A novel approach to assessing the risks from smokeless tobacco: looking at the evidence

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This distributable version of the slides has been edited slightly from the version used in that seminar, including collapsing multiple slides into one and changing text, to make certain points easier to understand when read without the accompanying oral presentation.

Background

Modern smokeless tobacco products cause very little health risk.

The evidence for this is overwhelming.

The risk appears to be 1% (+/- 1%) of that attributed to smoking
(more specifics on that later)

so, it is small compared to everyday hazards like:
french fries, driving, medical errors

Surprised?

Not surprising. A lot of people want you to believe ST is very unhealthy. (Confession: I was as surprised as anyone.)

Background, continued

Most self-proclaimed experts on the topic have never looked at the actual scientific evidence (thus the snarky title for the talk).

The "authoritative" summary reports (a.k.a. the "ancient texts")
(Surgeon General's Committee 1986, IARC 1985)
were written before the vast majority of the evidence existed.

The ostensible authorities who provide most of the popular information,
i.e., sources of most clinicians' and policy makers' knowledge,

(NCI, other U.S. govt, ACS, other U.S. advocacy groups)

provide consistently misleading information.

(see: Phillips et al. "You might as well smoke" 2005, Waterbor 2004).

Background, continued

Despite this, it is not difficult to learn what the evidence really says.

The literature is pretty straightforward.

Even a reader who cannot understand the major flaws in a few papers (which I will allude to), or otherwise critically evaluate, will quickly learn the basic message.

Textbooks and genuine experts are already starting to come around.

But the prevalent political propaganda will continue to make it difficult for people to *realize* that they don't know the truth.

Now you can realize.

Background on this talk

A talk is not really a good format for a literature review.

I was asked by the department to do this particular presentation.

Why?

Well, funny thing....

Background on this talk, continued

I am one of the more vocal critics of business-as-usual in health science research,

> including naive acceptance of what researchers claim to have found without multiple examinations of the evidence (see Phillips and Goodman 2006).

Alas, the request I present this is probably not the emergence of genuine healthy scientific scepticism in health research.

Rather, this burst of scientific caution and doubt about one person's assessment of the evidence seems limited to:

> claims that something is not really very bad for you,
> -especially if that exposure is politically incorrect,
> -esp if challenging claims of very rich organizations.

Background on this talk, continued

Ironically, the reason for the rare burst of healthy scepticism might be the research funding that I get from the smokeless tobacco industry (which is fairly modest and completely hands-off unrestricted).

(you may have heard about this)

Ironic because my small shop (and others who make these points) are taking on numerous government agencies and some of the richest health organizations in the world (who are lying to you).

But we are treated as if we are some kind of massively-funded leviathan who deserves extra scrutiny.

We are just what you see – nothing more.

Fortunately, overwhelming evidence is a great equalizer.

Background on this talk, continued

This presentation was solicited by the department, but the analysis is my own, uninfluenced by the department or my funders.

However, my work was assisted.

ASTER Group members who helped in preparing this talk:

Alfred Aung
Paul Bergen
Jennifer Dressler
Dunsi Rabiu
Chris Sargent

Overview

I will present the evidence about risks caused by ST for:

-oral cancer, incl pharynx and larynx (not established; clearly small)

-esophageal and gastric cancers (not supported; clearly small)

-pancreatic cancer (not established, but some evidence)

-breast cancer (sometimes claimed, but no evidence)

-lung cancer (not established, as well supported as most other sites)

-other cancers (speculative, clearly small)

-cardiovascular disease (possible; might be enough to be measurable, but not clearly established)

Overview, continued

While the presentation of the evidence is necessarily brief,

it is systematic and comprehensive (to my knowledge)
particularly for the most important disease endpoints,

(I and others have searched *a lot*)
(it is probably the most comprehensive review that exists)

and should leave little doubt about the main conclusions.

Important observation about scientific epistemology

There is much confusion about:

absence-of-evidence

vs.

evidence-of-absence

vs.

evidence-of-small-effect

(blame the use of statistical significance testing for much of this)

Important observation about practical epistemology, continued

If there is no evidence of a phenomenon,

but no one has ever looked for it,

then we do not know much (an absence of evidence).

