## Risk Factors for Histological Types and Anatomic Sites of Cutaneous Basal-Cell Carcinoma: An Italian Case-Control Study

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Different clinico-pathologic subtypes and anatomic sites of basal-cell carcinoma (BCC) may display distinct characteristics and mechanisms of development. However, scanty information exists on potential differences in etiological factors for BCC according to histotype and anatomic location. Thus, we analyzed data from an Italian case-control study, including 528 subjects with newly diagnosed, histologically confirmed BCC and 512 controls admitted to the same hospitals with acute conditions. The multivariate odds ratio (OR) of nodular (OR = 1.53) but not superficial (OR = 0.71) BCC was increased for occupational exposure to sunlight. Considering the anatomic site of BCC, the corresponding values were 1.46 for head/neck and 0.74 for truncal location. Direct associations were observed with recreational sunlight exposure, eye color, red hair, and number and early age of severe sunburn episodes, along with some differences in risk between histotypes and anatomic sites. This study confirmed the role of (intermittent) sun exposure and phenotypic characteristics as risk factors for BCC, and suggested etiological differences between nodular and superficial histotypes and between head/neck and truncal locations.

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#### **INTRODUCTION**

Basal-cell carcinoma (BCC) is the most frequent type of cancer occurring in Caucasians. The incidence of BCC is reported to be increasing in various countries (Tran *et al.*, 2003; Rubin *et al.*, 2005), but there are very scanty reliable data, as most skin cancers are not pathologically examined. The Cancer Registry of the Canton of Vaud is one of the few registration settings producing valid data on the issue, and incidence of BCC was around 70/100,000 (Levi *et al.*, 2001). Recognized risk factors for BCC include selected phenotypic characteristics, such as fair skin and light eyes, sunburns in childhood, immunosuppression, family history of skin cancer, and exposure to UV radiations, although many aspects of the latter are still unclear (Tran *et al.*, 2003; Wong *et al.*, 2003).

Nodular and superficial subtypes are the most common clinico-pathological variants of BCC, accounting for about 60 and 25% of cases, respectively (Tilli *et al.*, 2005). BCC most

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Abbreviations: BCC, basal-cell carcinoma; CI, confidence interval; OR, odds ratio

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frequently arises on the head/neck ( $\sim 80\%$  of cases) or the trunk (~15% of cases) (Rubin et al., 2005). In a large investigation conducted in France on more than 10,000 patients and about 13,500 cases of BCC, 79% of the cases were nodular and 15% were superficial BCC, 83% occurred on the head and neck and 11% on the trunk. BCC occurring on the head/neck was mainly of the nodular histotype, whereas truncal BCC was more frequently of the superficial histotype (Scrivener et al., 2002). This fact, as well as some different characteristics observed among clinico-pathologic subtypes (i.e., age at occurrence), lead to suggest that nodular and superficial BCC could have a different etiology (McCormack et al., 1997; Bastiaens et al., 1998). Different mechanisms of development were reported also for truncal and head/neck BCC, as development of truncal BCC appeared to be associated with a distinct predisposition (Ramachandran et al., 2001). Further, when the initial tumor was a truncal BCC with superficial histology, development of additional BCCs was faster (Lovatt et al., 2005).

However, only a few epidemiological studies to date investigated risk factors for BCC according to its major clinico-pathological variants and anatomic sites. With the aim to investigate the issue, we analyzed data from a case-control study conducted in Italy.

#### RESULTS

Table 1 gives information on BCC in the case group, according to clinico-pathologic variants, anatomic site, and

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sex. Considering the age distribution of cases, subjects with superficial and truncal BCC were younger than those with nodular and head and neck BCC, respectively. In fact, 11% of subjects with nodular BCC were <50, 47% were 50–69, and 42% were  $\geq$ 70 years old. The corresponding proportions in subjects with superficial BCC were 18, 54, and 28%, respectively. Considering the site of BCC, 9% of subjects with head and neck BCC were <50, 50% were 50–69, and 41% were  $\geq$ 70 years old. The corresponding values for truncal BCC were 23, 53, and 24%.

Table 2 reports the distribution of nodular and superficial BCC cases and controls, and the corresponding odds ratios (ORs) and 95% confidence intervals (CIs), according to pigmentary traits, presence of selected pigmentary lesions, skin sensitivity to the sun, indicators of sun damage to the skin, family history of skin and non-skin cancer, and history of radiotherapy. P-values for the difference between estimates of nodular and superficial BCC were also given. Risk of nodular BCC was higher in subjects with light-colored eyes (OR = 2.47 for gray/blue as compared to black/dark brown)eyes). The corresponding risk for superficial BCC was 1.45. The OR of nodular and superficial variants of BCC were 6.18 and 11.7, respectively, for having red as compared to black hair, whereas no increased risks were observed for blondhaired subjects. A fair/pale skin color at interview was related with a  $\sim$  50% increased risk of superficial BCC, but not with nodular subtype. Nodular BCC cases (77%) had solar lentigines anywhere on the body more frequently than superficial cases (66%, P=0.03) and controls (67%). The association between actinic keratosis and BCC was stronger in the superficial (OR = 3.41) than the nodular (OR = 1.71)subtype (P=0.005), whereas seborrheic keratosis was associated with an about 2-fold increased risk of both BCC subtypes. Considering skin reactions to sunlight exposure, significantly elevated ORs were observed for nodular and superficial BCC among subjects who always burn after first seasonal sun exposure (OR = 1.80 and 2.74, respectively), with no tan after sunburns (OR = 2.26 and 3.82) and reporting a severe sunburn episode before 18 years of age (OR = 6.94 and 3.27). Significant differences in risk were reported between nodular and superficial BCC according to

history of severe sunburns episodes (P=0.006), as well as age at first sunburn (P=0.016) and number of episodes (P=0.005). A family history of skin cancer in first-degree relatives was related with risk of nodular (OR = 8.42) and superficial BCC (OR = 4.87). Personal history of radiotherapy increased the risk of both clinical subtypes, as well (OR = 2.57 and 2.20, respectively).

