Can ultraviolet radiation act as a survival enhancer for cutaneous melanoma?

Cristina Fortes\textsuperscript{a}, Simona Mastroeni\textsuperscript{a}, Renan Bonamigo\textsuperscript{d}, Thomas Mannooranparampila\textsuperscript{a}, Claudia Marino\textsuperscript{c}, Paola Michelozzi\textsuperscript{c}, Francesca Passarelli\textsuperscript{b} and Mathieu Boniol\textsuperscript{e}

Some studies have suggested that sun exposure plays a protective role in melanoma survival. This created a paradox as the known carcinogen can act as a cancer promoter and also as a survival enhancer. The aim of this study was to investigate the effect of sun exposure on melanoma mortality using both ambient sun exposure and individual data. A 10-year cohort study was carried out on primary cutaneous melanoma cases ($n = 972$). Residential data were coupled with levels of ultraviolet radiation (UV) to provide a measure of individual exposure. Demographic, histological and clinical data were obtained for all participants. In a subsample, information on pigmentary characteristics, diet, medical history, phenotype and self-reported sun exposure was also collected. Survival analysis and Cox proportional hazards models were used to examine associations. No protective effect was found for UVB or individual sun exposure variables on melanoma mortality. However, an increased risk of mortality was found among patients with cutaneous melanoma located on the lower limbs and in the highest decile of UVB exposure ($\geq 3.298 \text{ J/cm}^2$) after controlling for sex, age and Breslow thickness (relative risk: 4.78; 95% confidence interval: 1.30–17.5). The increased risk of mortality for the highest decile of UVB was also confirmed in the subsample after controlling for sex, age, education, use of sun lamps, pigmentary characteristics and diet. The results of the study suggested no protective effect of sun exposure for melanoma mortality and showed that high sun exposure increases the risk of melanoma mortality among patients with melanomas located on the lower limbs. European Journal of Cancer Prevention 25:34–40 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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\textsuperscript{a}Clinical Epidemiology Unit, Istituto Dermopatico dell‘Immacolata, Rome, Italy, \textsuperscript{b}Pathology Unit Istituto Dermopatico dell’Immacolata, \textsuperscript{c}Department of Epidemiology of the Regional Health Service, Rome, Italy, \textsuperscript{d}Dermatology Department – Federal University of Health Sciences of Porto Alegre, Porto Alegre, Brazil and \textsuperscript{e}University of Strathclyde Institute of Global Public Health at IPRI, International Prevention Research Institute, Lyon, France

Correspondence to Cristina Fortes, BSc, MSc, PhD, Clinical Epidemiology Unit, Istituto Dermopatico dell’Immacolata, IDI Via dei Monti di Creta, 104 00187 Roma, Italia
Tel: + 39 06 66460 x4305; fax: +39 066 66460 x4307; e-mail: c.fortes@idi.it

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Background

Cutaneous melanoma (CM) has been one of the most rapidly increasing cancers in White populations over the past several decades and it is still increasing, in particular, among men and in Northern and Western Europe and Australia. The global incidence of CM among men has increased in 6 years from 2.8 to 3.1 per 100 000 inhabitants, whereas among women, the incidence has remained fairly constant (Ferlay et al., 2004, 2008). There were 232 130 new melanoma cases in 2012 worldwide. However, there is a striking variation in the risk of CM according to geographic location. Among white populations, an important difference in the incidence of melanoma exists between populations, with rates ranging from 35.1 new cases per 100 000 inhabitants in Australia/New Zealand to 8.1 new cases per 100 000 inhabitants in Southern Europe (Ferlay et al., 2012). These differences can be attributed to differences in the intensity of environmental exposure to ultraviolet radiation (UV), with residents of Australia receiving more than twice the intensity of UV radiation as in Europe under clear sky conditions (Gallagher and Elwood, 1994). There is no doubt that sun exposure plays a predominant role in the genesis of melanoma (http://www.skincancer.org). However, evidence suggests that sun exposure may also exert a protective effect on melanoma survival, probably because of vitamin D (Holick, 2004; Berwick et al., 2005; Rosso et al., 2008). This created a paradox as the known carcinogen can act as a cancer promoter and also as a survival enhancer.

