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Metabolic risk factors and skin cancer in the Metabolic Syndrome and Cancer Project (Me-Can)

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Summary

Background Little is known about the associations of metabolic aberrations with malignant melanoma (MM) and nonmelanoma skin cancer (NMSC).
Objectives To assess the associations between metabolic factors (both individually and combined) and the risk of skin cancer in the large prospective Metabolic Syndrome and Cancer Project (Me-Can).
Methods During a mean follow-up of 12 years of the Me-Can cohort, 1728 (41% women) incident MM, 230 (23% women) fatal MM and 1145 (33% women) NMSC were identified. Most NMSC cases (76%) were squamous cell carcinoma (SCC) (873, 33% women). Hazard ratios (HRs) were estimated by Cox proportional hazards regression for quintiles and standardized z-scores (with a mean of 0 and SD of 1) of body mass index (BMI), blood pressure, glucose, cholesterol, triglycerides and for a combined metabolic syndrome score. Risk estimates were corrected for random error in the measurements.
Results Blood pressure per unit increase of z-score was associated with an increased risk of incident MM cases in men and women [HR 1·17, 95% confidence interval (CI) 1·04–1·31 and HR 1·18, 95% CI 1·03–1·36, respectively] and fatal MM cases among women (HR 2·39, 95% CI 1·58–3·64). In men, all quintiles for BMI above the reference were associated with a higher risk of incident MM. In women, SCC NMSC risk increased across quintiles for glucose levels (P-trend 0·02) and there was a trend with triglyceride concentration (P-trend 0·09).
Conclusion These findings suggest that mechanisms linked to blood pressure may be involved in the pathogenesis of MM. SCC NMSC in women could be related to glucose and lipid metabolism.

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Skin cancer includes malignant melanoma (MM) and nonmelanoma skin cancer (NMSC). NMSC is a heterogeneous group, with the main histological subtypes being squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).[1] Skin cancer incidence, particularly NMSC, has been rising over the past years in most Western countries.[2–4] In Europe, the highest MM incidence rates are observed in the Scandinavian countries.[2] MM is frequently observed in young people and is thus economically relevant as a cause of death and productivity loss.[5] Because of increasing life expectancy in most developed

countries, risk factors for NMSC are also of interest, as 80% of the cases occur in people aged ≥ 60 years.[6] Exposure to ultraviolet (UV) radiation, particularly during childhood, is the major risk factor for skin cancer.[7] However, gender- and age-related differences in the localization of MM suggest that hormonal and lifestyle-related factors could also be involved in the disease pathogenesis.[8]

Evidence of the importance of metabolic alterations in the aetiology of skin cancer is emerging, although data from prospective investigations are sparse.[9] For MM, body mass index (BMI) has consistently been found to be associated with increased risk among men.[9–12] An association between high blood glucose levels and an increased risk of MM has been shown,[13] and an excess incidence of NMSC has been observed among patients with diabetes mellitus type 1[14] and among individuals with high blood pressure.[15]

The aim of this study was to assess the associations between metabolic factors (both individually and combined) and the risk of skin cancer in the large prospective Metabolic Syndrome and Cancer Project (Me-Can).

Material and methods

Study population

The Me-Can study has been described in detail previously.[16,17] In brief, data from seven longstanding cohorts in Austria (the Vorarlberg Health Monitoring and Prevention Programme), Norway (the Oslo Study I, the Norwegian Counties Study, the Cohort of Norway and the Age 40 programme) and Sweden (the Malmö Preventive Project and the Västerbotten Intervention Project) were pooled. All participating cohorts were set up as part of population-based surveillance/screening programmes for the prevention of chronic diseases such as cardiovascular disease and cancer,[16] and included at least one health examination. Blood concentrations of glucose, total cholesterol and triglycerides were quantified and information on smoking status recorded; anthropometric measurements were made in similar ways in each cohort, with participants wearing light indoor clothes and no shoes. For the present analysis, data of 578 700 persons collected between 1974 and 2005 were used. Incident cases of MM [International Classification of Diseases (ICD), seventh revision, ICD-7: 190] and NMSC (ICD-7: 191) were identified through linkages with the national cancer registries. ICD-O-2 codes 8051/3, 8070/3, 8071/3, 8072/3, 8074/3, 8075/3 and 8076/3 were used to identify SCC. In Norway, ICD-O-2 was applied from 1993 and MONTAC (Manual Of Tumor Nomenclature and Coding) before that date. Data on vital status were obtained from mortality registries. Causes of death were coded according to the Eurostat European shortlist for cause of death.[18] To reduce the possibility of reverse causation, follow-up started 1 year after the baseline examination. Thus, the analytical cohort comprised 541 254 subjects. Person-years under observation for each person were calculated until the date of diagnosis, migration or the date of death, whichever came first. Participants were censored for incident skin cancer by 31 December 2003 in Austria, 2005 in Norway and 2006 in Sweden, and for death from MM by 31 December 2003 in Austria, and 2004 in Norway and Sweden.

