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The association between residential pesticide use and cutaneous melanoma

Cristina Fortes[a,*], *Simona Mastroeni*[a], *Franco Melchi*[b], *Maria Antonietta Pilla*[a], *Massimo Alotto*[a], *Gianluca Antonelli*[a], *Diana Camaione*[a], *Simone Bolli*[a], *Elisabetta Luchetti*[a], *Paolo Pasquini*[a]

[a]*Clinical Epidemiology Unit, Istituto Dermopatico dell'Immacolata (IDI-IRCCS), Via dei Monti di Creta, 104, 00167 Rome, Italy*
[b]*VIII Dermatology Unit, Istituto Dermopatico dell'Immacolata (IDI-IRCCS), Rome, Italy*

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ABSTRACT

Occupational pesticide exposure has been linked to cutaneous melanoma in epidemiological studies. We studied the association between cutaneous melanoma and the residential use of pesticides. This is a case-control study of cutaneous melanoma (287 incident cases; 299 controls). Data on pesticide use was obtained with a standardised interview. An increased risk of melanoma was found for high use (⩾4 times annually) of indoor pesticides (odds ratio (OR) = 2.18; 95% confidence intervals (CI) 1.07–4.43) compared to low use (⩽1 times annually), after adjustment for sex, age, education, sun exposure and pigmentary characteristics. Subjects exposed for 10 years or more had two and a half times the risk (OR = 2.46; 95% CI 1.23–4.94) of those exposed for less than 10 years. A dose response was observed for the intensity of pesticides use (p_{trend} = 0.027). The results indicate that residential pesticide exposure may be an independent risk factor for cutaneous melanoma.

1. Introduction

Cutaneous melanoma is an increasingly common malignancy of the melanocytes, which has steadily increased over the past decades.[1] IARC data shows that the incidence of cutaneous melanoma changes according to sex and geographical location. In Europe the highest melanoma incidence is seen in northern Europe (11.9 and 14.3 cases per 100,000 inhabitants for males and females respectively) and the lowest in the south (8.5 and 8.4 cases per 100,000 inhabitants for males and females respectively). Although in subjects of 65 years and over the incidence of melanoma increases in both regions, in the south it is 22/100,000 for males and 19.4/100,000 for females, and in the north it is estimated to be 39.2/100,000 for males and 31.1/100,000 for females.[2]

The individual risk of cutaneous melanoma seems to depend upon two sets of factors: ultraviolet radiation exposure (e.g. sun exposure, tanning bed and sunlamps) and individual characteristics of each subject, including the high number of common nevi, the presence of atypical nevi, family history, fair eye and skin colour, inability to tan, high density of freckles, pre-malignant lesions and skin cancer lesions.[3,4]

It cannot be denied that sun exposure is the best identified environmental risk factor for melanoma; however, the proportion of cases attributable to sun exposure has been estimated as circa 30% of the risk.[5] This could be explained by either recall bias of sun exposure[6] or by other, little explored potential risk factors, such as pesticides.

Pesticides belong to a wide group of chemicals that are of increasing concern in public health debates. All pesticides are

* *Corresponding author*: Tel.: +39 6 6646 4305; fax: +39 6 6646 4307.
E-mail address: c.fortes@idi.it (C. Fortes).
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poisonous by definition with a risk related to the degree of chemical toxicity and exposure.[7,8] Absorption resulting from dermal exposure is the most important route of uptake for exposed subjects.[8]

Over the years many studies have suggested a link between pesticides and increased melanoma risk. In one study an excess risk of cutaneous melanoma (O/E 2.13) was found around a pesticide factory,[9] while in another it was reported as the predominant cancer in banana plantation workers with high pesticide exposure (SIR = 197; 95% CI: 94–362).[10] An increased incidence of melanoma was also observed in the Vietnam War veterans who performed aerial pesticide spraying,[11] and still other publications[12–14] have suggested that farmers, veterinarians and agricultural workers are at a particularly high risk of melanoma because of pesticide use.