Table 3 considers the same variables as Table 2, separately for the main anatomic sites where BCC occurred in cases. Risk of BCC on the head/neck was increased for those with hazel/green (OR = 2.31) or gray/blue eyes (OR = 2.72), and with red hair (OR = 6.43). Red-haired subjects also had a remarkably higher risk of trunk BCC (OR = 14.2). A high number of melanocytic nevi on the upper limbs were more frequently observed in subjects with BCC on the trunk (21.6%) than in controls (12.5%). The ORs of head/neck and trunk BCC were similarly increased in subjects with frequent burns after first seasonal sun exposure, no tanning after sunburns, early age and high number of severe sunburns episodes, and positive family history of skin cancers in firstdegree relatives. On the other hand, risk of trunk BCC was higher than risk of head/neck BCC in subjects with history of actinic keratosis (OR = 3.03 and 1.78, respectively, P=0.047) and seborrheic keratosis (OR = 2.80 and 1.47, P = 0.014).

Table 4 considers occupational, recreational, and total lifetime sunlight exposures. Thirty-six percent of subjects with nodular BCC, 20% of cases with superficial BCC, and 27% of controls had a relevant occupational exposure to sunlight during life. As a result, the multivariate OR for occupational sun exposure was higher for nodular (OR = 1.53, 95% Cl, 1.08–2.18) than for superficial (OR = 0.71, 95% CI)0.44–1.15) clinico-pathologic type (P-value for the difference between estimates of nodular and superficial BCC was 0.003). With reference to recreational sun exposure, a significantly increased risk of nodular BCC was found in ever-exposed subjects (OR = 1.75, 95% CI, 1.27-2.42). The corresponding OR of superficial BCC was 1.35 (95% Cl, 0.91-2.00). Subjects reporting at least one type of sun exposure had ORs of nodular and superficial BCC of 2.04 (95% Cl, 1.47-2.83) and 1.02 (95% Cl, 0.69-1.49),

|                | Nodular |     | Superficial |    |    | Others/Unknown <sup>1</sup> |    |    | All variants |     |     |            |
|----------------|---------|-----|-------------|----|----|-----------------------------|----|----|--------------|-----|-----|------------|
| Anatomic site  | м       | F   | All (%)     | м  | F  | All (%)                     | м  | F  | All (%)      | м   | F   | All (%)    |
| Head and neck  | 115     | 105 | 220 (75.6)  | 32 | 38 | 70 (42.2)                   | 23 | 24 | 47 (66.2)    | 170 | 167 | 337 (63.8) |
| Trunk          | 36      | 19  | 55 (18.9)   | 49 | 23 | 72 (43.4)                   | 7  | 5  | 12 (16.9)    | 92  | 47  | 139 (26.3) |
| Limbs          | 6       | 5   | 11 (3.8)    | 13 | 7  | 20 (12.0)                   | 2  | 6  | 8 (11.3)     | 21  | 18  | 39 (7.4)   |
| Multiple sites | 3       | 1   | 4 (1.4)     | 1  | 2  | 3 (1.8)                     | 3  | 0  | 3 (4.2)      | 7   | 3   | 10 (1.9)   |
| Unspecified    | 1       | 0   | 1 (0.3)     | 0  | 1  | 1 (0.6)                     | 1  | 0  | 1 (1.4)      | 2   | 1   | 3 (0.6)    |
| All sites      | 161     | 130 | 291 (100)   | 95 | 71 | 166 (100)                   | 36 | 35 | 71 (100)     | 292 | 236 | 528 (100)  |

Table 1. Frequency distribution of 528 cases of BCC according to clinico-pathologic variants, anatomic site, and sex

BCC, basal-cell carcinoma; F, females; M, males.

<sup>1</sup>The category "others" includes morphoeic or sclerosing, and infiltrative BCC.

