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The risk for cutaneous malignant melanoma, melanoma *in situ* and intraocular malignant melanoma in relation to tobacco use and body mass index

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Conflicts of interest
None declared.

Summary

Background The incidence of cutaneous malignant melanoma (CMM) and melanoma in situ (MIS) has been increasing during the last 50 years. Malignant melanoma (MM) is also the most common intraocular malignancy (IMM). Besides ultraviolet radiation, the cause of these tumours is largely unknown.
Objectives We designed a study to examine the effect of body mass index (BMI) and tobacco use on the risk for MM and MIS.
Methods Analyses were performed on a nationwide cohort of 339 802 Swedish construction workers. Exposure information was collected prospectively by questionnaires combined with personal interviews.
Results Follow up yielded a total of 7 663 400 person-years during which 1639 workers developed MM/MIS. The risk for MM/MIS was reduced in current or previous smokers compared with those who had never smoked, both when analysing all smoking tobacco products combined and when analysing cigarette and pipe smokers separately. The risk was further diminished with longer duration of smoking and greater quantity of tobacco smoked. The effect was more evident in CMM/MIS than in IMM. Snuff taking conferred a decreased risk for CMM/MIS, and a BMI over normal weight range conferred an increased risk for CMM.
Conclusions Tobacco smoking was found to be inversely associated with the risk for CMM and MIS. The mechanism of action is unknown but it has been suggested to be due to the immune suppressive effect that tobacco exerts which would be protective against deleterious immune reactions caused by, for example, the sun. Neither is the mechanism behind the higher risk for CMM due to being overweight known. One hypothesis is that it is an effect of a hormonal imbalance. Further studies are required to elucidate these mechanisms.

Cutaneous malignant melanoma (CMM) has been the most rapidly increasing malignancy in developed countries with large white-skinned populations over the last 50 years.[1–3] In Sweden, the incidence rate has increased by more than 300% since 1970.[4] Despite the rapidly growing number of malignant melanomas (MMs) the survival rate has improved substantially, a trend attributable mainly to earlier detection.[1,5] The lesions therefore tend to be thinner and are even classified as melanoma in situ (MIS) at diagnosis today. Intraocular MM (IMM) is an uncommon form of cancer, but it is still the most frequent intraocular tumour and it presents with a bad prognosis.[6] The only confirmed risk factors for CMM and MIS are phenotype, phototype and sunlight exposure, but other aetiological factors may also contribute.[7,8] The relation between sunlight exposure and CMM/MIS is complex: intermittent intense exposure (recreational) and sunburn history have been shown to confer an elevated risk, whereas some studies show that chronic sun exposure, e.g. occupational sun exposure, is inversely related to the risk for CMM/MIS.[9] No major causative agent has so far been established for IMM. There has been

some evidence for an association with racial characteristics and with sun exposure, but the results have been inconsistent.[10,11]

Tobacco constituents contain a wide range of carcinogenic substances and exert multiple toxic effects on the respiratory, cardiovascular and immunological systems.[12,13] There has been conflicting evidence for an association between CMM/MIS or IMM and smoking in previous studies.[7,14–21] Most of these studies have suffered from limited statistical power and have often been of the case–control design. Different specific tobacco products, such as pipe tobacco, cigars and oral moist snuff have rarely been investigated before.

The association between body mass index (BMI) and CMM has been explored previously and there has been some evidence for an increased risk with increasing BMI.[8,14,18,22] As these results are based on very few studies with limitations in their study designs, the relationship is still far from established.

With this very large, nationwide occupational cohort study, with prospectively collected exposure information, we aim to elucidate further the role of tobacco use and BMI in the development of CMM, IMM and MIS.

