IJC
International Journal of Cancer

Snus use, smoking and survival among prostate cancer patients

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Smoking is associated with prostate cancer mortality. The Scandinavian smokeless tobacco product snus is a source of nicotine but not the combustion products of smoke and has not been studied with respect to prostate cancer survival. The study is nested among 9,582 men with incident prostate cancer within a prospective cohort of 336,381 Swedish construction workers. Information on tobacco use was collected at study entry between 1971 and 1992, and categorized into (*i*) never users of any tobacco, (*ii*) exclusive snus: ever users of snus only, (*iii*) exclusive smokers: ever smokers (cigarette, cigar and/or pipe) only and (*iv*) ever users of both snus and smoking. Hazard ratios for prostate cancer-specific and total mortality for smoking and snus use based on Cox proportional hazards models adjusted for age, calendar period at diagnosis and body mass index at baseline. During 36 years of follow-up, 4,758 patients died—2,489 due to prostate cancer. Compared to never users of tobacco, exclusive smokers were at increased risk of prostate cancer mortality (HR 1.15, 95% CI: 1.05–1.27) and total mortality (HR 1.17, 95% CI: 1.09–1.26). Exclusive snus users also had increased risks for prostate cancer mortality (HR 1.24, 95% CI: 1.03–1.49) and total mortality (HR 1.19, 95% CI: 1.04–1.37). Among men diagnosed with nonmetastatic disease, the HR for prostate cancer death among exclusive snus users was 3.17 (95% CI: 1.66–6.06). The study is limited by a single assessment of tobacco use prior to diagnosis. Snus use was associated with increased risks of prostate cancer and total mortality among prostate cancer patients. This suggests that tobacco-related components such as nicotine or tobacco-specific carcinogens may promote cancer progression independent of tobacco's combustion products.

The medical community and the general public generally accept that cigarette smoking is a major determinant of mortality. Perhaps less appreciated, a pooled analysis of nearly one million people found that 17% of this excess mortality was due to causes of death not typically associated with smoking, including prostate cancer.[1] The 2014 Surgeon General's report found current or recent smoking was associated with an increased risk of advanced-stage prostate cancer and death from prostate cancer, although not associated with overall incidence of the disease.[2–7] Because the specific compounds in cigarettes that most strongly influence prostate cancer outcomes have not been identified, it is not clear the extent to which other tobacco products, some of which are increasing in popularity, also pose risks.

Key words: cancer survival, prostate cancer, smoking, snus, tobacco use
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DOI: 10.1002/ijc.30411
History: Received 25 May 2016; Accepted 10 Aug 2016; Online 1 Sep 2016
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Snus, a moist smokeless tobacco product common in Scandinavia, is of interest in the study of the biological effects of tobacco, as users are exposed to high levels of nicotine and other compounds over long periods of time, but without exposure to tobacco combustion products known to influence cancer risk and outcomes.[8,9] The potential effect of snus on cancer progression is also of policy interest, as snus is generally suggested as a risk-reducing alternative to smoking by authorities including the World Health Organization.[10–13] In fact, tobacco companies have introduced and promoted the use of snus outside of Sweden as a healthier alternative to smoking over the past decade and have sold it in the United States since 2006.

No study to date has investigated whether snus use is, in fact, a less detrimental alternative to smoking among men with prostate cancer. We used data from a cohort of male Swedish construction workers to study the associations of both smoking and snus use with prostate cancer mortality among 9,582 men diagnosed with prostate cancer between 1971 and 2007.

Patients and Methods

Study population and follow-up

The Swedish construction industry's Organization for Working Environment, Safety and Health (Bygghälsan) offered

What's new?

Snus, a smokeless tobacco product, is often promoted as a safe alternative to cigarettes as it lacks the combustion products of smoking that are generally associated with cancer risk. Here the authors show that snus use is independently associated with risks of overall and prostate cancer-specific mortality that are comparable to cigarette smoking. These findings may lead to a re-evaluation of the public health impact of smokeless tobacco products as they suggest that nicotine or possibly other tobacco ingredients play a role in the progression of prostate cancer.

annual preventive health check-ups to all construction workers in the industry between 1969 and 1992. A total of 343,811 male workers had at least one visit between 1971 and 1992. Each visit included detailed questions about tobacco use.

