Review of: "[Commentary] The WHO strategies to reduce tobacco-related deaths are insufficient"

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Potential competing interests: No potential competing interests to declare.

In view of the current data, which is summarized in the report below and

the research I have followed in many years, I am certainly in compliance with WHO

information on snus and all other tobacco and other smoked products use

consequences and do not agree with the author's point of view. Risk reduction is not a logical approach for tobacco use cessation in view of the very effective methods and drugs for cessation as monotherapy or in combination.

Health risks from snus use

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Report

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We were commissioned by the Ministry of Health and Care Services to update the 2014 report on health risks from snus use. The report presents updated figures on snus use in Norway, and assesses exposure and risk. The report is limited to the use of Swedish snus.

Health risks from use of Swedish snus

Based on systematic reviews of research on people who use Swedish snus compared to people who do not use snus, knowledge about the properties of the constituents (TSNA and nicotine), animal studies on snus and evidence about adverse health effects caused by use of other tobacco products, we conclude as follows:

Cancer

Use of Swedish snus probably increases the risk of oesophageal and pancreatic cancer.

It is possible that use of Swedish snus increases the risk of cancer of the stomach and rectum.

It is possible that use of Swedish snus increases mortality after a diagnosis of cancer (all types of cancer assessed together, and prostate cancer specifically), both when the cause of death is considered cancer-related and for all causes.

It is uncertain whether use of Swedish snus affects the risk of cancer of the oral cavity and pharynx, the lungs, the upper part of the stomach (cardia), colon and anus.

It is uncertain whether use of Swedish snus affects mortality after colon and rectal cancer.

There are no studies investigating whether use of Swedish snus affects the risk of cancer in women

Cardiovascular disease

Use of Swedish snus probably increases the risk of high blood pressure and lethality after myocardial infarction and stroke.

It is possible that stopping the use of snus after a heart attack may halve the risk of dying during the next two years.

It is possible that use of Swedish snus increases the risk of endothelial dysfunction and has immediate effects on cardiac function (reduced diastolic function).

It is uncertain whether use of Swedish snus affects the risk of myocardial infarction, stroke, atrial fibrillation and chronic heart failure.

There are no studies investigating whether use of Swedish snus affects the risk of cardiovascular disease in women.

Mental disorders

It is possible that use of Swedish snus increases the risk of non-affective psychosis.

It is uncertain whether use of Swedish snus affects the risk of schizophrenia.

There are no studies investigating whether use of Swedish snus affects the risk of mental illnesses in women.

Type 2 diabetes, obesity and metabolic syndrome

High consumption (> four boxes of snus per week) of Swedish snus among men probably results in a large increase in the risk of type 2 diabetes and metabolic syndrome.
It is uncertain if low consumption (<four boxes of snuff per week) of Swedish snus among men affects the risk of type 2 diabetes and metabolic syndrome.

It is possible that use of Swedish snus among men leads to weight gain and increases the risk of obesity.

Non-malignant changes in the oral cavity

The available studies are ambiguous regarding a possible association between caries occurrence and snus use.

Use of snus causes changes in the mucous membrane of the oral cavity.

Other health outcomes

It is possible that use of Swedish snus reduces the risk of Parkinson's disease.

It is uncertain whether use of Swedish snus affects groin hernia repair.

It is uncertain whether use of Swedish snus affects the risk of rheumatoid arthritis, or the risk of developing multiple sclerosis (MS).

Pregnancy outcomes

The use of Swedish snus probably increases the risk of premature births.

It is possible that use of Swedish snus during pregnancy increases the risk of stillbirths, being small for gestational age, reduced birth weight, cesarean section, neonatal apnea and oral cleft malformations, and levels of nicotine degradation products (cotinine) in the child's urine.

It is uncertain whether use of Swedish snus changes the risk of preeclampsia, early neonatal mortality, and cardiac arrhythmias in the newborn.

Snus use in Norway

Almost 20% of adult men and just over 5% of adult women use snus daily. In addition, about 5% of men and just under 5% of women sometimes use snus. Use of snuff is most common among young adults; 25% of men and 15% of women aged 16-24 years use snus daily.

The use of snus increased in the late 1990s among men and approximately ten years later among women. The growth in the proportion of snus users has slowed among young adults of both sexes. However, the proportion is still increasing among men aged 25-49.

