British Journal of Cancer (1996) 73, 1440-1446

The multicentre south European study '*Helios*' I: skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin

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Summary The aim of this study was to investigate constitutional and environmental determinants of non-melanocytic skin cancer among different populations from south Europe. Between 1989 and 1993 we interviewed incident cases and a random population sample of controls from five centres where a cancer registry was operating, whereas we selected a sample of hospital-based cases and controls from three other centres. Controls were stratified according to the age and sex distribution of cases. In all, 1549 cases of basal cell carcinoma (BCC), 228 of squamous cell carcinoma (SCC) and 1795 controls were interviewed. Both cancers affected primarily sun-exposed sites such as face, head and neck, but the prevalence of BCC on the trunk was higher than for SCC. Pigmentary traits such as hair and eye colour as well as tendency to sunburn were strong and independent indicators of risk for both BCC and SCC. In SCC, adjusted odds ratios (ORs) ranged from 1.6 for fair hair colour to 12.5 for red hair. Light-blonde hair entailed a risk of about 2 for BCC. Pale eye colour was associated with a risk of 1.8 for SCC and 1.4 for BCC. Subjects who always burn and never tan showed an adjusted OR of 2.7 for BCC and 2.0 for SCC. A history of sunburns and a young age at first sunburn were associated with an increased risk for BCC only (OR 1.7). Pigmentary traits and sun sensitivity of the skin confirmed their role as risk indicators. The effect of sunburns, as an indicator of both exposure and sun sensitivity of the skin, is less clear. Nevertheless, its association with BCC suggests, by analogy with melanoma, a relationship with intense sun exposure. Converseley, SCC would require prolonged exposure to sunlight.

Keywords: basal cell carcinoma; squamous cell carcinoma; pigmentation; sun burns; skin cancer

Non-melanocytic skin cancer is one of the commonest tumours in white populations. Standardised incidence rates in men, as measured by cancer registries in the late 1980s, ranged from about 40 cases per 100 000 in various European countries, to 100 and 200 cases per 100 000 respectively in North America and Australia (Parkin *et al.*, 1992). It is generally believed that incidence rates, as reported by cancer registries, are underestimated, because current notification systems miss some cases diagnosed and treated only as outpatients. Two surveys carried out in Australia, the highest risk area worldwide, found annual incidence rates to be over 1000 cases for 100 000 inhabitants (Kricker *et al.*, 1990; Stenbeck *et al.*, 1990).

Non-melanocytic skin cancers are classified into two major groups: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BCC is the most common cancer type in white populations, occurring rarely among black Africans, among whom SCC is a little more common that BCC though still rare (Oettlé, 1963). As reported by some surveys, the incidence of BCC has increased in British Columbia (Gallagher *et al.*, 1990), USA (Fears and Scotto, 1982), the Netherlands (Coebergh *et al.*, 1991) and Switzerland (Levi *et al.*, 1988) during the last two decades. In addition, these upward trends were especially marked for BCC on the trunk, while for SCC, they were limited to the head, face and neck (Gallagher *et al.*, 1990; Fears and Scotto, 1982; Coebergh *et al.*, 1991).

Risk factors for BCC and SCC have been examined in a few analytical studies. Pigmentary characteristics, skin sensitivity to sun and sun exposure emerged as the major risk factors, although the relationship among these highly correlated indicators is still controversial (Kricker *et al.*, 1994). None of the studies on skin cancer recently reviewed had sufficient SCC cases to test for differences between BCC and SCC with an adequate statistical power (IARC, 1992). Subsequently, a few other analytical studies have been published (Ron *et al.*, 1991; Kubasiewicz *et al.*, 1991), and recent analyses have included data on the qualitative and quantitative relationship between risk of BCC (Kricker *et al.*, 1995*a*, *b*; Gallagher *et al.*, 1995*a*), of SCC (Gallagher *et al.*, 1995*b*) and sun exposure.

