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Skin cancer as a marker of sun exposure associates with myocardial infarction, hip fracture and death from any cause

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Background Sun exposure is the single most important risk factor for skin cancer, but sun exposure may also have beneficial effects on health. We tested the hypothesis that individuals with skin cancer (non-melanoma skin cancer and cutaneous malignant melanoma) have less myocardial infarction, hip fracture and death from any cause, compared with general population controls.

Methods We examined the entire Danish population above age 40 years from 1980 through 2006, comprising 4.4 million individuals. Diagnoses of non-melanoma skin cancer ($n = 129\,206$), cutaneous malignant melanoma ($n = 22107$), myocardial infarction ($n = 327\,856$), hip fracture ($n = 129\,419$), and deaths from any cause ($n = 1\,629\,519$) were drawn from national registries.

Results In individuals with vs without non-melanoma skin cancer, multifactorially adjusted odds ratios were 0.96 (95% confidence interval: 0.94–0.98) for myocardial infarction and 1.15 (1.12–1.18) for hip fracture, and the multifactorially adjusted hazard ratio was 0.52 (0.52–0.53) for death from any cause. Risk of hip fracture was reduced (odds ratios were below 1.0) in individuals below age 90 years. In individuals with vs without cutaneous malignant melanoma, corresponding odds ratios were 0.79 (0.74–0.84) for myocardial infarction and 0.84 (0.76–0.93) for hip fracture, and the corresponding hazard ratio for death from any cause was 0.89 (0.87–0.91); however, cutaneous malignant melanoma was associated positively with death from any cause in some individuals.

Conclusions In this nationwide study, having a diagnosis of skin cancer was associated with less myocardial infarction, less hip fracture in those below age 90 years and less death from any cause. Causal conclusions cannot be made from our data. A beneficial effect of sun exposure *per se* needs to be examined in other studies.

Keywords Sun exposure, skin cancer, myocardial infarction, hip fracture, mortality, nationwide study

Introduction

Public health recommendations warn against high sun exposure in view of the risk of skin cancer in general and cutaneous malignant melanoma in particular. However, sun exposure has been reported to be associated with lower risk of cardiovascular diseases and with other beneficial effects on health.[1,2] Although the balance between positive and negative effects of sun exposure in the public debate currently leans towards the negative side, the scientific evidence for this balance is largely unclear.

Sun exposure is the single most important risk factor in the pathogenesis of skin cancer, accounting for an estimated 80–85% of both non-melanoma basal cell carcinoma and squamous cell carcinoma (here collectively referred to as non-melanoma skin cancer) and cutaneous malignant melanoma.[3,4] Constant and prolonged sun exposure patterns cause non-melanoma skin cancer, whereas overexposure as a child and high intensity intermittent sun exposure primarily cause cutaneous malignant melanoma.[5,6]

We tested the hypothesis that having a diagnosis of skin cancer was associated with less myocardial infarction, hip fracture and death from any cause, compared with general population controls. We chose to include these three hard outcomes because myocardial infarction and hip fracture (as a clinical marker of osteoporosis) almost always lead to hospitalization in Denmark and therefore are registered as described below, and because these two diagnoses are unlikely to be given to patients during a hospitalization without proper diagnostic tests. Furthermore, death is the hardest of all outcomes and is registered 100% in Denmark. We studied the entire Danish population above age 40 years from 1980 through 2006 and used information from the national Danish Cancer Registry, the national Danish Patient Registry, the national Danish Causes of Death Registry, the national Danish Civil Registration System and Statistics Denmark; all registries were complete during this period. We first used a cross-sectional design for the outcomes myocardial infarction and hip fracture and a prospective design for the outcome death from any cause, and secondly, a matched design to circumvent effects of time (calendar year) and changes in sun exposure habits and in treatment of cancer during the observation period.

Methods

We conducted a study of the entire Danish population above age 40 years from 1 January 1980 through 31 December 2006, comprising 4 412 568 individuals. Almost 90% of the Danish population are Whites of Danish descent. Denmark is situated in the northern hemisphere at latitudes 54–57N and has a mean of 1495 sun-h per year or a mean of 4.1 sun-h per day (www.dmi.dk). The national Danish Civil Registration System records all births, deaths, emigrations and immigrations in Denmark, recorded by a civil registration number unique to every person living in Denmark, including information about age and gender.

This study was approved by Herlev Hospital, Copenhagen University Hospital, Statistics Denmark and the Danish Data Protection Agency. Anonymous nationwide studies in Denmark do not require approval from ethical committees.

Exposures: non-melanoma skin cancer and cutaneous malignant melanoma

Diagnoses and dates of skin cancer were drawn from the national Danish Cancer Registry, which identifies 98% of cancer cases in Denmark from all hospitals and private practising pathologists; neither non-melanoma skin cancer nor cutaneous malignant melanoma diagnoses were based on self-reports.[7] All individuals with a diagnosis of non-melanoma skin cancer according to the International Classification of Diseases (ICD-7 until 31 December 2003, thereafter ICD-10; ICD-7: 191; ICD-10: C44) and cutaneous malignant melanoma (ICD-7: 190; ICD-10: C43) from 1 January 1980 through 31 December 2006 were identified.