|  | Clinico-patholo<br>no. of c | gic variants,<br>cases |                 | OR (95% Cl)      |                  |                              |  |
|--|-----------------------------|------------------------|-----------------|------------------|------------------|------------------------------|--|
| Variable   | Nodular                     | Superficial            | No. of controls | Nodular          | Superficial      | <i>P</i> -value <sup>1</sup> |  |
| Eye color <sup>2</sup>                           |                             |                        |                 |                  |                  |                              |  |
| Black/dark brown                                 | 76                          | 54                     | 207             | 1                | 1                |                              |  |
| Light brown                                      | 64                          | 25                     | 97              | 1.83 (1.17-2.86) | 0.93 (0.53-1.66) |                              |  |
| Hazel/green                                      | 72                          | 44                     | 111             | 1.97 (1.27-3.04) | 1.43 (0.86-2.38) | 0.152                        |  |
| Gray/blue  | 79                          | 43                     | 97              | 2.47 (1.54-3.95) | 1.45 (0.82–2.56) |                              |  |
| Hair color <sup>2</sup>                          |                             |                        |                 |                  |                  |                              |  |
| Black/dark brown                                 | 173                         | 97                     | 341             | 1                | 1                |                              |  |
| Light brown                                      | 90                          | 49                     | 131             | 1.09 (0.75-1.57) | 1.15 (0.73–1.80) |                              |  |
| Blond  | 24                          | 15                     | 39              | 1.02 (0.54-1.90) | 1.17 (0.55–2.51) | 0.857                        |  |
| Red  | 4                           | 5                      | 1               | 6.18 (0.65–58.9) | 11.7 (1.21–113)  |                              |  |
| Skin color at interview <sup>2,3</sup>           |                             |                        |                 |                  |                  |                              |  |
| Dark/olive                                       | 37                          | 16                     | 68              | 1                | 1                |                              |  |
| Intermediate                                     | 160                         | 88                     | 277             | 0.88 (0.54-1.41) | 1.46 (0.77–2.79) | 0.175                        |  |
| Fair/pale  | 94                          | 61                     | 165             | 0.73 (0.42–1.25) | 1.49 (0.73–3.05) |                              |  |
| Freckles <sup>2</sup>                            |                             |                        |                 |                  |                  |                              |  |
| No   | 155                         | 98                     | 293             | 1                | 1                |                              |  |
| Yes  | 136                         | 68                     | 219             | 1.00 (0.72–1.39) | 0.68 (0.45–1.04) | 0.094                        |  |
| Solar lentigines <sup>2</sup>                    |                             |                        |                 |                  |                  |                              |  |
| No   | 67                          | 56                     | 168             | 1                | 1                |                              |  |
| Yes  | 224                         | 110                    | 344             | 1.47 (1.03–2.09) | 0.89 (0.60–1.34) | 0.030                        |  |
| Melanocytic nevi on upper limbs <sup>2</sup>     |                             |                        |                 |                  |                  |                              |  |
| None   | 171                         | 101                    | 360             | 1                | 1                |                              |  |
| Few (1–5)  | 76                          | 35                     | 88              | 1.44 (0.98–2.12) | 1.05 (0.64–1.71) | 0.456                        |  |
| Many (≥6)  | 44                          | 30                     | 64              | 1.40 (0.88–2.22) | 1.30 (0.75–2.25) |                              |  |
| Actinic keratoses <sup>2</sup>                   |                             |                        |                 |                  |                  |                              |  |
| No   | 217                         | 110                    | 445             | 1                | 1                |                              |  |
| Yes  | 74                          | 56                     | 67              | 1.71 (1.14–2.57) | 3.41 (2.11-5.50) | 0.005                        |  |
| Seborrheic keratosis <sup>2</sup>                |                             |                        |                 |                  |                  |                              |  |
| No   | 88                          | 48                     | 233             | 1                | 1                |                              |  |
| Yes  | 203                         | 118                    | 279             | 1.80 (1.28–2.53) | 2.24 (1.45–3.45) | 0.361                        |  |
| Skin reaction to 1st sun exposure <sup>3,4</sup> |                             |                        |                 |                  |                  |                              |  |
| Never burns                                      | 127                         | 58                     | 261             | 1                | 1                |                              |  |
| Burns occasionally                               | 68                          | 42                     | 150             | 1.01 (0.69–1.46) | 1.16 (0.73–1.85) |                              |  |
| Burns frequently                                 | 59                          | 36                     | 55              | 2.44 (1.55–3.83) | 2.68 (1.56-4.61) | 0.642                        |  |
| Always burns                                     | 36                          | 30                     | 44              | 1.80 (1.06–3.07) | 2.74 (1.49-5.02) |                              |  |

# Table 2. Type of BCC: ORs and 95% CIs, according to pigmentary traits, presence of selected pigmentary lesions, skin sensitivity to the sun, indicators of sun damage to the skin, family history, and history of radiotherapy

Table 2 continued on following page

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Risk Factors for Histotype and Site of BCC

## Table 2. continued

|   | Clinico-patholo<br>no. of o | ogic variants,<br>cases |                 | OR (95% CI)      |                  |                              |  |
|---|-----------------------------|-------------------------|-----------------|------------------|------------------|------------------------------|--|
| Variable  | Nodular                     | Superficial             | No. of controls | Nodular          | Superficial      | <i>P</i> -value <sup>1</sup> |  |
| Skin reaction after sunburns <sup>3,4</sup>       |                             |                         |                 |                  |                  |                              |  |
| Never had sunburns                                | 105                         | 48                      | 211             | 1                | 1                |                              |  |
| Often/always tans                                 | 156                         | 91                      | 272             | 1.29 (0.92-1.79) | 1.29 (0.85–1.96) | 0.239                        |  |
| Never tans  | 30                          | 27                      | 28              | 2.26 (1.24-4.12) | 3.82 (1.97–7.42) |                              |  |
| SSEs <sup>3,4</sup>                               |                             |                         |                 |                  |                  |                              |  |
| Never   | 212                         | 134                     | 452             | 1                | 1                |                              |  |
| Ever  | 78                          | 32                      | 58              | 3.43 (2.28–5.15) | 1.70 (1.03–2.79) | 0.006                        |  |
| Age at first SSE <sup>3,4</sup>                   |                             |                         |                 |                  |                  |                              |  |
| <18   | 24                          | 10                      | 8               | 6.94 (2.97–16.2) | 3.27 (1.24-8.65) | 0.016                        |  |
| ≥18   | 50                          | 20                      | 47              | 2.83 (1.78-4.51) | 1.34 (0.74–2.41) |                              |  |
| No. of $SSE^{3,4}$                                |                             |                         |                 |                  |                  |                              |  |
| 1   | 48                          | 13                      | 38              | 3.23 (1.98-5.26) | 1.06 (0.54-2.11) | 0.005                        |  |
| ≥2  | 27                          | 17                      | 11              | 6.53 (3.08–13.8) | 4.53 (2.01–10.2) |                              |  |
| Family history of skin cancers <sup>5,6</sup>     |                             |                         |                 |                  |                  |                              |  |
| No  | 266                         | 157                     | 506             | 1                | 1                |                              |  |
| Yes   | 25                          | 9                       | 6               | 8.42 (3.35–21.2) | 4.87 (1.67–14.2) | 0.196                        |  |
| Family history of non-skin cancers <sup>5,6</sup> |                             |                         |                 |                  |                  |                              |  |
| No  | 191                         | 100                     | 349             | 1                | 1                |                              |  |
| Yes   | 100                         | 66                      | 163             | 1.18 (0.86–1.63) | 1.39 (0.95–2.04) | 0.446                        |  |
| Family history of all cancers <sup>5,6</sup>      |                             |                         |                 |                  |                  |                              |  |
| No  | 174                         | 96                      | 345             | 1                | 1                |                              |  |
| Yes   | 117                         | 70                      | 167             | 1.48 (1.09–2.04) | 1.49 (1.02–2.18) | 0.994                        |  |
| Radiotherapy <sup>4</sup>                         |                             |                         |                 |                  |                  |                              |  |
| No  | 273                         | 156                     | 499             | 1                | 1                |                              |  |
| Yes   | 18                          | 10                      | 13              | 2.57 (1.21-5.46) | 2.20 (0.92-5.25) | 0.713                        |  |

