Research article  

**Occupation and skin cancer: the results of the HELIOS-I multicenter case-control study**  

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**Abstract**

**Background:** Non-melanoma skin cancer (NMSC) is the most frequent tumour among Caucasian populations worldwide. Among the risk factors associated with this tumour, there are host-related factors and several environmental agents. A greater likelihood of high exposure to physical agents (with the exception of solar radiation) and chemical agents depends on the work setting. Our objective is to evaluate the role of occupational exposures in NMSC, with special emphasis on risk factors other than solar radiation and skin type.

**Methods:** We analysed 1585 cases (1333 basal cell carcinoma (BCC) and 183 squamous cell carcinoma (SCC)) and 1507 controls drawn from the Helios-I multicenter study. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression mixed models.

**Results:** For NMSC as a whole (both histological types), miners and quarrymen, secondary education teachers, and masons registered excess risk, regardless of exposure to solar radiation and skin type (OR 7.04, 95% CI 2.44–20.31; OR 1.75, 95% CI 1.05–2.89 and OR 1.54, 95% CI 1.04–2.27, respectively). Frequency of BCC proved higher among railway engine drivers and firemen (OR 4.55; 95% CI 0.96–21.57), specialised farmers (OR 1.65; 95% CI 1.05–2.59) and salesmen (OR 3.02; 95% CI 1.05–2.86), in addition to miners and quarrymen and secondary education teachers (OR 7.96; 95% CI 2.72–23.23 and OR 1.76; 95% CI 1.05–2.94 respectively). The occupations that registered a higher risk of SCC (though not of BCC) were those involving direct contact with livestock, construction workers not elsewhere classified (OR 2.95, 95% CI 1.12–7.74), stationary engine and related equipment operators not elsewhere classified (OR 5.31, 95% CI 1.13–21.04) and masons (OR 2.55, 95% CI 1.36–4.78).

**Conclusion:** Exposure to hazardous air pollutants, arsenic, ionizing radiations and burns may explain a good part of the associations observed in this study. The Helios study affords an excellent opportunity for further in-depth study of physical and chemical agents and NMSC based on matrices of occupational exposure.
Background
Non-melanoma skin cancer is the most frequent tumour among Caucasian populations worldwide. Nevertheless, the study of its frequency poses difficulties. As one of the basic data sources for identification of cases in population cancer registries are hospital and pathology records, the fact that non-melanoma skin cancer is often not grounds for hospital admission may well lead to under-registration of cases. Furthermore, being a disease that can progress with few symptoms and is basically manifested in persons of advanced age, it may never be diagnosed. Cure rates stand at around 99% [1], with the result that it is a tumour to which relatively little attention is paid and is often not included among cancers targeted by population cancer registries. Variability in incidence rates is very marked, something that might in part be due to greater or lesser comprehensiveness of the case registry, as well as differences in risk among populations. The highest European incidence rates correspond to cancer registries in Ireland and Geneva (Switzerland), with rates close on 100 per 100,000 population [2]. In surveys conducted in Australia, annual incidence rates were estimated to exceed 1,000 per 100,000 population [3,4].

In all, 80–85% of non-melanoma skin cancers are basal cell carcinomas (BCC) and the remaining percentage are squamous cell carcinomas (SCC), with the latter being the more invasive of the two and underlying most of the deaths attributable to these tumours [5]. Both histologic types consistently register a positive relationship with exposure to solar ultraviolet (UV) radiation and an inverse relationship with the degree of skin pigmentation in the population [6], though differences nevertheless do exist between the two histologic types in terms of risk of presenting with cancer by type of exposure (brief-intense in basal cell, and prolonged-accumulated in squamous cell carcinomas) [7]. Among the risk factors associated with this tumor, there are host-related factors, such as skin pigmentation, precursor lesions (actinic keratosis or Bowen’s disease), genetic predisposition, and immunologic factors. Physical agents (ultraviolet and ionizing radiations) [8-11] and chemical agents (polycyclic aromatic hydrocarbons, arsenic, and nitrosamines) [12-15], as well as diet-related factors, viruses and the predisposition generated by certain traumas, burns and scars have been identified as environmental etiologic agents [16-18].

A greater likelihood of high exposure to physical agents (with the exception of solar radiation) and chemical agents depends on the work setting. Hence, this study sought to evaluate the role of occupational exposures in non-melanoma skin cancer, with special emphasis on risk factors other than solar radiation, using data drawn from the Helios-I multicenter study for the purpose [7,8]. Such additional factors are connected with exposures to environmental chemical substances (e.g., chimney soot, arsenic compounds, polycyclic hydrocarbons), chronic skin irritation, viral infections, and immune factors that can predispose to this type of cancer [19-23].

Methods
The Helios I study was a European multicenter case-control study. Its design is briefly outlined below, with a more detailed description to be found in the reference section [7,8]

Selection of cases
We included all cases of non-melanoma skin cancer registered from November 1989 through June 1993 in the following 6 European regions: Turin (north-west Italy); Ragusa (Sicily); Trento (North-East Italy); Villejuif and Créteil (Paris); Besançon (Franche-Comté, France); Murcia (south-east Spain); and Granada (Andalusia, Spain). In Turin, Ragusa, Besançon, Murcia and Granada, population cancer registers that covered a total population of 3.5 million were used as the case source. In these areas, all incident cases aged 20 to 70 years with diagnosis of BCC, SCC or skin carcinoma identified by the reporting systems, were deemed eligible. In Paris, case data were collected at two specialist centers, the Gustave-Roussy Institute in Villejuif and the Henri Mondor Hospital in Créteil. Dermatologists as well as general practitioners asked cases for their consent to being interviewed on lifestyle and health. In population-based centers, cases were interviewed at the dermatology clinic itself or at home, whereas at hospital-based centers, they were interviewed during their stay in hospital. Morphologic diagnoses were validated by a panel of pathologists who carried out a blind review of the biopsies [24].