To elucidate further the aetiology of non-melanocytic skin cancers, in 1989 we planned a case–control study of sufficient size to evaluate the causal role of sun exposure, constitutional factors, occupational and iatrogenic exposures on SCC and BCC separately. The study was implemented among south European populations in order to increase variability of phenotypes and lifestyles and provide insight into the epidemiology of skin cancer in a population still little studied. In this paper we present results on pigmentary traits, skin sensitivity to sun exposure and sunburns.

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Received 21 August 1995; revised 20 December 1995; accepted 8 January 1996

Methods and subjects

Cases ascertainment

The recruitment of cases and controls took place in seven south European regions between November 1989 and June 1993: Turin (north-west Italy), Trento (north-east Italy), Ragusa (Sicily), Villejuif and Créteil (Paris), Besançon (Franche-Comté, France), Murcia (south-east Spain) and Granada (Andalusia, Spain). Population-based cancer registries are operating in Turin, Ragusa, Besançon, Murcia and Granada, covering a total population of over 3.5 million inhabitants. In these areas, all incident cases between 20 and 70 years of age with a diagnosis of BCC, SCC and carcinoma of skin adnexa, as identified by cancer registries' notification systems, were considered eligible. In Trento, cases were identified at the Dermatology Service of the main regional hospital, where virtually all skin cancer cases of the area are diagnosed and treated. In Paris, case recruitment was carried out in two specialised centres: Institut Gustave Roussy, Villejuif and Hôpital Henri Mondor, Créteil. Dermatologists or family physicians asked cases to consent to an interview about 'lifestyle and health'. When contact was made directly, informed consent was asked before interviews. In population-based centres cases were interviewed at dermatological clinics or at home, while in hospital-based centres cases were interviewed during their stay in hospital.

We collected the histological report of all interviewed cases, together with the slides whenever possible. A panel consisting of one pathologist from each centre was constituted in order to validate and evaluate reproducibility of morphological diagnoses. Each panel's participants reviewed diagnoses blindly, exchanging slides with each other and discussing discordant cases in plenary sessions. Cases with more than one concurrent skin cancer were assigned to the first occurring or diagnosed cancer.

Controls sampling

We drew the control group as an age- and sex-stratified random sample of respective general populations in areas covered by cancer registries, with strata proportional to the age and sex distribution of the skin cancers; samples were drawn from electoral rolls in Ragusa and Besançon, and from the population registries in Turin, Murcia and Granada. Control sampling was hospital-based in Paris and Trento, excluding patients with cancer or skin diseases. We contacted population controls by mail and interviewed them at home, at work or at cancer registry locations, whereas hospital controls were approached and interviewed during their stay in hospital.

Assessment of exposure

All subjects who agreed to collaborate were interviewed by a trained interviewer with a standard questionnaire. All interviewers were trained by the same senior interviewer, who replicated the same 4-day course in Italy, France and Spain, paying particular attention to ascertain exposures in a similar way among cases and controls in order to minimise misclassification. The senior interviewer checked their performances in the first interviews and then systematically reviewed occupational histories and internal consistency of outdoor activity histories. After data gathering in the central data base, quality checking was performed on missing values, extreme values, etc.

The questionnaire covered host factors (skin characteristics, pigmentary traits), history of past and present places of residence, life-long exposure to sunlight, occupational history, dermatological history, cosmetic habits (sunscreens, sunlamps, sand and mud bath), use of immune-suppressor and radiological exposures.

Measures of pigmentary traits were taken by assessing hair and eye colours. We graded hair colour against 11 samples of human hair provided by a cosmetic firm (L'Oréal). For subjects who were bald, had gone grey or dyed their hair, we assessed eyebrow hair, which, we consider, keeps its natural colour longer than scalp hair, or, if not possible, asked subjects to select the hair colour that would have matched their original or natural colour best. Eye colour was assessed on a three-level scale (black and brown; green; blue and grey).

