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INVITED REVIEW

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A systematic review of cancer risk among users of smokeless tobacco (Swedish snus) exclusively, compared with no use of tobacco

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Abstract

The main objective of this systematic review was to assess cancer risk, and mortality after cancer diagnosis, for exclusive users of Swedish snus, compared with non-users of tobacco. We followed international standards for systematic reviews and graded our confidence in the risk estimates using the GRADE approach. Our search gave 2450 articles, of which 67 were assessed in full text against our inclusion criteria. Of these, 14 cohort-studies and one case-control study were included in the review. The studies investigated risk of cancer in the oral cavity or oropharynx (3 studies), esophagus (1 study), stomach (1 study), pancreas (2 studies), colorectum (2 studies), anus (1 study) and lung (1 study), as well as malignant lymphoma (1 study), leukemia and multiple myeloma (1 study), melanoma (1 study), any cancer (1 study) and mortality after cancer diagnosis (4 studies). Cancer risk could only be evaluated in men as there was a general lack of data for women. All included studies were evaluated to have a moderate risk of bias, mostly related to validity of exposure information. An increased risk of cancer of the esophagus, pancreas, stomach and rectum as well as an association between use of snus and increased mortality after a cancer diagnosis was reported. Our confidence in the various risk estimates varied from moderate through low to very low.

KEYWORDS
cancer, smokeless tobacco, snus, tobacco

1 | INTRODUCTION

Tobacco smoking is a leading cause of preventable death in the world,[1] affecting almost every organ in the body, and associated with

Abbreviations: CI, confidence interval; CWC, construction worker cohort; HR, hazard ratio; IARC, International agency for research on cancer; IRR, incidence rate ratios; NNK, nicotine-derived nitrosamine ketone; NNN, N-nitrosonornicotine; OR, odds ratio; PAHs, polycyclic aromatic hydrocarbons; RR, relative risk; Snus, Swedish smokeless tobacco; TSNA, tobacco-specific nitrosamines.

a wide range of diseases such as cardiovascular disease, chronic obstructive pulmonary disease and various types of cancer.[2] Traditionally, these detrimental health effects have been linked to toxic chemicals in tobacco smoke, including polycyclic aromatic hydrocarbons (PAHs) typically formed during pyrolysis or incomplete combustion as well as tobacco-specific nitrosamines (TSNA) and nicotine.[2,3] Smoking has declined in many parts of the western world, while alternative nicotine products, such as electronic cigarettes, snus and other types of smokeless tobacco products have increased their market shares.[4] The term snus has been used for moist smokeless tobacco that comes in loose form or bags to be placed under the lip. In Sweden, a country with a long tradition for use of snus, the overall male prevalence of snus use is approximately 20%.[5] In Norway, Finland and the USA, the consumption has increased, especially among adolescents and young adults over the last two decades, reaching 29% and 12% in Norwegian men and women, respectively, in the age group 16-24.[6-8]

All tobacco products inclusive of Swedish snus contain TSNA, constituents associated with formation of DNA adducts and initiation of cancer.[9] Analyses have shown a reduction in TSNA levels in Swedish snus resulting from modification of the production process and storage conditions.[10] Despite a lower concentration of the carcinogenic nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK, nicotine-derived nitrosamine ketone) in Swedish snus compared with several American brands, one study reported the urine concentrations of the predominant NNK metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) among users of Swedish snus to be approximately half of that found in smokers and in users of snus with a higher content of TSNA.[11] Animal and in vitro studies have further suggested that exposure to nicotine through e-cigarette aerosol was associated with endogenous conversion of nicotine to TSNA, reduced DNA repair, subsequent DNA damage and cancer development.[12,13] In addition, some studies in animals suggest that nicotine is a tumor promotor and thus may promote biological selection of cells with oncogenic mutations acquired over an individual's lifetime due to endogenous processes, lifestyle factors and/or environmental exposures.[12] However, the cancer risks specifically related to nicotine exposure is currently not known and will likely depend on cancer type as well as the magnitude and length of nicotine exposure.

The main aim of the present systematic review was to identify, assess and summarize available human studies of the risk of cancer and the risk of death after a cancer diagnosis among exclusive users of Swedish snus compared with risks among non-users of tobacco.

2 | METHODS

2.1 | Protocol

The present systematic review on health risks from use of snus (PROSPERO CRD42021293500), was conducted in accordance with The Cochrane Handbook.[14]

2.2 | Search strategy

The literature search was conducted by a head librarian in May 2022. The search was built on previous searches conducted in 2004 (Norwegian Knowledge Centre for the Health Services. 2005), updated in 2013 (Norwegian Institute of Public Health. 2014) and 2018 (Norwegian Institute of Public Health. 2019), all conducted in accordance with Cochrane Handbook.[14] The following electronic databases were searched: Cochrane Database of Systematic Reviews, MEDLINE (Ovid), Embase (Ovid), PsycInfo, Cochrane Central register of controlled trials and Web of science. Terms related to geographical regions were used to restrict the search to the use of Swedish snus. In the Nordic countries, this is the predominant smokeless tobacco used. However, we did not exclude studies from other regions. The search strategy is presented in Table S1. In addition, we screened the references of included studies to identify potentially relevant studies not identified in our literature search.

2.3 | Study eligibility criteria

We included human studies, no restrictions on study design, of cancer risk, total mortality and cancer specific mortality for exclusive users of Swedish snus compared with never users of tobacco products and limited to publications in English, Norwegian, Swedish or Danish language. We used the risk estimates for current users of snus at the time when their tobacco habits were reported, when available (Table S2). We excluded studies reporting risk estimates based only on dual use of snus and cigarettes and studies conducted by researchers with link to the tobacco industry or sponsored by this industry.[15]

2.4 | Study selection

The identified titles and abstracts were screened against the inclusion criteria by two researchers independent of each other, discrepancies were resolved by discussion. Relevant papers were assessed in full text by two researchers independently and discrepancies resolved by discussion.

