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Physical activity and cutaneous melanoma risk: A Norwegian population-based cohort study

Flavie Perrier^{1,*}, perrier@medisin.uio.no, Reza Ghiasvand^{2,3}, Simon Lergenmuller¹, Trude E. Robsahm³, Adele C. Green^{4,5}, Kristin B. Borch⁶, Torkjel M. Sandanger⁶, Elisabete Weiderpass⁷, Corina S. Rueegg², Marit B. Veierød¹.

¹Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway;

²Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway;

³Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway;

⁴QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia;

⁵Cancer Research UK Manchester and Faculty of Biology, Medicine and Health, University of Manchester, United Kingdom;

⁶Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway;

⁷International Agency for Research on Cancer, Lyon, France.

* **Corresponding author at:** Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, PO Box 1122 Blindern, N-0317 Oslo, Norway flavie.

Abstract

Physical activity (PA) is an important factor in cancer prevention, but positive association between PA and risk of cutaneous melanoma found in recent studies may complicate this strategy. Ultraviolet radiation (UVR) exposure during outdoor PA is a plausible explanation for a positive association. We investigated the associations between PA, UVR and melanoma risk in the Norwegian Women and Cancer cohort. Overall PA was reported by 151,710 women, aged 30-75 at inclusion, using a validated 10-point-scale at enrolment and during follow-up, together with recent numbers of sunburns, indoor tanning sessions and weeks on sunbathing vacations. Seasonal outdoor walking and seasonal PAs were recorded in subsamples (n=102,671 and n=29,077, respectively). Logistic and Cox regression were used. Mean follow-up was 18.5 years, and 1,565 invasive incident melanoma cases were diagnosed. Overall PA was inversely associated with sunburns, while positively associated with sunbathing vacations and indoor tanning. Overall PA was not associated with melanoma risk in all body sites combined ($p_{\text{trend}}=0.61$), but reduced risk was found in upper limb melanomas (hazard ratio (HR)=0.70, 95% confidence interval (CI) 0.51-0.96; high versus low PA). Non-significant reduced risks

were found for seasonal outdoor walking >2 h/day versus 30-60 min/day (summer HR=0.81, 95% CI 0.66-1.00; autumn HR=0.74, 95%CI 0.55-1.01). Seasonal PAs were not associated with melanoma risk. In conclusion, we found positive associations between overall PA and sunbathing vacations and indoor tanning, and, unlike literature, inverse association between overall PA and sunburns. Our results do not support a positive association between PA and melanoma risk in Norwegian women.

Keywords

physical activity, ultraviolet radiation, cutaneous melanoma, cohort, women, Norway

List of abbreviation

BMI	body mass index
CI	confidence interval
CNR	Cancer Registry of Norway
DAG	directed acyclic graph
HR	hazards ratio
NOWAC	Norwegian Women and Cancer
OR	odds ratio
PA	physical activity
SSC	squamous cell carcinomas
UVR	ultraviolet radiation

1. Introduction

Incidence of cutaneous melanoma (hereafter, melanoma) has been rising in fair-skinned populations during the past decades (1). In 2020, about 324,635 new cases were diagnosed worldwide (2). Norway is the European country with the highest incidence rate, and the third leading country worldwide, after Australia and New Zealand.

Physical activity (PA) is a major component of cancer prevention promoted by public health authorities. PA is demonstrated to regulate body weight and hormones (sex steroids, insulin and insulin-like growth factors and adipokines), has positive impact on biological pathways (increased DNA repair capacity, decreased oxidative stress, reduced inflammation and enhanced immune function) (3), and is a well-recognized protective and modifiable risk factor for many diseases,

including several types of cancer (4, 5). There is convincing epidemiological evidence that PA decreases risk of colon, endometrium, bladder, breast, kidney, esophagus and stomach cancers, while accumulating evidence suggests that PA may also be protective for other cancers, including ovary, prostate and pancreatic cancers (6, 7). PA has been less studied in relation to melanoma, and inconsistent results have been reported. Notably, a pool of cohorts, a recent meta-analysis and a case-control study suggested that PA might be associated with increased risk of melanoma (4, 8, 9), while a case-control study found inverse association (10) and other studies found no association (11-14). The inconsistent findings in these studies might be partially explained by different geographical study localisations. Moreover, an absence (4, 9, 12, 14) or a broad assessment (8, 10, 11, 13) of ultraviolet radiation (UVR) exposure might also explain differences. Indeed solar UVR exposure is the major established melanoma risk factor (7). In 2012, population attributable fraction estimates for solar UVR were 65-90% in populations with predominantly European ancestry, including 89.5% in Northern Europe (15). UVR during outdoor PA is a plausible explanation for a positive association between PA and melanoma risk.

