

Letter to the Editor

A deficient study of smokeless tobacco use and cancer

Brad Rodu^{1*} and Philip Cole²

¹Department of Pathology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

²Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA

Dear Sir,

Boffetta *et al.*¹ presented relative risks (RR) for several forms of cancer among Norwegian men who were smokeless tobacco (SLT) users in the 1960s and they emphasized the RR of 1.67 for pancreas cancer. They employed unconventional SLT exposure groups, however, made no adjustment for alcohol consumption, and their unusual adjustment for smoking may have produced the implausible results that we describe below. A re-analysis of the data from this study is indicated.

Boffetta *et al.*¹ created a mixed referent group for the SLT analysis by combining never and occasional users. The designation of exposure groups, and especially of the referent group, greatly affects risk estimates in a study as small as this. For example, if occasional SLT users had a higher pancreas cancer rate than never users, their inclusion in the referent group would have resulted in an *underestimation* of pancreas cancer risks among SLT users. The authors should provide risk estimates using the 4 customary SLT exposure categories that they described in their Material and Methods section: never users (referent group), regular current, occasional current, and regular former users.¹ In any case, it is unwise to place confidence in results based on up to 40-year-old information on a lifestyle risk factor as inconstant as snus use. In one study at least 25% of snus users quit in less than a decade.²

The authors acknowledge that "Residual confounding...by other potential risk factors for pancreatic cancer, such as heavy alcohol intake...cannot be ruled out." In fact, alcohol consumption was reported as the strongest risk factor for pancreas cancer in the earlier report of this cohort, with odds ratios up to 10.8,³ and must be fully controlled in this update.

The procedure that was used to control smoking has 3 major limitations. First, the information on smoking is as out-of-date as that of SLT use. Further, smokers at cohort inception are even more likely than SLT users to have quit over the 40-year follow-up period.² Second, cigar and pipe smokers, who have very low risks for pancreas cancer, were combined with cigarette smokers, who have much higher risks. This is crucial because cigar and pipe smokers in this cohort were shown previously to be at low risk of pancreas cancer.³ Third, Boffetta *et al.*³ used daily cigarette smoking categories (1–9, 10–14, 15+ cigarettes) that seem inconsistent with the original survey's actual responses (1–9, 10–19, 20+).³

Failure to adjust fully for alcohol and for smoking may have contributed to the implausible results from this study, shown in our table. We compared the numbers of cancers observed among SLT users in the study with the number expected to occur if they had been never users. The expected numbers are derived directly from the smoking-adjusted RR in the article. For cancers of the oral cavity/pharynx, esophagus, stomach and pancreas the expected number is lower than that observed. For cancers of the lung, kidney and bladder, the expected number is actually higher than the observed number.

TABLE 1 – CASES OF CANCER OBSERVED AMONG SLT USERS BY BOFFETTA *ET AL.* AND CASES EXPECTED AMONG THEM AT THE RATES OF NEVER SLT USERS

Cancer (RR ¹)	Cases of cancer among SLT users		Observed minus expected
	Observed	Expected ²	
Oral-pharynx (1.10)	9	8.2	0.8
Esophagus (1.40)	9	6.4	2.6
Stomach (1.11)	74	66.7	7.3
Pancreas (1.67)	45	26.9	18.1
Lung (0.80)	72	90.0	–18.0
Kidney (0.72)	22	30.6	–8.6
Bladder (0.83)	69	83.1	–14.1
All cancers	300	311.9	–11.9

¹Relative risk for ever vs. never SLT use, adjusted for age and smoking (cigarettes, cigars, pipe), according to Boffetta *et al.*² At the rate of never users. Expected = observed/RR.

The net result from the table shows that SLT use is associated with 12 fewer cases of cancer among ever users than would have occurred at never-user rates, a 4% difference that is not statistically significant. The 20% deficit of lung, kidney and bladder cancers combined is statistically significant (RR = 0.80, 95% CI = 0.68–0.93). This would seem to indicate that SLT use lowers the risk of these cancers beyond its protection against smoking because the RR were adjusted for smoking. Boffetta *et al.*¹ may wish to provide an explanation for these reduced risks other than protection by SLT use. Any such explanation may require resolution of the fundamental analytic problems that we have described.

Yours sincerely,

Brad RODU and Philip COLE

References

- Boffetta P, Aagnes B, Weiderpass E, Andersen A. Smokeless tobacco use and risk of cancer of the pancreas and other organs. *Int J Cancer* 2005;114:992–5.
- Rodu B, Stegmayr B, Nasic S, Cole P, Asplund K. Evolving patterns of tobacco use in northern Sweden. *J Int Med* 2003;253:660–5.
- Heuch I, Kvåle G, Jacobsen BK, Bjelke E. Use of alcohol, tobacco, and coffee, and risk of pancreatic cancer. *Br J Cancer* 1983;48:637–43.

Funding/Conflict of Interest.

Drs. Rodu and Cole are supported in part by an unrestricted gift from the United States Smokeless Tobacco Company to the Tobacco Research Fund of the University of Alabama at Birmingham. Neither has any financial conflict of interest with regard to the sponsor. The sponsor had no scientific input or other influence in regard to this work, including design, analysis, interpretation or preparation.

*Correspondence to: SDB 81, University of Alabama at Birmingham, Birmingham, AL 35294-0007. Fax: +1-205-975-5200.

E-mail: rodu@uab.edu

Received 16 March 2005; Accepted 27 April 2005

DOI 10.1002/ijc.21323

Published online 4 October 2005 in Wiley InterScience (www.interscience.wiley.com).