To the authors' knowledge, no previous study has investigated the risk of residential pesticide exposure and cutaneous melanoma. The aim of our study is to evaluate the association between residential pesticide exposure and cutaneous melanoma in a non-occupational exposed population.

2. Patients and methods

A hospital-based case-control study of cutaneous melanoma was conducted at a referral hospital for skin diseases (IDI-San Carlo) in the Lazio region of Italy. Eligible cases were Caucasians aged 18 years or more, resident in Lazio and admitted to the hospital between May 2001 and May 2003, with a new histologically confirmed diagnosis of primary malignant cutaneous melanoma. Selection was confined to Caucasian subjects because of the limited numbers of other racial and ethnic groups. IDI-IRCCS ethical committee approved the study, and written informed consent was obtained from all participants.

Controls were selected from the patients admitted to the hospital during the same period, from the same geographical area and in the following hospital wards: General Surgery, Vascular Surgery, Orthopaedics, ENT, and General Medicine. The control subjects were frequency matched to cases by gender and age (in 5-year age strata).

A total of 652 subjects were approached (321 cases and 331 controls). The response rate was 94.7% among cases and 92.1 among controls. A total of 304 cases and 305 controls gave written consent. A full skin examination and interview were carried out. Among the 609 participants, 23 subjects (21 males and 2 females) were then excluded due to occupational pesticide exposure leaving 287 cases and 299 controls.

After obtaining informed consent, the participants were interviewed by two trained researchers with a structured questionnaire and then clinically examined for pigmented lesions. The questionnaire included socio-demographic characteristics, a personal medical history, phenotype traits (skin photo type; skin, hair and eye colour), familial history of skin cancer, lifetime sunlight exposure, sunburn history, sun bed and lamp use and residential pesticide use (both indoors and outdoors).

The pigmented lesions were identified and recorded according to the IARC protocol.[15] Acquired melanocytic nevi were defined as brown to black pigmented maculae or papules of 2 mm or more in diameter, darker in colour than the surrounding skin and clinically different from freckles, lentigines, cafe-au-lait spots, seborrheic keratoses, and pigmented basal cell carcinomas. The number of nevi (>2 mm) over the entire skin surface (except for the scalp, pubic region and perineum) were recorded and then classified as none, few (1–24), moderate (25–59), or many ($\geqslant$60).

An 'atypical naevus' was defined as a melanocytic lesion ($\geqslant$5 mm) with at least two of the following features: irregularity or ill defined borders, variegated or an irregular pigment distribution, background erythema, or accentuated skin markings. The atypical naevi found were recorded systematically and classified into two groups: none, $\geqslant$1. Other skin and individual characteristics such as freckles, solar lentigines, actinic keratoses and a past history of skin cancer were also recorded. Solar lentigines were classified as: none, few (limited to a single body part), moderate (two body areas), or many (more than two body areas).

The Fitzpatrick system was used to classify skin photo type (burning and tanning tendency).[16] Hair colour at 20 years old was classified as red and blonde, light brown, dark brown and black. The eye colour was divided into three categories: blue, grey and green; light brown; dark brown and black. Two categories were used for skin colour (dark and fair). A skin, eye and hair colour chart was used to help define skin, eye and hair colour during the interview.

Sun exposure history included the average daily hours spent outdoors in three different life periods: under 12 years, 12–18 years and 19 years and more. Indicators of intermittent exposure were: average daily hours spent outdoors during vacation, sunburn episodes and sun bed or lamp use. Chronic exposure indicators were: average daily hours spent outdoors in recreational activities, occupational sun exposure and lifetime sun exposure. Lifetime sun exposure was the sum of the average hours spent outdoors during lifetime. Average daily hours spent outdoors were divided into two categories ($\leqslant$5 and $\geqslant$6 h). Lifetime sun exposure was classified into terciles (low: <26; medium: 27–36; high: $\geqslant$37 h) based on the controls distribution. Occupational sun exposure was classified as only indoors or outdoors, or both.