Selection of controls
The group of controls was obtained by random sampling, duly stratified by age and sex, and conducted in the same regions in which the cases were recruited. The strata were proportional to the distribution of cases by age and sex. The sample was recruited on the basis of electoral censuses in Ragusa and Besançon and municipal rolls in Turin, Murcia and Granada. In the case of Paris, the controls were obtained by means of random sampling, based on hospital registers and excluding all patients with cancer or skin diseases. Controls were contacted by letter, and interviewed at home, in the workplace, or at the cancer registry. In the case of hospital controls, such interviews took place during their stay in hospital.

Assessment of exposure
Questionnaires were completed during an interview conducted by purpose-trained staff. A section of the questionnaire recorded information on participants’ work history, i.e., any job held during their lifetime with a minimum
duration of 6 months. They were asked about the type of work, the firm's activity, and the starting and finishing dates. In addition, this section included questions on outdoor work performed, hours per day and months worked in the periods May-September or October-April, whether subjects worked partly unclothed, whether they wore a head covering and, lastly, whether they wore socks or stockings during work done in summer. Another sections reported on participants' use of leisure time, and on their phenotype characteristics.

Occupations were classified and coded according to the International Standard Classification of Occupations (ISCO) [25]. Analyses were performed for 10 major occupational groups, defined by the first of the four digits code, and for occupations defined by the first three digits of the code. We selected a total of 157 three-digit occupations having a minimum of five exposed individuals with at least one case and one control.

Insofar as the "exposure to sun" variable was concerned, this was measured on a continuous scale, as total hours, in terms of solar exposure during vacations and during outdoor work, weighted and not weighted by season of exposure (on average, solar irradiation in summer is double that in winter). Quartiles were calculated and the "exposure to sun" variable categorized on this basis. A complete explanation of sun exposure recording can be consulted on Rosso et al. [7].

In addition, the models also included variables that had proven to be independent risk indicators in previous analyses [7,8,26], namely: color of eyes; natural hair color at age 20 years; and reaction of skin to solar exposure (history of sunburn). References to "phenotype" in the text are to these three components.

In the analysis, we assessed the effect of occupation on appearance of basal cell and squamous cell carcinomas, considered jointly and singly. ORs and their 95% confidence intervals (CI) were calculated using unconditional logistic regression mixed models. In a first analysis, estimates were adjusted for age and sex (variables matched by frequency), with exposure to solar radiation and phenotype being added subsequently. Center/town was included as a random effects term in all analyses [27].

At the time the study has been conducted ethical approval was not required for epidemiological studies in none of the involved countries. Written consent was obtained from every recruited subject, in order to both analyzing the data acquired and accessing the relevant diagnostic documents (e.g. pathology reports).

Results

The participation rate, as described elsewhere [8] was 85.8% among cases and 69.3% among controls. For this analysis, we included 3092 participants, with 1585 cases and 1507 controls. We excluded 297 cases and 288 controls since information on occupation was not available. Among the cases, 1333 presented with basal cell, and 183 with squamous cell carcinoma. Mean age was 60.5 years for cases and 58.2 years for controls. A total of 63% of cases and 62% of controls were men. Shown in Table 1 is the breakdown of the study by participant region, from which it will be seen that Turin was the region with the greatest contribution to the study, followed by Granada, Murcia and Besançon.

Table 2 shows the results of the analysis by major occupational group, defined by the first digit of the ISCO code, for: a) all cases; b) basal cell carcinomas; and, c) squamous cell carcinomas. Two effect estimates are shown, one adjusted for age and sex, and the other additionally adjusted for solar exposure and phenotype. Both estimates are adjusted for center as a random effects term (amounting to a conservative constraint). The analysis by major group yielded no statistically significant associa-
Table 2: Effect of occupation (major groups) on non-melanoma skin cancers. OR and 95% confidence intervals. Estimates adjusted for a) age group, sex and center; b) age group, sex, exposure to sun, skin type and center. All cases, basal cell and squamous cell

