

## Causal effects of smokeless tobacco on mortality in CPS-I and CPS-II?

Jonathan Foulds · Lars Ramstrom

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We congratulate Henley and colleagues for their excellent report on the mortality rates among men who reported using smokeless tobacco at the beginning of the CPS-I and CPS-II cancer prevention studies [1]. The report contained a number of unexpected results, which deserve further comment.

Firstly, neither study found a significant increase in the risk of death from oral cancer. While there may have been a lack of power to detect a statistically significant effect, the adjusted hazard ratio of 0.9 after 18 years of follow-up in 2,488 smokeless users with a median age of 57 at enrollment (and only one death due to this type of cancer in the follow-up period in the smokeless-using cohort, and none in former users), is not suggestive of a strong association between smokeless tobacco use and death from oral cancer. Given that 5-year survival from oral cancer has been around 50% for the past 30 years [2], it is unlikely that the lack of effect was due to a large number of incident cases occurring but not causing death.

On the other hand, these studies did find surprising associations between smokeless tobacco use at enrollment

and subsequent death from diseases of the lung. For example, in CPS-I there were significant adjusted hazard ratios for smokeless users and death from respiratory system diseases (HR = 1.28), and COPD (HR = 1.86), and in CPS-II there was a significantly increased risk of death from lung cancer (HR = 2.0). These results are surprising as the mechanism whereby use of smokeless tobacco in the mouth may cause cancer of the lung (but not of the oral cavity), and other lung diseases, is not clear. Even more perplexing was that the highest adjusted hazard ratio reported in the paper was for lung cancer deaths among never-smoking snuff users who were former chewers (HR = 9.78). Why would snuff users who formerly used another form of smokeless tobacco be at increased risk of lung cancer?

The authors quite correctly attempted to rule out confounds by adjusting for a host of other baseline variables. However, given that no further updated information on tobacco use or other lifestyle factors was analyzed during the follow-up period, it is plausible that changes in other unmeasured behaviors during the follow-up period may account for some of the findings. For example, despite controlling for baseline alcohol consumption, smokeless tobacco users were found to be at significantly increased risk of death from cirrhosis (HR = 3.02) in CPS-II.

The lack of a dose–response relationship between either frequency or duration of smokeless tobacco use and any endpoint also casts doubt over the likelihood that the significant relationships found in this study represent causal effects. As pointed out by the authors, this is in marked contrast to previous analyses examining the risk of death from various diseases in relation to tobacco smoking, which found clear dose–response relationships and much larger relative risks (e.g. male smoker/never-smoker relative risk for lung cancer death = 23.2 in CPS-II) [3].

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J. Foulds (✉)  
Tobacco Dependence Program, University of Medicine and  
Dentistry of New Jersey-School of Public Health,  
New Brunswick, NJ 08901, USA  
e-mail: fouldsja@umdnj.edu  
Tel.: 732-235-8213  
Fax: 732-235-8297

L. Ramstrom  
Institute for Tobacco Studies, Stockholm, Sweden

Perhaps the most likely confound in the study that could not be controlled for is potential differences in exposure to tobacco smoke between the never tobacco users and the smokeless tobacco users. This could have occurred via greater exposure to environmental tobacco smoke in smokeless tobacco users or via some of the smokeless users taking up smoking either before or after the follow-up period. The surprisingly high association between lung cancer and smokeless tobacco “switching” mentioned above may be because a history of switching tobacco products was a marker for switching to a smoked product later in the study. The signs of residual confounding in this study therefore cast doubt on the most plausible causal relationship suggested – that between smokeless tobacco use and mortality from heart disease and stroke.

The report cited one of our papers as proposing that spit tobacco should be marketed as a less hazardous alternative to smoking [4]. Although we did not actually make such a proposal in that paper, we agree that the health risks from use of smokeless tobacco products are markedly smaller than those from smoking tobacco products. We believe it would be helpful for health professionals and the public to be provided with best estimates of the relative risks of death from all causes and specific diseases, comparing exclusive smokeless tobacco users with exclusive smokers. It is a pity that opportunity was not taken in this report. We

agree that nicotine replacement therapy (NRT) is a preferable alternative to smoking, even although the most plausible causal effects of smokeless use suggested in this study (on heart disease and stroke) would likely also apply to long term NRT use.

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