Outcomes: acute myocardial infarction, hip fracture and death from any cause

Diagnoses and dates of myocardial infarction and hip fracture were drawn from the national Danish Patient Registry and the national Danish Causes of Death Registry, recording information on discharge diagnoses from all Danish hospitals including outpatients and causes of death reported by hospitals and general practitioners using the civil registration number.[7] Myocardial infarction (ICD-8: 410; ICD-10: I21) and hip fracture (ICD-8: 820; ICD-10: S72.0, S72.1, S72.2) from 1980 through 2006 were used in the study.

Information on death from any cause was drawn from the national Danish Civil Registration System, recording information about deaths in Denmark, using the civil registration number.

Other covariates

Statistics Denmark records information on descent coded as Danish or other descent, educational level and geographical residential city size for all persons living in Denmark. From 1 January 1980 through 31 December 1995, Statistics Denmark also recorded detailed information on occupation with 202 different categories. Each occupational category was assigned an estimated sun exposure level (low or high) and an estimated physical activity level (low, intermediate or high) based on general knowledge, and two variables were generated. For example,. farmers will be coded as high occupational sun exposure and high occupational physical activity and office workers will be low in both categories.

Statistical analysis

Statistical analyses were performed with STATA MP 11.1 software. We assessed the association between diagnoses of non-melanoma skin cancer and cutaneous malignant melanoma and the three outcomes, myocardial infarction, hip fracture and death from any cause, by surveillance of all individuals above age 40 years living in Denmark from 1 January 1980, from the 40th birthday or from time of immigration (whichever occurred last) to occurrence of the outcome investigated (e.g. myocardial infarction, hip fracture or death from any cause), emigration or 31 December 2006 (whichever occurred first). Individuals who first emigrated and later returned to Denmark were still included in the analyses. We used Kaplan–Meier curves and log rank tests. For the outcomes myocardial infarction and hip fracture, we used logistic regression models because of the temporality between the exposure and the outcomes, and odds ratios were calculated as measures of relative risk. For the endpoint death from any cause, we used Cox regression models with age as the time scale, implying that age is automatically adjusted for, and hazard ratios were calculated as measures of relative risk. The Cox regression models were left truncated (in 1980, at the 40th birthday or at immigration) with delayed entry, and individuals were censored at event, death, permanent emigration or end of follow-up. We assessed the assumption of proportional hazards graphically by plotting log (cumulative hazards) as a function of follow-up time. We detected no major violations until age 100 years for myocardial infarction, hip fracture or death from any cause, except for cutaneous malignant melanoma and death from any cause. To address potential modification by age, we also performed the above-mentioned analyses in age-strata of 10 years.

Both regression models were adjusted multifactorially for age, gender, descent, geographical residency, educational level, estimated occupational sun exposure and estimated occupational physical activity, and were also stratified by baseline characteristics.

To circumvent the effect of time (calendar year) and changes in sun exposure habits and in treatment of cancer during the past three decades, we performed a matched analysis matching each individual with non-melanoma skin cancer or cutaneous malignant melanoma to five general population controls on the basis of age, birth year and gender; we then used logistic regression modeling overall and in age-strata of 10 years.

Results

We included the entire Danish population above age 40 years from 1980 through 2006 comprising 4 412 568 individuals. Median surveillance time was 23 years. Baseline characteristics are shown in Table 1. We identified 129 206 individuals with non-melanoma skin cancer, 22 107 with cutaneous malignant melanoma, 327 856 with myocardial infarction, 129 419 with hip fracture and 1 629 519 individuals who died. Mean age of outcomes was 68 years for diagnosis of non-melanoma skin cancer, 59 years for cutaneous malignant melanoma, 69 years for myocardial infarction, 78 years for hip fracture and 76 years for death from any cause.

Myocardial infarction

Cumulative incidence of myocardial infarction as a function of age was lower among individuals with non-melanoma skin cancer (log rank, P-value $<2 \times 10^{-308}$) and individuals with cutaneous malignant melanoma (log rank, P-value $= 5 \times 10^{-67}$), than among individuals without (Figure 1).

In individuals with vs without non-melanoma skin cancer, the multifactorially adjusted odds ratio was 0.96 (95% confidence interval: 0.94–0.98) for myocardial infarction (Table 2, top). The corresponding odds ratio in individuals with cutaneous malignant melanoma compared with individuals without was 0.79 (0.74–0.84). Stratifying by baseline characteristics only changed odds ratios slightly in most strata (Table 2).

Hip fracture

Cumulative incidence of hip fracture as a function of age was lower among individuals with non-melanoma skin cancer (log rank, P-value $= 9 \times 10^{-233}$) and individuals with cutaneous malignant melanoma (log rank, P-value $= 1 \times 10^{-28}$), than among individuals without (Figure 1).

