Lifetime indoor tanning and subsequent risk of cutaneous squamous cell carcinoma

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Key Points

Question: Is there a dose-response association between lifetime indoor tanning and risk of cutaneous squamous cell carcinoma (SCC)?

Findings: In this prospective cohort study, a significant dose-response association was found between indoor tanning and risk of SCC. Cumulative exposure to indoor tanning was more important than duration of use and age at initiation.

Meaning: This work adds compelling evidence of increased SCC risk in indoor tanners, with a greater risk in women with higher cumulative number of indoor tanning sessions.

Abstract

Importance: No study has prospectively investigated a dose-response association between lifetime indoor tanning and risk of cutaneous squamous cell carcinoma (SCC).

Objective: To investigate if there is a dose-response association between lifetime indoor tanning and SCC risk, to investigate the effect of duration of use and age at initiation on SCC risk, and the association between age at initiation and age at diagnosis.

Design: Norwegian Women and Cancer cohort study established in 1991 with follow-up through 2015.

Setting: Population-based study.

Participants: We included 159,419 women, born 1927-1963. Baseline questionnaires were issued 1991-2007, and follow-up questionnaires every 5-7 years.

Exposures: Participants reported pigmentation factors. Sunburns, sunbathing vacations and indoor tanning were reported for childhood, adolescence and adulthood.

Main Outcomes and Measures: Information on all cancer diagnoses, and dates of emigration or death were obtained through linkage to the Cancer Registry of Norway, using the unique personal identification number of Norwegian citizens.

Results: During follow-up (mean 16.5 years), 597 women were diagnosed with SCC. SCC risk increased with increasing cumulative number of indoor tanning sessions. The adjusted hazard ratio (HR) for highest use versus never use was 1.83 (95% confidence interval [CI] 1.38-2.42; P_{trend}<0.001). A significantly higher risk of SCC was found both in women with ≤10 years (HR=1.41, 95%CI 1.08-1.85) and >10 years of use (HR=1.43, 95%CI 1.16-1.76) and in women with age at initiation ≥30 years (HR=1.36, 95%CI 1.11-1.67) and <30 years (HR=1.51, 95%CI 1.18-1.92) versus never users. There was no significant association between age at initiation and age at diagnosis.

Conclusion and Relevance: This cohort study provides evidence of a dose-response association between indoor tanning and SCC risk in women. Cumulative indoor tanning exposure was more important than duration of use or age at initiation. These results strengthen the justification for developing policies that regulate indoor tanning.

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Introduction

Cutaneous squamous cell carcinoma (SCC) is one of the most common types of cancer worldwide.[1] Norway, one of the few countries with national high quality SCC incidence data, had a nine-fold increase in age-standardized incidence in women and a six-fold increase in men since 1963.[2]

While development of SCC has been associated with cumulative solar ultraviolet radiation (UVR) exposure,[1,3,4] few studies have investigated its association with cumulative exposure to UVR from indoor tanning. Four meta-analyses (2006-2012), based on three to six studies,[5-8] reported a significant increased risk of SCC in ever vs. never users of indoor tanning devices (summary relative risk estimates 1.67-2.25). Two of the six investigated age at first indoor tanning exposure,[9,10] and only one examined a dose-response association.[10] Later, in a report from the Nurses' Health Study, a significant dose-response association was found for indoor tanning in adolescence and adulthood,[11] but information about indoor tanning was obtained several years after entry into the cohort, increasing the risk of recall bias. The same year, in the Norwegian-Swedish Women's Lifestyle and Health Cohort study, cumulated use of indoor tanning devices from age 10 to 49 years significantly increased SCC risk.[12] That cohort study included the first third of women enrolled in the Norwegian Women and Cancer (NOWAC) study, the cohort assessed in the current paper.

We recently studied the association between indoor tanning and cutaneous melanoma in the NOWAC study.[13] This cohort similarly provides a unique opportunity to examine prospectively the long-term risk of SCC in relation to indoor tanning. We aimed to investigate if there is a dose-response association between cumulative number of indoor tanning sessions and SCC, the effect of duration of use and age at indoor tanning initiation on SCC risk, and the association between age at initiation and age at diagnosis.

Material and methods

NOWAC cohort

The NOWAC cohort study was established in 1991, and has been described in detail.[13,14] Women were selected randomly from the Norwegian Population Register. Baseline questionnaires were issued in 1991-2007 and 171,725 (54%) women answered. First and second follow-up questionnaires were sent after 5-7 years (response 80% and 79%, respectively).

