

# The Results of Studies on the Health Effects of Smokeless Tobacco Funded by Tobacco Companies: A Meta-Analysis

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**Background:** This study aimed to examine the health impact of the use of smokeless tobacco in the context of research conducted by scholars with financial and organizational connections with tobacco companies. The study findings were intended to construct a foundation for regulating smokeless tobacco by contrasting such studies with investigations by researchers who did not declare any shared interest with tobacco companies in terms of funding or affiliation.

**Methods:** This systematic literature review established operational definitions to identify connections between researchers and tobacco companies. The affiliations of authors with leading tobacco companies were scrutinized using the Truth Tobacco Industry Documents. Internal documents released by tobacco companies were reviewed to ascertain whether any author of the relevant reviewed literature had received financial backing, participated in funding initiatives, or was an erstwhile employee of tobacco companies.

**Results:** The findings revealed that the reviewed studies reported a relatively high incidence rate of pancreatic cancer among smokeless tobacco users. However, studies by authors without competing interests concluded that smokeless tobacco users were more likely to develop cardiovascular diseases, lung cancer, as well as pancreatic cancer. In particular, a statistically significant difference was noted depending on the presence or absence of competing interest in the results reported for cardiovascular diseases, myocardial infarctions, and lung cancer.

**Conclusion:** Tobacco companies conduct their own research; they also fund various research centers and colleges to construct evidence that would be advantageous to their interests. Smokeless tobacco manufacturers rely on such evidence to promote their products as safe. Therefore, due attention must be paid to scholarly references to such findings and the inferences drawn from them.

**Keywords:** Tobacco; Smokeless; Systematic review; Snus; Tobacco company

## INTRODUCTION

Smokeless tobacco is a cigarette that is chewed or placed in the mouth so that nicotine can be absorbed without acting as a smoke cigarette [1]. Tobacco was developed in Sweden in the early 1600s and its sale is currently prohibited in European Union countries except for Romania, Denmark, and Sweden. Tobacco is imported to Korea through Snus Korea and Damoatobacco. It is mainly distributed through off-line tobacco-only dealers and Internet secondhand trading sites [2]. Smokeless tobacco manufacturers claim that their products help smoking cessation [3]. While many believe that they are induced to quit, there is no evidence that smokeless tobacco products help to stop smoking [4].

In Korea, the interest in smokeless tobacco and electronic cigarettes is increasing with strengthened regulations on tobacco, as indicated by the designation and expansion of non-smoking areas in all sales offices in 2015 and the increase in cigarette prices in January 2015. As regulations on the expansion of the smoking area and secondhand smoke are expanding, there is growing interest in smokeless tobacco, which can be smoked everywhere as there is no smoke coming out of a cigarette. Tobacco manufacturers are pursuing various marketing programs in different countries to increase the use of smokeless tobacco in countries where they are not well known. In countries in which promotions have been implemented, the use of smokeless cigarettes has skyrocketed, especially among young people and young adults [5]. The use of unleaded cigarettes in young people may eventually lead to smoking [5] and cigarette smokers may turn to smokeless cigarettes [6]. Smokeless tobacco is used in smoking-cessation areas, while cigarettes are used only in designated smoking areas [7].

The health risks associated with the use of

smokeless tobacco are lower than those of cigarettes [8]. However, they are still harmful to the health and are inadequate as an alternative method to smoking [1]. A 1986 US surgeon's report indicated that smokeless potentially caused cancer and had a 50-fold increased risk of developing oral and gingival cancer [9]. In addition, smokeless tobacco contains approximately 28 kinds of carcinogens and contains only nicotine-derived N-nitrosamines (TSNA), a carcinogen found in tobacco [10]. Smokeless tobacco also can cause health problems such as stroke (cerebral stroke) [11], periodontal disease [12], hypertension [13], myocardial infarction [11], etc., and its addiction is difficult to overcome [9]. Systematic literature reviews on smokeless tobacco have been conducted in various countries, including Europe and North America, where snus is used. Burkey et al. [14] reviewed research related to smokeless tobacco in Europe and South America, concluding that the use of smokeless tobacco affects pancreas cancer. Boffetta and Straif [11] reported that the use of smokeless tobacco increased the risks of fatal myocardial infarction and stroke in the US and Sweden. Critchley and Unal [15] reviewed studies conducted in the US and Europe, suggesting that the use of smokeless tobacco might be related to cardiovascular disease. In contrast, Hansson et al. [16], Lee [3], Lee [17], Colilla [18], Lee and Hamling [19], Kallischnigg et al. [20], Sponsiello-Wang et al. [21], Lee [22], Weitkunat et al. [23], Daniel Roth et al. [24], and Rodu and Cole [25] also conducted systematic literature reviews of research conducted in the US, Sweden, and neighboring European countries, concluding that the use of smokeless tobacco causes little harm to human health in relation to oral, pharynx, pancreas, and laryngeal cancer as well as cardiovascular disease, oral mucosal disease, and circulatory disease, and that the incidence rates of such diseases are lower than those for ordinary

smoking. However, the findings of these studies are unreliable since they were supported by tobacco companies [16,18,24,25] or their authors were employees of tobacco companies [3,17,19-23].