Statistical analysis

Cox proportional hazards regression models with age as the time variable were fitted to obtain hazard ratios (HRs) with 95% confidence intervals (CIs). Quintile cut points were determined for BMI, mid blood pressure [(systolic blood pressure + diastolic blood pressure)/2], glucose, cholesterol and triglyceride levels within the seven subcohorts, sex, and also for glucose, cholesterol and triglycerides in categories of fasting time (fasting: < 4, 4–8 and ≥ 8 h). The models were stratified for cohort (seven subcohorts) and for year of birth (five categories: ≤ 1929, 1930–9, 1940–9, 1950–9 and ≥ 1960) and adjusted for smoking status (four categories: never, former and current smokers, and unknown). Additional models were calculated adjusting for BMI and including all metabolic factors simultaneously. Test for trend was based on the Wald test for linear regression assigning the risk estimate of each quintile to the median exposure levels within the Me-Can cohort.

The variables BMI, mid blood pressure, glucose, cholesterol and triglycerides were standardized to a z-score variable with mean 0 and SD 1. The variables were standardized separately for the seven subcohorts, by sex and also for glucose, cholesterol and triglycerides by fasting time. Because glucose and triglycerides were skewed and had outliers, they were log-transformed before standardization. A metabolic syndrome score (MetS) was constructed by adding the individual z-scores and standardized separately for the seven subcohorts, sex and for fasting time. Risk estimates for MM, all NMSC, SCC NMSC and BCC NMSC were calculated. To explore potential differences by age stratified analyses in women by attained age (< 50 and ≥ 50 years) were performed.

We tested for interactions between the z-scores for the variables by applying likelihood ratio tests for the product term of MetS factors in the corresponding model. Two-sided P-values of 0·05 were considered statistically significant. Because of the small number of fatal MM, analyses for mortality in quintiles were performed for men and women combined. All calculations were carried out using the statistical software package SAS release 9.2 (SAS Institute, Cary, NC, U.S.A.) and R version 2.7.2 (http://www.r-project.org/) for random error calibration.

Correction of the measurement error

To account for the measurement error of the different exposures and their variation during follow-up, corrections have been made by calculation of the regression dilution ratio (RDR) and by applying the regression calibration method (RC).[19] In brief, based on the data of 133 820 subjects with repeated health examinations comprising 406 364 observations in the Me-Can cohort, calibrated values were calculated by linear mixed-effect models that considered age at

baseline, fasting time, smoking status, sex and time from baseline to repeated measurement as fixed effects and cohort as random effect.[20] Only repeated measurements with the same fasting time and from the same as the original subcohort with information on smoking status were used. Mean time since the baseline measurement was 6·9 (SD 3·9) years. Corrections of the HRs for RDR were obtained by exp [log (HR)/RDR]. The sex-specific RDR used in the analysis were in men and women, respectively: BMI (0·90, 0·90), blood pressure (0·52, 0·56), log blood glucose (0·28, 0·27), cholesterol (0·64, 0·66), log triglycerides (0·51, 0·50) and MetS score (0·68, 0·69).

A second correction method, RC, which also allows correction of random error of covariate measurements, was applied to models including *z*-scores of the metabolic variables and the MetS score. In RC, the exposures of interest were replaced by predicted values calculated by a regression model with age at baseline, fasting time, smoking status and time from baseline as fixed effects and cohort as random effect.[21]

Results

Among Me-Can participants with at least 1 year of follow-up 6 332 222 person-years were accrued for the current study. Mean age at baseline was 43·9 (SD 11·1) years for men and 44·1 (SD 12·3) years for women (Table 1). On average, participants were followed for 12·2 (SD 8·3) years. A total of 1728 (41% women) cases of MM and 1145 (33% women) NMSC, including 873 SCC (33% women) and 55 BCC (51% women) cases, were identified. Mean age at diagnosis was 57·4 (SD 12·3) years for MM and 68·6 (SD 11·3) years for NMSC cases. There were 230 MM deaths at a mean age of 61·8 (SD 11·7) years.

Malignant melanoma

Quintile analyses of individual metabolic factors in men (Table 2) showed that risk of incident MM was significantly increased in quintiles two to five of BMI and blood pressure, but no statistically significant linear trend across the quintiles

Table 1 Baseline characteristics of the Metabolic Syndrome and Cancer Project (Me-Can) cohort