The national Data Inspection Board and the Medical Ethical Committees of North Norway approved the NOWAC study.

Follow-up and endpoints

The cohort was linked to the Cancer Registry of Norway (CRN), using the unique personal identification number of Norwegian citizens.[15] Mandatory reporting of malignant diseases from independent sources (hospitals, laboratories, general practitioners, and the Cause of Death Registry) to the CRN ensures virtual completeness and high quality data with 99.7% of the non-melanoma skin cancers (excluding basal cell carcinoma) being morphologically verified.[16] Cutaneous SCC cases were identified by the International Classification of Diseases, 7th revision (ICD-7), coding 191, and the morphology codes 80703, 80713, 80763, 80953, 80513, 80723, and 80743. We excluded cases with the ICD-7 code 1914 (perineum, perianal), as they are unlikely to be related to UVR-exposure. Primary anatomical location of the tumor was categorized as head/face (1910: outer ear; 1911: eyelids (including eyelets); 1912: face and the rest of the head (including scalp, orbital region, chin and cheek)), neck/trunk (1913), upper limbs (1915), lower limbs (1916), multiple localizations (1918,

based on clinical notification of more than one tumor, within 4 months), and unspecified site (1919).

Indoor tanning

Use of an indoor tanning device (never, rarely, 1, 2, 3-4 times per month, >1 time per week) was obtained at baseline for childhood (<10 years), adolescence (10-19 years) and adulthood, and was updated in the follow-up questionnaires. We created five variables for indoor tanning exposure: cumulative number of sessions, ever/never use, current use (no, yes), duration of use (never, 1-10, >10 years), and age at initiation (never, ≥30, <30 years).[13] Cumulative number of sessions was calculated by converting reported frequencies for all age periods from age 10 to a yearly amount (never=0 sessions/year; rarely=1 session/year; 1 time/month=12 sessions/year; 2 times/month=24 sessions/year; 3-4 times/month=42 sessions/year; >1 time/week=60 sessions/year) and multiplying this with the number of years for the given period.[13] The sum was categorized to capture the heavy tail of the distribution (never use (0 sessions), lowest use (1-38 sessions), medium use (39-240 sessions), highest use (>240 sessions); 38 is the highest tertile and 240 the highest sextile).

Covariates

Ambient UVR exposure was categorized based on the average ambient UVR hours of the region of residence (latitudes 70° to 58°) as low (northern Norway), medium-low (central Norway), medium (southwestern Norway), and highest (southeastern Norway).[13,17] Participants reported education (≤10, 11-13, ≥14 years), smoking (never, former, current smoker), hair color (black/dark brown, brown, blond/yellow, red), freckling when sunbathing (no, yes), and untanned skin color (color scale from 1 (very fair) to 10 (very dark); categorized as light (1-3), medium (4-5), dark (6-8), and very dark skin (grades 9-10)). Skin reaction to acute and chronic sun exposure were recorded for a subsample of the cohort.

Annual number of sunburns that resulted in pain or blisters and subsequent peeling (never, 1, 2-3, 4-5, ≥6) and average annual number of weeks spent on sunbathing vacations (never, 1, 2-3, 4-6, ≥7 weeks/year) in low latitudes or within Norway/northern countries were reported for the same age periods as for indoor tanning, and updated by follow-up questionnaires. Cumulative number of sunburns was calculated similarly to indoor tanning, and categorized as none, lowest tertile (1-30 sunburns), middle tertile (31-54 sunburns), or highest tertile (>54 sunburns). Cumulative weeks spent on sunbathing vacations was calculated similarly and categorized as never, lowest tertile (1-74 weeks), middle tertile (75-149 weeks), or highest tertile (>149 weeks).[13] Finally, we calculated number of indoor and outdoor tanning sessions by dividing cumulative number of indoor tanning sessions and sunbathing vacations into quartiles, which were then summed (score 0-8), and categorized into 5 groups (1=lowest, 5=highest).

