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## Practice of Epidemiology

# Indoor Tanning and the *MC1R* Genotype: Risk Prediction for Basal Cell Carcinoma Risk in Young People

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Basal cell carcinoma (BCC) incidence is increasing, particularly in young people, and can be associated with significant morbidity and treatment costs. To identify young individuals at risk of BCC, we assessed existing melanoma or overall skin cancer risk prediction models and built a novel risk prediction model, with a focus on indoor tanning and the melanocortin 1 receptor gene, *MC1R*. We evaluated logistic regression models among 759 non-Hispanic whites from a case-control study of patients seen between 2006 and 2010 in New Haven, Connecticut. In our data, the adjusted area under the receiver operating characteristic curve (AUC) for a model by Han et al. (*Int J Cancer.* 2006;119(8):1976–1984) with 7 *MC1R* variants was 0.72 (95% confidence interval (CI): 0.66, 0.78), while that by Smith et al. (*J Clin Oncol.* 2012;30(15 suppl):8574) with *MC1R* and indoor tanning had an AUC of 0.69 (95% CI: 0.63, 0.75). Our base model had greater predictive ability than existing models and was significantly improved when we added ever–indoor tanning, burns from indoor tanning, and *MC1R* (AUC = 0.77, 95% CI: 0.74, 0.81). Our early-onset BCC risk prediction model incorporating *MC1R* and indoor tanning extends the work of other skin cancer risk prediction models, emphasizes the value of both genotype and indoor tanning in skin cancer risk prediction in young people, and should be validated with an independent cohort.

basal cell carcinoma; indoor tanning; *MC1R*; melanocortin 1 receptor; nonmelanoma skin cancer; risk prediction model; young adults

Abbreviations: AUC, area under the receiver operating characteristic curve; BCC, basal cell carcinoma; CI, confidence interval; *MC1R*, melanocortin 1 receptor gene; NMSC, nonmelanoma skin cancer.

Nonmelanoma skin cancers (NMSCs) are the most common cancers in white populations in the world (1). Basal cell carcinoma (BCC), which accounts for 70%–80% of NMSCs (2, 3), has increased dramatically in recent decades, notably among young women (1, 4–6). BCC is treatable and unlikely to result in death; however, it can be associated with both significant morbidity and health-care costs (2, 7). The ability to identify those at highest risk of early-onset BCC could focus public health efforts and mitigate the imminent epidemic.

There are few BCC risk prediction models (8, 9), yet several exist for melanoma (8–16) that typically evaluate demographic, phenotypic, and clinical factors. The melanocortin 1 receptor gene, *MC1R*, has been consistently associated with high-risk skin cancer phenotypes, including red hair and fair skin; however, common variants of *MC1R* are also now recognized as contributing to the risk of melanoma (9, 11, 17, 18) and NMSC (9, 19, 20) independent of phenotype. Consequently, the *MC1R* genotype has improved prediction in several melanoma (8, 9, 11, 12) and NMSC (8, 9) models.

Indoor tanning has recently emerged as an important risk factor for both melanoma (21, 22) and NMSC (23) and seems particularly relevant for skin cancer in younger populations (24–26). Of the 3 published prediction models that evaluated the additive prediction of indoor tanning (8, 11, 12), only 1 model, for melanoma, observed increased predictive ability (12).

Given the increase in indoor tanning in young populations and the high incidence of BCC, we were interested in evaluating whether *MC1R* and indoor tanning added to the predictive ability of BCC risk models, as seen in some melanoma risk models. Thus, we examined the utility of 2 existing skin cancer

risk prediction models that included *MC1R* and indoor tanning in the setting of early-onset BCC. We then built a novel risk prediction model in the same early-onset BCC case-control population, with careful consideration of the additive prediction of indoor tanning and the *MC1R* genotype.

