KEY MESSAGES

- Evidence from available studies of Swedish snus and risk of pancreatic cancer is limited because of contradictory findings in the two available studies. A recent study of smokeless tobacco products used in Western countries did not observe an increased risk of pancreatic cancer.
- Two public health agency reports have concluded that there is "sufficient evidence" that *smokeless tobacco* use causes pancreatic cancer in humans, but these conclusions were drawn before the most recent study of smokeless tobacco and pancreatic cancer was available.
- Two recent meta-analyses (a study that combines results of several studies that address a similar hypothesis) reported an increased risk of pancreatic cancer, while a third did not. Again, these analyses were conducted prior to publication of the most recent study.
- Much debate remains in the scientific community, so further research needs to be conducted before the question of whether or not the use of Swedish snus leads to increased risk of pancreatic cancer can be conclusively answered.

QUESTIONS AND ANSWERS

Why have researchers studied the relationship between snus use and pancreatic cancer?

Cigarette smoking is known to be associated with increased risk of pancreatic cancer. It is logical that researchers would be interested in the relationship between other types of tobacco products and pancreatic cancer. The development of pancreatic cancer is poorly understood. Cigarette smoking is the only established risk factor for the development of pancreatic cancer. Other possible risk factors include diet, obesity, diabetes, personal or family history of pancreatitis, personal or family history of pancreatic cancer, family history of genetic syndromes that can increase cancer risk, and age, sex, and race (Johns Hopkins Medicine 2008; Mayo Clinic 2008).

Is there evidence that snus use is associated with pancreatic cancer?

The evidence for an association between use of Swedish snus and risk of pancreatic cancer is limited by contradictory findings in the two available studies. No firm conclusions can be drawn at this time. Although two international public health organizations (IARC and SCENIHR) have concluded that there is *sufficient evidence* that *smokeless tobacco* use is associated with increased risk of pancreatic cancer, the epidemiological data for Swedish snus are inconsistent, and these conclusions were published before the most recent epidemiological study was published, discussed below.

Data specific to Swedish snus are available from two epidemiology studies, which analyzed snuff use and the risk of pancreatic cancer in Scandinavian men (Boffetta et al. 2005; Luo et al. 2007). Results from these two studies are inconsistent. Boffetta et al. (2005), who studied Norwegian men who may have used forms of snuff other than Swedish snus, found an increased risk of pancreatic cancer among snuff users after adjusting for smoking in a statistical model. In contrast, Luo et al. (2007) found an increased risk of pancreatic cancer among ever

snus users who had never smoked, but did not observe an increased risk among snus users after adjusting for smoking in a statistical model.

Inherent design and methodological limitations in the studies may have affected results, and these have been discussed considerably in the scientific literature (Boffetta et al. 2006; Nilsson 2006; Ramstrom 2006; Rodu and Cole 2006; Rutqvist and Lewin 2006; Sponsiello-Wang et al. 2008; Lee and Hamling 2009a,b) which resulted in scientific debate regarding these findings. Specifically, Lee (2010) stated that neither of these studies adjusted for alcohol consumption or history of diabetes, and that the smokeless tobacco consumed in the Norway cohorts study was not Swedish snus, but a poorly defined snuff probably characterized by a higher content of tobacco specific nitrosamines (TSNA) than comparable Swedish products.

A third study, which pooled data from 11 case-control studies of smokeless tobacco users throughout North America, Europe and Australia, was recently published by Bertuccio and colleagues (2011). Users of chewing and snuff tobacco were combined, though it is unlikely that Swedish snuff was a major product used in any of the populations included in the analysis. In this pooled study, no association between pancreatic cancer and use of smokeless tobacco was observed.

Three meta-analyses, which combine results of epidemiological studies, have been conducted, though all were published prior to the most recent study by Bertuccio and colleagues. Boffetta et al. (2008) conducted a meta-analysis of *smokeless tobacco* use and pancreatic cancer risk (Scandinavian studies noted above). Results revealed an increased risk overall (i.e., when U.S. and Scandinavian studies were combined), as well as when the analysis was restricted to the two Scandinavian studies (Boffetta et al. 2005; Luo et al. 2007). However, when the analysis was restricted to U.S. studies only, the increased risk was no longer statistically significant. Further study is needed to clarify these discrepancies.

An additional meta-analysis conducted by Sponsiello-Wang and colleagues (2008) also examined the risk of pancreatic cancer from the use of *smokeless tobacco* in Europe and North America. These researchers conclude that although some subgroup analyses suggest a possible association, the risk estimates are heavily dependent on the contribution from one specific study (Luo et al. 2007). Thus, these authors state that further research needs to be conducted to clarify discrepancies in the findings of the two studies available from Scandinavia.

Lee and Hamling (2009b) also conducted a meta-analysis that examined the risk of pancreatic cancer among North American and European *smokeless tobacco* users. No significantly elevated risk of pancreatic cancer was observed among users of snuff in Scandinavia, which included the Luo et al. (2007) and Boffetta et al. (2005) studies. The reason for the difference in results between meta-analyses is due to differences in the selection of the relative risk from each study. Selection of the appropriate relative risk to be used in a meta-analysis is the subject of debate (Lee and Hamling 2009a). These authors selected the smoking-adjusted relative risk as opposed to Boffetta and colleagues (2008) who selected the relative risk for never smokers from the Luo et al. (2007) study (Lee and Hamling 2009a). Lee and Hamling (2009a) noted that Boffetta and colleagues (2008) did not follow their own stated approach of selecting relative risks from never smokers when they selected the smoking-adjusted relative risk from the Boffetta et al. (2005) study, the higher of the two effect estimates. Lee (2010) concluded that for both whole population and never smokers, the meta-analyses only suggest a possible association.

What conclusions have been reached by public health agencies about the association between snus use and pancreatic cancer?

The International Agency for Research on Cancer (IARC) has concluded that there is "sufficient evidence" that *smokeless tobacco* causes pancreatic cancer in humans (Cogliano et al. 2004; IARC 2007). This conclusion was based on two case-control studies from the U.S. (Alguacil and Silverman 2004; Muscat et al. 1997) and two cohort studies, one from the U.S. (Zheng et al. 1993) and the one from Norway (Boffetta et al. 2005). Of note however, is that the overall risk for pancreatic cancer was not statistically significantly increased in the studies of Alguacil and Silverman (2004), Muscat et al. (1997), and Zheng et al. (1993).

The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR 2008) also has concluded that there is "sufficient evidence" that *smokeless tobacco* use causes pancreatic cancer. This conclusion was based on the studies as noted by IARC (see above), plus a study by Luo et al. (2007).

These agency conclusions are not based solely on Swedish snus, and do not include the most recent study published by Bertuccio and colleagues in 2011; the previously mentioned independent reviews reveal the body of evidence to be inconsistent and inconclusive, therefore, further research is needed before firm conclusions can be drawn.

Is there reasonable evidence of a biological mechanism by which snus could cause pancreatic cancer?[1]

Some investigators have suggested that the association between snus use and pancreatic cancer is biologically plausible (e.g., Boffetta et al. 2005; Luo et al. 2007) and that the pancreas is a likely target organ for carcinogenic action of tobacco specific nitrosamines (TSNAs) (Hecht 1998; Rivenson et al. 1988). However, at this time the mechanism by which snus exposure might be associated with pancreatic cancer development has not been characterized in detail.

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[1] When attempting to determine whether a substance causes a particular health effect, scientists seek a biological explanation, or mechanism, for how the effect could reasonably occur.

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