I.e., for an exposure that has not been well studied and that no one is particularly interested in,

failure to find evidence it is bad for you is not very informative.

Important observation about practical epistemology, continued

But, for an exposure that

> lots of well-funded people are actively trying to show to be bad,
>
> and many researchers would love to build their career on such findings,

then failure to find evidence of substantial harm is as informative as you can ask for in science (evidence of absence).

Important observation about practical epistemology, continued

Moreover, if there are high quality studies that show very small or no association,

then they actively rule out large effects (evidence that any effect is small, or that there is no effect at all).

I.e., just as confidence intervals can "rule out" the null, they can "rule out" strong positive associations.

General background on the literature

Most modern studies exclude smokers (a few stratify).
(smoking is a huge potential confounder for these studies)

Older studies did not, and are thus not very useful.

Fortunately, most of the potentially useful literature is modern.

Most studies of specific cancers are case-control.

There is some cohort data, particularly recent publications, and mortality followback data.

It is difficult to study a relatively rare exposure.

Most useful studies of modern Western ST products are from Sweden (where exposure is much more prevalent), with most of the rest from the US.

Oral Cancer - overview

Anti-ST advocates seem obsessed by OC risk, even though it is a relatively rare disease in the West,

and thus a moderately elevated RR is a small absolute risk.

~2% of cancer mortality, ~4 per 100,000 PYs
1000 deaths/year in Canada; 8000 in US

but the majority of these are attributed to smoking,
baseline rates for nonsmokers perhaps 1/3 of these

This is probably mostly rhetorical strategy because people seem willing to believe it,

though some of it stems from an early over-conclusion based on a bit of evidence.

Oral Cancer - the literature

Three studies with largest effective sample size (all case-control):

- Winn et al. 1981 (see below)
- Schildt et al. 1998 (found null association)
- Lewin et al. 1998 (found null association)

About 30 smaller studies (depending on exactly what you count)

- about 10 of which provide useful data.

(Wynder 1957a, Wynder 1957b, Peacock 1960, Vogler 1962, Vincent 1963, Martinez 1969, Williams 1977, Browne 1977, Wynder 1977, Whitaker 1979, Wynder 1983, Young 1986, Stockwell 1986, Spitz 1988, Blot 1988, MacKerras 1988, Falk 1989, Franco 1989, Sterling 1992, Maden 1992, Marshall 1992, Zahm 1992, Mashberg 1993, Kabat 1994, Bundgaard 1995, Muscat 1996, Schwartz 1998, Lee 2000, Accortt 2002/2005, Boffetta 2005, Henley 2005, Rosenquist 2005)

- Often include pharynx sites, sometimes larynx (some are just larynx)

Not too much apparent publication bias among big studies

- (might not be the case for other cancer sites)
- but seems to be some among smaller studies

Oral Cancer - literature summary

Literature to-date was systematically reviewed and statistically summarized by Rodu and Cole 2002

Main results:

Little or no association

For moist snuff,
results for all sites very close to null
summary estimates range of RRs: 0.7 to 1.2

For chewing tobacco,
also close to null
similar range (if we set aside one very old study)

(Compare: RR for OC (alone) from smoking is close to 10)

Oral Cancer - literature summary, continued

Rodu and Cole results, cont:

For dry snuff,
strong positive association found

For very old studies (weak methods; unknown exposure details; older products)
weak positive associations found

All publications subsequent to R&C 2002 (e.g., Rosenquist 2005) have further supported the near-null results for modern products as do several earlier studies that R&C could not include in their summary because inadequate statistics were reported.

(so, if anything, R&C overestimated the association)

Oral Cancer - note on the one piece of literature that is often mistaken for *the* literature

The outlier result for dry snuff in R&C is driven by the one large study that found a strong positive association, Winn 1981.