## METHODS

### Study population

The Yale Study of Skin Health is a case-control study of early-onset BCC conducted in Connecticut (27). Briefly, BCC cases and controls with minor benign skin conditions diagnosed between July 2006 and September 2010 were identified through Yale University's Dermatopathology database. Eligible participants had to be under the age of 40 years at skin biopsy, reside in Connecticut, speak English, and be (themselves or appropriate guardian) mentally and physically capable of completing study components. Participants completed a structured in-person interview and self-administered questionnaires, and they provided a saliva sample with ORAgene•DNA 2-mL saliva collection kits (DNA Genotek, Inc., Kanata, Ontario, Canada) (http://www.dnagenotek.com/index.html). Yale University's Institutional Review Board approved the study, and study participants (or guardians) provided written informed consent. The study enrolled 389 BCC cases (participation rate = 72.8%) and 458 (participation rate = 60.7%) randomly sampled controls who were frequency matched to BCC cases on age at biopsy, sex, and biopsy site.

We assessed self-reported eye color, skin color (inner upper arm), hair color (natural color), freckling on the arms (based on images), number of moles ≥5 mm in diameter on the back (clear acetate size template), mole removal, skin reaction to sunlight for the first time in the summer for 1 hour without sunscreen, skin reaction after repeated and prolonged exposure to sunlight, family history of melanoma and NMSC, and detailed data on indoor and outdoor ultraviolet exposure (24, 27).

### *MC1R* sequencing and variant classification

DNA was isolated from the saliva samples, and *MC1R* variants were obtained via sequencing, as described previously (27). Sequencing was conducted at the W. M. Keck Facility at Yale University by using Applied Biosystems 3730 capillary sequencing instruments (Life Technologies, Grand Island, New York). We classified *MC1R* in 5 ways: a 3-level variable for the total number of nonsynonymous variants from sequencing (0, 1, ≥2); a dichotomous variable for R151C variant status (≥1 vs. 0); separate ordinal variables for the status of the variants R151C, V60L, V92M, I155T, R160W, R163Q, and D294H; a combination of R160W, R151C, and D294H to define carriage of a red hair color variant; and all 7 variants evaluated in 1 model together with 1 variable for each allele, similar to the method of Han et al. (8).

### Statistical analysis

We restricted our sample to non-Hispanic whites (380 cases, 390 controls). Three BCC cases with Gorlin syndrome, which predisposes individuals to multiple BCCs early in life (28), and 8 individuals without genotype data were further excluded, leaving 759 individuals (376 cases, 383 controls).

*Early-onset BCC model.* Multivariate logistic regression with the factors in Table 1, excluding *MC1R* and indoor tanning variables, was performed with the likelihood ratio test at a significance level of 0.05 using forward selection and backward elimination to obtain a base model (combinations of levels of categorical variables were also explored). All models were adjusted for the study design matching variables: sex, age at diagnosis, and body site (Table 2).

The base model's predictive performance was assessed via summary measures of calibration, misclassification, and discrimination. Calibration measures the association between the model's predicted probability of disease and the true observed frequency of disease. This was assessed via the Hosmer-Lemeshow test, which indicates whether the model is better than a model with no predictors ($P \geq 0.05$ indicates a good fit). Misclassification is a measure of prediction error and ranges from 0 to 1, with lower scores indicating less error in prediction; here, it is based on a 10-fold cross-validation estimate.

Discrimination, assessed via the *C* statistic or area under the receiver operating characteristic curve (AUC), measures the model's ability to distinguish between diseased and nondiseased patients. The AUC ranges from 0.5 to 1.0, with higher scores indicating better prediction. Because prediction models perform best when built and assessed on the same data, we used bootstrapping to better reflect the AUC expected when the model is tested on an independent but similar set of patients. Bootstrapping entails sampling the observations with replacement (here stratified by case-control status), such that all resulting bootstrapped samples have the same number of observations, although many observations across samples are repeated. The entire model-building procedure is performed for each bootstrap sample, and the AUC calculated on the basis of those observations is excluded from the bootstrap sample. This estimate is referred to as the "out of bag" AUC.