	Men			Women		
	MM cases	NMSC cases	Total cohort	MM cases	NMSC cases	Total cohort
Subjects, n	1078	786	289 866	778	396	288 834
Age at baseline (years), mean (SD)	46·0 (10·1)	52·6 (12·4)	43·9 (11·1)	46·7 (12·1)	58·1 (14·1)	44·1 (12·3)
Cohort, n (%)						
Oslo (1972–73)	230 (21)	176 (22)	16 760 (6)	0 (0)	0 (0)	0 (0)
NCS (1974–83)	173 (16)	115 (15)	25 952 (9)	151 (19)	62 (16)	25 072 (9)
CONOR (1995–2003)	118 (11)	86 (11)	52 181 (18)	131 (17)	74 (19)	57 687 (20)
40-y (1994–99)	109 (10)	31 (4)	60 676 (21)	164 (21)	32 (8)	68 211 (23)
VHM&PP (1988–2002)	166 (15)	166 (21)	73 213 (25)	183 (24)	150 (38)	86 671 (30)
VIP (1985–2005)	65 (6)	21 (3)	38 843 (13)	68 (9)	14 (5)	40 669 (14)
MPP (1974–92)	217 (20)	191 (24)	22 241 (8)	81 (10)	64 (16)	10 524 (4)
Fasting time, n (%)						
< 4 h	510 (47)	342 (44)	120 510 (41)	356 (46)	133 (34)	122 319 (42)
4–8 h	103 (10)	57 (7)	30 769 (11)	91 (12)	35 (9)	26 802 (9)
> 8 h	465 (43)	387 (49)	138 587 (48)	331 (43)	228 (57)	139 713 (49)
BMI (kg m^{-2}), mean (SD)	25·4 (3·0)	25·3 (3·1)	25·7 (3·5)	24·9 (4·2)	25·2 (3·9)	24·9 (4·4)
Mid BP (mmHg), mean (SD)	109·8 (12·5)	112·0 (14·0)	106·9 (12·7)	105·3 (16·0)	110·1 (15·8)	101·8 (14·2)
Missing, n (%)	1 (0)	0 (0)	412 (0·1)	0 (0)	0 (0)	489 (0·2)
Glucose (mmol L^{-1}), median (IQR)	5·2 (4·7–5·7)	5·2 (4·7–5·8)	5·2 (4·7–5·7)	5·1 (4·6–5·7)	5·2 (4·7–5·8)	5·0 (4·6–5·5)
Missing, n (%)	2 (0)	1 (0)	420 (0·1)	1 (0)	1 (0)	359 (0·1)
Cholesterol (mmol L^{-1}), mean (SD)	5·9 (1·1)	6·0 (1·2)	5·8 (1·2)	5·7 (1·2)	6·3 (1·2)	5·6 (1·2)
Missing, n (%)	2 (0)	2 (0)	593 (0·2)	1 (0)	0 (0)	777 (0·3)
Triglycerides (mmol L^{-1}), median (IQR)	1·5 (1·1–2·2)	1·5 (1·1–2·2)	1·5 (1·1–2·3)	1·1 (0·8–1·5)	1·3 (0·9–1·9)	1·1 (0·8–1·6)
Missing, n (%)	23 (2)	8 (1)	7774 (3)	16 (2)	4 (1)	4533 (2)
Smoking status, n (%)						
Never	414 (38)	292 (37)	113 496 (39)	432 (56)	252 (64)	144 815 (50)
Former	351 (33)	217 (28)	86 086 (30)	197 (25)	55 (14)	72 600 (25)
Current	310 (29)	276 (35)	89 419 (31)	147 (19)	88 (22)	70 721 (25)
Missing	3 (0)	1 (0)	865 (0)	2 (0)	1 (0)	698 (0)

MM, malignant melanoma; NMSC, nonmelanoma skin cancer; Oslo, Oslo study I cohort; NCS, Norwegian County Study; CONOR, Cohort of Norway; 40-y, Age 40-programme; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme; VIP, Västerbotten Intervention Project; MPP, Malmö Preventive Project; BMI, body mass index; mid BP, mid blood pressure = [(systolic blood pressure + diastolic blood pressure)/2]; IQR, interquartile range.

Table 2 Hazard ratios (HRs) with 95% confidence intervals (CIs) of incident (stratified by sex) and fatal malignant melanoma (MM) by metabolic parameter in quintiles

