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Letter to the Editor

Possible carcinogenicity of smokeless tobacco

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Dear Sir,

The database on the possible carcinogenicity of smokeless tobacco has been limited for sites other than the head/neck region, and the contribution by Boffetta *et al.*[1] provides additional data with respect to cancers of the stomach, pancreas, lung, kidney and bladder in a cohort of 10,136 male subjects of Norwegian origin. The authors state that their results ''...are consistent with previous evidence in supporting the conclusion that it is unlikely that the use of smokeless tobacco products in Europe and the United States entails a substantial increase in the risk or oral and pharyngeal cancer.'' They also found no adequate evidence that snuff affects the incidence of cancers of the esophagus, stomach, bladder or kidney. Although the number of cases were limited, however, they found a statistically significant risk increase for pancreatic cancer. The ability of NNK to induce pancreatic cancer in rodents was cited as supporting mechanistic data.

Active smoking constitutes a major cause of pancreatic cancer and the interpretation of the results is by no means straight forward. An increase in pancreatic cancer was only found for *current smokers* who reported use of snuff in 1964–67 when they were enlisted for the study. Among never smokers there were only 3 cases of pancreatic cancer. There was no consistent follow-up of the tobacco habits because enrollment, a serious drawback that the authors acknowledge. The authors' supposition that changes of tobacco use since enrollment ''...is unlikely to have occurred differentially with respect to outcome'' is unwarranted. Due to nicotine dependence, common sense dictates that a user of snuff who gives up this habit would be much more inclined to switch to smoking than a study subject who quit this habit before 1964–67, or someone who never used smokeless tobacco. The studied cohort, 32% of whom were exposed to snuff, must have been highly selected, and certainly not representative of the either the Norwegian nor the United States male population where the normal prevalence of snuff use has been under 10% during the time period of study follow-up. Another anomaly is that the RR for pancreatic cancer was the same for former and current users of snuff. As to the capacity of NNK to induce pancreatic tumors in rodents, it is a well known fact that the target organ for carcinogenic action of a particular agent often varies from species to species.

That no apparent increase in lung cancer among ever users of snuff had been found was advanced as a main argument by the authors that there was no confounding by tobacco smoking. One factor to be considered here is a possible diagnostic bias. Pancreatic cancer is mostly diagnosed at a late stage of the disease. The outcome is rapidly fatal in the large majority of cases and the probability of positive verification of primary tumors in the pancreas and neoplasia of the lung have most probably been different in this cohort of smoking subjects, where information on histological verification is lacking. In addition, there is evidence that smoking markedly shortens the latency period for induction of pancreatic cancer,[2] implying an earlier appearance of this type of smoking associated tumor than for that of the lung. The impact of these confounding factors are difficult to assess quantitatively, especially in view of the absence of follow-up data on tobacco use for this cohort. The most damaging flaw, however, is the absence of information on alcohol abuse. Chronic alcoholism leading to pancreatitis is a well-known predisposing factor for neoplasia of this organ, and Gullo *et al.*[3] found that almost all patients with alcoholic pancreatitis were also heavy smokers. Preexisting diabetes constitutes another confounding factor that was not recorded.

Led by the Nobel Prize Laureate Sune Bergström, the Swedish Cancer Committee[4] estimated that about 50% of all pancreatic cancers can be ascribed to smoking. Thus, if the risk estimate for snuff use were true, and that is claimed by Boffetta *et al.*[1] to approach that for smoking, this would be expected to have an impact in a country like Sweden where about 20% of the grown up male population uses snuff. This is not so. Relying on the IARC EUCAN cancer database[5] 1998 estimates (www-dep.iarc.fr/eucan/eucan.htm), Swedish men do not have a higher incidence of pancreatic cancer than other European nations where snuff use hardly exists. The Swedish incidence/mortality is actually much lower than for a countries Finland where smoking also has decreased markedly during the last decade. Furthermore, although almost 20% of all Swedish men use snuff, only about 4% of the women have this habit. All the same, Swedish women have almost the same incidence of pancreatic cancer as men from this country.

The objections raised above do not exclude that snuff poses a certain risk for pancreatic cancer, but it will have to be much smaller than that cited by Boffetta *et al.*[1] Also, any such risk from low nitrosamine snuffs would under all circumstances be only a fraction of the total cancer risk caused by active smoking. Still, Boffetta *et al.*[1] do not favor the use of smokeless tobacco for the purpose of smoking cessation. In contrast, the prestigious United States Institute of Medicine, a main advisory body to *inter alia* FDA, concluded that

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oral snuff of the Swedish type '. . .should be evaluated as a possible harm reduction product.'[6] The authors also do not appreciate the fact that other nicotine replacement products like nicotine chewing gum, nicotine spray, *etc*. are simply not affordable for a major part of the population in *e.g*., the former socialist countries or in Asia. For heavy smokers in these regions, Boffetta et al.[1] would leave no other choice than to stop smoking or die.

Yours sincerely,

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