Reproducibility was good for freckling when sunbathing (kappa (κ)=0.77), skin color (intra class correlation=0.59), indoor tanning (weighted κ (κ_w)=0.70), and sunbathing vacations in low latitudes (κ_w=0.71), and fair for sunburns (κ_w=0.49) and sunbathing vacations in Norway/northern countries (κ_w=0.47) in the first follow-up questionnaire.[18] Age, education, and skin color did not affect reproducibility. The NOWAC study has been found to be representative of Norwegian women aged 45-74 with regard to total cancer incidence,[14] with no major selection bias[19] and with almost no selection of participants from the baseline questionnaire to the first follow-up questionnaire.[14]

Study sample

Of the 171,725 women, 160,657 were asked about indoor tanning use and pigmentation characteristics. We excluded women with very dark skin (*n*=290), prevalent SCC (*n*=90), or cutaneous melanoma (*n*=770) (Figure 1). The Cancer Registry of Norway does not record

information on basal cell carcinoma (BCC) routinely. We further excluded 88 women that emigrated or died before the date of questionnaire return, resulting in 159,419 women born in 1927-1963.

Statistical analysis

The association between use of indoor tanning devices and SCC was estimated by hazard ratios (HRs) and 95% confidence intervals (CIs), using Cox regression with age as timescale. We stratified by birth-cohort (1927-44, 1945-52, 1953-63) because calendar year of indoor tanning may influence the level of irradiance.[12] Person-years were calculated from date of entry to date of first primary SCC diagnosis, melanoma diagnosis (i.e. censoring at melanoma diagnosis), emigration, death, or end of follow-up (31.12.2015), whichever occurred first. We conducted sensitivity analysis excluding all prevalent cancers and censoring for all other cancers, to ensure that a history of cancer did not affect the effect estimates.

We modelled indoor tanning variables (except age at initiation) and cumulative number of sunburns and sunbathing vacations as time-varying variables. All exposure and covariate information was collected prior to disease diagnosis. The proportionality assumption was checked using Schoenfeld residuals. A likelihood ratio test was used to test for interaction between ever use of indoor tanning devices or cumulative number of indoor tanning sessions (collapsing medium and highest use) and birth cohort, residential ambient UVR exposure, hair color, untanned skin color and sunbathing vacations. We tested for trend by modelling the variables as continuous.

Based on a directed acyclic graph[20] (eFigure 1A in the Supplement), we adjusted for hair color, residential ambient UVR exposure, sunburns, and sunbathing vacations in the multivariable models. We conducted sensitivity analysis based on a DAG in which the arrow between sunbathing and indoor tanning was reversed (eFigure 1B in the Supplement), and

adjusted for hair color and residential ambient UVR exposure only. Additional adjustment for education, smoking, freckling, untanned skin color, and skin reaction to chronic and acute sun exposure did not change the results.

We investigated age at indoor tanning initiation and age at diagnosis using linear regression, and present regression-coefficient estimates ($\hat{\beta}$) and 95% CIs. The multivariable model included birth year, hair color, residential ambient UVR exposure, cumulative number of sunburns and sunbathing vacations.

We had missing information in 13% of participants for the cumulative number of indoor tanning sessions and up to 20% missing in the covariates of the multivariable model. We used multiple imputation with chained equations[21] to impute 40 datasets.

All tests were two-sided with 5% significance level. Statistical analyses were conducted using R software, version 3.5.2 (R Foundation for Statistical Computing).

Results

The 159,419 women had a mean follow-up of 16.5 years (range <1-25 years), during which 597 women were diagnosed with incident SCC. The first primary SCC was the first cancer diagnosis for 481 women, second for 98, third for 12, fourth for 3, and the fifth diagnosis for 3 women. Mean age at inclusion was 50 years (range 33-70), and mean age at SCC diagnosis was 66 years (range 42-89). Mean age at SCC diagnosis was similar for women with SCC as their first (66 years), second (67 years), or third to fifth (67 years) cancer diagnosis. Head (*n*=248) was the most common site (outer ear (*n*=13), eyelids (*n*=9), face/rest of the head (*n*=226)), followed by neck/trunk (*n*=141), lower limbs (*n*=82), upper limbs (*n*=66), multiple localizations (*n*=50) and unspecified site (*n*=10).

In total, 69% of the women reported ever-use of indoor tanning. Indoor tanning was more common in the younger birth-cohorts, in women living in northern and central Norway, current smokers, women with lighter hair color, and with lighter skin color (Table 1). Host characteristics were similar among women who answered the baseline questionnaire, first follow-up, and second follow-up (eTable 1 in the Supplement), except for birth cohort, due to the sampling procedure (women recruited earlier had more time to receive follow-up questionnaires).

