Tobacco use and cancer survival: A cohort study of 40,230 Swedish male construction workers with incident cancer

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Novelity and Impact Statements
We found that exclusive snus users had a 15% increased risk of cancer-specific death compared to never-users of tobacco, and the excess risk was of the same magnitude as among exclusive smokers. Whereas smokers had an increased risk of deaths that were not cancer-specific, this was not as evident for exclusive snus users. Thus, our empiric observations provide support for the hypothesis that tobacco use may affect cancer survival, possibly through specific effects of nicotine.

ABSTRACT

On theoretical grounds, nicotine has been implicated as a modifier of cancer progression. We investigated possible associations of smoking or use of Scandinavian moist snuff ('snus') with survival after cancer among Swedish male construction workers. Snus use is associated with substantial exposure to nicotine but not to the combustion products in smoke. Among 336,381 workers with detailed information on tobacco use in 1971-1992 we observed 40,230 incident cancers. Complete follow-up through 2007 was accomplished through linkage to population and health registers. Hazard ratios (HRs) and 95% confidence intervals (CIs) for death from any cause, cancer-specific death and death from other causes were derived from Cox proportional hazards regression models adjusted for age at diagnosis, body mass index at study entry and period of diagnosis. Never-users of any tobacco served as reference.

Increased risks of cancer-specific death were observed both among exclusive smokers ($HR_{all\ cancer}$ 1.15, 95% CI 1.10-1.21) and never-smoking snus users (1.15, 95% CI 1.05-1.26). As regards deaths due to other causes, exclusive smokers had higher relative risks than exclusive snus users (p=0.03). A history of tobacco use, even exclusive use of the seemingly benign snus, is associated with moderately increased cancer-specific mortality. While nicotine might play a role, the mechanisms warrant further investigation.

INTRODUCTION

Nicotine is not a carcinogen but has many biological effects that theoretically could promote cancer progression, such as changed regulation of the cell-cycle and apoptosis in several cell types, including lung and gastric cancer cells, as well as stimulation of proliferation, angiogenesis and invasiveness in various systems and models.[1-7] It is relevant to investigate into possible effects of nicotine on the prognosis of human cancer.

Previous studies have almost unanimously demonstrated poorer overall survival among current smokers than among never-smokers, but whether or not the poorer prognosis in smokers is importantly attributable to specific effects on tumour progression remains conjectural. Only a few clinical follow-up studies have been able to confirm a statistically significant association of smoking status with cancer-specific survival.[8-11] Hence, the clinical importance of the putative nicotine-induced stimulation of tumour progression remains largely unconfirmed.

To further narrow in on the importance of nicotine, exposure to Swedish moist snuff ('snus') is of particular interest. Oral use of this smokeless tobacco product produces peak levels of nicotine in venous blood comparable to those observed during smoking but with a considerably longer duration.[12] Since habitual users keep snus quids intraorally for several hours per day, the integrated nicotine dose is substantial. Although snus is not harmless,[13] there is general consensus that its overall adverse health effects are only a fraction of those attributed to smoking.[14]

Given that nicotine effects might influence tumor progression and possibly interfere with antitumor treatment,[5-7, 15-18] this study aimed to investigate associations of tobacco use, divided into smoking and snus

use, with cancer survival. Therefore, fatality according to self-reported tobacco use among new cases with any cancer was studied within a large cohort of male construction workers.

MATERIAL AND METHODS

Bygghälsan

The construction industry's Organization for Working Environment, Safety and Health, ("Bygghälsan"), offered preventive health check-ups to all blue- and white-collar workers in the Swedish construction industry between 1969 and 1992. Workers who participated in 1971-75 filled out a 200-item questionnaire with detailed questions about smoking and snus use. After a pause during 1976 through 1977, the collection of smoking and snus information was resumed in 1978 with a new form filled out by the Bygghälsan nurses after a short interview. All data were compiled in a computerized central register.

Identification of incident cancer cases

A total of 361,280 workers had at least one recorded visit between 1971 and 1993. Due to the small number of women (17,458), this study was restricted to men only.

The national registration numbers, unique personal identifiers assigned to all residents in Sweden, permitted follow-up through precise linkages to nationwide and essentially complete registers. To check the national registration numbers, we used the registers of total population, migration, and causes of death; if a national registration number could not be found in any of these registers it was deemed to be incorrect and the record was excluded. The Swedish National Cancer Register, established in 1958 and shown to be 96-98% complete,[19] was used to identify incident cases. It has coded malignant neoplasms according to the 7th revision of International classification of diseases (ICD7) throughout the study period. Since we only

considered first cancers, all cohort members recorded with a previous cancer at time of entry were excluded. Subsequent cancers were not considered in this analysis and accordingly follow-up was not censored at occurrence of secondary cancers.