Sunburn information (pain and erythema and/or blisters for more than 24 h) and sun protection behaviour such as the habitual use of sunscreens (SPF $\geqslant$15) and/or a hat and/or T-shirt was taken for each lifetime period. Sunburn episodes were classified into four categories (none; 1; 2–5; $\geqslant$6). Sun protection indicators were categorised as never/rarely and often/always.

Residential pesticide exposure was assessed by a 35-item questionnaire. All cases and controls were asked to indicate average frequency and length of pesticide use, type of pesticide used (e.g. insecticides, fungicides, rodenticides, herbicides) and commercial name. The questionnaire was divided into two sections: indoor pesticide (for mosquitoes, ants, flies, spiders, cockroaches, mice, wasps, moths, termites, mites) and outdoors pesticide use (terrace, yard, garden). Pesticide definition, purpose of use (e.g. herbicides to eliminate chickweed; rodenticides for mice and rat control, insecticides for ants and cockroaches; fungicides against fungi on plants), a list of commercial names and illustrations were used to help recall memory. The frequency of pesticide exposure indoors and outdoors was defined on a four-point scale as follows: never, once annually or less, two or three

times annually, four times and more annually. For each pesticide variable, the four-point categorical scale was combined. Combination of categories was based on the overall distribution among controls. For the frequency of use of pesticides, three categories representing low (⩽1 times annually), medium (2–3 times annually) and high exposure (⩾4

Table 1 – Socio-demographic, clinical and histological characteristics of the subjects participating in the study and diagnosis of the controls

	N = 287		N = 299	
	Cases[a]	%	Controls[a]	%
Sex				
Males	127	44.3	139	46.5
Females	160	55.7	160	53.5
Age(yr)				
< 25	8	2.8	21	7.0
25–34	36	12.5	38	12.7
35–44	52	18.1	52	17.4
45–54	57	19.9	54	18.1
55–64	65	22.6	63	21.1
65–74	50	17.4	56	18.7
⩾75	19	6.6	15	5.0
Education(yr)				
<8	44	15.4	63	21.1
8–13	179	62.6	205	68.6
>13	63	22.0	31	10.4
Residence				
City of Rome	240	83.6	266	89.0
Outside Rome	47	16.4	33	11.0
Anatomic site				
Head/neck	23	8.0	–	–
Trunk	137	47.7	–	–
Upper limb	43	15.0	–	–
Lower limb	84	29.3	–	–
Other specified sites	0	–	–	–
Types of melanoma				
Superficial spreading	220	76.7	–	–
Nodular	30	10.5	–	–
Acral lentiginous	2	0.7	–	–
Mixed	12	4.2	–	–
In situ	15	5.2	–	–
Unclassified	8	2.8	–	–
Cell type†				
Epithelioid	192	73.8	–	–
Naevocytic	4	1.5	–	–
Spindle	13	5.0	–	–
Clear	1	0.4	–	–
Mixed	23	8.8	–	–
Unclassified	27	10.4	–	–
Diagnosis				
Benign neoplasms	–	–	31	10.4
Endocrine system and disease at the immune system	–	–	4	1.3
Diseases of the nervous system and sense organs	–	–	11	3.7
Diseases of the circulatory system	–	–	82	27.4
Diseases of the respiratory system	–	–	15	5.0
Diseases of the digestive system	–	–	24	8.0
Diseases of the genitourinary system	–	–	36	12.0
Complications of pregnancy, child birth and the puerperium	–	–	1	0.3
Diseases of the skin & subcutaneous tissue	–	–	30	10.0
Diseases of the musculoskeletal system & connective tissue	–	–	42	14.0
Congenital abnormalities	–	–	10	3.3
Symptoms, signs & ill defined conditions	–	–	4	1.3
Jnjury	–	–	9	3.0

a Totals may vary because of missing value. † Only for invasive melanoma (Clark ⩾ II).

times annually) were formed when possible, while for duration only two categories were used.

Unconditional logistic regression was the method chosen for the statistical analysis. Using the low exposure category as a baseline, odds ratios (ORs) and 95% confidence intervals (CI) for the intermediate and high exposure categories were calculated.