In Korea, Article 25 of the Tobacco Business Act and Article 9 of the Enforcement Decree of the same act specify that the advertisement of tobacco (including tobacco substitute goods) online is prohibited in principle (Law on Tobacco Business Act: No. 14042, date of promulgation: March 2, 2016, effective date: March 3, 2017; Enforcement Decree of the Tobacco Business Act, Presidential Decree No. 27869: launch date February 28, 2017, effective date March 3, 2013). Although there is limited advertising, current portal blogs and articles contain advertisements for smokeless cigarettes such as snus [2]. In addition, the Ministry of Strategy and Finance indicated that according to the Tobacco Business Act, tobacco and tobacco substitute products do not support smoking cessation; nonetheless, blogs and articles report effects of smokeless cigarettes such as smoking cessation or health safety, etc. with unclear information [2]. In reality, tobacco companies fund studies that encourage their employees, including researchers and consultants, to present findings that support the idea that smokeless tobacco is not harmful to human health. However, there is no research or evidential material by which such findings can be supported or rejected.

Accordingly, the aims of these present study were to analyze the health effects of smokeless tobacco according to the interests shared with tobacco companies and to utilize these findings as the basis for the regulation of smokeless tobacco by identifying shared interests such as funding and affiliation with tobacco companies in comparison to the findings of studies that do not have a relationship with tobacco companies. The main object of this study is snus, a type of smokeless tobacco that has been claimed to be less harmful to health than

ordinary cigarette products and has even been reported to have positive effects on smoking cessation. This study assessed the differences in research findings depending on whether or not tobacco companies funded the studies.

## METHODS

This study conducted a systematic literature review based on the methodology described in the “Korea Health and Medical Research Institute” manual [26,27]. As systematic literature reviews do not collect raw patient data and are based on existing publications; this study was conducted with a written confirmation of exemption from deliberation procedures (EUIRB2016-14) issued by the institutional bioethics committee of Eulji University.

### 1. Key question

Is there a difference in the results of research on smokeless tobacco depending on whether tobacco companies funded the research?

### 2. Analysis method

#### 1) Operational definitions for the identification of interests shared with tobacco companies

In order to examine their relationships with the tobacco companies, the authors’ affiliations were searched using the internal ‘Truth Tobacco Industry Documents (TTIDs)’ of the tobacco companies. After searching the TTIDs, we examined internal documents to determine if any author had received any financial support from the tobacco company, had been involved in the tobacco company’s funding or had ever worked at the company. A clear indication that the authors or the research were involved with the tobacco company was considered evidence of a relationship with the tobacco company. Table 1

outlines the PICOTS-SD (population, intervention, comparator, outcome, time frame, setting, and study design) checklist for the present study.

### 2) Scope of document search

The literature search utilized the MedLine, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases without a limit on the search period. In addition, a systematic review of the literature and reference documents of selected documents were also performed and a search was conducted in parallel with the manual search. The search was conducted on June 20, 2016.

### 3) Search strategies

The related documents were identified using search terms including ‘smokeless tobacco’, ‘chewing tobacco’, ‘snuff’, ‘snus’, and ‘tobacco, smokeless’ without limiting the search period. Searches of domestic and foreign databases were carried out directly by the researchers. The search terms that are included in the MeSH (Medical Subject Headings) terminology for smokeless tobacco were summarized using an existing systematic literature review.

### 4) Document selection

The retrieved data were summarized using Endnote and Microsoft Excel 2016 (Microsoft,

Redmond, WA, USA). Two reviewers (the researcher and another researcher with a Master’s degree who performed the systematic literature review) independently applied the inclusion and exclusion criteria. In the initial literature selection process, studies were excluded as irrelevant to the research topic based on a review of the titles and abstracts. In the second stage, the abstracts of the documents were reviewed and the documents that met the selection criteria of the study were finally selected. In cases of disagreement, the reviewers reached a consensus by discussing with a third party (advisor).

