A biased and deficient study of snus use and esophageal/gastric cancer

Karyn K. Heavner, MSPH, PhD
Carl V. Phillips, MPP, PhD
Brad Rodu, DDS

Corresponding author:
Carl V. Phillips
8215 112th Street, Suite 215
Edmonton, Alberta T6G 2L9
Canada
E-mail: carl.v.phillips@ualberta.ca
Phone: 780.492.9068
Fax : 780.492.4911

Karyn K. Heavner
8215 112th Street, Suite 215
Edmonton, Alberta T6G 2L9
Canada
E-mail: heavner@ualberta.ca
Phone: 780.492.1389
Fax : 780.492.4911

Brad Rodu
4th Floor
James Graham Brown Cancer Center
University of Louisville
529 South Jackson Street
Louisville, KY 40202
E-mail: brad.rodu@louisville.edu
Phone: 502.561.7273
Fax: 502.852.4311

The study by Zendehdel et al.[1] of snus use and esophageal/gastric cancer is one of many analyses involving the large prospective cohort of Swedish construction workers. A comparison of the methodologic approach in this report to those in earlier reports that were based on the same cohort and dataset (with substantial overlapping authorship) reveals several noteworthy inconsistencies, including: (1) conflicting eligibility criteria (which greatly influences the size and age distribution of the sample); (2) incomplete and inconsistent analysis of snus use; and (3) several other important analytic irregularities. In particular, we compare the Zendehdel et al. study to others involving tobacco use and cutaneous squamous cancer,[2] melanoma,[3] leukemia and multiple myeloma,[4] mouth, lung, and pancreas cancer,[5] prostate cancer,[6] myocardial infarction [7] and amyotrophic lateral sclerosis. [8] This letter limits the comparison to studies that included an assessment of snus; more examples of the observations presented here will appear when the investigation is expanded to other reports based on the same cohort (to be presented in a less constrained format). The observed inconsistencies are sufficient that the scientific community should consider that the reports from this cohort are biased and generally uninformative until the issues discussed below are resolved.

(1) Conflicting eligibility criteria: The Zendehdel study included 336,381 male construction workers enrolled between 1971 and 1993. However, several of these authors recently published a study that excluded over 55,000 subjects who were enrolled prior to 1976 due to "ambiguities in the coding of smoking status in the questionnaires used during 1971–75," citing an unpublished observation by Zendehdel as the justification of the exclusions.[5]

It appears that the inclusion of these previously excluded subjects was necessary for Zendehdel's positive findings, because those enrolled between 1971 and 1975 contributed disproportionately to the 70+ person-time category in the analysis. Our estimates, based on numbers reported in the paper for age at enrollment, suggest that the 1971-75 enrollees account for more than one-third of that person-time. (This is necessarily a rough estimate; the authors should have reported it, or provided enough information to calculate it, but did not.). For Tables III and IV Zendehdel et al. stratify their analysis of snus use into what *appears to be* (see below) person-time accumulated before age 70 and among 70+ year olds. They show that most of the elevated relative risks were for snus users attaining 70+ years, and, were it not for those, the relative risks would generally show null or even protective effects. Thus, this confusing re-inclusion of 1971-75 enrollees in this study is not merely suspicious; there is affirmative evidence suggesting it substantially altered the apparent results, a noteworthy fact that was not addressed by the authors.

(Note: We say "*appears to be*" in the previous paragraph because the description of methods for stratification at age 70 years is ambiguous. In addition, while Table III reports person-time figures that are consistent with our interpretation, the person count implies that only those subjects who did not attain age 70 contributed person time to the under-70 analysis, since the number of persons in both strata sums to the total number (except where the numbers do not quite add up due to what we guess is a typographical error); we assume the latter represents a series of errors in the tables. We also observe that the tables report a baseline (referent group) for the all-ages analyses, but omit it for the age-specific analyses, creating the confusing impression that the same referent applies to all analyses.)

The authors justify this age cutpoint (which is not consistent with previous analyses (Table 1)) by stating that the relative risks diverged at age 70 and indicate that older men were more likely to have been exposed to different snus products that had higher levels of tobacco specific nitrosamines than contemporary products. This assertion provides additional support for the exclusion of men enrolled before 1976, as doing so would have made the overall findings more applicable to contemporary products, which is arguably a more relevant public health focus than earlier products. At a minimum this means that the under-70 results should be emphasized (in the abstract and elsewhere) as the only ones that provide information that is relevant to current policy.

(2) Snus exposure assessment: There are inconsistencies in how exposure to snus was defined and analyzed in the studies that emphasized that exposure. An earlier report by overlapping authors stated that, "Inconsistencies in the data on snuff taking were present in 7% of the workers". [3] But the Zendehdel article contradicts that observation by asserting: "The [exposure] data quality has been reviewed previously and was deemed to be satisfactory," citing an older study which included an analysis of only cigarette, cigar and pipe smoking, and does not appear to address snus exposure at all. [9] Zendehdel et al. postulated possible biases due to the inclusion of the 1971-1975 sample in the discussion. However, they did not provide any direct comparison of tobacco use or esophageal/gastric cancer between males enrolled prior to 1976 and those enrolled after 1977, which they easily could have done.