We did not measure skin colour directly because the two methods we tested (sample photos and direct reflectance measurement with opto-electronic colorimeter) turned out to be both unreliable and difficult to implement. Indeed, we considered grading skin colour against a set of six sample photos, and a direct reflectance measurement (Chroma-meter, Minolta). During the pilot period, the first method proved to be highly unreliable because of inter-observer variance. The second method was tested on a sample of about 50 subjects and proved to be highly variable according to skin site, age and sex of subjects. This is not surprising and is consistent with previous findings with objective measurements. The skin colour is not only dependent on pure melanin pigmentation, but is also influenced by body hair, thickness, moisture, superficial diffusion of blood vessels and tanning. Moreover, objective measurements are only weakly associated with skin cancers and actinic lesions, suggesting that it is not skin colour, but rather a combination of pigmentation and sensitivity to sun, that induces skin tumours (Green and Martin, 1990; Kricker *et al.*, 1991).

Skin characteristics were measured by asking questions about reaction to sun exposure and sunburns in childhood. Reaction to sun exposure was measured on a four-level scale and ranged from subjects who always tan and never burn to subjects who always burn when exposed to sun. As reaction to sun exposure varies during life according to the degree of melanin protection and skin thickness, we asked patients to report their skin reaction experience at 20 years old. Past experience of sunburns was assessed by asking questions about number of sunburns and age at first sunburning.

Scales construction and data analysis

In this analysis we evaluated the effect of skin characteristics and sunburns during different outdoor activities on both BCC and SCC. Since analysis was conducted on BCC and SCC separately and given the different control sampling schemes, we controlled the residual confounding effect of design variables by means of odds ratios adjusted for age, sex, and centre. Each factor was then analysed, including significant pigmentary traits and skin characteristics in unconditional logistic models with design variables to establish which factors were independent from all others.

Hair colour, eye colour and skin reaction to sun exposure were all measured on ordinal scales. Point estimations were computed at each level of the scale, then collapsing adjacent classes with similar estimates, in order to increase the efficiency of models, while saving degrees of freedom. Number of sunburns and age at first sunburn were both determined on an interval scale, but given the skewness of their distributions, we applied quartiles of distributions in exposed controls. Further, we tested linear trends of such reduced scales.

The effect was tested of different control sampling bases on odds ratios (population based in five centres and hospital based in three centres); results indicated that parameter estimates tended to aggregate according to national clusters rather than to their sampling basis. For this reason, when it was necessary to deal with more parsimonious models and controlling by centre effect, we grouped centres in three national groups.

The independent effect of risk factors was tested including all variables in a model and then evaluating if there were significant interaction terms. Only significant variables or confounders (i.e. with a relevant effect on other coefficients) were retained. Finally the model was further checked with the appropriate logistic regression diagnostics (Pregibon, 1981).

Results

We interviewed 1832 cases and 1795 controls. The response rate was 85.8% among cases and 69.3% among controls in population-based centres (Table I). About 8.8% cases refused to be interviewed and 3.0% cases could not be traced because of a change in residence or death. Among controls, 18.5% refused to be interviewed and 7.9% could not be traced. Response in population controls in the collaborating centres ranged from 55.6% in Besançon to 82.9% in Ragusa. A small proportion of cases and controls (about 3%) in the hospital-based centres refused to participate.

Case review by the pathologists' panel resulted in identification of 1549 BCC, 228 SCC and 20 carcinomas of the adnexa (not analysed here). Thirty-five (1.9%) cases already interviewed were then discarded from analysis since case review excluded malignancy. Another 38 cases (2.1%) were misclassified by histological type at the first reading. Further details on diagnostic concordance will be presented in a separate article.

The head was the most common site for both SCC (76.8% in men, 58.8% in women) and BCC (78.1% in men, 76.9% in women) (Table II). The rest of the SCC lesions were markedly different from those of BCC: the second most common site for SCC was lower limbs in women (25.5%) and upper limbs in men (7.9%), whereas for BCC the second most common site of lesions was the trunk in both men (14.1%) and women (10.1%).

Pigmentary traits and skin characteristics

Pigmentary traits showed a clear and independent association with both BCC and SCC (Table III), but hair colour had a stronger association than eye colour. In general, SCC exhibited elevated risks for subjects with blonde or red hair. Both BCC and SCC showed a 2-fold increase of risk in people who never tan and always get burned when exposed to sun (Table IV). The increase was not linear with the two intermediate categories showing similar estimates in BCC.