Ambient UV exposures, which vary markedly throughout the year (Boniol et al., 2006) and according to geographic location, may be highly informative in exploring the sun exposure phenomenon on melanoma survival. The sources of vitamin D are sunlight exposure and diet, with sunlight (UVB) being a major source for most individuals. Nevertheless, the potential protective effect of UV because of vitamin D on melanoma survival may also depend on other factors, such as the host susceptibility characteristics (e.g. skin pigmentation, phenotype), use of sun protection and use of vitamin D supplements.
of sun lamps, and diet (Calvo et al., 2005; Burke and Wei, 2009; Narayanan et al., 2010). However, using a semi-ecologic design that combines ambient UV exposures with individual-level data, we may disentangle the paradox described previously. Clearly, we cannot apply this study design to a large number of individuals, but having individual data, even on a small subsample, can provide valuable additional information. It may help to improve exposure estimation and modelling, which in turn should lead to improved assessment of risk (Jackson et al., 2006, 2008).

Few studies have examined the role of individual sun exposure (Berwick et al., 2005; Rosso et al., 2008) or ambient UV (Fears and Tucker, 2005) in melanoma mortality. To our knowledge, none has examined both individual and ambient sun exposure. As the effect of sun exposure on CM survival is still controversial (Fears and Tucker, 2005; Jayasekara et al., 2009), it was considered that further investigation of this factor would be important to improve exposure estimation and future recommendations.

Therefore, the aim of this study was to investigate the effect of history of sun exposure on melanoma survival using both ambient and individual sun exposure data.

**Methods**

Data were merged from the clinical Melanoma Registry of the Istituto Dermopatico dell’Immacolata (IDI). From January 2001 to December 2003, 972 patients with newly diagnosed CM and living in the Lazio region were registered at IDI. Demographic, histological, residential and clinical data were collected for all participants. Data on pigmented characteristics, diet and sun exposure history were also available for 256 out of 972 patients from a previous case-control study. The details of this study have been described previously (Fortes et al., 2008). In brief, information on sociodemographic characteristics, personal medical history, diet, phenotypic traits (skin type, skin, hair and eye colour) and family history of skin cancer, lifetime sunlight exposure, sunburn history and sun bed exposure was obtained. We combined medical and environmental data to improve risk assessment and control for potential confounding factors. The IDI-IRCCS ethical committee approved the study and written informed consent was obtained from the participants.

The histological type, tumour thickness, ulceration, regression and cellular types were recorded and followed the guidelines described elsewhere (Clark et al., 1969, 1989; Breslow, 1970; Barnhill, 1995). The International Classification of Diseases (ICD-9) was used to classify the anatomic site and cause of death.

After giving informed consent, study participants were interviewed by two trained dermatologists and were examined clinically to look for the presence of pigmented lesions. Pigmented lesions were identified by dermatologists and recorded according to the IARC protocol (English and Mac Lennan, 1990).

The Fitzpatrick system was used to classify skin phototype (burning and tanning tendency) (Freedberg et al., 1999). Three hair colour categories were created (red, blonde; light brown; dark brown, black). Three eye colour categories were created (blue, grey, green; light brown; dark brown and black).

Indicators of intermittent exposure were time spent outdoors during vacation, sunburn episodes and use of sun beds. Indicators of chronic exposure were time spent outdoors in recreational activities, occupational sun exposure and lifetime sun exposure. Occupational sunlight exposure was classified as indoors and outdoors. Information on sunburn episodes (number of sunburns causing pain and erythema and/or blisters for more than 24 h) was collected. Sunburn episodes were classified into two categories (no/yes).

Consumption of foods rich in vitamin D was classified into low and high consumption. The following categories were used: milk (more than daily vs. weekly consumption), cheese (≥3 times weekly vs. ≤2 times weekly) and fatty fish (less than weekly vs. weekly and more).

**Ambient UV radiation**

UV ambient radiation information was extracted from databases of the EuroSun project (2012). It provided an estimation of the daily average of UVA and UVB irradiation in Europe on the basis of satellite measurements for every 1’ of arc-angle. Data were reported as the 5-year average of monthly means of UV daily doses (1988–1992; 1993–1997; 1998–2002; 2003–2007) selected for counties in the Lazio region. The last 10 years of residential UV exposure before melanoma diagnosis (2001–2003) were considered for all participants. Individual UV exposure was calculated for each participant in the study as weighted mean by providing different weights on the basis of the numbers of years covered in the different 5-year periods (http://www.eurosun-project.org). Deciles were calculated and the reference category was defined as the lowest ninth.