| Occupation                                    | Exp | No exp | OR  | 95% CI     | OR  | 95% CI     |
|-----------------------------------------------|-----|--------|-----|------------|-----|------------|
| Physical scientists, architects and engineers, biological and health scientists, mathematicians and economists | Cases 129 | 1455 | 1.28 | 0.98–1.69 | 1.21 | 0.91–1.62 |
| Accountants, jurists, teachers, writers and artists | Cases 185 | 1400 | 1.13 | 0.90–1.41 | 1.11 | 0.88–1.40 |
| Administrative and managerial workers         | Cases 60 | 1524 | 1.32 | 0.88–1.97 | 1.30 | 0.86–1.96 |
| Clerical and related workers                  | Cases 287 | 1295 | 0.93 | 0.77–1.11 | 0.88 | 0.73–1.07 |
| Sales workers                                 | Cases 176 | 1406 | 0.90 | 0.72–1.13 | 0.89 | 0.71–1.11 |
| Service workers                               | Cases 283 | 1302 | 0.85 | 0.71–1.02 | 0.85 | 0.71–1.02 |
| Agriculture, animal husbandry and fishermen   | Cases 486 | 1097 | 1.06 | 0.91–1.25 | 1.18 | 0.96–1.45 |
| Miners, metalworker, woodworkers, chemical workers | Cases 288 | 1297 | 1.08 | 0.90–1.30 | 1.12 | 0.93–1.35 |
| Leather workers, welders, electricians and glass workers | Cases 289 | 1295 | 0.91 | 0.76–1.10 | 0.90 | 0.74–1.08 |
| Rubber workers, graphic artists, painters, builders, transport workers | Cases 431 | 1153 | 1.08 | 0.91–1.28 | 1.10 | 0.93–1.31 |
| Physical scientists, architects and engineers, biological and health scientists, mathematicians and economists | Cases 115 | 1217 | 1.38 | 1.04–1.83 | 1.26 | 0.94–1.69 |
| Accountants, jurists, teachers, writers and artists | Cases 152 | 1181 | 1.10 | 0.87–1.40 | 1.07 | 0.84–1.37 |
| Administrative and managerial workers         | Cases 50 | 1282 | 1.35 | 0.89–2.05 | 1.31 | 0.85–2.01 |
| Clerical and related workers                  | Cases 43 | 1464 | 0.97 | 0.80–1.17 | 0.90 | 0.74–1.10 |
| Sales workers                                 | Cases 253 | 1077 | 0.98 | 0.78–1.22 | 0.96 | 0.76–1.21 |
| Service workers                               | Cases 246 | 1087 | 0.88 | 0.73–1.06 | 0.88 | 0.73–1.07 |
| Agriculture, animal husbandry and fishermen   | Cases 394 | 939 | 1.04 | 0.88–1.23 | 1.21 | 0.97–1.50 |
tion, save for group 0 (professional, technical and related workers) in the case of basal cell carcinomas. However, this association became attenuated after adjustment for solar exposure and phenotype, and failed to attain significance. In the case of squamous cell carcinomas, the groups classified as clerical and related workers and sales workers registered a significantly lower risk than did the remaining occupations.

Tables 3 and 4 show the analysis for the three-digit occupations. We analyzed a total of 157 occupations that had a minimum number of exposed subjects, but Table 3 only lists the results of occupations that displayed statistical significance and/or an OR of 2 or higher.

### All Tumours (Table 3)

For the two histologic types taken jointly, the occupations that displayed an association with the disease were "Secondary education teachers" (OR 1.75, 95%CI 1.05–2.89,

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**Table 2: Effect of occupation (major groups) on non-melanoma skin cancers. OR and 95% confidence intervals. Estimates adjusted for a) age group, sex and center; b) age group, sex, exposure to sun, skin type and center. All cases, basal cell and squamous cell (Continued)**

| Occupation                                      | Controls | Cases | **Exp** | **No Exp** |
|------------------------------------------------|----------|-------|---------|------------|
| Miners, metalworker, woodworkers, chemical workers | 436      | 1069  |         |            |
| Cases                                           | 246      | 1087  | 1.10    | 0.90–1.33  |
|                                                 |          |       |         | 1.14       |
|                                                 |          |       |         | 0.93–1.39  |
| Leather workers, welders, electricians and glass workers | 258      | 1248  |         |            |
| Cases                                           | 250      | 1083  | 0.96    | 0.79–1.16  |
|                                                 |          |       |         | 0.93       |
|                                                 |          |       |         | 0.76–1.13  |
| Rubber workers, graphic artists, painters, builders, transport workers | 295      | 1211  |         |            |
| Cases                                           | 353      | 980   | 1.07    | 0.90–1.27  |
|                                                 |          |       |         | 1.10       |
|                                                 |          |       |         | 0.92–1.32  |
| Controls                                        | 387      | 1118  |         |            |

**SQUAMOUS CELL**

| Occupation                                      | Controls | Cases | **Exp** | **No Exp** |
|------------------------------------------------|----------|-------|---------|------------|
| Physical scientists, architects and engineers, biological and health scientists, mathematicians and economists | 98       | 1407  |         |            |
| Cases                                           | 16       | 167   | 0.81    | 0.46–1.43  |
|                                                 |          |       |         | 0.80       |
|                                                 |          |       |         | 0.43–1.48  |
| Accountants, jurists, teachers, writers and artists | 158      | 1349  |         |            |
| Cases                                           | 8        | 175   | 1.27    | 0.59–2.77  |
|                                                 |          |       |         | 1.43       |
|                                                 |          |       |         | 0.61–3.32  |
| Administrative and managerial workers            | 43       | 1464  |         |            |
| Cases                                           | 19       | 164   | 0.55    | 0.34–0.90  |
|                                                 |          |       |         | 0.58       |
|                                                 |          |       |         | 0.34–0.99  |
| Clerical and related workers                     | 292      | 1212  |         |            |
| Cases                                           | 12       | 170   | 0.48    | 0.26–0.88  |
|                                                 |          |       |         | 0.48       |
|                                                 |          |       |         | 0.25–0.92  |
| Sales workers                                    | 185      | 1321  |         |            |
| Cases                                           | 24       | 159   | 0.66    | 0.42–1.02  |
|                                                 |          |       |         | 0.65       |
|                                                 |          |       |         | 0.40–1.03  |
| Service workers                                  | 308      | 1196  |         |            |
| Cases                                           | 75       | 106   | 1.34    | 0.95–1.89  |
|                                                 |          |       |         | 1.00       |
|                                                 |          |       |         | 0.65–1.54  |
| Agriculture, animal husbandry and fishermen      | 436      | 1069  |         |            |
| Cases                                           | 30       | 153   | 1.01    | 0.67–1.53  |
|                                                 |          |       |         | 1.13       |
|                                                 |          |       |         | 0.73–1.75  |
| Miners, metalworker, woodworkers, chemical workers | 258      | 1248  |         |            |
| Cases                                           | 30       | 152   | 0.72    | 0.47–1.10  |
|                                                 |          |       |         | 0.79       |
|                                                 |          |       |         | 0.51–1.23  |
| Leather workers, welders, electricians and glass workers | 295      | 1211  |         |            |
| Cases                                           | 62       | 120   | 1.21    | 0.87–1.69  |
|                                                 |          |       |         | 1.19       |
|                                                 |          |       |         | 0.83–1.70  |
| Controls                                        | 387      | 1118  |         |            |
### Table 3: Non-melanoma skin cancer. OR and 95% confidence intervals associated with selected occupations*

