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Issues

1. Types of post-market studies to monitor and evaluate longer term health effects of new modified risk tobacco products.
2. Scientific standards in cancer clinical trials; Characteristics of a study for reliable evidence
3. Usage of modified risk tobacco products over time
4. The relationship between modified risk tobacco products and actual and relative health risk.

Post-market Studies

Studies Used for Drugs

- Anecdotal vs. Organized
  AERS vs. Formal Studies
- Observations vs. Interventions
  “Epidemiology” vs. (randomized) Clinical Trials

Post-Market Studies: What is a "Trial"?

As used, term is too vague to be meaningful:

- A randomized (organized, very formal) study

OR

- Any large study (often observational)

OR

- Any intervention study (no controls, not randomized)

Post-Market Studies

Unique Issues for Modified Risk Tobacco Products

- Acute adverse effects largely known/suspected
  (Interest is long-term effects: CVD, cancer, etc.)
- Time-varying, mixed exposures
- Need for behavioral endpoints
  (e.g. Uptake of higher risk products)
- Need for societal endpoints?
- Biomarker exposure and/or endpoints markers?

Post-Market Studies

Different Questions Need Different Studies

"Science"

- Does the product cause MI, Stroke, Cancer? (Is there risk? Less than for smoking?)

"Behavior"

- Does the product lead to smoking?
- Does the product facilitate smoking cessation?

"Bottom Line"

- Is there really less risk to society?

Post-Market Studies

Modified Risk Tobacco Products

- Need long term studies for many diseases
- Can’t use current administrative data
- Current behavioral surveys have limited utility
- Need detailed tobacco history (all products, over time)
- Biomarkers may help in some questions
- Small numbers exposed for new products

Post-Market Studies

(Randomized) Clinical Trials?

Not useful for most relevant questions:

- Randomization possible only for advice/access
- Long-term compliance will be difficult/impossible
- Long-term (decades) detailed follow-up difficult

Post-Market Studies

Will Have to Depend on the Product & Question

What Probably Won't Help:

- Adverse event reporting
- Randomized clinical trials

What Could Help in the Right Contexts:

- Series of (case-control) studies of CVD, cancer, etc
- Follow-up studies of product users, smokers, unexposed
- Detailed surveys of tobacco product use patterns

Post-Market Studies

What Will a Good Study Look Like?

- Focused appropriately
- Large enough to answer the question
  Need endpoint N's and exposed N's
- High response/follow-up rates

Analysis:

- User vs never user
- User vs never tobacco user
- User vs smoker
- Don't adjust for smoking in some analyses

Post-Market Studies

What Will a Good Study Look Like?

- Focused appropriately
- Large enough to answer the question
  Need endpoint N's and exposed N's
- High response/follow-up rates

CVD:

- Fairly rapid protective/adverse effects
- "Reliable" risk biomarkers

Post-Market Studies

What Will a Good Study Look Like?

- Focused appropriately
- Large enough to answer the question
  Need endpoint N's and exposed N's
- High response/follow-up rates

Cancer, COPD

- Long term exposure needed to document ↓ risk
- Follow-up studies possible but difficult
- Case-control studies might be productive

Post-Market Studies

What Will a Good Study Look Like?

- Focused appropriately
- Large enough to answer the question
  Need endpoint N's and exposed N's
- High response/follow-up rates

Behavioral Endpoints:

- Follow-up studies

Post-Market Studies

Summary

- Question-specific studies needed
- Product specific analyses essential (duration & intensity of use)
- Detailed, longitudinal tobacco history important
- Often need long, large studies