BCC, basal-cell carcinoma; CI, confidence interval; OR, odds ratio; SSE, severe sunburns episode.

 $^{1}P$ -value from Wald  $\chi^{2}$  statistic for the difference between estimates of head/neck and trunk BCC.

<sup>2</sup>ORs were computed using unordered polytomous logistic regression models, including terms for age, sex, study center, education, eye, hair, and skin color, freckles, solar lentigines, number of melanocytic nevi, actinic, and seborrheic keratosis.

<sup>3</sup>The sum does not add up to the total because of some missing values.

<sup>4</sup>ORs were adjusted for age, sex, study center, education, eye, hair, and skin color.

<sup>5</sup>ORs were adjusted for age, sex, study center, education, eye, hair, and skin color, and number of siblings.

<sup>6</sup>In first-degree relatives only.

respectively (P=0.001). There were no dose-response relations with occupational nor recreational sun exposures in any of the subtypes considered. Risks were not materially changed when we examined sunlight exposures during spring/summer and autumn/winter.

Table 5 gives the same information as Table 4, considering anatomic sites. The multivariate ORs for lifetime occupa-

tional sunlight exposure were 1.46 (95% CI, 1.04–2.05) for head/neck and 0.74 (95% CI, 0.44–1.24) for trunk BCC (P=0.013), those for lifetime recreational sun exposure were 1.88 (95% CI, 1.37–2.57) and 1.62 (95% CI, 1.06–2.45), respectively, and those for total sun exposure were 1.96 (95% CI, 1.44–2.68) and 1.21 (95% CI, 0.79–1.83), respectively (P=0.036).

|  | Anatomic site, n | o. of cases | _               | OR (95% CI)      |                  |                      |  |
|--|------------------|-------------|-----------------|------------------|------------------|----------------------|--|
| Variable   | Head/neck        | Trunk       | No. of controls | Head/neck        | Trunk            | P-value <sup>1</sup> |  |
| Eye color <sup>2</sup>                             |                  |             |                 |                  |                  |                      |  |
| Black/dark brown                                   | 81               | 53          | 207             | 1                | 1                |                      |  |
| Light brown  | 69               | 21          | 97              | 1.82 (1.18-2.80) | 0.94 (0.51–1.74) |                      |  |
| Hazel/green  | 92               | 25          | 111             | 2.31 (1.53-3.50) | 0.89 (0.50-1.61) | 0.020                |  |
| Gray/blue  | 95               | 40          | 97              | 2.72 (1.74-4.26) | 1.54 (0.85–2.77) |                      |  |
| Hair color <sup>2</sup>                            |                  |             |                 |                  |                  |                      |  |
| Black/dark brown                                   | 199              | 86          | 341             | 1                | 1                |                      |  |
| Light brown  | 99               | 36          | 131             | 0.96 (0.67-1.36) | 0.95 (0.57-1.57) |                      |  |
| Blond  | 34               | 12          | 39              | 1.09 (0.61–1.93) | 1.02 (0.43-2.40) | 0.734                |  |
| Red  | 5                | 5           | 1               | 6.43 (0.72–57.8) | 14.2 (1.44–141)  |                      |  |
| Skin color at interview <sup>2,3</sup>             |                  |             |                 |                  |                  |                      |  |
| Dark/olive   | 37               | 17          | 68              | 1                | 1                |                      |  |
| Intermediate                                       | 182              | 76          | 277             | 1.02 (0.63-1.64) | 1.13 (0.59–2.14) | 0.920                |  |
| Fair/pale  | 118              | 45          | 165             | 0.90 (0.53–1.54) | 1.06 (0.51-2.22) |                      |  |
| Freckles <sup>2</sup>                              |                  |             |                 |                  |                  |                      |  |
| No   | 182              | 82          | 293             | 1                | 1                |                      |  |
| Yes  | 155              | 57          | 219             | 0.87 (0.63–1.20) | 0.81 (0.52–1.27) | 0.759                |  |
| Solar lentigines <sup>2</sup>                      |                  |             |                 |                  |                  |                      |  |
| No   | 79               | 44          | 168             | 1                | 1                |                      |  |
| Yes  | 258              | 95          | 344             | 1.45 (1.03–2.02) | 1.00 (0.64–1.58) | 0.137                |  |
| Melanocytic nevi on upper limbs <sup>2</sup>       |                  |             |                 |                  |                  |                      |  |
| None   | 211              | 67          | 360             | 1                | 1                |                      |  |
| Few (1–5)  | 79               | 42          | 88              | 1.24 (0.85–1.81) | 1.84 (1.12-3.02) | 0.246                |  |
| Many (≥6)  | 47               | 30          | 64              | 1.26 (0.80–1.99) | 1.82 (1.03-3.24) |                      |  |
| Actinic keratoses <sup>2</sup>                     |                  |             |                 |                  |                  |                      |  |
| No   | 254              | 92          | 445             | 1                | 1                |                      |  |
| Yes  | 83               | 47          | 67              | 1.78 (1.20–2.65) | 3.03 (1.79–5.13) | 0.047                |  |
| Seborrheic keratosis <sup>2</sup>                  |                  |             |                 |                  |                  |                      |  |
| No   | 114              | 37          | 233             | 1                | 1                |                      |  |
| Yes  | 223              | 102         | 279             | 1.47 (1.07–2.02) | 2.80 (1.71-4.58) | 0.014                |  |
| Skin reaction to first sun exposure <sup>3,4</sup> |                  |             |                 |                  |                  |                      |  |
| Never burns  | 137              | 51          | 261             | 1                | 1                |                      |  |
| Burns occasionally                                 | 83               | 31          | 150             | 1.17 (0.82–1.67) | 0.90 (0.54–1.51) |                      |  |
| Burns frequently                                   | 75               | 30          | 55              | 2.86 (1.85-4.43) | 2.48 (1.39-4.45) | 0.238                |  |
| Always burns                                       | 41               | 27          | 44              | 1.88 (1.12–3.16) | 2.95 (1.54-5.65) |                      |  |
|  |                  |             |                 |                  |                  |                      |  |