To investigate whether indoor tanning and *MC1R* improved prediction performance over the base model, we followed recently published recommendations for evaluating improved prediction performance in biomarker evaluation studies (29). As such, we report the regression coefficients for the markers in the expanded risk model and the corresponding likelihood ratio test statistic (Table 2). Pepe et al. (29) show that, if the markers (here indoor tanning and *MC1R*) contribute to risk while controlling for the other variables as assessed via the likelihood ratio test statistic, the corresponding population value for the change in AUC cannot be zero. Given the concerns with valid tests for the difference in nested AUCs reported in the literature (29–31), we report *P* values for the likelihood ratio test and change in AUC but focus only on the former. All statistical tests were 2-sided, and analyses were performed in the statistical software R (version 3.0.2) (R Foundation for Statistical Computing, Vienna, Austria).

*Evaluation of existing models including genetic and indoor tanning data.* Han et al. (8) examined the odds ratio for the risk of skin cancer (melanoma, BCC, and squamous cell carcinoma, each separately) for having 1 additional variant in each of 7 *MC1R* polymorphisms controlling for 3 different sets of variables that are shown in models 1, 2, and 3 in Table 3. They then examined the predictive ability of all 7 *MC1R*

**Table 1.** Characteristics of Early-Onset BCC Cases and Controls, Yale Study of Skin Health, 2006–2010

| Characteristic | Cases ($n = 376$) | | | Controls ($n = 383$) | | |
|---|---|---|---|---|---|---|
| | No.[a] | % | Median (IQR) | No.[a] | % | Median (IQR) |
| Age at diagnosis, years | | | 36.3 (33.2–38.5) | | | 36.6 (32.6–38.5) |
| Female | 256 | 68.1 | | 270 | 70.5 | |
| Body site of skin biopsy | | | | | | |
| Head | 204 | 54.3 | | 161 | 42 | |
| Extremity | 72 | 19.2 | | 125 | 32.6 | |
| Trunk | 100 | 26.6 | | 97 | 25.3 | |
| Education | | | | | | |
| ≤ Some college | 105 | 28.2 | | 143 | 37.5 | |
| College graduate | 112 | 29.7 | | 111 | 29.1 | |
| ≥ Some graduate school | 158 | 42.1 | | 127 | 33.3 | |
| Eye color | | | | | | |
| Brown | 86 | 22.9 | | 150 | 39.2 | |
| Hazel | 64 | 17 | | 71 | 18.5 | |
| Green | 47 | 12.5 | | 37 | 9.7 | |
| Blue/gray | 179 | 47.5 | | 125 | 32.5 | |
| Hair color | | | | | | |
| Black/dark brown | 100 | 26.6 | | 157 | 41.9 | |
| Light brown | 136 | 36.2 | | 152 | 39.7 | |
| Blonde/fair | 100 | 26.7 | | 63 | 16.4 | |
| Red | 39 | 10.4 | | 11 | 2.9 | |
| Skin color (inner upper arm) | | | | | | |
| Olive | 15 | 4 | | 76 | 19.8 | |
| Fair | 212 | 56.4 | | 233 | 60.8 | |
| Very fair | 149 | 39.6 | | 74 | 19.2 | |
| Skin reaction with first summer sun exposure | | | | | | |
| Turn brown, no sunburn | 6 | 1.6 | | 31 | 8.1 | |
| Mild sunburn followed by tan | 142 | 37.8 | | 196 | 51.3 | |
| Painful sunburn peeling | 198 | 52.7 | | 142 | 37.1 | |
| Severe sunburn blistering | 30 | 8 | | 13 | 3.4 | |
| Skin reaction with prolonged sun exposure | | | | | | |
| Very brown, deeply tanned | 39 | 10.4 | | 69 | 18 | |
| Moderately tanned | 168 | 44.7 | | 220 | 57.4 | |
| Mildly tanned, peeling tendency | 123 | 32.7 | | 76 | 19.8 | |
| Freckled, no suntan | 46 | 12.2 | | 18 | 4.7 | |

**Table continues**

variants (represented by 1 variable for each allele and an interaction term for the R151C variant and hair color) with the covariates in model 3. This new model is described as model 4 (Table 3) (8). To compare, we fitted these 4 models (Table 3) in our population with adjustments based on the variables we had collected.

