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Obesity and the incidence of skin cancer in US Caucasians

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Abstract

Background—Limited information is available on the potential link between obesity and either melanoma or non-melanoma skin cancers.

Objective—To conduct a prospective study to examine the association between obesity and the risk of both melanoma and non-melanoma skin cancers.

Methods—Using pooled data from two large national cohorts in the US, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), we prospectively examined the incidence of melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) among participants grouped according to body mass index (BMI).

Results—Compared to participants with an updated BMI in the normal range, those with a BMI in the obese range had a 32 % lower risk of developing SCC, and those with a BMI in the morbidly obese category had a 37 % lower risk of developing SCC. The decrease in SCC risk was limited to women. Compared to participants with a BMI in the normal range, those with a BMI in the obese range had a 19 % lower risk of developing BCC, and those with a BMI in the morbidly obese category had a 29 % lower risk of developing BCC. The risk of developing melanoma did not statistically differ by BMI grouping. The results were similar using BMI measurements obtained 10 years prior to the diagnosis of skin cancer.

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Conflict of interest No conflicts of interest to disclose.

Conclusion—Obesity appears to be inversely associated with the development of non-melanoma skin cancers. Obesity is most likely a surrogate marker for lack of chronic sun exposure, which is a risk factor for non-melanoma skin cancers.

Keywords

Skin cancer; Melanoma; Squamous cell carcinoma; Basal cell carcinoma; Obesity; BMI; Prospective cohort

Introduction

In recent decades, there has been a significant increase in the prevalence of obesity in both adults and children in the United States [1–3]. Approximately 65 % of the adult population is overweight with a body mass index (BMI) greater than 25 kg/m^2, and 32 % of adults can be classified as obese with a BMI greater than 30 kg/m^2 [1]. Further, the number of overweight children tripled between 1980 and 2000 to 16 % [2, 4], and many of these children are likely to become obese adults [2, 4]. This trend has been shown to have substantial negative health consequences. One of these negative health consequences is an increase in the incidence of several internal cancers, such as those of the colon, breast, pancreas, stomach, ovary, and prostate, and kidney [5]. A prospective cohort study of more than 900,000 US adults reported looking at the link between BMI and the risk of death from cancer found that increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites [5]. In terms of mechanisms of carcinogenesis of obesity, it has been proposed that adipose tissue secretes several cytokines believed to promote inflammation, cell proliferation, and angiogenesis, and thereby tumor growth [3].

Non-melanoma skin cancer (NMSCs), including basal and squamous cell carcinoma, are the most common cancers in white populations. The most recently published peer-reviewed study estimates the total number of NMSCs in the US population in 2006 at 3,507,693, a dramatic increase from year prior [6]. Melanoma poses a similarly significant burden. The incidence of malignant melanoma is increasing faster than any other cancer in the United States as well as worldwide [7]. An estimated 70,230 Americans were diagnosed with melanoma in 2011, with an estimated 8,790 deaths due to the cancer [8]. In 1960, the lifetime risk of melanoma in the United States was 1 in 800. As of 2010, this risk was 1 in 39 for men and 1 in 58 for women [9].

Numerous studies have established that exposure of the skin to UV radiation is an important risk factor for the development of both melanoma and non-melanoma skin cancers. Though not yet well studied, a link has also been proposed between obesity and skin cancer [3, 10]. The purpose of this study therefore was to prospectively examine possible associations between obesity and the risk of melanoma and non-melanoma skin cancer in two large national cohorts: the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

Methods

Study population

The Nurses' Health Study began in 1976, when 121,700 registered, female nurses aged 30–55 years in 11 US states completed a baseline questionnaire regarding risk factors for cancer and cardiovascular diseases. Participants completed self-administered, mailed, follow-up questionnaires biennially with updated information on their lifestyle, medical history, and diet. The Health Professionals Follow-up Study (HPFS) began in 1986 when 51,529 US

male health professionals, including dentists, veterinarians, pharmacists, and optometrists aged 40–75 years completed a baseline questionnaire on lifestyle, diet, and medical conditions. The information was similarly updated biennially with follow-up questionnaires. Details of the two cohorts have been described previously [11, 12]. This study was approved by the Human Research Committee at the Brigham and Women's Hospital (Boston, MA, USA). Informed consent was previously obtained from all participants when they elected to participate in the NHS and HPFS and consented to data being used for subsequent analyses.

Identification of skin cancer cases

Skin cancer identification was performed routinely in both cohorts. Participants reported new diagnoses biennially. With their permission, participants' medical records were obtained and reviewed by physicians to confirm self-reported diagnoses. Only pathologically confirmed invasive cases of melanoma and SCC were included in this study. Medical records were not obtained for self-reported cases of BCC, as the validity of BCC self-reports was ≥90 % [13, 14].