### 5) Evaluation of uncertainty in the selected studies

Because the included studies were observational studies rather than randomized clinical trials, the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) version 2.0 [28] was used. This risk assessment tool was developed by the Health Insurance Review and Assessment Service of the National Institute of Health and was revised in 2013 to reflect the latest research trends such as Cochrane. The RoBANS evaluates selection bias (target group comparison possibility, target group selection, disturbance variable), execution bias (exposure measurement), result confirmation bias (blurring of result evaluator, evaluation of result), elimination

**Table 1.** PICOTS-SD (population, intervention, comparator, outcome, time frame, setting, and study design)

Category	Description
Population	- Smokeless tobacco smokers - 18 years of age or older
Interventions	- Snus
Comparison	- Non-smokers
Outcomes	- Primary outcomes: cardiovascular disease, cerebral stroke, myocardial infarction - Secondary outcomes: cancer (lung or pancreas)
Time	No limit
Setting	No limit
Study design	- Randomized controlled trials, controlled clinical trials - Non-comparable studies were excluded - Published in either Korean or English

bias (incomplete data), and reporting bias (reporting optional results). Based on the reported rationale for each item, the risk was evaluated as ‘low’, ‘high’, and ‘unclear’. Two reviewers independently performed the agreed inclusion and exclusion criteria. In cases of disagreement between the two reviewers, a consensus was reached following discussion with a third party (advisor).

## 6) Data analysis

The final selected texts were divided according to the core questions. Quantitative analysis (meta-analysis) was performed when possible, with qualitative analysis performed for studies that could not be included in the meta-analysis. In the meta-analysis, if the study population and arbitration methods were not homogenous, a random-effects model was used to generalize to a wide population. In addition, since the number of studies was low and the sample size in each study large, estimations were made using a generic inverse variance estimation method. Subgroup analysis was performed after analyzing the possible items according to research funding source. The sources of research funding were identified according to the division of interests with the tobacco company. Heterogeneity was first visually confirmed by forest plots and the statistical heterogeneity between studies was assessed by Cochrane Q ( $p < 0.10$ ) and  $I^2$  statistics ( $\geq 50\%$ ) [29]. Since the analysis included more than 10 articles, the publication bias was assessed by funnel plot [29]. The meta-analysis statistical program used RevMan 5.3.

## RESULTS

This study systematically reviewed the published literature to evaluate the reported health effects of smokeless tobacco according to the research funding. A total of 9,288 records were searched in

the major foreign electronic databases. A total of 6,069 records remained following the removal of duplicate records by means of Endnote and Microsoft Excel 2016. Following title review, 2,189 articles were selected, and 636 articles remained after reviewing the abstracts. The full texts of 636 documents were downloaded and reviewed, and 18 documents were finally selected. The literature selection process according to the selection exclusion criteria of this study is shown (Figure 1).

## 1. Study characteristics

### 1) Study characteristics

The present study included 14 cohort studies and three patient-control studies (Table 2) [16,30-46]. Of these, 16 studies were conducted in Sweden, one in the US, and one in Norway. Fourteen studies were conducted through self-reported questionnaires, three conducted by the North Sweden MONICA Center, and one by a hospital. Ten studies had an indirect interest in a tobacco company and eight studies did not have a relationship with the tobacco company.

## 2. Classification of interests shared with tobacco companies

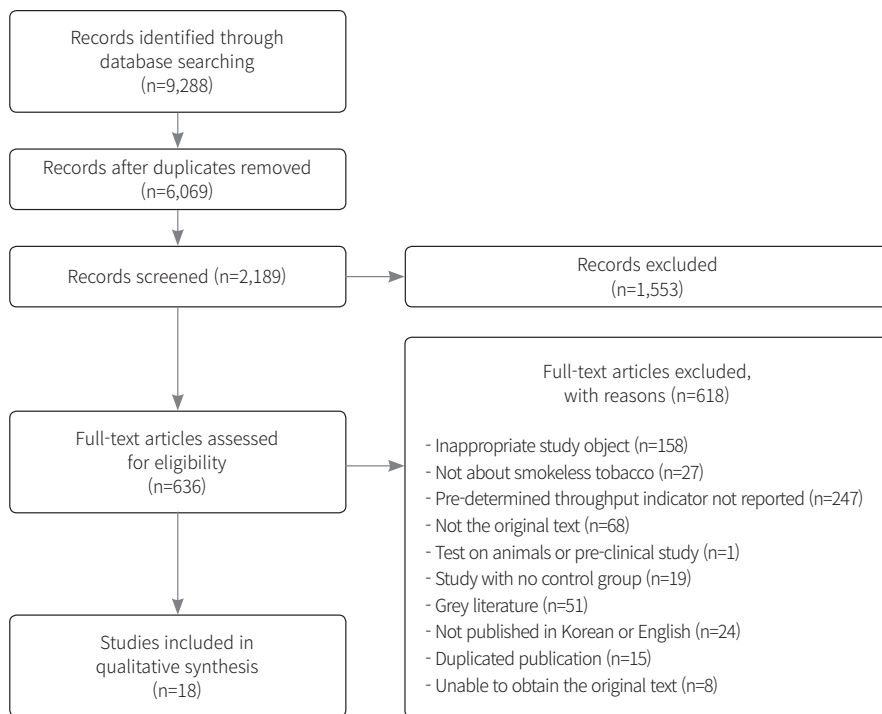
The 18 included studies were assessed for evidence of interest or relationship with tobacco companies. To identify the indirect interests of tobacco companies, we searched for all study authors in the TTIDs. This analysis revealed that one research institute had received research funding from tobacco companies. According to the internal articles of the Absolut Vodka tobacco company [47], The Swedish Tobacco Groups offered 20 million Skr to the Karolinska Institute in Stockholm to establish a chair in medical tobacco research (neurobiology, toxicology, biochemistry, or cell biology) [47]. The stated reason for this funding was that “The tobacco industry’s offer to the Karolinska Institute is an

