Supplemental Data

Supplemental Table 1. Case-case comparison of molecular 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]
P53 IHC [2]	less intensity and/or ≤ 10% cover	26 (72.2)	96 (75.0)	1.0 (ref)
	3+ intensity >10% cover	10 (27.8)	32 (25.0)	1.3 (0.6-3.0)
P53 mutation [3]	negative	23 (59.0)	86 (63.2)	1.0 (ref)
	positive	16 (41.0)	50 (36.8)	1.2 (0.6-2.5)
PTCH / LOH [4]	negative	8 (25.8)	20 (21.3)	1.0 (ref)
	positive	23 (74.2)	74 (78.7)	0.7 (0.3-1.9)

1. Odd ratios and 95% confidence intervals were estimated by logistic regression and adjusted by study phase and gender (male, female).
2. Tumor P53 immunohistochemistry was performed on 120 early onset BCC (Diagnosis age ≤ 50 years old) and 329 late onset BCC (Diagnosis age > 50 years old) subjects.
3. P53 mutations in the tumors were assessed on 39 early onset BCC (Diagnosis age ≤ 50 years old) and 136 late onset BCC (Diagnosis age > 50 years old) subjects.
4. PTCH-LOH assays on BCC tumors were 31 on early onset and 94 late onset (Diagnosis age > 50 years old) subjects.

Supplemental Table 2. Family history and ethnic risk factors for early and late onset basal cell carcinoma (BCC) compared to controls.

	Early onset (≤ 50 years old)			Late Onset (> 50 years old)		
Variable	Controls N (%)	Cases N (%)	OR (95% CI)[a]	Controls N (%)	Cases N (%)	OR (95% CI)[1]
Number of 1st degree relatives with melanoma [2]						
0	416 (92.2)	573 (87.3)	1.0 (ref)	931 (97.5)	817 (93.1)	1.0 (ref)
≥ 1	35 (7.8)	83 (12.7)	1.7 (1.1-2.6)	24 (2.5)	61 (6.9)	3.1 (1.9-5.0)
Number of Nevi[3]						
None	217 (50.7)	246 (39.7)	1.0 (ref)	382 (40.5)	297 (33.8)	1.0 (ref)
1-2	108 (25.2)	160 (25.8)	1.3 (1.0-1.8)	215 (22.8)	214 (24.3)	1.3 (1.0-1.7)
≥ 3	103 (24.1)	214 (34.5)	1.9 (1.4-2.5)	347 (36.8)	368 (41.9)	1.4 (1.2-1.8)
			$p_{trend} < 0.0229$			$p_{trend} < 0.1453$
Ethnicity[4]						
United Kingdom - full ancestry	11(5.0)	29 (8.0)	1.0 (ref)	117 (23.1)	123 (22.7)	1.0 (ref)
Northern Europe	86 (88.7)	161 (84.7)	0.7 (0.3-1.6)	103 (46.8)	139 (53.1)	1.4 (1.0-2.1)
Ireland	72 (86.7)	147 (83.5)	0.7 (0.3-1.7)	82 (41.2)	123 (50.0)	1.6 (1.1-2.4)
Germany	36 (76.6)	61 (67.8)	0.6 (0.2-1.4)	42 (26.4)	66 (34.9)	1.7 (1.0-2.8)
Latvia, Lithuania, Estonia	6 (35.3)	7 (19.4)	1.0 (0.2-7.0)	13 (10.0)	4 (3.1)	0.2 (0.1-0.9)

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. Family history of melanoma was missing in 64 controls and 44 cases.
3. Number of nevi was missing in 98 controls and 79 cases.
4. Ethnicity of parents and grandparents was missing in 503 controls and 361 cases.

Detailed Methods

Statistical Analyses

We examined risk factors in 1578 individuals in the New Hampshire Skin Cancer Study, a population-based case–control study of keratinocyte cancers. Subjects were frequency-matched on age classes (25–35, 36–45, 46–50 51–59, 60–64, 65–69, and 70–74 years) and gender to represent the combined distribution of BCC and SCC diagnoses. Early onset cases were diagnosed with BCC between 24 and 49 years of age, while late onset cases were diagnosed 50 years of age or older. Of the 1,823 cases and 2,062 controls confirmed eligible, 1,578 (86.6%) cases and 1497 (72.6%) controls were interviewed. We computed the odds ratio (OR) and 95% confidence interval (CI) of early onset BCC compared to later onset BCC associated with characteristics of tumors using unconditional logistic regression. We controlled for the potentially confounding effects by adjusting for reference age, gender and study phase (1993–1997, 1998–2000, and 2001–2002). To assess possible modifying effects, we 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. We used subgroup analyses by tumor characteristics to evaluate associations of molecular or histologic types of tumors and early disease onset. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Pathological Evaluation and Molecular Analysis

For diagnoses beginning in July 1998, diagnostic slides of the original paraffin embedded tumor were re-reviewed by a board-certified dermatopathologist (A.E.P.), who determined histologic subtype (including aggressive subtypes: infiltrative, sclerosing, morpheaform and micronodular) (Walling *et al*, 2004, Batra *et al*, 2002 and Sexton *et al 1986*), the presence of actinic keratoses and the severity of solar elastosis in the skin adjacent to each tumor. Basosquamous and metatypical subtypes were excluded to avoid confounding with basaloid SCCs and inadvertently misclassified SCCs (Webb *et al*. 2015). Solar elastosis in the papillary dermis was mild if present as single, scattered, blue-gray elastotic fibers; moderate if in isolated clumps of elastotic fibers; and severe if the dermis was replaced by clumped fibers or amorphous masses of elastotic material. Actinic keratosis was characterized by atypical epithelial cells present only in the epidermis of tissue adjacent to the tumor.

In a subset of tumors, immunohistochemical analysis of P53 was performed. P53 was coded positive when scored with 3+ intensity in >10% of the tumorous cells. From tumor DNA extracted using a standard protocol, we detected the presence of *TP53* mutations and *PTCH* LOH. In exons 5-9 of *TP53,* we used fluorescently labeled primers to conduct single strand conformation polymorphism (SSCP) analysis (Danaee *et al.*, 2006; Toguchida *et al.*, 1992; Torti *et al.*, 2011). For LOH analysis, five microsatellite loci, D9S15, D9S53, D9S196, D9S176, including an intragenic microsatellite in PTCH (exon 1a, 1AJL) were isolated from peripheral blood (Qiagen) (Danaee *et al.*, 2006; Louhelainen *et al.*, 1998).