This study aimed at examining the relationship between PA, UVR exposure and risk of melanoma in women using data from the Norwegian Women and Cancer (NOWAC) study, a large, well-characterized population-based cohort with information on PA and UVR exposure updated during follow-up. Firstly, we investigated the association between overall PA and UVR exposure, and secondly the associations between overall and seasonal PAs and melanoma risk.

2. Methods

2.1. NOWAC cohort

The NOWAC cohort recruited women between 1991 and 2007 (16). Questionnaires were sent to a sample of over 320,000 women, aged 30 to 75 years, randomly drawn from the Norwegian National Population Register. More than 172,000 participants answered and gave written informed consent to participate response (54%). The first and second follow-up questionnaires (response 80% and 79%, respectively) were sent after 5 to 7 years.

2.2. Physical activity (PA) assessment

Participants reported PA at recruitment and follow-up using a validated 10-point scale (17) following the description: "By physical activity we mean activity both at work and outside work, at home, as well as training/exercise and other physical activity, such as walking, etc. Please mark the number that best describes your level of physical activity; 1 being very low and 10 being very high" (18).

Based on this question, overall (global) PA refers to total amount of PA across different domains (recreation, occupation, transport and household), categorized as: very low (1-2), low (3-4), moderate (5-6), high (7-8) and very high (9-10) (19).

A subsample of the cohort (n=105,256) was asked to report, for each season of the year in Norway (summer, autumn, winter and spring), the average number of hours per day spent walking or strolling outdoors, recorded as <1/2 hour, 1/2-1 hour, 1-2 hours and >2 hours (hereafter, seasonal outdoor walking). Also, a subsample of participants (n=46,412) was asked to report the average number of minutes per day spent gardening, jogging/exercising and biking for each season recorded as a continuous variable (hereafter, seasonal PAs). We calculated the total time spent active by summarizing these three activities for each season. We then categorized seasonal PAs in three categories using the same cutoffs across seasons for comparability <50.0, 50.0-89.9 and ≥ 90.0 minutes/day. These cut-offs were chosen as a compromise between the tertiles of autumn and spring. The majority of women (91%, 82%, 51% and 90% for summer, autumn, winter and spring, respectively) were above the recommended 150 minutes of PA per week (20), making a categorization based on this cut-off less optimal for the purpose of our study.

2.3. Potential confounders

Questions about host characteristics and UVR exposure in NOWAC have been described in detail (21-23). Participants reported years of education (categorized as ≤ 10 , 11-13 and ≥ 14 years) and smoking status (never, former, current). Body mass index (BMI, kg/m²) was calculated from self-reported height and weight and categorized as normal weight <25.0, overweight 25.0-29.9 and obese ≥ 30.0 (24). Smoking and BMI were reported at baseline and updated during follow-up. Hair color (black/dark brown, brown, blond/yellow, or red) and untanned skin color (using a color scale graded from 1 (very fair) to 10 (very dark)) were also reported.

Ambient UVR of residence was categorized, based on mean ambient UVR hours of the region of residence (latitudes, 70°-58°), as low (northern Norway), medium-low (central Norway), medium (southwestern Norway) and highest (southeastern Norway) (23, 25). Severe sunburns and annual number of weeks spent on sunbathing vacation in countries of low (typically Southern European Countries) and high latitudes (within Norway/northern countries) during various periods of adulthood were recorded at baseline and updated during follow-up (23). For the most recent age period (5-10 years prior to the questionnaire), we categorized number of sunburns as never, 1 time/year and ≥ 2 times/year, and number of weeks of sunbathing vacations as never, 1, 2-3 and ≥ 4 weeks/year. Use of an indoor tanning device was collected for the same age periods, and average

frequency of indoor tanning in the most recent age period was categorized as never, rarely and ≥ 1 time/month.

2.4. Study samples

Baseline was defined as the first returned questionnaire (recruitment, first or second follow-up) with information on overall PA. Among 172,472 participants who answered the recruitment questionnaire, we excluded 8,559 women with missing information on PA in all questionnaires, women with melanoma (n=778) or other cancers (n=11,261) diagnosed prior to baseline, women who emigrated or died (n=18) before return of the baseline questionnaires, and women reporting very dark skin color (grades 9-10, n=146, Fig. 1) (26). In total, 151,710 participants were included in this study. Participants' baseline for overall PA was determined based on the questionnaire at recruitment for 96.2% (n=145,977), first follow-up questionnaire for 3.5% (n=3,374) and second follow-up questionnaire for 0.2% (n=383).

Baseline for seasonal outdoor walking (n=104,181) and seasonal PAs (n=30,533) was defined in the same way as for overall PA. Since these baselines were later than for overall PA, further exclusions for death, emigration and prevalent cancer before these baselines were performed (Fig. 1). In total, 102,671 participants were included in the study sample for seasonal outdoor walking and 29,077 participants in the study sample for seasonal PAs. Participants were included in these study samples if they reported such PAs for at least one season, with non-reported seasons set to missing. Seasonal outdoor walking was reported for the first time at recruitment (n=59,742, 58.2%), first follow-up (n=41,373, 40.3%) or second follow-up (n=1,556, 1.5%), while seasonal PAs were reported at recruitment (n=7,784, 26.8%) or at second follow-up (n=21,293, 73.2%) (Fig. 1).

