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Anthropometric factors and cutaneous melanoma: Prospective data from the population-based Janus Cohort

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The aim of the present study was to prospectively examine risk of cutaneous melanoma (CM) according to measured anthropometric factors, adjusted for exposure to ultraviolet radiation (UVR), in a large population-based cohort in Norway. The Janus Cohort, including 292,851 Norwegians recruited 1972–2003, was linked to the Cancer Registry of Norway and followed for CM through 2014. Cox regression was used to estimate hazard ratios (HRs) of CM with 95% confidence intervals (CIs). Restricted cubic splines were incorporated into the Cox models to assess possible non-linear relationships. All analyses were adjusted for attained age, indicators of UVR exposure, education, and smoking status. During a mean follow-up of 27 years, 3,000 incident CM cases were identified. In men, CM risk was positively associated with body mass index, body surface area (BSA), height and weight (all $p_{\text{trends}} < 0.001$), and the exposure-response curves indicated an exponential increase in risk for all anthropometric factors. Weight loss of more than 2 kg in men was associated with a 53% lower risk (HR 0.47, 95% CI: 0.39, 0.57). In women, CM risk increased with increasing BSA ($p_{\text{trend}} = 0.002$) and height ($p_{\text{trend}} < 0.001$). The shape of the height-CM risk curve indicated an exponential increase. Our study suggests that large body size, in general, is a CM risk factor in men, and is the first to report that weight loss may reduce the risk of CM among men.

The incidence rate of cutaneous melanoma (CM) has been increasing steeply during the past three decades,¹ and presents a major burden in fair-skinned populations worldwide.² CM is the third most common cancer in Europe after cancers of the colon/rectum and lung.³ Exposure to ultraviolet radiation (UVR) is recognized as the most important risk factor for CM.⁴ Further, pigmentation characteristics such as nevi, hair and eye color, and the skin's sensitivity to sunburns, greatly modify an individual's response to UVR exposure.⁵

Anthropometric factors such as high body mass index (BMI), large body surface area (BSA) and tall stature, have

all been associated with increased CM risk.^{6,7} In previous population-based large cohort studies, higher CM risk has been reported with increasing pre-diagnostic BSA and height in both genders,^{7,8} while for BMI a positive association has only been observed in men.^{7,9} The major strengths of these studies were the large numbers of incident CM cases and the pre-diagnostic measurement of height and weight. Other cohort studies investigated CM risk in both genders with respect to self-reported height and weight at baseline, and did not detect an association with BMI after adjustment for sun exposure and phenotype.^{10,11}

Mixed evidence has been provided on the associations between anthropometric factors and CM risk in case-control studies that relied on self-reported height and weight, but had detailed information on UVR exposure and pigmentation characteristics. Two studies have reported a positive association between BMI and CM risk in men,^{12,13} whereas another study found no such association.¹⁴ A pooled analysis of eight case-control studies in women found a positive association between CM risk and height and weight, but did not detect any associations with BMI or BSA.¹⁵ The most recent meta-analysis of obesity and CM risk found a moderate positive association between BMI and CM risk in men, but no association in women.¹⁶ The pooled effect estimates were similar for overweight and obese men, and the authors highlighted the need for further investigation with non-linear models to

Key words: body mass index, body surface area, height, weight change, cutaneous melanoma

Additional Supporting Information may be found in the online version of this article.

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What's new?

Anthropometric factors, such as height and weight, affect melanoma risk, according to new results. These authors looked at data from a large Norwegian cohort, including 3000 cases of cutaneous melanoma. They found that body mass index, body surface area, weight, and height all influence CM risk in males, with an exponential increase for all factors. In women, only height and body surface area correlated with cancer risk – possibly because women with higher weight and BMI sunbathe less. They further showed that men who reduced their weight by 2 kg or more also lowered their melanoma risk.

assess the shape of the exposure-response curve for BMI and CM risk. The lack of an association in women has been attributed to uncontrolled confounding by differences in sun seeking behavior between normal weight and obese women^{16,17}; this underscores the importance of adjustment for behavioral factors such as sunburns, sunbathing and solarium use.

The overall aim of the present study was to prospectively examine CM risk adjusted for UVR indicators, according to measured BMI, BSA, height, weight and weight change, in a large population-based cohort of Norwegian men and women. Further, we aimed to assess possible non-linear relationships between these anthropometric factors and CM risk, and to assess CM risk by anatomical site and by histological subtype.

Methods**Study population and study design**

The Janus Serum Bank Cohort (hereafter termed the Janus Cohort) is a population-based biobank for prospective cancer studies containing serum samples and data from health examinations, including measured anthropometry and questionnaire data from 292,851 Norwegians who participated in the following five surveys between 1972 and 2003. Detailed descriptions of the Janus Cohort, its data and establishment, have been published previously.¹⁸

1. The Oslo Study I, invited men aged 20–49 residing in Oslo aged 20–49 years during 1972–1973.
2. The Norwegian Counties Study was a three-wave survey (1974–1978, 1977–1983 and 1985–1988), inviting men and women aged 20–49 years residing in the counties Finnmark, Oppland and Sogn og Fjordane.
3. The Oslo Age 40 Program invited men and women aged 40 residing in Oslo during 1981–1999.
4. The National Age 40 Program triennially invited all men and women aged 40–42 years in all Norwegian counties during 1985–1999.
5. The TROFINN Health Study invited all men and women aged 30–75 years residing in the counties Troms and Finnmark during 2001–2003.