| Code | ISCO | Exp | No Exp | Exp | No Exp | OR  | 95% CI | OR  | 95% CI | OR  | 95% CI |
|------|------|-----|--------|-----|--------|-----|--------|-----|--------|-----|--------|
| 034  | Engineering Technicians | 6   | 1579   | 3   | 1504   | 1.90| 0.47–7.60| 1.86| 0.46–7.49| 2.07| 0.51–8.44 |
| 067  | Pharmacist | 2   | 1505   | 2.88| 0.58–14.36| 2.81| 0.56–14.02| 2.82| 0.55–14.43 |
| 132  | Secondary Education Teachers | 25  | 1482   | 1.80| 1.10–2.95| 1.78| 1.08–2.92| 1.75| 1.05–2.89 |
| 193  | Social Workers | 6   | 1579   | 3   | 1504   | 1.90| 0.47–7.60| 1.86| 0.46–7.49| 2.07| 0.51–8.44 |
| 212  | Factory Managers | 9   | 1576   | 4.37| 0.94–20.33| 4.24| 0.91–19.74| 3.46| 0.73–16.33 |
| 342  | Computer Operators | 7   | 1578   | 2   | 1505   | 3.52| 0.73–17.01| 3.46| 0.71–16.77| 3.07| 0.62–15.22 |
| 399  | Clerks n.e.c. | 6   | 1579   | 3   | 1504   | 1.97| 0.49–7.93| 1.96| 0.49–7.86| 2.08| 0.50–8.59 |
| 531  | Building Caretakers | 8   | 1577   | 2   | 1505   | 2.47| 0.48–12.79| 2.41| 0.46–12.47| 2.82| 0.55–14.43 |
| 551  | Cooks | 5   | 1580   | 2   | 1505   | 2.81| 0.58–14.36| 2.81| 0.56–14.02| 2.82| 0.55–14.43 |
| 612  | Specialized Farmers | 6   | 1579   | 3   | 1504   | 1.97| 0.49–7.93| 1.96| 0.49–7.86| 2.08| 0.50–8.59 |
| 711  | Miners and Quarrymen | 13  | 1572   | 5   | 1502   | 6.86| 2.40–19.6| 7.07| 2.47–20.24| 7.04| 2.44–20.31 |
| 728  | Galvanizers | 11  | 1574   | 4   | 1503   | 2.60| 0.82–8.20| 2.58| 0.82–8.16| 2.91| 0.91–9.25 |
| 749  | Chemical Workers | 5   | 1580   | 1   | 1506   | 4.58| 0.53–45.9| 4.51| 0.51–45.8| 4.51| 0.51–45.8 |
| 773  | Butchers and Meat Preparers | 8   | 1577   | 17  | 1489   | 0.45| 0.19–1.04| 0.44| 0.19–1.04| 0.41| 0.17–0.97 |
| 811  | Cabinetmakers | 3   | 1582   | 10  | 1497   | 0.28| 0.08–1.02| 0.28| 0.08–1.02| 0.27| 0.07–0.99 |
| 855  | Electricians | 9   | 1576   | 20  | 1487   | 0.42| 0.19–0.94| 0.42| 0.19–0.93| 0.38| 0.17–0.85 |
| 926  | Bookbinders | 7   | 1578   | 3   | 1504   | 2.26| 0.58–8.77| 2.26| 0.58–8.77| 2.12| 0.53–8.46 |
| 951  | Masons | 69  | 1516   | 47  | 1460   | 1.42| 0.97–2.08| 1.44| 0.98–2.13| 1.54| 1.04–2.27 |
| 983  | Railway Engine Drivers and Firemen | 10  | 1575   | 2   | 1505   | 4.55| 0.99–20.89| 4.49| 0.98–20.62| 4.14| 0.89–19.29 |
| 999  | Laborers n.e.c. | 122 | 1463   | 90  | 1417   | 1.32| 0.99–1.76| 1.34| 1.00–1.80| 1.37| 1.02–1.85 |

* Criterion: OR>2 or statistically significant OR (lower limit of OR adjusted for age, sex, exposure to sun and skin type ≥ 0.9 or upper limit <1).