	MM incidence						MM death	
	Men			Women			All	
Quintile	Mean (SD)	Cases (n)	HR (95% CI)[a]	Mean (SD)	Cases (n)	HR (95% CI)[a]	Cases (n)	HR (95% CI)[a]
BMI (kg m^{-2})								
1	21·5 (1·3)	151	1 (referent)	20·0 (1·2)	112	1 (referent)	34	1 (referent)
2	23·8 (0·8)	213	1·34 (1·07–1·70)	22·3 (0·8)	167	1·42 (1·09–1·86)	49	1·36 (0·84–2·21)
3	25·4 (0·8)	229	1·39 (1·11–1·75)	24·1 (0·8)	150	1·18 (0·90–1·56)	50	1·31 (0·81–2·13)
4	27·1 (0·9)	218	1·29 (1·03–1·63)	26·4 (1·0)	134	0·99 (0·74–1·32)	40	1·00 (0·60–1·67)
5	30·8 (2·8)	204	1·28 (1·01–1·62)	31·7 (3·8)	150	1·13 (0·85–1·49)	57	1·61 (1·00–2·61)
P-trend			0·402			0·851		0·290
Mid blood pressure (mmHg)								
1	91·1 (4·7)	124	1 (referent)	84·3 (4·4)	112	1 (referent)	26	1 (referent)
2	100·0 (2·2)	184	1·72 (1·12–2·65)	93·1 (2·6)	115	0·71 (0·44–1·13)	38	1·55 (0·62–3·89)
3	105·1 (2·4)	224	2·01 (1·33–3·05)	99·3 (2·5)	138	1·01 (0·64–1·59)	49	2·19 (0·91–5·27)
4	111·7 (2·8)	234	2·13 (1·41–3·23)	106·6 (3·5)	147	0·78 (0·50–1·24)	54	2·36 (0·99–5·64)
5	125·5 (9·5)	248	2·02 (1·33–3·07)	122·6 (11·0)	201	1·19 (0·76–1·87)	63	2·89 (1·21–6·91)
P-trend			0·125			0·421		0·005
Glucose (mmol L^{-1})								
1	4·2 (0·5)	195	1 (referent)	4·1 (0·5)	133	1 (referent)	35	1 (referent)
2	4·8 (0·3)	218	1·43 (0·72–2·84)	4·6 (0·3)	130	1·03 (0·42–2·51)	43	2·15 (0·43–10·75)
3	5·1 (0·3)	179	0·78 (0·38–1·59)	5·0 (0·3)	141	0·68 (0·28–1·64)	41	1·30 (0·26–6·64)
4	5·5 (0·3)	216	0·85 (0·43–1·70)	5·3 (0·3)	134	0·87 (0·36–2·12)	54	2·94 (0·63–13·70)
5	6·9 (2·0)	205	0·81 (0·40–1·63)	6·5 (1·7)	174	1·33 (0·57–3·10)	57	3·28 (0·71–15·16)
P-trend			0·431			0·363		0·050
Cholesterol (mmol L^{-1})								
1	4·3 (0·5)	193	1 (referent)	4·2 (0·4)	141	1 (referent)	48	1 (referent)
2	5·1 (0·3)	210	0·96 (0·71–1·30)	4·9 (0·2)	142	0·92 (0·64–1·31)	41	0·65 (0·34–1·22)
3	5·7 (0·3)	200	0·84 (0·61–1·14)	5·5 (0·3)	122	0·65 (0·45–0·95)	43	0·64 (0·34–1·21)
4	6·3 (0·3)	195	0·80 (0·59–1·10)	6·1 (0·3)	161	0·90 (0·63–1·28)	46	0·68 (0·36–1·28)
5	7·4 (0·8)	215	0·88 (0·65–1·20)	7·3 (0·9)	146	0·67 (0·46–0·98)	52	0·73 (0·39–1·36)
P-trend			0·199			0·192		0·438
Triglycerides (mmol L^{-1})								
1	0·80 (0·18)	185	1 (referent)	0·62 (0·11)	123	1 (referent)	39	1 (referent)
2	1·17 (0·20)	196	1·05 (0·71–1·56)	0·87 (0·08)	166	1·26 (0·79–2·01)	50	1·38 (0·60–3·16)
3	1·54 (0·26)	211	1·19 (0·81–1·75)	1·12 (0·11)	131	0·81 (0·49–1·32)	48	1·21 (0·52–2·81)
4	2·07 (0·37)	196	1·06 (0·71–1·57)	1·47 (0·17)	155	1·08 (0·67–1·74)	47	1·17 (0·50–2·73)
5	3·71 (1·71)	207	1·26 (0·85–1·87)	2·52 (1·07)	123	0·65 (0·39–1·09)	45	1·12 (0·47–2·65)
P-trend			0·097			0·194		0·879

BMI, body mass index. [a]Stratified for centre and year of birth (categories), and adjusted for age at recruitment (years), smoking status (never, former, current, unknown), and corrected for measurement error by regression dilution ratio.

was observed (P-trend for the RDR corrected values 0·40 and 0·13, respectively). One unit of increase in blood pressure was significantly associated with an increased risk of incident MM (per 1 increment of z-score: HR 1·17; 95% CI 1·04–1·31), also after adjustment for the other metabolic factors (HR 1·22; 95% CI 1·08–1·39) (Table 3). As observed in men, one unit increase in the blood pressure z-score was associated with an increased risk of incident MM (HR 1·18, 95% CI 1·03–1·36) in women. After adjustment for other metabolic factors the statistically significant association persisted (HR 1·27, 95% CI 1·09–1·48). In women only, the highest quintile of cholesterol concentrations was associated with a decreased risk of incident MM, but without a linear trend (HR 0·67; 95% CI 0·46–0·98; P-trend 0·19) and a unit increase in the z-score for cholesterol was not significantly associated with MM risk.