Smith et al. (12) examined the predictive ability of adding indoor/outdoor ultraviolet exposure and *MC1R* (labeled as model 6) (Table 3) to a conventional risk factor model (labeled as model 5) (Table 3) for melanoma (8, 12). To compare, we fitted 2 similar models (Table 3) for BCC. To adjust for the optimism reflected by estimating the coefficients and assessing a model on the same data, we used bootstrapping as described above.

## RESULTS

### Base model for BCC

The best base model included hair color, skin color, skin reaction with prolonged sun exposure, education, freckles on arm, family history of NMSC, and outdoor sun exposure in warm months. A goodness-of-fit test, the $\chi^2$ test with 8 df,

**Table 1.** Continued

| Characteristic | Cases ($n = 376$) | | | Controls ($n = 383$) | | |
|---|---|---|---|---|---|---|
| | No.[a] | % | Median (IQR) | No.[a] | % | Median (IQR) |
| No. of moles ≥5 mm in diameter on back | | | 1 (0–3) | | | 0 (0–2) |
| Moles removed | 166 | 44.5 | | 161 | 42.2 | |
| Freckles on arm | | | | | | |
| None | 81 | 21.5 | | 140 | 36.6 | |
| Very few | 115 | 30.1 | | 143 | 37.7 | |
| Few | 83 | 22.1 | | 53 | 13.8 | |
| Some | 42 | 11.2 | | 30 | 7.8 | |
| Many | 55 | 14.6 | | 17 | 4.4 | |
| *MC1R* nonsynonymous variants[b] | | | | | | |
| 0 variants | 65 | 17.3 | | 131 | 34.2 | |
| 1 variant | 173 | 46.1 | | 175 | 45.7 | |
| ≥2 variants | 138 | 36.7 | | 77 | 20.1 | |
| R151C nonsynonymous variants | | | | | | |
| 0 variants | 291 | 77.3 | | 346 | 90.3 | |
| 1 variant | 82 | 21.5 | | 35 | 9.1 | |
| 2 variants | 4 | 1.1 | | 2 | 0 | |
| Family history of NMSC | 234 | 62.2 | | 129 | 33.7 | |
| Family history of melanoma | 46 | 12.2 | | 34 | 8.9 | |
| Outdoor sun exposure in warm months, hours | | | 8,945 (3,426)[c] | | | 8,286 (3,231)[c] |
| Sunburns, no. | | | 6 (1–16) | | | 3 (1–9) |
| Sunbathing sessions, no. | | | 326 (58–719) | | | 280 (83–697) |
| Blisters, no. | | | 1 (0–3) | | | 0 (0–1) |
| Indoor tan, ever | 246 | 65.6 | | 245 | 64 | |
| Age at first indoor tan, years | | | 17 (16–21) | | | 17 (16–21) |
| Any painful burn from indoor tanning | 104 | 27.7 | | 89 | 23.3 | |
| Painful burns from indoor tanning, no. | | | 0 (0–1) | | | 0 (0–0) |
| Indoor tanning total sessions, no. | | | 9.5 (0–90) | | | 8 (0–103) |

Abbreviations: BCC, basal cell carcinoma; IQR, interquartile range; NMSC, nonmelanoma skin cancer; SD, standard deviation.

[a] May not sum to total because of missing values.

[b] *MC1R*, melanocortin 1 receptor gene.

[c] Mean (SD).

was 2.76 ($P = 0.95$), indicating adequate fit (Table 2). The "out of bag" AUC was 0.75 (95% confidence interval (CI): 0.72, 0.79), and the misclassification estimate was 0.31.