In individuals with vs without non-melanoma skin cancer, the multifactorially adjusted odds ratio was 1.15 (1.12–1.18) for hip fracture (Table 2, top). The corresponding odds ratio in individuals with cutaneous malignant melanoma compared with individuals without was 0.84 (0.76–0.93). Stratifying by baseline characteristics only changed odds ratios slightly in most strata (Table 2).

The odds ratio of 1.15 (1.12–1.18) for hip fracture in those with vs without non-melanoma skin cancer could be because those with skin cancer live longer and therefore eventually will fall and have a hip fracture, which is particularly common in the elderly. We therefore made a age-stratified analysis and estimated the odds ratio for hip fracture in age-strata of 10 years: up to age 80–89 years the odds ratio was below 1.0, whereas for age-strata 90–99 and >100 years the odds ratios were nominally above 1.0 (Figure 2).

Death from any cause

Cumulative incidence of death from any cause as a function of age was lower among individuals with non-melanoma skin cancer (log rank, P-value $< 2 \times 10^{-308}$) compared with individuals without (Figure 1). Cumulative incidence of death from any

Table 1 Baseline characteristics

	Individuals without skin cancer		Individuals with non-melanoma skin cancer		Individuals with cutaneous malignant melanoma[b]	
	Number	Percent within stratum	Number	Percent within stratum	Number	Percent within stratum
Total	4 261 345		129 206		22 017	
Gender						
Men	2 091 806	49%	64 147	50%	9696	47%
Women	2 169 539	51%	65 059	50%	12 321	53%
Descent						
Danish	3 988 308	94%	124 819	97%	21 354	97%
Other	261 784	6%	4372	3%	659	3%
Occupational sun exposure[a]						
Low	3 929 549	96%	118 642	95%	20 362	96%
High	172 451	4%	6342	5%	928	4%
Residential city size						
<12 000 inhabitants or rural	1 688 871	40%	45 412	35%	8399	38%
12 100 000 inhabitants	1 092 173	26%	33 574	26%	5882	27%
>100 000 inhabitants	1 466 266	34%	50 200	39%	7731	35%
Occupational physical activity[a]						
Low	2 418 807	59%	74 242	59%	11 699	55%
Intermediate	807 832	20%	26 144	21%	5001	23%
High	890 986	21%	24 709	20%	4635	22%
Highest level of education						
Unknown[c]	1 042 158	25%	45 722	35%	4225	19%
Primary school	1 206 611	29%	32 653	25%	6082	28%
High school	95 348	2%	1812	1%	418	3%
Vocational education	1 131 858	271%	29 141	23%	6510	30%
Short academic education	137 917	3%	3304	2%	770	4%
Medium academic education	405 957	10%	10 927	9%	2755	13%
Long academic education	175 194	4%	5549	5%	1173	5%

Baseline was at study inclusion in 1980, 40th birthday, or at immigration (whichever occurred last). Numbers of individuals vary slightly due to availability of data.

[a]From 1 January 1980 through 31 December 1995, Statistics Denmark also recorded detailed information on occupation, which allowed us to generate two composite variables: a variable of estimated occupational sun exposure (low or high) and a variable of estimated occupational physical activity (low, intermediate, or high).

[b]Individuals with both non-melanoma skin cancer and cutaneous malignant melanoma were counted only in the cutaneous malignant melanoma group.

[c]Information regarding education was not available if the education was completed prior to 1980 or abroad.

cause as a function of age was higher among individuals with cutaneous malignant melanoma (log rank, P-value $= 1 \times 10^{-28}$) compared with individuals without, except above age ~70 years (Figure 1).

In individuals with vs without non-melanoma skin cancer, the multifactorially adjusted hazard ratio was 0.52 (0.52–0.53) for death from any cause (Table 2, top). The corresponding hazard ratio in individuals with cutaneous malignant melanoma compared with individuals without was 0.89 (0.87–0.91). Stratifying by baseline characteristics only changed hazard ratios slightly in most strata (Table 2). For cutaneous malignant melanoma, stratifying by level of education showed reduced risk of death from any cause in the group with unknown educational level(dominated by older people), and higher risk of death from any cause in those with high school or more advanced educational level, largely reflecting domination by younger individuals in these latter groups. This pattern was also seen in the age-stratified analysis: among individuals