Subjects and methods

Study setting

The Construction Industry's Organization for Working Environment, Safety and Health (Bygghälsan) provided outpatient services to construction workers all over Sweden from 1969 to 1993. The organization was a joint venture launched by trade unions and the Swedish Construction Employers' Association. The basic units were stationary and mobile clinics typically staffed by a physician and a few nurses. The main activity was preventive health check-ups, offered to all blue- and white-collar employees in the building industry through regular (every second year during the early years, every third year thereafter) invitations and through visits or advertisements at virtually all major building sites. Although the programme was voluntary, 85–90% of eligible workers participated at least once.[23] Beginning in 1971 the information collected was stored in a computerized register.

Exposure information

Exposure information was collected by letting each worker complete a questionnaire before every visit. On average each cohort member underwent three health check-ups. To avoid misunderstandings or inconsistencies, the answers were double-checked by a nurse. During the period from 1971 to 1993 four different questionnaires were used. The questionnaires used during 1971–1974 are extensive with almost 200 items including a detailed history of smoking and snuff using, anthropometric measures and occupational coding in 200 categories. This questionnaire was removed during the period 1975–1977 but was resumed and expanded in 1978 to record an even more detailed smoking history from then on. The quality of the smoking data has been reviewed and when comparing answers from 2 to 3 years apart perfect concordance was found in 89%. There were missing values in 1·3% of current and 1·4% of previous smokers and inconsistencies were found in 2·6% of the smoking data.[24] Inconsistencies in the data on snuff taking were present in 7% of the workers. Information on BMI was missing in < 2% of the cohort.

Occupational exposure to sunlight has been assessed as previously described.[25] Briefly, an experienced industrial hygienist from the construction industry (N. Hallin) assessed the amount of sunlight exposure of every worker, using the extensive job task coding available in this cohort. Sunlight exposure was categorized into four exposure groups. Subjects with multiple occupations were assigned an average score based on the exposure levels of the component job tasks. We only used information on job task from the first visit but it has been shown that the workers seldom changed their duties and therefore 96·3% had the same exposure level throughout follow up.[25]

The cohort and follow-up

First visit defined entry into the cohort. As no information on smoking history was collected from 1975 to 1977 we included only workers who were registered between 1971 and 1975 and between 1978 and 1992. Over 95% of the cohort consisted of men; hence we restricted our study to male workers. After excluding 1232 persons who had developed cancer before entry into the cohort, 3258 individuals who emigrated before entry and 570 individuals with erroneous personal identification numbers we were left with 339 802 men for analyses.

Each cohort member was followed from date of entry into the cohort until cancer diagnosis, death, emigration, or end of follow up (31 December 2004), whichever occurred first. Follow up was made possible by the unique 10-digit personal identification number given to every Swedish citizen.[4] Identification numbers were checked exhaustively with usual techniques to ensure that they were complete and valid. The personal identification number was then used for record linkage to the National Death Registry (date and cause of death), the Migration Registry (date of emigration) and the Swedish Cancer Registry (SCR). The SCR, founded in 1958 and functional throughout this study, receives reports of all incident malignancies diagnosed in Sweden. By law, both treating physician and pathologist are required to report to the Registry, which ensures recording of > 98% of all malignant tumours, with histological verification of 97%.[4,26] There is no scientific study available on the quality and completeness of MIS registration in the SCR. The reporting of intraocular tumours has been studied previously.[27] With time, eye-saving treatments have become more usual and therefore histological verification of these tumours has varied, but it is not as high as for tumours registered in the SCR generally. During the period of this study the *International Classification of Diseases*, 7th edition (ICD-7) was in use and the following codes were used

for identifying incident cases of CMM and IMM: ICD-7: 190.1–190.9 (CMM; Pathological Anatomical Diagnosis, PAD 176 for CMM and 173/174 for MIS) and 192.0 (PAD 176 for IMM).

Statistical analyses

The distribution of BMI was categorized in four groups according to World Health Organization criteria: underweight, BMI < 18·5; normal weight, BMI 18·5–25; overweight, BMI 25–30; obese, BMI > 30. Because there were too few cases in the extreme categories, data were analysed in two groups: underweight/normal and overweight/obese.

The distribution of age was categorized in eight groups, each with a range of 5 years.

