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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 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, $P_{heterogeneity} = 0.01$). In conclusion, pre-diagnostic smoking, alcohol and obesity prior to KC diagnosis were associated with risk of SPCs.

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.

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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

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.