



Review

Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi

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Abstract

A systematic meta-analysis of observational studies of melanoma and one of the most important risk factors, the number of naevi, was conducted in order to clarify aspects of the aetiology of this disease. Following a systematic literature search, relative risks (RRs) were extracted from 46 studies published before September 2002. Dose–response random effects models were used to obtain pooled estimates. Sub-group analysis and meta-regression were carried out to explore sources of between-study variation and bias. Sensitivity analyses investigated the reliability of the results and any publication bias. Number of common naevi was confirmed an important risk factor with a substantially increased risk associated with the presence of 101–120 naevi compared with <15 (pooled Relative Risk (RR) = 6.89; 95% Confidential Interval (CI): 4.63, 10.25) as was the number of atypical naevi (RR = 6.36 95%; CI: 3.80, 10.33; for 5 versus 0). The type of study and source of cases and controls were two study characteristics that significantly influenced the estimates. Case-control studies, in particular when the hospital was the source for cases or controls, appeared to present much lower and more precise estimates than cohort studies.

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1. Introduction

The incidence of cutaneous malignant melanoma (*melanoma*) has been increasing worldwide in Caucasian populations for several decades; between the early 1960s and the late 1980s annual increments of 3–7% were observed in 24 populations of mainly European origin [1], making melanoma the most rapidly increasing cancer in

white populations, except for lung cancer in women [2]. However, there are recent trends showing a deceleration or levelling-off of the rate of increase in melanoma risk in cohorts born after 1950 in some of these populations [3–7]. As a result of the increasing incidence, melanoma is now one of the more common cancers in white populations. It ranks fourth, in men and third in women in high incidence areas such as Australia and New Zealand (non-Maoris) and about sixth in medium incidence areas like the white populations of the United States (US), Scandinavia and parts of Canada [8]. In the US, melanoma is the most common cancer in the “25–29 year” age group in females, and the second most common can-

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cer (after breast cancer) in the “30–34 year” age group [9].

A systematic meta-analysis of all published aetiological studies from 1966 to 2002 was carried out to assess all the major risk factors for cutaneous malignant melanoma: exposure to ultraviolet sun radiations, sunburns, indicators of actinic damage, family history of melanoma, phenotype characteristics, pigmented lesions and skin type. This systematic review of the literature to conduct a comprehensive meta-analysis for all main risk factors on melanoma allowed an in-depth exploration of the associations and interactions among the risk factors and provided some clues with regard to the Epidemiology of melanoma by looking extensively at the inconsistencies and variability in the estimates. Meta-analyses permit questions to be asked such as whether the association of melanoma with some risk factors may depend on the composition of the population under study, the level of exposure in the study population, the definition of disease employed in the studies, or the methodological quality of the studies.

In this manuscript, we present the results of a meta-analysis on cutaneous melanoma risk and common melanocytic and atypical naevi. Among Caucasians, a fairly large body of evidence suggested that the number of melanocytic naevi represents a very good predictor for cutaneous malignant melanoma and that atypical naevi may play an independent role [10–16]. Risk of melanoma rises with increasing number and clinical atypia of naevi, from a small risk in those with few common naevi, to a higher risk in those with larger numbers of common naevi, to a very high risk in those with multiple, clinically atypical naevi [17].

2. Patients and methods

2.1. Definition of the outcome and exposures

The outcome of this systematic meta-analysis was histologically confirmed melanoma, which is commonly divided into four histological types. These are superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma and acral lentiginous melanoma. Most melanomas (around 90%) are cutaneous lesions (superficial spreading and nodular melanomas). Mucosal melanoma and melanomas located on the palms, digits, soles, and nail beds (where acral lentiginous melanoma is found) are unique because they cannot be directly attributable to sun exposure and a different aetiology is involved [18]. Lentigo maligna melanoma, i.e., the invasive form of lentigo maligna, is related to substantial and repeated exposures over many years.

A melanocytic naevus is a benign tumour of melanocytes and naevus cells, which produce melanin, the brown-black skin pigment.

In 1990, the International Agency for Research on Cancer (IARC) proposed a detailed protocol to standardise methodologies in naevus epidemiological studies. It defined countable melanocytic lesions as “brown to black pigmented macules or papules which are reasonably well defined and are darker in colour than the surrounding skin. Countable lesions do not have the features of freckles, solar lentiginos, seborrhoeic keratoses, cafe-au-lait spots, or non-melanocytic lesions”.

Atypical naevi, present in 2–5% of Caucasian adults, are usually larger than common naevi with a more variegated appearance. The IARC protocol for identifying and recording naevi in epidemiological studies uses the following criteria to identify atypical naevi: there must be a macular component in at least one area; in addition, at least three of the following features must be present: (a) border not well defined, (b) size 5 mm or more, (c) colour variegated, (d) contour uneven, (e) presence of erythema.

The term “atypical naevus” is frequently used clinically raising the suspicion of naevi likely to be hiding underlying dysplasia within benign congenital or acquired naevi, whereas there is a poor concordance between the diagnosis of atypical naevi using the clinical phenotype and the histological criteria.

