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Risk of second primary cancer associated with pre-diagnostic smoking, alcohol, and obesity in women with keratinocyte carcinoma

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Abstract

Keratinocyte carcinoma (KC), which includes basal-cell carcinoma (BCC) and squamous-cell cancer (SCC), has been associated with an increased risk of second primary cancers (SPCs), although the reason for this increase is unknown. We assessed the effects of smoking, alcohol, and

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Conflict of interest statement

The authors have declared that no conflict of interests exist.

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Author contributions

Drs. Park and Cho had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design

All authors.

Analysis and interpretation of data

All authors.

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Park and Cho.

obesity prior to the diagnosis of KC on the development of SPCs, as these are well-established risk factors for multiple cancers and may also contribute to the increased risk of SPCs among those with KC. A total of 15,628 women with self-reported KC were identified in the Nurses' Health Study. Incident SPCs were assessed throughout the follow-up until June 2012. Cox proportional hazards models were used to calculate the hazard ratios (HRs) of SPC associated with pre-diagnostic smoking, alcohol and body mass index (BMI). We also compared these risk estimates to those for first cancers in all cohort participants. During 193,695 person-years of follow-up, we recorded 2839 SPC cases. Compared with never smokers, current smokers had a significantly elevated risk for SPC overall and specifically for lung, colorectal, and bladder cancers. We also found a positive association between higher BMI and risk for SPC overall as well as for endometrial and bladder SPCs. Women with KC who consumed alcohol 30 g/day had a marginally higher risk of SPC compared to non-drinkers. The associations between incident SPC risk among KC cases and smoking, alcohol, and obesity appeared similar to the associations between these risk factors and the incident first primary cancers in the whole cohort. Only in the heavy smoking (≥ 25 cigarettes/day) category was the HR for SPC after KC (2.34; 95% CI 1.98–2.76) slightly higher than that for the first cancer in the overall cohort (HR 1.86; 95% CI 1.75–1.98, $P_{\text{heterogeneity}} = 0.01$). In conclusion, pre-diagnostic smoking, alcohol and obesity prior to KC diagnosis were associated with risk of SPCs.

Keywords

Smoking; Alcohol; Body mass index; Second primary cancer; Keratinocyte carcinoma

1. Introduction

Keratinocyte carcinoma (KC), which includes basal-cell carcinoma (BCC) and squamous-cell cancer (SCC), is the most prevalent cancer [1,2], and the incidence of KC is increasing worldwide [2–5]. Although KC has a low mortality rate of 1/100,000 [1,2], several previous studies have suggested a positive association between the history of KC and the risk of subsequent second primary cancers (SPCs) in other organs [6–10]. A meta-analysis reported that KC was associated with about a 10% increased risk of SPCs [7].

These positive associations between KC and SPCs could be due to differences in lifestyle factors or increased susceptibility to carcinogenesis among those with KC. Common cancer risk factors such as smoking, alcohol consumption, and obesity may have a role in the increased risk of SPC among those with KC [16–23]. As sunlight exposure has an immunosuppressive effect [15] and is a well-established risk factor for KC, these common cancer risk factors may interact with weakened immune systems among those with KC. Several previous studies have demonstrated that pre-diagnostic smoking [11,12] and obesity [13,14] were associated with an increased risk of SPC among cancer survivors. However, little is known about the associations between these behavioral risk factors and risk of SPC among KC patients.

Using the Nurses' Health Study (NHS), we assessed the risk of incident SPCs after KC in relation to pre-diagnostic smoking, alcohol, and obesity. In a secondary analysis we

compared the association of these risk factors for SPCs after KC with their associations with first cancer in the overall NHS cohort.

2. Methods

2.1. Study population

The study population consisted of participants from an ongoing prospective cohort study. The NHS was established in 1976, when 121,700 US female registered nurses aged 30–55 years were enrolled. Baseline and follow-up questionnaires were sent every 2 years to update information on lifestyle factors and diagnosed diseases. Institutional Review Board (IRB) approval was obtained at the Brigham and Women's Hospital.