2.5 | Data extraction

One author collected information from the included studies whereas another author controlled that the right information was extracted correctly. Where we identified missing data or had questions regarding the analysis, we contacted authors of the studies to retrieve necessary information.

All studies reporting cancer risk, total mortality, and cancer-specific mortality for exclusive users of Swedish snus compared with never users of tobacco products are presented in text and Table S2.

2.6 | Study quality

Risk of bias in the included studies was assessed and discussed by two researchers. We used the checklist for cohort studies by The Joanna Briggs Institute, Critical Appraisal tools for Cohort studies and case-control studies.[16] Our confidence in the risk estimates was assessed using the GRADE approach.[17] Graded outcomes are presented in our GRADE tables (Tables 1 and S3). The GRADE tables were made using the GRADEpro software tool. We used the narrative statements as suggested by the GRADE working group for phrasing conclusions. For results of Moderate certainty, the words "probably" or "likely" were used. For results of Low certainty, the conclusion was phrased with the words "may" or "the evidence suggests". For results of Very Low certainty, we used the words "very uncertain".

Point estimates of effect in observational studies, which include most epidemiological cancer studies, are generally considered to be of "low confidence" when evaluated by GRADE. Studies were upgraded to a "moderate confidence", if the point estimates of risk were above 2.0 or below 0.5, and there had been no reason for downgrading of these studies (no serious problems with risk of bias, heterogeneity or

TABLE 1 Graded risk estimates for cancer associated with snus use compared with no use of tobacco.

Snus compared with no use of tobacco for cancer

Patient or population: Exclusive users of snus
Setting: Sweden
Intervention: Exclusive use of snus
Comparison: No use of tobacco

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no use of tobacco	Risk with snus				
Oral cancer	90 per 100 000	84 per 100 000 (53 fewer to 130 more)	HR 0.93 (0.59 to 1.44)	181 797 (1 observational study, Araghi et al[18])	⨁◯◯◯ Very low[a]	
Esophagus (squamous cell carcinoma)	16 per 100 000	55 per 100 000 (25 to 119 more)	HR* 3.5 (1.6 to 7.6)	142 891 (1 observational study, Zendehdel et al[19])	⨁⨁⨁◯ Moderate[b]	
Non-cardia stomach cancer	237 per 100 000	332 per 100 000 (261 to 451 more)	HR* 1.4 (1.1 to 1.9)	142 891 (1 observational study, Zendehdel et al[19])	⨁⨁◯◯ Low	
Pancreatic cancer, 27 years	72 per 100 000	151 per 100 000 (86 to 237 more)	RR 2.1 (1.2 to 3.3)	122 639 (1 observational study, Luo et al[20])	⨁⨁⨁◯ Moderate[c]	
Pancreatic cancer, 36 years	225 per 100 000	241 per 100 000 (174 fewer to 338 more)	HR 1.07 (0.77 to 1.50)	184 277 (1 observational study, Araghi et al[18])	⨁◯◯◯ Very low[a]	
Rectal cancer	339 per 100 000	468 per 100 000 (363 to 600 more)	HR 1.38 (1.07 to 1.77)	185 209 (1 observational study, Araghi et al[18])	⨁⨁◯◯ Low	
Rectal cancer	n.a	n.a	HR 1.10 (0.91 to 1.34)	(2 observational studies in combined meta-analysis, Nordenvall et al[21] and Araghi et al[18]	⨁⨁◯◯ Low	
Cancer specific mortality	2141 per 100 000	2395 per 100 000 (2141 to 2690 more)	HR 1.12 (1.00 to 1.26)	163 412 (1 observational study, Byhamre et al[22])	⨁⨁◯◯ Low	

Note: *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence—High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; HR, hazard ratio; * risk ratios reported as relative risk from Cox proportional hazard regression model in the studies was assumed to be HR; n.a. not available.

[a]We consider the outcomes of cancer and mortality to be such important harms that we did not decide a threshold value for harm, exemplified by how many more cancers should occur in the exposed vs the non-exposed group. Thus, we downgraded our certainty of the evidence when the risk estimates included both increased and reduced harm. We did not downgrade when the whole confidence interval was above unity.

[b]Downgraded due to very few events.

[c]Upgraded due to large effect (effect estimate ≥2) and/or dose response gradient.

directness). Studies were downgraded to "very low confidence" when the confidence intervals included both increased and reduced harm. We did not downgrade when the whole confidence interval was above unity.

All studies assessed by GRADE were based on follow-up of cohorts with prospectively recorded cancers analyzed according to baseline information. When several observational studies of the same outcome were performed in the same population, the study with the highest number of participants or the longest follow-up time was included. For pancreatic cancer, we additionally present informative results from a study with shorter follow-up time.

For rectal cancer, using the method of generic inverse variance, we performed a meta-analysis of the estimates from Araghi et al,[23] exchanging their 27-year follow-up of the CWC with a 10 years longer follow-up of the same cohort by Nordenvall et al.[21]

3 | RESULTS

3.1 | Cancer risk of snus use compared with no tobacco use

Our systematic literature search identified 2450 references. We considered 67 of these references potentially relevant for cancer and assessed them in full-text against our inclusion criteria. We included 14 studies from the literature search and included one more identified by screening the references from these studies. Fourteen of the studies were cohort studies and one was a case-control study.[24] The PRISMA flow chart is presented in Figure 1. Excluded studies are presented with their reason for exclusion in Table S4.

