Author's response to reviews

Title: Systematic review of the relation between smokeless tobacco and non-neoplastic oral diseases in Europe and the United States

Authors:

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Version: 2 Date: 18 February 2008

Author's response to reviews:

Dear Editor,

Following the helpful comments of the reviewers we have made extensive changes to the text and tables of the paper. What we have done is described below, where we give for each reviewer, their comments and our replies to them. We have also altered the title to make clear that it is a systematic review.

We hope that the revised paper is now acceptable.

Yours sincerely

Peter Lee - on behalf of my co-authors

1. REPLY TO AXELL

Reviewer's report
Title: Review of the relation between European and American smokeless tobacco and non-neoplastic oral disease
Version: 1 Date: 28 November 2007
Reviewer: Tony Axéll

Reviewer's report:
General

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Discretionary Revisions (which the author can choose to ignore)

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Kallischnigg G, Weitkunat, Lee PN

Review of the relation between European and American smokeless tobacco and non-neoplastic oral disease

Referee report

This study is an extensive and knowledgeable review concerning smokeless tobacco products in Europe, especially Scandinavia or Sweden, and USA. In order to be meaningful such a review has to be adequately structured and considering up-to-date consensus points of view. I find the present review lacking in some of these aspects.

General comments

We are extremely grateful to the reviewer for his comments. Following his comments and those of the other two reviewers, we have made extensive changes to the paper. The main ones are as follows:

1. Inclusion of seven later references [1-7] to make the review more up-to-date, and of five older references [8-12] cited in the very recent IARC Monograph 89 [13].

2. Splitting the original tables into separate tables for Scandinavia and the USA.

3. Adding two extra tables to clarify the definitions of the oral mucosal lesions considered in the different studies. We use the term snuff-induced lesions (SIL) where appropriate for those seen in virtually all the Scandinavian studies, but make clear the variation of endpoints used in the various US studies. We avoid the use of oral leukoplakia (or related lesions), which we used in the paper submitted originally, only referring to oral leukoplakia where that is how the original author described the lesion.

4. Separating the results more clearly into those relating to snuff, chewing tobacco (CT) and unspecified smokeless tobacco (ST), as well as separating results in relation to Scandinavia and the USA.

Especially three aspects have to be reconsidered. The authors throughout their article use the label leukoplakia in their review, even if they also consistently add or related lesions. This is unfortunate. Leukoplakia is a precancerous lesion and a precancerous trait has never been demonstrated concerning snuff induced lesions. (see e.g. Roosaar et al. 2006) On p. 19 the authors also state ST use
clearly increases the risk of oral leukoplakia, which thus is misleading. At several consensus meetings snuff induced lesions have been considered different from leukoplakias since they comprise a unique entity, since they are far from always white and since their precancerous potential is not clarified (Axéll et al 1984, Axéll et al. 1996, Zain et al. 1996). In the report by Zain et al. is stated

A localized lesion of the oral mucosa corresponding to the regular site of placement of a quid and characterized by one or more of the following characteristics: 1) change of normal color, 2) wrinkled appearance, 3) thickening of the mucosa, 4) scrapable or non-scrapable epithelial surface, and 5) presence of ulceration. Examples of such quid-induced lesions are: i. Tobacco and lime user’s lesion; ii. Snuff-induced lesions; and iii. Areca-quid lesion.

Thus, lesions caused by snuff should preferably be renamed for e.g. Snuff-induced lesions (SIL) suggested by Roosaar et al 2006.

See general comment 3.

Studies in Europe and US should be separated in the analyses primarily since the products used may differ considerably. Further, studies carried out on snuff (SIL) should be separately analysed from those carried out on chewing tobacco (CTIL?). Snuff and chewing tobacco are quite different products. For instance, using chewing tobacco in Sweden gives rise to only subtle mucosal changes (Axéll et al. 1992). Further, Swedish chewing tobacco may cause erosions on dental surfaces (Birkhed and Malmberg 1982).

See general comment 4.

The most extensive epidemiologic study on Swedish snuff (snus) users was published in 1976 (Axéll 1976). 1466 SILs were encountered, a prevalence of 8% in 20,333 individuals aged 15 years and over (16% in men and 0.2% in women). A lesion was found in almost all snus users. In 551 users consuming 11 g snus a day a SIL was not registered in 32 individuals (5.5%). On the other hand in 187 individuals or 1% of 18,701 individuals a SIL was registered in spite of the fact that they denied using snus. A sample of these 1466 SILs was followed for about 30 years. The result was published by Roosaar et al. 2006.