When assessing the total amount of tobacco smoked by a worker daily, cigarettes were assumed to contain 1 g of tobacco and cigars 6 g of tobacco. Snuff users and pipe smokers reported the amount of tobacco (in g) used every week.

Age-, BMI- and sun exposure-adjusted rate ratios (RRs) were estimated using the Cox proportional hazards regression model, which allows studying time to event data, accounting for censoring and loss to follow up; the relevant exposure factors were included as independent variables and their effects were estimated in separate models. Removing the variables birth cohort and sun exposure from the analyses did not alter the estimated incidence RRs or the 95% confidence intervals (CIs) significantly; however, they were kept in the models as they might be considered as potential confounders. Smoking status, duration of smoking, time since cessation of smoking and BMI were established on the date of entry.

Parameter estimates and 95% CIs were obtained by maximizing the partial likelihood, using the stset procedure in Stata 8.2 (StataCorp 2003: Stata Statistical Software, Release 8.2; Stata Corporation, College Station, TX, U.S.A.). Trend tests were calculated, when applicable, by taking the mean exposure in each class of the continuous variable, after categorization, and then including the new 'scored' variable as a continuous variable in the model. Interaction effects between biologically plausible exposures were also included in the model and the likelihood ratio test was used to assess their statistical significance.

The main underlying assumptions of the Cox model were assessed by looking at the distribution of Schoenfeld residuals and by the related test of proportionality; when these were not fulfilled a stratified Cox regression was fitted instead.

Results

The baseline characteristics of the study population are shown in Table 1. Mean age at entry was 34·2 years and the cohort members were followed on average for 22·6 years (range 0·01–33·53), yielding a total of 7 663 400 person-years of follow up. About 70% had ever used some kind of tobacco product. Forty-seven per cent used one tobacco product only (30% were pure cigarette smokers and 10% were pure snuff users) and 25% used two or more tobacco products—most frequently cigarettes and snuff (14%). The mean BMI in the cohort was 24·2 kg m^{-2}. Most workers had a low or medium amount of occupational sun exposure.

Table 1 Basic characteristics of study population

No. cases in the cohort	
CMM	1309
MIS	267
IMM	63
Total	1639
Person-years	7 663 400
Mean age at entry, years (range)	34·2 (14–82)
Mean BMI, kg m^{-2} (range)	24·2 (10·7–55·0)
Tobacco use (all melanoma cases combined), no. cases (person-years)	
Tobacco nonusers	599 (2 289 820)
Smoking tobacco combined[a]	
Former smokers	236 (811 380)
Current smokers	454 (2 468 390)
Pure cigarette smokers	440 (2 254 730)
Pure cigar smokers	15 (46 850)
Pure pipe smokers	88 (399 970)
Pure snuff users	96 (815 050)
Mixed tobacco users	401 (1 856 970)
Occupational sun exposure (during working days)	
Seldom or never	781 (3 616 800)
Intermittently	601 (2 633 280)
Continually	68 (408 980)
Incessantly	26 (125 130)

CMM, cutaneous malignant melanoma; MIS, melanoma *in situ*; IMM, intraocular malignant melanoma; BMI, body mass index. [a]Snuff users excluded.

Throughout follow up, a total of 1639 men developed MM/MIS. Of these, 1309, 267 and 63 men developed CMM, MIS and IMM, respectively. Table 2 displays the adjusted incident RRs and 95% CIs for MM/MIS due to the combined effect of tobacco smoking, including cigarettes, cigars and pipe smoking. Current smokers were at a 35–50% lower risk of developing all outcomes. Ex-smokers had a 25% decreased risk for CMM compared with those who had never smoked but there was no risk change observable for MIS or IMM. This effect of tobacco smoking is confirmed by the analyses of quantity smoked, accumulated quantity smoked and duration of smoking. With increasing duration of smoking, the risk for CMM and MIS decreased. Cessation of smoking within the last 10 years from entry into the cohort conferred approximately the same risk for CMM and MIS as smoking cessation of more than 10 years from entry into the cohort. The risk for IMM increased markedly with longer time since cessation but with a very wide CI. The risk for CMM, MIS and IMM was also decreased in the analyses of quantity smoked. The lowest estimate of CMM and MIS risk was detected in the category of moderate quantity smoked. By calculating accumulated