What is most inexplicable is the failure by Zendehdel et al. to report separately the risks for former and current snus use at the time of cohort induction. Other studies with overlapping authors [5, 7] prove that this information was available to Zendehdel et al., as were other important measures besides a dichotomous measure of lifetime (ever-never) use of snus. By contrast, Zendehdel et al. presented a dose response relationship for smoking, but not for snus use. This oversimplification of the exposure of interest must be viewed in the context of other studies from this research group that assessed intensity [5] or duration of snus use, [2, 3] and thus demonstrate that the authors are aware of the value of dividing this exposure into categories.

(3) Miscellaneous irregularities and inconsistencies: The study by Zendehdel et al. also differs from previous analyses in the definitions of BMI and smoking. They divide BMI into quartiles; while this was done by Nyren et al., [9] it differs greatly from the BMI variables used in most of the other analyses (Table I). [2-5] Zendehdel et al. used multiple definitions of smoking: 1) ever smokers versus those who never used any tobacco; 2) current (overall and divided into 3 categories: <10 grams (g)/day, 10–19 g/day and >=20 g/day) or previous (overall and divided into smoke free <5 years and smoke free >=5 year) smokers; and 3) smoked cigarette only, pipe only and cigar only. Dose response was analyzed by "… creating semicontinuous variables from medians of categories; in these analyses the never-users of any tobacco were omitted" but there is no indication of why this method was used or if the results changed when these variables were analyzed as continuous variables or as non-ordinal categorical variables. In addition, the referent groups for these analyses are unclear and the tables are constructed in a way that implies that males who never used tobacco are the referent group for all analyses. Overall there is little consistency between smoking variables included in different analyses of the Swedish construction workers' cohort.

Thus, the definitions of several variables vary substantially from report to report without explanation or even acknowledgement that it is being done. It is conceivable that changes in one minor covariate were considered unimportant enough to mention, though it is difficult to imagine this is the case for the main exposure of interest. It is even conceivable that the authors genuinely believed, without regard to the results in their data, that theories about the causes of different diseases justify different exposure definitions (though little evidence of such a rationale appears in the papers). But given the substantial deviations and even contradictions among the above cited studies, it is impossible to not strongly suspect that the model choices were made based on the results they produced.

It is a perennial problem in epidemiology that different studies use incompatible measures, and thus reach conclusions that can not be directly compared or even replicated. But it is particularly troublesome when the same authors publish numerous studies addressing a single exposure in a single cohort but use inconsistent measures of exposure without any acknowledgement of this change, let alone any attempt to explain why. The most obvious explanation is that the authors were practicing "publication bias in situ", [10] analyzing the data in many different ways and reporting only the particular model that produces results they most like or believe have the greatest likelihood of being published.

Zendehdel et al. provided no indication of whether their findings are robust enough to hold true if the alternative variable definitions – in particular, those used in their previous publications -- are used. While using different variable definitions in different analyses is defensible if it is based on plausible hypotheses about different patterns of effects or if small sample size necessitates combining categories, there is no evidence that those explanations apply in the present case. If the tobacco use variables were truly **"…** categorized prior to the analyses based on what was perceived as relevant in relation to factual consumption habits and biological effect," then some reference should have been made to the categories used in the previous studies (including an explicit acknowledgement of the differences). Absent such analysis, it is difficult to identify any explanation for the differing model choices other than an attempt to get a preferred result.

Beyond the choice of the statistic model, it is worth nothing that Tables III and IV include positive, negative and null relative risks, as would be expected from analyzing 60 different associations. The authors choose to focus on statistical significance as paramount and emphasize the outlier results that are significant. Even setting aside the possibility that the outlier point estimates and statistical significance result from the model choices noted above, the emphasis on data-driven outliers means that a correction for multiple hypothesis testing should be used. Such a correction would almost certainly make most or all of the results not statistically significant.

Readers of this series of papers might also be confused by the piecemeal approach that isolates exposure-outcome pairs and reports them in forms that are not comparable, mixes incidence and mortality, omits absolute risk level estimates, and makes it impossible to get a clear picture of comparative risks. While this is not necessarily wrong or unusual, it takes substantial work for a sophisticated reader to try to piece together this cohort's exposure and disease experience. Given the potential value of this cohort in providing a big picture, we wonder why these authors have

not attempted to, for example, report the overall mortality rates for people in different exposure categories, providing valuable perspective on snus use, smoking, and other exposures.