In our study, the following UV variables were considered: UVA mean daily irradiation premelanoma diagnosis, UVB mean premelanoma diagnosis, UVA peak in daily irradiation premelanoma diagnosis and UVB peak premelanoma diagnosis.

All UV variables were highly correlated. For example, the correlation between UVA mean and UVB mean was $\rho = 1.0; P < 0.0001$; the correlation between UVA peak and UVB peak was $\rho = 1.0; P < 0.0001$; and the correlation between UVB peak and UVB mean was $\rho = 0.95; P < 0.0001$. The UV measurements were expressed in J/cm². Then, we restricted the analysis to UVB exposure because it is the main source of vitamin D.
Vital status
Files from the Registry Office of the Department of Epidemiology of the Lazio region were examined to obtain information on vital status and cause-specific mortality. The length of follow-up for each participant was the number of days from the diagnosis of primary melanoma to the date of death or to 31 December 2009, whichever came first. Patients who were alive, or dead because of other causes, were considered censored.

Statistical methods
The outcome of interest was death from melanoma. The Kaplan–Meier method and the Cox proportional hazards model were the methods chosen for the statistical
analysis. UVB radiation was categorized into deciles of exposure. Using upper decile versus lower ninth deciles, the relative risk and 95% confidence intervals (CIs) were calculated. The potential for violation of the proportional hazards assumption was assessed graphically by comparing survival curves for each variable level. Scaled Schoenfeld and Martingale residuals were also used. The following variables were considered in the models as potential confounders: sex, age, Breslow’s thickness, presence of ulceration, histological type, mitotic rate, anatomic site, pre-existing naevus, latitude of residence, Rome/outside Rome, elastosis and self-reported sun exposure.

The likelihood ratio test was used to decide whether to retain each covariate in the model. Only the variables that made statistically significant contributions to the model were included \((P < 0.05)\). Effect modification by sex, age, Breslow, residence (Rome/outside Rome), pre-existing naevus, histological type, anatomic site of melanoma and UV radiation was considered. A stratified analysis by anatomic site was carried out. Data were analysed using STATA software (Stata 11.0; StataCorp LP, College Station, Texas, USA). Missing data were recorded as unclassified and risk estimates were calculated when possible.

### Results

In the study population, there were 150 deaths, 57 of which were because of melanoma. The median follow-up time was 7.4 years (ranging from 1.2 months to 9.0 years). The mean age of the participants was 55.8 years (SD = 16.3), and 52.3% of the population were women. Overall survival for melanoma was 93.8%, but when divided into four primary tumour thickness categories – equal and under 1.00 mm, 1.01–2.00 mm, 2.01–4.0 mm and over 4.0 mm – 10-year figures were 98.4, 89.0, 73.9 and 61.6% \((P_{trend} < 0.0001)\), respectively. Women had a better survival rate than men (95.2 vs. 92.3%). Survival decreased with increasing age \((P_{trend} < 0.001)\) (Table 1). The most powerful predictor of mortality after thickness was ulceration \([\text{hazard ratio (HR): 5.87; 95\% CI: 3.29–10.5}]\), followed by mitotic rate \((HR: 5.42; 95\% CI: 2.87–10.3)\). Nodular \((HR: 7.43; 95\% CI: 4.23–13.1)\) and ‘other’ types of melanoma \((HR: 7.38; 95\% CI: 2.60–20.9)\) were also associated with an increased risk. The presence of regression, the presence of pre-existing naevus, cell type and anatomical site were not associated with mortality.

Table 2 shows the characteristics of the entire sample of patients with CM, excluding in-situ and lentigo maligna melanoma, and the subsample. No significant differences were found for all variables studied, except for age. Patients were slightly younger in the subsample than in the total sample.