Fig. 1 Flow chart of the study samples from the Norwegian Women and Cancer (NOWAC) study for the analysis of physical activity (PA) and risk of melanoma, 1991-2018. * Additional exclusions due to the later baseline

2.5. Follow-up and endpoints

The NOWAC cohort is linked to the Cancer Registry of Norway (CRN) for information on cancer incidence, emigration and death, using the 11-digit unique identity number of Norwegian citizens (27), and 99.9% of the invasive melanoma diagnoses reported to the CRN are morphologically verified (28). Based on the International Classification of Diseases, Seventh Edition (ICD-7) codes,

anatomic location was categorized as head/neck (190.0), trunk (190.1 and 190.7), upper limb (190.2), lower limb (190.3 and 190.4), multiple sites (190.8) and unspecified site (190.9).

2.6. Statistical analyses

To assess the associations of overall PA with sunburns, sunbathing vacation and indoor tanning in the last decade, each of these UVR exposure variables was categorized as ever and never. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association of overall PA with each of the UVR exposure variables were obtained using a logistic regression model adjusted for age at baseline, recruitment period (1991-1992, 1996-1997 and 2003-2007), education and BMI. Analysis of sunbathing vacations in low and high latitudes was performed for the sub-group of participants with such information (n=72,192). The relationship between overall PA and melanoma risk was estimated by hazards ratios (HRs) with 95% CIs from Cox proportional hazards regression, stratified by recruitment period. These HRs refers to the average total effect (hereafter effect) of overall PA on melanoma risk in this cohort, conditional on the covariates included in analyses. We used age as time-scale, calculating person-years from baseline to date of diagnosis of first melanoma or any other primary cancer, emigration, death or end of follow-up (31st December 2018) whichever occurred first. Analysis without exclusion of prevalent squamous cell carcinomas (SCCs) and no censoring for SCC did not change the results (data not shown). Basal cell carcinoma could not be considered since not routinely recorded in the CRN. Model 0 is the age-adjusted model. A directed acyclic graph (DAG) (29) was used to further model the relationship between PA and melanoma risk, based on current knowledge on melanoma risk factors (Supplementary materials, Fig. S1). In model 1, we adjusted for education, smoking, and BMI (as a proxy of obesity), corresponding to the minimal set of covariates necessary to control for confounding when estimating the total effect of PA on melanoma based on the DAG. In model 2, we further adjusted for hair color as a proxy of sensitivity to UVR exposure (21), residential ambient UVR exposure, indoor tanning and height, corresponding to the maximal set of covariates based on our DAG. Only sunburns caused by the sun are recorded in NOWAC, thus we did not assume a causal path from indoor tanning to sunburn. Sensitivity analysis with sunbathing and sunburns as confounders instead of mediators was also carried out (DAG in Supplementary materials, Fig. S2).

Time-varying models were also implemented, using updated information from the first and second follow-up for overall PA, BMI, smoking status and indoor tanning, using the same adjustment set of covariates (models 0, 1 and 2).

Nonlinearity in the 10-scale overall PA was tested using cubic B-splines knots set at 5 and 6 (30).

To examine if PA is associated with melanoma risk for each anatomic site, Cox regression was conducted separately for melanoma located on the head/neck, trunk, upper limb and lower limb using the same models 0, 1 and 2. In these analyses, overall PA was regrouped into three categories because of smaller numbers: low (1-4), moderate (5-6) and high (7-10) (31).

Cox regression was used to analyze seasonal outdoor walking and seasonal PAs, separately for each season and with mutual adjustment for each season, using the same models 0, 1 and 2.

Statistical analyses were carried out using the R software (<https://www.r-project.org/>). We used two-sided tests and a 5% significance level.

3. Results

3.1. Characteristics of study participants

During an average follow-up of 18.5 years, 1,565 women were diagnosed with a first primary incident melanoma. Lower limb was the most common site of melanoma (n=591), followed by trunk (n=514), upper limb (n=264), head/neck (n=132) and multiple sites/unspecified (n=64). Mean age was 49.3 years at recruitment and 61.9 years at diagnosis (Table 1). Participants who reported the highest levels of PA were more likely to be recruited in the most recent calendar period and to have a lower BMI. Participants who reported the lowest level of PA were more likely to be in the lowest category of education and to be current smokers (Table 1).

Table 1 Characteristics of the study sample and ultraviolet radiation (UVR) exposure, by levels of overall physical activity at baseline in the Norwegian Women and Cancer study, 1991-2018. BMI=body mass index, SD=standard deviation, ^a Number of sunburns, number of weeks spent on sunbathing vacations and frequency of indoor tanning sessions during the last decade.

