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Clearing the air: summarizing the smoking-related relative risks of bladder and kidney cancer

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Cigarette smoking was established several decades ago as the major cause of bladder cancer, estimated to account for approximately half of all cases (1). Kidney cancer was more recently accepted as a tobacco-related malignancy, with approximately 20% of cases attributable to smoking (2). Despite the extensive epidemiologic evidence accumulated to date, it has proven challenging to characterize the magnitude of the relative risk from smoking for these cancers, as findings vary substantially owing to differences in study design, target population, time period, and other factors. Meta-analysis is a valuable tool for providing insight into the relationship between tobacco smoking and the risk of these two main cancers of the urinary tract.

In this month's issue of *European Urology*, Cumberbatch et al. report on the latest and most comprehensive meta-analyses to date of smoking and cancers of the bladder and kidney (3). The authors are to be commended for their exhaustive review, sifting through abstracts from over 2,600 publications to identify and summarize 107 relevant articles. The wide breadth of this project, summarizing the evidence for both of these urinary tract sites, is a particular strength. Importantly, the weaker associations for former smokers than for current smokers confirm the importance of smoking cessation as a means of reducing one's risk of developing these cancers.

One limitation complicating the interpretation of the findings of Cumberbatch et al. involves the substantial study heterogeneity present in their meta-analyses. Heterogeneity, often measured using the I^2 statistic, is defined as inconsistency beyond that expected by chance. In principle, the findings of a meta-analysis are valid only to the extent that the underlying study-specific results vary randomly around a consistent effect. In these meta-analyses, most summary effect measures for bladder cancer incidence are based on findings with considerable study heterogeneity, with I^2 statistics usually exceeding 75%. For kidney cancer, the heterogeneity is more moderate, with I^2 values generally between 30% and 65%.

Study design is an important source of heterogeneity. Cumberbatch and colleagues point out that misclassification of smoking can bias results of both case-control and cohort studies. However, case-control studies are more prone to differential recall of smoking habits, which may in part explain the higher pooled estimates of bladder cancer risk based on the case-control studies compared to those based on the reported cohort studies (3). Further, it is clear that additional factors are contributing to heterogeneity, as the I^2 statistics remained high in meta-analyses conducted separately for case-control and cohort studies. Similarly, I^2

statistics indicated substantial heterogeneity in meta-analyses stratified by sex and study region.

What other sources of heterogeneity are involved? Additional study design issues may play a role. The use of hospital controls may result in an overrepresentation of smokers compared to the actual source population of cases, leading to odds ratios biased towards the null (4). This is evident in the meta-analysis of current cigarette smoking and kidney cancer incidence, where 3 of the 4 findings from hospital-based case-control studies are weaker than the summary relative risk estimate, while only 1 of the 9 population-based case-control study findings is weaker than the summary estimate (3). Differences in case definition can also introduce heterogeneity; as an extreme example, the null finding for current smoking observed in the African study of bladder cancer by Vizcaino et al. is likely a reflection of the fact that nearly three-quarters of cases are squamous cell carcinomas, primarily caused by schistosomiasis (3, 5).

Why is there more study heterogeneity for bladder cancer than for kidney cancer? One possible reason is the potential importance of calendar period covered by the study. Findings from recent studies suggest that the relative risk of bladder cancer for current smokers has increased from about three times the risk of nonsmokers to about four- to five times the nonsmoker risk over the past two decades in the U.S. (1, 6, 7) and in Europe (8). It has been suggested that this trend may be due to changes in cigarette composition leading to a reduction tar and nicotine concentrations in cigarette smoke, but also to an apparent increase in the concentration of bladder carcinogens such as β -naphthylamine (9). Additional research is needed to further evaluate this provocative hypothesis. To our knowledge, no studies to date have evaluated whether smoking-related relative risks of kidney cancer have increased in recent years. Given the comparatively weak association with smoking for this cancer, any such change may be small and difficult to detect.

The differences in summary relative risks between former and current smokers observed by Cumberbatch et al. offer reassurance of the benefit of smoking cessation for bladder and kidney cancer patients. However, this finding begs additional questions requiring clarification through meta-analysis, such as the importance of timing of cessation (i.e., at how many years after cessation does risk begin to decrease, and by how much). Although little is known about the effects of cessation on kidney cancer risk, such effects have been evaluated in numerous bladder cancer studies. Some studies suggest that the risk of former smokers who stopped smoking for many years returns to the level of nonsmokers (5). In contrast, other studies suggest that a risk reduction occurs within 4 years of stopping, but that risk either does not continue to decrease with increasing time since stopping or does continue to decline but does not return to the level of nonsmokers even after 20 to 25 years of cessation (5, 7, 8).

The association between tobacco use and risks of urinary tract cancers will remain an important research priority as usage patterns change and new products emerge. Other important questions for future research include continuing the search for variants in our genome that modify the smoking-related relative risks for these tumors and characterizing the translational implications (10). Ultimately, developing more effective strategies to

prevent initiation of smoking and support successful smoking cessation efforts will be instrumental for the prevention of bladder cancer, and to a lesser extent, kidney cancer.

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References

1. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. *JAMA* 2011 8 17;306(7):737–45. [PubMed: 21846855]
2. Benichou J, Chow WH, McLaughlin JK, Mandel JS, Fraumeni JF, Jr. Population attributable risk of renal cell cancer in Minnesota. *Am J Epidemiol.* 1998 9 1;148(5):424–30. [PubMed: 9737554]
3. Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The Role of Tobacco Smoke in Bladder and Kidney Carcinogenesis: A Comparison of Exposures and Meta-analysis of Incidence and Mortality Risks. *Eur Urol* 2015 7 3.
4. Modern Epidemiology. Second Edition Philadelphia, PA: Lippincott-Raven; 1998.
5. Silverman DT, Devesa SS, Moore LE, Rothman N. Bladder Cancer. In: Schottenfeld D, Fraumeni JF, Jr., editors. *Cancer Epidemiology and Prevention Third Edition*. New York: Oxford University Press; 2006 p. 1101–27.
6. Baris D, Karagas MR, Verrill C, et al. A case-control study of smoking and bladder cancer risk: emergent patterns over time. *J Natl Cancer Inst* 2009 11 18;101(22):1553–61. [PubMed: 19917915]
7. Welty CJ, Wright JL, Hotaling JM, Bhatti P, Porter MP, White E. Persistence of urothelial carcinoma of the bladder risk among former smokers: results from a contemporary, prospective cohort study. *Urol Oncol* 2014 1;32(1):25 e1–5.
8. Bjerregaard BK, Raaschou-Nielsen O, Sorensen M, et al. Tobacco smoke and bladder cancer--in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer.* 2006 11 15;119(10):2412–6. [PubMed: 16894557]
9. Hoffmann D, Hoffmann I. The changing cigarettes: chemical studies and bioassays In: Shopland DR, Burns DM, Benowitz NL, Amacher RH, editors. *Risk Associated With Smoking Cigarettes With Low Machine-Measured Yields of Tar and Nicotine*. Bethesda, MD: U.S. NIH, National Cancer Institute, NIH Publication No. 02–5074; 2001 p. 159–91.
10. Garcia-Closas M, Rothman N, Figueroa JD, et al. Common genetic polymorphisms modify the effect of smoking on absolute risk of bladder cancer. *Cancer Res* 2013 4 1;73(7):2211–20. [PubMed: 23536561]