For MM mortality across quintiles of metabolic variables, we observed a higher risk with increasing blood pressure and glucose levels (P for trend 0·005 and 0·05, respectively) (Table 2). In analyses per unit z-score, blood pressure was associated with high MM mortality in women (HR 2·39; 95% CI 1·58–3·64), but not in men (HR 1·28; 95% CI 0·96–1·69) (Table 3).

Nonmelanoma skin cancer

The HRs and 95% CIs for all NMSC and SCC NMSC for metabolic factors in quintiles and NMSC subgroups for a one unit

Table 3 Hazard ratios (HRs) with 95% confidence intervals (CIs) of incident and fatal malignant melanoma (MM) by metabolic parameter (*z*-score) by sex

	Men		Women	
	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[a]	HR (95% CI)[b]
MM incidence				
n	1015		713	
BMI	1·05 (0·98–1·13)	1·01 (0·92–1·11)	0·98 (0·90–1·07)	0·96 (0·86–1·08)
Mid blood pressure	1·17 (1·04–1·31)	1·22 (1·08–1·39)	1·18 (1·03–1·36)	1·27 (1·09–1·48)
Glucose	0·82 (0·65–1·03)	0·78 (0·61–0·99)	0·97 (0·74–1·28)	0·92 (0·68–1·24)
Cholesterol	0·92 (0·83–1·02)	0·87 (0·78–0·98)	0·88 (0·78–1·00)	0·92 (0·80–1·05)
Triglycerides	1·07 (0·94–1·21)	1·11 (0·95–1·29)	0·86 (0·74–1·01)	0·87 (0·72–1·06)
MetS score	1·03 (0·93–1·14)	–	0·95 (0·84–1·07)	–
MM mortality				
n	177		53	
BMI	1·17 (0·99–1·38)	1·04 (0·84–1·29)	1·07 (0·79–1·45)	0·85 (0·58–1·25)
Mid blood pressure	1·28 (0·96–1·69)	1·18 (0·86–1·61)	2·39 (1·58–3·64)	2·50 (1·58–3·96)
Glucose	1·31 (0·77–2·23)	1·19 (0·68–2·08)	1·27 (0·48–3·35)	1·05 (0·37–2·99)
Cholesterol	0·79 (0·61–1·01)	0·72 (0·54–0·96)	1·38 (0·93–2·03)	1·36 (0·87–2·13)
Triglycerides	1·18 (0·88–1·59)	1·18 (0·82–1·69)	1·03 (0·59–1·80)	0·72 (0·36–1·41)
MetS score	1·17 (0·92–1·49)	–	1·59 (1·06–2·37)	–

BMI, body mass index; MetS, metabolic syndrome. [a]Stratified for centre and year of birth (categories), and adjusted for age at recruitment (years), smoking status (never, former, current, unknown), and corrected for measurement error by regression dilution ratio. [b]Stratified by centre and year of birth (categories), adjusted for age at recruitment (years), smoking status (never, former, current, unknown), BMI, blood pressure, total cholesterol, and triglyceride and corrected for measurement error by regression calibration.

increase in the z-scores by sex are presented in Tables 4 and 5, respectively. In men, only triglycerides by z-scores were significantly positively associated in the mutually adjusted model with SCC risk (HR 1·22; 95% CI 1·00–1·50). In women, the risk of SCC was significantly positively associated with high blood glucose concentrations by quintiles (5th vs. 1st quintile: RDR corrected, adjusted HR 6·37, 95% CI 1·40–29·03, P-trend 0·015), but the increase in risk associated with 1 unit of glucose z-score was not significant. Analyses by z-score revealed an inverse association for BMI in women (HR 0·86; 95% CI 0·74–0·99). Analyses limited to BCC were based on very small numbers and none of the associations reached statistical significance. For both MM and NMSC, results were similar in subgroups of attained age (< 50/≥ 50 years) (data not shown).

Discussion

In this prospective investigation, elevations in blood pressure were positively associated with increased risk of incident MM in both men and women and increased risk of fatal MM in women. High BMI was associated with an increased risk of incident MM in men for all quintiles above the first. For SCC NMSC, we found an inverse association with BMI z-score and a significant positive association with glucose quintiles and a trend for triglycerides in women.

The major strengths of our study are its prospective design, large size and standardized information of measured exposure factors which minimizes bias due to selection, recall and reverse causation. The follow-up for cancer occurrence among cohort members was ascertained through linkages with nation-wide, high-quality registers in Austria, Norway and Sweden.[22–24] We applied models using quintiles and z-scores of metabolic factors to assess the association between MetS and skin cancer risk.

The limitations of our study concern the lack of data on sun exposure, the major risk factor for skin cancer. However, for MM and SCC (the predominant NMSC in our data), the effect of sunburns during early childhood may be the most relevant exposure,[7,25] and this is unlikely to be strongly associated with the metabolic variables measured in adulthood. In addition, the role of UV radiation independent of the vitamin D-mediated protective effects against skin cancer is not completely understood.[26] The reporting of NMSC is not as rigorous as that for other cancer sites, particularly not for the most frequent, often indolent BCC. For the present analyses, data on BCC were only available in Sweden and Austria, the number of cases was small and risk estimates unstable and should be interpreted with caution.