Participants have reported new diagnoses of BCC and SCC from 1984. Women who reported SCC were asked for permission to obtain medical records, which were obtained and reviewed by study physicians to confirm the diagnoses. Medical records were not obtained for self-reported cases of BCC. However, previous validation studies in our cohorts demonstrated a high accuracy of self-reported BCC, with 96% confirmed by histopathology records [24,25].

The eligible study population for our primary analysis consisted of women with first incident KC diagnosed any time between the 1984 and the 2010 follow-up cycle with no previously diagnosed cancer ($n = 15,836$). We excluded individuals who had no information on pre-diagnostic smoking status, alcohol consumption, or body mass index (BMI). In the present analysis, we included 15,628 women with KC.

2.2. Case ascertainment

The primary endpoint of this study was newly diagnosed SPC other than KC. Self-reported information on incident cancers was obtained in each biennial questionnaire. Participants who reported a cancer diagnosis were asked for permission to access their medical and pathological records. We identified fatal cases from the National Death Index and from next of kin. Physicians blinded to participants' exposure information reviewed the records to confirm the diagnosis. We only included confirmed SPC cases.

2.3. Ascertainment of exposures and other life-style factors

Information on smoking status, weight, menopausal status, hormone replacement therapy use, and physician-diagnosed diabetes, hypertension, and dyslipidemia has been assessed biennially since the start of the study in 1976. Information on alcohol consumption and physical activity has been collected every 2–4 years. Age and adult height were assessed in 1976.

Information on pre-diagnostic smoking status, weight, and alcohol consumption was extracted from the biennial questionnaire of at least one follow-up cycle prior to the diagnosis of KC. Current smokers reported intensity of smoking (number of cigarettes per day). We classified participants as pre-diagnostic current, former, or never smokers. For current smokers, we also classified them on the basis of the number of cigarettes smoked per day. Alcohol intake was computed as the sum of the intake of beer, wine, and liquor. The

reproducibility and validity of alcohol intake assessed by dietary questionnaire have been previously documented [26]. BMI was calculated as pre-diagnostic weight divided by adult height squared (kg/m^2). The accuracy of self-reported anthropometric measures has been validated [27].

Information on other life-style factors was also collected at least 2 years prior to diagnosis of first KC.

2.4. Statistical analysis

We calculated person-years of follow-up from the date of first diagnosis of KC to the date of SPC diagnosis other than KC, death from any cause, or the end of follow-up (June 2012), whichever came first. For those who were lost to follow-up after the diagnosis of KC, we censored them at the date of return of the last questionnaire. Cox proportional-hazards models were used to determine the hazard ratios (HRs) of SPCs associated with pre-diagnostic smoking status, alcohol consumption, and BMI. The assumptions of proportionality were satisfied. We conducted analyses for total SPCs as well as the major individual SPCs with more than 70 cases, which included lung, colorectal, breast, endometrial, and bladder cancers, non-Hodgkin lymphoma, and melanoma.

For multivariate analyses, we adjusted for the following: age (continuous), smoking status (never [reference], past, current 1–14 cigarettes/day, current 15–24 cigarettes/day, or current 25 cigarettes/day), alcohol consumption (0 [reference], 0.1–4.9, 5.0–14.9, 15.0–29.9, or 30.0 g/day), BMI (<23 [reference], 23–25, 25–29.9, 30–34.9, or 35 kg/m^2), physical activity (quintiles), menopause status (yes/no), postmenopausal hormone use (yes/no), and history of hypercholesterolemia (yes/no), hypertension (yes/no) or type 2 diabetes (yes/no). Tests for trend were performed by assigning consecutive numbers for smoking status and median values for alcohol and BMI categories, and treating the new variable as a continuous term in the models. If there were less than five SPC occurrences in the category, the hazard ratio was not estimated because of power considerations.