The nationwide Swedish Cancer Register, established in 1958 and 96–98% complete,[14] was used to identify incident cases of prostate cancer to form the study population for this analysis. Men with previous history of any cancer at study entry were excluded. We included 9,582 workers with a diagnosis of prostate cancer after the time of the first study visit and between 1971 and 2007. Mortality and cause of death through 2007, the most recent date for which mortality data was available, were ascertained through linkage to the nationwide Swedish Death Register, which has been shown to have high reliability for cause-of-death among prostate cancer patients.[15–17] Follow-up for mortality in Sweden is essentially complete.

Information on tumor characteristics for men with newly diagnosed prostate cancer was available from the National Prostate Cancer Register (NPCR) of Sweden, which has been nation-wide since 1998 with a capture rate of 98% compared to the Swedish Cancer Register. Thus tumor characteristics were available for 5,346 men (56% of total). In this subset of cases, we defined risk categories using a modified version of the National Comprehensive Cancer Network Practice Guidelines in Oncology, Version.1.2010, based on stage, Gleason score and serum prostate specific antigen (PSA) at diagnosis.[18] Low risk was defined as clinical stage T1 or T2, Gleason score 2–6 and PSA <10 ng/ml. Intermediate risk was stage T1-T2, Gleason score 7 and/or PSA 10 to <20 ng/ml. High risk localized disease was stage T3-T4 and/or Gleason 8–10, and/or PSA 20-<50 ng/ml. Regionally metastatic disease was defined as N1 and/or PSA 50 to <100 ng/ml and M0/MX. Distant metastases was defined as M1 and/or PSA >=100 ng/ml.

Assessment of tobacco use

Between 1971 and 1975, participating workers filled out a 200-item questionnaire with detailed questions about smoking and snus use. Collection of information on tobacco use was not done in 1976–1977 but resumed in 1978 with a questionnaire completed by the examining nurse. All data were compiled in a central computerized register. The number of total visits per person ranged from 1 to 13. However, we limited our analysis to exposure information collected in the first visit because the number and timing of visits may be linked with mortality. Based on the first visit, never, past and current tobacco use was obtained and past and current users were combined. Therefore, men were classified as (*i*) never users of any tobacco, (*ii*) ever users of snus only ("exclusive snus"), (*iii*) ever smokers only: cigarette, cigar and/or pipe ("exclusive smoking") and (*iv*) ever users of both snus and smoking (either concurrently or sequentially).

Statistical analysis

Each worker contributed person-time from the date of prostate cancer diagnosis to the date of death, emigration, or end of study, December 31, 2007, whichever came first. The association between tobacco use and either prostate cancer-specific or total mortality was studied using Cox proportional hazards models with time since cancer diagnosis as the underlying time scale. Models were stratified by age at diagnosis (<60 years, 60–64, 65–69, 70–74, 75+ years) and time period of diagnosis (1971–1984, 1985–1994, 1995–2007) and were adjusted for body mass index (BMI) at baseline (continuous) and time between baseline examination and cancer diagnosis (continuous). In the subset of patients with clinical data, additional models were adjusted for stage, grade and PSA at diagnosis. We also studied the association between tobacco use and death among men diagnosed with nonmetastatic disease, *i.e.*, excluding those with evidence of regionally spread disease and distant metastases, under the hypothesis that lifestyle factors may play a greater role in survival among men with less advanced disease at diagnosis.

SAS statistical software (release 9.2) was used for the analysis. The study was approved by the Stockholm Regional Ethics Vetting Board.

Results

We identified 9,582 new cases of prostate cancer among workers with at least one clinic visit prior to diagnosis. Mean age at diagnosis was 70.2 years. During the study period 4,758 (50%) men died. Of those, 52% ($n = 2{,}489$) died of prostate cancer. The mean time from study entry/baseline examination to prostate cancer diagnosis was 20.6 years (range: 1 week–33.2 years), and the mean follow-up time after diagnosis was 4.5 years. 869 cases (9%) were diagnosed between 1972 and 1984, 2,674 (28%) between 1985 and 1994 and 6,039 (63%) from 1995 to 2004. Among the 5,346 cases included in The National Prostate Cancer Register (NPCR) of Sweden, the median PSA at diagnosis was 15.0 ng/ml, and

Table 1. Characteristics of the 9,582 prostate cancer cases by ever use of tobacco at study entry, Swedish Construction Workers cohort 1971–2007