The 15 included studies investigated risk of cancer in the oral cavity,[20,25,26] esophageal cancer,[19] stomach cancer,[19,27] pancreatic cancer,[20,23] colon, rectal and anal cancer,[18,21] lung cancer,[20] malignant lymphoma,[28] leukemia and multiple myeloma,[29] cutaneous melanoma, melanoma in situ, intraocular melanoma,[30] any cancer,[26] cancer-specific mortality,[22,26,31,32] as well as cancer-specific mortality and all-cause mortality after a cancer diagnosis.[18,31-33] Only one of these 15 studies reported risk estimates for women. For the included studies, there was a moderate risk of bias, mostly related to validity of exposure information. (Table S5). For all included studies, effect estimates, number of cases, user group charateristics and confounder adjustments are summarized in Table S2.

3.1.1 | Cancer of the oral cavity

We identified three studies reporting on use of snus and oral cancer. One of them was a pooled analysis of nine Swedish cohorts reporting an oral cancer risk of HR 0.93 (95% CI 0.59 to 1.44, 25 exposed cases).[25] This most recent and pooled study from 2021 was used for the GRADE evaluation (Table S3). A separate subanalysis of the pooled study presented an extended follow-up of the Swedish

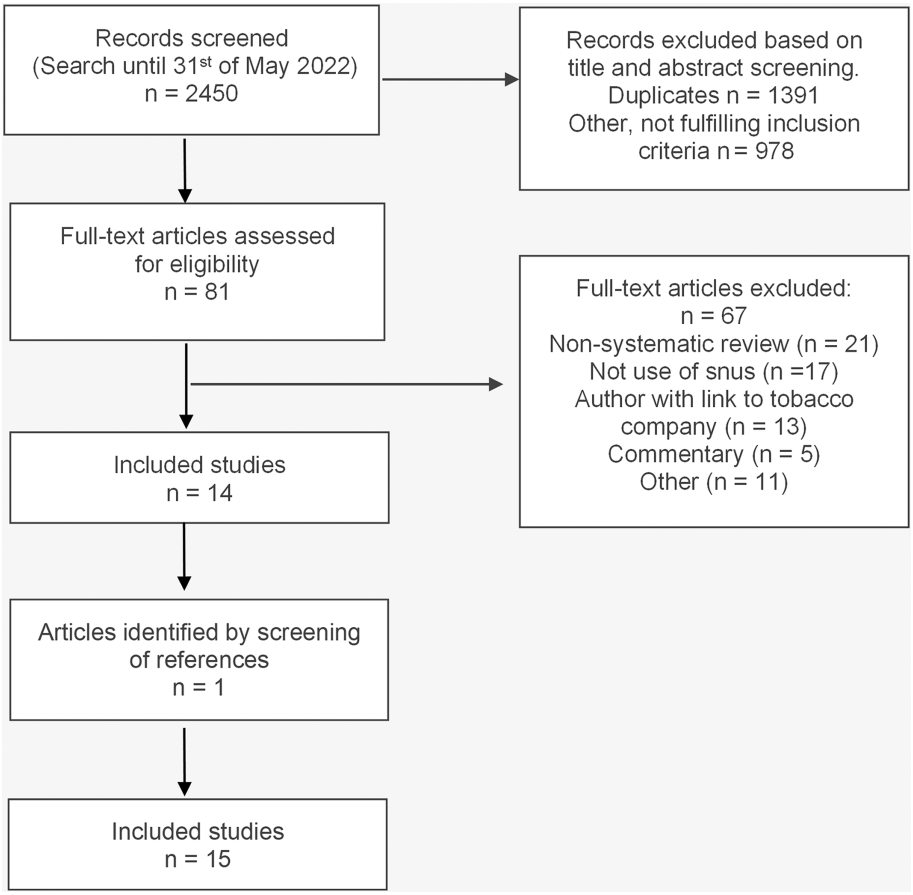

FIGURE 1 PRISMA flow charts 2450 records screened and 15 studies included.

Construction Workers Cohort (CWC), used separately in an earlier oral cancer study by Luo et al.[20] The most recent one had a maximum follow-up of 35 years and showed an oral cancer risk of HR 1.0 (95% CI 0.6 to 1.7, number of exposed cases not reported). The third study on oral cancer, reported a risk estimate for oral and pharyngeal cancers combined, restricted to never smoking, daily snus users, showing a risk of HR 2.3 (95% CI 0.7 to 8.3, 5 exposed cases).[26]

3.1.2 | Cancer of the esophagus

Zendehdel et al[19] reported a risk of esophageal squamous cell carcinoma for exclusive users of snus of 3.5 (95% CI 1.6 to 7.6, 10 exposed cases) based on the CWC (Table 1). The risk for esophageal adenocarcinoma was HR 0.2 (95% CI 0.0 to 1.9, 1 exposed case; Table S3).

3.1.3 | Cancer of the stomach

It is common to distinguish between cancers of the part of the stomach closest to the opening of the esophagus (cardia) and the rest of the gastric ventricle (non-cardia). Two studies reported on cancer of the stomach. A case-control study by Ye et al[27] reported for never smoking ever users of snus a risk of adjusted (a) OR 0.5 (95% CI: 0.2 to 1.2, 11 exposed cases) for combined cardia and non-cardia stomach cancer.

Based on the CWC, Zendehdel et al[19] reported a risk of non-cardia stomach cancer of RR 1.4 (95% CI 1.1 to 1.9, 68 exposed cases) for users of snus only compared with never users of tobacco (Table 1). The cancer risk estimated for cardia stomach cancer was RR 0.9 (95% CI 0.4 to 2.0, 8 exposed cases; Table S3).

3.1.4 | Cancer of the pancreas

Two partly overlapping epidemiological studies investigated associations between Swedish snus use and pancreatic cancer, using either incidence data or mortality and incidence combined in their main analysis. There appeared to be a time-dependent HR, and we present results from both studies.