	Overall physical activity					Total
	Very low	Low	Moderate	High	Very high	
Number of participants, n (%)	7,302 (5)	30,430 (20)	62,551 (41)	41,346 (27)	10,081 (7)	151,710
Melanoma cases, n (%)	65 (4)	299 (19)	664 (42)	438 (28)	99 (6)	1565
Age at recruitment, mean (SD)	49.7 (9.0)	49.4 (8.8)	49.2 (8.5)	49.4 (8.1)	49.1 (8.3)	49.3 (8.5)
Age at diagnosis, mean (SD)	62.4 (9.8)	62.4 (9.4)	62.3 (9.3)	61.1 (8.9)	60.6 (8.3)	61.9 (9.2)
Follow-up time (years), mean (SD)	18.6 (7.4)	18.7 (7.1)	18.7 (7)	18.1 (7.0)	18.6 (7.2)	18.5 (7.1)
Year of recruitment, %						
- 1991-1992	39.1	36.0	35.4	32.5	37.7	35.1
- 1997-1998	32.9	29.8	25.5	21.0	20.6	25.2

- 2003-2007	28.1	34.2	39.1	46.5	41.7	39.8
Education (years), %						
- ≤10	44.2	33.5	31.6	29.7	38.8	32.6
- 11-13	26.4	28.1	29.5	28.3	27.4	28.6
- ≥14	23.9	33.7	34.3	37.3	28.9	34.1
- Missing	5.6	4.8	4.6	4.7	4.9	4.7
Smoking, %						
- Never	28.7	34.8	35.6	35.3	32.7	34.8
- Former	30.8	32.6	34.9	37.9	36.5	35.2
- Current	40.3	32.5	29.3	26.7	30.5	29.9
- Missing	0.2	0.2	0.1	0.2	0.3	0.2
BMI (kg/m ²), mean (SD)	26.1 (5.5)	25.3 (4.5)	24.2 (3.7)	23.7 (3.4)	23.1 (3.3)	24.3 (4.0)
BMI (kg/m²), %						
- Normal and underweight (<25.0)	48.5	53.6	64.2	71.9	75.2	64.2
- Overweight (25.0-29.9)	29.3	30.9	26.6	21.7	18.5	25.7
- Obese (≥30)	19.8	13.4	7.3	4.5	3.7	8.1
- Missing	2.4	2.1	1.9	1.9	2.5	2.0
Hair color, %						
- Red	3.0	3.0	2.8	2.9	2.7	2.9
- Blond/yellow	34.8	45.6	36.5	36.8	37.5	36.4
- Brown	35.7	36.9	37.5	37.5	35.5	37.2
- Black/dark brown	17.5	15.5	15.3	15.9	18.2	15.8
- Missing	9.0	9.0	7.8	6.9	6.1	7.7
Ambient UVR of residence, %						
- Low (northern Norway)	23.2	22.3	20.9	20.0	21.0	21.0
- Medium-low (central Norway)	10.4	11.0	11.5	11.2	11.1	11.3
- Medium (southwestern Norway)	15.1	16.7	18.6	20.0	20.5	18.6
- Highest (southeastern Norway)	51.3	50.0	49.0	48.8	47.5	49.1
Sunburns (per year)^a, %						
- Never	44.2	42.6	44.5	47.6	50.5	45.3
- 1	35.3	39.9	39.5	37.4	34.1	38.4
- ≥2	5.2	5.0	4.2	4.0	3.6	4.3
- Missing	15.3	12.5	11.8	11.0	11.9	11.9
Sunbathing vacations (weeks/year)^a, %						
- Never	24.9	19.8	18.0	16.0	18.9	18.2
- 1	23.6	26.9	27.6	26.5	23.5	26.7
- 2-3	28.1	32.4	34.2	37.0	34.5	34.3
- ≥4	8.6	8.0	8.3	9.7	10.9	8.8
- Missing	14.8	12.9	11.9	10.8	12.2	12.0
Indoor tanning^a, %						

- Never	41.5	39.5	38.4	37.3	35.4	38.3
- Rarely	32.2	37.4	39.2	40.0	37.8	38.6
- ≥ 1 per month	13.1	12.0	12.0	13.3	17.0	12.7
- Missing	13.2	11.2	10.4	9.4	9.8	10.4

Among the 102,671 (29,077) participants who reported seasonal outdoor walking (seasonal PAs) for at least one season, 993 (259) were diagnosed with a first primary incident melanoma. Compared to the whole study sample, the seasonal outdoor walking sample was older and follow-up started later, they had higher education, slightly higher BMI and a larger proportion lived in the region of highest ambient UVR (Supplementary materials, Table S1). The seasonal PAs subsample had similar characteristics, with somewhat more contrast, except for a less common use of indoor tanning. For all seasons, the two subsamples had comparable scores on the overall PA to the main study sample (identical medians, 1st and 3rd quartiles: 6, 5 and 7, respectively, for all three samples).