For BCC, excess risk was located in "Secondary education teachers" (OR 1.76, 95%CI 1.05–2.94, p-value = 0.03), "Sales Engineers" (OR 3.02; 95%CI 1.05–8.66, p-value = 0.04), "Specialized farmers" (OR 1.65, 95%CI 1.05–2.59, p-value = 0.03), "Miners and Quarrymen" (OR 7.96, 95%CI 2.72–23.23, p-value = 0.0002) and "Laborers" (OR 1.39, 95%CI 1.01–1.89, p-value = 0.04). "Railway Engine Drivers and Firemen" registered a significant increase in risk (OR 5.08, 95%CI 1.09–23.65), which subsequently lost significance on adjustment for sun and phenotype. The protective effect encompassed "Cooks", "Building Caretakers", and "Butchers and Meat Preparers".

### Basal cell carcinomas (Table 4)

For BCC, excess risk was located in "Secondary education teachers" (OR 1.76, 95%CI 1.05–2.94, p-value = 0.03), "Sales Engineers" (OR 3.02; 95%CI 1.05–8.66, p-value = 0.04), "Specialized farmers" (OR 1.65, 95%CI 1.05–2.59, p-value = 0.03), "Miners and Quarrymen" (OR 7.96, 95%CI 2.72–23.23, p-value = 0.0002) and "Laborers" (OR 1.39, 95%CI 1.01–1.89, p-value = 0.04). "Railway Engine Drivers and Firemen" registered a significant increase in risk (OR 5.08, 95%CI 1.09–23.65), which subsequently lost significance on adjustment for sun and phenotype. The protective effect encompassed "Cooks", "Building Caretakers", and "Butchers and Meat Preparers".

### Squamous cell carcinomas (Table 4)

For SCC, the highest risk was detected in the occupations of "Construction worker" (OR 2.95, 95%CI 1.12–7.74, p-value = 0.03), "Miners and Quarrymen" (OR 7.96, 95%CI 2.72–23.23, p-value = 0.0002) and "Laborers" (OR 1.39, 95%CI 1.01–1.89, p-value = 0.04). "Railway Engine Drivers and Firemen" registered a significant increase in risk (OR 5.08, 95%CI 1.09–23.65), which subsequently lost significance on adjustment for sun and phenotype. The protective effect encompassed "Cooks", "Building Caretakers", and "Butchers and Meat Preparers".
Table 4: Basal cell (BCC) and squamous cell carcinoma (SCC). OR and 95% confidence intervals associated with each occupation

| CODE | ISCO          | BASAL CELL | SQUAMOUS CELL |
|------|---------------|------------|---------------|
|      |               | Controls BCC | Adjusted | SCC | Adjusted | Adjusted |
|      |               |             | for age | for age, | for age, | for age, |
|      |               |             | and sex | sex, | exposure to sun, | exposure to sun, |
|      |               |             |         | exposure to sun, | and phenotype | and phenotype |
|      |               | Exp | Exp | OR | 95% CI | OR | 95% CI | Exp | OR | 95% CI | OR | 95% CI |
| 023  | Electrical Engineer's | 3 | 4 | 1.50 | 0.34 – 6.74 | 1.10 | 0.24 – 5.05 |
| 033  | Surveyor's Assistant's | 4 | 2 | 0.58 | 0.11 – 3.18 | 0.46 | 0.08 – 2.64 |
| 039  | Engineer's Aides | 5 | 2 | 0.46 | 0.09 – 2.38 | 0.45 | 0.08 – 2.36 |
| 067  | Pharmacists | 2 | 4 | 2.17 | 0.39 – 11.89 | 1.98 | 0.34 – 11.44 |
| 111  | Professio nal Accountants | 42 | 34 | 0.92 | 0.58 – 1.48 | 0.99 | 0.61 – 1.60 |
| 132  | Secondary Educatio n Teachers | 25 | 41 | **1.88** | **1.13 – 3.11** | **1.76** | **1.05 – 2.94** |
| 133  | Teacher, Primary Teacher's | 36 | 28 | 0.86 | 0.52 – 1.43 | 0.79 | 0.47 – 1.32 |
| 139  | Teacher's n.e.c. | 7 | 7 | 1.14 | 0.40 – 3.26 | 0.96 | 0.33 – 2.79 |
| 193  | Social Workers | 2 | 5 | 2.87 | 0.55 – 14.86 | 2.45 | 0.46 – 13.24 |
| 202  | Memb Legislative Bodies, high civil servants | 2 | 2 | 1.13 | 0.16 – 8.05 | 1.25 | 0.17 – 9.06 |
| 211  | General Managers | 12 | 12 | 1.15 | 0.51 – 2.57 | 1.16 | 0.51 – 2.65 |
| 212  | Factory Managers | 2 | 8 | 4.68 | 0.99 – 22.16 | 3.52 | 0.73 – 16.92 |
| 219  | Manager's n.e.c. | 25 | 22 | 1.01 | 0.56 – 1.80 | 0.94 | 0.52 – 1.71 |
| 321  | Secretaries, Typists, Stenographers | 29 | 31 | 1.21 | 0.72 – 2.03 | 1.05 | 0.62 – 1.79 |
| 331  | Bookkeepers, Cashiers | 62 | 52 | 0.93 | 0.64 – 1.36 | 0.85 | 0.58 – 1.26 |