Using the information on tobacco habits obtained at the first visit at 'Bygghälsan', the cancer cases were classified as (i) never-users of any tobacco, (ii) never-smoking snus users ("pure snus users"), (iii) never snus-using smokers (cigarette, cigar, and/or pipe) ("pure smokers"), and (iv) users of both snus and smoking tobacco (concurrent or in sequence).

Follow-up of cancer cases

Each cancer case contributed person-time from the date of cancer diagnosis to the date of death, emigration, or end of study, December 31, 2007, whichever came first. For cancer-specific death, the cancer diagnosis recorded as the underlying cause of death had to be the same as the first cancer diagnosis, whereas for death from other causes, the underlying cause of death was other than cancer or a different cancer than the first cancer. Individuals with unspecified cancer (ICD7=199) were not included in the analyses of cancer-specific death and death from other causes.

Statistical analysis

Multivariably adjusted hazard ratios (HR) for overall death, cancer-specific death, and death from other causes, with 95% confidence intervals (CIs), were estimated using Cox proportional hazards regression models with time since cancer diagnosis as underlying time-scale. Never-users of any tobacco constituted the reference category. Adjustments were made for first recorded body mass index (BMI, kg/m^2), categorized into <25, 25-29.9, ≥30, as well as age (<50, 50-59, 60-69, 70-79, and ≥80 years) and calendar period (1971-

84, 1985-94, 1995-2007) at cancer diagnosis. To control for the fact that smokers (and possibly also snus users) have a different mix of cancers compared to never-users of tobacco, we also adjusted for cancer site. In the 'all cancer' cohort, site was divided into ICD7 140-48 (oral and pharyngeal); 150 (esophageal); 151 (gastric); 152 (small bowel); 153-154.0 (colorectal); 154.1 (anal); 155-56 (bilary and hepatic); 157 (pancreatic);158 (peritoneal); 160 (sinonasal); 161(larynx); 162-63 (pulmonary); 177 (prostate); 178 (testicular); 179 (male genital); 180 (renal); 181 (urinary tract); 190 (melanoma); 191 (cutaneous tumor); 193 (nervous system); 194 (thyroid); 195 (endocrine glands); 196 (skeletal); 197 (muscle and soft tissue); 200-8 (hematological); and the rest). The proportional hazards assumption was examined using Schoenfeld's partial residuals.[20] All variables were tested for each model. Age, calendar period, and cancer group did not fulfill the proportional hazards assumption and were entered in the model using the strata option, i.e., by assuming different baseline hazard for each combination of those variables.

To investigate into possible heterogeneity we separately analyzed five common cancers – cancer of the lung, stomach, prostate, and colorectum, as well as malignant melanoma.

Attribution of observed deaths to a specific cancer is sometimes problematic and misclassification could potentially be differential in regard to exposure status. As an alternative, we calculated relative survival ratios, [21] defined as the observed overall survival divided by the expected survival derived from the age- and calendar period-matched Swedish male population. This measure estimates total excess mortality directly and indirectly attributable to the cancer, but it should be noted that in analyses by tobacco user status the results are somewhat biased because both users and never-users of tobacco contribute to the expected survival. We used the Ederer II method with 1-year age and 1-year calendar period strata. [22]

Sensitivity analyses

To investigate if possible survival effects of tobacco use would be restricted to smoking-related cancers, we performed a set of analyses stratified into cancers considered to be smoking-related according to the current literature (oral, esophageal, gastric, colorectal, anal, hepatic, pancreatic, sinonasal, larynx, tracheal and lung, prostate, penile, renal and urinary tract cancers)[23, 24] and all other cancers.

To explore the importance of co-morbidity, a subanalysis was done using data obtained through linkage with the Swedish Inpatient Register.[25] We only considered inhospital diagnoses registered before, or on the date of cancer diagnosis. Patients were divided into three groups; (i) no recorded co-morbidity, (ii) any of chronic pulmonary disease, myocardial infarction or cerebrovascular disease, and (iii) other co-morbidity. Since data from the Inpatient Register could be accessed only until December 2004, cancer cases occurring after that were excluded in this subanalysis. Because nationwide coverage of the Inpatient Register was not attained until 1987, we only included patients covered by the registration for at least 5 years before cancer diagnosis.

Since we suspected that tobacco users and never-users might differ in their propensity to seek health care for early cancer symptoms, we tried to shed light on possible differences in their respective cancer stage distributions. Since TNM classification data were first introduced in the Swedish cancer registration in 2004, this analysis was restricted to 2004-2007.