Assessment of BMI and skin cancer risk factors

Obesity during adolescence and adulthood was assessed by BMI. On the baseline questionnaire (1976, NHS; 1986 HPFS), participants reported their current weight and height, followed by biennial updated reports on weight. Baseline and updated body mass indices were calculated for all participants by dividing weight in kilograms by height in meters squared. Participants were then categorized into one of five BMI categories (in kg/m^2): <18.5, 18.5–24.9, 25–29.9, 30–34.9, and 35 and greater.

Data on skin cancer risk factors were obtained from cohort questionnaires in both cohorts in the 1980s. All information on risk factors and exposures was collected via biennial questionnaires. The following information was collected: (1) childhood or adolescent tendency to burn after 2 h or more of sunlight exposure (classified into 1 of 3 categories: no reaction, burn, or painful burn/blister), (2) number of severe sunburns over lifetime (categories included: no burns, 1–2 burns, 3–5 burns, 6–9 burn, or 10+ burns), (3) natural hair color at age 20 years, (4) family history of melanoma in first-degree relatives, and (5) the number of nevi measuring 3 mm or larger on the limbs (categories included: no nevi, 1–2 nevi, 3–5 nevi, 6–9 nevi, or 10+ nevi).

Information on participants' current location of residence (US state), location at birth and at 15 and 30 years of age was also obtained on follow-up questionnaires. In order to estimate the UV exposure level of each location, an ultraviolet (UV) database for 50 US states was developed. The erythemal UV index (i.e., the UV index) is a method to estimate UV radiation reaching the earth's surface. When the sun is highest in the sky, UV irradiance is weighted by the action spectrum for erythema of white skin. Based on the mean UV index in North America for the month of August (by the National Oceanic and Atmospheric Administration), the 50 states (and the District of Columbia) were divided into the following 3 UV index groups: 5 or less (low UV index: Alaska, Maine, Michigan, Minnesota, New Hampshire, Oregon, Pennsylvania, Vermont, Washington, and Wisconsin); 6 (medium UV index: Connecticut, Delaware, Illinois, Indiana, Iowa, Maryland, Massachusetts, Missouri, Nebraska, New Jersey, New York, North Dakota, Ohio, Rhode Island, South Dakota, and West Virginia); and 7 or more (high UV index: Alabama, Arizona, Arkansas, California, Colorado, Florida, Georgia, Hawaii, Idaho, Kansas, Kentucky, Louisiana, Montana, Mississippi, Nevada, New Mexico, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Utah, Virginia, Washington, DC, and Wyoming). This grouping for northern, middle, and southern states remains the same for other months throughout the year [15]. The mean

solar radiation for each individual's past (at different age categories) and current residences was derived from the UV values measured at the nearest weather station.

In addition, we asked how many hours per week participants were outdoors in direct sunlight in the middle of the day in summer months, including work and recreation at different age intervals (high school/college, 25–35, 36–59, 60–65) in 2008 in the NHS and HPFS.

Physical activity

In both cohorts, participants were asked about physical activity (first with detail in 1986 in NHS, and 1986 in HPFS), and this information was updated every 2 years. Participants indicated the average time spent per week at various types of physical activity, such as walking, jogging, bicycling, lap swimming, playing tennis, doing calisthenics, aerobics, aerobic dance, rowing machine exercise, playing squash, and/or racquetball. Based on this information, we calculated energy expenditure in metabolic-equivalent tasks (METs) measured in hours per week [16]. Each MET-hour is the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram of weight per hour at rest. The reproducibility and validity of self-reported physical activity in both cohorts has been evaluated in detail in prior studies [17, 18]. The 2-year test–retest correlation for activity was 0.59 for the 147 samples in the NHS. Correlations between activity reported on recalls and that reported on questionnaire were 0.79. Similar results were observed in the HPFS.

Statistical analyses

Participants who did not report their date of birth, height, or weight at baseline (excluded 1,337 in NHS and 1,065 in HPFS) were excluded from analyses. Non-whites (excluded 4,517 in NHS and 2,386 in HPFS) were excluded due to insufficient sample sizes for those race categories for analyses. Also excluded were participants who had skin cancer before 1976 for the NHS ($n = 186$) and before 1986 for the HPFS ($n = 107$). The primary exposure was the participant's BMI, assessed at baseline and every 2 years thereafter. Participants contributed person-time from the date of return of the follow-up questionnaires. Accumulation of follow-up time ceased at the first report of BCC, the first report followed by confirmation of SCC, the first report followed by confirmation of melanoma, or the end of follow-up (NHS 2006 June; HPFS 2006 January), whichever came earlier. We used Cox proportional hazards models to calculate the hazard ratios (HRs) and 95 % confidence intervals (CIs) of each type of skin cancer using two BMI measurements for each participant: an updated BMI and a latent BMI. The updated BMI was measured one follow-up cycle prior to the diagnosis of skin cancer, and the latent BMI was the BMI measured l0 years prior to the diagnosis of skin cancer. In the multivariate analysis, we simultaneously controlled for the above-mentioned skin cancer risk factors and physical activity (quintiles). We used updated physical activity in the analysis for updated BMI, and physical activity 10 years prior to diagnosis in the analysis for BMI 10 years prior to diagnosis. In the combined analysis of the two cohorts, we additionally controlled for gender. Results for participants with a BMI <18.5 were not reported in analysis of hazard ratios of skin cancer due to the small number of participants in this BMI grouping. 153 and 3,218 participants at baseline for the HPFS and NHS, respectively, were excluded as they had BMI values <18.5.