Luo et al[20] based their analysis on never smoking CWC participants and reported a RR of 2.1 (95% CI 1.2 to 3.6, 18 exposed cases) among current users of snus at baseline with a maximum of 27 years follow-up (Table 1).[20] In a more recent pooled analysis of nine Swedish cohorts, where 2/3 of all participants and 72% of incident cases or deaths of pancreatic cancer originated from the CWC, the estimated risk in current users of Swedish snus at baseline was HR 1.07 (95% CI 0.77 to 1.50, 41 exposed cases) in a sensitivity analysis restricted to never smokers (Table 1).[23] The same study presented a sub-analysis of the CWC indicating a variable HR, dependent on the length of the observation period. The risk among current users of snus at baseline remained twice that of never-tobacco users until 2004, and subsequently seemed to drop: Follow-up 1978-1994, HR 1.98 (95% CI 0.97 to 4.03, 4 exposed cases),[23] follow-up 1978-2004, HR 2.1 (95% CI 1.2 to 3.6, 18 exposed cases)[20]; follow-up 1978-2013, HR 1.34 (95% CI 0.90 to 1.99, 31 exposed cases)[23] (Figure 2).

Since the study by Luo et al[20] showed a strong association between use of snus and pancreatic cancer and a dose-related risk pattern, we present both the study of Luo et al[20] and the study by Araghi et al[23] in Table 1.

3.1.5 | Cancer of the colon, rectum and anus

Nordenvall et al[21] reported risks of cancer of the colon, rectum and anus, with corresponding HRs of 1.08 (95% CI 0.91 to 1.29, 153 exposed cases), 1.05 (95% CI 0.85 to 1.31, 99 exposed cases) and 0.61 (95% CI 0.07 to 5.07, 1 exposed case), respectively, based on CWC with a maximum follow-up of 37 years (Table S3).

Araghi et al[18] used the same nine cohorts as those included in the study on pancreatic cancer, although with a shorter maximum follow-up time for CWC, 27 years. For exclusive current snus users compared with never users of tobacco, the authors reported for colon cancer and rectal cancer combined a HR of 1.16 (95% CI 0.97 to 1.37, 153 exposed cases; Table S3), for colon separately HR 1.02 (95% CI 0.81 to 1.29, 80 exposed cases; Table S3), and for rectal cancer HR 1.38 (95% CI 1.07 to 1.77, 73 exposed cases; Table 1). Furthermore, the risk of colorectal cancer (combined) among those reporting the highest daily snus consumption (seven cans or more per week) was HR 1.36 (95% CI 1.04

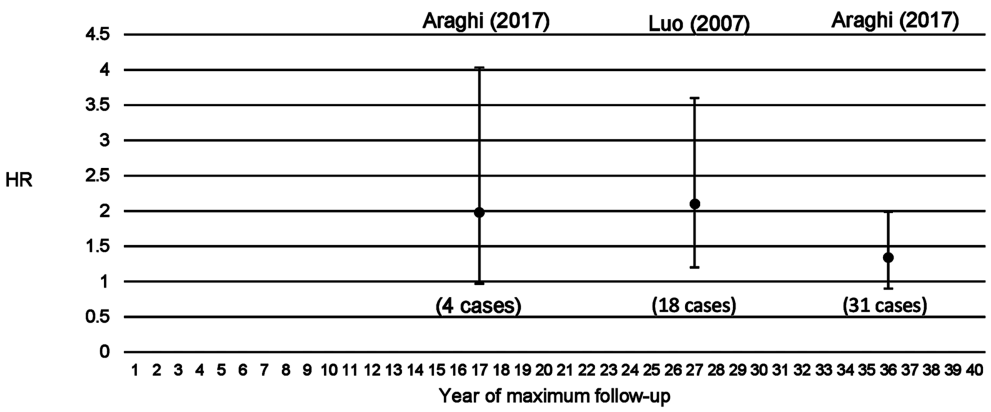

FIGURE 2 Time varying hazard ratios (HR) of pancreatic cancer from the construction worker cohort (CWC).

to 1.78, number of exposed cases not reported). Sensitivity analysis without the dominating large CWC gave a HR 1.22 (95% CI 0.91 to 1.64, 50 exposed cases) for colorectal cancer in current users of snus. This was quite similar to the overall HR 1.16 for colon cancer and rectal cancer combined. We also performed a meta-analysis of the rectal cancer estimates from Araghi et al[23] that had excluded the CWC with 27 years follow-up, combined with the risk estimate from Nordenvall et al[21] who had a 10 year longer follow-up time of the CWC. The new risk estimate was HR 1.10 (95% CI 0.91 to 1.34). Thus, the point estimate (HR) was reduced by almost 20% (from 1.38 to 1.10) with the 10 years maximum longer follow-up time (Figure 3).

3.1.6 | Cancer of the lung

One study investigated use of Swedish snus and the risk of lung cancer. Luo et al[20] reported a RR of 0.8 (95% CI 0.4 to 1.3, 15 exposed cases) for lung cancer among 34 818 men who currently used snus at baseline with a maximum 27-year follow-up of the CWC (Table S3).

3.1.7 | Malignant lymphoma

The CWC was used to investigate the role of smoking and use of snus on the risk for developing non-Hodgkin and Hodgkin lymphoma. Fernberg et al[28] reported a risk for non-Hodgkin lymphoma IRR 0.77 (95% CI 0.59 to 1.01, 66 exposed cases) and for Hodgkin lymphoma IRR 0.88 (95% CI 0.49 to 1.58, 15 exposed cases). The risk for Hodgkin lymphoma in men who had used snus for over 30 years was IRR 3.78 (95% CI 1.23 to 11.60:4 exposed cases). This study was the only one also reporting on women, however there were few participants, and no lymphoma cases were observed among women. The authors report that they used a Cox proportional hazard regression model, however they presented the results as the incidence rate ratios (IRR), thus we did not GRADE these results.

