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Ambient temperature and risk of first primary basal cell carcinoma: A nationwide United States cohort study

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ABSTRACT

The Earth's surface is warming and animal studies have shown higher temperatures promote ultraviolet radiation (UVR) skin carcinogenesis. There are, however, no population studies of long-term temperature exposure and basal cell carcinoma (BCC) risk. We linked average lifetime summer ambient temperatures (based on weather station data) and satellite-based UVR estimates to self-reported lifetime residences in the U.S. Radiologic Technologists' cohort. We assessed the relationship between time-dependent average lifetime summer ambient temperature (20-year lag) in quintiles and BCC in whites, using Cox proportional hazards regression. Risks were adjusted for time-dependent lagged average lifetime UVR and time outdoors, body mass index, eye color, and sex (baseline hazard stratified on birth cohort). During a median 19.4 years follow-up, we identified 3556 BCC cases. There was no significant trend in risk between temperature and BCC. However, BCC risk was highest in the fourth quintile of temperature (Q4 vs. Q1; hazards ratio (HR) = 1.18; 95% confidence interval (CI) = 1.06–1.31, *p*-trend = 0.09). BCC risk was strongly related to average lifetime ambient UVR exposure (Q5 vs. Q1; HR = 1.54 (95% CI = 1.35–1.75, *p*-trend = <0.001)). Future studies of temperature and BCC risk should include a broad range of UVR and temperature values, along with improved indicators of exposure to temperatures and UVR.

1. Introduction

Basal cell carcinoma (BCC) is the most common type of non-melanoma skin cancer (NMSC), and the most frequently diagnosed U.S. cancer [1]. The estimated U.S. incidence of NMSC is more than one million cases per year, of which about 70–80% are BCCs [2]. Although BCC is rarely fatal, it accounts for substantial disfigurement and health expenditures [1]. Epidemiologic studies of BCC have largely focused on the role of ultraviolet radiation (UVR), the main risk factor for BCC [2,3,1,4], but other factors are also involved [1].

Over several decades studies have suggested that temperature together with UVR might contribute to skin carcinogenesis [5–9]. Experimental animal studies demonstrated that elevated temperatures enhanced UVR carcinogenesis when UVR radiation was held constant [5,9]. Studies in human cell lines suggest that elevated temperatures may inhibit DNA repair in UV-irradiated cells [8] and may increase chromosomal aberrations in human keratinocytes [7]. One cross-sectional epidemiologic study found that NMSC incidence in 10 regions correlated with both ambient UVR and average daily maximum temperature in summer, despite a poor correlation between UVR and temperature in those areas [6].

Measurements show that the Earth's average surface temperature has risen 1.4° Fahrenheit (F) over the past 100 years, and additional warming of 2.0–11.5 °F over the 21st century is expected [10]. In 2010, The Interagency Working Group on Climate Change and Health, a U.S. governmental entity, outlined research needs in a report on the human health effects of climate change [11]. Among the cancer research needs identified was "elucidating the effects of ambient temperature on UVR-induced skin cancers, including the amplification of non-melanoma skin cancers."

The purpose of this study is to explore the association between long-term ambient temperature and subsequent BCC risk, while accounting for historic ambient UVR exposure, time outdoors, and other relevant factors. This study, which relies on data from the U.S. Radiologic Technologists (USRT) Study, a large nationwide cohort that draws members from all 50 states, is the first, to our knowledge, to assess BCC risk in a wide geographic population

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with estimates of historic ambient temperature and solar UVR exposures, and other key factors.

2. Materials and methods

2.1. Study population

The USRT Study comprises a cohort of U.S. radiologic technologists who were certified by the American Registry of Radiological Technologists for at least two years between 1926 and 1982 [12]. Detailed information on the study has been previously provided [12]. Three questionnaires were self-administered to the study members. A first questionnaire (1983–1989) provided information on height, weight, smoking behavior, as well as work history, cancer history, and other factors. A second questionnaire (1995–1998) also ascertained incident cancers and updated earlier information. The third survey (2003–2005) included information on eye and hair color, complexion, residential history and summer time outdoors, as well as cancer diagnoses. The USRT Study has been approved annually by the human subject review boards at the University of Minnesota and the National Cancer Institute and subjects gave their written, informed consent.

We restricted the study population to white participants who answered the first and/or second questionnaires, as well as the third questionnaire, and were cancer-free as of the baseline questionnaire (the earlier of the first or second questionnaire), $N = 66{,}362$. We then excluded participants who had omitted information on their residential locations ($N = 1792$) or for whom ambient UVR could not be calculated ($N = 4$), resulting in a study population of $N = 64{,}566$.