Below, we present the results from the multiple imputation analyses based on the multivariable model, except P-values for interaction, which were based on the complete-case analysis. The risk of SCC was significantly higher in ever users of indoor tanning devices than in never users (HR=1.43, 95%CI 1.17-1.74) (Table 2). Significant increased risk was also found in current users (HR=1.27, 95%CI 1.06-1.53). We found a significant dose-response association between cumulative number of indoor tanning sessions and SCC risk (HR=1.83, 95%CI 1.38-2.42, highest versus never use, P_{trend}<0.001). A significantly higher risk of SCC was found both in women with ≤10 years of use (HR=1.41, 95%CI 1.08-1.85) and >10 years of use (HR=1.43, 95%CI 1.16-1.76) and in women with age at initiation ≥30 years (HR=1.36, 95%CI 1.11-1.67) and <30 years (HR=1.51, 95%CI 1.18-1.92) versus never users. The dose-response association between indoor tanning and SCC risk was evident both in women with ≤10 years and >10 years of indoor tanning use, with no significant interaction ($P_{interaction}$=0.194; Table 2). We found no significant interaction between cumulative indoor tanning and age at initiation ($P_{interaction}$=0.823; result not shown). None of the tests for interactions between ever use of indoor tanning devices or cumulative number of sessions and birth cohort, residential ambient UVR exposure, hair color, untanned skin color and sunbathing vacations were significant ($0.231 \leq P_{interaction} \leq 0.837$; results not shown). There was a significant increasing trend in SCC risk with increasing number of indoor and outdoor

tanning sessions combined (HR=2.43, 95%CI 1.74-3.39, highest versus lowest category, P_{trend}<0.001; Table 2).

In the linear regression analysis, we found no significant association between age at initiation and age at diagnosis ($\hat{\beta}$=-0.09, 95%CI (-1.11,0.94) for ≥30 years and $\hat{\beta}$=-0.02, 95%CI (-1.27,1.22) for <30 years versus never use; Table 3).

Results from the sensitivity analysis based on the DAG in which the arrow between indoor tanning and sunbathing was reversed (eFigure 1B in the Supplement), were similar but with slightly higher HRs (eTable 2).

In the sensitivity analysis restricted to women with no history of cancer (n=148,444; 481 incident SCC; mean follow-up 15.9 years), the associations between indoor tanning and SCC were similar but with slightly weaker estimates (eTable 3 in the Supplement). Moreover, the analysis of age at initiation and age at diagnosis also gave almost identical estimates (eTable 4 in the Supplement).

Discussion

In this large prospective cohort, we found a significant dose-response association between cumulative number of indoor tanning sessions and SCC risk. The results suggest that cumulative exposure to indoor tanning is more important than duration of use or age at initiation.

Randomized controlled trials (RCTs) are the gold standard for investigating causal associations.[22,23] In our context, RCTs would be unethical, and cohort studies therefore provide the highest level of evidence. NOWAC is a well-characterized cohort of women randomly selected from the general population, with information about indoor tanning, sunburns and sunbathing vacations from all decades of life, and complete follow-up through

the CRN (>99% of SCCs morphologically verified[15,16]) linked by the unique personal identification number. Previous cohort studies[10-12] had indoor tanning exposure only for limited time periods. Here we have updated information on indoor tanning during follow-up and used cut-offs that took the heavy tail of the distribution into account, which make our results unique.

Our study confirms a significant association between ever use of indoor tanning devices and SCC risk, with a HR in agreement with the latest meta-analysis.[8] Moreover, we found a clear dose-response association after adjusting for sunburns and sunbathing vacations.

To our knowledge, no previous study has investigated the relationship between duration of indoor tanning and SCC risk. We found significant and similar HRs for ≤10 and >10 years of use, and no significant interaction between cumulative number of sessions and duration of use. Three studies investigated age at initiation of indoor tanning and SCC risk.[9,10,24] One found a significant association with initiation ≤35years but not for initiation later in life,[9] while no significant association was found between age at initiation and SCC risk in the other two studies.[10,24] In our study, both initiation ≥30 and <30 years were significantly associated with SCC risk, compared with never users. However, we found no significant interaction between cumulative number of sessions and age at initiation.