attempt to promote itself indirectly and to gain credibility”. The Swedish Tobacco Groups provided the Karolinska Institute over 20 million kroner (over 2.5 billion won) and this support was indirectly promoted as a reason to gain trust. Therefore, based on the results of the internal document search, researchers belonging to the Karolinska Institute had an indirect interest in tobacco companies.

### 3. Evaluation of the risk of bias

The final selection of 18 papers underwent a risk of bias assessment using RoBANS version 2 [28]. The evaluation results revealed that more than 20% of the items in the comparability category of the target group, which are considered to be important in observational studies, were evaluated as high or

uncertain. One document was considered to be ‘uncertain’ because no concrete method was described. In the target group selection area, all documents were judged to be ‘low’. The risk of assessment bias in the case of cohort studies was considered to be ‘low’ when there was no problem in the selection of the target group after confirmation from the homepage of the cohort, even if there was no description about the cohort investigation method. In order to determine the risk of assessment bias caused by inadequate confirmation and consideration of disturbance variables, a homogeneity test was performed between two groups. The risk of assessment was considered ‘low’ when statistical corrections were made when the results were not homogeneous. However, one document did not



**Figure 1.** Overview of the selected studies.

**Table 2.** Overview of included studies

No.	Study	Research period	Research design	Research country	Place of application	Name of smokeless tobacco	Conflict of interest	Total No. of objects	Age bracket (yr)
1	Asplund et al. [30]	1985-2000	Patient-control studies	Sweden	North Sweden MONICA Center	Snus	-	276	25-74
2	Boffetta et al. [31]	1964-2001	Cohort studies	Norway	Self-questionnaires	Snus	Indirect interests	12,431	Not specified
3	Bolinder et al. [32]	1971-1974	Cohort studies	Sweden	Self-questionnaires (CWC)	Snus	Indirect interests	135,036	65
4	Carlens et al. [33]	1978-1992	Cohort studies	Sweden	Self-questionnaires (CWC)	Snus	-	277,777	-
5	Fernberg et al. [34]	1971-1992	Cohort studies	Sweden	Self-questionnaires (CWC)	Snus	-	336,381	14-82
6	Haglund et al. [35]	1988-1989	Cross studies	Sweden	Self-questionnaires (Swedish Survey of Living Conditions)	Snus	-	5,002	16-74
7	Hansson et al. [16]	1978-2004	Cohort studies	Sweden	Self-questionnaires	Snus	Indirect interests	130,485	Not specified
8	Hansson et al. [36]	1998-2002	Cohort studies	Sweden	Self-questionnaires (Screening Across the Lifespan Twin Study, SALT)	Snus	Indirect interests	16,642	≥40
9	Hatsukami et al. [37]	Not specified	Patient-control studies	US	Self-questionnaires	Snus	-	998	Not specified
10	Hergens et al. [38]	1978-1993	Cohort studies	Sweden	Self-questionnaires (CWC)	Snus	Indirect interests	118,395	35-65
11	Hergens et al. [39]	1978-1993	Cohort studies	Sweden	Self-questionnaires (CWC)	Snus	Indirect interests	120,930	≥65
12	Huhtasaari et al. [40]	1994	Cohort studies	Sweden	North Sweden MONICA Center	Snus	-	687	25-64
13	Janzon and Hedblad [41]	1991-1996	Cohort studies	Sweden	Malmö Hospital	Snus	-	27,227	45-73
14	Johansson et al. [42]	1988-2000	Cohort studies	Sweden	Self-questionnaires (Swedish Annual Level-of-Living Survey)	Snus	-	3,120	30-74
15	Luo et al. [43]	1978-1992	Cohort studies	Sweden	Self-questionnaires (CWC)	Snus	Indirect interests	125,576	≥60
16	Nordenvall et al. [44]	1971-1992	Cohort studies	Sweden	Self-questionnaires (CWC)	Snus	Indirect interests	336,381	≥65
17	Wennberg et al. [45]	1985-1999	Patient-control studies	Sweden	North Sweden MONICA Center	Snus	Indirect interests	525	≥60
18	Zendejdel et al. [46]	1971-2004	Cohort studies	Sweden	Self-questionnaires (CWC)	Snus	Indirect interests	336,381	-