 Table 3. Site of BCC: ORs and 95% CIs, according to pigmentary traits, presence of selected pigmentary lesions, skin sensitivity to the sun, indicators of sun damage to the skin, family history, and history of radiotherapy

Table 3 continued on following page

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Risk Factors for Histotype and Site of BCC

## Table 3. continued

|   | Anatomic site, n | o. of cases | _               | OR (95% Cl)      |                  |                              |  |
|---|------------------|-------------|-----------------|------------------|------------------|------------------------------|--|
| Variable  | Head/neck        | Trunk       | No. of controls | Head/neck        | Trunk            | <i>P</i> -value <sup>1</sup> |  |
| Skin reaction after sunburns <sup>3,4</sup>       |                  |             |                 |                  |                  |                              |  |
| Never had sunburns                                | 108              | 42          | 211             | 1                | 1                |                              |  |
| Often/always tans                                 | 189              | 78          | 272             | 1.56 (1.13-2.16) | 1.15 (0.73–1.80) | 0.301                        |  |
| Never tans  | 40               | 19          | 28              | 2.86 (1.61-5.10) | 3.16 (1.51-6.62) |                              |  |
| SSEs <sup>3,4</sup>                               |                  |             |                 |                  |                  |                              |  |
| Never   | 248              | 101         | 452             | 1                | 1                |                              |  |
| Ever  | 88               | 38          | 58              | 3.40 (2.29–5.06) | 2.39 (1.46-3.91) | 0.157                        |  |
| Age at first SSE <sup>3,4</sup>                   |                  |             |                 |                  |                  |                              |  |
| <18   | 25               | 10          | 8               | 6.00 (2.57–14.0) | 4.15 (1.53–11.2) | 0.370                        |  |
| ≥18   | 58               | 26          | 47              | 2.93 (1.87-4.59) | 2.05 (1.17-3.58) |                              |  |
| No. of $SSE^{3,4}$                                |                  |             |                 |                  |                  |                              |  |
| 1   | 53               | 18          | 38              | 3.19 (1.97–5.17) | 1.68 (0.89–3.17) | 0.136                        |  |
| ≥2  | 31               | 18          | 11              | 6.56 (3.13–13.7) | 5.99 (2.65–13.5) |                              |  |
| Family history of skin cancers <sup>5,6</sup>     |                  |             |                 |                  |                  |                              |  |
| No  | 316              | 129         | 506             | 1                | 1                |                              |  |
| Yes   | 21               | 10          | 6               | 6.18 (2.41–15.8) | 6.34 (2.18–18.5) | 0.954                        |  |
| Family history of non-skin cancers <sup>5,6</sup> |                  |             |                 |                  |                  |                              |  |
| No  | 220              | 86          | 349             | 1                | 1                |                              |  |
| Yes   | 117              | 53          | 163             | 1.17 (0.86–1.60) | 1.30 (0.86–1.96) | 0.652                        |  |
| Family history of all cancers <sup>5,6</sup>      |                  |             |                 |                  |                  |                              |  |
| No  | 207              | 79          | 345             | 1                | 1                |                              |  |
| Yes   | 130              | 60          | 167             | 1.35 (1.00–1.83) | 1.56 (1.04–2.34) | 0.516                        |  |
| Radiotherapy <sup>4</sup>                         |                  |             |                 |                  |                  |                              |  |
| No  | 320              | 124         | 499             | 1                | 1                |                              |  |
| Yes   | 17               | 15          | 13              | 2.05 (0.96-4.38) | 4.01 (1.78–9.04) | 0.094                        |  |

BCC, basal-cell carcinoma; CI, confidence interval; OR, odds ratio; SSE, severe sunburns episode.

 $^{1}P$ -value from Wald  $\chi^{2}$  statistic for the difference between estimates of head/neck and trunk BCC.

<sup>2</sup>ORs were computed using unordered polytomous logistic regression models, including terms for age, sex, study center, education, eye, hair, and skin color, freckles, solar lentigines, number of melanocytic nevi, actinic, and seborrheic keratosis.

<sup>3</sup>The sum does not add up to the total because of some missing values.

<sup>4</sup>ORs were adjusted for age, sex, study center, education, eye, hair, and skin color.

<sup>5</sup>ORs were adjusted for age, sex, study center, education, eye, hair, and skin color, and number of siblings.

<sup>6</sup>In first-degree relatives only.