We additionally performed several sensitivity analyses. First, we excluded those diagnosed with SPCs within the first 2 years after KC diagnosis to minimize concerns of reverse-causation. Second, when we analyzed the associations between pre-diagnostic BMI and SPC risk, we stratified the associations by smoking history (never versus ever). Third, we evaluated the associations according to type of KC (BCC and SCC).

In a secondary analysis, we examined associations between smoking, alcohol and BMI and first cancer risk among the cancer-free participants in the NHS overall. This was done in order to compare the magnitude of the associations with post-KC SPC risk from our primary analysis. In this secondary analysis, all of the cohort participants with valid exposure data in 1984 and no previous cancer diagnosis were included ($n = 74,696$). Follow-up started in 1984 and continued until the diagnosis of a first non-KC cancer, KC, death, loss to follow-up, or end of follow-up in June 2012. *P* values for heterogeneity were calculated with the *Q* statistic.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). All statistical tests were two-tailed, and the significance level was set at $P < 0.05$.

3. Results

We included 15,628 women with KC (14,324 BCC cases and 1304 SCC cases) from June 1984 to June 2010 in NHS. These KC cases include both BCC and SCC. Table 1 lists the baseline (1984) characteristics of the study population of women with KC based on the development of SPC during follow-up. After 193,695 person years of follow-up, we documented 2839 cases with SPC (1071 with breast cancer, 232 with lung cancer, 199 with colon and rectum cancer, 157 with melanoma, 152 with non-Hodgkin lymphoma, 156 with endometrial cancer, and 71 with bladder cancer).

Pre-diagnostic smoking was associated with increased risk of overall SPC and several individual SPCs (Table 2). Compared with non-smokers, smoking before KC diagnosis had a significantly elevated overall SPC risk ($P_{\text{trend}} < 0.001$; HR 2.34; 95% CI 1.98–2.76 for current smokers ≥ 25 cigarettes/d) and risk for cancers of the lung ($P_{\text{trend}} < 0.001$; HR 22.10; 95% CI 13.68–35.71 for current smokers ≥ 25 cigarettes/d), colorectum ($P_{\text{trend}} = 0.003$; HR 2.78; 95% CI 1.57–4.93 for current smokers ≥ 25 cigarettes/d) and bladder ($P_{\text{trend}} = 0.009$; HR 2.47, 95% CI 1.26–4.86 for current smokers overall) in multivariate-adjusted analysis.

Alcohol consumption was associated with increased risk of SPCs ($P_{\text{trend}} = 0.02$, Table 3). There was a significant trend of increasing breast cancer risk associated with higher alcohol intake ($P_{\text{trend}} = 0.01$). Alcohol consumption was not significantly associated with cancer at other sites, although there was some suggestion of a linear trend with non-Hodgkin lymphoma ($P_{\text{trend}} = 0.04$).

BMI was positively associated with risk of SPCs overall (Table 4). We found positive linear trends in the associations between BMI and risk for SPCs overall ($P_{\text{trend}} < 0.001$), and breast ($P_{\text{trend}} = 0.02$) and endometrial SPCs ($P_{\text{trend}} < 0.001$). The associations between BMI and SPCs were similar by smoking history (never versus ever; Supplementary Table 1, $P_{\text{interaction}} = 0.33$).

In a sensitivity analysis excluding SPCs developed in the first 2 years ($n = 399$) after diagnosis of KC, the associations with behavioral risk factors remained essentially unchanged from the primary analysis (data not shown). In the sensitivity analysis stratified by KC subtype (BCC and SCC), no substantial differences in trends were found among BCC patients (Supplementary Fig. 1). Among SCC patients, the associations were attenuated with SPCs overall and could not be tested for specific cancers due to the small number of cases. A sensitivity analysis additionally adjusting for the number of KCs did not materially change the findings (data not shown).