The series of studies that are difficult to compare with numerous unexplained variations in eligibility criteria, variable definitions, and other choices create the appearance that the studies of snus using this cohort have degenerated into fishing expeditions. There is no apparent basis for the analytic choices that were made, other than biased reporting. Because there is no way for the interested reader to fully understand the choices, replicate the calculations, or otherwise examine the analyses, we are left speculating about such bias. Producing results based on incompletely explained and under-justified methods using data that is not available for the scientific community to reanalyze strains the definition of sound scientific publishing. At a minimum the authors should report the results that would be obtained for each of their disease endpoints (esophageal cancer, pancreatic cancer, etc.) using the models from all other relevant articles and report absolute risk (differences) so that different exposure-disease combinations can be compared and summed. Having done that, the authors would be free to argue that the specific models used in each report were the best for that particular analysis, and the scientific community could judge whether the model choices biased the reported results. Should the authors be unwilling to provide these basic comparisons, the dataset should be made publicly available so that the biases outlined in this letter can be refuted or confirmed.

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Table I: Comparison of variables included in analyses of the Swedish construction workers' study

Reference	Age	Snus use	BMI	Other tobacco use
1	Attained age Stratified analysis: <70, >=70 years old Incidence rates standardized using 5-year age groups Relative risks adjusted for age in years as the time scale.	Ever versus never	Quartiles	Ever or never Current, previous, or never Amount: <10 g/day, 10-19 g/day, >=20 g/day Product: cigarette only, pipe only, cigar only
5	Attained age Incidence rates standardized using 5-year age groups Relative risks adjusted for attained age (continuous) as time scale.	Never, previous, or current Grams of snus per day (<10 g or ≥10 g)	<25, 25–29, and ≥30	Never, previous, or current Grams of smoking tobacco per day (continuous)
3	Incidence rate ratios adjusted for age (possibly in 5-year age groups)	Pure snuff users vs tobacco nonusers (TNU) Duration of use (years): 1-29, >=30	Underweight: <18.5, normal: 18.5-25, overweight: 25-30 and obese: >30	Pure cigarette smokers vs TNU Amount of cigarette tobacco smoked daily: TNU, 1-9 g, 10-19 g, >=20 g Pure pipe smokers vs TNU Pure cigar smokers vs TNU Mixed tobacco use vs TNU
4	Incidence rate ratios adjusted for age in years as the time scale.	Never tobacco users versus pure snuff dippers	Underweight: <18.5, normal: 18.5-25, overweight: 25-30 and obese: >30	Current smokers, ex-smokers and TNU Amount currently smoked (g/day): <10, 10-20, >20 Pure cigarette smoker versus TNU Pure pipe smoking versus TNU
7	Stratified analysis: 35-54 and 55-65 years old Incidence rates standardized using 5-year age groups Relative risks adjusted for age as time scale.	Never, current, former Amount used by current users: <12.5 g/day, 12.5–24.9 g/day, 25–49.9 g day and >=50 g day Amount of snuff use	<20, 20-24, 25-30, 30+ (BMI was Adjusted for age distribution at entry)	Not included

Reference	Age	Snus use	BMI	Other tobacco use
		(g/week) Duration of snuff dipping Time since cessation of snuff use Regular snuff use: (>=1 g day) for at least 1 year Former snuff use: stopped using snuff more than 1 year before enrolment		
8	Incidence rates standardized by age group: <40, 40–44, 45–49, 50–54, 55–59, 60+ years old Estimated relative risks adjusted for age in 5-year categories	Pure snuff dipping versus non-tobacco use		Former, current, non-tobacco use Amount: <=15 g/day, >15 g/day Cigarette smoking, cigar, pipe or mixed smoking and non-tobacco use Only smoking, both smoking and snuff dipping and non-tobacco use Only smoking, snuff dipping only, both smoking and snuff dipping and non-tobacco use
2	Incidence rate ratios adjusted for age (possibly in 5-year age groups)	Snuff dipper vs TNU Years dipping snuff: TNU, <30, >=30	Underweight: <18.5, normal: 18.5-25, overweight: 25-30 and obese: >30	Previous, current vs TNU Smoking tobacco g/day: TNU, <=10, 11-15, >15 Years of smoking: TNU, <=15, 16-25, >25 Years since smoking cessation: TNU, <10, >=10 Cigarette smoker vs TNU Cigarettes/day: TNU, <10, 11-20, >=20 Cigar smoker vs TNU Pipe smoker vs TNU Pipe tobacco g/week: TNU, <80, >=80 Mixed user vs TNU

Reference	Age	Snus use	BMI	Other tobacco use
6	Rate ratios adjusted for age as a categorical variable (<45, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 80+ years old)	Never (includes cigarette, pipe and cigar smoking) and ever		Never, previous and current Cigarettes per day: 0, 1-4, 5-14, 15-24, >25 Duration among ex-smokers (years): never smokers (ref), 1-10, 11-20, >21 Duration among current smokers (years): never smokers (ref), 1-10, 11-20, 21-30, 31-40, >41 Pipe (g tobacco/week): never smokers (ref), <30, 30-100, >100

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