Table 3 shows no differences in survival between high \((\geq 3.298)\) and low UVB exposure \((\leq 3.297)\). The results show no effect of UVB radiation on melanoma mortality after controlling for sex, age and Breslow thickness \((HR\text{ for highest decile: 1.01; 95\% CI: 0.43–2.38})\). The effect of UVB radiation on mortality did not change after excluding melanoma in-situ and lentigo maligna \((HR: 1.02; 95\% CI: 0.43–2.41)\). We also did not find an association between UVB and overall survival or all-cause mortality (Supplementary Table 1). As an interaction was suggested between UVB ambient exposure and lower limbs \((HR: 6.71; 95\% CI: 1.02–44.3; P = 0.048)\), we carried out a stratified analysis. An increased risk of both melanoma mortality \((HR: 4.78; 95\% CI: 1.30–17.5)\) and all-cause mortality \((HR: 2.80; 95\% CI: 0.96–8.14)\) was found among patients with CM located on the lower limbs and in the highest decile of UVB exposure, in comparison with patients with CM located on the lower limbs and with lower UVB exposure, after controlling for sex, age and Breslow. The effect of both melanoma mortality \((HR: 5.09; 95\% CI: 1.39–18.6)\) and all-cause mortality \((HR: 3.03; 95\% CI: 1.04–8.83)\) increased slightly after excluding melanoma in-situ and lentigo maligna and after introducing ulceration, mitotic rate and histological type.

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**Table 2** Demographic and clinical characteristics of the participants in the study base population and in the subsample.

|                        | All \((N = 972)\) | Subsample \((N = 256)\) | \(P\)-value* |
|------------------------|------------------|----------------------|--------------|
| **Sex**                |                  |                      |              |
| Females                | 508 (52.3)       | 142 (55.5)           | 0.36         |
| Males                  | 464 (47.7)       | 114 (44.5)           |              |
| **Age [mean (SD)]**    | 56.8 (16.3)      | 52.4 (15.1)          | 0.003        |
| **Residence**          |                  |                      |              |
| City of Rome           | 582 (59.9)       | 166 (64.8)           | 0.15         |
| Outside Rome           | 390 (40.1)       | 90 (35.2)            |              |
| **UVB radiation**      |                  |                      |              |
| Low ≤ 9th decile, ≤ 3.297 J/cm² | 876 (90.1) | 230 (89.8) | 0.89 |
| High (10th decile, ≥ 3.298 J/cm²) | 96 (9.9) | 26 (10.2) | |
| **Anatomic site**      |                  |                      |              |
| Head/neck              | 126 (13.0)       | 19 (74)              | 0.19b        |
| Trunk                  | 354 (36.4)       | 96 (37.5)            |              |
| Upper limb             | 214 (22.0)       | 65 (25.4)            |              |
| Lower limb             | 274 (28.2)       | 75 (29.3)            |              |
| Unclassified           | 4 (0.4)          | 1 (0.4)              |              |
| **Breslow thickness (mm)** |                 |                      |              |
| 0.01–1.00              | 572 (69.9)       | 165 (67.9)           | 0.79b        |
| 1.01–2.00              | 103 (12.6)       | 36 (14.8)            |              |
| 2.01–4.00              | 81 (9.9)         | 25 (10.3)            |              |
| > 4.00                 | 44 (5.6)         | 14 (5.8)             |              |
| Unclassified           | 18 (2.2)         | 3 (1.2)              |              |
| **Mitic rate**         |                  |                      |              |
| Low (≤ 1 mitosis/mm²)  | 353 (43.2)       | 107 (44.0)           | 0.70         |
| High (≥ 1 mitoses/mm²) | 72 (8.8)         | 25 (10.3)            |              |
| Unclassified           | 393 (48.0)       | 111 (45.7)           |              |
| **Presence of ulceration** |                 |                      |              |
| No                     | 754 (92.2)       | 226 (93.0)           | 0.68         |
| Yes                    | 64 (7.8)         | 17 (7.0)             |              |

*\(P\)-value for \(\chi^2\)-test analysis between the study base population and the subsample.  
†\(P\)-value for Fisher’s exact test analysis between the study base population and the subsample.  
‡Excluding in-situ and lentigo maligna melanoma.
Table 3  Percentage survival and hazard ratio for mortality and 95% confidence intervals for high UV radiation: univariate and multivariate analysis