In our analysis of incident primary cancers in the cohort as a whole, we documented 13,628 primary cancer cases other than KC over 1,601,540 person-years of follow-up for 74,696 women. Overall associations between cigarette smoking and first cancer risk were similar to those observed for SPC risk after KC (Fig. 1). However, in the heavy smoking category (≥ 25

cigarettes/day) the HR for SPC among women with KC (2.34; 95% CI 1.98–2.76) was slightly higher than that for first cancer among all cohort participants (HR 1.86; 95% CI 1.75–1.98, $P_{\text{heterogeneity}} = 0.01$). In a similar comparison, the magnitude of the association between alcohol consumption ≥ 30 g/day and cancer risk was similar for SPC after KC (HR 1.20; 95% CI 1.02–1.41) versus first cancer (HR 1.25; 95% CI 1.16–1.34, $P_{\text{heterogeneity}} = 0.65$). The strength of the association between obesity and cancer risk was similar for SPC (HR 1.36; 95% CI 1.12–1.65 for BMI ≥ 35 kg/m²) versus first cancer (HR 1.39; 95% CI 1.28–1.51 for BMI ≥ 35 kg/m², $P_{\text{heterogeneity}} = 0.84$).

4. Discussion

In this large cohort study of women, we provided the first prospective investigation of the association between pre-diagnostic smoking, alcohol intake, and obesity and risk of SPC among KC patients. Pre-diagnostic smoking, alcohol consumption and obesity were independent risk factors for subsequent overall SPC as well as for several individual SPCs. The magnitude of these associations was similar to those seen for first primary cancer in the cohort overall.

Previous studies have demonstrated that a prior KC diagnosis was associated with increased risk of developing another type of cancer compared with the general population, which may be due to genetic predisposition, lifestyle factors, or increased susceptibility to carcinogenesis [6–9]. Unlike other cancers, KC is common, is rarely fatal, and is usually locally excised with minimal concern for elevated cancer risk due to the adverse effects of treatment [7,9]. Therefore, KC is an excellent first cancer to identify life-style risk factors for SPCs.

Our finding that pre-diagnostic smoking was an independent risk factor for SPCs in women with KC is consistent with findings of other studies suggesting that smoking increases the risk of SPCs, especially smoking-related cancers such as lung and bladder cancers [16–19]. For example, a recent pooled analysis of prospective cohort studies among survivors of smoking-related cancers found that cigarette smoking before first cancer diagnosis was associated with increased smoking-related SPC risk [11]. A Japanese cancer survivor cohort study also showed a similar positive association between pre-diagnostic smoking and risk of overall SPCs (incidence rate ratio 1.76; 95% CI 1.53–2.02) [12]. Meanwhile, although several studies have demonstrated that smoking is associated with an increased risk of colorectal cancer in the general population [28,29], little is known about this association among cancer survivors. We provide novel data showing that pre-diagnostic smoking is associated with elevated risk of colorectal cancer among women with KC.

We found that overall associations between cigarette smoking and first cancer risk were similar to associations identified for SPC risk among women with KC. Only in the heavy-smoking category was the HR for SPC slightly higher than that for the first primary malignancy. There could be modest increased susceptibility to smoking-related carcinogenesis among KC patients. It is possible that a personal history of KC may be a marker of genetic susceptibility to suboptimal DNA repair, which may increase the susceptibility to smoking-related cancers [6]. Furthermore, UV radiation, a well-known

cause of skin cancer, can also cause immunosuppression, which may interact with smoking and contribute to increase the risk of smoking-related cancers [30,31]. Further research is needed to replicate our findings and to clarify the mechanism.

Alcohol consumption is known to increase the risk of cancers of the upper aero-digestive tract [32,33], colorectum [34–37] and breast [20] in the general population. In our study, alcohol intake increased the risk of overall SPC and specifically of breast cancer. However, overall associations between alcohol consumption and first cancer risk were similar to the associations identified for SPC.