3.1.8 | Leukemia and multiple myeloma

A prospective cohort study reported risks of acute lymphocytic leukemia (ALL) IRR 1.24 (95% CI: 0.39 to 4.01, 4 exposed cases), acute myelogenous leukemia (AML) IRR 0.81 (95% CI: 0.41 to 1.60, 10 exposed cases), chronic myelogenous leukemia (CML) IRR 1.17 (95% CI: 0.60 to 2.28, 12 exposed cases) and multiple myeloma (MM) IRR 0.92 (95% CI: 0.61 to 1.40, 26 exposed cases).[29] The authors report that they used a Cox proportional hazard regression model, however they presented the results as the IRR, thus we did not GRADE these results.

3.1.9 | Cutaneous malignant melanoma, melanoma in situ, intraocular malignant melanoma

Odenbro et al[30] reported from the CWC on risk for all melanomas combined IRR 0.65 (95% CI, 0.52 to 0.82, 96 exposed cases), cutaneous malignant melanoma IRR 0.63 (95% CI: 0.48 to 0.81), melanoma in situ IRR 0.64 (95% CI: 0.36 to 1.14) and intraocular malignant melanoma IRR 1.14 (95% CI: 0.43 to 3.07). When stratified by duration of snus use (1 to 29 years and ≥ 30 years), similar estimates were reported, although with generally lower point estimates in long-term users. The authors report that they used a Cox proportional hazard regression model, however they presented the results as the IRR, thus we did not GRADE these results.

3.1.10 | Any cancer and smoking related cancer

The study by Roosaar et al[26] reported on risk for any cancer HR 1.1 (95% CI 0.9 to 1.4, 138 exposed cases) for ever daily users of snus, restricted to never smokers. The same study reported a risk for smoking-related cancer defined according to Levitz et al[34] HR 1.6 (95% CI 1.1 to 2.5, 39 exposed cases; Table S3).

3.1.11 | All-cause and cancer-specific mortality

Byhamre et al[22] investigated the relationship between snus use and all-cause and cause-specific mortality by retrieving cause of death by linkage to the National Cause of Death Register. The study included eight of the nine Swedish cohorts previously addressed in studies by Araghi et al.[23] Pooled analyses showed that exclusive current snus users had a risk of cancer-specific death HR 1.12 (95% CI 1.00 to 1.26, 332 exposed deceased) and of all-cause mortality HR 1.28 (95%

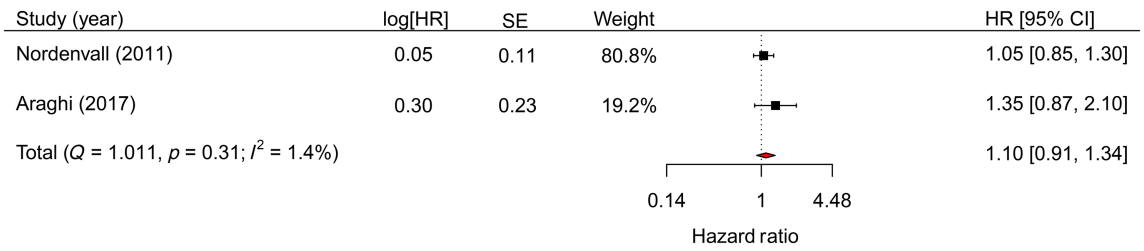

FIGURE 3 Meta-analysis of the estimates for rectal cancer based on HR at 27 and 37 years follow up time. Data from Araghi and co-workers that had excluded the CWC with 27 years follow-up, combined with the risk estimate from Nordenvall and co-workers who had a 10 year longer follow-up time of the CWC. [Color figure can be viewed at wileyonlinelibrary.com]

CI 1.20 to 1.35, 1410 exposed deceased; Table 1). Bolinder et al[31] have previously reported on all-cause and cancer-specific mortality based on the CWC but with shorter follow-up time than Byhamre et al.[22] The study by Roosaar et al[26] on a cohort not included by Byhamre and co-workers reported a risk for death any cause HR 1.23 (1.09 to 1.40, number of exposed deceased not reported) and risk of cancer specific mortality HR 1.28 (95% CI 0.96 to 1.69, number of exposed deceased not reported) for ever snus users among never smokers.

3.1.12 | Mortality after any cancer diagnosis

Nordenvall et al[32] investigated the survival of 40 230 male Swedish construction workers from the CWC diagnosed with incident cancer and compared the overall and cause-specific mortality among exclusive smokers and exclusive snus users with that of patients who never used tobacco. Participants classified as exclusive snus users at baseline had a risk of death regardless of cause (total mortality), of HR 1.13 (95% CI 1.05 to 1.20, 1060 exposed deceased). The risk of dying from cancer among users of snus was HR 1.15 (95% CI 1.05 to 1.26, 606 exposed deceased)[32] (Table S3). The analysis by Nordenvall et al[32] was adjusted for cancer site since prognosis varies according to site and there were differences in the frequency of cancer at each site.

3.1.13 | Mortality after prostate cancer

Wilson et al[33] studied survival among CWC participants with prostate cancer, to assess cancer-specific mortality and total mortality according to tobacco use at entry (snus, smoking, both snus and smoking or never use of tobacco). Never-smoking patients who used snus had an overall mortality risk, compared with patients who never used tobacco, of HR 1.19 (95% CI 1.04 to 1.37, 261 exposed deceased). Patients who used snus also had a higher risk of prostate cancer-specific death, HR 1.24 (95% CI 1.03 to 1.49, 141 exposed deceased). Nordenvall et al[32] had previously performed an analysis of cancer-specific death after prostate cancer based on the same cohort and follow-up time applying a slightly different statistical model. Nordenvall et al[32] reported a similar hazard ratio of HR 1.19 (95% CI 1.00 to 1.40). Additionally, Wilson et al[33] performed an analysis restricted to patients with non-metastatic prostate cancer and found a risk of death among snus users of HR 3.17 (95% CI 1.66 to 6.06, 14 exposed deceased; Table S2).