Roosaar [1] is now considered in our paper. See general comment 1, and also
In summary,
This review is an important, extensive and knowledgable one. It should preferably be restructured with emphasis on the following.
1. separate accounts for chewing and snuff (snus) products
2. separate accounts for USA and European studies
3. change of the label leukoplakia for other ones e.g. snuff induced lesion (SIL) and chewing tobacco induced lesion (CTIL)

We hope that the much revised paper adequately meets these points.

References

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'

References


2. REPLY TO RODU

Reviewer's report
Title: Review of the relation between European and American smokeless tobacco and non-neoplastic oral disease
Version: 1 Date: 3 December 2007
Reviewer: Brad Rodu

Reviewer's report:
1. Is the question posed by the authors new and well defined? Yes
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work? Yes
3. Are the data sound and well controlled? Yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes
6. Do the title and abstract accurately convey what has been found? Yes
7. Is the writing acceptable? Yes

This is an excellent review of the research literature regarding non-neoplastic oral conditions associated with smokeless tobacco use. It is important to understand to what extent smokeless tobacco use contributes to leukoplakia, periodontal disease and caries. As the authors reveal, the first condition is commonly associated with smokeless use. Periodontal disease and caries are the main focus of most dental practitioners, so this review should be of special interest to many dentists. It is welcome addition to the existing literature on smokeless tobacco use and health consequences.
General comments
We are extremely grateful to the reviewer for his comments. Following his comments and those of the other two reviewers, we have made extensive changes to the paper. The main ones are as follows:

1. Inclusion of seven later references [1-7] to make the review more up-to-date, and of five older references [8-12] cited in the very recent IARC Monograph 89 [13].
2. Splitting the original tables into separate tables for Scandinavia and the USA.
3. Adding two extra tables to clarify the definitions of the oral mucosal lesions considered in the different studies. We use the term snuff-induced lesions (SIL) where appropriate for those seen in virtually all the Scandinavian studies, but make clear the variation of endpoints used in the various US studies. We avoid the use of oral leukoplakia (or related lesions), which we used in the paper submitted originally, only referring to oral leukoplakia where that is how the original author described the lesion.
4. Separating the results more clearly into those relating to snuff, chewing tobacco (CT) and unspecified smokeless tobacco (ST), as well as separating results in relation to Scandinavia and the USA.

Compulsory Revisions:
Page 3, lines 12-15. I found this sentence to be out of place, especially in the abstract. This study only assessed smokeless use with respect to these diseases, not smoking. In fact, the discussion would benefit considerably by comparing the results found here with the incidence or risk among smokers for leukoplakia (the incidence may be lower but the risk for dysplasia/carcinoma greater), periodontal disease and caries.

We have removed the last sentence of the abstract. While the discussion might benefit from a comparison with the results for smokers, we have never considered this evidence in detail and would prefer to let the paper stand as it is.

Page 9, line 8-10. I am an oral pathologist, and this sentence makes no sense. Leukoplakia is predominantly a clinical term referring to a white plaque, and it is mucosal by definition.

We have removed the text giving our definition of lesions. Rather we have included tables to make clear the definitions used in the different papers, and
have commented on the extent to which we feel they suggest similar or different lesions. See also general comment 3.

Page 9-10, Various classifications of leukoplakia. These are awkward as they appear in the text. Table 2 (Endpoint) makes it pretty clear that all degrees of leukoplakia were the endpoints in all studies. I think the classifications could be listed in a table, in which similarities and differences could be appreciated.

See general comment 3 and Tables 3 and 5.

Page 11, line 11 and page 12, line 1. Both of these sentences refer to reference 8 (Fisher et al, 2005), but this study is missing from Table 2.

In fact Fisher [14] was not missing but was at the end of the old Table 2. It is now considered in Table 6 (and Table 5).

Page 13, line 11. This sentence refers to reference 1 (Larsson et al, 1991), but this study is missing from Table 2.

The original paper described the results of the experimental studies (including Larsson [15]) only in the text. The results from all the relevant studies are now described in Tables 4 and 6.

Page 15, Periodontal disease. The authors appear to have missed two important studies, Robertson et al (J Periodontol 61: 738, 1991) and Fisher et al (J Dent Res 84:705, 2005). I realize that the authors ended their search in December 2005, but it is a shame that this comprehensive review does not include the study by Bergström et al (J Clin Periodontol 33: 549, 2006).

See general comment 1.