Results

Eligible for analyses were 143,129 participants (102,748 female nurses and 40,381 male health professionals) in the NHS and HPFS. The mean follow-up time was 23.5 years (26.3 for NHS and 16.0 for HPFS). Baseline characteristics of participants in our study were

similar across BMI groupings assessed in 1986 (Table 1). Participants with BMI of 35 or greater had a higher number of moles and severe sunburns compared with the other BMI groupings.

In total, 925 participants developed melanoma, 1,930 developed SCC, and 27,200 developed BCC in the two cohorts. When looking at combined data from the NHS and HPFS, compared to participants with updated BMI in the range of 18.5–24.9, participants with BMI of 30–34.9 had a significantly lower risk of developing both SCC (multivariate-adjusted HR = 0.68; 95 % CI: 0.57, 0.80) and BCC (multivariate-adjusted HR = 0.81; 95 % CI: 0.77, 0.84). In the morbidly obese (BMI 35 or greater), the hazard ratios of SCC and BCC were even lower. The multivariate-adjusted HR was 0.63 for SCC (95 % CI: 0.48, 0.82, p for trend <0.0001), and the multivariate-adjusted HR for BCC was 0.71 (95 % CI: 0.66, 0.75, p for trend<0.0001). Similar results were obtained when hazard ratio was assessed using latent BMI values (Tables 2, 3). We observed a statistically significantly interaction between the updated BMI and gender ($p = 0.008$); women with a BMI of 35 or greater had a decreased risk of SCC (multivariate-adjusted HR = 0.59; 95 % CI: 0.43, 0.80). Men, however, did not have any altered risk of skin cancer (multivariate-adjusted HR = 1.07; 95 % CI: 0.64, 1.78).

The risk of developing melanoma did not statistically differ by BMI group in either of the two cohorts using updated BMI values (Table 4). Sixteen participants with melanomas (14 in the NHS and 2 in the HPFS) were excluded from the analysis as they had BMI values <18.5. Compared to participants with a BMI in the range of 18.5–24.9, the multivariate-adjusted HR of developing melanoma was 1.20 (95 % CI: 1.04, 1.38) for those with BMI in the range of 25–29.9, and 0.91 (95 % CI: 0.74, 1.13) for those with BMI of 30 and above (p for trend = 0.78). BMI was analyzed in 3 categories for melanoma given the small number of participants with BMI of 35 or greater that developed melanomas. Similar associations were found using the latent BMI (Table 4). We grouped BMI greater than 30 as one category in the baseline analysis because of the small number of individuals with BMI greater than 35 at baseline (Tables 2, 3, 4). The hazard ratios of melanoma, SCC, and BCC associated with BMI values were not substantially altered by multivariable adjustment for other known or suspected risk factors for skin cancer.

Additionally, we assessed whether the risk associated with obesity differed across different body sites of SCC. The inverse association between BMI and the risk of SCC was more apparent for SCC of the trunk, shoulders, or legs than for SCC of the head, neck, arms, or hands. Obese women had a lower risk of developing SCC on their trunk or shoulders as well as a lower risk of developing SCC on their legs. Also noted was an approximate 30 % lower risk of SCC of the head, neck, and arms among obese women, which was not significant (Table 5). No significant difference was observed between BMI and SCC according to different body sites among men (Table 5).

We also compared gender difference for SCC at different body sites. As shown in Table 5, compared with men, women had a much greater extent of decrease in SCC risk at head and neck, trunk and shoulder, and leg. There was no substantial difference in SCC risk at arm and hand between the two genders.

In the analysis of updated physical activity reports (2 years prior to the diagnosis of skin cancer), physical activity was associated with an increased risk of both SCC and BCC. The hazard ratio (top vs. bottom quintile) was similar between SCC (multivariate-adjusted HR = 1.22; 95 % CI: 1.04, 1.42, p for trend = 0.01) and BCC (multivariate-adjusted HR = 1.17; 95 % CI: 1.12, 1.22, p for trend <0.0001). The increased risk for melanoma was not statistically significant (top vs. bottom quintile, multivariate-adjusted HR = 1.24; 95 % CI: 0.99, 1.55, p for trend = 0.06). Overall, for each type of skin cancer, the association with physical activity

was more pronounced in women than in men. In the latency analysis (10 years prior to the diagnosis of skin cancer), physical activity was also significantly associated with increased risk of SCC and BCC with a magnitude similar to that observed in the updated analysis. The risk associated with melanoma was stronger with that with SCC or BCC (multivariate-adjusted hazard ratio = 1.72; 95 % CI, 1.26, 2.350, p for trend = 0.0007).