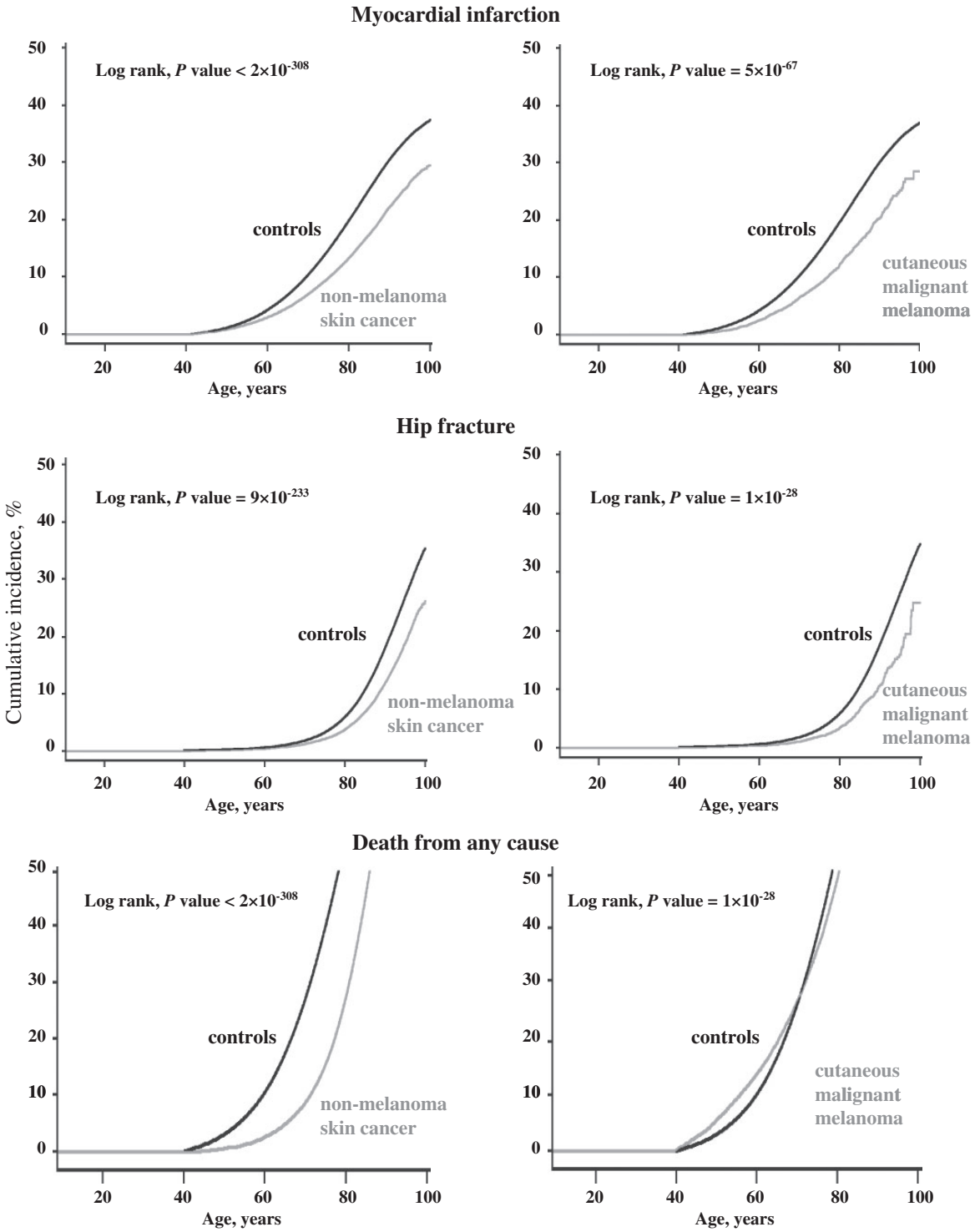

Figure 1 The cumulative incidence of myocardial infarction, hip fracture and death as a function of age in individuals above age 40 years ever diagnosed with non-melanoma skin cancer and cutaneous malignant melanoma. Cumulative incidence curves were generated from Kaplan–Meyer estimates, comparing individuals with non-melanoma skin cancer and cutaneous malignant melanoma vs individuals free of both diseases. *P*-values are for comparison between groups by log rank tests

Table 2 Odds ratios of myocardial infarction and hip fracture, and hazard ratios of death from any cause, in individuals ever diagnosed with non-melanoma skin cancer or cutaneous malignant melanoma in the entire Danish population above age 40 years stratified by baseline characteristic