The present study is based on a comprehensive research file created through linkage of measured anthropometric and questionnaire data from the Janus Cohort to individual information on education, occupation, cancer diagnoses, vital

status and cause of death, and to group level information on ambient UVR data and sun tanning habits. Details of the data sources and linkages are available in the published study protocol.¹⁹

Legal and ethical approvals were obtained from the Norwegian Data Inspectorate, the Regional Committee for Medical Research Ethics, and the Norwegian Directorate of Health.

Assessment of exposures

In the Janus Cohort, baseline measurements of height (to the nearest 1 cm) and weight (to the nearest 0.5 kg) were obtained by trained staff according to a standardized protocol. BMI was calculated as kg/m²; BSA (m²) was calculated using the DuBois and DuBois' equation (weight^{0.4253} × height^{0.7253} × 0.007184)²⁰; and weight change was calculated by subtracting the 1985–88 weight measure from the 1974–78 measure (median time between the weight measurements was 10 years). BSA, height and weight were categorized according to sex-specific quintiles, and BMI according to the World Health Organization's (WHO) BMI classification using the additional cut-points for normal range and overweight as recommended by the WHO Expert Consultation: underweight (<18.5 kg/m²), normal weight 1 (18.5–22.9 kg/m²), normal weight 2 (23.0–24.9 kg/m²), overweight 1 (25.0–27.4 kg/m²), overweight 2 (27.5–29.9 kg/m²) and obese (≥30.0 kg/m²).²¹ Weight change was categorized as <–2.0 kg, –2.0 to 2.0 kg, and >2.0 kg. The questions about smoking and physical activity were worded differently in each survey and were harmonized into the following categories for physical activity: inactive, low, medium, high, unknown; and for smoking status: current, former, never, unknown (see Supporting Information Material for physical activity and Hjerkind *et al.*¹⁸ for smoking).

Occupation at baseline (indoor, mixed, outdoor, unknown) and highest attained educational level at baseline (none, compulsory, upper secondary, college/university, unknown) were obtained by linkage to Statistics Norway using the 11-digit personal identification number (PIN) assigned to Norwegian citizens. The categorization of occupation followed Alfonso *et al.*²² who used these categories as proxies for occupational sun exposure.

Ambient UVR exposure was based on region-specific cumulated doses of ultraviolet-B (UVB) radiation between 1972 and 1991 (when 97.5% of the Janus Cohort was

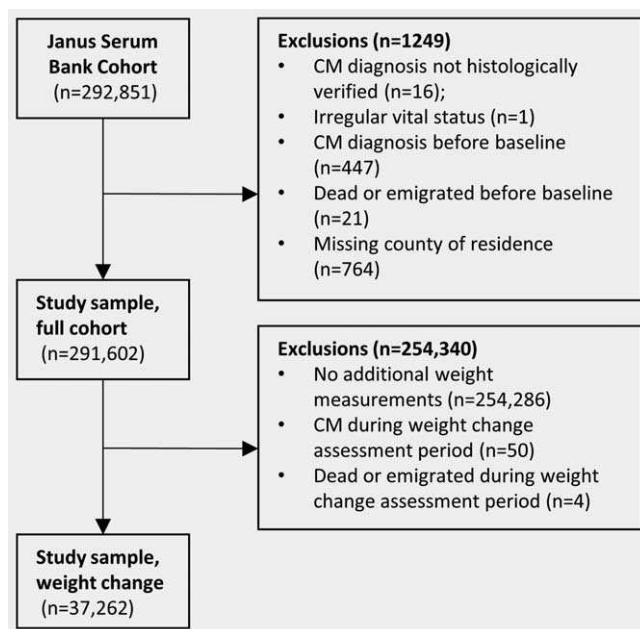


Figure 1. Overview of study samples and exclusions.

recruited), derived from reconstructed measurements and modelled values as described by Medhaug *et al.*²³ UVR exposure estimates were then linked to region of residence at baseline. Cumulative UVB doses were categorized as north, mid, southwest, southeast inland, southeast coast; decreasing doses were seen from north to south.

Data on the annual mean number of sunburns, sunbathing vacations, and solarium sessions (women only) from the Norwegian Women and Cancer study (NOWAC),^{19,24} were linked to the Janus Cohort on a group-level, based on combinations of age, county and time period. The rationale for conducting this group-level data linkage between the NOWAC (women only) and the Janus Cohort (men and women) was based on a survey conducted by the Norwegian Cancer Society,²⁵ showing only small gender differences for sunburns and sunbathing vacations, and that the solarium was more frequently used by women than men.