Discussion

Our prospective cohort results suggest that a BMI of 30 or greater is associated with a significantly lower risk of SCC and BCC compared with a BMI in the range of 18.5–24.9. Overall, we did not find any strong association between BMI and the risk of melanoma.

There is strong evidence for the role of obesity in cancer risk [19]. However, limited information is available on the potential link between obesity and either melanoma or non-melanoma skin cancers. In terms of the pathophysiological link between obesity and skin cancer, there is evidence that obesity-induced inflammation interacts with inflammation resulting from UV radiation to induce a state favorable to carcinogenesis. A study of inflammatory mediators secondary to UVB irradiation in mice found that UV-induced inflammatory responses were exacerbated in the skin of obese mice. In addition, levels of the proinflammatory cytokines TNF-α, IL-6, and IL-1β were higher in the UVB-exposed skin of obese mice, which further suggests a positive relationship between obesity and UVB-induced inflammation. The higher levels of proinflammatory cytokines may contribute to the development of various inflammation-associated cutaneous diseases [3], and chronic or sustained elevated levels of proinflammatory cytokines have been implicated in skin cancer risk [20–22]. Our results, however, indicate an inverse relationship between obesity and non-melanoma skin cancers, indicating that behavioral influences as discussed below may play a stronger role in skin cancer development and may counteract any biological mechanisms in favor of carcinogenesis.

The well-known risk factors for non-melanoma skin cancer can be classified as genotypic, phenotypic, or environmental. Established host risk factors for skin cancer include family history of skin cancer, fair skin color, inability to tan, susceptibility to burn, and light hair color. Individuals at greatest risk are those who reside in geographic areas with high UV indices and who are most susceptible to UV radiation secondary to certain phenotypic characteristics such as lighter hair color or inability to tan [23]. These risk factors were equally distributed among the various BMI groupings in our study. Although UV radiation is the most important risk factor for pathogenesis of both BCC and SCC, studies have shown the effect on risk of SCC to be greater [24]. Cumulative lifetime sun exposure has a strong dose–response association with SCC [24, 25]. The relationship between sun exposure and development of BCC remains unclear, and epidemiological studies suggest that the quantitative effect could be small. This evidence is consistent with our results; compared with BCC, the risk of SCC is reduced to a greater extent in obese individuals. This reduced risk among the obese may be secondary to the following: obese individuals were shown to have lower levels of physical activity. One could argue that obese individuals are less active outdoors and thus have less cumulative lifetime sun exposure, with morbidly obese women (BMI >35) being the least active outdoors given our results. Obesity has shown to be inversely associated with physical activity [26]. Martinez-Gonzalez et al. [27] estimated the association between leisure time activity and weight status (BMI >30) in a representative sample of the 15 member states of the European union and found that individuals in the highest quintile for leisure time physical activity were approximately 50 % less likely than those in the lowest quintile to be classified as obese [27]. Similar findings have been reported in several other studies [28–30]. Moreover, physical activity has been linked to higher 25-hydroxyvitamin D blood levels, which mechanistically may be a surrogate for sun

exposure [31]. Thus, obesity is related to decreased physical activity, which in turn may lead to decreased levels of cumulative sun exposure and therefore a lower risk of non-melanoma skin cancers as cumulative sun exposure is a major risk factor for the development of these cancers. For this reason, BMI 10 years prior to diagnosis was examined to determine whether any potential link existed between a chronic overweight state and/or obesity and the development of skin cancer as skin in addition to BMI one follow-up cycle prior to a skin cancer diagnosis as it may be surrogate for cumulative sun exposure secondary to it relation to physical activity.

Host risk factors for melanoma include eye color, hair color, skin color, the number of nevi, and skin reaction to chronic and acute sun exposure [32]. As mentioned above, these host risk factors were controlled for in our study. Compared to chronic lifetime exposure, which has been identified as a risk factor for non-melanoma skin cancer, an intermittent pattern of sun exposure, especially childhood and adolescent sunburns, is more frequently associated with an increased risk for melanoma [33]. Results of many studies have suggested that childhood is a critical period for sun exposure [33], and ecologic studies have shown consistent associations between childhood sun exposure and melanoma risk [34]. However, chronic sun exposure may also play a role in the development of melanoma. Thus, it is justifiable to examine obesity in relation to melanoma given that obesity may serve as a surrogate marker for cumulative sun exposure as discussed previously.