Although people with sun-sensitive skin type tend to avoid sun exposure, they too could have experienced some sunburns. As a consequence, we analysed number of lifelong sunburns and age at first occurrence as a mixed indicator of both skin reaction and sun exposure.

Number of sunburns showed a highly significant association with BCC, which was however, attenuated by allowance for pigmentary traits and skin type (Table V). Subjects who experienced sunburns before age 15 had a significant, although moderate, increase of risk for BCC, also after allowance for pigmentary traits and skin type (Table V). In addition, age at first sunburn emerged as a significant risk factor for BCC, even after controlling for number of sunburns, while the effect of number of sunburns was no longer significant when age at first sunburn was included in models. Conversely, number of sunburns and age at first sunburn did not seem to be risk indicators for SCC.

Subjects with fair hair and tendency to burn showed a 5-

Table I Recruitment of cases and controls by collaborating centre

	Identified	Refused interview	(%)	Untraceable (including death)	(%)	Interviewed	(%)
Cases							
Turin	555	93	16.8	3	0.5	459	82.7
Ragusa	146	15	7.5	0	0.0	131	92.5
Trento	149	–	–	–	–	149	100.0
Granada	358	4	1.1	11	3.1	343	95.8
Murcia	374	38	10.2	36	9.6	300	80.2
Besançon	295	33	11.2	12	4.1	250	84.7
Villejuif	100	–	–	–	–	100	100.0
Créteil	100	–	–	–	–	100	100.0
Total	2077	183	8.8	62	3.0	1832	88.2
Controls							
Turin	663	232	35.0	9	1.4	422	63.6
Ragusa	158	19	12.0	8	5.1	131	82.9
Trento	141	–	–	–	–	141	100.0
Granada	428	41	9.6	38	8.9	349	81.5
Murcia	397	36	9.1	60	15.1	301	75.8
Besançon	452	124	27.4	77	17.0	251	55.6
Villejuif	100	–	–	–	–	100	100.0
Créteil	100	–	–	–	–	100	100.0
Total	2439	452	18.5	192	7.9	1795	73.6

Table II Site distribution of basal cell carcinomas and squamous cell carcinomas

	Men		Women	
Site	BCC (%)	SCC (%)	BCC (%)	SCC (%)
Head	668 (78.1)	136 (76.8)	516 (76.9)	30 (58.8)
Neck	26 (3.0)	6 (3.4)	20 (3.0)	–
Trunk	124 (14.1)	4 (2.3)	68 (10.1)	4 (7.8)
Abdomen	13 (1.5)	1 (0.6)	24 (3.6)	1 (2.0)
Lower abdomen	–	7 (3.9)	5 (0.7)	–
Upper limbs	15 (1.7)	14 (7.9)	10 (1.5)	3 (5.9)
Lower limbs	14 (1.6)	9 (5.9)	28 (4.2)	13 (25.5)
Total	878 (100.0)	177 (100.0)	671 (100.0)	51 (100.0)

Table III Odds ratios (ORs) of BCC and SCC by pigmentary traits

	No. of controls	*No. of BCCs*	*No. of SCCs*	*BCC OR[a] (95% CI)*	*BCC OR[b] (95% CI)*	*SCC OR[a] (95% CI)*	*SCC OR[b] (95% CI)*
Hair colour							
Black	154	99	12	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Brown	699	544	80	1.24 (0.94–1.64)	1.16 (0.87–1.53)	1.59 (0.84–3.02)	1.51 (0.79–2.88)
Light brown	597	514	67	1.41 (1.06–1.87)	1.20 (0.89–1.60)	1.83 (0.95–3.52)	1.54 (0.80–2.99)
Blonde	253	257	30	1.69 (1.23–3.30)	1.29 (0.93–1.78)	2.19 (1.07–4.48)	1.63 (0.79–3.40)
Light blonde	81	121	29	2.47 (1.68–3.63)	1.78 (1.20–2.66)	6.93 (3.25–14.84)	4.88 (2.24–10.63)
Red	11	16	10	2.37 (1.05–5.35)	1.58 (0.69–3.62)	18.02 (6.12–52.98)	12.50 (4.13–37.86)
P-value (linear trend)				<0.001	0.008	<0.001	<0.001
Eye colour							
Black/dark brown	542	332	39	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Light brown/green	816	764	106	1.52 (1.28–1.81)	1.37 (1.15–1.64)	1.80 (1.18–2.76)	1.75 (1.12–2.71)
Blue/hazel/grey	437	453	83	1.71 (1.41–2.08)	1.35 (1.09–1.67)	2.60 (1.66–4.07)	1.83 (1.11–3.03)
P-value (linear trend)				<0.001	0.002	<0.001	0.049