Sex, age, years of school attendance, hair colour, skin photo type, freckles, nevi and sun burn episodes in childhood were considered in the regression models as potential confounders. The likelihood ratio test was used to help decide whether to keep each covariate in the model.

To test if the effect of pesticide exposure on melanoma would increase systematically with the level of exposure, we included frequency of use of pesticides as an ordinal variable in the logistic regression and tested for trend (Wald test). Since the non-exposed subjects may differ from the exposed subjects on uncontrolled confounders, and this fact could cause biased estimates, we also performed the dose-response analysis omitting the non-exposed subjects (category zero).

We also evaluated effect modification by sex, age, phenotype characteristics and sun exposure variables for each pesticide variable.

All analyses were performed using the statistical software package PC-STATA (Stata 9.0; StataCorp LP, College Station).

3. Results

The mean age of cases and controls was 52.7 years (standard deviation (SD) = 15.4) and 51.1 years (SD = 16.1), respectively.

Table 2 – Association between subjects' pigmentary characteristics and cutaneous melanoma

	N = 287		N = 299		OR[bc]	95%CI[bc]
	Cases[a]	%	Controls[a]	%		
Hair colour						
Black/dark brown	117	40.8	201	67.2	1	
Light brown	113	39.4	74	24.7	2.74	1.87 to 4.02
Fair/blond/red	57	19.9	24	8.0	4.33	2.53 to 7.42
Eye colour						
Black/dark brown	98	34.1	138	46.2	1	
Light brown	62	21.6	63	21.1	1.42	0.91 to 2.21
Blue/grey/green	127	44.3	98	32.8	1.92	1.32 to 2.81
Skin colour						
Dark	46	16.0	125	42.2	1	
Fair	241	84.0	171	57.8	3.93	2.64 to 5.86
Skin photo type[d]						
III–IV	95	33.2	174	58.2	1	
I–II	191	66.8	125	41.8	2.89	2.04 to 4.09
Presence of freckles						
No	157	57.5	236	81.4	1	
Yes	116	42.5	54	18.6	3.38	2.28 to 5.00
Solar lentigines						
None	12	4.2	32	10.8	1	
Few/moderate	36	12.7	91	30.6	1.08	0.50 to 2.35
Many	236	83.1	174	58.6	3.94	1.91 to 8.12
Common nevi (*n*)						
0–24	104	36.2	206	68.9	1	
25–59	69	24.0	53	17.7	3.35	2.10 to 5.34
⩾60	114	39.7	40	13.4	8.02	4.95 to 13.0
Atypical nevi (*n*)						
0	195	67.9	259	86.9	1	
⩾1	92	32.1	39	13.1	3.58	2.31 to 5.56
Actinic keratosis/non melanoma skin cancer						
No	240	86.0	258	89.6	1	
Yes	39	14.0	30	10.4	1.37	0.79 to 2.39
Family history of skin cancer						
No	270	95.7	284	96.3	1	
Yes	12	4.3	11	3.7	1.14	0.49 to 2.66

a Totals may vary because of missing value.
b OR, odds ratio; CI, confidence intervals.
c Odds ratio adjusted for age and sex.
d I: always burns, never tans; II: often burns, tans minimally; III: rarely burns, tans well; IV: never burns, tans profusely.

