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

Dorothea T. Barton[1,2], **Michael S. Zens**[3], **Heather H. Nelson**[4], **Brock C. Christensen**[3,5], **Craig A. Storm**[2], **Ann E. Perry**[2], and **Margaret R. Karagas**[3]

[1]Section of Dermatology, Department of Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH

[2]Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, NH

[3]Department of Epidemiology, Geisel School of Medicine at Dartmouth, Hanover, NH

[4]Masonic Cancer Center, University of Minnesota, Minneapolis, MN

[5]Department of Pharmacology and Toxicology, Geisel School of Medicine at Dartmouth, Hanover, NH

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

Corresponding author: Dorothea Torti Barton, MD, Section of Dermatology, Department of Surgery and Department of Pathology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, Phone: (603) 650-3100, Fax: (603) 650-3174, ; Email: Dorothea.T.Barton@hitchcock.org

old) ([Karagas et al., 1999; Karagas et al., 2002; Karagas et al., 2010; Karagas et al., 2007]). 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., 2014; 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 *PTCH* and *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 *PTCH* and *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.

Acknowledgements

Abbreviations

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 subtype[2]	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 N (%)	Cases N (%)	OR (95% CI)[a]	Controls N (%)	Cases N (%)	OR (95% CI)[1]
Sun sensitivity to first solar exposure[2]						
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)
			$p_{trend} < 0.0001$			$p_{trend} < 0.0001$
Number of painful sunburns in childhood[3]						
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 (18.4)	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)
			$p_{trend} < 0.0001$			$p_{trend} < 0.0001$
Number of blistering sunburns in childhood[4]						
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)
			$p_{trend} < 0.0001$			$p_{trend} < 0.013$
Recreational sun exposure – proportion of lifetime[5]						
< 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)
			$p_{trend} < 0.0164$			$p_{trend} < 0.0011$

[1] Odd ratios and 95% confidence intervals were estimated by logistic regression and adjusted by study phase, age at diagnosis and gender (male, female).

[2] 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.

[3] The number of painful sunburns in child hood was missing in 126 controls and 112 cases.

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

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