Page 16, line 11. ¿Dental caries, demineralization of the tooth surface.¿ This is not technically correct and is inadequate. I suggest revising to ¿Dental caries is a microbial disease causing demineralization and destruction of teeth, and it can occur on the crown and root surfaces.¿

We have removed the text giving our definition of the lesions and have presented the results in terms of the terminology used in the source papers.

Page 21, only paragraph. Unless they have evidence to the contrary, the authors should more strongly state that adequate control of confounding is rarely achieved in studies addressing smokeless tobacco use and periodontal disease,
despite the fact that it has been standard practice for over two decades to control for education and SES in periodontal disease studies (Ismail et al, JADA 106: 617, 1983). As we pointed out in our critique of the Fisher et al study cited above (J Dent Res 84:705, 2005), education and socio-economic status (SES) are two of the strongest correlates of periodontal disease that are also strongly and inversely correlated with SLT use in the U.S.

We totally agree that adequate control of confounding is rarely achieved. The tables make it clear which factors have been adjusted for and confounding is considered towards the end of paragraph 1 on page 21, and again in the second paragraph on page 23.

Another perspective worth mentioning is that periodontal disease is highly correlated with age. It is extremely uncommon in children and young adults, so if smokeless use was a strong risk factor the Ernster, Sinusas, Robertson and Rolandsson studies might have detected it. On the other hand, perio disease is much more common at older ages, so it is important to control account for differences in age structure between control and exposed populations.

Age is considered in the texts referred to in the reply to the previous comment.

Minor edits:
Page 5, line 4. ¿With gingival recessions¿. Change to ¿recession¿.
Amended ¿ see line 1 on p 5.

Page 8, line 3. ¿On oral leukoplakia of quitting smoking.¿ Don¿t you mean ¿quitting snuff use¿?
It should actually be ¿quitting ST use¿. This is now on line 7 of paragraph 1 on page 8.

Page 13, line 11. ¿Leukoplakia areas had completed resolved clinically.¿ Should be ¿completely¿.
This text no longer exists anyway, as the results of the experimental studies appear in the Tables (4 and 6).

Page 21, line 6. ¿Factors associated with poorer dental health¿. Don¿t you mean ¿poor¿?
Corrected ¿ see near end of page 23.

What next?: Accept after minor essential revisions
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
My research is supported by unrestricted grants from smokeless tobacco manufacturers to the University of Louisville (US Smokeless Tobacco Company and Swedish Match AB). The terms of the grants assure that the grantors are unaware of, and have no scientific input or other influence over the research or other related activities. I have no financial or other personal relationship with regard to the grantors.

References


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[http://monographs.iarc.fr/]


3. REPLY TO TOMAR
Reviewer’s report
Title: Review of the relation between European and American smokeless tobacco and non-neoplastic oral disease
Version: 1 Date: 28 November 2007
Reviewer: Scott L. Tomar
Reviewer’s report:
General comments
This paper is a relatively thorough review of the published literature on the association between European and North American non-neoplastic oral diseases. There is some confusion by the authors on disease terminology. Some conclusions extend beyond the focus of the review. Two of the authors are employees of Philip Morris International, a tobacco company that now markets
moist snuff in addition to cigarettes, which may explain the company¿s interest in commissioning these recent meta-analyses.

General comments

We are extremely grateful to the reviewer for his comments. Following his comments and those of the other two reviewers, we have made extensive changes to the paper. The main ones are as follows:

1. Inclusion of seven later references [1-7] to make the review more up-to-date, and of five older references [8-12] cited in the very recent IARC Monograph 89 [13].
2. Splitting the original tables into separate tables for Scandinavia and the USA.
3. Adding two extra tables to clarify the definitions of the oral mucosal lesions considered in the different studies. We use the term snuff-induced lesions (SIL) where appropriate for those seen in virtually all the Scandinavian studies, but make clear the variation of endpoints used in the various US studies. We avoid the use of oral leukoplakia (or related lesions)¿, which we used in the paper submitted originally, only referring to oral leukoplakia¿ where that is how the original author described the lesion.
4. Separating the results more clearly into those relating to snuff, chewing tobacco (CT) and unspecified smokeless tobacco (ST), as well as separating results in relation to Scandinavia and the USA.

MINOR ESSENTIAL REVISIONS

1. It would be more accurate in the title to describe the smokeless tobacco included in this review as European and North American. There are forms of smokeless tobacco used in parts of South America that are not considered here, and moist snuff is available in Canada as well as USA.

As our literature search only found studies relevant to the USA and Europe (mainly in Sweden, but a few from Finland, Denmark and England), we have altered the title to make this more precise. The results section starts by making it clear that we found no other North American or European studies.