### Contribution of indoor tanning and *MC1R*

Next, via a combination of forward selection and backward elimination, we identified 2 out of 6 indoor tanning variables (Table 1) that significantly added to the base model: ever–indoor tanning and painful burns from indoor tanning, as well as R151C status (≥1 vs. 0). With the addition of these 3 variables to the base model, freckles on arm became insignificant ($P = 0.09$) and was dropped (Table 2). The likelihood ratio test assessing the addition of the 3 variables was highly significant ($P < 0.005$), indicating that indoor tanning and the *MC1R* R151C variant contribute to risk while controlling for the other variables. The "out of bag" AUC for the base plus tanning and genetics model was 0.77 (95% CI: 0.74, 0.81). The $\chi^2$ goodness-of-fit test with 8 df was 6.07 ($P = 0.64$), indicating adequate fit, and misclassification was estimated to be 0.298. In the 373 cases, the extended model (compared with the base model without freckles on arm) appropriately reclassified 106 cases upward to a higher risk decile, but it incorrectly reclassified 102 cases downward to a lesser risk decile. In the 380 controls, the extended model inappropriately reclassified 48 controls upward but 113 cases correctly downward.

We conducted the same procedures with a variable for all *MC1R* nonsynonymous variants detected via sequencing, as well as a variable indicating carriage of a red head color variant; however, these variables did not improve prediction

**Table 2.** Risk Estimates for Early-Onset BCC, Yale Study of Skin Health, 2006–2010

| Characteristic | Base Model[a,b,c] | | Base Model Plus Indoor Tanning and Genetics Model[a,c,d,e] | |
|---|---|---|---|---|
| | Odds Ratio | 95% CI | Odds Ratio | 95% CI |
| Hair color | | | | |
| Light/dark brown and black | 1 | Referent | 1 | Referent |
| Red and blonde or fair | 1.85 | 1.27, 2.68 | 1.76 | 1.21, 2.59 |
| Skin color | | | | |
| Olive | 1 | Referent | 1 | Referent |
| Fair or very fair | 3.02 | 1.65, 5.83 | 3.15 | 1.72, 4.13 |
| Skin reaction with prolonged sun exposure | | | | |
| Very brown, deeply tanned, or moderately tanned | 1 | Referent | 1 | Referent |
| Mildly tanned, peeling tendency | 1.85 | 1.26, 2.73 | 2.05 | 1.40, 3.04 |
| Freckled, no suntan | 2.40 | 1.27, 4.72 | 3.43 | 1.80, 6.78 |
| Education | | | | |
| College graduate or less | 1 | Referent | 1 | Referent |
| Master's or doctoral degree | 1.50 | 1.04, 2.16 | 1.73 | 1.19, 2.50 |
| Family history of NMSC | | | | |
| No | 1 | Referent | 1 | Referent |
| Yes | 2.80 | 2.03, 3.89 | 2.95 | 2.12, 4.13 |
| Outdoor sun exposure in warm months, per 200-hour increment | 1.02 | 1.00, 1.03 | 1.02 | 1.01, 1.03 |
| Freckles on arm | | | | |
| None/very few | 1 | Referent | | |
| Few/some/many | 1.54 | 1.08, 2.2 | | |
| Painful burns from indoor tanning, per 1-burn increase | | | 1.06 | 1.02, 1.11 |
| Indoor tan | | | | |
| Never | | | 1 | Referent |
| Ever | | | 1.52 | 1.03, 2.26 |
| R151C nonsynonymous variants | | | | |
| 0 variants | | | 1 | Referent |
| 1 or 2 variants | | | 2.09 | 1.31, 3.39 |

Abbreviations: AUC, area under the receiver operating characteristic curve; BCC, basal cell carcinoma; CI, confidence interval; NMSC, nonmelanoma skin cancer.

[a] Adjusted for study design matching variables: age at diagnosis, body site, and sex.

[b] AUC (via 1,000 bootstrap samples) = 0.75 (95% CI: 0.72, 0.79).