Table 2 Age-, sunlight exposure-, birth cohort- and body mass index-adjusted incidence rate ratios (RRs) and 95% confidence intervals (CIs) for developing melanoma due to smoking tobacco exposure

	All melanoma combined		Cutaneous malignant melanoma		Melanoma *in situ*		Intraocular malignant melanoma	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Tobacco nonusers	1		1		1		1	
Smoking status								
Previous	0·80	0·68–0·94	0·75	0·63–0·91	0·97	0·66–1·43	1·05	0·52–2·13
Current	0·63	0·55–0·72	0·66	0·58–0·77	0·47	0·33–0·67	0·57	0·28–1·13
Quantity of tobacco smoked per day (g)[a]								
1–5	0·76	0·62–0·94	0·75	0·60–0·95	0·71	0·42–1·21	0·92	0·36–2·32
6–15	0·62	0·53–0·73	0·63	0·53–0·75	0·56	0·38–0·82	0·78	0·39–1·58
> 15	0·69	0·59–0·81	0·71	0·60–0·85	0·63	0·42–0·95	0·50	0·20–1·25
	$P_{trend} = 0·18$		$P_{trend} = 0·32$		$P_{trend} = 0·23$		$P_{trend} = 1·00$	
Duration of smoking (years)								
1–10	0·74	0·62–0·89	0·76	0·62–0·93	0·67	0·43–1·05	1·07	0·42–2·76
11–20	0·74	0·63–0·87	0·75	0·62–0·89	0·59	0·39–0·91	1·23	0·59–2·52
> 20	0·59	0·49–0·70	0·60	0·50–0·73	0·58	0·37–0·90	0·39	0·17–0·90
	$P_{trend} < 0·001$		$P_{trend} < 0·001$		$P_{trend} = 0·006$		$P_{trend} = 0·03$	
Accumulated quantity smoked (duration × quantity, g)								
1–499	0·82	0·71–0·93	0·82	0·71–0·96	0·69	0·49–0·97	1·19	0·64–2·18
500–999	0·55	0·46–0·66	0·56	0·46–0·68	0·61	0·40–0·94	0·17	0·04–0·72
> 999	0·38	0·28–0·52	0·41	0·29–0·58	0·28	0·11–0·68	0·22	0·03–1·62
	$P_{trend} = 0·15$		$P_{trend} = 0·25$		$P_{trend} = 0·34$		$P_{trend} = 0·84$	
Recency of smoking cessation (years)								
1–10	0·80	0·66–0·96	0·75	0·61–0·94	1·03	0·66–1·59	0·72	0·27–1·93
> 10	0·87	0·68–1·12	0·77	0·58–1·04	1·12	0·61–2·07	1·76	0·74–4·17
	$P_{trend} = 0·55$		$P_{trend} = 0·64$		$P_{trend} = 0·13$		$P_{trend} = 0·07$	

[a]Combined quantity from cigarette (one cigarette = 1 g), cigar (one cigar = 6 g) and pipe smoking.

quantity smoked (quantity smoked × duration of smoking) a decreasing risk trend for CMM, MIS and IMM was again observed, although the RR estimates for IMM were based on few cases.