CWC, construction workers cohort.

confirm the results; thus, the risk of bias was considered high. In the case of exposure metrics to evaluate the performance bias, all 18 documents had not previously been exposed to mediation, indicating that the risk of bias risk was low. The risk of bias in one of the categories for assessment of the evaluator's blindness, an unbiased evaluation area, was 'uncertain' because the relevant information was

not reported in all documents. In the case of the outcome evaluation category, one of the documents did not report the assessment risk and was evaluated as uncertain. The risk of assessment due to incomplete data due to the exclusion of research participants or analysis was high in two studies, while two other studies had an uncertain risk because the risk of assessment bias could not



be evaluated. Uncertainty arising from selective outcome reports was due to the lack of content reporting in some documents.

#### 4. Analysis results

##### 1) Cardiovascular disease

Among the studies reporting on cardiovascular disease, two were included in the analysis. Categorizing of these studies based on a relationship of interest with tobacco companies revealed one study with no interest and one study with interest. A meta-analysis showed that smokeless tobacco smokers had a higher incidence of cardiovascular disease (odds ratio [OR], 1.02) than that of non-smokers, but the difference was not statistically significant (95% confidence interval [CI], 0.33-3.13). However, subgroup analysis according to the presence or absence of interest revealed that the incidence of cardiovascular disease (OR, 1.80; 95% CI, 1.54-2.11) in the study with no interest was higher than that in the study with interest (OR, 0.57; 95% CI, 0.47-0.70). The difference between the two groups was statistically significant ( $\chi^2=76.72$ ,  $df=1$ ;  $p<0.001$ ).

##### 2) Stroke

A total of five studies were included in the literature reporting on stroke. Categorization of studies according to interests with tobacco companies revealed two studies with no interest and three studies with interest. A meta-analysis showed a high heterogeneity between the studies ( $I^2=87%$ ) and that the smokeless smokers had a significantly lower incidence of stroke than that of non-smokers (OR, 0.48; 95% CI, 0.37-0.61). However, subgroup analysis according to the presence or absence of interest revealed that the incidence rate of stroke (OR, 0.70; 95% CI, 0.42-1.17) in the studies with no interest was higher than that in the studies with

interest (OR, 0.38; 95% CI, 0.33-0.44). The difference between the two groups was statistically significant ( $\chi^2=5.15$ ,  $df=1$ ;  $p=0.02$ ).

##### 3) Myocardial infarction

A total of four studies were included in the analysis of myocardial infarction. Categorization of studies according to interests with tobacco companies revealed three studies with no interest and one study with interest. A meta-analysis showed a high heterogeneity between the studies ( $I^2=95%$ ) and that smokeless tobacco users had a lower incidence of cardiovascular disease than that of non-smokers (OR, 0.69), although the difference was not statistically significant (95% CI, 0.35-1.36). Subgroup analysis according to the presence or absence of interest revealed that the incidence of myocardial infarction (OR, 0.90; 95% CI, 0.71-1.14) in the studies with no interest was significantly higher than that in the study with interest (OR, 0.33; 95% CI, 0.30-0.36;  $\chi^2=57.45$ ,  $df=1$ ;  $p<0.001$ ).

##### 4) Lung cancer

A total of two studies reporting on lung cancer were included in the analysis. Categorization of the studies according to interest with tobacco companies revealed one document with no interests and one with interests. A meta-analysis showed that a high heterogeneity between the studies ( $I^2=100%$ ) and that there was no statistical correlation between the lung cancer incidence rates of non-smokers and smokeless tobacco users (OR, 2.47; 95% CI, 0.13-46.39). Subgroup analysis according to the presence or absence of interest revealed that the incidence of lung cancer (OR, 11.00; 95% CI, 9.24-13.10) in the study without interest was significantly higher than that in the study with interest (OR, 0.55; 95% CI, 0.40-0.76;  $\chi^2=255.3$ ,  $df=1$ ;  $p<0.001$ ).



5) Pancreatic cancer

A total of three studies reporting on pancreatic cancer were included in the analysis. Categorization of the articles according to interest in tobacco companies revealed two studies with no interest and one with interest. A meta-analysis showed a high heterogeneity between the studies ( $I^2=84%$ ) and that smokeless smokers had higher pancreatic cancer

incidence rates (OR, 2.18; 95% CI, 1.05-4.51). Subgroup analysis according to the presence or absence of interest revealed that the incidence of pancreatic cancer (OR, 2.62; 95% CI, 1.02-6.71) in the study with no interest was higher than that in the studies with interest (OR, 1.57; 95% CI, 0.99-2.47), although the difference was not statistically significant ( $\chi^2=0.93$ ,  $df=1$ ;  $p=0.34$ ) (Figure 2).

