Distinct histologic subtypes and risk factors for early onset basal cell carcinoma: A population-based case control study from New Hampshire

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To the Editor

Basal cell carcinoma (BCC) is the most prevalent cancer diagnosed in the United States. A subset of BCC behave more aggressively and are associated with a higher risk of recurrence, local tissue destruction, deeper invasion, subclinical spread, morbidity and local and distant metastasis risk (Walling et al., 2004). An important indicator of potential for aggressive clinical behavior is the histologic subtype of BCC. Aggressive histologic subtypes include infiltrative, sclerosing, morpheaform, basosquamous and micronodular types, which often require more vigorous therapeutic regimens (Batra and Kelley, 2002; Blixt et al., 2013). The increase in incidence rates of BCC among younger individuals, particularly women, has spurred renewed interest in early onset BCC (Arits et al., 2011; Christenson et al., 2005; Karagas et al., 2014).

We examined tumor characteristics and risk factors in the New Hampshire Skin Cancer Study, a population-based case–control study of keratinocyte cancers. Cases were identified through comprehensive surveillance of dermatology and dermatopathology practices along with pathology laboratories in New Hampshire. Controls were randomly selected from lists of state residents provided by the New Hampshire Department of Transportation (individuals < 65 years old) and the Center for Medicaid and Medicare services (individuals ≥ 65 years old).
Early onset cases were diagnosed with BCC between 24 and 49 years of age, while late onset cases were diagnosed at ≥50 years of age. Of the 1,823 cases and 2,062 controls confirmed eligible, 1,578 (86.6%) cases and 1497 (72.6%) controls were interviewed. Odds ratios (OR) were calculated using unconditional logistic regression, controlling for potentially confounding effects of age, gender, and study phase. Modifying effects were calculated on subjects stratified by gender, study phase, anatomic site, sun exposure (sun sensitivity to first solar exposure, number of painful sunburns in childhood, recreational sun exposure) and subject characteristics including family history of melanoma, number of nevi, hair color, eye color, skin color, freckling and ethnicity. Subgroup analyses were used to evaluate associations of molecular or histologic subtypes and disease onset. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc, Cary, NC) (Karagas et al.; Torti et al., 2011); details are provided in Supplemental data). A board-certified dermatopathologist (A.E.P.) confirmed histologic subtype (including aggressive subtypes: infiltrative, sclerosing, morpheaform and micronodular) (Batra and Kelley, 2002; Sexton et al.; 1990, Walling et al., 2004), presence of actinic keratoses and severity of solar elastosis. Basosquamous and metatypical subtypes were excluded to avoid confounding with basaloid SCCs and inadvertently misclassified SCCs (Webb et al., 2015). Molecular analyses for \textit{PTCH} and \textit{TP53} were performed as described (Danaee et al.; 2006, Louhelainen et al.; 1998, Torti et al.; 2011); also see Supplemental data.

Of 1,578 newly-diagnosed cases of BCC, 674 were early onset (≤50 years) and 904 were later onset (> 50 years) at diagnosis. These were compared to 460 controls ≤50 years and 1,010 controls >50 years. Mean age at diagnosis was 43.3 ± 5.5 years and 64.0 ± 6.7 years for early versus late onset BCC, respectively. Demographics and tumor characteristics are compared in Table 1. Patients with early onset BCC were more likely to be women (61.6% versus 41.3%; OR 2.2, 95% CI 1.7–2.7) and exhibit an aggressive histological subtype (7.6% of early onset cases versus 2.1% of late onset cases (OR 3.9, 95% CI 1.9–8.0). Anatomical localization differed, with a higher percentage of early onset BCC tumors localized on the head or neck (93.3% vs 83.6%; OR 2.8 95% CI 1.9–4.2). The frequency of genetic alterations in \textit{PTCH} and \textit{TP53} were not different (Supplemental Table 1).

We also compared known BCC risk factors (Table 2). Risk factors linked to sun exposure including skin sensitivity to first solar exposure, number of painful sunburns in childhood, number of blistering sunburns in childhood and recreational sun exposure, were associated with both early and late onset BCC. However, the strength of associations for sun sensitivity to first solar exposure and number of blistering sunburns in childhood was approximately twice as strong in the early onset BCC cases. Other risk factors were similar (Supplemental Table 2).