Only the Norwegian-Swedish Women's Lifestyle and Health Cohort study has evaluated the association between combined indoor and outdoor UVR exposure and SCC risk, and found a significant increase in SCC risk with increasing exposure.[12] There is some overlap of women with the present study. Notably, we have used the whole NOWAC cohort with updated exposure during follow-up, which provided stronger evidence that cumulative indoor and outdoor UVR exposure is important in the etiology of SCC.[1] We found no evidence of an effect of age at initiation on age at SCC diagnosis, in contrast to our previous

finding for melanoma.[13] To our knowledge, no other study has investigated the association between age at initiation and age at SCC diagnosis.

We conducted sensitivity analysis on women with no history of cancer, resulting in a more direct, less confounded effect of indoor tanning on SCC risk. The results were in line with the results in the whole cohort, but with slightly lower HRs and wider CIs, due to the reduced sample size and person-years of follow-up. One previous cohort study included only women with no history of cancer,[10,11] but they did not censor by date of diagnosis of any incident non-SCC cancer, as done in the present study.

Limitations

Type (UVA, UVB) and intensity of ultraviolet radiation vary largely between tanning devices,[25-27] and we did not have information on the types of indoor tanning devices used and lengths of sessions. The NOWAC cohort includes only women, and while indoor tanning is more common among women than men,[28,29] another study found similar estimates for the association between indoor tanning and SCC for men and women.[9] Nonetheless, generalizability to men may be limited. The information on exposure was collected retrospectively, thus some misclassification is likely to have occurred. However, the chosen cutoffs should limit this by placing low users in the same category, while differentiating higher users, thereby focusing on cumulative indoor tanning exposure, and, importantly, all information was collected prior to SCC diagnosis. In contrast, case-control studies may be limited by the potential for differential bias in recall of exposure between cases and controls.[30,31] In our age-adjusted model, assuming non-differential, non-systematic errors, the effect of misclassification would be to attenuate the HR of the higher indoor tanning use category,[32] i.e. that the true effect of this category (compared to the lower) is likely to be even

higher than reported in Table 2. Moreover, in this model, under the same assumptions, the test for trend will be valid.[32]

Unfortunately, we could not distinguish lip SCC, which may be related to smoking,[33] but there was no change in estimates when smoking was included as a covariate, so it is unlikely to have affected the results. Finally, this cohort is still young with respect to SCC incidence. Excluding BCC and melanoma, the median age at diagnosis for skin cancers (mostly SCC) in Norwegian women was 80 years in 2012-16 (obtained from CRN), compared to 66 years in our study.

Conclusions

While the association of indoor tanning with SCC has received far less attention than its association with melanoma, our results from this large prospective study strengthen the evidence of a causal effect of indoor tanning on SCC risk. It appears that cumulative indoor tanning exposure is more important than duration of use or age at initiation. Avoidance of indoor tanning can help prevent not only melanoma[13] but also SCC and our results strengthen the justification of developing policies that regulate indoor tanning.

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the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. No conflicts of interest to declare.

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Figure 1: Flow chart of study sample from the Norwegian Women and Cancer study.

Abbreviations: NOWAC: Norwegian Women and Cancer; SCC: Squamous cell carcinoma.

Table 1: Host characteristics stratified by cumulative number of indoor tanning sessions, Norwegian Women and Cancer study (*n*=138,474), 1991-2015.

	Cumulative no. of indoor tanning sessions			
	Never use	**Lowest use**	**Medium use**	**Highest use**
No. participants (%)	42,922 (31.0)	63,979 (46.2)	15,666 (11.3)	15,907 (11.5)
Total person-years of follow-up	694,707	1,036,626	285,634	262,108
Mean person-years of follow-up	16.2	16.2	18.2	16.5
Mean age at inclusion	51.3	49.1	47.8	49.0
Mean age at diagnosis	68.6	64.0	63.3	64.9
Incident SCC cases (%)	152 (30.8)	207 (42.0)	65 (13.2)	69 (14.0)
	%[a]	%[a]	%[a]	%[a]
Birth cohort				
1927-1944	43.7	36.3	10.6	9.4
1945-1952	29.7	46.5	11.8	12.0
1953-1963	25.0	51.9	11.1	12.0
Residential ambient UVR exposure				
Low (northern Norway)	25.8	47.6	13.4	13.1
Medium-low (central Norway)	25.5	49.5	13.2	11.8
Medium (southwestern Norway)	36.2	47.0	8.5	8.3
Highest (southeastern Norway)	32.5	44.5	11.0	11.9
Education, years (*n*=131,909)				
≤10	33.7	41.8	11.2	13.2
11-13	26.1	48.7	12.3	12.8
≥14	31.9	48.5	10.7	8.9
Smoking status at baseline (*n*=138,093)				
Never	39.6	42.5	9.5	8.4
Former	27.2	48.8	12.0	12.0
Current	25.4	47.4	12.6	14.5
Hair color (*n*=137,521)				
Black/dark brown	35.2	44.8	9.7	10.2
Brown	29.5	47.3	11.6	11.6
Blond/yellow, red	30.4	45.9	11.7	12.0
Freckling when sunbathing[b] (*n*=121,018)				
No	30.5	46.3	11.4	11.7
Yes	27.2	48.0	12.5	12.2
Untanned skin color[b] (*n*=118,311)				
Dark	31.8	46.2	10.6	11.4
Medium	28.1	47.7	12.2	11.9
Light	26.7	47.7	12.8	12.7
Skin reaction to acute sun exposure[b] (*n*=74,874)				
Brown	27.9	42.1	15.4	14.6
Red	31.0	43.3	14.7	11.0
Red with pain	35.7	43.7	12.5	8.2
Red with pain and blisters	37.5	41.3	12.0	9.1