The most consistent finding in our study is the positive association of blood pressure with the risk of incident MM in both men and women, and fatal MM among women. To date, only two very small studies including about 50 MM and 110 NMSC cases have reported on the association of skin cancer with elevated blood pressure.[15,27] In the first study from Sweden, no association between measured hypertension and risk of MM in men was observed.[15] In the second, the incidence of both MM and NMSC among hypertensive patients in Finland was similar to that expected in Finland.[27] However, for other cancers, associations with hypertension have been

Table 4 Hazard ratios (HRs) with 95% confidence intervals (CIs) of all nonmelanoma skin cancer (NMSC) and squamous cell carcinoma (SCC) by metabolic parameter in quintiles stratified for sex

	NMSC[a]						SCC			
	Men			Women			Men		Women	
Quintile	Mean (SD)	Cases (n)	HR (95% CI)[b]	Mean (SD)	Cases (n)	HR (95% CI)[b]	Cases (n)	HR (95% CI)[b]	Cases (n)	HR (95% CI)[b]
BMI (kg m^{-2})										
1	21·5 (1·3)	123	1 (referent)	20·0 (1·2)	61	1 (referent)	97	1 (referent)	44	1 (referent)
2	23·8 (0·8)	162	1·21 (0·93–1·58)	22·3 (0·8)	73	0·92 (0·62–1·36)	123	1·12 (0·84–1·51)	50	0·90 (0·57–1·42)
3	25·4 (0·8)	182	1·22 (0·94–1·58)	24·1 (0·8)	63	0·62 (0·42–0·93)	142	1·17 (0·87–1·56)	49	0·65 (0·41–1·03)
4	27·1 (0·9)	166	1·05 (0·81–1·37)	26·4 (1·0)	107	0·84 (0·58–1·21)	127	0·97 (0·72–1·30)	74	0·79 (0·51–1·21)
5	30·8 (2·8)	152	1·00 (0·77–1·31)	31·7 (3·8)	91	0·69 (0·48–1·01)	98	0·78 (0·57–1·06)	69	0·71 (0·46–1·10)
P-trend			0·672			0·234		0·133		0·397
Mid blood pressure (mmHg)										
1	91·1 (4·7)	89	1 (referent)	84·3 (4·4)	42	1 (referent)	73	1 (referent)	27	1 (referent)
2	100·0 (2·2)	127	1·37 (0·82–2·30)	93·1 (2·6)	48	0·70 (0·32–1·52)	98	1·24 (0·70–2·21)	35	0·74 (0·30–1·84)
3	105·1 (2·4)	158	1·50 (0·91–2·47)	99·3 (2·5)	48	0·55 (0·25–1·21)	115	1·19 (0·68–2·07)	36	0·61 (0·24–1·52)
4	111·7 (2·8)	184	1·54 (0·95–2·51)	106·6 (3·5)	93	0·69 (0·34–1·42)	135	1·19 (0·69–2·05)	62	0·57 (0·24–1·34)
5	125·5 (9·5)	227	1·43 (0·88–2·30)	122·6 (11·0)	165	0·80 (0·40–1·61)	166	1·04 (0·61–1·78)	126	0·74 (0·33–1·69)
P-trend			0·214			0·660		0·972		0·343
Glucose (mmol L^{-1})										
1	4·2 (0·5)	161	1 (referent)	4·1 (0·5)	47	1 (referent)	123	1 (referent)	31	1 (referent)
2	4·8 (0·3)	126	0·43 (0·18–0·99)	4·6 (0·3)	56	2·73 (0·63–11·86)	86	0·31 (0·12–0·83)	44	3·62 (0·66–19·80)
3	5·1 (0·3)	155	0·98 (0·44–2·18)	5·0 (0·3)	86	3·68 (0·94–14·41)	111	0·84 (0·33–2·11)	60	3·73 (0·75–18·56)
4	5·5 (0·3)	174	0·76 (0·35–1·65)	5·3 (0·3)	78	3·21 (0·80–12·91)	132	0·77 (0·32–1·85)	55	3·18 (0·62–12·26)
5	6·9 (2·0)	168	0·57 (0·26–1·26)	6·5 (1·7)	128	5·37 (1·46–19·71)	134	0·64 (0·26–1·55)	95	6·37 (1·40–29·03)
P-trend			0·485			0·013		0·686		0·015
Cholesterol (mmol L^{-1})										
1	4·3 (0·5)	132	1 (referent)	4·2 (0·4)	33	1 (referent)	97	1 (referent)	21	1 (referent)
2	5·1 (0·3)	151	0·83 (0·57–1·20)	4·9 (0·2)	59	1·59 (0·81–3·11)	105	0·76 (0·50–1·17)	38	1·62 (0·72–3·64)
3	5·7 (0·3)	155	0·74 (0·51–1·07)	5·5 (0·3)	65	1·22 (0·63–2·37)	118	0·77 (0·51–1·17)	51	1·52 (0·70–3·31)
4	6·3 (0·3)	172	0·78 (0·54–1·12)	6·1 (0·3)	98	1·49 (0·79–2·81)	131	0·82 (0·54–1·24)	70	1·53 (0·71–3·27)
5	7·4 (0·8)	173	0·73 (0·51–1·05)	7·3 (0·9)	141	1·47 (0·79–2·74)	134	0·78 (0·51–1·17)	106	1·66 (0·79–3·49)
P-trend			0·095			0·352		0·326		0·188
Triglycerides (mmol L^{-1})										
1	0·80 (0·18)	131	1 (referent)	0·62 (0·11)	36	1 (referent)	94	1 (referent)	25	1 (referent)
2	1·17 (0·20)	167	1·26 (0·80–1·98)	0·87 (0·08)	66	1·48 (0·64–3·40)	129	1·46 (0·87–2·45)	46	1·55 (0·58–4·10)
3	1·54 (0·26)	144	0·84 (0·53–1·35)	1·12 (0·11)	72	1·32 (0·58–2·98)	106	0·90 (0·52–1·56)	54	1·33 (0·51–3·45)
4	2·07 (0·37)	168	1·21 (0·77–1·90)	1·47 (0·17)	89	1·46 (0·66–3·24)	134	1·47 (0·87–2·46)	64	1·31 (0·51–3·37)
5	3·71 (1·71)	167	1·32 (0·83–2·07)	2·52 (1·07)	129	2·14 (0·99–4·63)	120	1·42 (0·84–2·41)	95	1·99 (0·80–4·93)
P-trend			0·338			0·018		0·415		0·087