Snus users increasingly prefer portion snus rather than loose snus. In the period 2015-2017, almost 70% of men and almost all women responded that they only used portion snus. Eight percent of men and almost no women responded that they only used loose snus in the same amount of time.

The snus sold on the Norwegian market in 2015 contained on average more nicotine per gram than the one sold in 2005. At the same time, there is an ever greater variation in portion sizes. This means that the degree of nicotine exposure

depends on the type of snus used.

There are few tobacco users who smoke and use snus at the same time. Of those who had ever used snus and who were interviewed in the period 2016-2018, 33% of men and 40% of women had no previous experience with smoking. This is an increase from the period 2004-2006; then 23% of men and 12% of women who had used snus had not smoked before.

A review of the literature on the global burden of disease (GBD) shows that there is not yet sufficient evidence to estimate the burden of disease related to snus use according to GBD's criteria. The latest available version of GBD did not include any estimates of the burden of disease caused by use of snus (GBD 2017).

Health effects of constituents of snus

Tobacco specific nitrosamines (TSNA)

The tobacco-specific nitrosamines N-Nitrosonornicotine (NNN) and 4-(N-Methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) as well as the NNK degradation product 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) are important and potent carcinogens in tobacco. A number of studies have unequivocally shown that laboratory animals develop cancer after exposure to NNN, NNK and NNAL. In many cell types, including cells in the liver, lungs and oral cavity, these nitrosamines can be converted into reactive products by activation or detoxification enzymes. These metabolic transformation products can bind to DNA and cause irreversible damage. This may be an early step in cancer development. Both animal and human cells are capable of forming such DNA binding products. This indicates that the mechanism of cancer development in humans is similar to that seen in laboratory animals. International Agency for Research on Cancer (IARC) classifies NNK and NNN as carcinogenic to humans. This is based on evidence from studies in cell lines and animals, and population studies which have found a correlation between the degree of exposure to NNK and NNN and cancer risk in smokers.

Nicotine

Nicotine is one of the most important active substances in tobacco and has considerable addictive potential. Nicotine acts primarily by stimulating nicotinic cholinergic receptors and secondly by increased release of various signaling molecules in and outside the central nervous system. The nicotinic cholinergic receptors activate multiple cellular signaling pathways involved in physiological functions. However, nicotine activation of these receptors will also mediate many of the undesirable effects of nicotine.

Nicotine and addiction: Nicotine is highly addictive and it is nicotine that mediates addiction in tobacco use. Withdrawal symptoms when trying to quit smoking are the typical signs that nicotine use leads to physical dependence. The use of nicotine also leads to development of nicotine tolerance. In some individuals, nicotine addiction can develop very quickly. There are indications that differences in nicotine dependence in the population may be related to genetic predisposition.

Nicotine and cancer: There is insufficient data from animal studies to conclude if nicotine is a complete carcinogen or not. Cell studies have shown that nicotine activates a number of signaling cascades in the cells that are relevant in terms of whether nicotine can promote cancer development (promoter effect) when such development is first initiated by known

carcinogens. Experimental studies in animals indicate that nicotine may be a promoter, that is, nicotine may promote already initiated cancer development. Animal studies have shown that nicotine can reduce the effects of cancer treatments by growth factor receptor blockade, chemotherapy and radiation therapy.

Lung development: Nicotine use during pregnancy will also expose the unborn child to nicotine. Several animal studies have shown that nicotine exposure during pregnancy has harmful effects on lung development and lung function after birth.

Immune system*:* Nicotine has a variety of immunological effects of both stimulant and suppressive nature. The effects are likely to be affected by the amount and duration of exposure, route of exposure, organ systems involved in the immune response, stage and type of disease, and the degree of autoimmune and inflammatory mechanisms involved. Gender, age and disease manifestations may alter the effects of nicotine.

Cardiovascular effects: Nicotine exposure increases heart rate and blood pressure. Nicotine can reduce insulin sensitivity, which in turn can increase the risk of atherosclerosis. Overall, nicotine may contribute to an increased risk of cardiovascular disease both in smokers and snus users.

Cognitive functions and mental health: Animal studies and human studies have shown that nicotine can alter cognitive functions. This is especially true when exposed during pregnancy through maternal nicotine use, as well as during childhood and adolescence where the brain is developing and thus extra vulnerable. Hypotheses have been made that nicotine use may alleviate mental disorders by enhancing cognitive functions (the self-medication hypothesis), while other data indicate that nicotine may be a risk factor for mental illness since it affects some of the same biological mechanisms underlying such disease. There are also studies indicating that there are common genes that provide vulnerability to nicotine addiction and mental illness.

