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Letter to the Editor

Flawed methods

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Dear Sir,

In a recent issue of the *Journal of Cancer*, Bofetta *et al.*[1] presented an update of cancer incidence relative to the use of smokeless tobacco in a cohort of Norwegian males. They claimed that use of non-smoking tobacco was associated with an increased risk of pancreatic cancer (RR = 1.67, 95% = 1.12–2.50) whereas no significant association was observed for 7 other selected cancers.

Unfortunately, the article includes several methodological flaws that make the conclusions tenuous and in some respects even misleading. Because the methodological shortcomings are quite obvious, we regret that the *Journal of Cancer's* peer review process, on this occasion, seems to have performed less well. Our main points of criticism are summarized below.

A previous report on this cohort (as well as numerous other studies) showed a strong association between pancreatic cancer and the use of alcohol.[2] For instance, the odds ratio for frequent use *vs.* no use was 10.8 (adjusted for smoking). It is enigmatic why Bofetta *et al.*[1] elected not to include alcohol use in their statistical analysis despite the fact that alcohol probably is a strong confounding factor. Moreover, data on alcohol use are obviously available for this cohort.

The confounding effect of alcohol is particularly worrying in view of the selection bias in the studied cohort. The reported prevalence of regular use of non-smoking tobacco in the cohort was 20%. The population prevalence of such use, however, was probably only a few per cent among adult Norwegian males at the time when the cohort was formed. This wide discrepancy makes it likely that the cohort was selected also on the basis of other factors related to use of tobacco, for instance, alcohol intake.

The article claims to have studied cancer risks related to "snus" that is a Scandinavian type of moist, non-smoking tobacco with a documented low content of putatively carcinogenic nitrosamines. "Snus" dominates the market today for non-smoking tobacco in northern Europe. Until the early 1980s, however, a completely different type of smokeless tobacco was common on the Norwegian market ("skrå"). Previous reports on the same cohort indicated that the questionnaires used to collect information on exposure made no distinction between different types of smokeless products. This circumstance detracts from the validity of the results reported by Bofetta *et al.*[1] because it remains unclear to which product their results should be ascribed, that is, whether the results are relevant for the type of product that now dominates the market in northern Europe.

A diagnosis of pancreatic cancer can be difficult to establish unequivocally because many patients are inoperable at clinical presentation. This implies that some of the reported cases are not verified histologically and may represent other types of abdominal malignancies misclassified as "pancreatic cancer." In the mentioned previous report on the association between alcohol use and pancreatic cancer based on the same cohort, the odds ratio (frequent use *vs.* no use) was substantially higher when the analysis was restricted to cases with histological verification compared to when all cases were included (10.8 *vs.* 2.7). This observation supports that there is a true association. The proportion of non-verified cases was 35%. It is problematic that Bofetta *et al.*[1] do not mention the proportion of histologically verified cases in their analysis, nor do they present results separately for such cases.

Bofetta *et al.*[1] report results for 8 selected cancer sites. No significant increase in risk associated with use of non-smoking tobacco was observed for 7 of these (head-neck, esophagus, stomach, lung, lung adenocarcinoma, kidney and urinary bladder). This confirms and extends results from several previous studies. It is unclear how many cancer sites have actually been analyzed in this cohort. We suggest that it is likely that Bofetta *et al.* or previous researchers who have been involved with this cohort, have studied all cancer sites reported by the Norwegian Cancer Registry, as this is readily done in a cohort study using computerized record linkages with a population-based cancer registry. The number of such sites is about 40–50. This raises the possibility of "mass significance" as an explanation to the reported significant association. A full disclosure of how this cohort have been analyzed over the years remains unavailable.

In view of the mentioned circumstances, we disagree with the conclusion that the article establishes a causal relationship between "snus" and pancreatic cancer, particularly because there were no data on dose-effect relationships that is a key element in causal inferences. In fact, the methodological flaws summarized in this letter may well explain the moderate increase of the reported odds ratio.

Finally, we believe that Bofetta *et al.*[1] do provide arguments in favor of the role of smokeless tobacco products to reduce the burden of smoking-related cancer. The consistent lack of an association between non-smoking tobacco and several major, smoking-related cancers clearly illustrates the "harm reduction" potential of the type of smokeless products currently used in northern Europe.

Yours sincerely,

Lars Erik Rutqvist, and Freddi Lewin

References

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