(also two small results contribute - clearly null results distorted by "publication bias *in situ*" as I have discussed elsewhere)

Winn 1981 reported a RR of about 4,
far outside the CI of the rest of the literature
(i.e., that RR is "ruled out" as implausible by the rest of the literature)

-unusual exposure (early/mid-20th c. dry snuff; very heavy use)

-unusual population (mostly rural Appalachian women)

Oral Cancer - the one piece of literature that is often mistaken for *the* literature, continued

Most RR numbers in the lay media are from Winn (only)
(moreover, many overstate what Winn found)

(Note again that even RR of 4 is still quite small compared to smoking)

Sadly, a huge portion of references and RRs in the health science literature are also from just this one source (and most are misinterpretations of what was found)

though driven by advocacy, this reflects common bad practice in the health literature:

-"ratchet effect"
-literature reviews that treat any published result as Truth
(regardless of what else is known)

Aside: Nitrosamines

Often identified as the main potential carcinogens in ST.

This is based on chemistry/toxicology alone,
since the actual evidence does not support the claim that modern Western ST causes cancer.

-widespread misunderstanding about suggestive findings versus real epidemiology
(when we have data on the actual exposure of people and their disease endpoints, it makes little sense to return to the merely suggestive data from chemistry/toxicology)

Concentrations of nitrosamines in ST have dropped by more than an order of magnitude over the last few decades

appear to be much higher in dry snuff (and non-Western products) than currently popular Western products

Does this mean that some products cause measurable risks for OC?

Quite possibly, particularly non-Western products.

The Winn outlier could be due to:

-study error, extreme levels of exposure, unusual population,

or

-genuine differences among products

(one possible explanation is nitrosamines, but there are others)

Stronger evidence exists in epidemiology from Africa and South Asia,

where they use very different dip products,

showing strong association with OC,

which could be due to:

-other ingredients in the dip,

-differences in tobacco processing (perhaps nitrosamines),

-different co-risk-factors (much higher baseline risks).

Oral Cancer - conclusions

For modern Western products:

The results in the literature are consistent with no association (i.e., it is not clear there is any risk at all).

They are not consistent with the claim that of a 4-fold or even 2-fold increase in risk. Even a 50% increase is extremely unlikely.

The risk is so close to null that we cannot distinguish it from null.

It is plausible (though clearly not established) that there is a RR of 1.1 or 1.2.

For archaic Western products (who cares?),
risks might have been higher (or the data might be due to study error or other differences in the exposure and population)

For non-Western products, risks seem to be higher.

Other Cancers - overview

Any association of ST use and all-site-cancer is difficult to detect

Cohort studies:

Henley 2005 (CPS I data) - very small positive association

Henley 2005 (CPS II data) - small positive assoc (mostly lung)

Accortt 2002/2005 (NHANES) - null association

Sterling 1992 (NMFS) - fairly strong protective (negative) association

Other Cancers - overview

Specific sites most often mentioned (in addition to OC):

- -esophageal
- -gastric
- -pancreatic
- -breast
- -lung

(will briefly review each of these)

Research exists also for:

-bladder	(a fair bit of data, no association)
-kidney	(results tend a bit positive, but inconclusive)
-colon and rectal	(no evidence of assoc, but not much data)
-prostate	(mixed results, mostly null, not much data)

Esophageal Cancer

Biologically plausible site to consider.

Results from 13 studies

(Wynder 1957, Wynder 1961, Martinez 1969, Williams 1977, Wynder 1977, Pottern 1981, Sterling 1992, Gammon 1997, Lewin 1998, Lagergren 2000, Lee 2000, Boffetta 2005, Henley 2005)

(some group multiple digestive system sites)

show a consistent pattern of null results,

(one old study showed a significant positive association)

results from larger studies very close to the null.

Small increase in risk is possible, but speculative.

Large increase in risk is ruled out.

Gastric (stomach) Cancer

Biologically plausible site to consider.

Results from 10 studies

(Williams 1977, Weinberg 1985, Kneller 1991, Hansson 1994, Ye 1999, Lagergren 2000, Accortt 2002/2005, Chao 2002, Boffetta 2005, Henley 2005)

(some group multiple digestive system sites)

show clear clustering around the null.