We found significant dose-dependent relationships between pre-diagnostic BMI and SPCs. Obesity is a well-known risk factor for cancer of multiple organs, including colon and rectum [21,22], breast [21,38], endometrium [21], kidney [23], and bladder [39]. Obesity has been studied in relation to SPC risk, although this work has largely been confined to survivors of breast cancer [40] or colorectal cancer [13]. The present study adds evidence that pre-diagnostic obesity may be a risk factor for SPCs at several cancer sites – including breast, endometrium, and bladder – among women with KC. We also found that the magnitude of the association between obesity and SPC risk was similar to that for first cancer risk in the cohort. As smoking is usually inversely associated with body weight [41], it could distort the link between obesity and SPC risk. However, the associations between obesity and the risk of SPC showed a similar trend in the stratified analysis by smoking status.

As health behaviors may be influenced by a diagnosis of cancer, the ideal assessment of the etiology of SPC would be a large prospective study with detailed data on exposures before the first KC diagnosis. The strengths of our study included the prospective cohort design with more than 15,000 women with KC and detailed assessment of the pre-diagnostic life-style risk factors.

Our study has several limitations. First, BCC cases were based on self-report. However, as the participants in this study were registered nurses, the validity of their reports is expected to be high, as shown in previous validation studies [24,25]. Still, we cannot exclude the possibility of under-reporting and misclassification of BCC. Second, our cohort of KC largely consisted of BCC cases, with SCC cases making up only 8.3%. Therefore, the associations were largely driven by associations with BCC. The small number of SCC cases also limited our stratified analysis by KC subtype. Third, although we defined SPC as cancer after first diagnosis of KC, there was some uncertainty as to which was the first cancer. However, when we conducted the analyses after excluding cancer cases that occurred within 2 years after KC diagnosis, the results remained similar.

In conclusion, our study showed that pre-diagnostic smoking, alcohol and obesity were risk factors for SPCs overall as well as for several individual SPCs (lung, colorectal, and bladder cancers for smoking; bladder and endometrial cancers for obesity) among women with KC. Our findings may be important for revealing previously unrecognized cancer risks among KC patients with the ultimate goal of promoting early detection of SPCs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.canep.2017.02.002>.

Fig. 1.

Associations between pre-diagnostic smoking (a), alcohol (b), and obesity (c) and risk of either a second primary cancer among women with keratinocyte carcinoma or a first cancer among women without cancer history in the Nurses' Health Study. Abbreviations: HR, hazard ratio.

*The multivariate relative risk model for total second primary cancers among keratinocyte carcinoma patients used Cox proportional analysis and adjusted for age (continuous variable), smoking status (never, past, current 1–14 cigarettes/day, current 15–24 cigarettes/day, or current 25 cigarettes/day), alcohol consumption (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, or 30.0 g/day), BMI (<23, 23–25, 25–29.9, 30–34.9, or 35 kg/m²), physical activity (quintiles), menopause status, postmenopausal hormone use, and history of hypercholesterolemia, hypertension or type 2 diabetes from the questionnaire of at least one biennial follow-up cycle prior to first keratinocyte carcinoma diagnosis.

†The multivariate relative risk model for first cancers among the cancer-free participants used Cox proportional analysis and adjusted for age (continuous variable), smoking status (never, past, current 1–14 cigarettes/day, current 15–24 cigarettes/day, or current 25 cigarettes/day), alcohol consumption (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, or 30.0 g/day), BMI (<23, 23–25, 25–29.9, 30–34.9, or 35 kg/m²), physical activity (quintiles), menopause status, postmenopausal hormone use, and history of hypercholesterolemia, hypertension or type 2 diabetes from the questionnaire in 1984.

Table 1

Baseline (1984) characteristics of the study population with keratinocyte carcinoma based on the development of second primary cancer during follow-up in the Nurses' Health Study.