Since we only used exposure information collected at entry into the cohort, there is a possibility that never-smoking snus users compared to never-users of any tobacco were more inclined to take up smoking in the follow-up period. Although repeat visits with renewed exposure assessment occurred with vastly varying frequency and most likely were differential both in relation to tobacco user status and disease outcome, thus

prohibiting valid utilization of updated exposure information, we crudely assumed that any mentioning of smoking at any repeat visit would indicate that the worker was either erroneously classified as a never-smoker at entry or had subsequently taken up smoking. In a previous paper,[26] we reported that 13.2% of never-smoking snus users (with an average of 3.7 repeat visits) had at least 1 repeat record that indicated current or previous smoking. The corresponding percentage among never-users of any tobacco (with average 3.3 repeat visits) was 6.7%. Even though the data should be interpreted with caution due to the risk of selection bias and misclassification, we adjusted the observed association between pure snus use and cancer-specific death hazard as proposed by Schneeweiss.[27]

SAS statistical software (release 9.2) was used in most analyses, except that STATA 9 was used for relative survival analyses. The study was approved by the Stockholm Regional Ethics Vetting Board.

RESULTS

Among 336,381 workers followed for a total of 8,208,741 person-years (longest follow-up 37 years) a total of 40,496 new first cancers were diagnosed (Figure 1). Of these cases, 266 died on the day of diagnosis, leaving 40,230 in the final cancer patient cohort. Pure smokers tended to be diagnosed with cancer at an earlier age (median age 65 years) compared to pure snus users and never-users of any tobacco (median age 67 and 67 years, respectively, Table 1). Among all members of the cancer patient cohort, the median BMI at the first health check-up at Bygghälsan was slightly lower in pure smokers (24.6) than in never-users of any tobacco (25.1) and pure snus users (25.4, Table 1).

Smokers exhibited a significant excess risk of dying (any cause); the risk was 21% higher than among never-users of any tobacco (Table 2). A significant 13% excess was noted also among pure (never-smoking) snus

users. The risk for cancer-specific death was significantly elevated by 15% both among pure smokers and pure snus users. While the risk for death from other causes was increased by 26% among pure smokers the corresponding risk elevation was 12% among pure snus users.

Modeling of HRs for single cancer sites was hampered by imprecision due to insufficient numbers of observed events (Supplementary Figure 1). Point estimates of HR for cancer-specific death due to smoking-related cancers tended to be higher among pure snus users (1.21, 95% CI 0.71-2.08 for lung cancer and 1.28, 95% CI 0.96-1.72 for stomach cancer) than among pure smokers (0.98, 95% CI 0.78-1.24, and 0.95, 95% CI 0.81-1.11, respectively). Excesses of borderline significance were observed for prostate cancer-specific death both among pure snus users (HR 1.19, 95% CI 1.00-1.40) and pure smokers (HR 1.13, 95% CI 1.04-1.23). Neither snus users nor smokers exhibited risk elevations for cancer-specific death due to malignant melanoma or colorectal cancer.

The cumulative relative survival ratios in the cohort of all cancer are presented by tobacco habit in Figure 2, and show the cohort members' survival in relation to the survival in the age- and calendar period-matched Swedish male population. The curves diverged already within the first year after cancer diagnosis, and the gap between them widened only marginally in the following years. Never-users of any tobacco fared best and pure smokers worst. The curve for pure snus users was below that for never-users of any tobacco, but closer to the latter than to that for pure smokers.

Sensitivity analyses

The subcohort of smoking-related cancer consisted of 29,458 cases. In this subcohort there were 18,692 deaths, of whom 11,344 died from their primary cancer. Median age at diagnosis was 68 years. The risk of

cancer-specific death was increased among pure smokers (HR 1.16) as well as pure snus users (HR 1.17) (Supplementary table 1). Whereas smokers in this subcohort exhibited a clear excess also of death from other causes (HR 1.25), pure snus users did not (HR 1.11).

Among the other cancer cases (10,772) the median age at diagnosis was 63 years. The risk of cancer specific risk death was similar among pure smokers and pure snus users but the latter did not reach statistical significance, HR 1.11, 95%CI 1.01-1.22, and HR 1.10, 95%CI 0.92-1.32 respectively (Supplementary table 1). Similar to the subcohort of smoking-related cancers, the risk for death from other causes was higher for pure smokers.

Using Cox regression models for overall death and cancer-specific death, with separate analyses for each co-morbidity stratum, we examined the importance of recorded comorbidity among 27,253 cancer cases (any site) with the required information; (i) 4,374 with no recorded co-morbidity (ii) 5,941 with any of chronic pulmonary disease, myocardial infarction or cerebrovascular disease, and (iii) 16,938 with other co-morbidity (Table 3). There were no important differences between the groups; in particular there were generally small differences in point estimates of HRs for cancer-specific death.

TNM stage data from 2004-2007 in the 'all cancer' cohort revealed no important differences between never-users of any tobacco and pure snus users, whereas the T-stage distribution among smokers was shifted towards more advanced stages (Supplementary Table 2). Similarly, while the N- and M-stage distributions did not differ much between never-users of any tobacco and pure snus users, there was a tendency for more advanced stages among smokers. However, for N and M stage, about 50% of the data points were missing.