	Non-melanoma skin cancer			Cutaneous malignant melanoma		
	Myocardial infarction OR (95% CI)	Hip fracture OR (95% CI)	Death from any cause HR (95% CI)	Myocardial infarction OR (95% CI)	Hip fracture OR (95% CI)	Death from any cause HR (95% CI)
All	0.96 (0.94–0.98)	1.15 (1.12–1.18)	0.52 (0.52–0.53)	0.79 (0.74–0.84)	0.84 (0.76–0.93)	0.89 (0.87–0.91)
Gender						
Men	0.96 (0.94–0.98)	1.17 (1.11–1.22)	0.52 (0.51–0.53)	0.76 (0.70–0.82)	0.79 (0.65–0.95)	0.90 (0.87–0.93)
Women	0.96 (0.93–0.99)	1.15 (1.11–1.19)	0.53 (0.53–0.54)	0.82 (0.75–0.91)	0.87 (0.78–0.98)	0.89 (0.86–0.92)
Descent						
Danish	0.96 (0.94–0.98)	1.14 (1.11–1.18)	0.52 (0.52–0.53)	0.79 (0.74–0.84)	0.85 (0.77–0.93)	0.89 (0.87–0.91)
Other	1.04 (0.93–1.17)	1.36 (1.15–1.60)	0.55 (0.52–0.58)	0.86 (0.60–1.23)	0.59 (0.27–1.26)	1.03 (0.90–1.17)
Occupational sun exposure						
Low	0.97 (0.95–0.99)	1.17 (0.99–1.38)	0.52 (0.52–0.53)	0.80 (0.75–0.85)	0.84 (0.76–0.93)	0.88 (0.86–0.90)
High	0.89 (0.83–1.06)	1.15 (1.11–1.18)	0.58 (0.55–0.60)	0.68 (0.54–0.86)	0.80 (0.45–1.42)	1.03 (0.94–1.13)
Residential city size						
<12 000 inhabitants or rural	0.94 (0.91–0.97)	1.15 (1.09–1.20)	0.55 (0.54–0.56)	0.71 (0.64–0.85)	0.91 (0.78–1.07)	0.97 (0.93–1.00)
12–100 000 inhabitants	0.96 (0.92–1.00)	1.14 (1.08–1.21)	0.53 (0.52–0.54)	0.84 (0.75–0.94)	0.78 (0.64–0.96)	0.90 (0.86–0.94)
>100 000 inhabitants	0.98 (0.95–1.01)	1.15 (1.10–1.20)	0.50 (0.50–0.51)	0.84 (0.76–0.93)	0.82 (0.70–0.96)	0.82 (0.79–0.84)
Occupational physical activity						
Low	0.99 (0.83–0.91)	1.15 (1.11–1.18)	0.55 (0.54–0.57)	0.84 (0.77–0.91)	0.84 (0.75–0.94)	1.01 (0.97–1.06)
Intermediate	0.85 (0.81–0.89)	1.03 (0.94–1.13)	0.52 (0.51–0.54)	0.66 (0.58–0.76)	0.68 (0.50–0.93)	1.04 (0.99–1.10)
High	0.87 (0.83–0.96)	1.06 (0.97–1.15)	0.52 (0.51–0.52)	0.73 (0.65–0.82)	0.88 (0.69–1.12)	0.81 (0.79–0.84)
Highest level of education						
Unknown[a]	0.91 (0.90–0.94)	1.14 (1.10–1.18)	0.52 (0.52–0.53)	0.73 (0.66–0.81)	0.86 (0.76–0.97)	0.71 (0.68–0.73)
Primary school	0.82 (0.79–0.86)	0.90 (0.83–0.97)	0.52 (0.51–0.53)	0.72 (0.64–0.80)	0.74 (0.59–0.91)	0.98 (0.94–1.02)
High school	0.86 (0.68–1.08)	0.91 (0.61–1.38)	0.49 (0.43–0.55)	1.05 (0.62–1.77)	0.90 (0.32–2.46)	1.38 (1.13–1.67)
Vocational education	0.81 (0.77–0.85)	0.95 (0.85–1.05)	0.51 (0.50–0.52)	0.71 (0.62–0.81)	0.64 (0.46–0.88)	1.15 (1.10–1.21)
Short academic education	0.93 (0.80–1.09)	0.75 (0.52–1.08)	0.53 (0.49–0.58)	0.58 (0.36–0.93)	0.90 (0.37–2.19)	1.46 (1.25–1.71)
Medium academic education	0.76 (0.68–0.84)	1.00 (0.82–1.22)	0.53 (0.50–0.56)	0.60 (0.46–0.80)	0.51 (0.27–0.99)	1.40 (1.28–1.52)
Long academic education	0.94 (0.83–1.06)	1.08 (0.84–1.39)	0.57 (0.54–0.61)	0.74 (0.53–1.05)	0.69 (0.31–1.57)	1.24 (1.10–1.40)

OR, odds ratio; HR, hazard ratio; CI, confidence interval.

Odd ratios are from logistic regression analysis and hazard ratios are from Cox regression analysis, both including the entire population above age 40 years and adjusted multivariate for age, gender, descent, occupational sun exposure, residential city size, occupational physical activity and highest level of education.

[a]Information regarding education was not available if the education was completed prior to 1980 or abroad.