3.2. Overall PA and UVR exposure

Sunburns tended to decrease by increasing PA, while the opposite was found for sunbathing vacations and indoor tanning (Table 1). Women in the very high PA category had lower odds of having ever experienced sunburns (OR=0.77, 95% CI 0.74-0.81) and higher odds of having ever used indoor tanning (OR=1.12, 95% CI 1.07-1.17) compared to moderately active women (Fig. 2). Women in the low PA category had lower odds of having ever been on sunbathing vacations and ever used indoor tanning compared to moderately active women. Analysis without adjustment for period of recruitment and education did not change the results, while BMI adjustment gave slightly weaker effect estimates (Supplementary materials, Table S2). Analysis of sunbathing in low and high latitudes gave similar results (Supplementary materials, Fig S3).

Fig. 2 Odds ratios (ORs) and 95% confidence intervals (CIs) for overall physical activity and ultraviolet radiation exposure, the Norwegian Women and Cancer study, 1991-2018. Logistic regression of ultraviolet radiation exposures during the last decade (ever versus never) on overall physical activity, adjusted for age at baseline, period of recruitment, education and body mass index.

3.3. Overall PA and melanoma risk

Overall PA was not significantly associated with melanoma risk in any of the models (HR=0.89, 95% CI 0.69-1.14 for very high versus moderate PA, $p_{\text{trend}}=0.277$; time-dependent analysis, model 2; Table 2).

The spline model did not indicate non-linearity of the association between PA and melanoma (Supplementary materials, Fig. S4). In the site-specific analyses, we found no significant associations between PA and head/neck, trunk or lower limb melanomas in any of the models ($0.242 \leq p_{\text{trend}} \leq 0.665$; Table 3). Compared with moderate PA, high PA was associated with significantly decreased risk of upper limb melanoma (HR=0.70, 95%CI 0.51-0.96, model 2), but with no indication of a trend ($p_{\text{trend}}=0.187$; Table 3).

Table 2 Hazard ratios (HRs) and 95% confidence intervals (CIs) for overall physical activity and melanoma risk, the Norwegian Women and Cancer study, 1991-2018. ^a Model 0: Cox proportional hazards regression stratified by year of recruitment, and with age as time scale. ^b Model 1: model 0 + education, smoking status and body mass index, ^c Model 2: model 1 + indoor or tanning, hair colour, ambient ultraviolet radiation of residence and height, ^d Physical activity, smoking status, body mass index and indoor tanning modelled as time dependent, ^e p_{trend} was obtained using the median of the original 10-scale physical activity in each level (very low: 1-2, low: 3-4, moderate: 5-6, high: 7-8, very high: 9-10) and modelled as a continuous variable in each model.

		Overall physical activity					
		Very low (1-2)	Low (3-4)	Moderate (5-6)	High (7-8)	Very high (9-10)	Continuous
	n	5,625	24,145	50,598	33,899	8,171	122,438
Baseline	No. of cases	51	242	546	351	83	1,273
Model 0^a	HR (95% CI)	0.85 (0.64-1.14)	0.93 (0.80-1.08)	1.00	0.99 (0.87-1.13)	0.95 (0.75-1.20)	1.012 (0.983-1.042)
	p_{trend}^e						0.511
Model 1^b	HR (95% CI)	0.90 (0.67-1.20)	0.94 (0.81-1.09)	1.00	0.99 (0.87-1.13)	0.97 (0.77-1.22)	1.010 (0.980-1.040)
	p_{trend}^e						0.621
Model 2^c	HR (95% CI)	0.90 (0.67-1.20)	0.94 (0.81-1.09)	1.00	0.99 (0.86-1.13)	0.98 (0.78-1.23)	1.010 (0.980-1.041)
	p_{trend}^e						0.614
Time dependent^d							
Model 0^a	HR (95% CI)	0.79 (0.58-1.07)	0.86 (0.74-1.00)	1.00	1.02 (0.90-1.16)	0.86 (0.67-1.11)	1.016 (0.987-1.047)
	p_{trend}^e						0.220
Model 1^b	HR (95% CI)	0.83 (0.61-1.12)	0.87 (0.75-1.00)	1.00	1.02 (0.89-1.16)	0.88 (0.68-1.13)	1.011 (0.981-1.041)

1^b	CI)	1.14)	1.02)		1.16)	1.13)	1.043)
	P_{trend}^e						0.320
Model	HR (95%	0.83 (0.61-	0.87 (0.75-		1.02 (0.89-	0.89 (0.69-	1.013 (0.982-
2^c	CI)	1.13)	1.02)	1.00	1.16)	1.14)	1.044)
	P_{trend}^e						0.277

Table 3 Hazard ratios (HRs) and 95% confidence intervals (CIs) for overall physical activity and melanoma risk by anatomic sites, the Norwegian Women and Cancer study, 1991-2018. ^a Model 0: Cox proportional hazards regression stratified by year of recruitment, and with age as time scale, ^b Model 1: model 0 + education, smoking status and body mass index, ^c Model 2: model 1 + indoor tanning, hair colour, ambient ultraviolet radiation of residence and height, ^d p_{trend} was obtained using the median of the original 10-scale physical activity in each level (low: 1-4, moderate: 5-6, high: 7-10) and modelled as a continuous variable in each model.