Small increase in risk is possible, but speculative.

Large increase in risk is ruled out.

Pancreatic Cancer

Not an intuitive biological connection

and never (or almost never) mentioned until:

Alguacil and Silverman 2004

possibly the best ever example of "publication bias *in situ*"
(as I presented previously)

Their data clearly supports the null, but they figured out how to portray it as a strong positive association.

Pancreatic Cancer, continued

Shortly thereafter, Boffetta 2005 also reported a positive association
(this study has also been sharply criticized, including for PBIS)

Other studies have found no association
(Williams 1977, Farrow 1990)

But a few are weakly suggestive of increase
(Zheng 1993, Muscat 1997)

Studies that lump together digestive system cancers tend to find very low or no increased risk
(Sterling 1992, Accortt 2002/2005, Henley 2005)

Pancreatic Cancer - conclusions

Difficult to make sense of this, but unless the recent suspect study results are interpreted naively (i.e., misinterpreted), we cannot interpret the evidence as showing an association.

But a positive association is consistent with the published results.
(not clear if there are negative results that were not published)

The published studies suggests RR is well under 2.

(Note that RR for pancreatic cancer from smoking is typically estimated in the range of 2.)

Breast Cancer

There is no evidence of association, but worth mentioning because:

One study (Spangler 2001) claimed to find a strong association

but this was completely retracted as an error (Spangler 2002).

Despite this and the lack of any other reports of associations (to our knowledge), a few anti-ST advocates still claim a causal link.

Lung Cancer

No obvious biological plausibility.

Interesting because recent cohort studies (Accortt 2002/2005, Henley 2005) found positive associations, much stronger than for OC or other sites.

(other studies did not find assoc - Williams 1977; Wynder 1977; Boffetta 2005)

Seems more plausible that this is evidence of confounding by smoking exposure (measurement error) - (second hand smoke?)

rather than an actual causal relationship.

Cardiovascular disease - overview

Despite the emphasis on cancer (particularly one relatively rare cancer),

if ST use causes any substantial mortality risk, it is via CVD.

Plausible: nicotine has acute CV effects.

Limited information,

cannot distinguish between null and risk level that might be of some (small) consequence,

but enough to rule out large increase in risk.

Cardiovascular disease - the evidence

Current concern is primarily due to Henley 2005 (CPS I and CPS II)

Reported RRs around 1.2 for all CVD

higher for stroke, lower for heart disease

Very large studies

(so a naive interpretation of statistics say that their results are extremely accurate)

But the data and analysis have other substantial limitations (e.g., the impressive lung cancer risk)

(I have written another paper that points out the limitations of that article, but beyond the present scope)

Cardiovascular disease - the evidence, continued

Other cohort results:

Bolinder 1994/1998, Swedish construction workers
showed higher association, about 1.5

Johansson 2005, SALLS
showed about 1.2 (smaller effective sample size)

Accortt 2002/2005, NHANES I
showed a null-to-protective association

Cardiovascular disease - the evidence, continued

Swedish case-control studies of MI
- Huhtasaari 1992
- Huhtasaari 1999
- Hergens 2005

and of Stroke
- Ahmed 2000
- Asplun 2003

and Swedish ecological study of MI
- Gyllerup 1991

all found near-null (mostly somewhat protective) associations

Cardiovascular disease – conclusions

Despite the flaws in Henley, we should not feel completely comfortable ruling out an RR as high as their 1.2.

The evidence does not support an RR higher than that (stroke may be higher in the 1.x range, but heart disease is lower by an equivalent amount)

(for comparison, RR for CVD from smoking is roughly double that for nonsmokers)

However, most results have been lower, so the totality of the evidence supports a lower RR than 1.2,
though biological plausibility means that we should not be quick to conclude the null.

If there is any substantial mortality risk from ST, it is to be found here.

What does this all mean?

To make this somewhat intuitive, compare to risk from smoking.