Experimental animal studies on snus

Snus cause changes in the oral mucosa (snus-induced lesion) in rats, as well as an increased number of cancers outside the oral cavity compared with those found in animals not exposed to snus. In animal studies with mice, exposure to snus or nicotine alone seems to affect the ability of the blood vessels to repair and to heal wounds. Exposure to snus in animal studies affects the immune system by reducing the white blood cell count and altering levels of various inflammatory markers. Such changes may affect the body's defence and repair when exposed to illnesses or harmful effects.

Discussion

We have prepared systematic reviews of available research on health risks from use of Swedish snus. Most studies were included in the report on snus from the Norwegian Institute of Public Health in 2014. The new studies have strengthened the conclusions of the previous report that the use of snus may increase the risks of some serious adverse health outcomes and some less serious adverse health outcomes, as shown in the results section.

The carcinogenic properties of the constituents, as shown in animal studies and cell studies, support the results of the population studies.

Available studies, on which we have based our conclusions, have varying design and length of follow-up. All follow-up studies identified the tobacco habits at the start of the studies, that is whether the participants used or had used snus, whether they smoked or had smoked, whether they neither smoked nor used snus, or both used snus and smoked (alternating or simultaneously).

We rarely know how long the individuals who answered that they were using snus, had used snus before they were included in the study. Neither do we know how many of those who used snus at the start of the study, still used snus at the time of follow-up. Some may have quit, some may have changed to higher / lower consumption, and some may have switched to smoking or started to smoke in addition to using snus. Those who, at the start of their studies, said that they did not use snus or other tobacco products may also have started later, and may have used snus (or smoked or both) for many years before the risk analysis was conducted.

For some health outcomes (cancer of the pancreas, colon and rectum) we have a follow-up time of up to 36 years, and it is possible that some would have answered differently to questions about their tobacco habits at the end of the study than they did at the start of the study. For several of the health risks that we have considered, it takes a long time before the disease has progressed so far that the diagnosis is made. For example, more than half of those diagnosed with pancreatic, colon and rectal cancer are over 70 years of age. With increasing age, there is a greater chance of dying from other causes, making any risk associated with snus use more difficult to estimate in older age groups. Long follow-up time will therefore have both strengths and weaknesses. We must also remember that people who choose to use snus may be different from those who choose not to use snus in many other respects. We do not have a complete overview of the factors that may be involved, and thus we do not have an overview of whether and how these factors may influence the same health outcomes.

Conclusion

There has been an increase in the use of Swedish snus in Norway in recent decades, especially among young adults, and especially among young women during the last decade. The majority of snus users are former smokers, but in the past 15 years there has been an increase in the proportion of snus users without prior smoking experience. In the period 2016-2018, 33% of men and 40% of women had not smoked before starting snus use. This is an increase from the period 2004-2006, when 23% of men and 12% of women who had used snus had never smoked.

Studies in animals and cells have shown that tobacco-specific nitrosamines are carcinogenic. Nicotine cause a variety of effects that may have adverse health consequences of varying severity.

Research on the health risks associated with use of Swedish snus in humans mainly comes from observational studies. Even with the inherent limitations of such studies, we conclude that systematically summarized research shows that the use of Swedish snus:

- probably increases the risk of cancer of the oesophagus and pancreas, and possibly increases the risk of cancer of the stomach and rectum
- possibly increases mortality after a cancer diagnosis (all types of cancer combined, and for prostata cancer specifically), both when the cause of death is considered cancer-related and for all causes
- probably increases the risk of high blood pressure
- probably increases lethality during the weeks after a heart attack or stroke, and may increase the long-term risk of dying after stroke
- may halve the risk of dying among those who stop using snus after a heart attack.
- may increase the risk of non-affective psychosis, weight gain and obesity
- high consumption of Swedish snus probably increases the risk of type 2 diabetes and metabolic syndrome

Women who use Swedish snus during pregnancy have:

- probably increased risk of premature births
- possible increased risk of stillbirths, being small for gestational age, reduced birth weight, cesarean section, neonatal apnea and oral cleft malformations, and levels of nicotine degradation products (cotinine) in the child's urine.

https://www.fhi.no/en/publ/2019/health-risks-from-snus-use2/