The effect on MM/MIS incidence by the exclusive use of one type of tobacco product is shown in Table 3. Compared with those who had never used tobacco, pure cigarette smokers had an RR of 0·7 (0·6–0·8) of developing CMM, an RR of 0·7 (0·5–0·9) of developing MIS and an RR of 0·9 (0·5–1·6) of developing IMM. In the same setting pure pipe smokers were at a 0·6 (0·5–0·8) risk for CMM, a 0·4 (0·2–0·7) risk for MIS, and a 0·6 (0·2–1·7) risk for IMM. The analysis on pure cigar smoking was based on small numbers but cigar smoking did not appear to confer significant risk changes for CMM or MIS and the risk could not be estimated for IMM. Pure snuff using reduced the risk for CMM and MIS by 40% but had no detectable effect on IMM. The results on amount of pure cigarette tobacco smoked per day were very similar to those on combined smoking tobacco. The impact of the amount of pipe tobacco smoked per week and number of cigars smoked per day was hard to evaluate due to small numbers of MM/MIS in the exposure categories. Risk of CMM and MIS decreased with increasing duration of snuff using. The RR for CMM was 0·7 (0·5–0·9) for 1–29 years' duration and 0·5 (0·2–1·0) for ≥ 30 years' duration, while the risk for MIS did not reach statistical significance. The risk for MIS was not altered by duration of using snuff.

The risk for CMM was significantly increased in the overweight/obese group compared with the underweight/normal weight group (Table 4). There was no association between BMI and MIS, and the slightly increased risk for IMM was based on very few cases.

Biologically plausible interactions, mainly between age and tobacco exposure category, were tested when possible and did not reveal any modification of the main effects.

Discussion

With this large cohort of Swedish male construction workers we have shown consistent evidence of a decreased risk for CMM and MIS by tobacco smoking and snuff using. A BMI above the normal weight range conferred an increased risk for CMM but not for MIS or IMM.

Ultraviolet (UV) radiation is the only established risk factor for CMM/MIS. It is generally accepted that characteristics related to ethnicity, such as skin type and eye colour, number of atypical naevi and sunlight exposure have a strong impact on the risk of developing CMM and MIS.[9]

Tobacco smoke contains a number of carcinogenic compounds and has been shown to have an aetiological role in a

Table 3 Age-, body mass index-, birth cohort- and sunlight exposure-adjusted incidence rate ratios (RRs) and corresponding 95% confidence intervals (CIs) for developing melanoma according to the use of different tobacco products separately

	All melanoma combined		Cutaneous malignant melanoma		Melanoma *in situ*		Intraocular malignant melanoma	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Tobacco nonusers	1		1		1		1	
Pure cigarette smokers	0·69	0·61–0·79	0·69	0·59–0·80	0·67	0·49–0·94	0·86	0·45–1·62
Quantity of cigarette tobacco smoked daily (g)								
1–9	0·73	0·61–0·86	0·73	0·60–0·88	0·68	0·45–1·04	0·86	0·38–1·96
10–19	0·62	0·51–0·76	0·61	0·49–0·76	0·56	0·33–0·93	1·19	0·52–2·72
≥ 20	0·73	0·57–0·92	0·72	0·55–0·94	0·92	0·51–1·66	0·46	0·11–2·02
	$P_{trend} < 0·001$		$P_{trend} < 0·001$		$P_{trend} = 0·10$		$P_{trend} = 0·79$	
Pure pipe smokers	0·58	0·46–0·74	0·62	0·48–0·81	0·35	0·17–0·73	0·64	0·24–1·72
Pure cigar smokers	0·79	0·46–1·38	1·00	0·57–1·73	-		-	
Pure snuff users	0·65	0·52–0·82	0·63	0·48–0·81	0·64	0·36–1·14	1·14	0·43–3·07
Duration of snuff use (years)								
1–29	0·71	0·55–0·90	0·70	0·53–0·92	0·67	0·37–1·23	1·17	0·33–4·10
≥ 30	0·51	0·27–0·98	0·47	0·22–1·00	0·39	0·05–2·88	1·05	0·23–4·79
	$P_{trend} < 0·001$		$P_{trend} < 0·001$		$P_{trend} = 0·08$		$P_{trend} = 0·75$	
Mixed tobacco use[a]	0·71	0·62–0·81	0·71	0·61–0·82	0·75	0·55–1·05	0·57	0·28–1·16

[a]Cigarette smoking and snuff taking was the most common combination.