Table 3 – Association between sun exposure and cutaneous melanoma

	N = 287		N = 299		OR[bc]	95%CI[bc]
	Cases[a]	%	Controls[a]	%		
Intermittent sun exposure						
Time spent outdoors during vacation in childhood (hours)						
⩽5	33	12.0	23	8.0	1	
⩾6	242	88.0	265	92.0	0.64	0.36 to 1.12
Time spent outdoors during vacation in adolescence (hours)						
⩽5	41	14.9	39	13.4	1	
⩾6	234	85.1	251	86.6	0.92	0.56 to 1.49
Time spent outdoors during vacation in adulthood (hours)						
⩽5	66	23.3	87	29.8	1	
⩾6	217	76.7	205	70.2	1.50	1.02 to 2.21
Sunburns in childhood						
None	125	55.6	196	75.7	1	
1	16	7.1	17	6.6	1.63	0.72 to 3.03
2–5	50	22.2	30	11.6	2.83	1.58 to 4.33
⩾6	34	15.1	16	6.2	3.60	1.88 to 6.92
Sunburns in adolescence						
None	128	53.6	184	69.4	1	
1	26	10.9	25	9.4	1.58	0.86 to 2.90
2–5	55	23.0	40	15.1	2.08	1.28 to 3.38
⩾6	30	12.6	16	6.0	2.69	1.39 to 5.19
Sunburns in adulthood						
None	121	47.6	175	62.9	1	
1	34	13.4	33	11.9	1.47	0.85 to 2.52
2–5	58	22.8	47	16.9	1.76	1.12 to 2.77
⩾6	41	16.1	23	8.3	2.49	1.41 to 4.41
Use of SPF15 sunscreens in childhood						
Never/rarely	200	82.0	225	84.9	1	
Often/ever	44	18.0	40	15.1	1.92	1.06 to 3.48
Use of SPF15 sunscreens in adolescence						
Never/rarely	225	83.0	241	84.6	1	
Often/ever	46	17.0	44	15.4	1.18	0.72 to 1.94
Use of SPF15 sunscreens in adulthood						
Never/rarely	157	55.5	181	62.8	1	
Often/ever	126	44.5	107	37.2	1.38	0.95 to 2.01
Use of hat and/or T-shirt in childhood						
Never/rarely	166	67.5	193	69.4	1	
Often/ever	80	32.5	85	30.6	1.07	0.73 to 1.57
Use of hat and/or T-shirt in adolescence						
Never/rarely	201	71.0	220	74.6	1	
Often/ever	82	29.0	75	25.4	1.35	0.86 to 2.11
Use of hat and/or T-shirt in adulthood						
Never/rarely	220	80.3	245	85.1	1	
Often/ever	54	19.7	43	14.9	1.14	0.78 to 1.66
Use of artificial sun bed and/or sunlamp in adulthood (times/yr)						
Never	224	78.0	239	79.9	1	
⩾1	63	22.0	60	20.1	1.32	0.84 to 2.08
Chronic sun exposure						
Time spent outdoors during recreational activities in childhood (hours)						
⩽5	113	41.2	111	38.4	1	
⩾6	161	58.8	178	61.6	0.86	0.60 to 1.23
Time spent outdoors during recreational activities in adolescence (hours)						
⩽5	138	50.7	154	52.9	1	
⩾6	134	49.3	137	47.1	1.11	0.79 to 1.57

Table 3 – *continued*

	N = 287		N = 299		OR[bc]	95%CI[bc]
	Cases[a]	%	Controls[a]	%		
Time spent outdoors during recreational activities in adulthood (hours)						
⩽5	198	70.0	202	68.9	1	
⩾6	85	30.0	91	31.1	1.02	0.70 to 1.47
Lifetime sun exposure (hours)						
Low (⩽26)	104	39.0	95	33.3	1	
Medium (27–36)	74	27.7	102	35.8	0.67	0.44 to 1.01
High (⩾37)	89	33.3	88	30.9	0.95	0.62 to 1.45
Occupational exposure						
Indoor	212	74.1	206	69.4	1	
Indoor/outdoor	41	14.3	54	18.2	0.74	0.47 to 1.18
Outdoor	33	11.5	37	12.5	0.84	0.49 to 1.43

a Totals may vary because of missing value.
b OR, odds ratio; CI, confidence intervals.
c Odds ratio adjusted for age and sex.

In our study, 71% of subjects reported use of at least one pesticide product in the home. Pyrethroid compounds were the most common (34%) followed by carbamates (29%).

Table 1 shows subjects' main demographic characteristics, the diagnosis of the hospital controls, the anatomic site and the frequency distribution of histological types of cutaneous melanoma. Cases were more highly educated than controls. The superficial spreading cutaneous melanoma was the most frequently seen (77%) and the trunk was the most common site (48%).