Recalculation of the hazard ratio with allowance for misclassification of smoking during follow-up had little impact on our estimates. Among pure snus users the estimate of HR for cancer specific death changed from 1.15 to 1.14.

DISCUSSION

While a 21% increase in risk of all-cause deaths among smokers may come as no surprise, the significant 13% risk elevation among users exclusively of snus, with much fewer and weaker general health effects,[14] is noteworthy. The relative excesses of cancer-specific death among snus users were generally of a similar magnitude as among smokers, whereas the excesses of deaths due to other causes tended to be lower. The relative survival curves for pure snus users were consistently below the curves for never-users of any tobacco. However, in analyses of five common single sites, a link between tobacco use and risk of cancer-specific death could only be statistically confirmed for prostate cancer. The observed association of tobacco use with poor prostate cancer-specific survival is in line with recent data from the Health Professionals Follow-Up Study,[10] but the absence of an evident association with poor colorectal cancer-specific survival is at odds two recent reports.[11, 28]

Before even tentatively attributing the observed finding to biological effects directly on the tumors, the possibilities of systematic differences between users and never-users of tobacco in regard to diagnostic delay and/or burden of co-morbidity must be entertained. We could only address these issues very crudely. In addition to hypothetical biases due to variations in diagnostic zeal and effectiveness, our analysis was limited by the fact that we only had data on tumor stage for a small subset of the most recent cancer cases, with much missing data. Our observations indicated that the smoker category, indeed, contained a greater proportion of more advanced cases compared to the group of never-users of any tobacco, whereas the

admittedly sparse data for pure snus users did not support a similar shift in stage distribution. We also lacked data on treatment and other clinical factors that may affect outcome. Our stratifications by co-morbidity status showed surprisingly small effects on the HRs for cancer-specific deaths and thus it is unlikely that the observed association between tobacco use and survival is explained entirely by confounding by co-morbidity.

Low socio-economic status (SES) is associated with higher cancer mortality independently of smoking habits.[29] One of the strengths of this study is the restriction to a narrow range of SES, with limited variation possibly also in regard to many lifestyle factors, such as e.g. physical activity. However, the results may not be generalizable to women, and a healthy worker effect cannot be disregarded.

To our knowledge, this is the first study that explores the effect of snus on cancer survival. However, the exposure information typically emanated from long before cancer occurrence. While this effectively precludes reverse causation, changes in tobacco habits might have occurred after the initial report. The resulting non-differential misclassification of the exposure is likely to entail some underestimation of associations. To start smoking at the age of 25 or later is rare, whereas the onset of snus use occurs during a longer period; it has been shown that about one third of all smokers switch to a combination of cigarette and snus use.[30] It is possible that some of the smokers in this cohort started to use snus during follow-up, which would affect the estimates for pure smokers, but it is less likely that the estimates for pure snus users are affected. A previous analysis in the Construction Worker Cohort suggested that pure snus users may be slightly more likely than never-users of any tobacco to show indications of being or having been smokers at one or more repeat visits during follow-up.[26] However, this possibly differential misclassification seemed to

have negligible impact on the hazard ratio in our sensitivity analysis. Since we lacked data on the intensity of tobacco use at cancer diagnosis, we were not able to estimate any dose-response relationships.

Whether or not the risk elevations pertain to all cancer sites remains conjectural. For most single sites, the power was insufficient to detect clinically relevant risk elevations. Albeit with an obvious risk of type-II error, our results weakly suggest that snus use is not associated with an increased risk of cancer-specific death in all cancers sites. This, in turn, suggests that a possibly causal effect may carry at least some degree of specificity towards certain types of cancer.

In conclusion, use of tobacco, also the less harmful moist snuff (snus),[15] is associated with moderately increased cancer-specific mortality. Our data provide little guidance in regard to the mechanisms, which warrant further investigations, but our results concerning snus users seem to narrow in on nicotine as a conceivable culprit.

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FIGURE LEGENDS

Figure 1. Overview of the origin of the incident cancer cohort, nested within the Construction Worker Cohort, and the follow-up of cancer cases.

Figure 2. Cumulative relative survival among all cancer cases (N=40,230) stratified by tobacco type.

Supplementary Figure 1. Forest plots exhibiting hazard ratios (with 95% confidence intervals) among exclusive smokers (left) and exclusive snus users (right), relative to never-users of any tobacco, for cancer-specific deaths due to lung cancer (3,459 cancer cases of whom 2,178 died of this cancer), stomach cancer (1,489 cases, 1,004 deaths), prostate cancer (12,395 cases, 3,102 deaths), malignant melanoma (1,560 cases, 271 deaths), and colorectal cancer (4,393 cases, 1,731 deaths). Adjustments in the multivariable Cox regression models were made for age at cancer diagnosis, calendar period of diagnosis, and BMI.