	Never-users	Exclusive snus	Exclusive smoking	Used snus and smoked
N (%)	2,762 (29)	460 (5)	4,833 (50)	1,527 (16)
No. prostate cancer deaths (%)	640 (23)	141 (31)	1,336 (28)	372 (24)
No. deaths (%)	1,207 (44)	261 (57)	2,539 (53)	751 (49)
Mean age at diagnosis (years)	70.4	71.3	70.3	69.3
Time period of diagnosis				
1972–1984	197 (7%)	46 (10%)	486 (10%)	140 (9%)
1985–1994	701 (25%)	143 (31%)	1,412 (29%)	418 (27%)
1995–2004	1,864 (67%)	271 (59%)	2,935 (61%)	969 (63%)
Mean time between study entry and dx (years)	20.8	20.2	20.3	20.9
Mean follow-up time (from diagnosis, years)	4.6	4.4	4.6	4.4
Tobacco use at study entry				
Mean cigarettes/day	–	–	9.3	7.9
Mean pipes/week	–	–	20.7	14.6
Mean cigars/day	–	–	0.3	0.3
Mean duration of smoking (at examination)	–	–	24.7	23.0
Mean duration of snus use (at examination)	–	24.3	–	15.2
Mean BMI (kg/m^2)	25.5	26.3	25.1	25.4
Tumor characteristics				
N in NPCR[1]	1,668 (60%)	243 (53%)	2,580 (53%)	866 (56%)
Risk category (%)[2]				
Low risk	21	19	19	24
Intermediate risk	21	21	21	20
High risk	28	30	30	29
Regional spread	11	9	9	10
Distant metastases	20	22	21	17%
Gleason score 8–10 (%)[3]	20	20	20	18
Median PSA at dx (ng/ml)	15.0	16.0	16.0	13.6

[1]Data for 5,346 men diagnosed after 1995 from the National Prostate Cancer Register of Sweden. [2]Risk category classification: low risk: T1–2, Gleason 2–6 and PSA <10; intermediate risk: T1–2, Gleason = 7 and/or PSA 10 to <20; high risk: T3–4 and/or Gleason 8–10 and/or PSA 20 to <50; regionally metastatic: N1 and/or PSA 50 to <100 and M0 or MX; distant metastases: M1 and/or PSA 100+. [3]Among those in prostate cancer registry with nonmissing Gleason data.

20% had Gleason 8–10 disease. 20% of cases were diagnosed with distant metastases and another 10% with regionally spread disease.

Table 1 describes the study population according to tobacco use at study entry. Never users accounted for 29% of the population, while 5% were exclusive snus users, 50% were exclusive smokers (cigarettes, pipe and/or cigars) and 16% both used snus and smoked. Mean age at diagnosis was slightly higher among exclusive snus users and slightly lower among users of both. Mean BMI at study entry was slightly higher among exclusive snus users than in other groups. Mean duration of snus use at baseline among exclusive snus users was 24.3 years and 15.2 years among users of both. Mean duration of smoking was 24.7 years among exclusive smokers and 23.0 years among users of both. The frequency of Gleason score 8–10 at diagnosis was similar across groups. PSA at diagnosis was 15.0 ng/mL among never users, 16.0 ng/mL among exclusive smokers, 16.0 ng/mL among exclusive snus users and 13.6 ng/mL among users of both. Users of both snus and smoking were slightly more likely to be in lower risk groups at diagnosis, while distribution of risk groups was similar in the other three groups.

Compared to never users, men in all three groups of tobacco use were at increased risk of overall mortality (Table 2; HR 1.19, 95% CI: 1.04–1.37 for exclusive snus; HR 1.17, 95% CI: 1.09–1.26 for exclusive smoking; HR 1.17, 95% CI: 1.06–1.28 for both). Exclusive snus users and exclusive smokers were at increased risk of prostate cancer-specific mortality, with a hazard ratio of 1.24 (95% CI: 1.03–1.49) for exclusive snus users and 1.15, (95% CI: 1.05–1.27) for

Table 2. Hazard ratios and 95% confidence intervals of the association of overall and prostate cancer-specific mortality according to category of ever use of tobacco at study entry, Swedish Construction Workers cohort 1971–2007