Models	Overall physical activity			P _{trend} ^d
	Low (1-4)	Moderate (5-6)	High (7-10)	
Head/Neck (n=121 275, 110 cases)				
Model 0^a	0.95 (0.59-1.54)	1.00	1.10 (0.72-1.69)	0.547
Model 1^b	0.91 (0.56-1.48)	1.00	1.13 (0.74-1.75)	0.384
Model 2^c	0.91 (0.56-1.48)	1.00	1.13 (0.74-1.75)	0.386
Trunk (n=121 580, 415 cases)				
Model 0^a	0.95 (0.74-1.23)	1.00	1.10 (0.89-1.37)	0.242
Model 1^b	0.98 (0.75-1.27)	1.00	1.10 (0.88-1.37)	0.365
Model 2^c	0.98 (0.76-1.27)	1.00	1.09 (0.88-1.36)	0.373
Upper limb (n=121 379, 214 cases)				
Model 0^a	0.80 (0.57-1.13)	1.00	0.70 (0.51-0.97)	0.265
Model 1^b	0.83 (0.59-1.17)	1.00	0.70 (0.51-0.96)	0.190
Model 2^c	0.83 (0.59-1.17)	1.00	0.70 (0.51-0.96)	0.187
Lower limb (n=121 642, 477 cases)				
Model 0^a	0.87 (0.69-1.10)	1.00	0.96 (0.79-1.18)	0.564
Model 1^b	0.89 (0.70-1.12)	1.00	0.97 (0.79-1.19)	0.622
Model 2^c	0.89 (0.70-1.12)	1.00	0.96 (0.78-1.19)	0.665

3.4. Seasonal outdoor walking, seasonal PAs and melanoma risk

Significantly reduced HRs were observed for outdoor walking in summer and autumn when comparing highly (>2 hours/day) and moderately active walkers (30-60 minutes/day) in model 1 (HRs (95%CI) 0.78 (0.63-0.96) and 0.70 (0.52-0.94), respectively; Table 4) with slightly weaker effect estimates after adjustment for UVR exposure (0.81 (0.66-1.00) and 0.74 (0.55-1.01), model 2). Similar results were found in summer after mutual adjustment for seasonal outdoor walking (0.67 (0.43-1.03), Supplementary materials, Table S3). HRs in the second highest category (1-2 h/day) of seasonal outdoor walking tended to be different from the HRs in the highest category (>2 h/day) (Table 4), and this was most evident for outdoor walking in winter in the mutually adjusted analyses (Supplementary materials, Table S3).

Table 4 Hazard ratios (HRs) and 95% confidence intervals (CIs) for seasonal outdoor walking and seasonal physical activities^a and melanoma risk, Norwegian Women and Cancer study, 1991-2018. min=minutes, h=hours, PA=physical activity, ^a Seasonal PAs refers to the sum of time (in minutes/day) spent cycling, jogging and gardening, in each season, ^b Model 0: Cox proportional hazards regression stratified by year of recruitment, and with age as time scale, ^c Model 1: model 0 + education, smoking status and body mass index, ^d Model 2: model 1 + indoor tanning, hair colour, ambient ultraviolet radiation of residence and height.

Models	Seasonal outdoor walking (per day)				Seasonal PAs (per day)		
	<30 min	30-60 min	1-2 h	>2 h	<50 min	50-89.9 min	≥90 min
	Summer, n=90,868, 877 cases				Summer, n=26,811, 245 cases		
Model 0^b	1.01 (0.82-1.24)	1.00	0.97 (0.82-1.13)	0.77 (0.62-0.95)	1.00	0.90 (0.63-1.30)	1.09 (0.80-1.49)
Model 1^c	1.02 (0.83-1.26)	1.00	0.97 (0.83-1.13)	0.78 (0.63-0.96)	1.00	0.88 (0.61-1.26)	1.08 (0.79-1.48)
Model 2^d	1.01 (0.83-1.25)	1.00	0.99 (0.84-1.15)	0.81 (0.66-1.00)	1.00	0.89 (0.62-1.27)	1.09 (0.80-1.49)
	Autumn, n=90,772, 876 cases				Autumn, n=25,100, 233 cases		
Model 0^b	0.99 (0.84-1.17)	1.00	1.05 (0.89-1.23)	0.68 (0.51-0.92)	1.00	1.21 (0.88-1.68)	1.17 (0.86-1.59)