[c] Difference in AUC (via 1,000 bootstrap samples) = 0.01 (95% CI: 0.002, 0.030).

[d] Likelihood ratio test: $\chi^2$ (3 df) = 26.7 ($P < 0.005$).

[e] AUC (via 1,000 bootstrap samples) = 0.77 (95% CI: 0.74, 0.81).

more than what was observed for R151C alone (data not shown). Interactions between genotype and phenotype were explored, but none was significant.

### Comparison with existing risk prediction models

Han et al. (8) reported an association between BCC and V60L variant alleles in model 1 and an association with R151C and R163Q variants in models 1–3 (Table 3). In our early-onset BCC population, we found an association between BCC and R151C variants for model 1 (odds ratio = 2.58, 95% CI: 1.73, 3.92), model 2 (odds ratio =1.74, 95% CI: 1.13, 2.72), and model 3 (odds ratio = 1.75, 95% CI: 1.10, 2.82). In addition, including 7 nonsynonymous variants in *MC1R* and an interaction of the R151C variant with hair color (model 4) (Table 3), the Han et al. (8) AUC increased to 0.69 ($\Delta = 0.01$; $P = 0.05$). In our population, the "out of bag" AUC decreased from 0.73 (95% CI: 0.67, 0.79) to 0.72 (95% CI: 0.66, 0.78); this was expected as the $P$ values for the added coefficients were greater than 0.05.

Smith et al. (12) reported that indoor and outdoor ultraviolet exposure and *MC1R* improved the predictive ability of their melanoma risk model (model 6) over a model that included only conventional risk factors (model 5) by 3%

**Table 3.** Existing Skin Cancer Risk Prediction Models and Comparable Variables in an Early-Onset BCC Population, Yale Study of Skin Health, 2006–2010

| Model for Melanoma and BCC[a] | | | | Model for Melanoma[b] | | | |
|---|---|---|---|---|---|---|---|
| Original Model | | BCC Population[c] | | Original Model | | BCC Population[c] | |
| Variable | Models in Which Variable Is Included | Variable | Models in Which Variable Is Included | Variable | Models in Which Variable Is Included | Variable | Models in Which Variable Is Included |
| | | *Sociodemographic Factors* | | | | | |
| Age | 1, 2, 3, 4 | Age | 1, 2, 3, 4 | Age | 5, 6 | Age | 5, 6 |
| Race | 1, 2, 3 | Race[d] | | | | | |
| | | Sex | 1, 2, 3, 4 | Sex | 5, 6 | Sex | 5, 6 |
| | | *Phenotype* | | | | | |
| Skin color | 2, 3, 4 | Skin color | 2, 3, 4 | Skin color | 5, 6 | Skin color | 5, 6 |
| Hair color | 2, 3, 4 | Hair color | 2, 3, 4 | Hair color | 5, 6 | Hair color | 5, 6 |
| Childhood tendency to burn | 3, 4 | Skin reaction with first exposure to summer sun for 1 hour | 3, 4 | | | | |
| Palpable moles on arms | 3, 4 | Mole count (0, ≥1) | 3, 4 | Mole density (none, few, some, many) | 5, 6 | Mole count | 5, 6 |
| | | | | Freckling | 5, 6 | Freckling density | 5, 6 |
| | | | | Eye color | 5, 6 | Eye color | 5, 6 |
| | | *Family History* | | | | | |
| Family history of skin cancer (yes, no) | 3, 4 | Family history of NMSC (yes, no) | 3, 4 | Family history of melanoma | 5, 6 | Family history of melanoma (yes, no) | 5, 6 |
| | | *Ultraviolet Exposure* | | | | | |
| No. of blistering sunburns (0, 1–5, 6–11, >11) | 3, 4 | No. of blistering sunburns (0, 1–5, 6–11, >11) | 3, 4 | | | | |
| Sunlamp use or tanning salon attendance (yes, no) | 3 | Ever–indoor tanning (yes, no) | 3 | Indoor tanning (<10 hours, ≥10 hours) | 6 | Indoor tanning (<10 hours, ≥10 hours) | 6 |
| Cumulative sun exposure when wearing bathing suit (tertiles) | 3 | No. of sunbathing sessions | 3 | Outdoor ultraviolet exposure | 6 | Lifetime hours of ultraviolet exposure during warm months | 6 |
| Geographical region | 3 | Geographical region[d] | | | | | |
| | | *Genetic Factors* | | | | | |
| Each of 7 *MC1R*[e] variants evaluated individually (R151C, V60L, V92M, I155T, R160W, R163Q, and D294H) | 1, 2, 3 | Each of 7 *MC1R* variants evaluated individually (R151C, V60L, V92M, I155T, R160W, R163Q, and D294H) | 1, 2, 3 | | | | |
| 7 *MC1R* nonsynonymous variants together; each represented by 1 variable (R151C, V60L, V92M, I155T, R160W, R163Q, and D294H) | 4 | 7 MC1R nonsynonymous variants together; each represented by one variable (R151C, V60L, V92M, I155T, R160W, R163Q, and aD294H) | 4 | *MC1R* | 6 | All *MC1R* nonsynonymous variants detected via sequencing (0, 1, 2 or more) | 6 |
| Interaction of R151C and hair color | 4 | Interaction of R151C and hair color | 4 | | | | |
| Risk prediction statistics | | | | | | | |
| AUC for BCC = 0.69 | 4 | $AUC_{adj}$ = 0.72 (95% CI: 0.66, 0.78) | 4 | AUC = 0.75 (95% CI: 0.72, 0.84) | 6 | $AUC_{adj}$ = 0.69 (95% CI: 0.63, 0.75) | 6 |
| AUC for melanoma = 0.73 | 4 | | | | | | |