Table 2 shows that approximately 59% of cases had fair hair and 84% fair skin, whereas the controls were 33% and 58%, respectively. The OR for subjects with light brown hair was found to be 2.74 (95% CI 1.87–4.02) and for blonds and red hairs 4.33 (95% CI 2.53–7.42) versus subjects with dark brown and black hair. Fair skin versus dark complexion had an approximately four-fold risk of cutaneous melanoma (3.93; 95% CI 2.64–5.86). The OR for those with skin photo types II and I was 2.89 (95% CI 2.04–4.09) when compared to subjects with skin photo types III and IV.

The presence of freckles (OR: 3.38; 95% CI 2.28–5.0), light colour eyes (blue, green, grey) (OR 1.92; 95% CI 1.32–2.81) and many solar lentigines (OR: 3.94; 95% CI 1.91–8.12) were all associated with an increased cutaneous melanoma risk, as was an elevated number of common nevi (25–59 nevi, OR: 3.35; 95% CI 2.10–5.34; ⩾60 nevi, OR: 8.02; 95% CI 4.95–13.0) and one atypical nevi or more (OR: 3.58; 95% CI 2.31–5.56). The presence of actinic keratosis lesions and/or a past history of nonmelanocytic skin cancer and familial history of skin cancer were associated with an increased risk, although not statistical significant.

Table 3 shows that sunburn at any time was associated with an increased risk of melanoma. Subjects who reported two or more sunburn episodes in childhood had circa a three-fold risk of cutaneous melanoma (OR: 2.83, 95% CI 1.58–4.33). An increased risk was also found for subjects spending 6 h or more daily outdoors while on vacation during adult life (OR: 1.50, 95% CI 1.02–2.21), although it is not statistically significant. An increased risk, although not statistical significant, was found for sun lamp or bed use. No effect was found for sun protection measures.

Lifetime sun exposure, occupational sun exposure, and the number of hours spent outdoors in recreational activities, were not associated with an increased risk for melanoma.

Table 4 depicts the association between residential pesticides use and melanoma. The most frequent products used were insecticides. Subjects highly exposed (⩾2 times annually) to pesticides indoors and/or outdoors, had a 63% increased risk for melanoma. A two-fold increased risk was observed for those exposed to indoor pesticides for four times or more annually (OR: 2.0; 95% CI 1.23–3.24). Subjects exposed to indoor pesticides for 10 years or more were at an increased risk (OR: 1.62; 95% CI 1.10–2.38) in comparison to subjects exposed to less than 10 years. An increased risk, although not statistically significant, was observed for pesticide use outdoors.

Table 5 reports the results of the multivariate analysis for all participants and for only exposed subjects. The risk associated with intensity and duration of indoor pesticide use remained statistically significant after adjustment for sex, age, education, pigmentary characteristics and sun exposure. An increased risk of melanoma was found for high use (⩾4 times annually) of indoor pesticides (OR = 2.18; 95% CI 1.07–4.43) compared to low use (⩽1 times annually). Subjects exposed to 10 years or more had two and a half times the risk (OR: 2.46; 95% CI 1.23–4.94) in comparison to subjects exposed to less than 10 years. A significant trend was observed for intensity of use of pesticides indoors (p_{trend} = 0.027). The increased risk observed for intensity and duration of use of pesticides outdoors disappeared after adjustment for confounders.

When we restricted the analysis to only invasive cutaneous melanoma the risk associated with frequency and duration of indoor pesticides remained statistically significant (model 3, OR: 2.08; 95% CI 1.01–4.28; model 4, OR: 2.43; 95%CI 1.20–4.90).