Table 1. Characteristics of the total cohort of incident cancer cases identified among the construction workers 1971-2007. .

	All	*Never-users of any tobacco*	*Pure Snus Users*[a]	*Pure Smokers*[a]
All	40,230	9,578	1,946	22,321
Period of diagnosis: 1971-1984	5,200	955	224	3,204
1985-1994	11,004	2,296	540	6,421
1995-2007	24,026	6,227	1,182	12,696
Median year of diagnosis	1997	1998	1997	1996
Median age at diagnosis (range)	67 (19-100)	67 (19-97)	65 (20-95)	67 (20-100)
Median BMI (range)[a]	24.8 (16-46)	25.1 (17-43)	25.4 (17-41)	24.6 (16-45)
Number of deaths	24,826	4,994	1,060	14,913
Number of cancer-specific deaths	13,940	2,720	606	8,492

[a]At first health check-up at Bygghälsan in 1971-93.

Table 2. Hazard ratios (HRs) of any death, cancer-specific death and death from other causes by pattern of tobacco use among all cancer cases. Adjustments in the multivariable Cox regression models were made for age at cancer diagnosis, calendar period of diagnosis, cancer site, and body mass index recorded at the first health check-up at Bygghälsan.

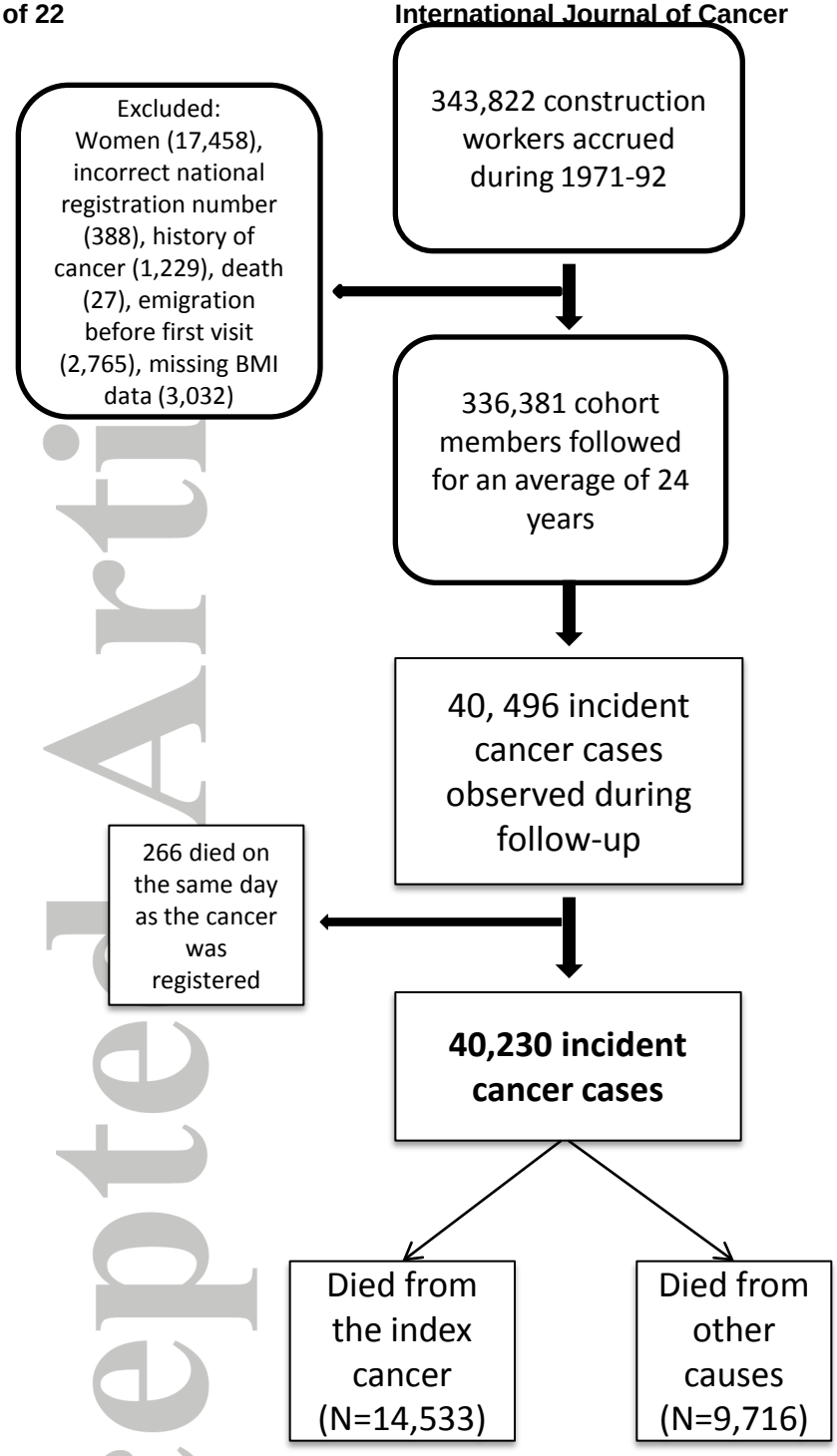
***TOBACCO USER STATUS*[e]**	***ALL CANCER COHORT*[d]**								
	RELATIVE RISK (HR) OF DEATH								
	OVERALL[a]			CANCER SPECIFIC[b]			DEATH FROM OTHER CAUSES[c]		
	Deaths	HR	95%CI	Deaths	HR	95%CI	Deaths	HR	95%CI
Never-users of any tobacco	4,994	Ref		2,720	Ref		2,073	Ref	
Ever tobacco users	19,832	1.19	1.15-1.23	11,220	1.14	1.09-1.19	7,643	1.25	1.19-1.32
-pure snus users	1,060	1.13	1.05-1.20	606	1.15	1.05-1.26	410	1.12	1.01-1.25
-pure smokers	14,913	1.21	1.17-1.25	8,492	1.15	1.10-1.21	5,654	1.26	1.19-1.32
-combined users[f]	3,859	1.17	1.12-1.22	2,122	1.08	1.02-1.15	1,579	1.29	1.21-1.38
ALL	**24,826**			**13,940**			**9,716**		