BMI, body mass index. [a]81 with other NMSC, and for 54 cases no morphology was available. [b]Stratified for centre and year of birth (categories), and adjusted for age at recruitment (years), smoking status (never, former, current, unknown), BMI in quintiles and corrected for measurement error by regression dilution ratio.

found.[28,29] Hypertension and cancer aetiology could share biological mechanisms. Examples include antiapoptotic effects involved in the growth of vascular smooth muscle cells and mitogenic effect of neurohormones such as angiotensin II.[30] Another potential shared mechanism may be related to decreased oxygen supply and increased vascular endothelial growth factor (VEGF) receptor production. Experimental research has shown that low oxygen supply in the melanocyte microenvironment stimulates oncogenic transformation.[31] Tumour hypoxia is associated with increased synthesis of proangiogenic factors such as VEGF receptor[32] and recently it has been shown that VEGF is involved in the initiation of skin cancers in mice.[33] Preliminary findings from animal experiments also indicate that impaired VEGF signalling could be related to hypertension.[34] Alternatively, the association of blood pressure with risk of both MM and NMSC (in men) could reflect confounding by some unmeasured factor.

Our observation that obesity is associated with the risk of incident MM among men is in line with a previous meta-analysis including seven prospective studies reporting increased risk of MM among men but not among women.[10,11] Several additional large prospective studies from Europe and the

Table 5 Hazard ratios (HRs) with 95% confidence intervals (CIs) of all nonmelanoma skin cancers (NMSC), squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) by metabolic parameter (z-score) stratified by sex

	Men		Women	
	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[a]	HR (95% CI)[b]
NMSC[c]				
n	785		395	
BMI	0·98 (0·90–1·06)	0·91 (0·82–1·01)	0·87 (0·77–0·98)	0·79 (0·67–0·92)
Mid blood pressure	1·17 (1·03–1·34)	1·19 (1·04–1·37)	0·97 (0·80–1·17)	0·96 (0·79–1·17)
Glucose	0·93 (0·72–1·19)	0·93 (0·72–1·20)	1·29 (0·93–1·79)	1·31 (0·92–1·86)
Cholesterol	0·90 (0·80–1·01)	0·84 (0·73–0·96)	1·12 (0·96–1·30)	1·10 (0·93–1·30)
Triglycerides	1·06 (0·92–1·23)	1·16 (0·97–1·39)	1·15 (0·93–1·41)	1·14 (0·88–1·47)
MetS score	1·01 (0·90–1·14)	–	1·05 (0·90–1·24)	–
SCC				
n	586		286	
BMI	0·91 (0·82–1·00)	0·84 (0·74–0·94)	0·86 (0·74–0·99)	0·78 (0·65–0·93)
Mid blood pressure	1·09 (0·93–1·26)	1·11 (0·95–1·31)	0·96 (0·77–1·19)	0·95 (0·76–1·19)
Glucose	0·97 (0·73–1·29)	1·01 (0·75–1·34)	1·37 (0·95–1·98)	1·41 (0·95–2·09)
Cholesterol	0·95 (0·83–1·08)	0·89 (0·76–1·03)	1·17 (0·99–1·39)	1·16 (0·96–1·41)
Triglycerides	1·10 (0·93–1·30)	1·22 (1·00–1·50)	1·12 (0·88–1·43)	1·08 (0·80–1·45)
MetS score	0·99 (0·87–1·13)	–	1·07 (0·89–1·28)	–
BCC				
n	27		28	
BMI	0·87 (0·55–1·38)	0·55 (0·30–1·02)	0·93 (0·60–1·44)	1·06 (0·59–1·88)
Mid blood pressure	1·53 (0·80–2·93)	1·42 (0·67–3·03)	0·62 (0·30–1·29)	0·54 (0·24–1·22)
Glucose	1·03 (0·28–3·88)	1·14 (0·29–4·43)	1·12 (0·32–3·96)	1·43 (0·36–5·69)
Cholesterol	1·19 (0·66–2·14)	0·83 (0·41–1·71)	1·38 (0·82–2·31)	1·70 (0·97–3·00)
Triglycerides	1·69 (0·78–3·65)	2·02 (0·79–5·20)	1·06 (0·48–2·33)	0·86 (0·32–2·28)
MetS score	1·19 (0·64–2·23)	–	1·03 (0·56–1·88)	–