When the analysis was restricted only to exposed cases and controls, the ORs increased. The ORs for high indoor

Table 4 – Association between residential pesticides use and cutaneous melanoma

	N = 287		N = 299		OR[bc]	95%CI[bc]
	Cases[a]	%	Controls[a]	%		
General use of pesticides						
Ever use						
No	97	34.2	111	37.6	1	
Yes	187	65.8	184	62.4	1.16	0.82 to 1.64
Frequency of use (times/yr)						
Low (⩽1)	181	68.6	212	77.7	1	
High (⩾2)	83	31.4	61	22.3	1.63	1.10 to 2.41
Duration(yr)						
<10	135	56.0	163	64.9	1	
⩾10	106	44.0	88	35.1	1.43	0.99 to 2.08
Pesticides used indoor						
Pesticides use by type						
Mosquitoes[d]	41	23.2	34	20.9		
Ants[d]	20	11.3	38	23.3		
Flies[d]	6	3.4	5	3.1		
Spider and cockroaches[d]	3	1.7	5	3.1		
Mice[d]	3	1.7	1	0.6		
Wasps[d]	0	–	0	–		
Moths[d]	1	0.6	1	0.6		
Termites[d]	0	–	0	–		
Mites[d]	0	–	1	0.6		
Mixed use[e]	103	58.2	78	47.9		
Frequency of use (times/yr)						
Low (⩽1)	153	57.5	192	68.1	1	
Medium (2–3)	59	22.2	54	19.1	1.38	0.89 to 2.13
High (⩾4)	54	20.3	36	12.8	2.00	1.23 to 3.24
Duration(yr)						
<10	138	59.7	182	70.8	1	
⩾10	93	40.3	75	29.2	1.62	1.10 to 2.38
Pesticides used outdoor						
Pesticides use by type						
Herbicides[d]	3	4.2	2	3.1		
Insecticides[d]	46	64.8	44	68.8		
Fungicides[d]	4	5.6	4	6.3		
Mixed use[e]	18	25.4	14	21.9		
Frequency of use (times/yr)						
Low (⩽1)	240	89.2	250	89.6	1	
High (⩾2)	29	10.8	29	10.4	1.00	0.58 to 1.73
Duration (yr)						
<10	233	86.3	245	89.7	1	
⩾10	37	13.7	28	10.3	1.32	0.77 to 2.27

a Totals may vary because of missing value.
b OR, odds ratio; CI, confidence intervals.
c Odds ratio adjusted for age and sex.
d Exclusive use.
e Use of more than one pesticides type.

pesticide exposure (⩾4 times yearly) and duration (⩾10 years) increased to 2.78; 95% CI 1.29–5.98 ($p_{trend} = 0.006$) and to OR: 2.77; 95% CI 1.31–5.85, respectively.

Common nevi, hair colour, skin photo type, presence of freckles and sunburn in childhood remained statistically significant in the six models.

There was no evidence of confounding by other sun exposure variables. We also controlled, one at a time in the model, for other potential melanoma risk factors, such as eye and skin colour, atypical nevi, solar lentigines, presence of actinic keratosis and/or a past history of skin cancer, time spent outdoors during vacation, the use of sun protective measures and the use of protection while using pesticides (e.g. gloves, filter face masks, special clothes). None of these variables made any statistical contribution to the model.

We checked the effect modification by age, sex and sun exposure variables. No statistical interaction was seen.

Table 5 – Residential pesticides use and cutaneous melanoma: multivariate analysis

Model	Variables	OR[ab]	95%CI[ab]	p-value [c]
General use of pesticides				
	Frequency of use (times/yr)			
1	(⩽1)	1		
	High (⩾2)	1.53	0.89 to 2.61	
	Duration (yr)			
2	<10			
	⩾10	1.98	1.06 to 3.71	
Pesticides used indoors				
	Frequency of use (times/yr)			
3	Low (⩽1)	1		*0.027*
	Medium (2–3)	1.61	0.82 to 3.15	
	High (⩽4)	2.18	1.07 to 4.43	
	Duration (yr)			
4	<10			
	⩾10	2.46	1.23 to 4.94	
Pesticides used outdoors				
	Frequency of use (times/yr)			
5	Low (⩽1)	1		
	High (⩾2)	0.91	0.48 to 1.73	
	Duration (yr)			
6	<10			
	⩾10	1.01	0.54 to 1.88	

a OR, odds ratio; CI, confidence intervals.
b Odds ratio adjusted for age, sex, education, hair colour, skin photo type, presence of freckles, number of nevi, sunburn episodes in childhood and an indicator of pesticides use.
c Test for trend (Wald test).