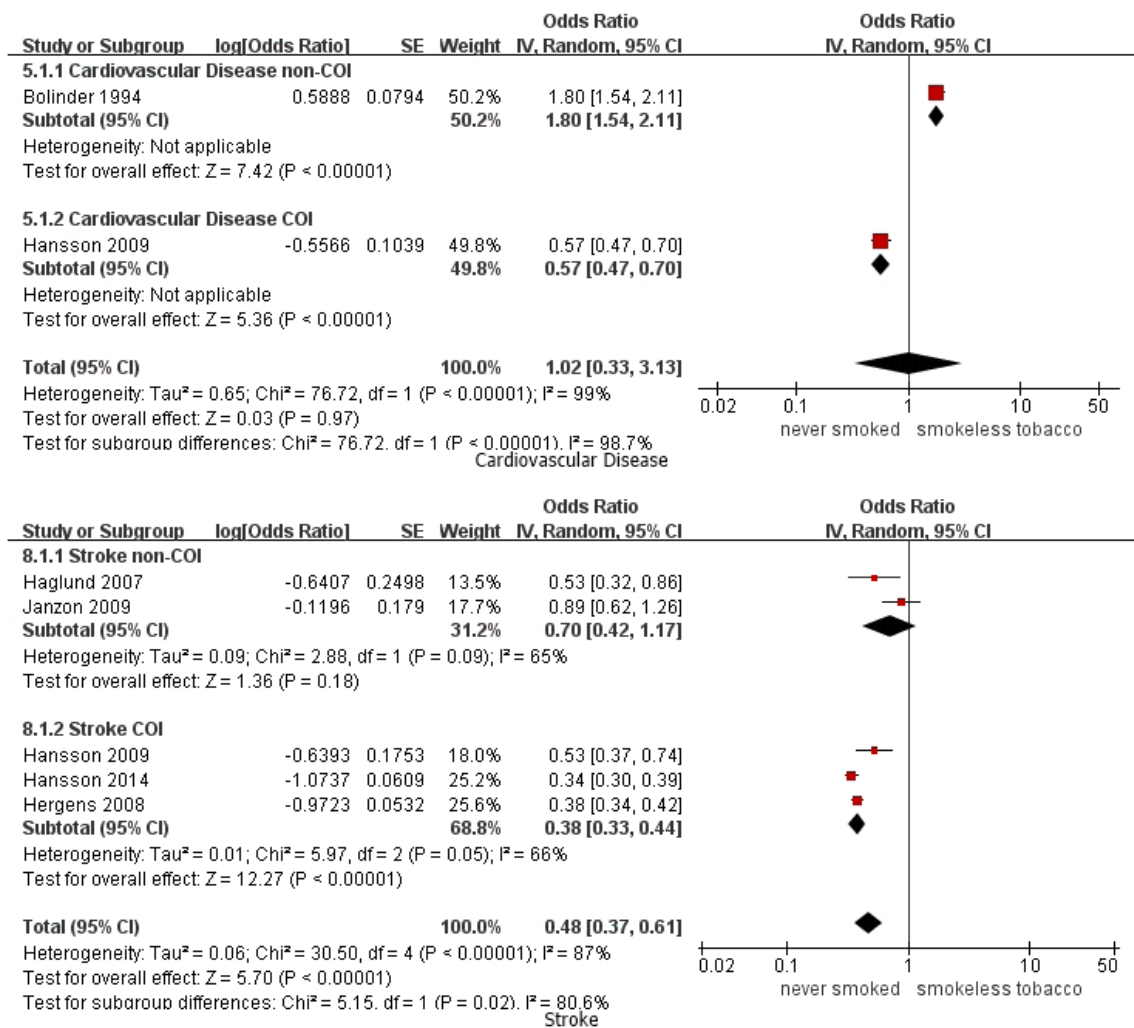


Figure 2. Results of the meta-analysis.