[a] Logistic regression estimates with terms for age, sex and centre. [b] Logistic regression estimates with terms for sex, age, centre, hair colour or eye colour, and skin reaction to sun exposure.

Table IV Odds ratios (ORs) of BCC and SCC by sun sensitivity

Skin reaction to sun exposure	*No. of controls*	*No. of BCCs*	*No. of SCCs*	*BCC OR[a] (95% CI)*	*BCC OR[b] (95% CI)*	*SCC OR[a] (95% CI)*	*SCC OR[b] (95% CI)*
Tan, no burn	518	299	44	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Rare burn then tan	288	278	27	1.72 (1.38–2.13)	1.69 (1.35–2.10)	0.97 (0.55–1.71)	0.91 (0.51–1.62)
Often burn then tan	800	665	114	1.52 (1.26–1.82)	1.43 (1.19–1.72)	1.73 (1.14–2.57)	1.50 (0.98–2.22)
Burn, never tan	184	299	43	3.09 (2.43–3.94)	2.71 (2.11–3.47)	3.28 (1.98–5.49)	2.04 (1.18–3.53)
P-value (linear trend)				<0.001	<0.001	<0.001	<0.001

[a] Logistic regression estimates with terms for age, sex and centre. [b] Logistic regression estimates with terms for sex, age, centres, hair colour and eye colour.

Table V Odds ratios (ORs) of BCC and SCC by number of sunburns and age at first sunburn

	No. of controls	*No. of BCCs*	*No. of SCCs*	*BCC OR[a] (95% CI)*	*BCC OR[b] (95% CI)*	*SCC OR[a] (95% CI)*	*SCC OR[b] (95% CI)*
Number of sunburns in a lifetime							
Never	1345	1053	169	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1	305	316	38	1.31 (1.09–1.57)	1.13 (0.94–1.36)	1.08 (0.70–1.65)	0.78 (0.49–1.23)
2	65	78	10	1.53 (1.08–2.15)	1.30 (0.92–1.84)	1.33 (0.61–2.87)	0.89 (0.38–2.08)
3+	80	102	11	1.65 (1.21–2.24)	1.30 (0.95–1.78)	0.86 (0.40–1.85)	0.54 (0.24–1.21)
P-value (linear trend)				<0.001	0.031	0.298	0.529
Age at first sunburn							
More than 15 years old or never	1741	1458	218	1 (Reference)	1 (Refrence)	1 (Reference)	1 (reference)
15 years old or less	54	91	10	2.05 (1.45–2.88)	1.68 (1.17–2.39)	1.90 (0.90–4.03)	1.26 (0.56–2.80)

[a]Logistic regression estimates with terms for age, sex and centre. [b] Logistic regression estimates with terms for sex, age, centre, hair colour, eye colour, and skin reaction to sun exposure.

fold to 10-fold increased risk for BCC if they experienced sunburns before age 15 (Table VI). The risk for SCC was substantial in people with fair hair and blue, hazel or grey eyes and a tendency to sunburn, as shown by an odds ratio of 54 for subjects with blue eyes, red hair, who never tanned and always burnt (Table VII).