Note: Bold indicates statistically significant ORs.
| Occupation               | OR   | 95% CI Lower | 95% CI Upper | Estimate | 95% CI Lower | 95% CI Upper |
|-------------------------|------|--------------|--------------|---------|--------------|--------------|
| Financial Clerks        | 339  | 0.57 - 2.07  | 0.98 - 1.88  | 1       | 0.48 - 0.77  | 0.57 - 2.07  |
| Computer Operators      | 342  | 0.82 - 2.77  | 0.66 - 1.88  | 1       | 0.48 - 0.77  | 0.57 - 2.07  |
| Mail Distribution on Clerks | 370  | 0.34 - 1.19  | 0.33 - 1.18  | 2       | 0.58 - 0.99  | 0.6 - 2.39   |
| Stokers Attendants      | 391  | 0.49 - 1.86  | 0.42 - 1.66  | 4       | 1.69 - 1.95  | 0.62 - 6.14  |
| Clerks Clarks n.e.c.    | 393  | 0.77 - 1.44  | 0.73 - 1.41  | 8       | 0.95 - 1.91  | 0.45 - 2.00  |
| Clerks n.e.c.           | 399  | 0.58 - 1.06  | 0.59 - 1.05  | 6       | 0.69 - 1.22  | 0.27 - 1.76  |
| Shop Keepers            | 410  | 0.47 - 1.06  | 0.46 - 1.05  | 6       | 0.69 - 1.22  | 0.27 - 1.76  |
| Sales Managers          | 421  | 0.81 - 8.58  | 0.69 - 7.50  | 0       | -            | -            |
| Sales Engineers         | 431  | 1.07 - 8.49  | 1.05 - 8.66  | 0       | -            | -            |
| Traveling Salesmen      | 432  | 0.95 - 1.68  | 0.92 - 1.59  | 4       | 1.37 - 1.74  | 0.49 - 1.91  |
| Sales Clerks            | 451  | 0.67 - 1.35  | 0.64 - 1.31  | 3       | 0.41 - 1.32  | 0.13 - 1.30  |
| News Vendors            | 452  | 0.50 - 1.58  | 0.48 - 1.57  | 2       | 0.56 - 1.48  | 0.14 - 0.81  |
| Bar, Hotel Managers     | 500  | 0.77 - 1.83  | 0.77 - 1.86  | 3       | 0.73 - 1.87  | 0.29 - 2.43  |
| Restaurant Owners       | 510  | 0.31 - 1.27  | 0.32 - 1.35  | 2       | 0.92 - 1.26  | 0.22 - 4.92  |
| Cooks                   | 531  | 0.36 - 0.81  | 0.39 - 0.87  | 0       | -            | -            |
| Waiters                 | 532  | 0.63 - 1.87  | 0.59 - 1.80  | 4       | 1.37 - 1.94  | 0.47 - 3.98  |
| Service Workers         | 540  | 0.52 - 1.21  | 0.53 - 1.26  | 1       | 0.31 - 1.46  | 0.04 - 2.16  |
| Building Caretakers     | 551  | 0.23 - 1.03  | 0.22 - 0.99  | 1       | 0.38 - 1.05  | 0.05 - 2.16  |
| Charworkers             | 552  | 0.76 - 1.66  | 0.79 - 1.74  | 2       | 0.61 - 0.71  | 0.15 - 3.10  |
| Laundriers              | 560  | 0.32 - 2.37  | 0.36 - 2.70  | 1       | 1.38 - 4.24  | 0.17 - 18.49 |
| Hairdressers, barbers, etc. | 570  | 0.23 - 1.22  | 0.22 - 1.23  | 0       | -            | -            |
| Memb. Armed Forces n.e.c. | 580  | 0.60 - 1.66  | 0.56 - 1.60  | 5       | 0.91 - 3.04  | 0.34 - 2.52  |
| Policemen               | 582  | 0.40 - 1.32  | 0.36 - 1.22  | 2       | 0.45 - 1.18  | 0.11 - 3.56  |
| Protective Service Workers | 589  | 0.68 - 2.82  | 0.66 - 2.82  | 3       | 1.16 - 2.00  | 0.33 - 4.00  |
| Other service workers   | 599  | 0.75 - 2.50  | 0.71 - 2.42  | 1       | 0.48 - 2.00  | 0.07 - 3.47  |
| General Farmers         | 611  | 0.63 - 1.23  | 0.65 - 1.32  | 2       | 1.76 - 1.95  | 1.04 - 2.55  |
| Specialized Farmers     | 612  | 0.99 - 2.39  | 1.05 - 2.69  | 7       | 1.06 - 2.06  | 0.46 - 2.35  |
| General Farm Workers    | 621  | 0.76 - 1.14  | 0.83 - 1.31  | 37      | 0.94 - 1.22  | 0.63 - 1.94  |
| Field Crop Workers      | 622  | 0.70 - 1.17  | 0.72 - 1.79  | 4       | 0.74 - 1.91  | 0.26 - 3.08  |
| Palmwine Harvesters     | 623  | 0.67 - 1.97  | 0.67 - 2.01  | 6       | 1.35 - 1.94  | 0.33 - 1.68  |
| Livestock Workers       | 624  | 0.52 - 1.35  | 0.54 - 1.44  | 14      | 2.11 - 1.11  | 1.11 - 1.58  |
| Makers                 | 625  | 0.50 - 2.68  | 0.49 - 2.77  | 5       | 3.64 - 2.26  | 0.57 - 10.83 |
| Foremen                | 700  | 0.64 - 1.91  | 0.61 - 1.89  | 2       | 0.47 - 1.19  | 0.11 - 2.95  |
| Code | Occupation                        | Workers | Cases | OR     | 95% CI Lower | 95% CI Upper | P | OR   | 95% CI Lower | 95% CI Upper | P |
|------|-----------------------------------|---------|------|--------|-------------|-------------|---|------|-------------|-------------|---|
| 728  | Galvinizers                       | 8       | 2    | 8.17   | 2.53 – 33.69| 1.03 – 27.83| .03| .14  | 1.03 – 27.83| 1.03 – 27.83| .03|
| 729  | Metal Processors                  | 8       | 1    | 8.70   | 2.65 – 38.70| 1.05 – 29.75| .03| .17  | 1.05 – 29.75| 1.05 – 29.75| .03|
| 749  | Chemical Workers                  | 4       | 1    | 1.46   | 0.46 – 7.29 | 0.01 – 9.03 | .96| .53  | 0.01 – 9.03 | 0.01 – 9.03 | .96|
| 773  | Butchers and Meat Preparers       | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 774  | Cashiers                          | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 776  | Confectionery Makers              | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 791  | Tailors and Dressmakers           | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 795  | Sewing Machine Operators          | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 796  | Upholsterers                      | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 832  | Tool and Die Makers               | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 834  | Machine Operators in Factory      | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 845  | Machinists or Fitters             | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 846  | Instrumakers                      | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 849  | Machinists, fitters, machine assem blers and precision instrument makers | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 855  | Electricians                       | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 872  | Welders                           | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 873  | Sheet-Metal Workers               | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 874  | Structural Steel Workers          | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 892  | Potters                           | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 902  | Tire Makers and Vulcanizers       | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 910  | Paper and paperboard product makers | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 922  | Printing Pressmen                 | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 926  | Bookbinders                       | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 931  | Painters, Construction            | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 942  | Basketweavers                     | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 951  | Masons                            | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|
| 954  | Carpenters                        | 4       | 1    | 1.58   | 0.50 – 7.88 | 0.02 – 9.70 | .96| .50  | 0.02 – 9.70 | 0.02 – 9.70 | .96|