Identification of cancer cases

Using PINs, the Janus Cohort was linked to the Cancer Registry of Norway (CRN) to provide a complete cancer history (1953–2014) in all individuals with a CM diagnosis. Linkage to the Norwegian National Population Register provided data on vital status, year of death, and year of emigration. Reporting of incident cancers to the Cancer Registry is compulsory in Norway, and data from several sources ensure high quality data.^{26,27}

Cases were required to be (i) histologically verified as CM, (ii) to have no cancer prior to their CM diagnosis and (iii) to occur after start of follow-up. Cases occurring before start of follow-up ($n = 447$) or during the weight change period ($n = 50$) were excluded. Information on skin cancer

localization was based on a local CRN modified version of the International Classification of Diseases, 7th revision (ICD-7 codes 1900–1909), converted into ICD-10 codes (head and neck = C43.0–4; trunk = C43.5; upper limbs = C43.6; lower limbs = C43.7; not otherwise specified = C43.9). Subtypes of CM were defined by using histology codes from ICD-Oncology, 3rd edition (superficial spreading melanoma = 8743; nodular melanoma = 8721; other = 8000, 8723, 8730, 8742, 8744, 8745, 8770, 8772; not otherwise specified = 8720).

Study samples and follow-up

From the full Janus Cohort ($n = 292,851$), we excluded 1,249 individuals, leaving 291,602 individuals available for analysis of CM risk in relation to BMI, BSA, weight and height (Fig. 1). CM risk according to weight change was examined in a subsample of 37,262 individuals with repeated anthropometric measurements (Fig. 1).

For the full cohort, start of follow-up (baseline) was defined as the year of first participation in the Janus Cohort between 1972 and 2003. For the subsample with repeated measurements ($n = 37,262$), baseline was defined as the year of the second weight measurement conducted between 1985 and 1988. End of follow-up was December 31, 2014.

Data analysis

To examine the relationship between the anthropometric factors and CM risk, Cox regression was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Entry time was age at baseline, and exit time was age at CM diagnosis, emigration, death, or end of follow-up, whichever occurred first. To account for group level data (ambient UVR, sunburns and solarium use), standard errors that allow for intragroup correlation were used (cluster option in the specification of the variance-covariance matrix in Stata).²⁸ Age was used as the time scale with entry at age at start of follow-up. To check for cohort effects, we also ran Cox regression stratified by 10 year birth cohorts. The multivariable models were adjusted for attained age (as the time scale), BMI, height, ambient UVR of residence, average intensity of sunburns, occupation, physical activity, education and smoking status (specified in each result table). In women, the multivariable models were additionally adjusted for the average intensity of solarium sessions. In an initial model, the average intensity of sunbathing vacations was also included to check whether this improved the adjustment provided by UVR exposure indicators.

Tests of interactions between sex and anthropometric factors were carried out by including a product term in each regression model. To check whether BMI at first measurement altered the effect of weight change on CM risk, we tested for interaction by including a product term of weight change and BMI at first measurement. In these analyses, BMI was categorized as $<27.5/\geq 27.5$ kg/m² in men and $<25/\geq 25$ kg/m² in women, as women are likely to have a higher percentage of body fat than men at equal BMI.²⁹

Restricted cubic splines were incorporated into the Cox models to assess the shape of the exposure-CM risk relationships using the Stata commands `-rcs-` and `-partpred-`.^{30,31} Population attributable fractions (PAFs) of CM associated with BMI, BSA, height and weight were estimated by the `-punafcc-` command in Stata.³²

Tests for linear trend across categories were performed by entering ordinal variables as continuous in the regression models. The proportional-hazards assumption was evaluated by Schoenfeld residuals and log-log plots. Tests for significance were two-sided, and p -values of <0.05 were considered to represent statistical significance. All data analyses were performed using Stata version 14.2 (StataCorp, College Station, TX).

Results

During an average follow-up of 27 years (range <1 –43 years), 3,000 first primary CM cases were identified in the Janus Cohort. Average year of birth was 1942 (range 1900–1976) in men and 1944 (range 1900–1976) in women. Average age at baseline was 42 years (range 15–89 years) and age at diagnosis was 69 (range men 20–102; women 20–101) in both sexes (Table 1). In men, 59% of the CMs were located on the trunk, while in women the most common location was the lower limbs (Supporting Information Table S1).

We found statistically significant interaction terms between sex and anthropometric factors (results not shown), and all results are therefore shown stratified by sex. Table 2 shows risk of CM according to BMI, BSA, height and weight, by sex. In men, CM risk increased significantly with increasing levels of BMI, BSA, height and weight ($p_{\text{trends}} < 0.001$). In both sexes, positive significant associations were seen for BSA, although the strongest effect was seen in men with a 58% increase in CM risk for Quintile 5 compared to Quintile 1. We also found significant positive associations for height, with over 50% increased CM risk for Quintile 5 compared to Quintile 1 in both sexes. Among women, no associations were found for BMI and weight in relation to CM risk.

The associations between CM risk and anthropometric factors were also assessed using restricted cubic splines. In men (Fig. 2a), the HR showed a slight exponential increase according to BMI (reference 23 kg/m², HR = 1.00). For BSA (reference 1.85 m²), the HRs increased exponentially with statistical significance until a BSA of around 2.65 m². For height (reference 172 cm), CM risk increased with statistical significance until a height of 195 cm, and then declined. For weight (reference 70 kg), CM risk showed a slight exponential increase with statistical significance until 115 kg. In women (Fig. 2b), CM risk according to BMI increased towards the null at 23 kg/m², and then declined. For BSA, the CM risk increased exponentially from the null at 1.60 m², plateaued around 1.80 m² and then remained statistically significant until 2.00 m². CM risk according to height increased exponentially with statistical significance from around 170 to 180 cm, and then declined. CM risk according to weight decreased slightly with increasing weight, although this was not statistically significant.