Our analysis of updated physical activity reports indicated an increased risk of BCC and SCC, but no association with melanoma. However, analysis of latent physical activity reports similarly suggest increased risk of BCC and SCC, but an even stronger elevated hazard ratio of melanoma. Thus, our results indicate that individuals who engaged in more physical activity, and thus were more likely to spend more extended time outdoors, were at an increased risk for SCC and BCC due to increased levels of chronic sun exposure. Further, earlier sun exposure is more relevant to melanoma development. Increased sun exposure earlier in life is linked to an increased risk of melanoma, a fact that has been well studied. Female gender was significantly associated with a lower risk of SCC; obese women have a lower risk of SCC than obese men. Among women, obese participants are less likely to develop SCCs on their trunk, shoulders, and legs. These body sites are less frequently exposed to the sun than the head, neck, arms, or hands, which are more chronically exposed. Obese women more so than obese men may be even less willing secondary to body image concerns to expose areas such as the trunk, shoulders, and legs, thus resulting the gender discrepancy in SCC among body sites described above.

Our results indicate that obesity is associated with a decreased risk of non-melanoma skin cancers. However, a causal link between obesity and skin cancer is unlikely. Rather, obesity may serve as a surrogate endpoint for other skin cancer risk factors (e.g., time spent outdoors, chronic sun exposure). Obese individuals may be likely to spend less time outdoors with less chronic sun exposure. The levels of childhood and adolescent sun exposure may not significantly vary among obese adults and non-obese adults, thus supporting our results of non-significant association between obesity and melanoma.

To date, ours is the first prospective study investigating the relationship between BMI and both melanoma and non-melanoma skin cancers. One of the major strengths of our study is its prospective assessment of obesity and physical activity. Another strength of our study is the large study population and the high follow-up rate. Also, the availability of many risk factor covariates allows us to assess the association while controlling for potential confounding within each BMI group. Limitations include the study population being relatively homogenous group of nurses and health professionals, and therefore, their sun-related behaviors may not represent those of the population-at-large, which may affect

generalizability of results obtained. Also, BMI rather than a more sensitive measure of central obesity, such as waist/hip ratio, was employed in the analysis. Body surface area measurements were also not directly examined in analysis.

Although participants were not a random sample of US women and men, it seems unlikely that the basic biological relations among participants in these cohorts will differ from those of the general population. Indeed, our skin cancer incidence is very similar to the national data, suggesting that these participants are reasonably representative of US population. The American Cancer Society estimates approximately 0.6 % probability of developing melanoma in the age range of 40–59 in 2004–2006 [8]. Our incidence rate of melanoma was 0.65 % during our follow-up period. Current estimates are that 1 in 5 Americans will develop skin cancer in their lifetime [35]. Our incidence rate of non-melanoma skin cancer during our follow-up period is 20 %.

In conclusion, prospective data from two large cohort studies demonstrated a statistically significant association between a BMI of 30 or greater and a lower risk of both SCC and BCC. In terms of public health implications, it is important to emphasize that the findings of this study are not in any way meant to recommend obesity as a healthy physical state. Instead, it must be seen as a potential surrogate marker of chronic sun exposure. It should be emphasized that obesity is a risk factor for several other types of cancers as well as cardiovascular disease, among many other disorders. Further studies of potential mechanisms underlying different associations between obesity and various skin cancers also are needed to illuminate skin cancer carcinogenesis.

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Table 1

Age-adjusted baseline characteristics of the nurses' health study and health professionals follow-up study combined by BMI grouping in 1986

Characteristics	BMI			
	18.5–24.9	25.0–29.9	30–34.9	35+
Number of subjects				
NHS	59,303	28,635	10,118	4,692
Mean time to skin cancer diagnosis, years	26	28	30	30
HPFS	18,410	18,495	2,924	552
Mean time to skin cancer diagnosis, years	14	16	20	20
Total	77,713	47,130	13,042	5,244
Mean age, years	52.4	53.9	53.6	52.7
Female, %	72.6	70.6	72.7	78.3
Physical activity (METs)	20.1	16.3	12.4	10.4
Red or blond hair, %	15.3	14.7	14.9	14.7
Childhood/adolescent sunburn reaction, %[a]	44.3	46.8	47.8	50.0
6+ lifetime severe sunburns, %	44.8	47.0	48.8	53.6
3+ moles on arms, %	11.4	13.2	15.0	18.3
Family history of melanoma, %[b]	2.7	3.0	3.0	3.2
College/high school sun exposure ≥ 11 h/week in summer, %	22.8	24.7	22.9	23.3
Age 25–35 ≥ 11 h/week sun exposure in summer, %	17.4	18.7	17.4	18.0
Age 36–59 ≥ 11 h/week sun exposure in summer, %	14.2	14.8	12.9	12.4
Age 60 ≥ 11 h/week in summer, %	13.0	12.6	10.3	8.9
Birth, high UV residence (%)	15.2	14.2	14.1	11.7
Age 15 years, high UV residence (%)	15.7	14.6	14.3	11.1
Age 30 years, high UV residence (%)	20.2	18.2	17.8	14.4