**Table 4: Basal cell (BCC) and squamous cell carcinoma (SCC).** OR and 95% confidence intervals associated with each occupation.
value = 0.03), "Stationary engine and related equipment operators" (OR 5.31, 95%CI 1.34–21.04, p-value = 0.02) and "Mason" (OR 2.55, 95%CI 1.36–4.78, p-value = 0.03, p-value = 0.004). In the case of "General farmers" (OR 1.76, 95%CI 1.04–2.98), "Livestock Workers" (OR 2.11, 95%CI 1.11–4.03), "Milkers" (OR 3.64, 95%CI 1.22–10.83) and "Miners and Quarrymen" (OR 4.98, 95%CI 1.23–20.18), there was an increase in risk on adjustment for age and sex, yet this rise in risk ceased to be significant when adjustment was subsequently made for solar exposure and phenotype. We detected no occupation with risk less than expected.

In the analysis of the three-digit occupations by center, the excess risk in miners was concentrated in Murcia, a province that accounted for 50% of all cases exposed, with an adjusted OR of 7.85 (95%CI, 1.57–39.26) among men. A possible high risk was also detected in Granada and Turin, but given the low frequency of this occupation, there was no exposed control in each case. Analysis of miners by time of exposure yielded an OR of 3.62 (95%CI 1.01–13.16) for those who had worked as miners for less than 5 years, and 15.89 (95%CI 2.10–120.35) for those who had worked for 5 years or more (trend p-value 0.0008).

Dose-response analysis by time of exposure (no exposed, <5 years and 5 or more) for secondary education teachers, for masons and for laborers was statistically significant (trend p-value 0.01, 0.03 and 0.03 respectively).

In Besançon, the association was observed for secondary education teachers, with a risk of developing non-melanoma skin carcinoma of 3.23 (95%CI 1.02–10.23). Another center in which significant results were observed was Turin, with an OR -in this instance protective- of 0.10 (95%CI 0.01–0.76) for cooks.

### Discussion

This study analyzes the association between non-melanoma skin cancer and ISCO-coded occupations. Analysis of the major occupational groups showed that, in the context of basal cell carcinoma, professionals and technicians have an increased risk of developing this type of cancer. When all occupations and both histologic types were analyzed jointly, miners and quarrymen, secondary education teachers and masons registered excess risk. Separate analysis of the results by type showed a higher risk of basal cell carcinoma for railway engine drivers and firemen, farmers and salesmen, in addition to the above three occupations. The occupations that registered a higher risk of SCC were those involving direct contact with livestock, and the groups encompassing other construction workers not elsewhere classified (ISCO: 959) and stationary engine and related equipment operators not elsewhere classified (ISCO: 969).

This study include all incident cases registered in five of the participating centers that account for the 88% of the cases. This design prevent the existence bias based on occupational recruitment patterns. However, one possible source of bias could be the different population bases of the control sample; although a certain degree of distortion cannot be completely ruled out, consistency among centers was checked [8] and the country proved to be a stronger confounder than study design (hospital or population basis).

Multicenter studies such as this are an example of the indication of the use of mixed models. These models take the covariance structure or interdependence of data (characteristics not registered at each study center) into account, whereas fixed effects models assume that all observations are independent. The ensuing estimates and standard
errors may possibly be more conservative, but the inferences that can be drawn from the results are wider.