### **DISCUSSION**

This study found an increased risk of nodular, but not superficial, clinical subtype of BCC in subjects reporting occupational sun exposures, but there was no duration-risk relation. Likewise, there was a direct relation between occupational sun exposure and risk of head/neck BCC, but not truncal BCC. This is consistent with a Puerto Rican study, where a direct relation between UV exposure and development of non-melanoma skin cancer was found for head/ neck neoplasms only (Ramos *et al.*, 2004). As the occurrence of truncal BCC is linked to a genetic susceptibility (Ramachandran *et al.*, 1999, 2001), and a reduced DNA repair capacity increases the risk of BCC (Wei *et al.*, 1993), Ramos *et al.* (2004) suggested that non-melanoma skin

|   | -Clinico<br>variants, ı | pathologic<br>no. of cases |                 | <b>OR</b> (95% Cl) <sup>1</sup> |                  |                              |  |
|---|-------------------------|----------------------------|-----------------|---------------------------------|------------------|------------------------------|--|
| Variable  | Nodular                 | Superficial                | No. of controls | Nodular                         | Superficial      | <i>P</i> -value <sup>2</sup> |  |
| Lifetime occupational sun exposure <sup>3,4</sup> |                         |                            |                 |                                 |                  |                              |  |
| No occupational exposure                          | 186                     | 133                        | 372             | 1                               | 1                |                              |  |
| Had occupational exposure                         | 105                     | 33                         | 140             | 1.53 (1.08–2.18)                | 0.71 (0.44–1.15) | 0.003                        |  |
| Short duration                                    | 51                      | 20                         | 65              | 1.66 (1.08-2.55)                | 0.92 (0.52–1.62) | 0.010                        |  |
| Long duration                                     | 52                      | 13                         | 74              | 1.35 (0.85–2.14)                | 0.50 (0.25–1.00) |                              |  |
| Lifetime recreational sun exposure <sup>3,4</sup> |                         |                            |                 |                                 |                  |                              |  |
| No recreational exposure                          | 162                     | 96                         | 346             | 1                               | 1                |                              |  |
| Had recreational exposure                         | 129                     | 70                         | 166             | 1.75 (1.27–2.42)                | 1.35 (0.91–2.00) | 0.227                        |  |
| Short duration                                    | 69                      | 32                         | 79              | 2.08 (1.39-3.12)                | 1.30 (0.79–2.16) | 0.210                        |  |
| Long duration                                     | 59                      | 37                         | 87              | 1.44 (0.96–2.17)                | 1.34 (0.83–2.17) |                              |  |
| Lifetime sun exposure (overall)                   |                         |                            |                 |                                 |                  |                              |  |
| No  | 86                      | 75                         | 236             | 1                               | 1                |                              |  |
| Yes   | 205                     | 91                         | 276             | 2.04 (1.47-2.83)                | 1.02 (0.69–1.49) | 0.001                        |  |
| Either occupational or recreational exposure      | 176                     | 79                         | 246             | 1.97 (1.41-2.74)                | 1.00 (0.68–1.47) | 0.005                        |  |
| Both exposures                                    | 29                      | 12                         | 30              | 2.93 (1.58-5.44)                | 1.20 (0.55–2.61) |                              |  |

## Table 4. Type of BCC: ORs and 95% CIs according to sunlight exposures

BCC, basal-cell carcinoma; CI, confidence interval; OR, odds ratio.

<sup>1</sup>ORs from unordered polytomous logistic regression models, adjusted for age, sex, study center, education, eye, hair, and skin color.

<sup>2</sup>*P*-value from Wald  $\chi^2$  statistic for the difference between estimates of nodular and superficial BCC.

<sup>3</sup>The sum does not add up to the total because of some missing values.

<sup>4</sup>Subjects who had any occupational (recreational) exposure were further subdivided into two groups, using the median number of lifetime hours of occupational (recreational) exposure as cut-point, with reference to no occupational (recreational) exposure as the baseline.

cancer of sun-protected anatomic sites may occur in individuals with decreased DNA repair capacity. The lower mean age at occurrence of truncal BCC observed in our investigation and other studies (Lear *et al.*, 1997a; Scrivener *et al.*, 2002) could also be related and further support this hypothesis. Therefore, it could be important to differentiate BCC according to the anatomic site in future studies, also keeping in mind that in a previous report from this study where data were not disaggregated no association was found between lifetime occupational sun exposure and risk of BCC (Naldi *et al.*, 2000).

On the other hand, we observed no important differences between risk of clinico-pathologic variants nor of anatomic site of BCC in relation to recreational sun exposure. The higher risks observed for recreational than occupational sun exposure are consistent with findings of Kricker *et al.* (1995a), that suggested that in poor tanners an exposure spread during the whole week may allow to develop defensive mechanisms. On the other hand, our data do not agree with results from a UK study, that is, a northern European population with different phenotypic characteristics, where frequent sunbathing increased 5-fold the risk of truncal as compared to head/ neck BCC and risks for the yearly average number of hours of exposure were similar in the two groups (Lovatt *et al.*, 2004), and with another report from an Australian case–control study of Kricker *et al.* (1995b) where risk of BCC on the head/neck decreased with high lifetime hours of sun exposure and BCC of the trunk was associated with hours of sun exposure on the same site.

We found that severe sunburns episodes were directly related with risk of both clinical subgroups, with a stronger association for nodular BCC. In agreement with some (Gallagher et al., 1995; Kricker et al., 1995a; Zanetti et al., 1996), but not all studies (Corona et al., 2001), subjects reporting frequent episodes of severe sunburns and those with a first episode during childhood or early teenage had higher risks of BCC. In this study, these were both 7-fold and 3- to 4fold elevated for nodular and superficial BCC, respectively. The observation that severe sunburns episodes, as well as solar lentigines, are significantly more strongly related to nodular than superficial BCC is consistent with the observation that UV exposure is a strong determinant of nodular BCC. On the other hand, limited differences emerged between risk of head/neck and truncal BCC in relation to history of severe sunburns episodes, as in a previous report from Lovatt et al. (2004).