The final model for pigmentary traits and skin characteristics included terms for hair colour, eye colour and skin reaction to sun exposure in both types of skin cancer, with the highest risks in SCC, whereas young age at first sunburn was present only in the BCC model. Table VIII shows parameter estimates from a logistic model. This model would

Table VI Odds ratios (ORs) and 95% confidence intervals (CI) of basal cell carcinoma[a] by age at first sunburn and skin reaction to sun exposure in some high-risk pigmentary traits

Hair colour		*Black/dark brown*		*Blonde*		*Light blonde*		*Red*	
Age at first sunburn	*Skin reaction*	*Dark eyes*	*Blue eyes*	*Dark eyes*	*Blue eyes*	*Dark eyes*	*Blue eyes*	*Dark eyes*	*Blue eyes*
More than 15 years old	Tan, no burn	1 (Reference)	1.36 (1.15–1.62)	1.44 (1.07–1.95)	1.97 (1.45–2.68)	1.51 (1.08–2.12)	2.06 (1.47–2.89)	1.58 (1.09–2.30)	2.16 (1.49–3.13)
15 years old or less	Sunburn then tan	2.77 (1.92–3.99)	3.78 (2.54–5.62)	4.01 (2.54–6.31)	5.47 (3.48–8.61)	4.19 (2.60–6.77)	5.73 (3.57–9.19)	4.39 (2.66–7.27)	6.00 (3.65–9.84)
15 years old or less	Sunburn, never tan	4.44 (2.94–6.70)	6.06 (3.92–9.37)	6.42 (3.97–10.39)	8.76 (5.44–14.11)	6.72 (4.07–11.10)	9.17 (5.60–15.04)	7.04 (4.17–11.89)	9.61 (5.74–16.07)

[a] Logistic regression estimates with terms for sex, age, centre, hair colour, eye colour, skin reaction to sun exposure, and age at first sunburn.

Table VII Odds ratios (ORs) and 95% confidence intervals (CI) of squamous cell carcinoma[a] by skin reaction to sun exposure in some high-risk pigmentary traits

Hair colour	*Black/dark brown*		*Blonde*		*Light blonde*		*Red*	
Skin reaction	*Dark eyes*	*Blue eyes*	*Dark eyes*	*Blue eyes*	*Dark eyes*	*Blue eyes*	*Dark eyes*	*Blue eyes*
Tan, no burn	1 (Reference)	1.78 (1.16–2.74)	4.34 (1.03–18.25)	7.75 (1.77–33.88)	6.79 (1.61–28.61)	12.11 (2.76–53.19)	13.97 (2.93–66.75)	24.93 (4.98–124.72)
Sunburn then tan	1.47 (1.16–1.87)	2.62 (1.62–4.25)	6.40 (1.53–26.77)	11.41 (2.63–49.52)	9.99 (2.38–41.80)	17.82 (4.10–77.45)	20.56 (4.36–97.10)	36.68 (7.44–180.89)
Sunburn, never tan	2.16 (1.34–3.50)	3.86 (2.57–7.81)	9.42 (2.17–40.86)	16.79 (3.75–75.25)	14.70 (3.40–63.55)	26.22 (5.86–117.24)	30.27 (6.25–146.56)	53.98 (10.72–271.86)

[a] Logistic regression estimates with terms for sex, age, centre, hair colour, eye colour, and skin reaction to sun exposure.

Table VIII Odds ratios (ORs) of BCC and SCC including independently significant variables and adjusting for age, sex and centre

	No. of controls	*No. of BCCs*	*No. of SCCs*	*BCC OR (95% CI)*	*SCC OR (95% CI)*
Hair colour					
Black	154	99	12	1 (Reference)	1 (Reference)
Brown	699	544	80	1.13 (0.90–1.51)	1.50 (0.79–2.86)
Light/brown	597	514	67	1.19 (0.89–1.59)	1.57 (0.81–3.04)
Blonde	253	257	30	1.24 (0.90–1.72)	1.64 (0.79–3.42)
Light blonde	81	121	29	1.72 (1.16–2.57)	5.02 (2.30–10.94)
Red	11	16	10	1.31 (0.57–3.03)	13.00 (4.29–39.38)
Eye colour					
Black/dark brown	542	332	39	1 (Reference)	1 (Reference)
Blue/hazel/grey/green	1253	1217	189	1.38 (1.16–1.63)	1.65 (1.11–2.43)
Skin reaction to sun exposure					
Tan, no burn	518	299	44	1 (Reference)	1 (Reference)
Burn, then tan	1088	943	71	1.49 (1.26–1.78)	1.35 (0.93–1.96)
Burn, never tan	184	299	43	2.70 (2.10–3.47)	1.97 (1.19–3.26)
Age at first sunburn					
More than 15 years old or never	1741	1458	218	1 (Reference)	–
15 years old or less	54	91	10	1.65 (1.16–2.36)	–

