counseling.[47] When doctors asked their patients about smoking, patients increased their attempts to quit. While 36% of patients reported spontaneous attempts to quit, 47% who had been asked about their smoking habits reported at least 1 attempt.[48] In modeling based on the 2001 National Health Information Survey some physician advice to quit smoking was associated with an increase in the percent of patients quitting of 6.9% to 14.7% in the 12 months after the advice.[49] Even simple interventions can help patients make successful attempts to quit.

While brief physician encounters may provide an impetus for a patient to attempt to quit smoking, long-term quitting rates are improved by various medical and behavioral supports for smoking cessation. Nicotine replacement therapy increased the chance of stopping smoking by 50% to 70% in a meta-analysis of 132 randomized trials with more than 40,000 participants.[50] The use of bupropion or nortriptyline approximately doubles the odds of successfully quitting cigarette smoking but their long-term impact in combination with nicotine replacement has not been fully established.[51] As an adjunct to medical therapy, individual and group counseling can help patients quit smoking but group counseling seems to have better results.[52,53] Thus, various options exist for physicians to help their patients achieve successful smoking cessation. The figure shows a schematic for smoking cessation therapy.

ISSUES IN PATIENT EDUCATION

The lack of patient education by health care providers on the causal role of cigarette smoking in bladder cancer would not be a problem if patients received this information from other sources. Unfortunately in the general public these associations are much less appreciated. Even among patients with bladder cancer and other urological diseases these risks are not known. While 98% of patients surveyed knew that smoking was a risk factor for lung cancer, only 36% knew that smoking was a risk factor for bladder cancer.[2] Of patients with bladder cancer only 22% knew that smoking was a risk factor for the disease.[45] A gap exists between patient knowledge and actual risk. For successful interventions to decrease the bladder cancer incidence this lack of knowledge must be rectified.

CONCLUSIONS

Cigarette smoking is the most consistent etiological factor implicated in bladder cancer. Robust epidemiological evidence supports a role for cigarette smoke in the initiation and the progression of bladder cancer. Eliminating cigarette smoking from the population would be expected to decrease the bladder cancer incidence by at least 50%. As the influence of occupational exposure decreases in developed nations, the proportion of bladder cancer cases attributable to cigarette smoking is expected to increase.

Fortunately interventions can help decrease the morbidity of bladder cancer related to smoking. Smoking cessation likely decreases superficial disease recurrence but the impact on bladder cancer progression and mortality is less clear. Furthermore, the future incidence of bladder cancer can be decreased through smoking cessation. Unfortunately urological patients are not being informed of the risk of their smoking habits and public education has not occurred through nonphysician sources. Thus, as urologists, we must accept a responsibility to provide cigarette smoking cessation counseling to rectify the information deficit and improve the health of our patients.

APPENDIX

Risk Reduction after Smoking Cessation

Bladder cancer[18,40]	40% Decrease in risk within 4 years of smoking cessation Risk higher than in never smokers for at least 25 years
Lung cancer[40]	Lower risk in former smokers compared to current smokers apparent within 5 to 9 years
Heart disease[40]	Relative risk reduction of 35% in former smokers compared to continued smokers within 2 to 4 years of quitting Risk in former smokers may be similar to never smokers after 10 to 15 years of abstinence
Cerebrovascular disease[40]	Risk reduction within 2 to 5 years Risk in former smokers returns to that of never smokers within 5 to 10 years in most studies
Chronic bronchitis[40]	Symptoms decrease within a few months of stopping smoking Prevalence of symptoms the same as in never smokers within 5 years

Abbreviations and Acronyms

PAR = population attributable risk

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EDITORIAL COMMENT

The financial burden of bladder cancer on the American public has been estimated to exceed $1 billion annually,[1] while the human burden is also immense. That tobacco use is well established as the principal risk factor for bladder cancer presents urologists with a unique opportunity to engage in preventive medicine. Indeed, counseling our patients to quit smoking may be the single most important thing that we do as physicians to alleviate preventable death and disability.[2] These authors summarize the epidemiology of the problem as well as how we can intervene. Patients advised by their physicians to stop smoking are twice as like to quit within 12 months (reference 49 in article). Our Hippocratic oath compels us to implore them to do so.

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