Subjects were classified as having a positive family history of melanoma if they reported one, or more, affected first-degree relative. Families with multiple cases of melanoma often exhibit the dysplastic naevus syndrome, a syndrome characterised by multiple atypical moles that continue to appear in adulthood. It was reported worldwide that persons with the atypical mole (dysplastic naevus) syndrome are at much higher increased risk. Greene [19] estimates that a person who has dysplastic naevi and at least two family members with melanoma has a 500-fold increase in their melanoma risk. However, so few people have this syndrome that in unselected series they account for less than 5% of the total melanoma incidence. Furthermore, one must take into account the fact that, in many of these families, dysplastic naevi as well as environmental factors are involved. In this work, we did not consider studies that analysed cases with atypical mole syndrome because these subjects are already monitored with particular care.

2.2. Data sources, search strategy and selection of articles

Bibliographic searches were conducted using two databases until September 30, 2002:

1. MEDLINE (National Library of Medicine, Bethesda, MD, USA) using PUBMED (www.nlm.nih.gov/entrez/query.fcgi) as the query interface, from January 1966.

2. EMBASE (Elsevier Science, Amsterdam, Holland) using OVID (www.ovid.com/) as the query interface, from January 1988.

No language restrictions were applied. The MEDLINE search was conducted using the following key words: *nevi**, *naevi**, *nevo**, *naevo**, *nevu**, *naevu**, *mole*, *moles*, *pigmented lesion**, *skin lesion**, *cutaneous lesion**, *melanocytic lesion**, in combination with *melanoma* and *case control**, *case-control**, *cohort**, *cross-section**, *cross-section**, *follow up stud**, *follow-up stud**. Successively, we used the following mesh term: *naevus*, *moles* associated with *melanoma* and *case-control studies*, *cohort studies*, *cross-sectional studies*, and *prospective studies*. Similar strategies were used to search EMBASE. The search was limited to human studies only.

Other sources were found in the reference lists of the retrieved articles and preceding reviews on the topic [20–23]. All the retrieved references were entered into the bibliography management software Reference Manager 9 [24] to facilitate the search for duplicate references.

Primary inclusion criteria were developed for the selection of all relevant articles, which were: case-control, cohort or cross-sectional studies published as an original article. Ecological studies, case reports, reviews and editorials were not considered eligible. On the basis of primary inclusion criteria, the initial relevance of all retrieved articles was evaluated by one of us on the basis of the title and abstract.

At the second step, some further inclusion criteria were identified, to obtain a group of studies, each with at least minimal information and comparable results:

1. The studies had to provide sufficient information to estimate the Relative Risk (RR) and 95% Confidence Intervals (CI) (i.e. they had to publish the Odds Ratios (ORs) or RRs or crude data and corresponding standard errors, variance, CIs or *P*-value of the significance of the estimates) for the number of common and/or atypical naevi.
2. The studies had to be independent in order to avoid giving double weight to some studies.
3. For the naevi counts, the results reported had to be comparable. For this reason, the study [48], which analysed the presence of only large naevi in twins was excluded. Congenital naevi were not considered in this meta-analysis because the presence of large congenital naevi is associated with a very high risk of melanoma and such patients already need to be monitored with particular care, whereas there are many anamnestic difficulties in finding small congenital naevi [23]. Tucker *et al.* [14], Rodenas *et al.* [25] and Grob *et al.* [16] reported ORs separated for common naevi with diameters smaller and greater than 5 mm separately; the first estimate was included in the meta-analysis. Bain *et al.* [26] showed two estimates

of risk for palpable and total self-reported naevus count; the first one was considered for the meta-analysis, but the choice was considered unimportant because, as stated in the paper, both may be biased.

4. It was necessary that the populations studied to be homogeneous, at least for the main risk factors for melanoma. Studies could include only cutaneous melanoma and papers [27,28] which considered only cases of palms, plantar foot and vulva were excluded because a distinct aetiology for non-sun-exposed sites was suggested [29]. Studies [30,31] conducted exclusively on melanoma in young subjects (aged less than 19 years) were excluded because they are few in number, as melanoma in childhood is very rare. Childhood melanoma very often arises from a giant naevus that exhibits different pathological characteristics and children with *Xeroderma Pigmentosa* [19] are subject to completely different risk factors, that are mainly genetic [30]. Furthermore, the mean age of the study population, for the other papers included in the meta-analysis, was around 50 years.

Instead of using strict inclusion criteria or quality scores to deal with differences among the studies, we decided to consider wide inclusion criteria in order to start from the premise of using as much data as possible. This allowed us more data in order to investigate more closely any possible sources of variations and inconsistencies, heterogeneity analysis being the primary issue to take into consideration for this meta-analysis. By contrast, the inclusion and exclusion of single studies was evaluated in the sensitivity analysis to investigate their influence on the pooled results and to exclude any potential biases.

2.3. Extraction and unification of the data

A questionnaire was developed to collect some information about each study:

- General information: year of publication, study design, study location, latitude of the region and mean age of the study population.
- Exposure information: definition of common naevi used, definition of atypical naevi used, body region where the naevi were counted, number and profession of observers and categorisations adopted.
- Case information: inclusion or exclusion of specific histological types of melanoma, inclusion of cases with family history of melanoma, number and source of cases, participation rates of cases and percentages of fair-skinned people in the cases and controls.
- Case-control study information: number and source of controls, matching design, blinding of interviewers and response rates of controls.