also be useful in building a parsimonious set of controlling variables that can make up the basis for testing other risk factors.

Discussion

Previous results have shown the relationship between sun exposure, skin characteristics and non-melanocytic skin cancer, but they were mainly based on Anglo-Saxon populations. We investigated several risk factors in a wide south European population in which different skin types, sun exposure patterns and histological subtypes confirmed by a panel of pathologists are sufficiently represented for statistical purposes.

The anatomical site distribution, with a substantial proportion of BCC on the trunk (14.1% in men and 10.1% in women), is consistent with previous observations in the Canton of Vaud, Switzerland (Levi *et al.*, 1988), The Netherlands (Coebergh *et al.*, 1991) and Tasmania (Kaldor *et al.*, 1993), although to a lesser extent in Norway (27.6% in men and 25.2% in women) (Magnus, 1991) and in Western Australia (32% in men and 21% in women) (Kricker *et al.*, 1990). Indeed, data from Western Australia were collected through a specific survey, whereas other studies relied upon routinely collected data from cancer registries. Although the anatomical site distribution of SCC was rather stable over time, several surveys showed that BCC lesions on the trunk increased in the last decade (Fears and Scotto, 1982; Levi *et al.*, 1988; Gallagher *et al.*, 1990; Coebergh *et al.*, 1991; Magnus, 1991).

Skin characteristics are considered as risk indicators for skin cancer as sun exposure produces skin cancer at different rates for skin types with different sun sensitivity. In general, apart from rare forms of skin cancer (basal cell syndrome in xeroderma pigmentosum), sun exposure is considered essential in inducing skin cancers. Nevertheless, identification of high-risk groups through easily detectable skin characteristics can help in targeting preventive interventions.

In the present study, we used hair colour, eye colour and skin reaction to sun exposure as indicators of skin type. These indicators have the advantage of being easier to use and more accurate than skin colour, and are therefore, more suitable for risk assessment and in messages to the public. Conversely, skin colour is difficult to measure reliably either subjectively or objectively. Although a high correlation would be expected between pigmentary traits, our results showed an independent effect, even if estimates were sensibly attentuated after adjustment for mutual confounding effects.

Comparison with other studies is made difficult by phenotype differences between study populations and the use of different measurement scales. Indeed, given the characteristics of the Mediterranean population, it is possible that in the baseline category our study included subjects with darker complexion than other studies. In general, eye colour and skin sun sensitivity showed similar results in both BCC and SCC with OR for eye colour ranging from 1.2 (Hogan *et al.*, 1989; Kricker *et al.*, 1991) to 3.4 (Vitasa *et al.*, 1990), and ORs for sun sensitivity ranging from 1.3 in subjects with 'an average tan' (Hunter *et al.*, 1990) to 6.1 in subjects who 'always burn' (Marks *et al.*, 1993).

For hair colour other studies used less expanded scales with similar results for BCC (Hogan *et al.*, 1989; Hunter *et al.*, 1990; Green and Battistutta, 1990; Kricker *et al.*, 1991). Odds ratios for SCC lower than ours, particularly in subjects with red hair, were however found with a maximum OR of 3.3 in a study based on only 21 SCCs (Green and Battistutta, 1990).

The lower ORs found for eye colour, as compared with hair colour, might simply indicate the greater difficulty in assessing eye colour with consequently larger measurement error.