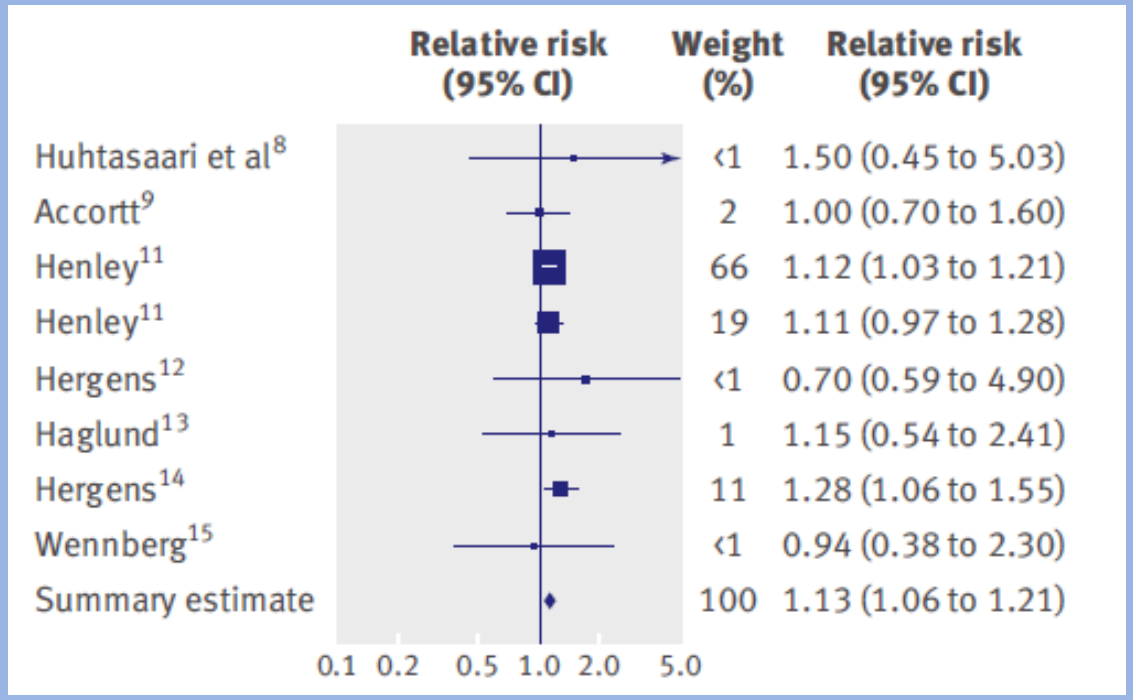
Smokeless Tobacco

Disease Associations

- In general, lower risks than smoking
- Smoking an important confounding factor

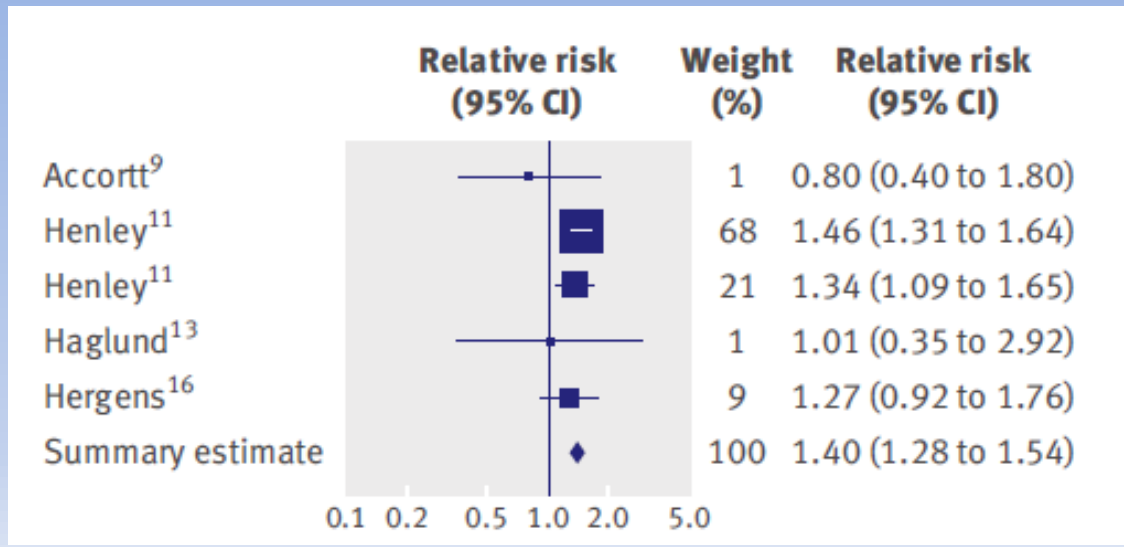
- Cancer: small ↑ risk upper GI (?)
- MI, stroke risks: Small increase in risk vs. non-users (?)

Smokeless Tobacco Use & CVD



Fatal MI

Fatal Stroke



Any use; men
Boffetta & Straif, 2009

Smokeless Tobacco Use & Cancer

Ever Use

	Countries	Number of risk estimates	p*	Relative risk (95% CI)	p†
Oral cancer	Overall	13	<0·001	1·8 (1·1–2·9)	..
	USA	9	<0·001	2·6 (1·3–5·2)	..
	Nordic countries	4	0·4	1·0 (0·7–1·3)	0·01
Oesophageal cancer	Overall	5	0·3	1·6 (1·1–2·3)	..
	USA	1	..	1·2 (0·1–13)	..
	Nordic countries	4	0·08	1·6 (1·1–2·4)	0·8
Pancreatic cancer	Overall	6	0·08	1·6 (1·1–2·2)	..
	USA	4	0·3	1·4 (0·7–2·7)	..
	Nordic countries	2	0·6	1·8 (1·3–2·5)	0·5
Lung cancer	Overall	5	0·005	1·2 (0·7–1·9)	..
	USA	3	0·07	1·8 (0·9–3·5)	..
	Nordic countries	2	1·0	0·8 (0·6–1·0)	0·02

Nordic countries include Norway and Sweden. *Test of heterogeneity in individual studies. †Test of heterogeneity between geographical regions.

Table 2: Summary relative risk of selected cancers for ever use of smokeless tobacco in the USA and northern Europe

Boffetta et al, 2008

Smokeless Tobacco & Disease

Summary

- Almost certainly less risky than cigarettes
- Gateway?
- Smoking cessation?