To calculated the comparative risk, we used U.S. government estimates of smoking mortality and prevalence, and estimates of RRs for ST from the literature review.

The results of this more complete calculation confirmed previous rough calculations:

> The mortality risk from ST is most likely about 1/100th that from smoking.
>
> Even the worst-plausible-case estimates of the RRs for ST do not yield a risk as high as 5% that from smoking.

[Note: More detailed estimates from our calculations were presented in the talk. They do not appear in these slides because they were very preliminary, but by the time you read this, more complete and updated results from our calculations will be available elsewhere.]

Conclusions

ST is clearly less harmful than most people think.

-indeed, there is no definitive evidence that it causes any life-threatening disease.

-best estimates put the risk in the range of many everyday hazards,

in a completely different league from smoking, poor nutrition, overweight, exercise, most recreational drugs

Did you catch the bit about risk from smoking for OC alone being *much* higher than that from ST.

-double even the usual overstatement of the risk of ST

-about 20× the highest plausible risk from ST

Conclusions, continued

Even though the low risk becomes clear as soon as you actually look at the literature, there are good reasons that many people do not know it:

-believing that ST causes substantial health risks has a certain *truthiness* to it (faith-based knowledge is in vogue these days)

so it is easy to be convinced
(but that still requires someone trying to convince you)

-most Anglophone popularizers of health science information look to the US government and US advocacy groups to interpret the research,

-but those entities do not provide honest information

Conclusions, continued

-it would not occur to most clinicians, public health officials, etc. that they are being lied to, so they pass on the information

-those receiving the information also have no reason to believe that the supposed experts they are hearing from are actually not expert

Key: with all that going for the claim that ST causes substantial health risk,

why would someone even think to doubt it?

Conclusions, continued

Now you know you should doubt it.

Conclusions, continued

Now you know you should doubt it.

Even if you did not find this brief presentation enough information to reach a new conclusion,

it should be quite enough to show that you should doubt the common conclusion that ST causes substantial risk of life-threatening disease.

Conclusions, continued

Having heard what the literature really says, it would be extremely naive to keep believing the conventional wisdom without looking more carefully.

It is clearly unethical to claim clinical or public health expertise and tell people that ST is a major health hazard:

-either you are claiming expertise you do not have

-or you are lying (sorry - no way to be polite about that)

Conclusions, continued

Smokeless tobacco is not a safe alternative to smoking....

Conclusions, continued

Smokeless tobacco is not a safe alternative to smoking....

...but it is very, very close.

Conclusions, continued

Smokeless tobacco is not a safe alternative to smoking....

...but it is very, very close.

(No one claims that ST is 100% harmless - that is pure straw man)

Driving carefully and properly is not a safe alternative to speeding while drunk through a school zone and not wearing your seatbelt...

...but it is also very close

Conclusions, continued

ST is clearly so much less harmful than cigarettes that encouraging smokers to switch is obviously good health advice.

This "harm reduction" approach is nothing new or radical:

Most activities (driving, eating, work, play) create some risk.
Risks can be reduced.
Public health is mostly about reducing (seldom eliminating) risks.

Public health practitioners can usually only dream of achieving as much harm reduction as the switch from cigarettes to ST.

Conclusions, continued

But it is not just harm reduction for smokers,

or the risk of telling ST users they might as well switch to cigarettes because ST is just as harmful:

Focusing on ST as a major risk consumes resources (budgets, clinical time, people's limited willingness to be lectured to) that could be spent on risk factors that matter,

People simply have a right to the truth, so they can make their own health and risk decisions.

Conclusions, continued

Are tobacco and nicotine so different from other things people do and consume that they justify:

-abandoning the core principle of modern health ethics:
informed individual autonomy?
-ignoring the scientific evidence?
-twisting the interpretation of data?
-wasting huge amounts of scarce resources?
-lying and resorting to *ad hominem* attacks when the truth is not on your side?
-trying to censor competing views?
-requiring researchers to compile, critically review, and present the evidence?

(well, actually that last one is always a good idea
everyone should give it a try)