A major problem of this type of exploratory study is that a large number of studied associations could produce some spurious significant results, the so-called mass-significance phenomenon. In order to deal with the problem of multiple comparisons, p-values are provided in results section. The number of statistically significant associations found exceed very little the results expected by chance, but we consider that these results in addition to the dose-response effect with exposure time for some of the occupations, could stimulate the research about the influence of occupational exposures on this tumours.

One of the aims of this analysis was to assess the risk due to exposures other than solar radiation, yet adjustment for solar radiation and phenotype did not substantially modify the effect estimates (Tables 3 and 4). Some of the associations detected were in outdoor occupations (construction workers or farmers); exposure to sun is inherent in such occupations and may thus account for the fact that adjustment has scant influence on the result. However, in the case of other occupations for which an effect was detected, such as mining, possible explanations must be sought elsewhere.

Relatively few studies have addressed occupation and exposures other than solar radiation, in the case of these tumours. In NMSC, the role of exposure to various chemical substances has been reported. Elevated risks of squamous cell carcinoma have been detected among subjects exposed to pesticides and by-products of petroleum, lubricants and other substances. In the case of basal cell carcinoma, higher risks have also been documented in subjects exposed to fiberglass dust and dry-cleaning agents [15], though stress has nonetheless been laid on the greater importance of exposure to arsenic versus other chemical substances in the etiology of these tumours [28].

It has also been reported that 2% of such tumours could be associated with exposure to radon in the UK [29]. The results of our study show a strong association between the occupation of miner and both histologic types of NMSC, with the strength of association for BCC being double that for SCC. The explanation for this result might partly lie in the above-mentioned exposure to radon in the case of BCC [30], and possibly lie in exposure to arsenic in the case of SCC [13,28]. However, a rise in risk of precancerous skin lesions has been reported among workers in open-work lignite mines, a finding that could be attributable to the long-term increase in the risk of skin cancer [31]. The OR estimations shown wide confidence intervals, reflecting some data instability and we can not discard the effect of uncontrolled confounders.

Although this type of cancer has not been shown to be more frequent in specific social groups [32], the association between NMSC and ionizing radiations has indeed been described on a number of occasions [33-36] and is reputedly greater with BCC than with SCC [29,34]. Occupational exposure to UV radiation among outdoor workers has a direct relationship with the appearance of these types of tumours [37-40]. In our study, farmers/animal husbandry workers were observed to register an increased risk of developing both BCC and SCC, despite our efforts to adjust for exposure to solar radiation. It is well known, however, that farmers suffer from multiple exposures [41], ranging from pesticides to hazardous air pollutants (HAPs), due to their use of different types of machinery and plants. The raised risk of basal cell carcinoma among railway engine drivers and firemen has been reported in other studies [19]. Though somewhat rare, it is acknowledged that occupational skin cancer can appear in the case of scars formed as a consequence of industrial burns [21].

The results show that the possible confounding effect generated by such solar exposure is very small, since OR magnitudes varied very little after this variable was adjusted for. Phenotype likewise failed to modify risk levels, with adjustment for it leading to no important variations vis-à-vis the crude effect. Moreover, we do not know the magnitude of the residual confounding effect of solar exposure. However, our questionnaire, for skin characteristics measurements and reported sun exposure history, received a validation study and there was a good reproducibility [42].

Among workers in direct contact with livestock, risk is apparently higher for SCC. Although there is a slight possibility of false diagnoses of SCC in the case of viral warts, such a problem would seem unlikely, in view of the fact that the cases were reviewed by a panel of pathologists who verified the diagnoses. These results evinced a high degree of concordance (99.5%), with a Kappa index (KI) of 0.85 (95%CI 0.77–0.94) in the assessment of the degree of concordance (99.5%), with a Kappa index (KI) of 0.85 (95%CI 0.77–0.94) in the assessment of the differentiation of major morphologic groups, BCC and SCC was also high (KI = 0.85; 95%CI 0.82–0.89) [24]. There is limited evidence in humans for the carcinogenicity of HPV genus-beta types in skin (squamous-cell carcinoma). In the rare case of patients with epidermodysplasia verruciformis, there is compelling evidence for the carcinogenicity of HPV genus-beta types 5 and 8 in skin (squamous-cell carcinoma)[43].

**Conclusion**

This study shows the association between non-melanoma skin cancer and certain occupations. For NMSC as a whole (both histologic types), miners and quarrymen, secondary education teachers, and masons register excess risk,
regardless of exposure to solar radiation and phenotype. BCC proves more frequent among railway engine drivers and firemen, farmers and salesmen, in addition to the above-mentioned 3 occupations. The occupations that register a higher risk of SCC (though not of BCC) are those involving direct contact with livestock, other construction workers not elsewhere classified and stationary engine and related equipment operators not elsewhere classified. Exposure to HAPs, arsenic, ionizing radiations and burns might well explain a good part of the associations observed in this study. The Helios Project affords an excellent opportunity for further in-depth study based on matrices of occupational exposure.

Competing interests
The author(s) declare that they have no competing interests.

Authors' contributions
BS and GLA performed the statistical analysis and wrote the first draft of the manuscript to which all authors subsequently contributed. RZ, SR, CM, CN, MJH, HSG, JW, LG, SS were responsible for the development of intellectual content and the multicenter study design and conducting. All authors made contribution to statistical analyses and interpretation of results, and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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