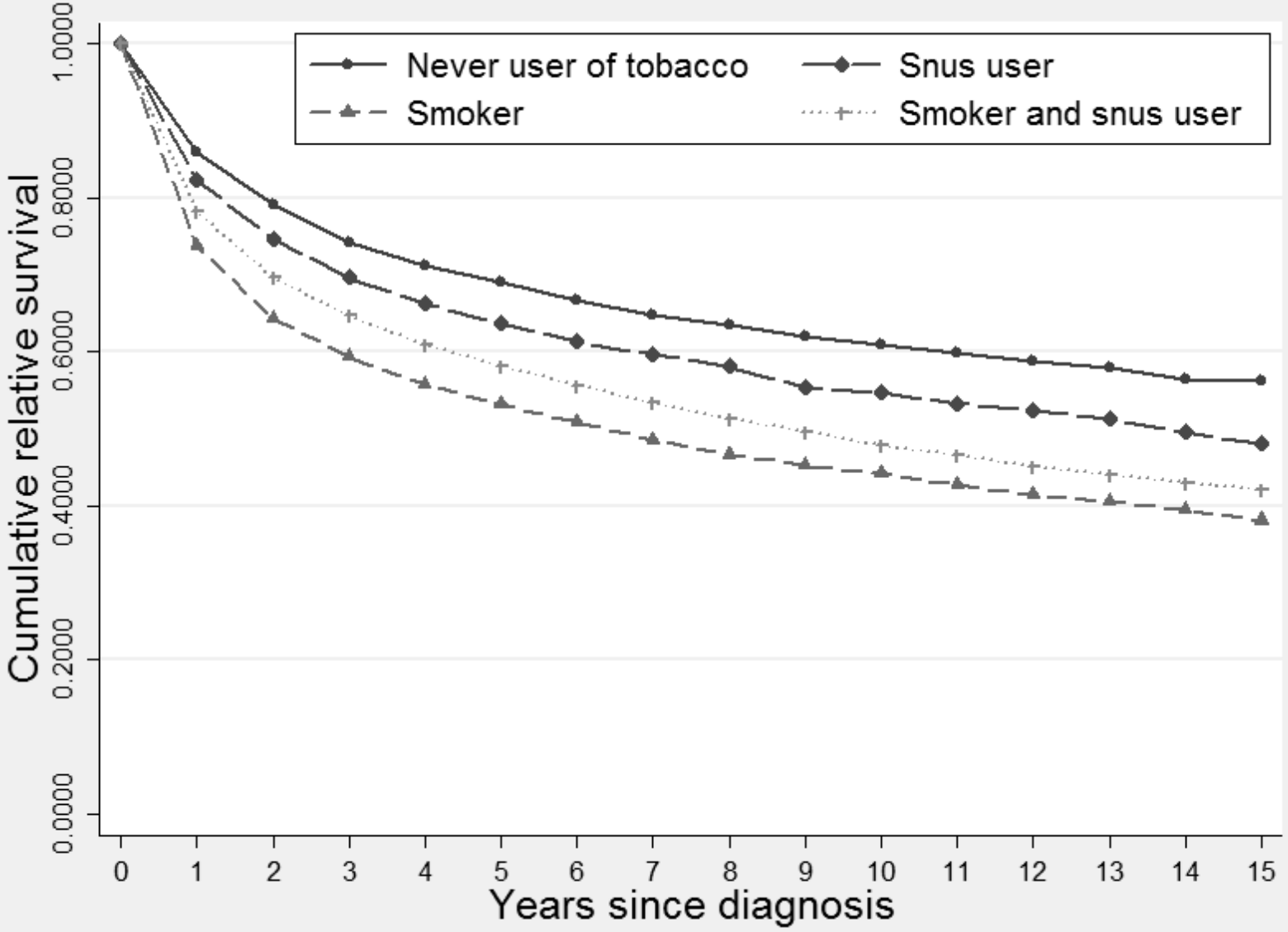
[a]Death from any cause. [b]Cause of death was cancer at the same site as the primary cancer. [c]Cause of death was not cancer, or cancer of another site than the primary cancer. [d]1,400 unspecified cancer cases which led to 1,170 deaths were excluded from the analyses of cancer-specific deaths and deaths of other causes. [e]User status as recorded at the first health check-up at Bygghälsan. [f]Both snus user and smoker, concurrently or in sequence.