3.1.14 | Mortality after colorectal cancer

Araghi et al[18] reported on mortality among colorectal cancer patients from a pooled analysis of the previously mentioned nine Swedish cohorts. Colorectal cancer patients who were exclusive current snus users had an overall mortality of HR 1.16 (95% CI 0.89 to 1.50, 66 exposed deceased), and a cancer-specific mortality of HR 1.00 (95% CI 0.66 to 1.53, 29 exposed deceased) compared with men who did not use tobacco products (Table S3). Based on CWC only, Nordenvall et al[32] had previously reported no elevated risk for cancer-specific mortality among colorectal cancer patients using snus. Araghi et al[18] also performed a sensitivity analysis excluding CWC, which was the largest and had the longest follow-up time from registration of snus habits of the nine cohorts. In the restricted analysis, they, found a risk of death from any cause, HR 1.89 (95% CI 1.21 to 2.94, 22 exposed deceased) among colorectal cancer patients recorded as exclusive current snus users compared with patients who did not use tobacco.

3.1.15 | Grading our confidence in the results on cancer risk from use of snus

Our GRADE assessments are shown in Tables 1 and S3 where footnotes explain the two estimates we upgraded for large effect and the estimates we downgraded for imprecision.

4 | DISCUSSION

Use of snus probably increases the risk for cancer of the esophagus and pancreas. Use of snus may increase the risk for cancer of the stomach and rectum, and the evidence suggests an increased risk for cancer-specific mortality as well as increased overall mortality after a cancer diagnosis (all types of cancer combined). We are very uncertain if use of snus affects the risk for cancer of the other organs investigated. Precise estimates of risk for rare cancers that may increase 10%-30% above the risk in non-exposed populations, are challenging to obtain. Only one study, on malignant lymphoma, assessed the risk of cancer for female users of snus. However, no cases were identified. For other cancers and mortality, no data on women was reported. Hence, we do not know how the use of snus affects the risk of cancer or mortality for women.

4.1 | Grading the results

For our GRADE assessment, we included studies that compared the risk of cancer and mortality for exclusive snus users with that of never users of tobacco. The alternative approach, with adjustment for smoking in analyses of study samples that also include smokers and dual users, has been shown to distort risk estimates for snus users most likely because of residual confounding by smoking. This was illustrated by Luo et al,[20] who chose a priori to analyze exclusive users of snus compared with participants who had never smoked. Dual users of cigarettes and snus with nicotine dependency, would tend to replace any reduction of their cigarette consumption with snus, and vice versa to obtain a more stable serum nicotine concentration. A lower-than-average consumption of cigarettes in a minority of dual users

would, in the absence of quantitative exposure data (amount and duration), tend to give snus an apparently protective effect whenever the risk associated with smoking surpassed that of snus. Data on smoking in the reviewed studies was merely qualitative, reflecting smoking status at entry as "current", "former" or "never" smoker. Where available, we chose to use risk estimates for current use of snus at the time of recruitment into the cohort to reduce uncertainty associated with former use (duration, dose and changes in constituents) and a potential attenuation of risk after quitting snus.

Point estimates may have confidence intervals that includes both a possible increase and decrease of risk or harm which implies that authors must consider downgrading due to imprecision.[35] We consider the outcomes of cancer and mortality to be such important harms that we did not decide a threshold value for harm, exemplified by how many more cancers should occur in the exposed vs the non-exposed group. Thus, we downgraded our certainty of the evidence when the risk estimates included both increased and reduced harm. This was the main reason why some of the results had "very low" confidence. We did not downgrade when the whole confidence interval was above unity. Since the cancer and mortality outcomes, as mentioned above, are considered important harms, our conclusions in these cases often concur with P-value considerations. Our considerations were supported by estimates suggesting increased cancer risk and by experimental studies of effects from the ingredients of snus, such as TSNAs and other hazardous constituents including nicotine, and by studies of other types of smokeless tobacco.[36]

4.2 | Impact of exposure information

The main aim in this review was to evaluate the evidence of cancer hazard associated with use of snus. Since important information on smoking habits such as amounts and duration, was not always included in the analyses, we restricted our hazard identification to data on non-smokers using snus. Residual confounding from smoking could otherwise distort the risk estimates from the use of snus as described by Luo et al.,[20] which was also suspected in other studies where smoking adjusted estimates were available (Table S2). In this systematic review based on Swedish cohort studies, the exposure information in the primary studies relied on a single recording of tobacco habits at baseline (start of follow-up). This approach secured a prospective design, but the results depended on the accuracy of self-reported data at one point in time and were vulnerable to potential changes in tobacco habits during follow-up. This may be especially challenging when participants are young at baseline, and the study must allow for a long observation time because cancer usually appears after the age of 50.

A study from Sweden reported that approximately 30% of exclusive snus users may quit their habit, or even change to smoking.[37] Additionally, there is not much documentation whether the risk of cancer changes after quitting use of snus. For smoking, the risk of cancer may wane after cessation but the slope of the risk reduction may depend on cancer type and smoking history.[38] The CWC was the largest cohort, contributing the highest number of snus users, cancer cases and deaths. The snus users, however, constituted the smallest subgroup of tobacco users and more than 75% of exclusive snus users were younger than 30 years at entry, while the proportion of smokers younger than 30 was only 31%. Only a small proportion of snus users was traced beyond the age of 70, even in the most recent studies of the CWC. Thus, the chance of precise and unbiased risk estimates may easily be smaller for snus users than for smokers.[19]

Potential misclassification of smoking status in the CWC by using data from 1971 to 1975 has been discussed both by authors of the primary literature using the CWC as well as authors of other reviews. The main concern raised regarding tobacco exposure information was that it is not possible to distinguish between no-use and non-response based on the data from these years. Seven of the 14 included studies in the present review included participants that entered the CWC from 1971 to 1975. The CWC had a pause from 1976 to 1977, but in 1978, a new questionnaire was used that included smoking and snus use and the registrations were filled in by the staff. As Nordenvall et al[21] points out, if the tobacco habits were changed, between the different periods, the questions on tobacco habits tended to be unanswered. Thus, the cohort participant may be incorrectly coded as a non-user. Authors using data from the CWC must choose between restricting the inclusion of participants to those entering the cohort after 1977, thus have a study with shorter follow up and less participants or include the participants entering the cohort between 1971 and 1975.