Table 1: Host characteristics stratified by cumulative number of indoor tanning sessions, Norwegian Women and Cancer study (*n*=138,474), 1991-2015. (continued)

	Cumulative no. of indoor tanning sessions			
	Never use	**Lowest use**	**Medium use**	**Highest use**
	%[a]	%[a]	%[a]	%[a]
Skin reaction to chronic sun exposure[b] (*n*=74,930)				
Deep brown	25.4	45.2	15.4	13.9
Brown	29.4	43.5	15.0	12.1
Light brown	36.6	41.3	13.0	9.1
Never brown	60.9	28.8	6.3	4.1
Cumulative no. of sunburns (*n*=118,642)				
None	39.6	41.1	9.2	10.1
Lowest tertile	28.6	48.5	10.9	12.0
Middle tertile	28.1	48.5	12.2	11.2
Highest tertile	29.6	45.9	11.9	12.6
Cumulative no. of weeks on sunbathing vacations (*n*=129,810)				
None	67.1	24.9	4.4	3.6
Lowest tertile	32.2	46.5	12.2	9.1
Middle tertile	25.3	50.4	11.8	12.6
Highest tertile	24.8	48.5	11.6	15.2

Abbreviations: SCC: squamous cell carcinoma, UVR, ultraviolet radiation.

[a]Row percentages. Due to rounding, percentages may not sum up to 100%.

[b]Recorded for a subsample of the cohort.

Table 2: Hazard ratios (HRs) and 95% confidence intervals (CIs) for indoor tanning and risk of cutaneous squamous cell carcinoma, Norwegian Women and Cancer study, 1991-2015.

			Complete-case analyses		**Multiple-imputation analysis[c]**
			Age-adjusted[a]	Multivariable model[b]	
	No. of participants (%) (*n*=113,290)	No. of cases (*n*=366)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Ever use of indoor tanning device					
Never	33,721 (29.8)	101	1.00	1.00	1.00
Ever	79,569 (70.2)	265	1.50 (1.19-1.90)	1.45 (1.14-1.85)	1.43 (1.17-1.74)
Current use of indoor tanning device					
No	44,971 (39.7)	146	1.00	1.00	1.00
Yes	68,319 (60.3)	220	1.27 (1.02-1.57)	1.22 (0.98-1.52)	1.27 (1.06-1.53)
Cumulative no. of sessions					
Never use	33,721 (29.8)	101	1.00	1.00	1.00
Lowest use	53,458 (47.2)	167	1.41 (1.10-1.82)	1.38 (1.07-1.78)	1.29 (1.04-1.60)
Medium use	12,809 (11.3)	47	1.57 (1.11-2.23)	1.54 (1.08-2.19)	1.60 (1.20-2.15)
Highest use	13,302 (11.7)	51	1.78 (1.27-2.51)	1.68 (1.19-2.38)	1.83 (1.38-2.42)
P_{trend}			<0.001	0.002	<0.001
Duration of use					
Never	33,721 (29.8)	101	1.00	1.00	1.00
≤10 years	15,682 (13.8)	49	1.56 (1.10-2.22)	1.54 (1.08-2.20)	1.41 (1.08-1.85)
>10 years	63,887 (56.4)	216	1.49 (1.17-1.89)	1.43 (1.12-1.84)	1.43 (1.16-1.76)
P_{trend}			0.002	0.007	0.001
Age at initiation					
Never	33,652 (29.7)	101	1.00	1.00	1.00
≥30 years	52,910 (46.7)	188	1.50 (1.17-1.91)	1.45 (1.13-1.86)	1.36 (1.11-1.67)
<30 years	26,728 (23.6)	77	1.41 (1.04-1.91)	1.36 (1.00-1.86)	1.51 (1.18-1.92)
P_{trend}			0.011	0.028	<0.001
Duration of use and cumulative no. of tanning sessions					
Duration: ≤10 years of use					
Never use	33,721 (29.8)	101	1.00	1.00	1.00
Lowest use	13,362 (11.8)	37	1.39 (0.95-2.05)	1.38 (0.93-2.03)	1.27 (0.94-1.71)
Medium/Highest use	2,320 (2.0)	12	2.49 (1.36-4.56)	2.45 (1.33-4.49)	1.99 (1.28-3.08)
Duration: >10 years of use					
Never use	33,721 (29.8)	101	1.00	1.00	1.00
Lowest use	40,096 (35.4)	130	1.42 (1.09-1.85)	1.38 (1.05-1.80)	1.30 (1.03-1.63)
Medium/Highest use	23,791 (21.0)	86	1.60 (1.20-2.15)	1.53 (1.14-2.07)	1.66 (1.29-2.13)
$P_{interaction}$[d]			0.204	0.194	