Abbreviations: AUC, area under the receiver operating characteristic curve; $AUC_{adj}$, adjusted AUC; BCC, basal cell carcinoma; CI, confidence interval; NMSC, nonmelanoma skin cancer.

[a] Model for melanoma and BCC by Han et al. (8).

[b] Model for melanoma by Smith et al. (12).

[c] All BCC models include study design matching variables: sex, age at diagnosis, and body site of skin biopsy.

[d] Race and geographic region were not included as all BCC participants were Caucasian and from Connecticut.

[e] *MC1R,* melanocortin 1 receptor gene.

(AUC = 0.75, 95% CI: 0.72, 0.84; $P = 0.001$). In our data, the "out of bag" AUC for model 6 was 0.69 (95% CI: 0.63, 0.75), with only a 0.2% increase over the AUC for model 5.

## DISCUSSION

We constructed novel, well-performing risk prediction models for early-onset BCC. We assessed the importance of adding indoor tanning and *MC1R* on risk prediction compared with a simpler base model and found that both indoor tanning and *MC1R* (R151C variant status) independently improved our ability to predict risk of early-onset BCC.

Despite the good discrimination of our base model including phenotype and outdoor ultraviolet exposure, one of our primary goals was to evaluate a risk prediction model that considered additional important modifiable risk factors, in particular, indoor tanning. Although there is a strong genetic component for early-onset BCC (demonstrated by the predictive performance of *MC1R*, family history of NMSC, and phenotypic characteristics in our model), both indoor tanning and outdoor ultraviolet exposure also increased the predictive value of the model. Therefore, clinicians should assess and counsel young people on behaviors that increase ultraviolet exposure in addition to the typical skin cancer characteristics. Similarly, the melanoma model of Smith et al. (12) performed particularly well in their younger individuals, with a 5% increase in the AUC, when outdoor ultraviolet exposure, *MC1R*, and indoor tanning were added.