- Follow-up information: source study population, years of follow-up, blinding on exposure status and completeness of follow-up.
- Statistical information: statistical methods used, adjusting for confounding variables (demographic factors such as age and gender, baseline host characteristics such as hair, eye and skin colour and inherent tendency to burn or tan easily, atypical moles, common moles, sun exposure) and type of effect estimates (OR, RR, and standardised incidence ratio) with corresponding measures of precision, according to the specific exposure category.

All of this information was used to investigate heterogeneity and in the sensitivity analysis.

The distinction among the various measures of RR (e.g. OR, rate ratio and risk ratio) was ignored on the assumption that melanoma is a rare disease. Consequently, every measure of association, adjusted for the maximum number of confounding variables concerning each level of naevi count, and the corresponding CI were translated into log RR ($\log(\text{RR})$) and corresponding variance with the formula proposed by Greenland in [32]. When estimates were not available from the paper, they were calculated from the published crude data. To obtain the standard error of the log odd ratio ($\text{SE}(\log(\text{OR}))$) from the crude data, Woolf's formula was implemented. For Standardised Incidence Rates (SIR), the number of cases could be used to estimate the standard error of the log(SIR). If only the *P*-value was published then a "test-based" estimate was considered [32].

Results from the population controls were chosen for the analysis where data from case-control studies were presented separately for hospital and population controls. Patients, who were hospitalised even for other diseases, may be unrepresentative of the exposure distribution in the source population [36].

2.4. Data analysis strategy

The data obtained were used for the statistical analysis performed in a two-step procedure.

In the first-step, a linear model was fitted, within each study, to estimate the RR, per one naevus of increase. The model was fitted according to the method proposed by Greenland and Longnecker in [37], which provides the natural logarithm of RR, and an estimator of its standard error ($\text{SE}(\log(\text{RR}))$), requiring the estimates and the number of subjects at each category of naevi counts. This dose-response model takes into account the fact that the estimates for separate naevi categories depend on the same reference group. When the number of subjects at each category of naevi count was not available from the papers, coefficients were calculated ignoring the correlation between the estimates of risk in the separate exposure levels.

Since the count of naevi was given by a range, we had to assign to each class the number of naevi corresponding to the midpoint of the range, in order to obtain a numeric value representing each category. Highest categories of naevi count are often open, therefore, a value for the maximum number of naevi had to be specified. When no information about the distribution of common naevi was available, a fix value of 125 was set as the maximum number. The effect of this assignment on this estimate was evaluated in the sensitivity analysis. For the upper categories of atypical naevi, the same amplitude as the preceding category was assigned, because the risk estimate is more sensitive to changes of small numbers of atypical naevi. A dichotomous categorisation was also evaluated. Marrett *et al.* [38] used a self-administered whole-body diagram to assess naevus density with qualitative indications and the four categories "none", "few", "moderate" and "many" were transposed into the following numerical categories: "0", "1–24", "25–49" and "50+", respectively.

In the second-step, the summarised RR was estimated pooling the study-specific estimates by the classical fixed effects and random effects models [32,39]. The homogeneity of the effect across studies is assessed using the large sample test based on the *Q* (Chi-squared) statistic [32,39]. A further analysis was carried out estimating pooled RR for common and atypical naevi together, through the bivariate approach proposed by van Houwelingen *et al.* [40]. Covariance between common and atypical naevi risk estimates was not available, and independence was assumed in the model. An estimate of the covariance was obtained from the model. Log (RR) was fitted with Proc MIXED in SAS [41].

Possible sources of heterogeneity were investigated; sub-group analyses and analysis of variance models were carried out to investigate between-study heterogeneity. Main effects and interactions between the factors were explored by an analysis of variance model. Proc GLM in SAS was used to fit the random effect models on the $\log(\text{RR})$ [41]. Sensitivity analysis was carried out to evaluate whether the results could have been influenced by violations of the inclusion criteria, variations in assignments for mid-points and upper limits, or changes on sub-group heterogeneity analysis. The influence of single papers was also assessed.

Finally, the hypothesis that publication bias might affect the validity of the estimates was tested by funnel-plot-based approaches using the adjusted rank correlation method (Begg's method) [42] and linear regression analysis on radial plot (Egger's method) [43]. "Trim and fill" [44] and Copas and Shi [45] methods were also applied. Estimates of the likely number of missing studies and of the adjusted RRs, calculated by inputting suspected missing studies, were provided.

3. Results

3.1. Literature search and selection

After elimination of duplicates, we obtained five hundred and ninety studies from the MEDLINE and EMBASE searches. Using primary inclusion criteria, fifty-seven articles were identified to be potentially included in the meta-analysis; thirteen additional articles were identified by means of the reference bibliographies, thereby totalling seventy articles. Of those, forty-six were identified as fulfilling the secondary inclusion criteria. The total number of datasets analysed was higher (forty-seven) because MacKie *et al.* [46] reported adjusted OR separately for males and females and these were considered as two independent estimates.