Zendehdel et al[19] reported that 6.7% of never users of tobacco and 13.2% of never smoking users of snus had at least one repeat record that indicated current or previous smoking. However, their sensitivity analysis showed that 60% of the snus users would have to be smokers to shift a null association with esophageal squamous cell carcinoma to the reported risk, when assuming no misclassification among never users of any tobacco. Similarly, Nordenvall et al[21] reported small changes in risk estimates caused by potential misclassification of smoking before and after 1977.

The CWC included construction workers, electricians, painters, sheet metal workers, and other construction industry employees in the whole of Sweden. The invitation to the voluntary medical examination was sent out by the construction site staff and about 75% responded to it. Occupational exposure may represent a cancer risk per se and may thus potentially confound the observed effects from the use of tobacco. However, in two case-control studies of lung cancer and exposure to asbestos among members of the CWC, the degree of confounding from smoking was found to be low, except in subanalyses with few cases.[39,40] Smoking is recognized as a potentially strong confounder of lung cancer risk, and the low degree of confounding indicates that tobacco habits and occupational exposures were independently distributed among the cohort members. Thus, we find it reasonable to believe that confounding from occupational exposure should be negligible in the current setting. Another bias of cancer risk could be differences in socioeconomic status The CWC cohort is considered rather uniform in this respect, which is also expected to reduce potential confounding.

4.3 | Specific cancer sites

In general, cohort studies of rare diseases are often hampered by low statistical power. For oral cancer, we did not identify any analysis restricted to cancer subsites within the oral cavity. The exact site of cancer relative to the most common place for the snus pouch (under the upper lip), was not available in the data. However, in a Swedish case series of long-term users of snus, oral cancer was observed at the same locations as where the portions had been placed.[41] A study by Axell and co-workers, not included in this review as the authors did not specify whether snus users were exclusive users of snus, suggested an incidence of 0.5 cases of oral cancer per 100 000 users of snus per year (see reference in Table S4). Oral cancer constitutes 0.7% to 0.8% of all cancers in Nordic countries,[42] and no information on relevant subsites is reported by routine. The public health impact from this relatively rare disease is expected to be limited in a Scandinavian population.

The risk of pancreatic cancer according to snus use in the CWC seemed to vary with length of follow-up, or time from baseline to year of observation.[20,23] The reason for this phenomenon is not known, but could plausibly involve age-dependent cessation of snus followed by an individual decreasing risk of pancreatic cancer in quitters, similar to the reversal of pancreatic cancer risk seen in former smokers.[38] The problem may be larger if tobacco habits were recorded early in life, and the disease occurs late in life. A possible explanation could also be that participants vary in their susceptibility to cancer development, leaving the more resistant ones for long-term observation.

Regarding colorectal cancer and use of snus, the number of studies and the strength of the data were not sufficient to confirm a causal relationship. However, at least for rectal cancer, there is reason to believe that a causal link may exist, considering the results from Araghi et al.[18] As observed for pancreas cancer in the CWC, it seems to be a time-varying HR for rectal cancer with a decreasing point estimate with longer follow-up time.

Odenbro et al[30] reported a reduced risk for cutaneous melanoma and melanoma in situ similar for both snus and smoking. However, a discussion of a potential biological mechanisms to explain this observation would be beyond the scope of this review.

4.4 | Cancer-specific death and all-cause mortality

Based on eight Swedish cohorts, Byhamre et al[22] reported an increased risk of cancer-specific death and all-cause mortality among snus users. Bolinder et al[31] had previously reported increased risks from the CWC, suggestively for cancer mortality RR 1.1 (95% CI 0.9 to 1.4, 96 exposed deceased) and more clearly for all-cause mortality RR 1.4 (95% CI 1.3 to 1.8, 440 exposed deceased) among snus users compared with non-users of tobacco. Another Swedish cohort, not included in the study by Byhamre et al,[22] also reported an increased risk for all-cause mortality HR 1.23 (95% CI 1.09 to 1.40, number of exposed deceased not reported), restricted to never-smoking ever users of snus compared with never users of snus.[26] For the same comparison, a HR 1.15 (95% CI 0.97 to 1.37, number of exposed cases not reported) was found for cancer related deaths. These associations may be linked to different user characteristics such as socioeconomic factors, diet or other user associated vulnerabilities, or to constituents in the snus products.