Eligible cases included only first primary BCC cases that were ascertained from the second or third questionnaires. BCC was defined as ICD-10 = C44 and morphology = 809–811×. Among the 3330 respondents reporting BCC, pathology reports and medical records were obtained for 1598 (48%). Of these, records validated the BCC diagnosis for 1527 (96%). We excluded 71 cases that were incorrectly reported as BCC and added 297 subjects with BCC found after validating other cancers. Based on the high validation rate, we included BCCs for which medical records were unavailable ($n = 1732$), bringing the total to 3556 BCC cases.

2.2. Data collection

The baseline questionnaires provided sex, body mass index (BMI), smoking history, and education at baseline. Occupational ionizing radiation skin dose to the head and neck, the most common sites for BCC [1], was estimated based on badge records and other factors [13]. The third survey provided data on eye and hair color, complexion, and residential history, as well as summer time outdoors.

UVR exposures derived from linking residential locations for up to five age groups (<13; 13–19; 20–39; 40–64; ⩾65 years) with the Total Ozone Mapping Spectrometer (TOMS) database (http://toms.gsfc.nasa.gov) maintained by the National Aeronautics and Space Administration (NASA). Residential locations (based on a 1.25° by 1° (longitude × latitude) grid) were linked to daily ambient UVR based on an estimated erythemal exposure level, which is an index of biological damage of Caucasian skin to sunburn (erythema). Values were averaged over the period collected by one satellite, Nimbus-7, (1978–1993), for June 1 through August 31 each summer, to provide stable estimates for each location ($n = 903$) and because satellite measurements were limited to some exposure periods. Temperatures were derived from meteorological data collected by U.S. weather stations and maintained by the National Climatic Data Center (NCDC) of the National Oceanic and Atmospheric Administration. Summer average daily mean temperatures (June 1–August 31) were averaged over 1971–2000 for each weather station, with a total of 7937 U.S. weather stations (NCDC Data set 9641C), again to provide stable estimates and because temperature data was limited to some exposure years. For each participant, average lifetime summer ambient temperatures and UVR levels were assigned based on combinations of residence and age at residence (over the five age groups set forth above), using data from the nearest weather station and TOMs grid cell, respectively, using ArcGIS 9.1 software (ESRI 2005).

2.3. Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed using Cox proportional hazards regression, with age as the time-scale, which adjusts for age in all models to permit a time-dependent analyses of covariates [14]. Subjects were followed from baseline until the earliest of the third questionnaire or the diagnosis of the first cancer. In our primary analysis, we used time-dependent average lifetime ambient summer temperature, average lifetime ambient summer UVR and average lifetime summer time outdoors, all with a 20-year lag period because studies suggest that the latency for BCC may be 20 or more years [15–20]. Thus, for example, if a subject entered the study at age 40, that person's average cumulative exposure at entry was calculated at age 20 and changed as they aged if they subsequently moved. HRs with unlagged exposures were also calculated. In all analyses, cut-points for time-dependent variables were based on quintile cut-points defined at the end of follow-up (or the end of follow-up lagged by 20 years, if a lagged analysis), so that cut-points were fixed over time, but individual exposures could move between time-dependent categories.

We examined characteristics presented in Table 1 as potential confounders. In the principal analysis, in addition to lagged average lifetime summer ambient temperature, all models *a priori* included age (as the time-scale), sex, average lifetime summer ambient UVR (continuous, similarly lagged), average lifetime summer time outdoors (quintiles, also lagged), with the baseline hazard stratified on birth cohort (5-year groups). BMI (<25, 25–<30, ⩾30; unknown, kg/m^2) at baseline was chosen *a priori* because BMI is strongly negatively related to BCC risk in this cohort [21]. The only additional factor to be included in the final model was eye color (blue; green/blue; grey/green; hazel; light brown; dark brown; other; unknown) because it changed the HRs by more than 10%. The other variables did not change the HRs by more than 10% and were not included (i.e., every smoker (yes; no; unknown); complexion (light; medium; dark; other; unknown); hair color (blonde; red; brown; black; other; unknown); education (grade school; high school; rad tech program; college; graduate school; other; unknown); occupational ionizing radiation dose (continuous). Tests for trend treated quintiles as a continuous ordinal variable. The same covariates above were included in all the analyses (i.e., age, sex, ambient UVR, ambient temperature, time outdoors, BMI, eye color, and birth cohort in the baseline hazard).

Missing values for variables were coded as a separate "missing" category except for average lifetime summer ambient temperature, average lifetime summer ambient UVR, and average lifetime time outdoors. For these, values were imputed based first on the values for the nearest subsequent age interval with available values and then, on the nearest earlier age interval, if subsequent data were unavailable. A separate missing category was created for time outdoors only when no values were available for any age interval (<5% of participants).

In addition, we assessed the HRs for average lifetime summer ambient temperature by quintile of average lifetime summer ambient UVR exposure to examine whether temperature was