Table 4 Age-, body mass index (BMI)-, birth cohort-, sunlight exposure- and tobacco product usage-adjusted incidence rate ratios (RRs) and corresponding 95% confidence intervals (CIs) for developing melanoma according to different levels of BMI

	All melanoma combined		Cutaneous malignant melanoma		Melanoma *in situ*		Intraocular malignant melanoma	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI								
Underweight/normal	1		1		1		1	
Overweight/obese	1·27	1·14–1·42	1·34	1·19–1·52	0·95	0·72–1·25	1·22	0·72–2·07

number of malignancies.[28–30] Smoking also decreases cutaneous blood flow and has been demonstrated to depress immune responses.[31] However, the evidence for an association with CMM/MIS is contradictory. Most studies have been of case–control design and therefore might have been prone to bias and were limited by small sample sizes. Freedman *et al.*[18] found a decreased risk for melanoma in men who had ever smoked that was consistent in measurements of quantity smoked and duration of smoking. They also performed a review of epidemiological studies and found an indicated pattern of decreased risk for melanoma in tobacco smokers. A possible explanation to the apparently negative association with smoking could be its immune depressive effect that hypothetically would protect the melanocytes from the inflammatory reaction induced by UV radiation. An alternative explanation of this finding is the fact that smokers are less physically active than nonsmokers and therefore spend more time indoors.[32,33] Pipe smoking conferred a decreased risk for CMM/MIS/IMM in this study. There was no effect on CMM risk of cigar smoking and this association could not be evaluated for MIS or IMM as there were too few cases. Only three case–control studies have previously investigated the effect of pure pipe and cigar smoking on the development of CMM/MIS/IMM.[7,15,21] These studies showed no association with pipe or cigar smoking; they did, however, suffer from poor statistical precision.

Oral moist snuff is a form of smokeless tobacco primarily used in Sweden. It has been suggested that snuff may be involved in the aetiology of some cancers.[28,29] However, we failed to find any previous studies on the relationship between snuff and CMM/MIS or IMM. Our study provides novel evidence of a decreased risk for CMM and MIS in snuff users, which appears to be independent from the effect of tobacco smoking.

In this study, a BMI > 25 kg m^{-2} was associated with an increased risk for CMM but had no effect on MIS or IMM. This is supported by a few other studies and hormonal factors have been suggested as one possible explanation.[8,14,18,22]

The main strengths of this study are the large size, the long and meticulous follow up, and the prospective, detailed

collection of exposure information. There are also a few limitations to this study. We did not have direct information on the amount of occupational or recreational sunlight exposure. Almost all construction workers during this period were, however, in approximately the same socioeconomic class and the recreational tanning behaviour ought not to differ considerably among workers born close in time to each other. Therefore, the recreational sunlight exposure can, to a large extent, be dealt with by adjusting for birth cohort. The occupational sunlight exposure was adjusted for by creating a sun exposure matrix. Any remaining misclassification of sunlight exposure is most likely not to differentiate between tobacco users and nonusers and would therefore bias our results towards the null. The lack of assessment of the quality and completeness of MIS reporting in the SCR as well as the limited histological verification of IMM are also limitations to this study, and the results on MIS and IMM should therefore be interpreted with caution. There is, however, no reason to believe that reporting depends on smoking status and eventual bias would therefore also be nondifferential. We were unable to perform analyses on women in this cohort. In two previous studies the relationship between the BMI and CMM found in men could not be detected in women.[8,18] Neither could the male relationship to smoking be replicated in women in the article by Freedman *et al.*[18] Lastly, this cohort had a mean age of 34·2 years at entry and was followed for an average of 22·6 years. The cohort is therefore relatively young and some of the workers had not reached the mean age for melanoma diagnosis. This will not affect the studied association with tobacco but considerably more cases can be expected to accrue with longer follow up and thereby add more power to future analysis.

In conclusion, with this large cohort study we have presented evidence of a decreased risk for CMM and MIS in tobacco users and an increased risk for CMM related to obesity. The biological mechanisms behind these findings are unclear. Future studies might therefore include experimental parts to increase our understanding.

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