Table 2: Hazard ratios (HRs) and 95% confidence intervals (CIs) for indoor tanning and risk of cutaneous squamous cell carcinoma, Norwegian Women and Cancer study, 1991-2015. (continued)

			Complete-case analyses		**Multiple-imputation analysis**[c]
			Age-adjusted[a]	Multivariable model[b]	
	No. of participants (%) (*n*=113,290)	No. of cases (*n*=366)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Cumulative no. of indoor and outdoor tanning sessions[e,f]					
1 (lowest)	14,897 (13.1)	44	1.00	1.00	1.00
2	30,122 (26.6)	95	1.47 (1.03-2.11)	1.39 (0.97-1.99)	1.42 (1.02-1.98)
3	37,127 (32.8)	106	1.43 (1.00-2.04)	1.34 (0.94-1.92)	1.48 (1.08-2.02)
4	14,970 (13.2)	57	2.02 (1.36-3.00)	1.89 (1.27-2.82)	1.79 (1.24-2.59)
5 (highest)	16,174 (14.3)	64	2.21 (1.50-3.27)	2.03 (1.38-3.01)	2.43 (1.74-3.39)
P_{trend}			<0.001	<0.001	<0.001

[a]Cox regression with age as the time scale and stratified by birth cohort.
[b]Additional adjustments for residential ambient UVR exposure, hair color and cumulative number of sunburns and sunbathing vacations.
[c]Analysis with multiple imputation of missing data conducted using chained equations and a total of 40 imputed datasets, with the same adjustments as the multivariable model (n=159,419; 597 cases).
[d]Testing interaction between number of sessions and duration of use.
[e]Based on the sum of quartiles of both variables (resulting in a score from 0 to 8), categorized as: (0,1), (2,3), (4,5), 6, (7,8).
[f]For this variable, the multivariable model included residential ambient UVR exposure, hair color and cumulative number of sunburns.

Table 3: Linear regression analysis of the association between age at initiation of indoor tanning and age at diagnosis, Norwegian Women and Cancer study, 1991-2015.

		Complete-case analyses		Multiple-imputation analysis[b]
		Crude	Adjusted[a]	
	No. cases	$\hat{\beta}$ (95% CI)	$\hat{\beta}$ (95% CI)	$\hat{\beta}$ (95% CI)
Age at initiation	366			
Never	101	0.00	0.00	0.00
≥30 years	188	-2.78 (-4.83,-0.73)	-0.33 (-1.47,0.82)	-0.09 (-1.11,0.94)
<30 years	77	-3.00 (-5.52,-0.49)	0.18 (-1.24,1.61)	-0.02 (-1.27,1.22)

$\hat{\beta}$: estimated regression coefficient;

Abbreviation: CI, confidence interval.

[a]Adjusted for birth year, residential ambient UVR exposure, hair color, cumulative number of sunburns and sunbathing vacations.

[b]Analysis with multiple imputation of missing data conducted using chained equations and a total of 40 imputed datasets, with the same adjustments as [a] (597 cases).