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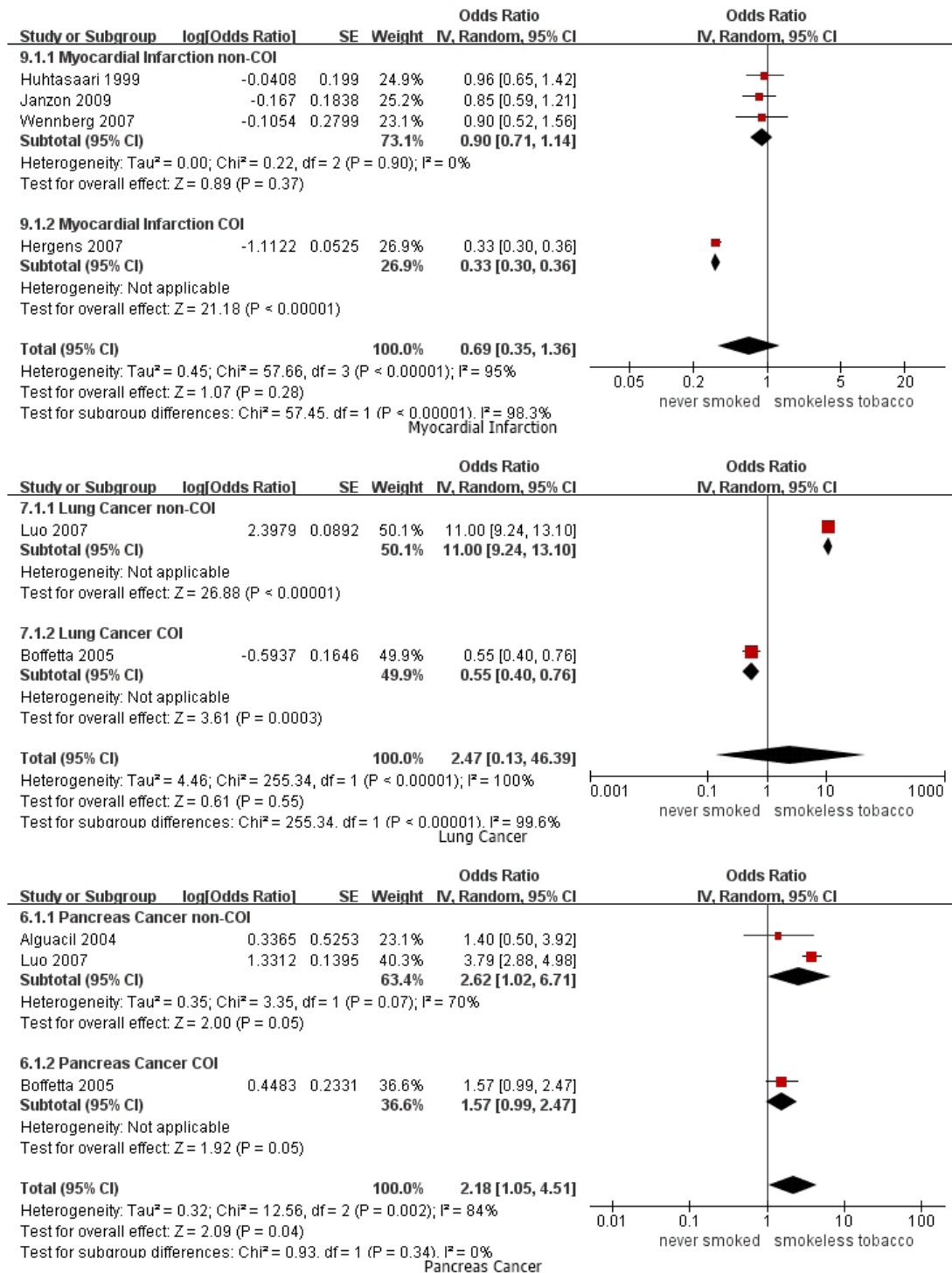


Figure 2. Continued

## DISCUSSION

This study was conducted to analyze the negative effects of smokeless tobacco and identify the basis for the regulation of smokeless tobacco considering interests shared with tobacco companies. According to the findings of the meta-analyses, the incidence rate of pancreas cancer incidence among smokeless tobacco users was relatively high. However, according to the studies with no interest, smokeless tobacco smokers were more likely to develop cardiovascular disease, lung cancer, and pancreatic cancer. In particular, there was a statistically significant difference in results of cardiovascular disease, myocardial infarction, and lung cancer depending on the presence or absence of interest.

There were different association by shared interests. In studies with no interest, the incidence rate of cardiovascular disease was higher among smokeless tobacco users, while studies with interests reported that the use of smokeless tobacco decreased the incidence rate. This finding should be interpreted with caution because of the heterogeneity among the studies. According to existing research in animals and humans, nicotine in smokeless tobacco products causes a short-term impact on blood pressure and cardiac impulse. However, the correlation between the long-term use of smokeless tobacco products and cardiovascular disease has yet to be confirmed [48]. In addition, previous study explained there was limitation to explain association between the use of smokeless tobacco and fatal cardiovascular disease due to the number of study objects with cardiovascular disease [32]. Hansson et al. [36], with shared interests, reported that there was limitation to explain association between the use of smokeless tobacco and fatal cardiovascular disease due to the lack of a sufficient number of study objects with cardiovascular disease. They also pointed out that some