Although, number of sunburns life-long is very difficult to recall and can be seriously underestimated, history of sunburns can be considered a comprehensive indicator of skin sensitivity and sun exposure, as sunburn is caused by an exposure that exceeds the skin's reparation ability. Few sunburns life-long, therefore, can indicate true skin resistance as well as a tendency to avoid sun exposure as a result of skin sensitivity. In our study the relationship with number of sunburns life-long was present only in BCC with OR similar to those found elsewhere (Hogan *et al.*, 1989; Hunter *et al.*, 1990; Kricker *et al.*, 1995*a*). However, the association was not significant after controlling for skin characteristics. Allowance for these variables is open to criticism as sunburns, as previously noted, occur only if exposure exceeds skin protection (Green *et al.*, 1985; Kricker *et al.*, 1995*a*).

Age at sunburn has been replaced, as a proxy, by age of arrival in sunny areas. For example, in previous studies in Australia it was found that immigration at age 10 years or less implied a slight risk increase (Armstrong, 1983; Kricker *et al.*, 1991). A recent study reported a similar risk increase for severe sunburns in childhood (Gallagher *et al.*, 1995*a*), and another study estimated that the strongest effect of sunburns on BCC was at 10–14 years of age (Kricker *et al.*, 1995*a*). Again, young age at sunburn is an indicator not only of the direct effect of sun exposure, but also of early starting of heavy exposure or a sign of sun sensitivity in subjects who can develop a darker and less sensitive complexion with ageing. This variable, therefore, can explain the marginal contribution to the risk of BCC in subjects not belonging to traditional high-risk groups. This result also mimics what has been found in cutaneous melanoma, in which history of past sunburn during childhood has been associated with a 2-fold increased risk (Østerlind, *et al.*, 1988; Elwood *et al.*, 1990; Zanetti *et al.*, 1992; Weinstock *et al.*, 1991).

Although SCC occurs mainly in old age, we restricted eligibility to 20–70 years because of the difficulty in gathering reliable information in elderly subjects; nevertheless, we were able to collect 228 SCC cases. The discrepancy between median incidence age of SCC in the general population and the median age in our data set is unlikely to bias the present results, as the control sample was balanced for age with cases and the residual effect of age was allowed for by adjusting odds ratios for the exact annual age.

Another possible source of bias was the different population bases of the control sample; although a certain degree of distortion cannot be completely ruled out, we checked for consistency among centres, and by aggregating centres by country. Country proved to be a stronger confounder than study design (hospital or population basis).

Compliance among cases was high for all centres. We had a lower response rate among controls in Besançon (55.6%) and Turin (63.6%) although still similar to those in other population-based case–control studies (Engel *et al.*, 1988; Green *et al.*, 1988; Hogan *et al.*, 1989; Marks *et al.*, 1989; Hunter *et al.*, 1990; Vitasa *et al.*, 1990). However, the interview setting was similar for cases and controls (at home or outpatient clinics), thus minimising possible sources of bias.

In summary, the present study confirms the role of constitutional factors in high-risk groups for both BCC and SCC. However, a somewhat stronger association with phenotypic characteristics emerged for SCC than for BCC. Conversely, sunburns were a more important risk factor for BCC than for SCC, partly as a consequence of the different pattern of sun exposure relevant to these two skin cancer types, which will be discussed in a companion paper (Rosso *et al.*, 1996).

Acknowledgements

This study has been supported by a research grant from Europe Against Cancer (contract nos. 890139, 910539, 920584) and by Associazione Italiana per la Ricerca sul Cancro (AIRC), Italy; Fondo de Investigacion Sanitaria de la Securidad Social (FISS), Spain (contract no. 90E0720); Ligue Nationale Contre le Cancer, France; Consiglio Nazionale delle Ricerche (CNR), Italy; Institut National de la Santé et de la Recerche Médicale (INSERM), France. We thank Mrs M Casale for her valuable help in preparing the questionnaire and in training interviewers and Dr BK Armstrong for his useful comments on the manuscripts. We are also grateful to the numerous colleagues, dermatologists, pathologists and general practitioners who allowed access to patients and histological material.

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