Table 3. Hazard ratios (HRs) of any death and cancer-specific death by pattern of tobacco use among all cancer cases stratified into three groups depending on the presence or absence of recorded comorbidity. Analyses were adjusted for age at cancer diagnosis, calendar period of diagnosis, cancer site, and body mass index recorded at the first health check-up at Bygghälsan. .

TOBACCO USER STATUS[d]	*NO COMORBIDITY*						
	All cancer cases	**RELATIVE RISK (HR) OF DEATH**					
		OVERALL			CANCER-SPECIFIC[b]		
		Deaths	HR	95%CI	Deaths	HR	95%CI
Never-users of any tobacco	1,254	547	Ref		360	Ref	
Ever users of any tobacco	3,120	1,704	1.22	1.10-1.36	1,133	1.21	1.06-1.37
-pure snus users	222	93	1.10	0.86-1.40	61	1.07	0.80-1.43
-pure smokers	2,266	1,298	1.24	1.11-1.38	859	1.21	1.00-1.39
-combined users[e]	632	313	1.20	1.04-1.40	213	1.24	1.03-1.48
	4,374	2,251			1,493		
	CHRONIC PULMONARY/CEREBROVASCULAR DISEASE/ MYOCARDIAL INFARCTION						
	All cancer cases	**RELATIVE RISK (HR) OF DEATH**					
		OVERALL			CANCER-SPECIFIC[b]		
		Deaths	HR	95%CI	Deaths	HR	95%CI
Never-users of any tobacco	1,120	722	Ref		333	Ref	
Ever users of any tobacco	4,821	3,568	1.13	1.04-1.23	1,830	1.09	0.96-1.23
-pure snus users	227	153	1.08	0.89-1.29	77	1.20	0.92-1.56
-pure smokers	3,636	2,727	1.16	1.06-1.26	1,414	1.11	0.98-1.26
-combined users[e]	958	688	1.07	0.96-1.20	339	1.00	0.85-1.17
	5,941	4,290			2,163		
	OTHER COMORBIDITY						
	All cancer cases	**RELATIVE RISK (HR) OF DEATH**					
		OVERALL			CANCER-SPECIFIC[c]		
		Deaths	HR	95%CI	Deaths	HR	95%CI
Never-users of any tobacco	4,152	2,216	Ref		1,360	Ref	
Ever users of any tobacco	12,786	8,261	1.17	1.12-1.23	5,116	1.10	1.03-1.17
-pure snus users	828	459	1.15	1.04-1.27	285	1.14	1.00-1.30
-pure smokers	9,296	6,232	1.19	1.13-1.25	3,861	1.11	1.04-1.19
-combined users[e]	2,662	1,570	1.12	1.05-1.19	970	1.04	0.96-1.13
	16,938	10,477			6,476		

[a] 105 unspecified cancer cases which led to 79 deaths were excluded from the cancer-specific analyses.
[b]254 unspecified cancer cases which led to 231 deaths were excluded from the cancer-specific analyses.
[c]670 unspecified cancer cases which led to 566 deaths were excluded from the cancer-specific analyses.
[d] User status as recorded at the first health check-up at Bygghälsan. [e]Both snus user and smoker, concurrently or in sequence.




Never user of tobacco
Snus user
Smoker
Smoker and snus user
Cumulative relative survival
0.0000
0.2000
0.4000
0.6000
0.8000
1.0000
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Years since diagnosis

Supplementary table 1. Hazard ratios (HRs) of any death, cancer-specific death and death from other causes by pattern of tobacco use among all cancer cases in the subcohort of smoking-related cancers and other cancers. Adjustments in the multivariable Cox regression models were made for age at cancer diagnosis, calendar period of diagnosis, cancer site, and body mass index recorded at the first health check-up at Bygghälsan.