3.2. Study characteristics

An overview of the forty-seven datasets included in the selected group is given in Table 1. These forty-seven datasets included a total of 10 499 cases and 14 256 controls. Among the thirty-eight datasets dealing with common naevi, twenty-six presented the risk estimates for the whole body naevus count and seventeen for naevi counts on the arms. Twenty-seven datasets published the risk estimates for atypical naevi. Twenty-four studies were carried out in European countries, fourteen in North America, seven in Australia and one in Argentina. There were eight cohort studies, all dealing with atypical naevi, thirty-seven case-control studies and two nested case-control studies.

Eleven case-control studies were hospital-based (both cases and controls were from hospitals), whereas eight were population-based (both cases and controls were from the population). Six studies comprised hospital cases with controls drawn from the population, five comprised cases drawn from the population and controls from hospitals, two used controls drawn from visitors to hospitals and one used controls drawn from the neighbourhood. Three case-control studies used both, i.e., population and hospital-based controls. For one study, information on source of cases and controls was not available.

Of the thirty-eight datasets dealing with common naevi, nine presented estimates of risk based on a self-assessment of the naevi count, while for all the twenty-seven datasets on atypical naevi, the assessment of the naevi count was performed by physicians.

Of the total number of papers on common naevi only, five presented estimates adjusted for chronic sun exposure, eighteen adjusted for intermittent sun exposure, twenty-seven adjusted for phenotypic or phototypical factors and one [33] published data with only a crude estimate. Of the total number of the papers on atypical naevi only, five presented estimates adjusted

for chronic sun exposure, eight adjusted for intermittent sun exposure, twenty-two adjusted for phenotypic or photo-typical factors and three [33,23,35] published data with only a crude estimate.

3.3. Relative risk estimates

Calculated dose–response RRs estimates and their corresponding 95% CIs for the melanoma risk, associated with common naevi on the whole body and arms, are presented in Figs. 1 and 2, respectively. RRs for atypical naevi and melanoma are presented in Fig. 3.

We found that χ^2 estimates, which evaluate between-study heterogeneity, were all significant ($\chi^2 = 181.97$, degrees of freedom (df) = 25, $P < 0.001$, for common naevi on the whole body; $\chi^2 = 111.74$, df = 16, $P < 0.001$, for common naevi on arms; $\chi^2 = 390.148$, df = 27, $P < 0.001$, for atypical naevi). This is an indication that the homogeneity assumption is probably not correct and random effects models were performed for common naevi on the whole body, common naevi on the arms and for atypical naevi, to take into account the variation among the studies.

Pooled RRs and CIs, calculated from dose–response models, for common naevi (whole body and arms) are presented for the different classes in Table 2. In Table 3, pooled RRs are described for the thirteen studies that presented a dichotomous categorisation (absence/presence) of atypical naevi and for the fifteen studies that published results for a continuous type of categorisation. Statistically significant associations were found between naevi (common and atypical) count and melanoma. Summary estimates for common naevi, counted on whole body, indicate a significant risk for melanoma even for a medium-low number of naevi, indicated by the category “16–40” naevi compared with “0–15” naevi (pooled RR = 1.47; 95% CI: 1.36, 1.59). People with very high naevi density (“101–120” naevi) present a highly significant risk, almost seven times greater (pooled RR = 6.89; 95% CI: 4.63, 10.25) than people with very few naevi (“0–15” naevi).

The count on an anatomical region (arms) confirms the association between common naevi and melanoma. Risk for people with (“11–15”) common naevi on their arms is almost five times greater than risk for people with no naevi on arms (pooled RR = 4.82; 95% CI: 3.05, 7.62).

Atypical naevi count is confirmed to be a highly significant risk factor for melanoma. Presence of any atypical naevus increased the risk 10-fold compared with the absence of atypical naevi (RR = 10.12; 95% CI: 5.04, 20.32). Even summary RRs for having only one atypical naevus are already considerable (RR = 1.60; 95% CI: 1.38, 1.85), rising up to 10.49 (95% CI: 5.05, 21.76) for 5 atypical naevi (Table 3).