	Tobacco exposure			
	Never-users *N*=2,762	Exclusive snus *N*=460	Exclusive smoking *N*=4,833	Used snus and smoked *N*=1,527
Overall mortality				
No. deaths	1,207	261	2,539	751
HR (95% CI) full cohort[1]	1.00 (ref)	1.19 (1.04–1.37)	1.17 (1.09–1.26)	1.17 (1.06–1.28)
HR (95% CI) with clinical data[2]	1.00 (ref)	1.15 (0.88–1.51)	1.15 (1.01–1.31)	1.15 (0.96–1.39)
Cancer-specific mortality				
No. prostate cancer deaths	640	141	1,336	372
HR (95% CI) full cohort[1]	1.00 (ref)	1.24 (1.03–1.49)	1.15 (1.05–1.27)	1.08 (0.95–1.23)
HR (95% CI) with clinical data[2]	1.00 (ref)	1.28 (0.88–1.88)	1.06 (0.87–1.30)	1.11 (0.84–1.45)
Among nonmetastatic risk groups[3]				
Total no.	1,087	160	1,691	586
Overall mortality				
No. deaths	107	25	272	80
HR (95% CI) with clinical data[2]	1.00 (ref)	1.36 (0.88–2.11)	1.53 (1.22–1.91)	1.65 (1.23–2.21)
Cancer-specific mortality				
No. prostate cancer deaths	28	14	60	23
HR (95% CI) with clinical data[2]	1.00 (ref)	3.17 (1.66–6.06)	1.33 (0.85–2.08)	1.93 (1.11–3.35)

[1]"Full cohort" includes all 9,582 men diagnosed with prostate cancer during follow-up. Models are stratified by age group at dx and time period of dx, and adjusted for BMI (continuous) and time between examination and dx. [2]Subcohort "with clinical data" includes 5,346 men diagnosed after 1995 with available tumor characteristics from the National Prostate Cancer Register. Models are stratified by age group at dx and adjusted for BMI (continuous), time between examination and dx and clinical risk category. [3]Includes men in "low," "intermediate" and "high" categories, excludes "regionally metastatic" and "distant metastases."

exclusive smokers. Users of both were at nonsignificantly increased risk of prostate cancer death (HR 1.08, 95% CI: 0.95–1.23).

When the analysis was restricted to men with available tumor characteristics, results were largely similar, though some associations were no longer statistically significant, likely due to smaller numbers of events (Table 2).

In the subgroup of men diagnosed with nonmetastatic disease, men in all three groups of tobacco use were at increased risk of total mortality, with somewhat greater hazard ratios than observed for the total patient cohort (Table 2). The association between tobacco use and prostate cancer-specific death was also more pronounced. Exclusive snus users had a hazard ratio of 3.17, 95% CI: 1.66–6.06, exclusive smokers had a hazard ratio of 1.33, 95% CI: 0.85–2.08, and users of both had a hazard ratio of 1.93, 95% CI: 1.11–3.35.

Discussion

Data from this large cohort study provides further support that tobacco use increases the risk of total mortality as well as prostate cancer-specific mortality among men newly diagnosed with prostate cancer.[2–4] For the first time, we also show an excess risk of overall and cancer-specific mortality among snus users, a noteworthy observation as snus is generally considered and has been promoted, as a healthier and less carcinogenic alternative to smoking.[10–13] Indeed, among men who never smoked, snus use was positively associated with overall and prostate cancer-specific mortality.

A previous study in this cohort[19] among all cancer cases found an excess risk of cancer specific death among exclusive snus users, exclusive smokers and combined users (snus and smoking), with a 24% increased risk among exclusive snus users. A study in Uppsala county, Sweden among men without cancer at baseline found an increased risk of all-cause mortality for those who reported any snus use and a suggestion of an increased risk of cancer mortality for exclusive snus use (HR: 1.28, 95% CI: 0.96–1.69).[20]

There are many hypothesized mechanisms behind the association between snus use and prostate cancer progression, although the exact mechanism is unclear. While snus users are not exposed to the combustion products of tobacco, they are exposed to nicotine and to multiple carcinogens present in smokeless tobacco, such as tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons (PAHs), volatile aldehydes and *N*-nitrosamino acids (NNAs), which have been shown to form DNA adducts.[21–25] Furthermore, they also contain aldehydes and metals, which have been associated with inflammation and increased cell proliferation.[25]

Snus users have blood levels of nicotine metabolites similar to those seen in cigarette smokers.[26] Experimental evidence from *in vitro* and *in vivo* studies suggests that nicotine, while not carcinogenic, may promote cancer progression at concentrations relevant to tobacco use.[27] Nicotine binds to nicotinic acetylcholine receptors (nAChR), which are present in various nonneuronal tissues.[28] A broad range of laboratory findings show that nicotine promotes cell proliferation and angiogenesis through its effects on nAChR in breast and lung cancer cell lines and in animal models of breast and colon cancer.[7,27,29–35]

Nicotine and nAChR expression has not been studied in prostate cancer models. However, a variety of signaling cascades downstream of nAChR play important roles in prostate cancer, including the c-Src, PI3K/AKT/mTOR, MAPK and HIF-1alpha.[36–41] These effects of nicotine could explain, in part, the association of smoking and snus with prostate cancer progression, but lack of association with cancer incidence.