|                          | Participants | Deaths | Survival | Any anatomic sites | Lower limbs | Other sites combined |
|--------------------------|--------------|--------|----------|--------------------|-------------|----------------------|
|                          | N  | %  | N  | %  | P-value* | HR (95% CI) | HR (95% CI)* | HR (95% CI)* | HR (95% CI)* |
| All (N = 972)            |    |    |    |    |          |           |             |             |             |
| UVB radiation            |    |    |    |    |          |           |             |             |             |
| Low (≤ 9th decile, ≤3.297) | 876 | 90.1 | 51 | 93.8 | 0.87 | 1 | 1 | 1 | 1 |
| High (10th decile, ≥3.298) | 98  | 9.9 | 6  | 93.7 | 1.07 (0.46–2.50) | 1.01 (0.43–2.39) | 4.78 (1.30–17.5) | 0.36 (0.08–1.51) |
| Excluding in-situ and lentigo melanoma (N = 818) |    |    |    |    |          |           |             |             |             |
| UVB radiation            |    |    |    |    |          |           |             |             |             |
| Low (≤ 9th decile, ≤3.297 J/cm²) | 738 | 90.2 | 51 | 92.7 | 0.84 | 1 | 1 | 1 | 1 |
| High (10th decile, ≥3.298 J/cm²) | 80  | 9.8 | 6  | 92.4 | 1.09 (0.47–2.54) | 1.02 (0.43–2.41) | 5.09 (1.39–18.6) | 0.36 (0.08–1.51) |

CI, confidence interval; HR, hazard ratio.
*Log-rank test.
*HR adjusted for sex, age and Breslow thickness.
†Head/neck, trunk and upper limbs.

Table 4 Subsample analysis – multivariate analysis for high UV radiation in melanoma of the lower limbs

|                          | All melanoma | Excluding in-situ and lentigo maligna melanoma |
|--------------------------|--------------|-----------------------------------------------|
| Model 0: UV radiation, sex, age and Breslow thickness | 11.7 (1.94–71.1) | 11.6 (1.91–70.3) |
| Model 1: Model 0 + education | 11.9 (1.73–82.0) | 11.8 (1.71–81.0) |
| Model 2: Model 1 + time spent outdoors during vacation in adulthood | 11.3 (1.53–83.6) | 11.2 (1.51–82.6) |
| Model 3: Model 1 + use of sun bed and/or sunlamp | 9.68 (1.39–67.4) | 9.49 (1.36–66.2) |
| Model 4: Model 1 + sunburns in total life | 18.6 (1.30–265.8) | 18.2 (1.28–260.0) |
| Model 5: Model 1 + time spent outdoors during recreational activities in childhood | 15.5 (1.97–122.8) | 15.3 (1.94–120.0) |
| Model 6: Model 1 + solar elastosis | 10.1 (1.39–78.2) | 9.98 (1.32–75.8) |

CI, confidence interval; HR, hazard ratio.

in the model. No increased risk of mortality was found for patients with invasive CM located in other anatomical sites (trunk, HR: 0.48; 95% CI: 0.06–3.64; upper limbs, HR: 0.69; 95% CI: 0.08–6.01). Risk estimates could not have been calculated for head and neck alone. Most cases located on the head and neck were in-situ melanomas and no death was observed in the highest decile of UVB exposure. No increased risk of mortality was found for patients with CM located in other anatomic sites combined (trunk, head and neck and upper limbs) (HR: 0.36; 95% CI: 0.08–1.51).

Table 4 presents the adjusted hazard ratios predicting the risk of death due to melanoma among the subsample by UVB radiation. The increased risk of mortality associated with high UVB exposure among patients with melanoma on the lower limbs was confirmed in the subsample (HR: 9.68; 95% CI: 1.39–67.4) after controlling for sex, age, education, Breslow thickness and sun bed use. We also controlled, one at a time, in the model for other potential confounders such as clinical solar elastosis, chronic and intermittent sun exposure variables, skin phototype, ‘red hair/fair skin’ phenotype, occupational sun exposure, family history of skin cancer, and foods rich in vitamin D, and the effect remained. No differences in age, Breslow thickness, mitotic rate and the presence of ulceration were found between melanomas located on the lower limbs and other anatomical sites (P=0.53) (Supplementary Table 2).

**Discussion**

Although some studies have evaluated associations between latitude (Crocetti et al., 2012) or ambient UV radiation and melanoma mortality (Fears and Tucker, 2005), only a few studies have examined individual-level data (Berwick et al., 2005; Rosso et al., 2008). This is the first study to elucidate the contribution of sun exposure to melanoma mortality using both ambient and individual sun exposure data. No increased risk of mortality was associated with UVB or sun exposure variables. However, patients with CM located on the lower limbs and exposed to high levels of ambient UVB had a four-fold increased risk of mortality after controlling for all possible risk factors for mortality.