4. Discussion

Pesticides are used extensively in agriculture with a wide range of compounds used as insecticides, herbicides, fungicides, and rodenticides; however, pest control is not restricted to agriculture, since they are also used in domestic settings. Epidemiological studies in the United States and Europe[17,18] estimated that around 80% of families use pesticides in or around the home and therefore health concerns arise from chronic exposure to pesticides. Results from animal studies show that several pesticides are carcinogens,[8] and exposure to pesticides has been associated with decreased cell-mediated immunity in farmers.[19,20] Studies suggested an association between pesticide exposure in the household and different types of paediatric tumours, such as brain, leukaemia and non-Hodgkin's lymphoma.[21,22]

In the literature, the relationship between occupational pesticide exposure and cutaneous melanoma has been already demonstrated.[23–25] However, no previous study has investigated the risk of residential pesticide exposure and cutaneous melanoma.

In this study we began by investigating the known cutaneous melanoma risk factors such as number of common nevi, phenotypic traits and sun exposure. Our results found an increased risk for light brown, blond and red hair, fair skin colour, blue, green and grey eyes, skin photo types I and II, freckles, solar lentigines, common nevi, a history of sunburn and intermittent sun exposure, all of which agree with previous findings.[26,27] These factors were then incorporated in the model to test the consistency of the association between residential pesticide exposure and cutaneous melanoma. None of these variables had any influence on the results obtained, whether adjusted separately or together.

Our study shows that residential pesticide exposure may be an important risk factor for cutaneous melanoma. Indoor pesticide exposure, particularly, was found to be associated with an increased melanoma risk, even after the careful control of several sun exposure related variables, phenotype traits and number of common nevi. We found that subjects exposed four times or more annually to indoor pesticides had twice the risk of melanoma. The risk was elevated with the increasing use of pesticides indoors and was especially evident in subjects exposed to these products for 10 or more years. Pesticides are a source of reactive oxygen species and melanocytes are extremely susceptible to the dangerous effects of free radicals that can induce DNA damage.[28]

In our study, pyrethroids and carbamates were the most common compounds of indoor pesticides. Pyretroids and carbamates have been shown to be immunosuppressive and neurotoxic in animals and humans.[29,30] Malignant melanoma develops in melanocytes. Embryologically, melanocytes are taken together with nerve cells, from both the upper cranial and lower truncal regions of the neural crest. Since the precursor cell of melanocytes, the melanoblast, is a differentiated nerve cell and the specific target of most insecticides is the nervous system[8,21] it could be hypothesised that insecticides can affect the melanocytic function as they do with nerve cells. In fact, pesticide exposure in the household has been associated with brain cancer.[21]

This study has some strengths and limitations. Epidemiological studies with a low level of participation are particularly vulnerable to selection bias and this may threaten the internal validity of these studies. Our study achieved high study participation. Recall bias is an inevitable problem in case-control studies. The influence of current sun exposure habits may lead to bias where the sun exposure habits of cases, but not controls, change as a result of diagnosis; however, the use of incident cases in this study may have decreased the possibility of this sort of bias. Misclassification of pesticide exposure could be also a problem; however, we evaluated the reproducibility of the questionnaire on residential pesticide exposure used in this case-control study (Fortes C, IDI-IRCCS). Overall, there was a fair to good reproducibility between answers given in two different periods (12 months apart). Agreement for duration and frequency of use of pesticides indoors was 75% and 77%, respectively and it did not vary by case/control status.

In conclusion, our results indicate that residential pesticide exposure may be an independent risk factor for cutaneous melanoma. The findings reinforce the hypothesis already suggested in occupational studies that pesticides may play a role in the aetiology of cutaneous melanoma. Further studies are needed to further confirm this finding.

Conflict of interest statement

None declared.

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