Cancer Epidemiology 46 (2017) 66–72

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Body mass index, height and early-onset basal cell carcinoma in a case-control study

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ARTICLE INFO

Article history:
Received 28 July 2016
Received in revised form 30 November 2016
Accepted 14 December 2016
Available online 28 December 2016

Keywords:
Basal cell carcinoma
Non-melanoma skin cancer
Height
Body mass index
Epidemiology

ABSTRACT

Introduction: Basal cell carcinoma (BCC) is the most common malignancy in the US. Body mass index (BMI) and height have been associated with a variety of cancer types, yet the evidence regarding BCC is limited. Therefore, we evaluated BMI and height in relation to early-onset BCC (under age 40) and explored the potential role of ultraviolet (UV) radiation exposure and estrogen-related exposures in the BMI-BCC relationship.

Methods: BCC cases (n = 377) were identified through a central dermatopathology facility in Connecticut. Control subjects (n = 389) with benign skin conditions were randomly sampled from the same database and frequency matched to cases on age (median = 36, interquartile range 33–39), gender, and biopsy site. Participants reported weight (usual adult and at age 18), adult height, sociodemographic, phenotypic, and medical characteristics, and prior UV exposures. We calculated multivariate odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression models.

Results: Adult BMI was inversely associated with early-onset BCC (obese vs. normal OR = 0.43, 95% CI = 0.26–0.71). A similar inverse association was present for BMI at age 18 (OR = 0.54, 95% CI = 0.34–0.85). Excluding UV exposures from the BMI models and including estrogen-related exposures among women only did not alter the association between BMI and BCC, indicating limited mediation or confounding. We did not observe an association between adult height and BCC (OR per cm = 1.00, 95% CI = 0.98–1.02).

Conclusions: We found a significant inverse association between BMI and early-onset BCC, but no association between height and BCC. This association was not explained by UV exposures or estrogen-related exposures in women.

1. Introduction

Non-melanoma skin cancer (NMSC) is the most common form of cancer in the US, exceeding all other cancer types combined [1,2]. Basal cell carcinoma (BCC), the most common type of NMSC [3], has been rising in incidence in many countries during the past several decades [4–9], with notable increases among young people under age 40 [5,8–10]. Incidence data in the US for NMSC are limited as it is not reported to cancer registries. Recent analyses using the population-based National Ambulatory Medical Care Survey and the Centers for Medicare & Medicaid Services Physicians Claims databases estimated 5.4 million NMSCs in the US in 2012 [2].

Obesity has been positively associated with various types of cancers in humans. In the setting of skin cancer, obesity has been positively associated with melanoma in men, but not women [11,12]. Similarly, evidence from epidemiologic research regarding the association between body mass index (BMI) and NMSC combined or only BCC is mixed, with several studies finding an inverse relationship [13–18], and other studies being null [19–22]. Some studies of melanoma [12,21,23] and one of BCC [21] have also investigated body surface area (BSA) as an alternate

Abbreviations: BCC, basal cell carcinoma; BMI, body mass index; BSA, body surface area; UV, ultraviolet; OR, odds ratios; CI, confidence intervals; NMSC, non-melanoma skin cancer; IGF, insulin-like growth factors.

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http://dx.doi.org/10.1016/j.canep.2016.12.007
1877-7821/

anthropometric measure, with results generally mirroring the BMI findings in each population.

For skin cancer, an association with being overweight/obese could have both biological and behavioral underpinnings. Biologically, a higher BMI is associated with elevated circulating estrogen levels [24], which have been associated with lower risk of NMSC in mouse models [25]. From a behavioral standpoint, ultraviolet (UV) radiation exposure, the primary risk factor for skin cancer, may vary by BMI due to differing levels of physical activity [26]. Also, leaner individuals might be more likely to expose their skin to UV light in public settings, and are also more likely to tan indoors [27]. Although UV and/or estrogen-related exposures may act as mediators of the relationship between BMI and skin cancer, only a few of the existing studies on BMI and skin cancer have considered UV [13–15,20,21] and none considered markers of estrogen exposure.

Similar to BMI, adult height has been positively associated with several types of malignancies in epidemiologic studies, including melanoma [28–34]. Specific to NMSC, adult height was associated with an increased risk of NMSC in a pooled European study [34] and BCC in one US cohort [14], but no association with BCC was reported in another cohort study and two case-control studies [15,19,20]. Possible underlying mechanisms for an association between height and cancer risk involve high caloric intake, especially early in life, leading to alterations in hormones and growth factors, such as insulin-like growth factors (IGF) that increase both height and cancer cell proliferation [35]. Another potential mechanism is that height simply indicates a larger number of cells that could potentially undergo abnormal proliferation [36].