Table 3 shows CM risk according to weight change in a subsample of the Janus Cohort. In men, a weight loss of >2 kg was associated with a 53% decrease in CM risk (HR 0.47, 95% CI: 0.39, 0.57). In women, neither weight gain nor weight loss was associated with CM risk. No significant interaction was found between weight change and BMI at first measurement (men: $p_{\text{interaction}} = 0.295$; women: $p_{\text{interaction}} = 0.054$). The weight change study sample ($n = 37,262$) differed from the rest of the cohort ($n = 254,340$) in that it was one of the earliest surveys in the Janus Cohort. Persons in the weight change sample were born earlier, were younger at baseline and older at diagnosis, and were shorter and lighter weight at baseline (Supporting Information Table S2).

Table 4 shows PAFs of CM associated with BMI, BSA, height and weight. In men, a BMI >25 kg/m² was estimated to account for 2% of the CM cases, while in women no statistically significant PAF was found. BSA above the median was estimated to account for 14 and 8% of the male and the female CM cases, respectively. Height above the median was estimated to account for 10% of the male and 6% of the female CM cases, respectively. Weight above the median was estimated to account for 7% of the male CM cases, while in women no statistically significant PAF was found.

We also examined CM risk according to anthropometric factors by anatomical site and histological subtype (Supporting Information Material). In men (results not shown in table), significant positive trends were found for trunk CMs according to all anthropometric factors, and head and neck CMs according to height ($p_{\text{trends}} < 0.001$). In women (Supporting Information Table S3), significant positive trends were found for all anthropometric factors in relation to CM of the upper limbs ($p_{\text{trends}} \leq 0.001$ –0.028). For lower limb CMs, significant positive trends were seen for BSA and height ($p_{\text{trends}} 0.046$ and <0.001 , respectively). Women with BMI 27.5–29.9 kg/m² had an 83% increased risk of upper limb CM compared to those with BMI 18.5–22.9 kg/m².

For CM risk by histological subtype in men (results not shown in table), significant dose-related risks were found for superficial spreading melanoma ($p_{\text{trends}} \leq 0.001$ –0.011) and nodular melanoma ($p_{\text{trends}} \leq 0.001$ –0.002) according to all the anthropometric factors. In women, dose-related risks of superficially spreading melanoma and nodular melanoma were seen for BSA ($p_{\text{trends}} 0.004$ and 0.010, respectively) and height ($p_{\text{trends}} < 0.001$ and 0.003, respectively).

Models including stratification on 10-year birth cohorts were also tested, but the results did not change materially (not shown). In an initial model, the average intensity of sunbathing vacations and sunburns were included in the same model, but no effect was seen from sunbathing vacations (results not shown) and it was hence not included in the final models.

Discussion

This study prospectively examined risk of CM according to pre-diagnostic BMI, BSA, height, weight and weight change in a large population-based cohort of Norwegian men and

Table 1. Characteristics of the study population

	Men	Women
Participants, <i>n</i> (%)	152,012 (52)	139,590 (48)
Year of birth, mean (range)	1942 (1900–1976)	1944 (1900–1976)
Age at baseline, mean years (range)	42 (15–89)	42 (15–89)
Years of follow-up, mean (range)	27 (<1–43)	27 (<1–41)
Age at diagnosis, mean (range)	69 (20–102)	69 (23–101)
BMI, mean kg/m ² (SD) ¹	25.2 (3.1)	24.2 (4.0)
BSA, mean m ² (SD) ¹	1.98 (0.15)	1.72 (0.14)
Height, mean cm (SD) ¹	177.7 (6.7)	164.8 (6.1)
Weight, mean kg (SD) ¹	79.6 (11.3)	65.7 (11.2)
Weight change, mean kg (SD) ²	3.0 (5.6)	3.2 (6.0)
Ambient UVR of residence, <i>n</i> (%)		
North	21,556 (14)	21,118 (15)
Mid	18,841 (13)	19,875 (14)
Southwest	21,148 (14)	21,048 (15)
Southeast inland	67,198 (44)	52,401 (38)
Southeast coast	23,269 (15)	25,148 (18)
Sunburns, mean (SD) ³	0.88 (0.13)	0.88 (0.14)
Sunbathing vacations, mean (SD) ³	1.21 (0.36)	1.17 (0.34)
Solarium sessions, mean (SD) ³	NA	1.05 (0.52)
Occupation, <i>n</i> (%)		
Indoor	81,230 (54)	89,793 (64)
Mixed	50,491 (33)	30,196 (22)
Outdoor	18,185 (12)	5,037 (4)
Unknown	2,106 (1)	14,564 (10)
Physical activity, <i>n</i> (%)		
Inactive	29,721 (19)	28,764 (20)
Low	79,539 (52)	95,301 (68)
Medium	37,516 (25)	13,855 (10)
High	4,349 (3)	710 (1)
Unknown	887 (1)	960 (1)
Smoking status, <i>n</i> (%)		
Never	68,578 (45)	55,456 (40)
Former	40,381 (27)	25,246 (18)
Current	40,134 (26)	55,199 (39)
Unknown	2,919 (2)	3,689 (3)
Education, <i>n</i> (%)		
None	512 (0.3)	458 (0.3)
Compulsory	45,896 (30.2)	46,823 (33.5)
Upper secondary	74,466 (49.0)	69,584 (49.9)
College/university	30,539 (20.1)	22,268 (16.0)
Unknown	599 (0.4)	457 (0.3)

Abbreviations: BMI: body mass index; BSA: body surface area; NA: not applicable, SD: standard deviation; UVR: ultraviolet radiation.