Characteristics	Second primary cancer development during follow-up (1984–2012)	
	Yes (n = 2836)	No (n = 12,792)
Age (years)		
Mean (standard deviation)	52.2 (6.8)	51.7 (6.8)
Smoking status		
Non-smoker	42.2%	43.9%
Past smoker	37.8%	35.8%
Current smoker:	20.0%	20.0%
1–14 Cigarettes per day	6.9%	6.7%
15–24 Cigarettes per day	7.3%	8.2%
25+ Cigarettes per day	5.7%	5.4%
Body mass index, kg/m ²		
Mean (standard deviation)	25.0 (4.5)	24.6 (4.3)
Normal (<25.0)	59.5%	63.9%
Overweight (25.0–29.9)	27.0%	25.6%
Obese (≥ 30)	13.5%	10.5%
Alcohol consumption, gram/day		
Mean (standard deviation)	7.2 (11.1)	7.8 (11.5)
History of physician diagnosed comorbidity		
Type 2 diabetes mellitus	1.7%	1.5%
Hypertension	8.6%	3.9%
Dyslipidemia	3.9%	8.5%

Information about the history of physician-diagnosed hypercholesterolemia, hypertension or type 2 diabetes mellitus was collected from the questionnaire.

Adjusted hazard ratio (aHR) of second primary cancer (SPC) by pre-diagnostic smoking status in women with keratinocyte carcinoma in the Nurses' Health Study (1984–2012).

Table 2

Site of second primary cancer	Pre-diagnostic smoking status				No. of cigarettes/d of current smokers			P for trend ^a
	Never	Former	Current					
				1–14	15–24	25		
All								
number of SPCs	1067	1195	577		167	236	174	
aHR (95% CI) ^b	1.0	1.16 (1.07–1.27)	1.72 (1.55–1.92)		1.36 (1.15–1.60)	1.74 (1.51–2.02)	2.34 (1.98–2.76)	<0.001
Lung								
number of SPCs	31	79	122		27	48	47	
aHR (95% CI) ^b	1.0	2.63 (1.72–4.00)	12.27 (8.16–18.47)		7.27 (4.30–12.29)	12.59 (7.90–20.07)	22.10 (13.68–35.71)	<0.001
Colon and rectum								
number of SPCs	76	83	40		8	16	16	
aHR (95% CI) ^b	1.0	1.21 (0.88–1.66)	1.56 (1.04–2.34)		0.90 (0.43–1.88)	1.51 (0.87–2.62)	2.78 (1.57–4.93)	0.003
Non-Hodgkin lymphoma								
number of SPCs	75	64	13		4	6	3	
aHR (95% CI) ^b	1.0	0.85 (0.60–1.19)	0.56 (0.31–1.02)		NA ^c	0.66 (0.28–1.53)	NA ^c	0.06 ^d
Melanoma								
number of SPCs	60	81	16		8	5	3	
aHR (95% CI) ^b	1.0	1.30 (0.92–1.83)	0.72 (0.41–1.27)		0.99 (0.47–2.09)	0.55 (0.22–1.38)	NA ^c	0.72 ^d
Breast								
number of SPCs	471	447	153		52	59	42	
aHR (95% CI) ^b	1.0	0.97 (0.85–1.11)	0.99 (0.82–1.19)		0.93 (0.69–1.24)	0.93 (0.71–1.23)	1.18 (0.85–1.63)	0.91
Endometrium								
number of SPCs	73	67	16		5	8	3	

Site of second primary cancer	Pre-diagnostic smoking status						<i>P</i> for trend ^a
	Never			Current			
	No. of cigarettes/d of current smokers						
				1-14	15-24	25	
aHR (95% CI) ^b	1.0	0.93 (0.66-1.32)	0.67 (0.38-1.17)	0.58 (0.23-1.45)	0.80 (0.38-1.68)	NA ^c	0.20 ^d
Bladder							
number of SPCs	21	34	16	4	8	4	
aHR (95% CI) ^b	1.0	1.61 (0.92-2.81)	2.47 (1.26-4.86)	NA ^c	2.95 (1.28-6.81)	NA ^c	0.009 ^d

HR, hazard ratio; CI, confidence interval; NA, not applicable.

Information on pre-diagnostic smoking status was obtained from the questionnaire of at least one biennial follow-up cycle prior to diagnosis of keratinocyte carcinoma.