***TOBACCO USER STATUS*[e]**	***SUBCOHORT OF SMOKING-RELATED CANCER***								
	RELATIVE RISK (HR) OF DEATH								
	OVERALL[a]			CANCER SPECIFIC[b]			DEATH FROM OTHER CAUSES[c]		
	Deaths	HR	95%CI	Deaths	HR	95%CI	Deaths	HR	95%CI
Never-users of any tobacco	3,467	Ref		2,004	Ref		1,463	Ref	
Ever tobacco	15,225	1.19	1.14-1.23	9,340	1.15	1.09-1.20	5,884	1.24	1.17-1.32
-pure snus users	764	1.15	1.06-1.24	458	1.17	1.06-1.30	306	1.11	0.98-1.26
-pure smokers	11,556	1.20	1.15-1.25	7,181	1.16	1.11-1.23	4,374	1.25	1.17-1.33
-combined users[f]	2,905	1.15	1.09-1.21	1,701	1.08	1.01-1.15	1,204	1.27	1.18-1.37
ALL	**18,692**			**11,344**			**3,301**		

	***SUBCOHORT OF OTHER CANCER*[d]**								
	RELATIVE RISK (HR) OF DEATH								
	OVERALL[a]			CANCER SPECIFIC[b]			DEATH FROM OTHER CAUSES[c]		
	Deaths	HR	95%CI	Deaths	HR	95%CI	Deaths	HR	95%CI
Never-users of any tobacco	1,527	Ref		716	Ref		610	Ref	
Ever tobacco	4,607	1.21	1.14-1.29	1,880	1.11	1.02-1.21	1,759	1.29	1.17-1.42
-pure snus users	296	1.08	0.95-1.22	148	1.10	0.92-1.32	104	1.17	0.94-1.45
-pure smokers	3,357	1.22	1.15-1.30	1,311	1.11	1.01-1.22	1,280	1.28	1.16-1.42
-combined users[f]	954	1.23	1.13-1.33	421	1.12	0.99-1.27	375	1.36	1.19-1.56
ALL	**6,134**			**2,596**			**2,368**		

[a]Death from any cause. [b]Cause of death was cancer at the same site as the primary cancer. [c]Cause of death was not cancer, or cancer of another site than the primary cancer. [d]1,400 unspecified cancer cases which led to 1,170 deaths were excluded from the analyses of cancer-specific deaths and deaths of other causes. [e]User status as recorded at the first health check-up at Bygghälsan. [f]Both snus user and smoker, concurrently or in sequence.

Supplementary table 1. TNM classification for all cancers diagnosed in 2004-2007.

	Non-users of any tobacco	***Pure snus users***	***Pure smokers***	***Combined users***
T0	4 (0.2%)	2 (0.6%)	13 (0.4%)	2 (0.2%)
T1	749 (40.9%)	154 (43.5%)	1,092 (31.2%)	407 (35.8%)
T2	502 (27.4%)	82 (23.2%)	890 (25.7%)	306 (26.9%)
T3	336 (18.4%)	64 (18.1%)	769 (22.2%)	246 (21.6%)
T4	132 (7.2%)	32 (9.0%)	423 (12.2%)	108 (9.5%)
Ta	32 (1.8%)	9 (2.5%)	127 (3.4%)	32 (2.8%)
Tis	11 (0.6%)	1 (0.3%)	14 (0.4%)	2 (0.2%)
Tx	64 (3.5%)	10 (2.8%)	129 (3.7%)	34 (3.0%)
∑	1,830	354	3,457	1,137
Missing	561	118	967	363
N+	3 (0.2%)	1 (0.3%)	6 (0.2%)	2 (0.2%)
N0	470 (25.8%)	91 (25.9%)	975 (28.4%)	322 (2.5%)
N1	92 (5.1%)	20 (5.7%)	252 (7.3%)	86 (7.6%)
N2	70 (3.8%)	18 (5.1%)	244 (7.1%)	60 (5.3%)
N3	8 (0.4%)	5 (1.4%)	122 (3.6%)	23 (2.0%)
Nx	1,178 (64.7%)	217 (6.7%)	1,832 (53.4%)	637 (56.4%)
∑	1,821	352	3,431	1,130
Missing	570	120	993	370
M0	637 (36.1%)	132 (38.5%)	1,328 (39.5%)	447 (40.8%)
M1	151 (8.5%)	42 (12.2%)	580 (17.3%)	151 (13.8%)
Mx	979 (55.4%)	169 (49.3%)	1,452 (43.2%)	499 (45.5%)
∑	1,767	343	3,360	1,097
Missing	624	129	1,064	403