Beyond nicotine, snus users are exposed to multiple tobacco-derived carcinogens. The TSNA content of snus is comparable to cigarette smoke.[9,42–44] TSNAs, including 4-(methylnitrosamino)−1–(3-pyridyl)−1-butanone (NNK) and *N*′-nitrosonornicotine (NNN), are carcinogenic compounds formed during the processing of tobacco and have been shown to cause lung, nasal and esophageal tumors in various rodent models and to induce DNA adducts.[22,45] In addition, these compounds, like their precursor nicotine, bind to nAChR to promote tumor progression through multiple pathways.[46,47]

While our results are suggestive, particularly in light of previous cell line studies, animal models and epidemiological studies, it is important to note several important limitations of this work. First, we have only a single assessment of tobacco use, recorded an average of 20 years before cancer diagnosis. This leaves room for substantial misclassification of tobacco use closer to and after the cancer diagnosis. It is likely that some users in all three tobacco use categories quit after the examination or after their diagnosis, given general trends over time. Such measurement error would result in an underestimation of the true effect of snus use and smoking on mortality. In addition, if smokers were more likely to quit than snus users, due to the perception that snus is less harmful, then the extent of the underestimation might be greater for smoking groups than for the exclusive snus group. The lack of detailed smoking history prevents us from evaluating a dose-response relationship or examining whether quitting is eventually associated with lower prostate cancer mortality, which is an important public health question. However, despite these limitations of the data, this unique cohort adds to our understanding of tobacco and prostate cancer survival.

Our study is also limited by the lack of covariate data, such as leisure-time physical activity. However, because few lifestyle factors have been strongly related to prostate cancer mortality, the lack of lifestyle information is less likely to substantially influence the results than for other causes of mortality. We did adjust for BMI at study entry, as exclusive snus users had slightly higher mean BMI at this point; however, we lack information on BMI at later time points, which may be important given evidence that obesity plays a role in prostate cancer progression.[48] Unfortunately, we did not have information on the use of PSA screening among the men in this study, preventing us from ruling out differences in screening according to tobacco use at study entry. However, median PSA at diagnosis was similar between tobacco use groups, and the associations remained when we adjusted for stage and grade, and when we restricted the analysis to patients in lower risk categories at diagnosis. With that said, the number of prostate cancer deaths among exclusive snus users is low when restricted to lower-risk categories.

In addition to adding to our understanding of the biology of prostate cancer, our findings have important implications for public health policy. Snus has been marketed as a less harmful alternative to smoking,[10–13,49,50] and is sometimes promoted as a smoking cessation aid, despite several studies finding no benefit.[51] Indeed, the US Food and Drug Administration (FDA) received and rejected an application from Swedish manufacturers seeking approval to modify language on snus warning labeling to state: "No tobacco product is safe but this product presents substantially lower risks to health than cigarettes."[52] However, the content of TSNAs and other carcinogens in snus is quite variable and is not labeled or routinely monitored.[24] Other smokeless tobacco products are also increasing in popularity. Particularly, e-cigarettes are increasingly common, with recent surveys reporting 12.6% of adults ever tried an e-cigarette and e-cigarette use tripling among adolescents in just one year.[53–58] In addition, a recent survey of high school students found those who had ever used e-cigarettes were more likely to report use of combustible tobacco products.[59] E-cigarettes are marketed as safer than cigarette smoking, with companies claiming they are healthier, cheaper and cleaner than cigarettes.[60,61] However, the concentration of nicotine in e-cigarette liquid varies widely across and even within products,[62] and some e-cigarettes also contain TSNAs and other toxicants.[63]

Conclusions

We found that a history of both smoking and snus use was associated with increased risk of prostate cancer-specific mortality and total mortality among men with prostate cancer in a large cohort in Sweden. Our results suggest that nicotine or other carcinogens in smokeless tobacco products may promote cancer progression independent of the combustion products of tobacco smoke and may have implications for the regulation of smokeless tobacco products.

Acknowledgements

KMW, JRR and LAM are supported by Prostate Cancer Foundation Young Investigator Awards. SCM is supported by a T32 training award from the National Cancer Institute (NIH T32 CA09001).

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