2. p. 4. The statement that moist snuff used in Scandinavia and the USA is composed solely of tobacco (in contrast to other parts of the world where tobacco is mixed with other substances) is not accurate. Nearly 600 additives (or as the tobacco companies call them, ingredients) are added to smokeless tobacco products in the US and Canada, based on industry reports to the U.S. Department of Health and Human Services. These are highly engineered products that contain much more than just tobacco, although the manufacturers
do not report the specific additives or their quantity in any individual product. Therefore, separating purely tobacco effects from the oral health effects of the many other chemicals in these products is just as problematic as in other countries.

We did not actually say originally that moist snuff used in Scandinavia and the USA is composed solely of tobacco, though the text could be read to imply this. While we accept of course that there are additives/ingredients in ST, we feel that the situation in USA/Scandinavia differs markedly from that in countries where users take ST jointly with major contributions from other substances. We have, however, rewritten the sentence in the background paragraph 1 (see page 4) as follows:

¿As in some other reviews of ST effects (e.g. ¿) results from areas (such as India, South Asia, Africa and Saudi Arabia) where the tobacco chewed is often mixed with other substances, such as betel quid and areca nut are not considered.¿

This also makes it clear that what we are doing in separating off USA/Scandinavia is not unusual. Referees for our other papers on oral cancer [14] and circulatory disease [15] have accepted our approach before.

3. p. 9. That definition of oral leukoplakia is incomplete. The actual WHO definition of leukoplakia adopted in 1978 was ¿a white patch or plaque that cannot be characterized clinically or pathologically as any other disease.¿ It is essentially a diagnosis made after exclusion of other possible diagnoses. There have been several subsequent congresses that reconsidered the definition, and most oral pathology experts consider the lesions associated with smokeless tobacco use to be distinct from leukoplakia because its etiology is often fairly clear and it is clinically distinct from more typical leukoplakias.

We have removed the text giving our definition of lesions. Rather we have included tables to make clear the definitions used in the different papers, and have commented on the extent to which we feel they suggest similar or different lesions. See also general comment 3.

4. p. 15. The definition of ¿periodontal disease¿ is incorrect. Periodontal diseases and gingival diseases are considered to be distinct entities. See, for example, the taxonomy developed by the American Academy of Periodontology [1999 International Workshop for Classification of Periodontal Diseases and Conditions-Annals of Periodontology Vol. 4]. It is briefly described in: Armitage
GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4:1-6. Also, periodontal attachment loss is not a separate disease entity, but a clinical feature of periodontitis. The term is used most appropriately in longitudinal studies in which changes over time in the clinical attachment level at a specific periodontal site are calculated.

Again, we have removed the text giving our definition of the lesions and have presented the results in terms of the terminology used in the source papers.

5. p. 15. The results may appear to be quite conflicting to the authors because they have lumped together a number of different disease endpoints. Periodontal destruction (i.e. periodontitis) or gingival recession can occur in the absence of gingivitis. Indeed, there is considerable evidence that cigarette smoking may suppress gingival inflammation (as measured by gingival bleeding on probing), but smoking is probably the major preventable risk factor for chronic periodontitis. Old periodontal indices such as Russell’s Periodontal Index were based on the concept of there being one type of periodontal disease, but that concept is very dated and largely abandoned. Therefore, studies whose outcome measure was non-descript periodontal disease may not be interpretable in light of modern disease concepts, depending on how the disease was operationally defined.

We have reorganized the relevant tables (now Tables 7 and 8) so that results for the various endpoints considered are grouped together, and have modified the text in line with this.

6. p. 16. The definition of dental caries is incomplete. Dental caries is bacterially-mediated demineralization of hard tooth structure. There are conditions that involve non-bacterially-mediated demineralization of tooth structure that are not dental caries, such as dental erosion. Caries is typically measured by DMFT/DMFS, not assessed by that index. DMF for an individual is simply a count. There are many limitations to the DMF index, particularly in adults, though it remains the most widely used measurement for caries.

Again, we have removed the text giving our definition of the lesions and have presented the results in terms of the terminology used in the source papers.

7. p. 20. The clinical reversal of oral mucosal keratosis (erroneously called leukoplakia here, which typically does not resolve) does not necessarily mean
there is little clinical significance. Squamous cell carcinoma arises from genetic alterations; resolution of the clinical lesion does not necessarily mean the absence of cellular damage.

We had only said originally that reversal of the lesion on quitting suggests that presence of the lesion may not necessarily be of clinical significance. We appreciated that it need not imply the lack of long-term problems. The relevant text (starting near the bottom of page 22) has in any case been altered here, partly to include the findings of Roosaar [1].