Overall, early onset BCC was more frequently associated with aggressive histologic BCC subtypes (infiltrative, sclerosing, morpheaform and micronodular), occurred more commonly on the head and neck, and among women. In addition, risk factors such as sensitivity to first solar exposure and number of blistering sunburns in childhood, appeared to increase susceptibility to early onset BCC to a greater extent than late onset BCC, suggesting there may be an interplay between inherent susceptibility and environmental
exposure in early onset BCC. We did not find a corresponding increase in mutations or LOH affecting the tumor suppressors p53 or PTCH in early onset BCC, which have been reported in sporadic BCCs and in some small studies of early onset BCCs (Zhang et al., 2001). Additional data are needed to define the molecular landscape of this disease.

Our study has limitations. The average age of individuals who we defined as early onset BCC was approximately 43 years. Although this is approximately 20 years younger than our late onset cases, it is older than the average age of early onset BCC used in several previous studies (Christenson et al., 2005; Ferrucci et al., 2012). Nevertheless, our ability to identify meaningful differences between these two populations suggests that this is a reasonable cut point.

One hypothesis for the increasing incidence rates of early onset BCC has been increased awareness and skin surveillance. However, lesion size has not decreased over time, as might be anticipated if earlier detection were the underlying cause of increased incidence (Christenson et al., 2005). Our results likewise suggest that early onset BCC is associated with aggressive histologic characteristics, as opposed to a less aggressive phenotype that might be expected if surveillance bias were operating. Although additional studies are needed, these results suggest there may be underlying biological differences between early and late onset BCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

| Abbreviation | Description               |
|--------------|---------------------------|
| BCC          | Basal Cell Carcinoma      |
| SCC          | Squamous Cell Carcinoma   |
| NMSC         | Non-melanoma Skin Cancer  |

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Table 1

Case-case comparison of demographic and tumor characteristics of early onset basal cell carcinoma (BCC) compared to later onset BCC.

| Variable          | Early onset (≤50 years old) N (%) | Late onset (> 50 years old) N (%) | OR (95% CI)¹ |
|-------------------|-----------------------------------|-----------------------------------|--------------|
| Gender            |                                   |                                   |              |
| male              | 259 (38.4)                        | 540 (59.7)                        | 1.0 (ref)    |
| female            | 415 (61.6)                        | 364 (40.3)                        | 2.2 (1.7–2.7) |
| Histologic subtype² |                                   |                                   |              |
| nonaggressive BCC | 463 (92.4)                        | 467 (97.9)                        | 1.0 (ref)    |
| aggressive BCC    | 38 (7.6)                          | 10 (2.1)                          | 3.9 (1.9–8.0) |
| Solar elastosis   |                                   |                                   |              |
| low/moderate      | 42 (40.4)                         | 65 (25.0)                         | 1.0 (ref)    |
| severe            | 62 (59.6)                         | 195 (75.0)                        | 0.5 (0.3–0.8) |
| Anatomic Site     |                                   |                                   |              |
| trunk             | 33 (5.0)                          | 110 (12.5)                        | 1.0 (ref)    |
| lower limbs       | 5 (0.8)                           | 14 (1.6)                          | 1.1 (0.4–3.3) |
| upper limbs       | 6 (0.9)                           | 20 (2.3)                          | 1.2 (0.4–3.2) |
| head or neck      | 611 (93.3)                        | 734 (83.6)                        | 2.8 (1.9–4.2) |

¹ Odd ratios and 95% confidence intervals were estimated by logistic regression and adjusted by study phase and gender (male, female).
² Tumor morphology was reviewed by a single pathologist in phase 2 and phase 3 of the study on the 978 subjects whose tumor material was available. The aggressive histology types are 8092.1/3 8092.2/3 8092.3/3.
Table 2

Risk factors for early and late onset basal cell carcinoma (BCC) compared to controls.