BMI, body mass index. MetS, metabolic syndrome. [a]Stratified for centre and year of birth (categories), and adjusted for age at recruitment (years), smoking status (never, former, current, unknown), and corrected for measurement error by regression dilution ratio. [b]Stratified for centre and year of birth (categories), and adjusted for age at recruitment (years), smoking status (never, former, current, unknown), BMI, blood pressure, total cholesterol, and triglyceride and corrected for measurement error by regression calibration. [c]81 with other NMSC, and for 54 cases no morphology was available.

U.S.A., however, showed no association between increasing BMI and MM.[12,35–37] In men, obesity could be related to differences in sun exposure according to social class or social behaviour among obese male and female subjects.[11] Differences among genders could be related to sunbathing and sun protection. In addition, hormonal factors may contribute to sex differences in MM risk.[38] In some studies in women, a potential effect modification of the association of MM with BMI by age was suggested.[39] However, in our data, risk estimates were similar in analyses stratified by attained age.

A potential mechanism underlying the association of MM with BMI may involve an increase in leptin concentrations, as obesity is associated with the development of leptin resistance and increased concentrations of this adipokine in the circulation. Experimental studies have shown that leptin can promote melanoma tumour growth.[40] In an age- and gender-matched case–control study, blood leptin concentrations were positively associated with melanoma, independently of BMI.[41] For SCC NMSC, there was an inverse association with the BMI z-score, but not in analysis by quintiles and it could be a chance finding. For BCC NMSC, only a few studies, with mixed results, exist.[42–44] In the literature, no differential associations for BCC between men and women have been reported. The absence of statistical significance of a linear trend for BMI could be related to differences in the statistical covariance related to social position and behaviour. Our findings could be by chance due to the small numbers, and need to be replicated in larger studies.

The lack of association of glucose concentrations with the risk of incident MM in either men or women in our data is in line with some previous reports.[45,46] For SCC NMSC, a positive association with glucose was observed only in women, similar to the results of a case–control study.[47] A registry-based study found an increased risk of NMSC in patients (both men and women) with type 1 diabetes mellitus,[14] although no increased risk in patients with type 2 diabetes was reported.[46] A different distribution of the morphological subtypes (SCC and BCC) and the severity of glucose alterations in type 1 and type 2 diabetes could explain some of the inconsistency in the results of the few published studies so far.

In our study, there was a trend for a positive association of triglycerides with the risk of SCC NMSC among women. We found no evidence for an association between cholesterol and skin cancer risk. Indirect evidence that fat metabolism is associated in the pathogenesis of NMSC comes from a study on

dietary fat intake, showing that total fat intake is positively associated with risk of NMSC among persons with a history of SCC of the skin.[48] Triglycerides were also associated with other cancer sites.[49,50] It is open to speculation whether or not the altered lipid metabolism is related to an infectious component in the pathomechanism, as human papilloma virus infections are associated with NMSC.[1,51]

In conclusion, the results from this large prospective study suggest that elevated blood pressure may be associated with an increased risk of incident and fatal MM. Further research is necessary to understand the potential mechanisms of such an association. The role of metabolic factors in NMSC is unclear, although elevated glucose and triglyceride concentrations may be associated with increased risk for this cancer type in women.

What's already known about the topic?

- High body mass index is associated with increased risk of malignant melanoma.
- High blood glucose levels are associated with increased risk of malignant melanoma.

What does this study add?

- Elevated blood pressure is associated with increased risk of incident and fatal malignant melanoma.
- In women, elevated glucose and triglyceride concentrations may be associated with increased risk for nonmelanoma skin cancer.

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