In this Mediterranean population, we observed significant associations between selected pigmentary traits and risk of BCC (Naldi *et al.*, 2000). The light-eyes phenotype was directly related with the nodular-head/neck profiles of BCC, whereas no association emerged with risk of superficial and truncal BCC. Risk of truncal BCC in red-haired subjects was

|   | Anatomic site, n | o. of cases |                 | OR (95% Cl) <sup>1</sup> |                  |                              |  |
|---|------------------|-------------|-----------------|--------------------------|------------------|------------------------------|--|
| Variable  | Head/neck        | Trunk       | No. of controls | Head/neck                | Trunk            | <i>P</i> -value <sup>2</sup> |  |
| Lifetime occupational sun exposure <sup>3,4</sup> |                  |             |                 |                          |                  |                              |  |
| No occupational exposure                          | 218              | 112         | 372             | 1                        | 1                |                              |  |
| Had occupational exposure                         | 119              | 27          | 140             | 1.46 (1.04–2.05)         | 0.74 (0.44–1.24) | 0.013                        |  |
| Short duration                                    | 61               | 17          | 65              | 1.69 (1.12-2.56)         | 0.91 (0.49–1.68) | 0.029                        |  |
| Long duration                                     | 57               | 9           | 74              | 1.20 (0.77–1.88)         | 0.48 (0.22–1.07) |                              |  |
| Lifetime recreational sun exposure <sup>3,4</sup> |                  |             |                 |                          |                  |                              |  |
| No recreational exposure                          | 188              | 68          | 346             | 1                        | 1                |                              |  |
| Had recreational exposure                         | 149              | 71          | 166             | 1.88 (1.37-2.57)         | 1.62 (1.06-2.45) | 0.504                        |  |
| Short duration                                    | 73               | 39          | 79              | 2.06 (1.38-3.05)         | 1.80 (1.09–2.98) | 0.703                        |  |
| Long duration                                     | 75               | 31          | 87              | 1.71 (1.16–2.52)         | 1.36 (0.80–2.30) |                              |  |
| Lifetime sun exposure (overall)                   |                  |             |                 |                          |                  |                              |  |
| No  | 106              | 53          | 236             | 1                        | 1                |                              |  |
| Yes   | 231              | 86          | 276             | 1.96 (1.44-2.68)         | 1.21 (0.79–1.83) | 0.036                        |  |
| Either occupational or recreational exposure      | 194              | 74          | 246             | 1.85 (1.35-2.55)         | 1.18 (0.77–1.81) | 0.069                        |  |
| Both exposures                                    | 37               | 12          | 30              | 3.35 (1.86-6.03)         | 1.49 (0.67–3.31) |                              |  |

## Table 5. Site of BCC: ORs and 95% CIs according to sunlight exposures

BCC, basal-cell carcinoma; CI, confidence interval; OR, odds ratio.

<sup>1</sup>ORs from unordered polytomous logistic regression models, adjusted for age, sex, study center, education, eye, hair, and skin color.

<sup>2</sup>*P*-value from Wald  $\chi^2$  statistic for the difference between estimates of head/neck and truncal BCC.

<sup>3</sup>The sum does not add up to the total because of some missing values.

<sup>4</sup>Subjects who had any occupational (recreational) exposure were further subdivided into two groups, using the median number of lifetime hours of occupational (recreational) exposure as cut-point, with reference to no occupational (recreational) exposure as the baseline.

higher than risk of head/neck BCC, but the number of redhaired subjects was too small to allow valuable considerations on this trait. We did not find any significant relation with skin color in all subgroups of BCC, whereas other studies reported an increased risk for having a fair/pale skin (Green *et al.*, 1996; Lear *et al.*, 1997b). A likely explanation for these findings is that in the Mediterranean population it is difficult to distinguish skin phenotypes, whereas eyes and hair color may be easier to classify.

Another interesting finding of this study is the substantial excess risk of BCC, particularly of the nodular subtype, for subjects with a family history of skin cancer in first-degree relatives. This association may reflect a true genetic predisposition or the sharing of common environmental factors, or may be due to a more careful recall of family history of skin cancer in subjects with such a diagnosis. Although a general association has been described in a number of studies, the different risk reported for family history of skin cancer in the clinical subgroups is of interest, even if the direct comparison of subgroups of BCC using polytomous logistic regression did not confirm major differences.

The risk of truncal BCC (OR = 4.0) was twice that of head/ neck BCC (OR = 2.0) for history of radiotherapy, whereas risks were similar for different clinical types of BCC. We had no available information on the site where radiation therapy was performed.

As actinic keratosis is related to sun exposure (Naldi et al., 2006), the stronger association with trunk BCC is difficult to explain, as is the difference in risks for seborrheic keratosis between anatomic sites of BCC. Chance may play a role, in view of the large number of variables that were considered. Although the sample size of this study was large, in fact, this is inadequate to analyze differences across subgroups. Further, cases and controls may recall in a different way their lifestyle habits and personal characteristics, but this potential bias would not compromise the comparison between subgroups of cases, as it is unlikely that such differences exist between subjects with nodular and superficial BCC or head/neck and truncal BCC. Information on family history was self-reported and was not validated, and may thus be inaccurate. On the other hand, the common hospital setting of cases and controls, and hence the similar attention to medical history, may improve the comparability of information (MacMahon and Trichopoulos, 1996). Moreover, we asked for family history of skin cancer to avoid confusion between melanoma and other more common skin neoplasms. Among the strengths of the study are the almost complete response rate, the similar catchment area of cases and controls, and the administration of a standard questionnaire under similar conditions.