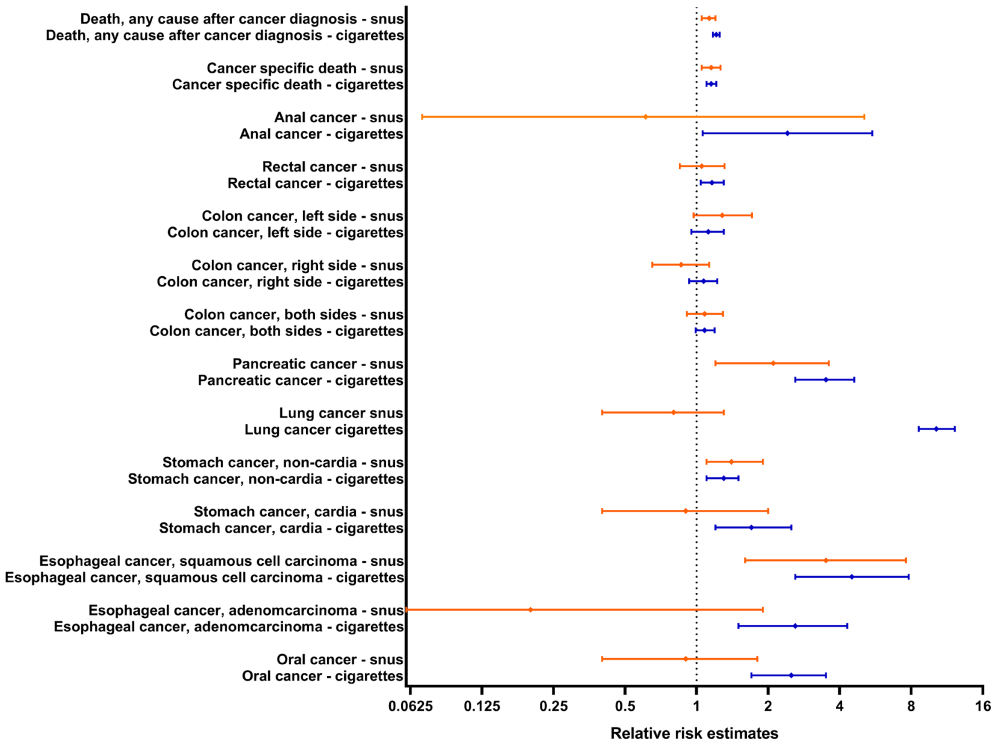

FIGURE 4 Compared risk between cancer outcomes for snus and cigarettes compared with same control group. The risk estimates originate from Nordenvall et al[32] (cancer specific death and any cause), Nordenvall et al[21] (colon cancer, rectal cancer and anal cancer), Luo et al[20] (oral cancer, lung cancer and pancreatic cancer) and Zendehdel et al[19] (esophagus cancer and stomach cancer). [Color figure can be viewed at wileyonlinelibrary.com]

4.5 | Comparison of cancer risk in exclusive users of snus and exclusive users of cigarettes

Switching completely from smoking to exclusive use of snus has been advocated as a harm reduction strategy, and obviously, this will reduce the pulmonary exposure to toxicants in the cigarette smoke. Still, respiratory function and pulmonary health can also be impacted by conditions not acting through the airways.

Some of the included studies in our systematic review reported the risk of cancer from smoking in parallel with use of snus. We collated the relative risk of cancer from studies where smoking and snus were compared with the same control group of never tobacco users, and adjusted for the same potentially confounding factors (Figure 4). An exception occurred in the study by Luo et al.,[20] where combined use of snus and smoking was included in the analysis of risk among smokers (about one third of the smokers combined snus and smoking). The reference group however was still never-users of tobacco, and the analyses of smoking-related risks were adjusted for snus. Overall, the risk estimates for cancer were higher for smokers than for snus users for most of the recorded cancer sites. Except for lung cancer, all confidence intervals were overlapping with those for smoking.

For those who stop smoking before age 40, it has been reported that more than 90% of the excess mortality risk is avoided compared with those who continue to smoke, whereas quitting at ages 45 to 64 years is associated with reductions of approximately 66% of the excess risk.[43] How much switching from smoking to exclusive use of snus would diminish the reduction in risk expected from quitting all use of tobacco is a highly relevant, complex question where the answer is currently not known. As snus contains carcinogens and the suggested tumor promotor nicotine[44] the specific reduction of risk following a switch to snus probably will depend on the tumor type, smoking history, the susceptibility of the host as well as accumulated damage.

4.6 | Biological plausibility of the results: TSNA, nicotine and other chemicals

Tobacco-specific nitrosamines (TSNA) including NNN (N-nitrosonornicotine), NNK (4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone), and the NNK degradation product NNAL (4-(methyl-N-nitrosamino)-1-(3-pyridyl)-1-butan-1-ol) are recognized carcinogens identified in Swedish snus. For both NNK and NNN, an important mode of action involved in cancer development is their conversion to reactive substances that can form DNA adducts.[45] TSNAs have also been suggested to contribute to carcinogenesis via binding to nicotine cholinergic- and other receptors that may enhance cancer development.[36]

The IARC monograph program does not classify nicotine as a human carcinogen. However, experimental studies provide evidence that nicotine may act as a tumor promotor.[46,47] Furthermore, endogenous nitrosation of nicotine may occur as indicated in vitro with human cells from the lung and bladder showing that nicotine and NNK gave similar DNA adducts.[13] A follow-up study, reported that inhalation of nicotine-containing e-cigarette aerosol caused lung cancer and precancerous lesions in the urinary tract in mice.[12] Our findings with snus are in agreement with previous evaluations of cancer risk in snus users, expressed by IARC and the US National Cancer Insitute.[9,36]

5 | SUMMARY OF EVIDENCE FOR CANCER RISK

Some of the studies retrieved in this systematic review, reported an increased risk of cancer of the esophagus, pancreas, stomach and rectum as well as cancer-specific death associated with the use of Swedish snus. Our confidence in the various risk estimates varied from moderate to very low. However, precise risk estimates for rare cancers with a moderate risk, are challenging to achieve. Swedish snus contains carcinogenic constituents such as TSNAs, although in lower levels compared with some other smokeless tobacco products. We conclude that use of snus entails a cancer hazard where the magnitude of cancer risk may be affected by user history and the susceptibility of the host.

AUTHOR CONTRIBUTIONS

Håkon Valen: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing—original draft, writing—review & editing. Rune Becher: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, writing—original draft, writing—review & editing. Gunn Elisabeth Vist: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, writing—original draft, writing—review & editing. Jørn Andreas Holme: investigation, writing—review & editing. Ibrahimu Mdala: formal analysis, software, writing—review & editing. Ida Kristin Ørjasæter Elvsaas: data curation, investigation, methodology, writing—review & editing. Jan Alexander: conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, writing—original draft, writing—review & editing. Vigdis Underland: data curation, investigation, writing—review & editing. Bendik Christian Brinchmann: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—original draft, writing—review & editing. Tom Kristian Grimsrud: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, writing—original draft, writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

All the authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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