¹Missing: BMI and BSA (*n* = 717); height (*n* = 576); weight (*n* = 695).

²Weight change only available in a subsample with repeated measurements (*n* = 37,262).

³Group-level data (age-, county- and time period-specific) on average intensity of yearly sunburns, sunbathing vacations and solarium use (women only) from birth to baseline.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of cutaneous melanoma according to body mass index, body surface area, height and weight in 291,602 Norwegian men and women in the Janus Cohort

Exposure	Men				Women			
	C	HR ¹	HR ² (95% CI)	<i>p</i> _{trend} ³	C	HR ¹	HR ^{2,4} (95% CI)	<i>p</i> _{trend} ³
Body mass index (kg/m²)⁴								
Continuous (per 5)		1.08	1.15 (1.08,1.22)	<0.001		0.95	1.00 (0.93, 1.07)	0.892
<18.5	3	0.51	0.56 (0.16, 1.95)		20	0.78	0.85 (0.56, 1.30)	
18.5–22.9	357	1.00	1.00 (reference)		567	1.00	1.00 (reference)	
23.0–24.9	508	1.21	1.21 (1.07, 1.38)		323	1.06	1.10 (0.98, 1.25)	
25.0–27.4	495	1.17	1.21 (1.08, 1.35)		208	0.93	0.99 (0.88, 1.11)	
27.5–29.9	215	1.17	1.29 (1.13, 1.48)		100	0.90	1.00 (0.83, 1.20)	
≥30.0	101	1.11	1.26 (1.01, 1.57)		92	0.83	0.95 (0.76, 1.17)	
Body surface area (m²)								
Continuous (per 0.05)		1.08	1.06 (1.05, 1.07)	<0.001		1.04	1.03 (1.01, 1.05)	0.002
Q1 (M: 1.09–1.85; W: 0.78–1.60)	249	1.00	1.00 (reference)		216	1.00	1.00 (reference)	
Q2 (M: 1.85–1.93; W: 1.61–1.68)	305	1.25	1.12 (0.96, 1.29)		242	1.12	1.04 (0.91, 1.18)	
Q3 (M: 1.93–2.00; W: 1.69–1.75)	345	1.44	1.25 (1.10, 1.42)		262	1.23	1.11 (0.91, 1.35)	
Q4 (M: 2.01–2.10; W: 1.76–1.83)	370	1.61	1.36 (1.21, 1.52)		309	1.46	1.30 (1.12, 1.52)	
Q5 (M: 2.11–2.95; W: 1.84–2.72)	410	1.90	1.58 (1.41, 1.78)		281	1.37	1.22 (1.01, 1.47)	
Height (cm)⁵								
Continuous (per 5)		1.21	1.13 (1.09, 1.17)	<0.001		1.20	1.18 (1.07, 1.17)	<0.001
Q1 (M: 124–172; W: 100–160)	261	1.00	1.00 (reference)		232	1.00	1.00 (reference)	
Q2 (M: 173–176; W: 161–163)	310	1.18	1.04 (0.90, 1.21)		232	1.42	1.28 (1.12, 1.47)	
Q3 (M: 177–179; W: 164–166)	308	1.46	1.24 (1.01, 1.52)		263	1.42	1.23 (1.06, 1.43)	
Q4 (M: 180–183; W: 167–170)	377	1.57	1.27 (1.09, 1.49)		302	1.50	1.25 (1.05, 1.48)	
Q5 (M: 184–210; W: 171–195)	423	2.01	1.55 (1.36, 1.77)		282	1.93	1.52 (1.31, 1.76)	
Weight (kg)⁴								
Continuous (per 5)		1.08	1.04 (1.02, 1.07)	<0.001		1.02	1.00 (0.97, 1.03)	0.993
Q1 (M: 33–70; W: 24–57)	263	1.00	1.00 (reference)		236	1.00	1.00 (reference)	
Q2 (M: 71–76; W: 58–61)	329	1.16	1.00 (0.81, 1.24)		252	1.25	1.12 (0.89, 1.43)	
Q3 (M: 77–81; W: 62–66)	341	1.41	1.16 (0.98, 1.38)		278	1.23	1.07 (0.89, 1.27)	
Q4 (M: 82–88; W: 67–74)	386	1.54	1.22 (1.06, 1.40)		286	1.35	1.14 (0.94, 1.38)	
Q5 (M: 89–182; W: 75–173)	360	1.59	1.24 (1.05, 1.47)		258	1.26	1.08 (0.87, 1.33)	

Abbreviations: C: cases; M: men; Q: quintile; W: women.