[a]Childhood or adolescent tendency to burn after 2 h or more of sunlight exposure, classified into 1 of 3 categories: no reaction, burn, or painful burn/blister

[b]Family history of melanoma in first-degree relatives

Table 2

Age-adjusted and multivariable-adjusted hazard ratios and 95 % confidence intervals for squamous cell carcinoma by BMI

Characteristics	BMI				*p* value for trend
	18.5–24.9	25.0–29.9	30–34.9	35+	
Squamous cell carcinoma—updated BMI[a]					
NHS, age-adjusted	1.0	0.79 (0.70, 0.91)	0.62 (0.51, 0.76)	0.54 (0.40, 0.73)	<0.0001
NHS, multivariate-adjusted[b]	1.0	0.80 (0.70, 0.91)	0.65 (0.53, 0.80)	0.59 (0.43, 0.80)	<0.0001
HPFS, age-adjusted	1.0	0.97 (0.84, 1.13)	0.78 (0.59, 1.02)	0.92 (0.56, 1.52)	0.19
HPFS, multivariate-adjusted[b]	1.0	1.00 (0.86, 1.16)	0.82 (0.62, 1.08)	1.07 (0.64, 1.78)	0.44
Combined, age-adjusted[b,c]	1.0	0.94 (0.85, 1.03)	0.66 (0.56, 0.78)	0.56 (0.44, 0.73)	<0.0001
Combined, multivariate-adjusted[b,c]	1.0	0.86 (0.78, 0.94)	0.68 (0.57, 0.80)	0.63 (0.48, 0.82)	<0.0001
Combined no. of cases	956	733	178	40	
Squamous cell carcinoma—BMI 10 years prior to diagnosis					
NHS, age-adjusted	1.0	0.78 (0.67, 0.89)	0.64 (0.51, 0.81)	0.43 (0.29, 0.64)	<0.0001
NHS, multivariate-adjusted[b]	1.0	0.77 (0.67, 0.89)	0.65 (0.52, 0.82)	0.44 (0.29, 0.66)	<0.0001
HPFS, age-adjusted	1.0	0.89 (0.74, 1.07)	0.80 (0.56, 1.15)	0.63 (0.26, 1.53)	0.02
HPFS, multivariate-adjusted[b]	1.0	0.93 (0.77, 1.12)	0.84 (0.58, 1.22)	0.75 (0.30, 1.83)	0.07
Combined, age-adjusted[b,c]	1.0	0.88 (0.79, 0.98)	0.68 (0.56, 0.82)	0.42 (0.29, 0.61)	<0.0001
Combined, multivariate-adjusted[b,c]	1.0	0.82 (0.73, 0.91)	0.69 (0.57, 0.84)	0.48 (0.33, 0.69)	<0.0001
Combined no. of cases	881	500	180	30	
Squamous cell carcinoma—baseline BMI[d]					
NHS, age-adjusted	1.0	0.63 (0.53, 0.74)	0.53 (0.39, 0.72)	0.60 (0.37, 0.97)	<.0001
NHS, multivariate-adjusted[b]	1.0	0.67 (0.57, 0.79)	0.60 (0.44, 0.82)	0.68 (0.42, 1.11)	<.0001
HPFS, age-adjusted	1.0	0.86 (0.74, 1.00)	0.87 (0.65, 1.17)	0.30 (0.10, 0.93)	0.017
HPFS, multivariate-adjusted[b]	1.0	0.88 (0.76, 1.02)	0.95 (0.70, 1.28)	0.37 (0.12, 1.15)	0.088
Combined, age-adjusted[b,c]	1.0	0.90 (0.81, 1.00	0.73 (0.59, 0.90)	0.52(0.33, 0.80)	0.0003
Combined, multivariate-adjusted[b,c]	1.0	0.75 (0.67, 0.83)	0.71 (0.58, 0.88)	0.56 (0.36, 0.88)	<.0001
Combined no. of cases	1,254	509	95	20	

[a]BMI measured one follow-up cycle prior to the diagnosis of skin cancer

[b] Multivariate-adjusted for sunburn reaction, family history of melanoma, number of severe sunburns, number of moles, hair color, sun exposure at different age intervals, UV index at residence at different ages, physical activity (quintiles), and history of cardiovascular diseases, type 2 diabetes, and cancer

[c] The combined analysis of the two cohorts additionally controlling for gender

[d] BMI measured from baseline questionnaire (1976 for NHS, 1986 HPFS)

Table 3

Age-adjusted and multivariable-adjusted hazard ratios and 95 % confidence intervals for basal cell carcinoma by BMI