Thus, these data support results from other studies (Kricker et al., 1995a; Rosso et al., 1996; Zanetti et al., 1996)

indicating a more important role of sunburns, and therefore intense sun exposure, than of prolonged sun exposure in both clinical subtypes and anatomic sites of BCC. Selected findings, including those for occupational and total lifetime exposures to sunlight, suggest a few differences in etiological factors for BCC according to histotype and anatomic site.

## MATERIALS AND METHODS

The study was conducted within the framework of the Italian Group for Epidemiological Research in Dermatology (GISED). This group is a collaborative network of hospital-based dermatology and oncology centers in Italy. A total of 16 centers (nine in the North and seven in the South of the country) participated. During the period March 1995 through December 1996, consecutive patients with a new diagnosis of histologically confirmed BCC were asked to participate in the study. Cases with a previous diagnosis of BCC, assessed by a question on history of skin diseases, were excluded. Controls were patients admitted to the same hospitals with newly diagnosed acute conditions not related to neoplastic diseases (e.g., traumatic injuries) or for an elective procedure, which was not related to neoplastic diseases. Controls were age- and sex-matched to cases.

A total of 528 eligible cases and 512 controls entered the study. Fewer than 3% of cases and controls refused to participate. There were no important differences between participants and nonparticipants in terms of geographic origin, diagnoses, and age and sex distribution. Information on BCC in the case group is reported in Table 1. The median age was 65 years in both the case group (67 years for nodular and 63 years for superficial BCC; 66 years for head and neck and 61 years for truncal BCC) and the control group. Of the control series, 25% were admitted for traumatic conditions or acute orthopedic disorders, 21% had acute diseases of the digestive or genito-urinary system, 17% were admitted for acute infections, mainly respiratory, and 37% had miscellaneous other illnesses, such as disorders of the eye, ear, nose, throat, or teeth. The study was conducted in accordance with the Declaration of Helsinki Principles.

BCC was classified into superficial, nodular, and other varieties (e.g., morphoeic or sclerosing, and infiltrative), based on clinicopathological correlations and a standardized collection form by participating dermatologists. Superficial BCC was defined as a welldemarcated erythematous plaque, characterized, histologically, by multifocal buds of neoplastic basaloid cells emanating from the basal layer of the epidermis, peripheral palisading, and a mucinous stroma. Nodular BCC was defined as a dome-shaped papule or nodule, with teleangiectatic surface, sometimes crusted or ulcerated, exhibiting, on histological examination, large, well-defined masses of basaloid cells with obvious peripheral palisading and a mucinous stroma (Sexton *et al.*, 1990).

A standardized questionnaire was administered to both cases and controls by trained interviewers. Questions concerned personal habits (e.g., smoking), the lifetime history of sun exposure for recreational and occupational reasons, clothing while in the sun, exposure to nonsolar sources of ultraviolet radiation (e.g., sunbeds/ lamps, fluorescent lights), the pattern of reaction to sun exposure (i.e., whether the skin of the subject tended to tan after a sunburn episode), use of sunscreens, history of sunburns including the number and severity, exposure to ionizing radiation, past dermatologic complaints, excision of skin lesions, and family and personal history of selected tumors. Cases and controls were also examined by trained dermatologists who collected data on pigmentary traits, solar lentigo, actinic keratosis, and the number of melanocytic nevi equal to or greater than 2 mm in diameter on the upper arms. A simple instrument called a "nevometer" was used to assess the diameter (2 mm) (Naldi et al., 1992). Concordance of nevus counts among assessors and within each assessor in two independent trials was evaluated and judged to be satisfactory with both intra- and inter-observer intraclass correlation coefficients between 0.78 and 0.96. Skin color was evaluated by means of a three-grade scale (light, medium, and dark) based on comparison with representative sample photographs. Judgment on hair color was made on a sixcategory scale by asking for the natural hair color during teenage and at interview to evaluate the reliability of the answer. Judgment on eye color was made on a seven-category scale. Freckles were assessed by comparison with drawings showing schematic patterns and classified on a seven-category scale (from none to widespread).

Sunlight exposure history was collected by asking about occupational and recreational activities, including vacations. Each job lasting 6 months or more was entered in the lifetime occupational history. For each occupation, the usual number of hours per week of outdoor work in the periods from May to September and from October to April was recorded separately. The usual exposure of limbs and trunk to the sun was also recorded. Habitual recreational activities were also assessed in two separate periods, from May to September and from October to April. Information on the average number of days per week, weeks per month, and months per year spent in each activity and the number of years of duration of the activity was collected.

#### Data analysis

For each variable, we computed the ORs of BCC as estimates of relative risks and the corresponding 95% CI using unordered polytomous logistic regression models (Allison, 1999; Hosmer and Lemeshow, 2001), to allow a direct comparison between different clinico-pathologic subtypes and anatomic sites of BCC. We adjusted for potentially confounding factors, that were a priori identified as relevant for BCC in earlier studies (Naldi et al., 2000). The regression models always included terms for age (categorized in quinquennia, i.e. <50, 50–54, 55–59, 60–64, 65–69, 70–74, ≥75 years), sex, study center (Northern, Central and Southern Italy), education (<6, 6-9,  $\geq$  10 years), eye (four groups), hair (four groups) and skin color (three groups). Moreover, when the analyses were conducted on pigmentary traits, presence of selected pigmentary lesions, skin sensitivity to the sun and indicators of sun damage to the skin, further terms for freckles (no/yes), solar lentigines (no/yes), number of melanocytic nevi on upper limbs (none, 1–5,  $\geq$ 6), actinic and seborrheic keratosis (no/yes) were included in the models. When the analyses were conducted on family history of cancer, a term for number of siblings  $(0, 1-2, \ge 3)$  was added in the models.

#### **CONFLICT OF INTEREST**

The authors state no conflict of interest.

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