^aTests for trends were performed by assigning consecutive numbers to smoking status (never, past, current 1–14 cigarettes/day, or current 15–24 cigarettes/day, or current 25 cigarettes/day) and treating the new variable as a continuous variable.

^bThe multivariate relative risk model used Cox proportional analysis and adjusted for age (continuous variable), alcohol consumption (0, 1–4.9, 5.0–14.9, 15.0–29.9, or 30.0 g/day), BMI (<23, 23–25, 25–29.9, 30–34.9, or 35 kg/m²), physical activity (quintiles), menopause status (yes/no), postmenopausal hormone use (yes/no), and history of hypercholesterolemia, hypertension or type 2 diabetes from the questionnaire of at least one biennial follow-up cycle prior to first keratinocyte carcinoma diagnosis.

^cIf there were fewer than five second primary cancer occurrences in the category, the hazard ratio was not estimated because of low case numbers.

^dTests for trends were performed by assigning consecutive numbers for smoking status (never, past, or current) because of low second primary cancer occurrence in some categories of number of cigarettes/day among current smokers.

Table 3

Adjusted hazard ratios (aHRs) of second primary cancer (SPC) by pre-diagnostic alcohol consumption in women with keratinocyte carcinoma in the Nurses' Health Study (1984–2012).

Site of second primary cancer	Pre-diagnostic alcohol consumption (grams/day) ^a					P for trend
	0	0.1–4.9	5.0–14.9	15.0–29.9	30.0	
All						
number of SPCs	941	833	637	242	186	
aHR (95% CI) ^b	1.0	0.98 (0.89–1.08)	1.03 (0.93–1.15)	1.05 (0.91–1.21)	1.20 (1.02–1.41)	0.02
Lung						
number of SPCs	75	60	49	26	22	
aHR (95% CI) ^b	1.0	0.82 (0.58–1.16)	0.78 (0.53–1.12)	1.08 (0.68–1.71)	0.84 (0.51–1.39)	0.89
Colon and rectum						
number of SPCs	75	55	44	11	14	
aHR (95% CI) ^b	1.0	0.83 (0.58–1.18)	0.94 (0.64–1.38)	0.60 (0.31–1.14)	1.10 (0.61–2.00)	0.98
Non-Hodgkin lymphoma						
number of SPCs	55	34	39	13	11	
aHR (95% CI) ^b	1.0	0.70 (0.45–1.08)	1.18 (0.77–1.82)	1.09 (0.58–2.03)	1.62 (0.83–3.16)	0.04
Melanoma						
number of SPCs	43	47	45	13	9	
aHR (95% CI) ^b	1.0	1.08 (0.71–1.65)	1.49 (0.96–2.30)	1.12 (0.59–2.12)	1.38 (0.66–2.87)	0.30
Breast						
number of SPCs	342	325	232	108	64	
aHR (95% CI) ^b	1.0	1.06 (0.91–1.24)	1.08 (0.91–1.28)	1.35 (1.08–1.69)	1.31 (0.99–1.72)	0.01
Endometrial						
number of SPCs	46	56	36	12	6	
aHR (95% CI) ^b	1.0	1.42 (0.95–2.11)	1.47 (0.93–2.32)	1.34 (0.70–2.59)	1.09 (0.46–2.59)	0.77
Bladder						

Site of second primary cancer	Pre-diagnostic alcohol consumption (grams/day) ^a					P for trend
	0	0.1–4.9	5.0–14.9	15.0–29.9	30.0	
number of SPCs	19	22	18	7	5	
aHR (95% CI) ^b	1.0	1.29 (0.69–2.40)	1.37 (0.70–2.67)	1.42 (0.58–3.45)	1.48 (0.54–4.10)	0.44

HR, hazard ratio; CI, confidence interval.

^aPre-diagnostic alcohol consumption was estimated from the questionnaire of at least one biennial follow-up cycle (one or two) prior to diagnosis of keratinocyte carcinoma. In the United States, a standard alcoholic drink contains 14.0 g of alcohol.