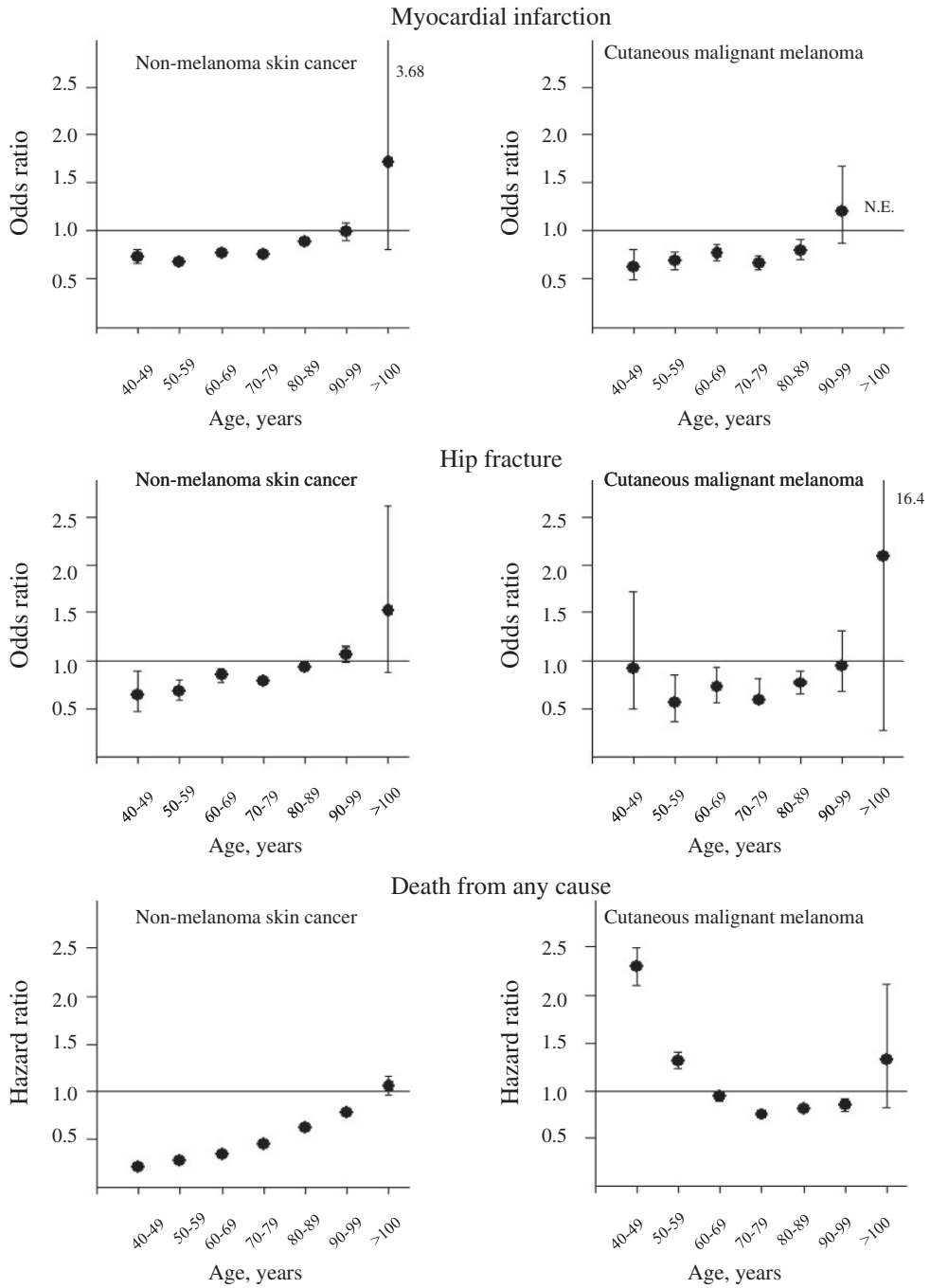

Figure 2 In the entire Danish population above age 40 years, odds ratios for myocardial infarction and hip fracture and hazard ratios for death from any cause within 10-years age-strata. N.E., no estimation due to limited statistical power

aged 40–59 years there was an increased risk of death from any cause, whereas this was not the case for individuals at age 60 and above (Figure 2).

Birth year-, age- and gender-matched case-control study

To circumvent the effect of time (calendar year), changes in sun exposure habits and changes in treatment of cancer during the observation period, we also examined the risk of myocardial infarction, hip fracture and death from any cause in individuals with non-melanoma skin cancer or cutaneous malignant melanoma matched with five general population controls on birth year, age and gender. For these analyses only myocardial infarction and hip fracture events following a diagnosis of non-melanoma skin cancer or cutaneous malignant melanoma entered into the analysis, whereas events before skin cancer were excluded.

Table 3 Odds ratios of myocardial infarction, hip fracture and death from any cause in individuals above 40 years with non-melanoma skin cancer and cutaneous malignant melanoma

	Non-melanoma skin cancer		Cutaneous malignant melanoma	
	Age-adjusted OR (95% CI)	Multifactorially adjusted OR (95% CI)	Age-adjusted OR (95% CI)	Multifactorially adjusted OR (95% CI)
Myocardial infarction	0.87 (0.85–0.90)	0.90 (0.88–0.92)	0.72 (0.66–0.78)	0.74 (0.68–0.81)
Hip fracture	0.97 (0.92–1.00)	0.99 (0.95–1.02)	0.70 (0.61–0.79)	0.71 (0.62–0.81)
Death from any cause	0.96 (0.95–0.97)	0.97 (0.96–0.99)	1.55 (1.50–1.60)	1.96 (1.89–2.04)

OR, odds ratio; CI, confidence interval.
To circumvent the effect of time (calendar year), changes in sun exposure habits and change in treatment of cancer during the past three decades, individuals with non-melanoma skin cancer or cutaneous malignant melanoma were each matched with five general population controls of the same birth year, age and gender. Birth year was matched beside age to also take into account that people born at different time periods throughout history have used sun exposure to a different degree.