Table 1
Characteristics of the studies on melanocytic naevi and melanoma

First author	Year of publication	Country	Study design	No. of cases	No. of controls	Cases source	Controls source	Common naevi		Atypical naevi
								Body	Arms	
Rhodes [47]	1980	USA	CC	138	217	N.A.	N.A.	–	–	Yes
Beral [66]	1983	Australia	CC	287	574	Hosp	Pop	Yes	–	–
Holman [18]	1984	Australia	CC	511	511	Pop	Pop	–	Yes	–
Green [10]	1985	Australia	CC	183	183	Pop	Pop	–	Yes ^a	–
Sorahan [67]	1985	England	CC	58	182	Hosp	Hosp	–	Yes ^a	–
Elwood [68]	1986	England	CC	83	83	Pop	Hosp	Yes	Yes	–
Swerdlow [11]	1986	Scotland	CC	180	197	Hosp	Hosp	Yes	Yes	–
Cristofolini [69]	1987	Italy	CC	103	205	Hosp	Hosp	Yes	–	Yes
Holly [12]	1987	USA	CC	121	139	Hosp	Hosp	Yes	–	Yes
Bain [26]	1988	USA	N CC	98	190	Pop	Pop	–	Yes	–
Osterlind [70]	1988	Denmark	CC	474	926	Pop	Pop	–	Yes	–
Roush [71]	1988	Australia	CC	246	134	Hosp	Pop + hosp	Yes	–	Yes
Garbe [72]	1989	Germany	CC	200	200	Hosp	Hosp	Yes	–	Yes
MacKie [46]	1989	Scotland	CC	181	181	Pop	Hosp	Yes	–	Yes
Women										
MacKie [46]	1989	Scotland	CC	99	99	Pop	Hosp	Yes	–	Yes
Men										
Rigel [73]	1989	USA	Co	1	281	–	–	–	–	Yes
Dubin [74]	1990	USA	CC	289	527	Hosp	Hosp	Yes	–	–
Elwood [75]	1990	England	CC	195	195	Pop	Hosp	–	Yes	–
Grob [16]	1990	France	CC	207	295	Hosp	Pop	Yes	Yes ^a	Yes
Augustsson [76]	1991	Sweden	CC	121	378	Pop	Pop	Yes	–	Yes
Halpern [77]	1991	USA	CC	105	181	Hosp	Pop	Yes	–	Yes
Tiersten [53]	1991	USA	Co	4	157	–	–	–	–	Yes
Weiss [78]	1991	Germany	CC	1079	778	Hosp	Hosp	Yes	–	Yes
Marrett [38]	1992	Canada	CC	583	608	Pop	Pop	Yes	–	–
Zaridze [79]	1992	Russia	CC	96	96	Hosp	Visit to hosp	–	Yes	–
Halpern [80]	1993	USA	Co	2	89	–	–	–	–	Yes
MacKie [55]	1993	Scotland	Co	5	116	–	–	–	–	Yes
Autier [81]	1994	Bel, Fr, Ger.	CC	420	447	Hosp	Neigh.	–	Yes	–
Garbe [82]	1994	Ger, Au, Swi.	CC	513	498	Hosp	Hosp	Yes	–	Yes
Kang [83]	1994	USA	Co	2	155	–	–	–	–	Yes
Marghoob [54]	1994	USA	Co	–	124	–	–	–	–	Yes
White [84]	1994	USA	CC	256	273	Pop	Pop	–	Yes	–
Westerdahl [85]	1995	Sweden	CC	400	640	Pop	Pop	–	Yes ^a	–
Bataille [86]	1996	England	CC	426	416	Pop	Hosp	Yes	–	Yes
Chen [87]	1996	USA	CC	548	494	Pop	Pop	–	Yes	–
Gulich [13]	1996	Australia	CC	242	276	Hosp	Pop + hosp	Yes	Yes	Yes
Rodenas [25]	1996	Spain	CC	105	138	Hosp	Visit to hosp	Yes	–	Yes
Dabkowski [33]	1997	Poland	CC	74	300	Hosp	Pop	Yes	–	Yes
Kelly [88]	1997	Australia	Co	20	278	–	–	–	–	Yes
Moore [34]	1997	USA	N CC	69	69	Pop	Pop	Yes	–	Yes
Tucker [14]	1997	USA	CC	716	1014	Hosp	Hosp	Yes	–	Yes
Carli [63]	1999	Italy	CC	131	176	Hosp	Pop	Yes	–	Yes
Snels [89]	1999	Holland	Co	3	166*	–	–	–	–	Yes
Mastrangelo [90]	2000	Italy	CC	99	104	Hosp	Pop	–	Yes	–
Naldi [91]	2000	Italy	CC	542	538	Hosp	Hosp	Yes	–	–
Landi [92]	2001	Italy	CC	183	179	Hosp	Pop + hosp	Yes ^b	–	Yes
Loria [93]	2001	Argentina	CC	101	249	Hosp	Hosp	Yes	Yes	–

N.A., not available; Pop, population; Hosp, Hospital; Neigh., neighbourhood; CC, case-control study; Co, cohort study; N CC, nested case-control; Bel, Fr, Ger: Belgium, France and Germany; Ger, Au, Swi.: Germany, Austria and Switzerland; Visit to hosp: visitors to hospitals; USA, United States of America.

^a Only one arm.

^b Only back

* Cohort size.

To make a more reliable comparison between the two types of naevi, a further analysis was conducted on the nineteen studies that published both estimates only, on both common and atypical naevi. This bivariate approach

gave us an indication of a substantial correlation ($r = 0.36$), suggesting that risk for common naevi and the risk for atypical naevi are correlated. We obtained similar results to the ones obtained in the univariate

