Are cohort data on smokeless tobacco use and pancreatic cancer confounded by alcohol use?

In the meta-analysis of pancreatic cancer case–control studies reported by Bertuccio et al. [1], the authors found no association between use of smokeless tobacco (ST) and risk of pancreatic cancer. This finding contradicts two large cohort studies from northern Europe [2, 3]. The authors speculate about possible differences in ST products but emphasise as the most likely explanation for the discrepancy that the case–control studies, as opposed to the cohort studies, adjusted for major confounding factors, including ethnicity, education, body mass index (BMI), diabetes and alcohol consumption. The results have prompted a proponent for ST to exclaim “… almost significant for a PROTECTIVE EFFECT” and “… directly addresses a persistent question about the integrity of previous studies” (http://rodutobaccotruth.blogspot.com/). Therefore, we feel obliged to comment on the authors’ interpretation.

First, the difference in control for confounding is more apparent than real. Through restriction (ethnically homogenous population of male construction workers), the control for ethnicity, education and most socioeconomic-related factors in the Swedish cohort study [3] was likely even more rigorous than that in the case–control studies. Moreover, in addition to attained age, the Swedish cohort study also adjusted for BMI. And in analyses restricted to never-smoking users of snus (the Swedish variant of ST) compared with never users of any tobacco, the control for smoking is likely to have been as good as that in the meta-analysis. The real difference, thus, concerns adjustments for self-reported diabetes and alcohol use in the case–control studies. People with type I [4] and type II [5] diabetes have an approximate twofold increase in the risk of pancreatic cancer. However, some evidence...
support a link between ST use and risk of type II diabetes [6], albeit one study did not attain statistical significance [7]. Hence, the adequacy of controlling for diabetes might be challenged because this condition could be in the causal pathway. So what remains is the inability of the Swedish study to control for alcohol use. Although the association of alcohol use with pancreatic cancer risk has been observed in several studies, the causality remains doubtful in view of possible confounding by smoking [8]. After control for all other covariates, did Bertuccio et al. note any important change of the relative risk estimate when they added the total alcohol consumption variable to their pooled regression model?

Several fallacies threaten the validity of case–control studies as opposed to cohort studies, one being recall bias, another reverse causation (if symptoms of the emerging tumour or its precursor states would change the tobacco habits). A third fundamental validity issue, in hospital-based case–control studies, is that the controls may not be representative of the population that generated the cases. In particular, the control sample might be biased towards over-representation of tobacco users. A fourth concern is non-participation, which corresponds to losses to follow-up in the cohort study and thus becomes a threat to the internal validity. With essentially complete register-based follow-up, the Swedish cohort study was clearly superior to all case–control studies in the meta-analysis. Thus, in view of existing strong cohort data, the discrepant results in case–control studies must be interpreted cautiously.

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