				0.70			
Model 1^c	1.00 (0.85-1.19)	1.00	1.05 (0.89-1.24)	(0.52-0.94)	1.00	1.19 (0.86-1.64)	1.18 (0.87-1.60)
				0.74			
Model 2^d	1.00 (0.84-1.18)	1.00	1.07 (0.91-1.27)	(0.55-1.01)	1.00	1.18 (0.85-1.62)	1.17 (0.86-1.59)
	Winter, n=91,025, 876 cases				Winter, n=22,179, 199 cases		
				0.59			
Model 0^b	0.92 (0.80-1.06)	1.00	1.15 (0.93-1.42)	(0.34-1.03)	1.00	0.99 (0.67-1.47)	1.15 (0.70-1.90)
				0.60			
Model 1^c	0.93 (0.81-1.07)	1.00	1.16 (0.93-1.43)	(0.34-1.04)	1.00	0.97 (0.65-1.43)	1.15 (0.69-1.90)
				0.62			
Model 2^d	0.93 (0.81-1.08)	1.00	1.17 (0.94-1.44)	(0.35-1.07)	1.00	0.98 (0.66-1.45)	1.10 (0.67-1.82)
	Spring, n=90,750, 876 cases				Spring, n=26,264, 241 cases		
				0.81			
Model 0^b	0.93 (0.78-1.12)	1.00	0.97 (0.81-1.14)	(0.61-1.07)	1.00	1.10 (0.78-1.55)	1.04 (0.77-1.42)
				0.82			
Model 1^c	0.95 (0.79-1.13)	1.00	0.97 (0.83-1.15)	(0.62-1.09)	1.00	1.06 (0.75-1.50)	1.04 (0.76-1.43)
				0.84			
Model 2^d	0.96 (0.80-1.15)	1.00	0.99 (0.84-1.16)	(0.63-1.11)	1.00	1.06 (0.75-1.50)	1.04 (0.76-1.42)

Seasonal PAs were not significantly associated with melanoma risk in any models (Table 4; Supplementary materials, Table S3)).

Sensitivity analysis adjusting for sunbathing and sunburns gave similar results for the three PA assessments (Supplementary materials, Tables S4 and S5).

4. Discussion

We investigated the associations between PA, patterns and level of UVR exposure and melanoma risk in a large Norwegian prospective female cohort with comprehensive data on UVR exposure and up to three assessments of PA: overall PA, seasonal outdoor walking and seasonal PAs. Compared to

moderate overall PA, very high PA was associated with reduced odds of sunburns and increased odds of indoor tanning while very low PA was associated with decreased odds of ever been on sunbathing vacation. Overall PA was not associated with melanoma risk in all body sites combined, nor in specific parts of the body, except a reduced risk in upper limb melanomas. Walking outdoor in summer and autumn for >2 h/day was associated with decreased melanoma risk compared to 30-60 min/day, but these associations were weaker after adjusting for UVR exposure. No significant associations were found between seasonal PAs and melanoma risk.

The inverse association between PA and sunburns in our study differs from findings from countries with other climates, where PA was associated with increased risk of sunburns (32-35). Moreover, these studies reported decreased risk of experiencing sunburns with increasing age, and less sunburns in women than men (32, 33, 35). Inadequate sun protection behavior have been reported by athletes who train outdoors, and thus are more susceptible to experiencing sunburns (36, 37). As NOWAC includes women living at northern latitudes, older and likely less active than the participants in Jardine et al. and Gilchrist et al., our participants may be less prone to sunburns. However, we found positive association between PA and sunbathing vacations (except for very high PA) which has also been reported in a study of Swedish women aged 40-61 (38). The higher use of indoor tanning devices found in physically active Swedish women (38) and in a recent review (39) is in line with our results. Physically active women may have more concerns about their body image than inactive women (40) and in pursuit of attractiveness, they may tend to use indoor tanning devices despite the risk of negative health consequences (41).

Two previous Norwegian cohort studies did also not find association between PA and melanoma risk (11, 12). Similar results, indicating no association between PA and melanoma risk were reported in case-control studies from Washington State (13) and the Montreal area (men only) (14). However, no consensus has been established. A Greek case-control study found protective effect of PA on melanoma risk (OR=0.70, 95% CI (0.51-0.94), per 30 minutes/day) (10). On the contrary, occupational PA was associated with increased odds of melanoma (OR=1.59, 95% CI (1.10-2.47), 5th versus 1st quintile) in a Canadian study (8). More recently, a meta-analysis of three cohort and five case-control studies, found positive association in the cohort studies (relative risk=1.27, 95% CI (1.16-1.40), high versus low PA) but no association in the case-control studies (9). In a pooled study of eight American and four European cohorts, PA was positively associated with melanoma (HR=1.27, 95% CI (1.16-1.40), 90th versus 10th percentile) with stronger association in high UVR areas (4).