objects could be excluded from the analysis because cases of cardiovascular disease diagnosed in the early stage of the research period might be omitted due to the incompleteness of discharge records at the hospital. In addition, the risks were underestimated since biased results were classified as missing values. In studies without interests, the stroke incidence rate was not correlated, while studies with interests involved reported that the use of smokeless tobacco decreased the incidence rate of stroke. Boffetta and Straif [11] distinguished stroke that resulted in mortality from those that did not, reporting increased risks of fatal stroke among smokeless tobacco users. In studies without interests, the myocardial infarction incidence rate was irrelevant, while studies with interests involved reported that the use of smokeless tobacco decreased the incidence rate of myocardial infarction. Hergens et al. [38] suggested the significance of interests shared with tobacco companies, stating that substances with protective effects on myocardial infarction such as fatty acid, flavonoids, and nitrate were included, and that there was a correlation between smokeless tobacco use and non-fatal myocardial infarction. In studies with no interests, the lung cancer incidence rate was higher among smokeless tobacco users than that in studies with involved interests, the use of smokeless tobacco reportedly decreased the lung cancer incidence rate. However, reports implying a decreased lung cancer incidence rate also caution the need for caution in the interpretation since only a small number of lung cancer cases were analyzed and that the carcinogenic effects of smokeless tobacco on the lungs should not be neglected. Hence, the relationship between smokeless tobacco and lung cancer has yet to be clarified and additional analysis is required in reference to more baseline data.

Meanwhile, the incidence rate of pancreas cancer in smokeless tobacco users was higher than that of

non-smokers. This result was the same whether or not there were shared interests. N-nitrosamines, N-nitroso compounds generated by smokeless tobacco, is a major element of smokeless tobacco that induces pancreas cancer and is frequently found in the pancreas of smokeless tobacco users [49]. The association between pancreas cancer and smokeless tobacco was the same regardless of shared interests with tobacco companies, indicating that smokeless tobacco is a risk factor for pancreas cancer.

This study has a limitation in that the search is limited to studies published before 2015. However, this study was able to shed light on the indirect interests shared between tobacco companies and researchers or organizations involved in studies mentioned in the TTIDs and internal literature of tobacco companies. Future studies that aim to investigate anti-smoking policies or cigarettes should consider identifying any covert activities of tobacco companies by referencing their internal literature to distinguish research findings that may have been influenced by tobacco companies. It is essential to conduct a comprehensive analysis of these interests to promote transparency in research and minimize the risk of bias. The results of the present study have the following implications. Regarding the internal documents of tobacco companies, this study clarifies the differences in research findings depending on whether or not there were interests shared with tobacco companies. This result can be utilized as a basis for regulatory policies regarding the use of smokeless tobacco products, whose use is increasing gradually.

This study provides evidence that research conducted directly by tobacco companies assert that as smokeless tobacco increases, the risks of various diseases are reduced, as the main causes are products used in the past or other factors such as drinking and smoking. They publicize that their smokeless tobacco products are safe. Such research also asserts that smokeless tobacco is safe since a far smaller quantity of

tobacco is used compared to ordinary cigarette products. However, it is hard to accept this view as studies have reported higher risks of diseases such as myocardial infarction and stroke in smokeless products compared to those in smokers using ordinary cigarettes only. Attention must be paid to this type of research since the interpretation and implication is that replacing cigarettes with smokeless tobacco is advantageous. Tobacco companies not only conduct their own research but also fund various research centers and colleges with the aim to make evidence advantageous to themselves [50,51]. Since such evidence is used by smokeless tobacco manufacturers to promote their products as if such products are safe; thus, attention must be paid when such findings are referred to and interpreted. The types of smokeless tobacco vary according to country and region. As there are no consistent findings on the risks of diseases according to smokeless tobacco types, it is uncertain whether such results can be generalized. Smokeless tobacco companies claim that, as they have developed their smokeless tobacco manufacturing techniques for many decades, the levels of carcinogenic substances generated have decreased drastically. Tobacco manufacturers in the US and Sweden have continually reported their research findings. Hence, future research findings may differ from those available now and some time may be required to verify the effects of new types of smokeless tobacco on health. While smokeless tobacco may have no powerful carcinogenic effects, it remains controversial whether the use of smokeless tobacco products should be recommended as an alternative to smoking [52]. As asserted by tobacco companies, the results of studies with shared interests imply that the incidence rates of stroke, myocardial infarction, etc. among smokeless tobacco users are lower than those of non-smokers, but the mechanism for these findings is not clear. In addition, studies that share no interests with tobacco companies

report opposite findings. Therefore, it is not recommended to use smokeless tobacco products as a measure to reduce the incidence rates of cigarette-related diseases as well as the risk of death. Since the effects of smokeless tobacco on health are classified based on a pre-viously invisible aspect of tobacco companies; that is, research funding, the findings of the present study can be utilized to respond to various arguments by tobacco companies. In addition, this study presents one way to utilize the internal documents of tobacco companies. Tobacco-related studies that appear to have no direct interests shared directly with tobacco companies are currently regarded and cited as such.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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