

Letter to the Editor

Response to comments by Drs. Rutqvist, Lewin, Nilsson, Ramström, Rodu and Cole further to the publication of the manuscript "Smokeless tobacco use and risk of cancer of the pancreas and other organs"

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Dear Sir,

We are pleased to be able to clarify some aspects of our recent study on snus use and cancer risk in a cohort of Norwegian men.¹

Drs. Rutqvist and Lewin raise the issue of possible confounding by alcohol drinking. Contrary to their hypothesis, alcohol drinking does not seem to be a confounder of the association between snus use and pancreatic cancer risk in this cohort. The relative risk of pancreatic cancer for ever snus use, adjusted for alcohol drinking in 3 levels (non-drinkers, 1–3, and 4 or more drinks/week), in addition to age and tobacco smoking, was 1.67 (95% confidence interval = 1.12–2.50).

They also question the use of the term 'snus' to identify the smokeless tobacco product used by the members of the cohort. The products used in Norway during the period of enrollment of our study population were called 'snus' and 'skrå.' Snus was placed in the upper gum, whereas skrå was a chewing product. They contained, however, comparable amounts of carcinogenic substances. We think that their characteristics were sufficiently close to those of smokeless tobacco products used in Norway and other countries to justify the use of a generic name.

As mentioned in the Material and Methods section of our article, cases diagnosed on the basis of a clinical examination or death certificate only were excluded. Among cases of pancreatic cancer retained in the analysis, 61% were confirmed by a pathology report, 23% were based on surgery, and the rest had a diagnosis based on X-rays.

We appreciate Rutqvist and Lewin's suggestion to analyze all possible types of cancer, but we restricted our analysis to 8 types cancer selected *a priori* for a possible association with snus use (with the exception of lung cancer, which was selected as a negative control). An association with pancreatic cancer was our strongest hypothesis given the results of an early analysis of our study² and the experimental evidence of a carcinogenic effect on the pancreas of tobacco-specific nitrosamines. We have reported full results of these 8 types of cancer.

We agree with most comments raised by Dr. Nilsson, and we believe we have been sufficiently cautious in our article to avoid over-interpretation of our results. We agree in particular that the small number of cases of pancreatic cancer among snus users who did not smoke is an important limitation of our study.

We do not wish to comment on the evaluations of authoritative panels on the risks and benefits of snus use, but we think that it is the duty of cancer researchers to contribute to the accumulation of the evidence. We have reviewed in details in our article earlier results on pancreatic carcinogenicity of snus. The data available before our study were mainly based on retrospective

studies. We think that the best way to either confirm or falsify our results is to conduct additional prospective studies.

Dr. Ramström comments on the number of cases of snus users among never- and ever-smokers and on the nomenclature of skrå vs. snus. We have already addressed these comments. In addition, he discusses the possible misclassification between tobacco smoking and snus use, which might have occurred in our study because of lack of data on changes of these habits during the follow-up. We ignore whether the trends he describes actually occurred in our study population, but we think that switching from smoking to snus use would dilute our risk estimate for snus use, because many supposedly unexposed individuals would indeed have become exposed during the follow-up (this justifies by the way our emphasis on the opposite change, from snus use to smoking).

Drs. Rodu and Cole are correct in stating that inclusion of occasional snus users in the reference category insight have led to underestimation of the relative risk of pancreatic cancer among snus users. We think that a conservative risk estimate is preferable when new hypotheses are presented. They also raise issues on potential confounding by alcohol drinking and misclassification of data on snus use and tobacco smoking we have already addressed. Cigar and pipe smoking are risk factors of pancreatic cancer,³ and we have stratified for amount of tobacco smoked as cigarettes, cigars and pipe. We believe it is acceptable to use different cutpoints to categorize continuous variables. We are not sure that the table proposed by Drs. Rodu and Cole adds to the interpretation of our results because it presents data in form of numbers of observed and expected cases (and their differences) instead of numbers of observed cases, relative risks and confidence intervals. The last row refers to all cancers considered in our analysis, not to all cancers that occurred among cohort members.

We think that our original conclusion that our study provides evidence of a carcinogenic effect of snus use on the pancreas, which should be taken into account in the assessment of the health effects of this type of products, was justified.

Yours sincerely,

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