Missing: weight (*n* = 695); height (*n* = 576); body mass index and body surface area (*n* = 717).

¹Adjusted for age (as the time scale).

²Adjusted for age (as the time scale), ambient UVR of residence, average intensity of sunburns, occupation, physical activity, education, smoking status.

³Modeled as a continuous variable to test for linear trend.

Additionally adjusted for average intensity of solarium sessions.

⁴Adjusted for height in addition to covariates in ² and ⁴.

⁵Adjusted for body mass index in addition to covariates in ² and ⁴.

women, with 3,000 incident CM cases occurring during an average follow-up of >26 years. In men, we found dose-related increases in CM risk for all anthropometric factors, and confirmed that weight loss was associated with a decreased CM risk. In women, CM risk increased significantly with increasing BSA and height.

The positive association between BMI and CM risk seen in men is consistent with other large population-based cohort

studies using pre-diagnostic measurements of height and weight.^{7,9} smaller Danish cohort study with 188 male CM cases found no statistically significant association, although CM risk increased with increasing BMI.³³ Another cohort study, relying on self-reported height and weight, could not detect a BMI–CM risk association in men.¹¹ Our finding of no association between BMI and overall CM risk (all anatomical sites combined) in female participants corresponds

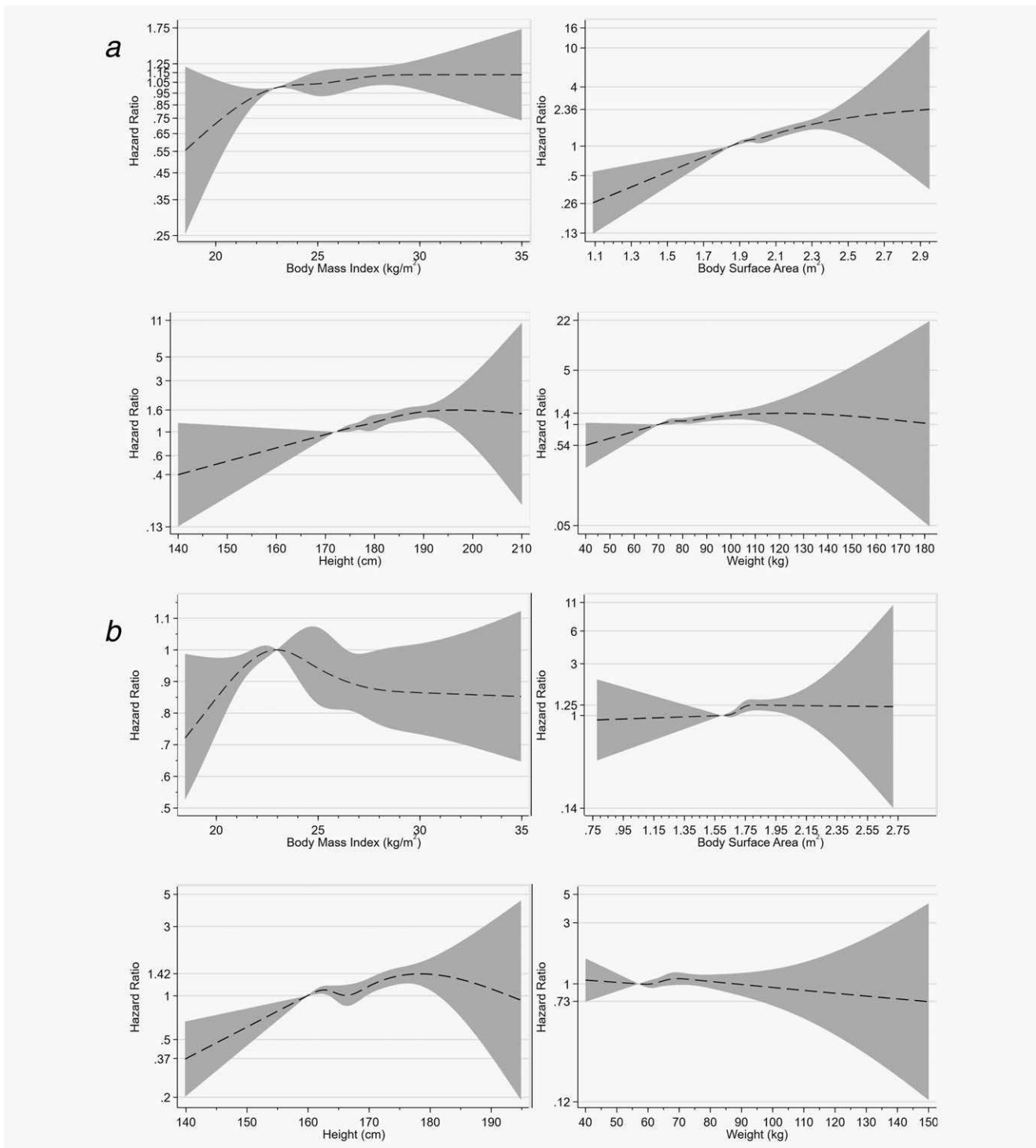


Figure 2. (a) *Men:* Restricted cubic splines displaying hazard ratios of CM risk with 95% confidence intervals according to anthropometric factors in men, adjusted for age (as the time scale), ambient UVR of residence, average intensity of sunburns, occupation, physical activity, education and smoking status. (b) *Women:* Restricted cubic splines displaying hazard ratios of CM risk with 95% confidence intervals according to anthropometric factors in women, adjusted for age (as the time scale), ambient UVR of residence, average intensity of sunburns, average intensity of solarium sessions, occupation, physical activity, education and smoking status.