8. p. 20. The authors cite their recently published meta-analysis as evidence that western forms of smokeless tobacco carry little or no increased risk for oral cancer. In reality, the most relevant analysis in that review was the effect estimates among never smokers (Table 6) because it is highly questionable whether an effect as strong and as collinear with ST use as smoking can be adequately controlled in multivariate modeling. The analysis in that table curiously omitted Winn et al. (1981), although that study provided data for snuff use and oral cancer among non-smokers. In any event, there were very few exposed cases, the confidence interval for the random effect estimates were relatively wide, and about a 2-fold elevation in risk. Little evidence of risk is not equivalent to evidence of little risk. The recent IARC review reached a different conclusion concerning the carcinogenicity of these products (Cogliano et al. 2004).

While we appreciate the difficulties in adequately adjusting for the effects of smoking (and also alcohol and other variables), we do not share the reviewer’s view that Table 6 of our earlier paper is the most relevant analysis, as it is based on so few cases of oral cancer. Table 6 was restricted to analyses for subjects who had never smoked; the analysis of Winn et al [16] that the reviewer had in mind was, according to our reading of the paper, for nonsmokers, i.e. only current and not former smokers had been removed. The reviewer’s comment that little evidence of risk is not equivalent to evidence of little risk may be correct, but we did not say that and, in any case, we feel that there is quite a lot of evidence that any risk is at most modest. Our published review is far more comprehensive than the single page statement of Cogliano et al [17] in the Lancet, citing an unpublished IARC Monograph (though we note that this Monograph[13] has very recently appeared).

9. p. 20. As stated earlier, there is no such thing as general periodontal disease.
We do not now use the term "general periodontal disease" and, where talking of the diseases considered in Tables 7 and 8 refer to them in various places as "periodontal and gingival diseases."

10. p. 21. Actually, the data are fairly consistent for gingival recession in adult populations. The studies that found no association were all conducted among young people.

We have expanded the discussion on gingival recession (see pages 15-17 and page 24) and now consider it probably related to snuff use. There are now nine studies which provide relevant evidence on the relationship of snuff (or undefined ST use) to gingival recession, three conducted in Sweden, and six in the USA. The studies which found no association were not all conducted among young people (cf. Wickholm 2004 [2]), and some studies in young people did find a relationship (cf. Offenbacher 1985 [18] in 10-17 year olds, which found a 60% prevalence and a huge relationship with ST use.)

11. p. 22. In light of the authors’ discussion of ST carrying lower risk for disease than smoking, can we expect Philip Morris to abandon the cigarette business? There are ethical issues to be considered when a manufacturer conducts a study that concludes that its major product is carcinogenic and toxic and another product it now manufactures carries much lower risks. In any other industry, such observations would lead the manufacturer or regulatory authorities to take action.

That cigarette smoke is causally related to an increased risk for lung cancer, COPD, and a number of cardiovascular diseases is incontestable and has been known for many years. The problem is that if Philip Morris were to stop manufacturing cigarettes, either existing or new companies would simply fill the resulting void. This can be well illustrated by the success of a number of small manufacturers who were able to make a very respectable profit in the US in the last 15 years, since they were exempt from the Master Settlement Agreement, did not need to make the required payments, and could sell their products at a significantly reduced price. Therefore, for Philip Morris to stop would accomplish nothing. The only alternative is to continue to develop and offer products that reduce the risk of smoking and that can replace the current cigarette. Although smokeless tobacco is one such product, there are many smokers who will not switch from smoking to smokeless products. We are investing very heavily in a program that will not only develop risk-reduced products but will also utilize modern molecular biological and modelling techniques to demonstrate that the risk of one or more smoking-related diseases is truly reduced. This is a challenging objective, but the fact that we have close to 500 R&D scientists and support people working on the project is proof positive that we take it very seriously.
Discretionary Revisions
1. p. 4. Chewing tobacco really isn’t ‘chewed’; it is typically mixed with saliva and
then ‘parked’ in the buccal pouch (or as the authors call it, the gingival buccal
area). Moist snuff in North America is frequently placed in the lower labial fold.

The text on p 4 merely says that, in the US, moist snuff or CT is ‘held in the
gingival buccal area’.

What next?: Accept after minor essential revisions
Level of interest: An article whose findings are important to those with closely
related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a
statistician.
Declaration of competing interests:
I have served and currently serve as an expert witness for plaintiffs in law suits
brought against smokeless tobacco manufacturers.

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