The results of our study did not confirm the results of two studies that suggested a protective role for sun exposure in melanoma survival after taking into consideration UVA and UVB radiation data and individual chronic and intermittent sun exposure, and after controlling for all possible confounding factors such as pigmentary characteristics, phenotype and diet. In a 5-year follow-up study of 528 melanoma patients who participated in a US case-control study in the 1990s, Berwick and colleagues...
observed that mortality from melanoma was approximately half among those with signs of elastosis in comparison with those without solar elastosis. In our study, elastosis was not associated with a protective effect on mortality. In the study by Rosso et al. (2008) with 260 melanoma cases, intermittent sun exposure, measured by number of weeks over a lifetime on the beach, was protective for melanoma mortality. In our study, time spent outdoors during vacations was not associated with melanoma mortality.

Fears and Tucker (2005) considered 24,888 melanoma patients and studied UVB flux and survival, and found no evidence for an association between melanoma survival and UVB flux. We also did not find an association between UVB and melanoma mortality. However, we observed that patients with CM located on the lower limbs and exposed to high levels of ambient UVB had a four-fold increased risk of mortality after controlling for all possible risk factors for mortality. In addition, our results were fairly stable even after adjustment for pigmentary characteristics, sun exposure variables and high intake of foods rich in vitamin D.

Ambient UVB radiation at diagnosis may not be the best measure of individuals’ sun exposure, but within the subsample, we also had individual sun exposure data. However, misclassification of sun exposure could also be a limitation of our study. To overcome the problem, we validated our questionnaire using two independent measures as suggested elsewhere (Fortes, 2002). It has been suggested that total sun exposure is associated with elastosis, and sunburns and intermittent sun exposure predict the number of naevi (Bernstein et al., 1996; Lee et al., 2006; Dodd et al., 2007; Gefeller et al., 2007). We compared sun exposure variables assessed by the questionnaire with skin damage variables assessed by a dermatologist following the IARC protocol (English and Mac Lennan, 1990). We found that total sun exposure and occupational sun exposure were highly associated with elastosis, sunburns in childhood with number of naevi in adults and time spent in the sun during holidays in childhood with number of naevi (Fortes et al., 2011).

From our results, we cannot confirm the hypothesis suggested elsewhere (Berwick et al., 2005) that melanomas induced by chronic sun exposure have a less aggressive phenotype than tumours that are not induced by chronic sun exposure. It is likely that high UV exposure causes a more aggressive melanoma in small groups with a certain phenotype and/or genotype. In our study, patients with melanomas located on the lower limbs were more likely to have the phenotype ‘red hair and fair skin colour’ (12 vs. 5%) than patients with melanomas located in other anatomic sites. It has been suggested that the NRAS mutation, in contrast to the BRAF mutation, is associated with chronic sun exposure and with tumour locations such as the extremities (Lee et al., 2011). However, we do not have data on genetics to confirm these findings. Our findings suggest that UV exposure plays a limited role as a risk factor for melanoma mortality. High sun exposure should not be recommended for patients diagnosed with melanoma to enhance survival. Sun-protection behaviour is necessary and is unlikely to place patients at risk of vitamin D deficiency.

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Conflicts of interest
There are no conflicts of interest.