with previous cohort studies,^{7,11,33} and with a pooled analysis based on eight case-control studies.¹⁵ However, when looking at upper limb CM risk in females, we also found significant

associations for BMI (p_{trend} 0.028) and weight (p_{trend} 0.019); this suggests that confounding by differences in sun seeking behavior between normal weight and obese women is

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) of cutaneous melanoma according to weight change in a subsample of 37,262 Norwegian men and women in the Janus Cohort

Weight change (kg)	Men (n = 18,332)			Women (n = 18,930)		
	C	HR ¹	HR ² (95% CI)	C	HR ¹	HR ^{2,3} (95% CI)
<-2.0	10	0.45	0.47 (0.39, 0.57)	21	1.01	1.09 (0.70, 1.68)
-2.0 to 2.0	61	1.00	1.00 (reference)	48	1.00	1.00 (reference)
>2.0	101	1.07	1.10 (0.84, 1.44)	80	0.92	0.95 (0.59, 1.53)

Abbreviations: C: cases; CI: confidence interval; HR: hazard ratio.

¹Adjusted for age (as the time scale).

²Adjusted for age (as the time scale), height, ambient UVR of residence, average intensity of sunburns, occupation, physical activity, education, smoking status.

³Additionally adjusted for average intensity of solarium sessions.

Table 4. Population attributable fractions (PAFs) and 95% confidence intervals (95% CIs) of cutaneous melanoma associated with anthropometric factors

Exposure	Men PAF ¹ (95% CI)	Women PAF ^{1,2} (95% CI)
BMI ³ >25.0 kg/m ²	0.02 (0.002, 0.04)	-0.02 (-0.05, 0.02)
BSA >median (men >1.97 m ² ; women >1.71 m ²)	0.14 (0.10, 0.17)	0.08 (0.04, 0.13)
Height ⁴ >median (men >178 cm; women >165 cm)	0.10 (0.06, 0.14)	0.06 (0.01, 0.11)
Weight ³ >median (men >79 kg; women >64 kg)	0.07 (0.02, 0.10)	0.03 (-0.02, 0.08)

Abbreviations: BMI: body mass index; BSA: body surface area.

¹Adjusted for age (as the time scale), ambient UVR of residence, average intensity of sunburns, occupation, physical activity, education, smoking status.

²Additionally adjusted for average intensity of solarium sessions.

³Adjusted for height in addition to covariates in ¹ and ².

⁴Adjusted for body mass index in addition to covariates in ² and ³.

restricted to anatomical sites more often covered by clothing. Confounding by sun seeking behavior may thus be the main reason for the differences in CM risk seen between men and women in our data.

The latest meta-analysis on anthropometric factors and CM risk found similar risk estimates for BMI 25–30 kg/m² and BMI ≥30 kg/m²,¹⁶ and highlighted the need for an assessment of a possible non-linear relationship in future studies, which to our knowledge has not been conducted previously. Consistent with this suspected underlying plateau in risk estimates, our spline-models revealed that CM risk increased and then levelled off with increasing BMI in men, and identified a twofold increased risk in men with a BSA of >2.60 m². The exponential increase in CM risk according to BSA found in our female participants corresponds well with the findings from two other Nordic cohorts,^{7,34} and with the 50% increased risk reported in the meta-analysis.¹⁶ As pointed out by Dennis *et al.*¹⁰ BSA is a measure of body surface that potentially can receive UVR exposure and it is a proxy of the number of skin cells able to convert to cancer cells and not necessarily a measure of obesity in relation to CM risk. Our analyses of BSA showed increased risk of CM in both sexes, which is in agreement with an effect both from obesity and UVR dose.

To our knowledge, this is the first study to report CM risk in relation to weight change in men. Interestingly, a 53% lower CM risk was seen with a weight loss of >2 kg over a

median time period of 10 years. This suggests that weight loss interventions may be an effective means of reducing CM risk in men. In women, however, we did not find any association between weight change and CM risk. Hormone use may be a potential confounding factor, which we were unable to consider in our analyses. A recent study, found that progestins reduced CM risk, while estrogens increased CM risk.³⁵ If hormone use explains our results for weight change in women, the proportion of progestin users should be larger among those who gain weight than those who lose weight. Moreover, the risk-reducing effect of progestin should also be stronger than the risk-increasing effect of estrogens. However, this remains unclear and should be further examined in a dataset with individual data on hormone use.