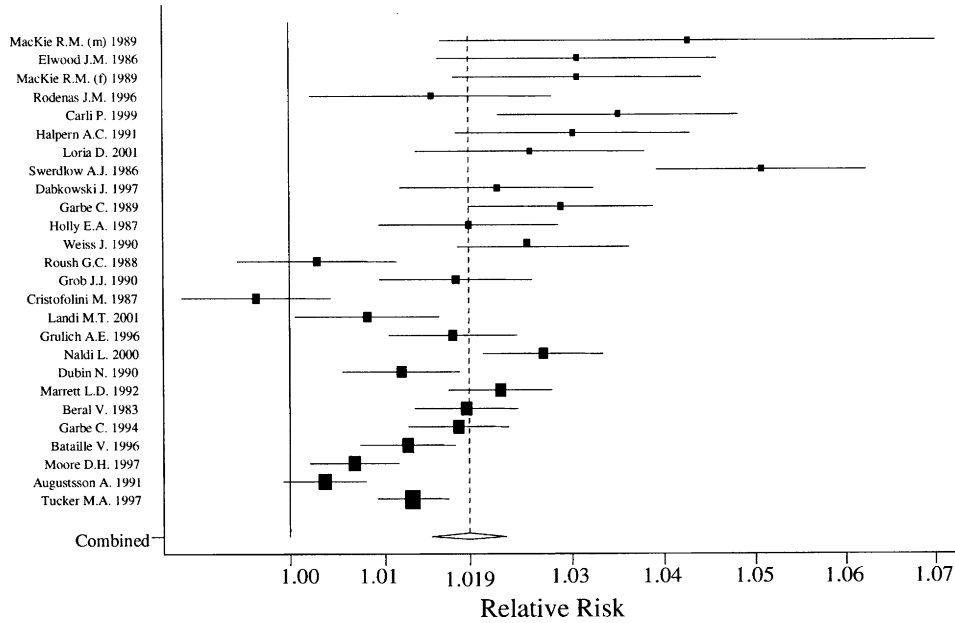


Fig. 1. Dose–response Relative Risks (RRs) and 95% Confidence Intervals (CIs) (95% CIs were calculated using SE(log RR) (standard error of the log add ratio), estimated from the published CI with the formula proposed by Greenland in [37].) of Melanoma associated with Common naevi (whole body). m, male; f, female.

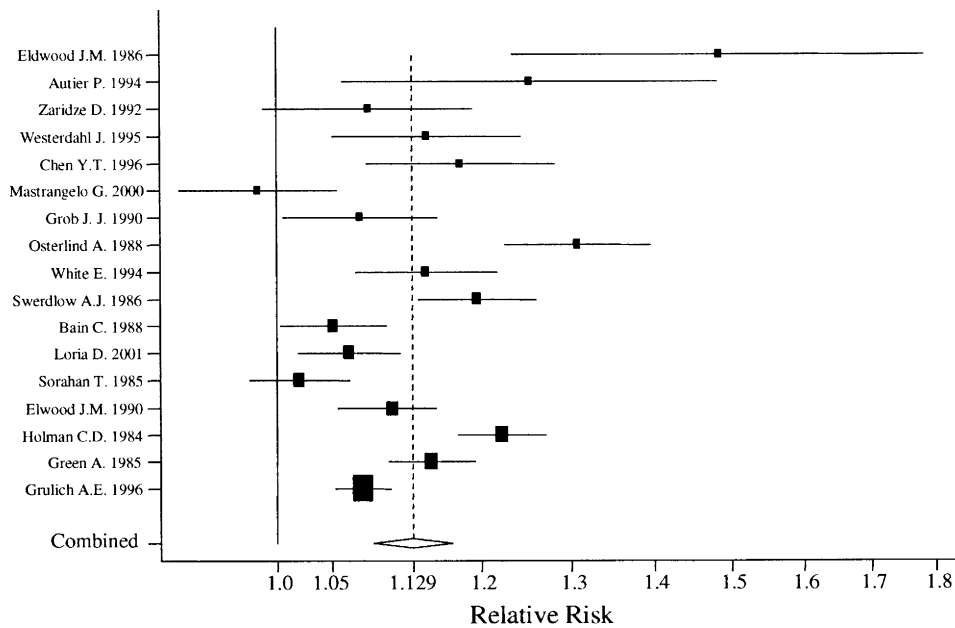


Fig. 2. Dose–response Relative Risks (RRs) and 95% Confidence Intervals (CIs) (95% CIs were calculated using SE(log RR), estimated from the published CI with the formula proposed by Greenland in [37].) of Melanoma associated with Common naevi (Arms).

analysis: the pooled estimate for the increase of one atypical naevus (RR = 1.51 and 95% CI: 1.37, 1.67) is much higher ($P < 0.001$) than that for the increase of one common naevus (RR = 1.02 and 95% CI: 1.01, 1.02).

3.4. Heterogeneity

Studies included in this work vary in a number of aspects of their design and analysis. As previ-

ously stated, several factors, which may have induced differences in outcomes, were investigated with sub-group analyses and analysis of variance models.