In individuals with vs without non-melanoma skin cancer, the multifactorially adjusted odds ratios were 0.90 (0.88–0.99) for myocardial infarction, 0.99 (0.95–1.02) for hip fracture and 0.97 (0.96–0.99) for death from any cause (Table 3). In individuals with vs without cutaneous malignant melanoma, the multifactorially adjusted odds ratios were 0.74 (0.68–0.81) for myocardial infarction, 0.71 (0.62–0.81) for hip fracture, and 1.96 (1.89–2.04) for death from any cause (Table 3). In sensitivity analyses, corresponding odds ratios in 10-year age strata are shown in Figure 3.

Discussion

In a nationwide study of 4.4 million individuals above age 40 years, having a diagnosis of skin cancer was associated with less myocardial infarction, less hip fracture in those below age 90 years and less death from any cause. However, cutaneous malignant melanoma was associated positively with death from any cause in some individuals. As skin cancer is a marker of a substantial sun exposure, these results indirectly suggest that sun exposure might have beneficial effects on health. However, causal or mechanistic conclusions cannot be drawn from this study design and a potential beneficial effect of sun exposure *per se* needs to be examined in other studies.

Mechanistically, one could however speculate that our findings theoretically could be explained by an association between increased sun exposure and more outdoor physical activity. In accordance with this, there is an inverse linear dose-response between physical activity and risk of cardiovascular disease, osteoporosis and all-cause mortality.[8,9] In further support of this idea are the findings in the present study of the lowest risk of myocardial infarction and death from any cause in individuals with a high level of occupational physical activity.

Another theoretically possible explanation of our findings relates to the fact that increased sun exposure also associates with increased vitamin D synthesis. Vitamin D exerts both direct and indirect endocrine, immunomodulatory and neurohormonal effects on the cells of the cardiovascular system, potentially leading to an overall protection against cardiovascular disease.[10–12] An association between high levels of vitamin D and lower cardiovascular morbidity and mortality has been reported in several epidemiological studies,[13] whereas randomized controlled trials show no effect of supplementation with vitamin D on risk of cardiovascular mortality.[14] Reports on vitamin D and risk of osteoporosis are ambiguous; results from epidemiological studies show that high levels of vitamin D associate with decreased risk of hip fracture, whereas results from meta-analyses of randomized controlled trials have failed to show an effect on risk of hip fracture.[15,16] However, a meta-analysis of vitamin D and calcium supplementation combined concludes that this treatment lowers risk of hip fracture.[17] The association between high levels of vitamin D and lower mortality has been demonstrated both in epidemiological studies and in several randomized controlled trials with mortality as a secondary outcome.[18,19]

In the present study, age is a potential effect modifier; to address this possibility we have restricted all analyses to age above 40 years, adjusted for age in the logistic regression analyses, in the Cox regression analysis used age as the underlying intensity and in the matched study matched on age. Moreover, we have performed age-stratified analyses in age-strata of 10 years. For hip fracture, although the overall odds ratio was 1.15 (95% CI: 1.12–1.18), among those below age 90 years odds ratios in those with vs without non-melanoma skin cancer were below 1.0. This suggests that individuals with non-melanoma skin cancer, which is most often a benign condition, sometimes live longer with a consequent increase in risk of hip fracture at very old age. Although, in our data, individuals with cutaneous malignant melanoma and high occupational sun exposure showed no association with mortality from any cause, including from cancer, it has been shown that sun exposure may increase survival from malignant melanoma; this suggests that cutaneous malignant melanoma may be

