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RESEARCH HIGHLIGHT

Smoking and prostate cancer survival and recurrence

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Smoking is associated with several major benign and malignant diseases, representing one of the most important modifiable risk factors. Among urothelial neoplasms, smoking is pivotal in tumor carcinogenesis, but its role in prostate cancer is still controversial. Many authors have failed to demonstrate an association between smoking and prostate cancer.[1–3] However, large epidemiological studies have shown that smoking is associated with higher risk of developing and dying of prostate cancer.[4] Thus, large sample sizes and long follow-ups are important when studying prostate cancer given that its natural history can be quite long. In selected clinical scenarios, smoking has been reported to be related to worse disease after diagnosis. For example, prostate cancer was associated with more aggressive disease at diagnosis[5] and after surgical treatment,[6] higher recurrence rates after surgery[7,8] and radiotherapy,[9] increased risk of metastatic disease after radiotherapy[10] and worst overall survival.[1,11] However, large epidemiological studies are still required to confirm these findings and elucidate the role of cigarette smoking on prostate cancer progression after diagnosis.

Recently, Kenfield *et al.*,[12] using data from the Health Professionals Follow-Up Study, published a paper investigating the association of prostate cancer with overall, disease-specific and disease-free survival. In that study, they evaluated a cohort of 5366 prostate cancer cases over a follow-up of 22 years. All patients provided detailed information on smoking status before cancer diagnosis. Smoking exposure such as cumulative tobacco exposure (pack-years), smoking status (current, former, never) and time since quitting and prostate cancer outcomes including biochemical recurrence, overall survival, prostate cancer-specific mortality (PCSM) and cardiovascular mortality were analyzed. At cancer diagnosis, current smokers had higher clinical stage and grade compared with non-smokers ($P<0.001$). In addition, they found that smokers exercise less, drink more coffee, consume more saturated fat and less calcium and tend to have less previous screening for prostate cancer. Smokers had higher risk of biochemical recurrence (HR=1.61), PCSM (HR=1.61), cardiovascular mortality (HR=2.13) and all-cause mortality (HR=2.28). At 5 years of follow-up, a higher disease-specific mortality among smokers was already noted and persisted throughout the study interval. Non-smokers and former smokers who had quit for more than 10 years before cancer diagnosis had a better prognosis than current smokers or more recent quitters. The absolute crude mortality rates per 1000 person-years were 9.6 and 10.3 respectively for non-smokers and long-term former smokers, and 13.8 and 15.3 respectively for more short-term former smokers and current smokers. A dose–effect relationship between smoking and disease-specific mortality was observed. Interestingly, former smokers who quit less than 10 years before cancer diagnosis and smoked less than 20 pack-years had similar risks to current smokers for biochemical recurrence, but their risks of dying from prostate cancer were comparable to never smokers.

The authors hypothesize that the deleterious effects of smoking on prostate cancer mortality are due to worst stage and grade at diagnosis. Given that prostate cancer stage is altered by screening,[13] it is conceivable that smokers present with more advanced disease in part due to the lower screening rate observed in the study. This suggests that smokers may be less attentive to preventive measures than non-smokers which may have deleterious consequences later, given that patients with locally advanced disease are known to have worst survival[14] and screening practices for prostate cancer have impact on mortality.[15,16] This is also supported by the fact that no differences in PCSM between smokers and non-smokers were observed after adjustment for cancer stage and grade and screening. Moreover, the authors speculate that the biological effects of smoking on cancer progression may be mediated by direct action of carcinogens, modulation of sexual hormones, epigenetic gene expression changes, nicotine-induced angiogenesis or the interplay among them. Although all these hypotheses are plausible, their data do not favor any specific pathway. Thus, it will be interesting to see further studies looking at these mechanisms by which smoking affects prostate cancer.

The study is not without limitations. One of the caveats is that, being a cohort of health professionals, the prevalence of smoking is only 5.2%—three times lower than many other series. Thus, it is possible that in populations with higher prevalence of smoking the differences in PCSM between groups may be diluted or attenuated, given that the strength of the association found was much higher for cardiovascular mortality and all-cause mortality. In those populations, patients might die of other smoking-related diseases before developing end-stage prostate cancer, reducing the effect of smoking on PCSM. Another limitation is that primary therapies for prostate cancer were not explored in detail. Given that smoking is associated with comorbidities which, in turn, may be correlated with treatment option, it is important to take into consideration that treatments may vary among smoking groups and that may modify the disease course. Finally, no information about smoking habits changes after diagnosis was available. Given the long natural history of prostate cancer, changes in smoking habits

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such as quitting smoking may also affect disease progression and ideally should be accounted for.

In conclusion, this is one of the largest studies that demonstrated an association between smoking at the time of diagnosis and adverse prostate cancer events. Its strengths include the large sample size, long follow-up, consistency of findings and dose–effect relationship of their results. The authors found that smoking was associated with worst overall and PCSM mainly due to its effect on tumor differences at diagnosis in this population of low prevalence of current smokers. The effect of smoking on PCSM seems to be reversible after 10 years of cessation of cigarette consumption before a prostate cancer diagnosis. Their conclusions reinforce the benefits of counseling patients for smoking cessation, especially before diagnosis of prostate cancer, but in the current era of highly screened populations and stage migration to better clinical profiles at diagnosis, its role in this type of contemporary setting of early screening-detected cancers remains to be determined in present prospective cohorts.

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