Heterogeneity may be investigated in several ways. When we looked at the χ^2 tests that evaluated any differences among groups (this compared pooled estimates of each subgroup with the overall pooled estimate) [32], we noticed that nearly all of the factors considered contrib-

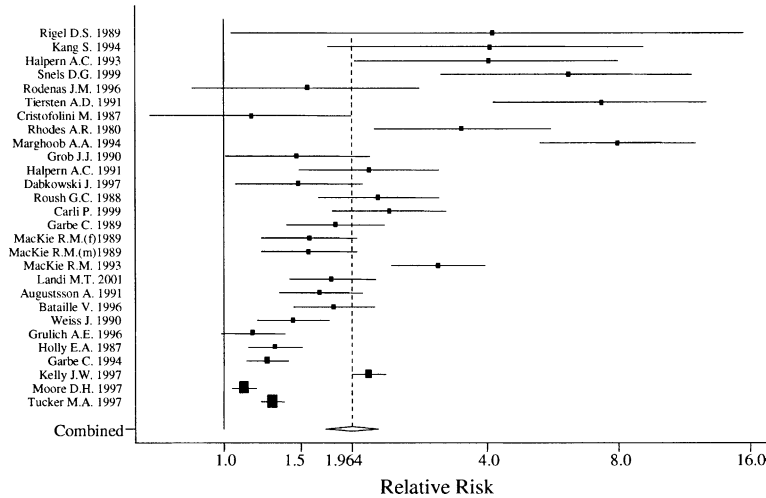


Fig. 3. Dose–response Relative Risks (RRs) and 95% Confidence Intervals (CIs (95% CIs were calculated using SE(log RR), estimated from the published CI with the formula proposed by Greenland in [37].)) of Melanoma associated with Atypical naevi.

Table 2
Pooled estimates for risk of melanoma for an increasing number of common naevi

No. naevi	RR	Lower 95% CI	Upper 95% CI
<i>Whole body</i>			
0–15	1.00		
16–40	1.47	1.36	1.59
41–60	2.24	1.90	2.64
61–80	3.26	2.55	4.15
81–100	4.74	3.44	6.53
101–120	6.89	4.63	10.25
<i>Arms</i>			
0	1.00		
1–5	1.44	1.29	1.60
5–10	2.48	1.90	3.23
11–15	4.82	3.05	7.62

For whole body, No. of studies = 26, Heterogeneity $\chi^2 = 181.970$, $P < 0.001$. For arms, No. of studies = 17, Heterogeneity $\chi^2 = 111.738$, $P < 0.001$.

No., number; 95% CI, 95% Confidence Interval; RR, Relative Risk.

uted significantly to the between-subgroup heterogeneity (data not shown). Among studies considering common naevi in all body, only “dichotomisation of exposure” and “adjustment for chronic sun” did not explain any between-study variability ($\chi^2 = 0.451$ with $P = 0.502$ and $\chi^2 = 0.011$ with $P = 0.918$, respectively). In publications analysing atypical naevi, “adjustment for intermittent sun exposure” and “adjustment for chronic sun exposure” did not seem to play a significant role ($\chi^2 = 1.721$ with $P = 0.19$ and $\chi^2 = 0.133$ with $P = 0.715$, respectively).

We investigated between-study heterogeneity by meta-regression on common naevi over the entire body, on the arms, and on atypical naevi. In order to make comparisons among factors considered for the heterogeneity analysis, we had to consider the “per naevus” analysis to obtain comparable estimates. RR estimates, for one common and atypical naevus, by sub-group factors, are shown in Tables 4 and 5, respectively. One study [47]

Table 3
Pooled estimates of melanoma risk for increasing number of atypical naevi in all body

Naevi	N.	RR	Lower 95% CI	Upper 95% CI	Heterogeneous χ^2	P-value for χ^2
<i>Dichotomous</i>						
Absent	13	1.00			85.34	<0.001
Present		10.12	5.04	20.32		
<i>Continuous</i>						
0	15	1.00			221.87	<0.001
1		1.60	1.38	1.85		
2		2.56	1.91	3.43		
3		4.10	2.64	6.35		
4		6.55	3.65	11.75		
5		10.49	5.05	21.76		

N., number of studies.