| Variable | Early onset (≤50 years old) | Late Onset (>50 years old) |
|----------|-----------------------------|-----------------------------|
|          | Controls | Cases | OR (95% CI) | Controls | Cases | OR (95% CI) |
| Sun sensitivity to first solar exposure<sup>2</sup> |          |       |             |          |       |             |
| tan      | 59 (12.9) | 26 (3.9) | 1.0 (ref) | 196 (19.6) | 88 (9.8) | 1.0 (ref) |
| mild burn then tan | 218 (47.7) | 290 (43.5) | 3.0 (1.8–4.9) | 505 (50.6) | 437 (48.8) | 1.9 (1.4–2.6) |
| burn then peel | 154 (33.7) | 301 (45.2) | 4.4 (2.6–7.2) | 231 (23.1) | 306 (34.2) | 2.9 (2.1–3.9) |
| burn then blister | 26 (5.7) | 49 (7.4) | 4.2 (2.1–8.1) | 67 (6.7) | 64 (7.2) | 2.1 (1.4–3.2) |
| Number of painful sunburns in childhood<sup>3</sup> |          |       |             |          |       |             |
| None     | 203 (47.1) | 218 (36.0) | 1.0 (ref) | 507 (55.5) | 393 (45.7) | 1.0 (ref) |
| 1–3      | 79 (18.3) | 77 (12.7) | 0.9 (0.6–1.3) | 168 (1 8.4) | 139 (16.2) | 1.0 (0.8–1.3) |
| 4–9      | 74 (17.2) | 121 (20.0) | 1.5 (1.1–2.2) | 162 (17.7) | 183 (21.3) | 1.4 (1.1–1.8) |
| ≥10      | 75 (17.4) | 190 (31.4) | 2.5 (1.8–3.5) | 76 (8.3) | 145 (16.9) | 2.6 (1.9–3.5) |
| **p<sub>total</sub>** | **<0.0001** | | | | | **<0.0001** |
| Number of blistering sunburns in childhood<sup>4</sup> |          |       |             |          |       |             |
| None     | 345(79.9) | 407(66.9) | 1.0 (ref) | 722(78.8) | 593(69.0) | 1.0 (ref) |
| 1        | 49(11.3) | 74(12.2) | 1.3(0.9–1.9) | 84(9.2) | 102(11.9) | 1.4(1.1–2.0) |
| 2–6      | 14(3.2) | 35(5.8) | 2.1(1.1–4.0) | 39(4.3) | 68(7.9) | 2.0(1.4–3.1) |
| ≥7       | 24(5.6) | 92(15.1) | 3.3(2.0–5.2) | 71(7.8) | 96(11.2) | 1.7(1.2–2.3) |
| **p<sub>total</sub>** | **<0.0001** | | | | | **<0.013** |
| Recreational sun exposure – proportion of lifetime<sup>5</sup> |          |       |             |          |       |             |
| < 0.495   | 52(12.1) | 86(14.3) | 1.0 (ref) | 278(31.3) | 213(25.3) | 1.0 (ref) |
| 0.495 to < 0.673 | 99(23.0) | 115(19.1) | 0.7(0.5–1.1) | 228(25.7) | 197(23.4) | 1.1(0.8–1.4) |
| 0.673 to < 0.844 | 144(33.5) | 185(30.7) | 0.8(0.5–1.2) | 186(21.0) | 200(23.8) | 1.4(1.1–1.8) |
| ≥0.844   | 135 (31.4) | 217 (36.0) | 1.0 (0.6–1.5) | 195 (22.0) | 231 (27.5) | 1.6 (1.2–2.1) |
| **p<sub>total</sub>** | **<0.0164** | | | | | **<0.0011** |

<sup>1</sup> Odd ratios and 95% confidence intervals were estimated by logistic regression and adjusted by study phase, age at diagnosis and gender (male, female).
In sun sensitivity to first solar exposure, 11 controls and 9 cases are missing in late onset BCC; 3 controls and 8 cases missing from early onset BCC. These same subjects were missing in all other exposure variables.

The number of painful sunburns in childhood was missing in 126 controls and 112 cases.

The number of blistering sunburns in childhood was missing in 129 controls and 118 cases.

Recreational sun exposure was missing in 153 controls and 134 cases.