In contrast to many cancer sites, epidemiologic evidence on the relationship between anthropometric measures and BCC is limited and inconsistent. In the present study, we evaluated the relationship between BMI, BSA, and height and early-onset BCC. We also focused on evaluating potential confounding and mediation by UV exposure (indoor and outdoor) in the full sample, and estrogen-related exposures in women.

2. Methods

2.1. Yale Study of Skin Health in Young People

The Yale Study of Skin Health in Young People is a case-control study of early-onset BCC conducted in Connecticut. A detailed description of the study design is available elsewhere [37]. BCC cases and control subjects with benign skin conditions diagnosed between July 2006 and September 2010 under age 40 (age range 12–39 years) were identified through Yale University's Dermatopathology database. Control subjects were randomly selected from the database and frequency matched to BCC cases on gender, age at biopsy, and body site of biopsy. Control conditions were non-UV related minor benign skin conditions, of which the three most common diagnoses were cyst (16.4%), seborrheic keratosis (16.2%), and wart (11.4%); with all other conditions present in $<10\%$ of controls. A total of 389 cases (participation rate = 72.8%) and 458 controls (participation rate = 60.7%) enrolled in the study. Study participants completed an in-person interview using a structured questionnaire, several mailed questionnaires, and provided a saliva sample for buccal cell DNA (98.9% of participants). The study was approved by Yale University's Institutional Review Board and study participants (or guardians) provided written informed consent.

2.1.1. Inclusion and exclusion criteria

We restricted the analytic sample to non-Hispanic Whites: 380 (97.7%) cases and 390 (85.2%) controls. We further excluded three cases with Gorlin Syndrome, which predisposes individuals to multiple BCCs early in life [38]. One control subject was further excluded due to missing weight data. The final study population included 766 individuals (377 cases and 389 controls).

2.2. Data collection

Participants were asked to report their weight (usual weight and weight at age of 18) and adult height during the structured interview. Personal phenotype characteristics were also ascertained during the interview including: skin color (very fair, fair, light olive, dark olive, brown, very dark brown/black), hair color (black/dark brown, light brown, blonde/fair, red), and skin reaction with prolonged sun exposure (deeply tanned, moderately tanned, mildly tanned, freckled without tan). Participants also provided information about UV exposures, including frequency of outdoor sunbathing during three time periods (ages 8–15, 16–25, and 26 or older), frequency of indoor tanning during four time periods (ages 11–15, 16–20, 21–30, and 31 or older), as well as time spent outdoors during warm months (June through August). In addition to UV-related behaviors, we collected information on education level, smoking status, and family history of skin cancer. Female participants additionally reported age at first menstrual period, number of live births, and oral contraceptive use.

2.3. Statistical analysis

Descriptive statistics were performed to evaluate differences between BCC cases and controls. Odds ratios (ORs) and related confidence intervals (CIs) were computed to compare risk associated with BMI, BSA, and height, using unconditional multivariate logistic regression models. Adult BMI was classified into three categories (<25 – normal weight, 25–29.9 – overweight, and ≥ 30 – obese). BMI at age 18 was divided into two levels (<25 and ≥ 25) due to the small number of obese individuals at age 18 in our sample. We calculated BSA using a standard formula [39] and then created quartiles based on the distribution in the controls. Height was evaluated as a continuous variable (centimeters).

Covariates in the models consisted of the study matching variables (age, gender, biopsy site), as well as variables which altered risk estimates by at least 10% or risk factors for BCC in our population, including smoking, skin color, skin reaction to prolonged UV exposure, family history of skin cancer, time spent outdoors in warm months, indoor tanning sessions, and outdoor sunbathing sessions. Height and BMI were mutually adjusted in their respective models. We evaluated the multivariate models in the overall sample, and then in men and in women separately, based on sex-specific associations in other populations. Tests for trend were conducted for BMI by including ordinal variables in the models.

We also evaluated the potential mediating and/or confounding effect of UV exposure by removing those variables from the multivariate model. We also tested effect modification of the BMI and BCC relationship by body site, as this is likely indicative of UV exposure patterns. In addition, to explore the potential effect of estrogen-related exposure on the BMI-BCC association among women, we evaluated a model which additionally adjusted for age at first menstrual period, number of live births, and years of oral contraceptive use, each of which affects estrogen exposure. All analyses were conducted using SAS software (SAS, Version 9.3, SAS Institute Inc., Cary, NC) and reported p-values are two-sided.

3. Results

In our study sample of 766 participants, 69.2% were female, and the median age at skin biopsy was 36 years. Compared with