

Review with meta-analysis relating North American, European or Japanese
smokeless tobacco or snus use to major smoking-related diseases

Supplementary material

This document gives full details of the search procedures used and the results
obtained.

Study inclusion and exclusion criteria

Attention was restricted to publications in English in the years 1990 to 2020 which present results relating current use of smokeless tobacco or moist snuff (“snus”) in non-smokers to the risk of lung cancer, COPD, IHD/AMI or stroke, based on epidemiological case-control studies conducted in North America, Europe or Japan, and involving at least 100 cases of the disease of interest. The studies selected should not be restricted to individuals with specific other diseases.

Literature searches

The first step was to carry out separate literature searches on Medline for lung cancer, COPD and cardiovascular disease, the aim being to identify from these searches not only publications that described studies satisfying the inclusion criteria, but also meta-analyses and reviews that may themselves cite other relevant publications. The search strings used were as follows:

Lung cancer

((((tobacco, smokeless[MeSH Terms] AND (english[Filter])) OR (smokeless tobacco AND (english[Filter]))) OR (snus AND (english[Filter])) AND (english[Filter])) AND ((lung cancer AND (english[Filter])) OR (lung neoplasm[MeSH Major Topic] AND (english[Filter])) AND (english[Filter]))

COPD

((((tobacco, smokeless[MeSH Terms] AND (english[Filter])) OR (smokeless tobacco AND (english[Filter]))) OR (snus AND (english[Filter])) AND (english[Filter])) AND (((((pulmonary disease, chronic obstructive[MeSH Terms] AND (english[Filter])) OR (lung diseases, obstructive[MeSH Terms] AND (english[Filter]))) OR (COPD AND (english[Filter]))) OR (bronchitis AND (english[Filter]))) OR (emphysema AND (english[Filter])) AND (english[Filter]))

Cardiovascular disease

((((tobacco, smokeless[MeSH Terms] AND (english[Filter])) OR (smokeless tobacco AND (english[Filter]))) OR (snus AND (english[Filter])) AND (english[Filter])) AND (((cardiovascular disease AND (english[Filter])) OR (heart disease AND (english[Filter]))) OR (stroke AND (english[Filter])) AND (english[Filter]))

Then, for each of the three searches, a print-out of the Medline output for title and abstract was examined by KJC to identify publications of possible relevance, the selection then being checked by PNL, with any disagreements resolved in discussion. For each selected publication, the Medline output notes whether there are other linked publications. Linked publications may be those which comment on the selected publication, or those which the selected publication is itself a comment on. These linked publications may or may not have been selected elsewhere in the search.

For the next stage, examination of full text output, a printout was obtained not only of each selected publication, but also of any other linked publication not selected elsewhere. The full text output (including relevant supplementary files) was then examined by PNL, with the publication classified as either an accepted publication containing relevant data, a reject (giving a reason), a relevant review or a relevant meta-analysis. The suggested rejects were then checked by KJC, with any disagreements resolved.

The reference list of each accepted publication, review and meta-analysis was then examined, after first eliminating multiple copies of publications detected in more than one search, with the aim of detecting accepted publications containing relevant data that had not previously been considered.

Examination of the accepted publications describing results from relevant studies

The combined list of accepted publications was then examined to eliminate those which provided data superseded by a later publication on the same study, those which were only comments on other accepted publications and provided no new data, those which did not separate out results for IHD/AMI and for stroke (only considering overall cardiovascular disease), those that only gave results by specific type of the four diseases of interest, and those which did not give results for non-smokers. The final set of accepted papers was then separated into those providing data on snus and those providing data on smokeless tobacco.

Results of literature searches

Tables 1, 2 and 3 summarize the results of the literature searches for, respectively, lung cancer, COPD and cardiovascular disease. For lung cancer, 131 publications

were identified in the Medline searches, with 10 accepted as providing apparently relevant study data, and 22 describing related meta-analyses or reviews. For COPD, 46 publications identified in the searches led to only 1 new acceptance and no new reviews. For cardiovascular disease, 308 identified publications, led to 24 new acceptances and 40 new meta-analyses or reviews.

Examination of reference lists in accepted publications, reviews and meta-analyses led to 10 further publications being considered possibly relevant, but only one of these^[1] was accepted as a paper describing relevant results (for COPD).

The total of 36 accepted papers for the diseases combined, was then reduced to 26, as four^[2-5] did not give results for non-smokers, one^[6] did not separate results for IHD and stroke, and five^[7-11] were only comments on other accepted papers and provided no new data. Of the 26 papers, 18^[1, 12-28] gave results for snus, and eight^[29-36] gave results for US smokeless.

TABLE 1 Search results for lung cancer

Description	N	References
Papers identified from Medline search	131	
First examination of titles and abstracts		
Rejected	97	
Accepted	34	
Second examination		
Rejected	2	
Total accepted	32	
Add linked comments	11	
Full text papers examined	43	
Papers rejected for various reasons	11	
Not to do with ST	2	[37, 38]
Not to do with disease	1	[39]
Only considers oral cancer	1	[40]
Only considers pancreatic cancer	2	[41, 42]
Only considers NNK and cancer	1	[43]
Only considers switchers to ST	1	[44]
Comparison of national rates	1	[45]
Results only relate to genotypes	1	[46]
Comment with no results of citations	1	[47]
Papers accepted as providing apparently relevant data	10	[7, 8, 10-13, 29-32]
Meta-analysis	3	[48-50]

Description	N	References
Reviews	19	[51-69]

TABLE 2 Search results for COPD

Description	N	References
Papers identified from Medline search	46	
First examination of titles and abstracts		
Rejected	38	
Accepted	8	
Second examination		
Rejected	2	
Total accepted	6	
Add linked comments	0	
Full text papers examined	6	
Papers considered in Table 1	4	[44, 46, 53, 66]
Papers rejected for various reasons		
Cross sectional study	1	[70]
Papers accepted as providing apparently relevant data	1	[2]

TABLE 3 Search results for cardiovascular disease

Description	N	References
Papers identified from Medline search	308	
First examination of titles and abstracts		
Rejected	228	
Accepted	80	
Second examination		
Rejected	0	
Total accepted	80	
Add linked comments	17	
Full text papers examined	97	
Papers considered in Tables 1 or 2	17	[7, 29, 30, 32, 43, 44, 50-53, 55, 57-59, 64, 65, 69]
Papers rejected for various reasons	16	
Study on snus users with MI	3	[71-73]
Only considered switchers to ST	1	[74]
Irrelevant correction	4	[75-78]
Relates to Australia	1	[79]
No relevant results	3	[40, 80, 81]
Does not consider risks	1	[82]
Only considers nasal snuff	1	[83]
Publication in 2021	1	[84]
Not in English	1	[85]
Papers accepted as providing apparently relevant data	24	[3-6, 9, 14-24, 26-28, 33-36, 86]

Description	N	References
Meta-analyses	5	[87-91]
Reviews	35	[86, 92-125]

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