Characteristics	BMI				*p* value for trend
	18.5–24.9	25.0–29.9	30–34.9	35+	
Basal cell carcinoma—updated BMI[a]					
NHS, age-adjusted	1.0	0.88 (0.86, 0.91)	0.82 (0.78, 0.86)	0.72 (0.67, 0.77)	<0.0001
NHS, multivariate-adjusted[b]	1.0	0.88 (0.85, 0.91)	0.81(0.78, 0.85)	0.70 (0.65, 0.75)	<0.0001
HPFS, age-adjusted	1.0	0.88 (0.84, 0.93)	0.79 (0.73, 0.86)	0.74 (0.62, 0.87)	<0.0001
HPFS, multivariate-adjusted[b]	1.0	0.89 (0.85, 0.94)	0.83 (0.76, 0.90)	0.83 (0.70, 0.98)	<0.0001
Combined, age-adjusted[b,c]	1.0	0.92 (0.89, 0.94)	0.81 (0.77, 0.84)	0.68 (0.64, 0.73)	<0.0001
Combined, multivariate-adjusted[b,c]	1.0	0.88 (0.85, 0.90)	0.81 (0.77, 0.84)	0.71 (0.66, 0.75)	<0.0001
Combined no. of cases	13,817	9,531	2,844	1,008	
Basal cell carcinoma—BMI 10 years prior to diagnosis					
NHS, age-adjusted	1.0	0.89 (0.86, 0.93)	0.81 (0.76, 0.86)	0.73 (0.66, 0.79)	<0.0001
NHS, multivariate-adjusted[b]	1.0	0.89 (0.86, 0.92)	0.79 (0.74, 0.83)	0.70 (0.64, 0.76)	<0.0001
HPFS, age-adjusted	1.0	0.88 (0.83, 0.94)	0.77 (0.68, 0.87)	0.61 (0.46, 0.82)	<0.0001
HPFS, multivariate-adjusted[b]	1.0	0.89 (0.84, 0.95)	0.79 (0.70, 0.89)	0.70 (0.52, 0.94)	<0.0001
Combined, age-adjusted[b,c]	1.0	0.93 (0.90, 0.96)	0.79 (0.75, 0.84)	0.68 (0.63, 0.74)	<0.0001
Combined, multivariate-adjusted[b,c]	1.0	0.88 (0.86, 0.91)	0.78 (0.74, 0.82)	0.69 (0.64, 0.76)	<0.0001
Combined no. of cases	11,408	6,177	1,657	570	
Basal cell carcinoma—baseline BMI[d]					
NHS, age-adjusted	1.0	0.82 (0.79, 0.85)	0.72 (0.67, 0.77)	0.58 (0.52, 0.66)	<.0001
NHS, multivariate-adjusted[b]	1.0	0.83 (0.80, 0.86)	0.74(0.69, 0.79)	0.58 (0.51, 0.65)	<.0001
HPFS, age-adjusted	1.0	0.89 (0.85, 0.94)	0.71(0.64, 0.79)	0.64 (0.51, 0.81)	<.0001
HPFS, multivariate-adjusted[b]	1.0	0.90 (0.86, 0.94)	0.76 (0.69, 0.84)	0.76 (0.60, 0.97)	<.0001
Combined, age-adjusted[b,c]	1.0	0.93 (0.90, 0.95	0.75 (0.71, 0.79)	0.60 (0.53, 0.66)	<.0001
Combined, multivariate-adjusted[b,c]	1.0	0.85 (0.82, 0.87	0.74 (0.70, 0.78)	0.61 (0.54, 0.68)	<.0001
Combined no. of cases	17, 768	7,062	1,346	330	

[a]BMI measured one follow-up cycle prior to the diagnosis of skin cancer

[b] Multivariate-adjusted for sunburn reaction, family history of melanoma, number of severe sunburns, number of moles, hair color, sun exposure at different age intervals, UV index at residence at different ages, physical activity (quintiles), and history of cardiovascular diseases, type 2 diabetes, and cancer

[c] The combined analysis of the two cohorts additionally controlling for gender

[d] BMI measured from baseline questionnaire (1976 for NHS, 1986 HPFS)

Table 4

Age-adjusted and multivariable-adjusted hazard ratios and 95 % confidence intervals for melanoma by BMI