Among previous studies of PA and melanoma risk, some adjusted for individual UVR exposure (8, 13), some for UVR of residence (11), but most did not have such adjustments (4, 9, 10, 12, 14). Studies also differed as regards PA type (recreational, occupational or a combination) and also age, sex, and

education level of participants, which alter PA habits and UVR-related behaviors (33, 38, 42, 43). Moreover, some adjusted for sun sensitivity (10, 13) while the majority did not (4, 8, 9, 11, 12, 14). Based on our DAG, we did not adjust for sunburns and sunbathing vacations as we assumed they are mediators on the pathway from PA to melanoma risk. In our analyses of overall PA and seasonal PAs, adjusting for indoor tanning, ambient UVR of residence and sun sensibility, did not change the results. An explanation might be that overall PA and seasonal PAs (running/exercising, cycling and gardening) referred to both indoor and outdoor activities, while seasonal outdoor walking referred exclusively to outdoor PA. In that case, for whichever season, the inverse association between seasonal outdoor walking and melanoma risk was always weaker when further adjusting for UVR exposure and tended to go towards the null.

We excluded participants diagnosed with melanoma or SCC prior to baseline as their UVR exposure might have changed after diagnosis (44) and they have higher risk of developing melanoma as a second cancer than the general population (45). We found similar results in a sensitivity analyses including participants with SCC diagnosis before baseline and without censoring participants at SCC diagnosis. PA has been reported to improve well-being and survival after cancer diagnosis and to reduce relapse (46), especially for breast (47), colorectal (48) and prostate cancer (49). Our analysis excluded participants diagnosed with another cancer type before baseline and censored at the incidence of another cancer type during follow-up, since their level of PA might have changed after the cancer diagnosis.

Our study is population based and representative of Norwegian women aged 30-75 years (18). In addition to the large cohort, a major strength is the use of comprehensive data on solar and artificial UVR exposure. Overall PA was measured at recruitment with up to two follow-ups, which allowed us to conduct time-dependent analysis. Major limitations of this study are the inability to differentiate indoor and outdoor PA, and the lack of information on sun protection (use of clothing, shade or sunscreen use) during outdoor PA and other unmeasured confounding factors that might alter our results. However, unmeasured mediating factors such as DNA capacity repair, are not affecting the estimate of the total effect of PA. Our analysis of outdoor PA was limited to walking and strolling which did not represent the total amount of outdoor PA. Further studies including other outdoor activities such as running, cycling, kayaking, skiing, etc. are needed to better understand the link between outdoor PA, UVR exposure and melanoma risk. Misclassification of exposures, inevitable in epidemiologic studies, is likely non-differential in a cohort study. Overall PA was reported with a 10-point scale where participants were asked to report the number that best describes their level of PA. Such a scale may be interpreted differently by each woman and the actual activity level of women within the same class on the scale might differ. However, this scale has been validated to rank PA

levels in the Norwegian female population (17), and is therefore considered a suitable measure to differentiate overall PA levels in our study. The NOWAC study includes only women and cannot be generalized to men. Compared to men, women are less physically active (42) and less prone to sunburns (33, 38), use more indoor tanning (43) and have a lower age-standardized melanoma specific mortality (50). However, previous studies of melanoma risk did not test for interaction between PA and gender.

5. Conclusion

In summary, overall PA was associated with UVR exposure: positively with sunbathing vacations and indoor tanning and, unlike literature findings, inversely with sunburns. Importantly, these prospective data do not support that PA increases melanoma risk in women. In order to reduce melanoma incidence, public health messages promoting PA should include advice on sun safety during outdoor PA.

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Ethics approval and consent to participate

The participants of the Norwegian Women and Cancer Study have all signed a broad informed consent to study risk factors and cancer, and the cohort has been approved by the local Medical Ethical Committee and the National Data Inspection Board. This project received only anonymous data.

Author contributions

Conceptualization: all authors

Data curation: FP, RG, SL, KBB, TMS, CSR, MBV

Formal analysis: FP

Funding acquisition: MBV

Investigation: TMS

Methodology: all authors

Project administration: MBV

Resources: TMS, MBV

Software: FP, RG, SL, CSR

Supervision: all authors

Visualization: all authors

Roles/Writing - original draft: FP

Writing - review & editing: all authors

Disclaimer

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Supplementary data

Supplementary material

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Highlights

- Recent studies found positive association between PA and risk of cutaneous melanoma
- Large population based cohort representative of Norwegian women aged 30-75 years
- Physically active women reported less sunburns and more indoor tanning use
- Overall physical activity did not increase risk of cutaneous melanoma
- Walking outdoor more than 1 h/day in summer and autumn decreased melanoma risk