Biologic mechanisms that might explain the effect of obesity and weight change seen in our data include the release and function of insulin and leptin, which are both linked to a positive energy balance.³⁶ Obesity-induced chronic activation of insulin enhances the milieu for oncogenic transformation by driving cell growth and proliferation, and by inhibiting apoptosis.^{36,37} Leptin is released by adipose tissue and plays an important role in the regulation of insulin sensitivity and body weight.^{38,39} Increased diagnostic serum levels of leptin have been associated with increased CM risk, possibly caused by a leptin-induced increase in neoangiogenesis, reduction in melanogenesis and decrease in the melanocytes' capacity of DNA repair.^{40,41}

The dose-response relations between height and CM risk seen in our data for both men and women are similar to those reported by others.^{7,42,43} However, we found distinct differences between the sexes with respect to anatomical site. In men, the clearest associations with height were found for head, neck and trunk CMs, while in women dose-response relations with height were only seen for CMs located on the limbs. The latter finding differs from the pooled analysis by Olsen *et al.*¹⁵ who found no differences in risk according to height across anatomical sites in women. Also, the shape of the height-CM risk curve (all anatomical sites combined) differed. In men, the curve increased towards 190 cm, plateaued and then declined for the tallest individuals (200–210 cm), whereas in women the risk increased towards the 180 cm and then declined.

Several underlying mechanisms have been suggested to explain the association between height and CM risk. One hypothesis is simply that height is a proxy of the number of cells in the body that may develop into neoplasms.⁴⁴ Our results were fairly similar for height and BSA, and thereby support the hypothesis that a larger number of melanocytes increases the risk of CM. Another possible explanation is that tall stature as an adult is an indicator of nutritional status during childhood, and that energy excess may activate obesity-related mechanisms (*i.e.*, cell proliferation, inhibition of apoptosis and angiogenesis).⁴⁵ Moreover, early life caloric restriction has been shown to have a lasting influence on the prevalence of neoplasms in rats.⁴⁶ A role for the endocrine system has also been suggested, as height has been associated with circulating levels of insulin-like growth factor binding protein 3 (IGFBP-3).⁴⁷ As pointed out by Kabat *et al.*⁴⁸ 80% of the variation in height in Western populations has been ascribed to genetics and at least 180 loci have been found to influence adult height.⁴⁹ However, it is unclear whether genetics may also be a shared etiologic factor for both height and CM risk.

Although it has been estimated that over 85% of the CM cases may be attributed to UVR exposure (based on UK data),⁴ we find it interesting from a public health perspective that 7% of our male CM cases could be ascribed to weight >79 kg, and that 14% and 8% of the CM cases could be ascribed to BSA above 1.97 m² and 1.71 m² in men and women, respectively. As with various other cancer forms, these findings indicate that reduction in body weight may also play a role for reduction in CM risk, at least in males. However, it is important to bear in mind that PAFs of CM estimated for different exposures may not add up to 100%, as the estimation will depend on the exposure assessment.

Strengths of our study include the prospective design and long follow-up period; the inclusion of 3000 first primary CM cases from a population-based cancer registry based on compulsory reporting of incident cancers; and the pre-diagnostic measurements of height and weight performed by trained personnel according to a standardized protocol. In this setting, pre-diagnostic measurements of height and weight are considerably more reliable than self-reports⁵⁰;

Self-reported height and weight are likely to be over- and underreported, respectively, which in turn would lead to under- and overestimations of risk.²⁹

An important limitation of this study is the lack of individual information on sun tanning habits. We accounted for some of the variation in sunburns and solarium sessions by using group level data (specific to age, period, and county of residence), but residual confounding cannot be excluded. Confounding may explain the results in women as we found no association between BMI or weight and CM risk in anatomical sites usually covered by clothing. The exposure-CM risk curves suggested a decline in risk with increasing BMI and weight, possibly caused by differences in sun tanning habits between normal weight and obese women. Still, adjustment for regional measures of ambient UVR, and for indoor/outdoor occupation and physical activity, seemed to capture a fair amount of the variation as the CM risk estimates were significantly associated with increasing values of these UVR indicators (results not shown). Information on phenotype and nevi, which are known CM risk factors,⁵ were not available and may have resulted in residual confounding if they were disproportionately distributed across anthropometric factors. Moreover, we did not have information on hormone use, and were hence unable to adjust for the potential confounding effect of progestin, which was recently found to reduce CM risk.³⁵ The weight change study sample ($n = 37,262$), based on the Norwegian Counties Study, differed from that of the remaining full cohort sample ($n = 254,340$) in several aspects (*i.e.*, year of birth, age at baseline, age at diagnosis, and height and weight at baseline). However, the Norwegian Counties Study included the counties Finnmark, Sogn og Fjordane and Oppland, located in northern, western and southeastern Norway, respectively, and represented the diversity in population density and sources of income at the time.⁵¹

In summary, this large population-based cohort provided evidence that BMI, BSA, height and weight are positively associated with CM risk in males. Our study also provides new insights into the shape of the exposure-risk curves, and indicates an exponential increase in CM risk for all anthropometric factors in males. This study is the first to report that men may benefit from weight loss in order to decrease their CM risk. In women, dose-response associations for CM risk were found with BSA and height. Further, by inspection of the BMI-CM risk curve in women, we found indications of confounding by sun tanning habits, which in turn warrants further study with meticulous UVR adjustment by use of individual and repeated UVR exposure data for an assessment of possible time-dependent effects.

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