The Authors’ Response to Dr. Behrens regarding “Urinary bladder cancer risk factors in Egypt: a multicenter case-control study”

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To the Editors:

We have carefully reviewed the letter by Dr. Thomas Behrens regarding our epidemiological study of bladder cancer. Dr. Behrens raises an interesting question concerning apparent inconsistencies between our results regarding tobacco association and the results of studies in Europe and the United States, especially since neither of the recent articles he cites were available at the time we submitted our paper to this journal. As we noted in the Discussion section of our paper (1), “Worldwide, urothelial carcinoma is the predominant type of urinary bladder cancer (>90%) and cigarette smoking is a well-established risk factor;” and we noted and referenced aspects of cigarette smoking dose and behavior that have been previously
associated with increased risk. Dr Behrens correctly observes that our results from the study in Egypt are different from most previous work, and indeed we discussed this point in our paper. Several of these differences between our study population and Western populations are worth repeating (2,3): “It should be noted that cigarette smoking habits are different in Egypt compared with the developed countries and are characterized by lower levels of pack-years and a large proportion of nondaily smokers ... In our study population, 83% of smokers smoked less than 20 cigarettes (1 pack) per day and less than 5% of the smokers smoked 40 cigarettes (2 packs) or more per day, consistent with previous reports of low levels of pack-years smoking among Egyptian men. Therefore, the observed association between cigarette smoking and the risk of urothelial carcinoma among Egyptian men may partly reflect the overall low levels of exposure.” We also pointed out that, among current smokers in our study, those who smoked 2 or more packs per day had 4.4 times higher risk of urothelial carcinoma (UC) than never smokers -- a level of risk comparable with what has been observed in the developed countries.

We also had a unique opportunity to include cases of squamous cell carcinoma (SCC) in our study, which have not been included in previous reports due to its rarity in the developed countries. Even within Egypt and other countries where SCC is more prevalent, some previous reports, including those cited by Dr. Behrens, did not clearly distinguish SCC from other histological subtypes, furthering underscoring the uniqueness of our findings. In addition, we were able to assess the risks associated with environmental tobacco smoke (ETS), which is also different in Egypt compared the developing countries and well documented in the Discussion section of our paper. To summarize, in Egypt the vast majority of smokers are adult males, living with their families in small, cramped housing where they smoke cigarettes and waterpipes freely.
Even in public places, clean air regulations are just beginning to be enacted and enforced, and the dangers of ETS exposures have yet to be effectively communicated to the public. As a result, levels of ETS in Egypt are very high and reflect both cigarette and waterpipe consumption (2), exposing millions of smokers and nonsmokers, in contrast to previous studies elsewhere that have often lacked statistical power to detect elevated odds ratios or relative risks associated with ETS. It is therefore plausible that the associations we observed between ETS and bladder cancer risk are more evident in our study than elsewhere. ETS was also associated more strongly with UC than SCC, similar to active smoking.

Dr. Behrens also raised study design issues. We are gratified that he noted the “surprisingly high response among controls” that was achieved through the talent and dedication of our Egyptian colleagues and field staff who recruited a population-based sample of the general population. The results from the questionnaires they administered provided reliable data on smoking behavior and ETS exposure that are comparable to prevalence rates from previous tobacco surveys in Egypt, as cited in our paper. Although his concern about possible “overadjustment” regarding the inclusion of both place of residence and rural vs. urban status in our statistical models is theoretically plausible, we observed empirically that place of residence (at the level of the governorate) did not correlate strongly with the urban or rural status of the household, since all the governorates in Egypt where we conducted our study contain both urban and rural areas. Finally, the time lag in pathological confirmation of some of the participating cases, suggested by Dr. Behrens as a possible methodological concern, was the result of our strict requirement of having the same pathologist review the specimens and records from all the cases. Considering the large number of cases in this ongoing study, not all of them were confirmed by the time we submitted the manuscript; however, the unconfirmed are very similar to the confirmed ones, in
terms of socio-demographic characteristics (referred to in the paper). We plan to include them in future reports.

In summary, we agree with Dr. Behrens that observational studies in general need to be considered in light of their study-specific strengths and weaknesses, which were carefully detailed in the paper. On the other hand, those findings that were mentioned as being in apparent contradiction with the literature are, in fact, either quite consistent with previous studies (as in the case of heavy smoking and UC risk), unreported previously (our detailed findings regarding SCC), or possibly unique to the study population (regarding heavy ETS exposures).

References


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