^bThe multivariate relative risk model used Cox proportional analysis and adjusted for age (continuous variable), smoking status (never, past, current 1–14 cigarettes/day, current 15–24 cigarettes/day, or current ≥25 cigarettes/day), BMI (<23, 23–25, 25–29.9, 30–34.9, or ≥35 kg/m²), physical activity (quintiles), menopause status, postmenopausal hormone use, and history of hypercholesterolemia, hypertension or type 2 diabetes from the questionnaire of at least one biennial follow-up cycle prior to first keratinocyte carcinoma diagnosis.

Adjusted hazard ratio (aHR) of second primary cancer by pre-diagnostic body mass index (BMI) in women with keratinocyte carcinoma in the Nurses' Health Study (1984–2012).

Table 4

Site of second primary cancer	Pre-diagnostic BMI (kg/m ²) ^a					P for Trend
	<23	23–24.9	25–29.9	30–34.9	35	
All						
number of SPCs	958	561	854	338	128	
aHR (95% CI) ^b	1.0	1.02 (0.92–1.14)	1.07 (0.98–1.18)	1.23 (1.08–1.41)	1.36 (1.12–1.65)	<0.001
Lung						
number of SPCs	86	54	67	20	5	
aHR (95% CI) ^b	1.0	1.10 (0.77–1.55)	0.93 (0.66–1.29)	0.73 (0.44–1.22)	0.54 (0.21–1.38)	0.06
Colon and rectum						
number of SPCs	65	47	59	19	9	
aHR (95% CI) ^b	1.0	1.22 (0.84–1.79)	0.99 (0.69–1.43)	0.90 (0.52–1.53)	1.23 (0.59–2.56)	0.79
Non-Hodgkin lymphoma						
number of SPCs	57	23	52	14	6	
aHR (95% CI) ^b	1.0	0.68 (0.42–1.14)	1.05 (0.71–1.55)	0.83 (0.45–1.53)	1.06 (0.44–2.56)	0.86
Melanoma						
number of SPCs	53	34	44	20	6	
aHR (95% CI) ^b	1.0	1.17 (0.76–1.81)	1.09 (0.72–1.64)	1.44 (0.83–2.48)	1.28 (0.53–3.09)	0.31
Breast						
number of SPCs	351	216	336	124	44	
aHR (95% CI) ^b	1.0	1.09 (0.92–1.29)	1.21 (1.03–1.41)	1.31 (1.06–1.63)	1.33 (0.95–1.84)	0.02
Endometrium						
number of SPCs	46	21	41	29	19	
aHR (95% CI) ^b	1.0	0.85 (0.50–1.43)	1.24 (0.81–1.92)	2.84 (1.73–4.65)	5.90 (3.25–10.71)	<0.001
Bladder						

Site of second primary cancer	Pre-diagnostic BMI (kg/m ²) ^a				P for Trend
	<23	23–24.9	25–29.9	30–34.9	35
number of SPCs	20	17	22	6	6
aHR (95% CI) ^b	1.0	1.51 (0.78–2.89)	1.28 (0.69–2.38)	1.05 (0.41–2.71)	3.03 (1.12–8.16)

HR, hazard ratio; CI, confidence interval.

^aInformation on pre-diagnostic body mass index (BMI) was estimated from the questionnaire of at least one biennial follow-up cycle prior to the keratinocyte carcinoma diagnosis.

^bThe multivariate relative risk model used Cox proportional analysis and adjusted for age (continuous variable), smoking status (never, past, current 1–14 cigarettes/day, current 15–24 cigarettes/day, or current 25 cigarettes/day), alcohol consumption (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, or 30.0 g/day), physical activity (quintiles), menopause status, postmenopausal hormone use, and history of hypercholesterolemia, hypertension or type 2 diabetes from the questionnaire of at least one biennial follow-up cycle prior to the first keratinocyte carcinoma diagnosis.