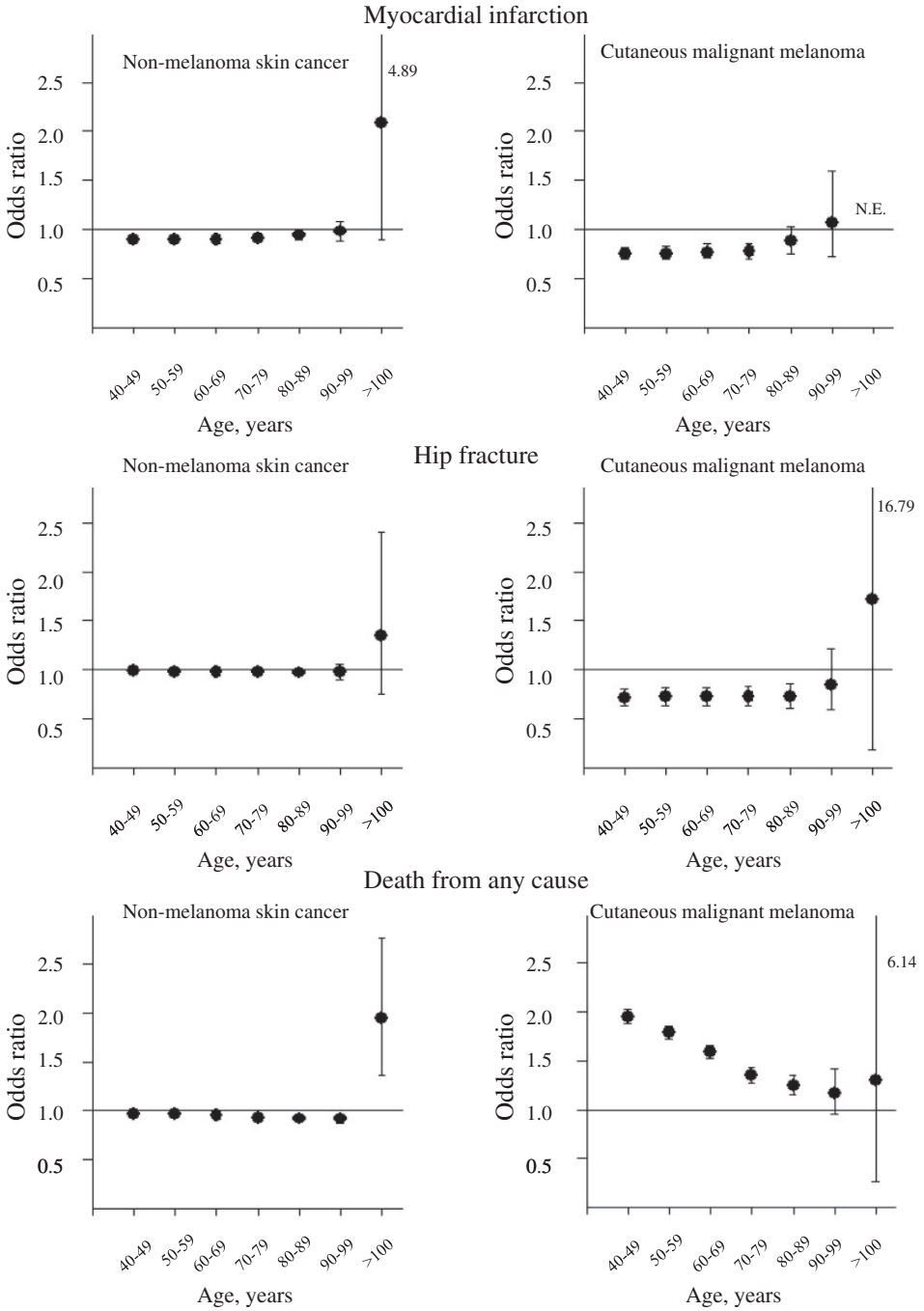

Figure 3 In a matched study within the entire Danish population above age 40 years, odds ratios for myocardial infarction, hip fracture and death from any cause within 10-years age-strata. Individuals with non-melanoma skin cancer or cutaneous malignant melanoma were each matched with five general population controls of the same birth year, age and gender. N.E., no estimation due to limited statistical power

biologically more benign if it occurs in association with high levels of sun exposure.[20] The difference in estimates between individuals with a diagnosis of non-melanoma skin cancer and individuals with a diagnosis of cutaneous malignant melanoma could be due to the fact that non-menaloma skin cancer is most often a benign condition, and thus individuals with this diagnosis live longer and have 'the full benefit' of sun exposure throughout life, as opposed to individuals with cutaneous malignant melanoma, who often die early.

A strength of the present study is the use of a large nationwide cohort, with complete registration of diagnoses, death and migration and with a median

follow-up time of 23 years. Limitations include that the study population mostly consists of Whites and results may therefore not necessarily apply to other ethnic groups. Also, a limitation of the use of skin cancer diagnoses as a proxy for sun exposure is that not all skin cancers are caused by sun exposure. This presumably smaller fraction of skin cancers could have their own association to the outcomes studied, and may therefore cause both under- and overestimation of the observed associations. Moreover, there is a large variability in the genetic susceptibility to development of skin cancer upon ultraviolet radiation exposure,[21] and therefore some individuals with very high level of sun exposure may not develop skin cancer whereas other individuals with low levels of sun exposure develop skin cancer. This would in both cases lead to an attenuation of the observed associations, and therefore cannot explain the present findings. Furthermore, for the outcome myocardial infarction, our results could be biased by cases of silent myocardial infarction leading to differential misclassification: it is not unlikely that cases of silent myocardial infarction would be more frequently registered in cancer patients in contact with the Danish health care service, and this could either overestimate or underestimate the true association. Finally, a limitation is that we did not have information from Statistics Denmark on smoking status and we cannot adjust for smoking status in our analyses; smoking could be an important confounder or effect modifier associated with exposures as well as outcome variables.

In conclusion, the present study suggests that having a diagnosis of skin cancer was associated with less myocardial infarction, less hip fracture in those below age 90 years and less death from any cause compared with general population controls. Although some individuals with cutaneous malignant melanoma experience increased risk of death from any cause, the overall data indirectly suggest that sun exposure for many individuals may have beneficial health effects, and therefore also question the widespread advice that sun exposure should avoided. Nevertheless, a potential beneficial effect of sun exposure per se needs to be examined in other studies.

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KEY MESSAGES

- In a nationwide study of 4.4 million individuals above age 40 years, having a diagnosis of skin cancer was associated with less myocardial infarction, less hip fracture and less death from any cause.
- As skin cancer is a marker of a substantial sun exposure, these results indirectly suggest that sun exposure might have beneficial effects on health.
- However, causal or mechanistic conclusions cannot be drawn from this study design and a potential beneficial effect of sun exposure per se needs to be examined in other studies.

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