References
Barnhill RL (1996). Pathology of melanocytic nevi and malignant melanoma. Boston, MA: Butterworth-Heinemann.
Berstein EF, Underhill CB, Hahn PJ, Brown DB, Utto J (1996). Chronic sun exposure alters both the content and distribution of dermal glycosaminoglycans. Br J Dermatol 135:255–262.
Berwick M, Armstrong B, Ben-Porat L, Fine J, Kricker A, Eberle C, et al. (2005). Sun exposure and mortality from melanoma. J Natl Cancer Inst 97:195–199.
Bonici M, Armstrong BK, Doré JF (2006). Variation in incidence and fatality of melanoma by season of diagnosis in new South Wales, Australia. Cancer Epidemiol Biomarkers Prev 15:524–526.
Breslow A (1970). Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 172:902–908.
Burke KE, Wei H (2009). Synergistic damage by UVA radiation and pollutants. Tissue Res Health 25 (4–5):219–224.
Calvo MS, Whiting SJ, Barton CN (2005). Vitamin D intake: a global perspective of current status. J Nutr 135:310–316.
Clark WH Jr, From L, Bernardino EA, Mihm MC (1969). The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res 29:705–727.
Clark WH, Elder DE, Guerry D, Bratman LE, Trock BJ, Schultz D, et al. (1989). Model predicting survival in stage I melanoma based on tumour progression. J Natl Cancer Inst 81:1893–1904.
Croectedi E, Buzzoni C, Chiarugi A, Nardini P, Pimpinelli N (2012). Relationship between latitude and melanoma in Italy. ISRN Oncol 2012:84680.
Dodd AT, Morelli J, Mokrohisky ST, Asdigian N, Byers TE, Crane LA (2007). Melanocytic nevi and sun exposure in a cohort of Colorado children: anatomic distribution and site-specific sunburn. Cancer Epidemiol Biomarkers Prev 16:2136–2143.
English DR, Mac Lennan R (1990). Epidemiological studies of melanocytic naevi; protocol for identifying and recording naevi. IARC internal report n 98/002. Lyon, France: International Agency for Research on Cancer.
Eurosun project (2012). Measuring the exposure of individuals and populations in Europe to UV radiation by using the data of meteorological satellites. Available at: http://www.eurosun-project.org. [Accessed 10 November 2012].
Fears TA, Tucker MA (2005). Re: Sun exposure and mortality from melanoma. J Natl Cancer Inst 97:1789–1790.
Ferlay J, Bray F, Pisani P, Parkin DM, GLOBOCAN (2004). Cancer incidence, mortality and prevalence worldwide IARC cancer base No 5, version 2.0. Lyon: IARC Press.
Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM, GLOBOCAN (2008). Cancer incidence and mortality worldwide: IARC cancer base No 10 [Internet] 2010. Lyon, France: International Agency for Research on Cancer.
Ferlay J, Soerjomataram I, Ervik M, et al., GLOBOCAN (2012). Cancer incidence and mortality worldwide: IARC cancer base No 11. Lyon, France: IARC.
Fortes C (2002). Reproducibility of skin characteristic measurements and reported sun exposure history. Int J Epidemiol 31:446–448.

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Fortes C, Mastroeni S, Melchi F, Pilla MA, Antonelli G, Camaioni D, et al. (2008). A protective effect of the Mediterranean diet for cutaneous melanoma. Int J Epidemiol 37:1018–1029.

Fortes C, Mastroeni S, Bozza P, Innocenzi L, Antonelli G, Giovinazzo R, et al. (2011). GSTM1, GSTT1 polymorphisms, sun exposure and the risk of melanoma. Acta Derm Venereol 91:284–289.

Freedberg IM, Eisen AZ, Wolf K (1999). Fitzpatrick’s dermatology in general medicine, 5th ed. New York: McGraw-Hill.

Gallagher RP, Elwood JM (1994). Epidemiological aspects of cutaneous malignant melanoma; tables of ambient solar ultraviolet radiation for use in epidemiological studies of malignant melanoma. Boston, MA: Kluwer Academic Publishers.

Gefeller O, Tarantino J, Lederer P, Uter W, Pfahlberg AB (2007). The relation between patterns of vacation sun exposure and the development of acquired melanocytic nevi in German children 6-7 years of age. Am J Epidemiol 165:1162–1169.

Holick MF (2004). Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 80 (Suppl):1678S–1688S.

Jackson C, Best N, Richardson S (2006). Improving ecological inference using individual-level data. Stat Med 25:2136–2159.

Jackson CH, Richardson S, Best NG (2008). Studying place effects on health by synthesizing individual and area-level outcomes. Soc Sci Med 67:1995–2006.

Jayasekara H, Karahalios E, Thursfield V, Giles GG, English DR (2009). Season of diagnosis has no effect on survival from malignant melanoma. Int J Cancer 125:488–490.

Lee EY, Williamson R, Watt P, Hughes MC, Green AC, Whiteman DC (2006). Sun exposure and host phenotype as predictors of cutaneous melanoma associated with neval remnants or dermal elastosis. Int J Cancer 119:636–642.

Lee JH, Choi JW, Kang YS (2011). Frequencies of BRAF and NRAS mutations are different in histologic types and sites of origin of cutaneous melanoma: a meta-analysis. Br J Dermatol 164:776–784.

Narayanan DL, Saladi RN, Fox JL (2010). Ultraviolet radiation and skin cancer. Int J Dermatol 49:978–986.

Rosso S, Sera F, Segnan N, Zanetti R (2008). Sun exposure prior to diagnosis is associated with improved survival in melanoma patients: results from a long-term follow-up study of Italian patients. Eur J Cancer 44:1275–1281.

Skin Cancer Foundation (2012). Melanoma causes and risk factors. Available at: http://www.skincancer.org. [Accessed 31 October 2012].