Several other studies have also evaluated *MC1R* and/or indoor tanning in risk prediction models for melanoma and BCC. In an Australian population-based case-control study, *MC1R* (in addition to age and sex) improved prediction for melanoma, squamous cell carcinoma, and BCC by 0.1% (AUC = 0.56; $P = 0.69$), 2.7% (AUC = 0.73; $P < 0.01$) and 6.7% (AUC = 0.61; $P < 0.01$), respectively; however, indoor tanning was not evaluated (9). Han et al. (8) also observed modest improvement of 2.0% in risk prediction for melanoma (AUC = 0.73; $P = 0.004$), but not squamous cell carcinoma, when *MC1R* was included in a model that included indoor tanning. Although indoor tanning was associated with early-onset melanoma risk in another Australian study (26), indoor tanning did not improve prediction in this same population, but *MC1R* did (11).

It is not clear for most of the existing studies, except that by Cust et al. (11), whether reported AUCs were adjusted for the optimism of building and assessing on the same data or whether they were validated in an independent test; thus, they may be overestimated. Nonetheless, our final early-onset BCC risk prediction model with an "out of bag" bootstrapped AUC of 0.77 (95% CI: 0.74, 0.81) has the highest AUC of the published (and possibly overestimated) BCC risk models (8, 9) and higher than the model of Smith et al. (12) for melanoma that included both indoor tanning and *MC1R*. This modest improvement in AUC and final achieved AUC is typical of cancer risk models, the majority of which reach a final AUC of less than 0.75. Given the lack of a true independent data set, it is important that in the future our model be independently replicated.

When we assessed how well the existing skin cancer risk models that incorporated genetic and ultraviolet exposure data (8, 12) performed in our early-onset BCC study, we found an adjusted AUC of 0.72 and 0.69 for the models of Han et al. and Smith et al., respectively. These were lower than the bootstrapped AUC for our best model derived from our data. Our findings may signify that the BCC AUC ascertained by Han et al. (8) is accurate and now validated, despite the model's having been built for melanoma and NMSC. In contrast, the reported melanoma AUC estimate for the model by Smith et al. was either overestimated or simply indicates that this model built solely for melanoma does not generalize as well to early-onset BCC, despite having performed well for younger individuals in their study population. As mentioned above, future research should entail testing our reported model with an independent test set, similar to how we assessed the model by Han et al. This type of replication work will be fostered by consortia efforts recently supported by the National Cancer Institute to bring together NMSC researchers (32).

Our study had several strengths, including a wide range of genetic and nongenetic data on almost all participants. This is also the first risk prediction model for early-onset BCC, which is becoming an increasingly important skin cancer outcome (33). Despite the lack of independent data sets for testing our model, through bootstrapping we were able to calculate more accurate and generalizable AUCs. Other strengths can be attributed to the study design: Interviewer blinding limited bias by case-control status in assessing risk factors; young participants were likely better able to recall lifestyle factors (e.g., indoor tanning) than older populations; and identifying subjects from a centralized dermatopathology facility captured control subjects representative of our source population (i.e., young people who see a dermatologist for a skin condition) who were very likely to be skin cancer free.

The limitations of our study include the following: the inability to assess the effects of our study matching variables (age, sex, body site) on risk; a sample size that precluded us from creating test and validation samples; and self-reported phenotype and lifestyle factors. Also, although we had many of the same variables that the published models included, as noted in the Methods section, we had to substitute a few closely related variables. Finally, our study was restricted to young people in Connecticut who represent a well-educated population, with unknown generalizability to a broader population.

In conclusion, we found that incorporation of the *MC1R* variant R151C and indoor tanning history, particularly ever–indoor tanning and painful burns from indoor tanning, provided benefit in predicting early-onset BCC. With personalized genotyping on the horizon, our results and those of others for melanoma and NMSC suggest that considering genotype may aid in risk prediction. Also, as indoor tanning and outdoor ultraviolet exposure are important predictors of risk, interventions, such as broader indoor tanning restrictions in minors and educational campaigns in young adults, provide a strategy to reduce early-onset BCC incidence, consistent with the Surgeon General's call to action to prevent skin cancer.

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