Characteristics	BMI			*p* value for trend
	18.5–24.9	25.0–29.9	30+	
Melanoma—updated BMI[a]				
NHS, age-adjusted	1.0	1.23 (1.03, 1.46)	0.91 (0.72, 1.15)	0.84
NHS, multivariate-adjusted[b]	1.0	1.34 (1.12, 1.60)	1.06 (0.83, 1.36)	0.24
HPFS, age-adjusted	1.0	1.02 (0.80, 1.29)	0.76 (0.50, 1.15	0.77
HPFS, multivariate-adjusted[b]	1.0	1.04 (0.82, 1.33)	0.75 (0.49, 1.15)	0.78
Combined, age-adjusted[b,c]	1.0	1.21 (1.05, 1.40)	0.85 (0.69, 1.04)	0.84
Combined, multivariate-adjusted[b,c]	1.0	1.20 (1.04, 1.38)	0.91 (0.74, 1.13)	0.78
Combined no. of cases	440	363	122	
Melanoma—BMI 10 years prior to diagnosis				
NHS, age-adjusted	1.0	1.12 (0.90, 1.39)	0.80 (0.58, 1.09)	0.64
NHS, multivariate-adjusted[b]	1.0	1.19 (0.96, 1.48)	0.89 (0.65, 1.22)	0.70
HPFS, age-adjusted	1.0	0.99 (0.70, 1.38)	0.81 (0.43, 1.49)	0.71
HPFS, multivariate-adjusted[b]	1.0	1.04 (0.74, 1.47)	0.90 (0.48, 1.70)	0.44
Combined, age-adjusted[b,c]	1.0	1.14 (0.95, 1.36)	0.78 (0.59, 1.04)	0.94
Combined, multivariate-adjusted[b,c]	1.0	1.13 (0.94, 1.36)	0.85 (0.64, 1.14)	0.63
Combined number of cases	316	200	60	
Melanoma—baseline BMI[d]				
NHS, age-adjusted	1.0	1.12 (0.93, 1.34)	1.14 (0.87, 1.49)	0.21
NHS, multivariate-adjusted[b]	1.0	1.16 (0.96, 1.41)	1.20(0.91, 1.59)	0.097
HPFS, age-adjusted	1.0	0.93 (0.74, 1.19)	0.84(0.54, 1.32)	0.42
HPFS, multivariate-adjusted[b]	1.0	0.97 (0.76, 1.24)	0.85(0.53, 1.36)	0.50
Combined, age-adjusted[b,c]	1.0	1.17 (1.02, 1.35)	1.09(0.87, 1.38)	0.054
Combined, multivariate- adjusted[b,c]	1.0	1.06 (0.91, 1.24)	1.05(0.83, 1.34)	0.46
Combined number of cases	601	282	83	

[a] BMI measured one follow-up cycle prior to the diagnosis of skin cancer

[b] Multivariate-adjusted for sunburn reaction, family history of melanoma, number of severe sunburns, number of moles, hair color, sun exposure at different age intervals, UV index at residence at different ages, physical activity (quintiles), and history of cardiovascular diseases, type 2 diabetes and cancer

[c] The combined analysis of the two cohorts additionally controlling for gender

[d] BMI measured from baseline questionnaire (1976 for NHS, 1986 HPFS)

Table 5

Multivariable-adjusted hazard ratios and 95 % confidence intervals for SCC according to body site using updated BMI

Cohort	Body site	BMI	18.5–24.9	25.0–29.9	30+	*p* value
NHS						
	Head and neck	No. of cases	242	148	72	
		Person years	1,554,610	816,537	469,103	
		HR(95 % CI)	1.0	0.88 (0.71, 1.08)	0.73 (0.55, 0.96)	0.08
	Trunk and shoulder	No. of cases	81	36	14	
		Person years	1,554,749	816,637	469,158	
		HR (95 % CI)	1.0	0.61 (0.41,0.91)	0.42 (0.23, 0.77)	0.02
	Arm and hand	No. of cases	128	67	39	
		Person years	1,554,692	816,613	469,143	
		HR (95 % CI)	1.0	0.73 (0.54, 0.98)	0.71 (0.49, 1.05)	0.08
	Leg	No. of cases	119	60	18	
		Person years	1,554,711	816,621	469,154	
		HR (95 % CI)	1.0	0.73 (0.53, 1.00)	0.39 (0.23, 0.65)	<0.0001
HPFS						
	Head and neck	No. of cases	182	220	47	
		Person years	268,305	311,134	77,819	
		HR (95 % CI)	1.0	1.08 (0.88, 1.32)	0.96 (0.69, 1.34)	0.78
	Trunk and shoulder	No. of cases	43	37	8	
		Person years	268,439	311,294	77,850	
		HR (95 % CI)	1.0	0.80 (0.51, 1.25)	0.72 (0.33, 1.59)	0.21
	Arm and hand	No. of cases	76	93	16	
		Person years	268,418	311,261	77,844	
		HR (95 % CI)	1.0	0.99 (0.72, 1.35)	0.66 (0.37, 1.15)	0.34
	Leg	No. of cases	21	14	5	
		Person years	268,463	311,316	77,854	
		HR (95 % CI)	1.0	0.58 (0.29, 1.18)	0.93 (0.33, 2.63)	0.52

Multivariate-adjusted for sunburn reaction, family history of melanoma, number of severe sunburns, number of moles, hair color, sun exposure at different age intervals, UV index at residence at different ages, physical activity (quintiles), and history of cardiovascular diseases, type 2 diabetes, and cancer