Table 4
Heterogeneity: sub-group analysis for common naevi

Common naevi (whole body)						Common naevi (arms)				
Variables	No. of studies	RR	Lower 95% CI	Upper 95% CI	P-value	No. of studies	RR	Lower 95% CI	Upper 95% CI	P-value
<i>Country</i>										
Australia	3	1.013	1.005	1.002		3	1.147	1.065	1.235	
North America	6	1.016	1.010	1.022		3	1.117	1.041	1.198	
North Europe	6	1.027	1.013	1.041		6	1.178	1.084	1.281	
Mediterranean Europe	7	1.017	1.008	1.027		3	1.045	0.993	1.101	
Central Europe	4	1.022	1.017	1.028	0.594	2	1.146	0.999	1.315	0.485
<i>Publication year</i>										
83-89	9	1.023	1.012	1.034		7	1.168	1.107	1.232	
90-01	17	1.018	1.013	1.022	0.383	2	1.100	1.051	1.152	0.163
<i>Matching</i>										
Individual matching	9	1.026	1.018	1.035		9	1.153	1.096	1.214	
Frequency matching	8	1.017	1.013	1.021		7	1.109	1.051	1.17	
No matching	8	1.012	1.005	1.019	0.103	1	1.078	1.006	1.154	0.602
<i>Source of cases</i>										
Hospital	19	1.019	1.015	1.024		8	1.080	1.036	1.125	
Population	7	1.018	1.010	1.025	0.738	9	1.172	1.117	1.229	0.052
<i>Source of control</i>										
Hospital	14	1.022	1.016	1.028		5	1.125	1.049	1.207	
Population	8	1.018	1.011	1.026		10	1.143	1.086	1.202	
Other	4	1.011	1.004	1.018	0.259	2	1.080	1.055	1.106	0.726
<i>Family history of melanoma</i>										
No	6	1.016	1.008	1.024		2	1.060	1.019	1.102	
Yes	19	1.019	1.015	1.024	0.448	15	1.139	1.096	1.184	0.297
<i>Dichotomous exposure</i>										
No	16	1.018	1.013	1.023		14	1.146	1.095	1.199	
Yes	10	1.021	1.014	1.028	0.485	3	1.039	1.011	1.068	0.095
<i>Self count of moles</i>										
No	20	1.018	1.013	1.023		13	1.144	1.098	1.193	
Yes	5	1.020	1.015	1.025	0.434	4	1.081	1.023	1.143	0.277
<i>Adjusted for phenotype characteristics</i>										
No	12	1.016	1.011	1.022		6	1.082	1.021	1.147	
Yes	14	1.021	1.015	1.027	0.355	11	1.155	1.105	1.207	0.145
<i>Adjusted for chronic sun exposure</i>										
No	22	1.019	1.015	1.024		16	1.132	1.091	1.175	
Yes	4	1.018	1.011	1.025	0.915	1	1.078	1.006	1.154	-
<i>Adjusted for acute sun exposure</i>										
No	17	1.017	1.012	1.022		8	1.157	1.100	1.218	
Yes	9	1.023	1.015	1.031	0.254	9	1.103	1.049	1.158	0.258
<i>Adjusted for atypical naevi</i>										
No	15	1.022	1.016	1.028						
Yes	11	1.015	1.010	1.020	0.229					

P-values: Significance of factor from analysis of variance models; RR for melanoma and one common naevus.

did not publish much information on the study design and was not included in several sub-groups examined for heterogeneity analysis.

For common naevi on the arms, we noticed that only the source of cases was an important factor that significantly affected the estimates. Studies with cases drawn from hospitals presented estimates lower than the ones from studies with cases drawn from the population (Fig. 4). Thus, the pooled estimate, for the increase of

one naevus on the arms, for the former (RR = 1.08, 95% CI: 1.04, 1.13) was significantly lower ($P = 0.05$, Table 4) than the estimate for the latter (RR = 1.17, 95% CI: 1.12, 1.23).

For atypical naevi, we obtained similar results (Table 5): when controls were drawn from hospitals, the pooled estimate, for one naevus of increase, was significantly ($P = 0.02$) lower (RR = 1.42, 95% CI: 1.31, 1.55) than the pooled estimate of studies with controls drawn from

Table 5
Heterogeneity: sub-group analysis for atypical naevi

Variables	No of studies	RR	Lower 95% CI	Upper 95% CI	P-value
<i>Type of study</i>					
Case-control	20	1.56	1.41	1.72	
Cohort	8	4.35	2.82	6.69	<0.001
<i>Dichotomous exposure</i>					
No	15	1.60	1.38	1.85	
Yes	13	2.86	2.05	3.99	0.01
<i>Country</i>					
Australia	3	1.77	1.14	2.76	
North America	10	2.52	1.94	3.26	
North Europe	6	2.09	1.58	2.76	
Mediterranean Europe	5	1.72	1.37	2.15	
Central Europe	4	1.44	1.24	1.69	0.45
<i>Publication year</i>					
80–89	8	1.76	1.42	2.18	
90–94	10	2.63	1.85	3.76	
96–01	10	1.69	1.38	2.07	0.22
Case-control studies only					
<i>Matching</i>					
Individual matching	5	1.40	1.18	1.65	
Frequency matching	6	1.47	1.28	1.70	
No matching	7	1.74	1.45	2.08	0.302
<i>Source of cases</i>					
Hospital	14	1.52	1.37	1.69	
Population	5	1.51	1.18	1.92	0.179
<i>Source of controls</i>					
Hospital	9	1.42	1.31	1.55	
Population	6	1.64	1.23	2.19	
Other	3	1.63	1.17	2.26	0.023
<i>Family history of melanoma</i>					
No	6	1.75	1.39	2.20	
Yes	13	1.46	1.31	1.62	0.265
<i>Adjusted for phenotype characteristics</i>					
No	8	1.59	1.36	1.86	
Yes	11	1.46	1.31	1.62	0.517
<i>Adjusted for chronic sun exposure</i>					
No	14	1.55	1.37	1.76	
Yes	5	1.43	1.21	1.67	0.716
<i>Adjusted for acute sun exposure</i>					
No	11	1.59	1.36	1.85	
Yes	8	1.42	1.29	1.56	0.494
<i>Adjusted for common naevi</i>					
No	8	1.51	1.22	1.87	
Yes	11	1.51	1.36	1.68	0.830

P-values: Significance of factor from analysis of variance models; RR for melanoma and one atypical naevus.

the population (RR = 1.64, 95% CI: 1.23, 2.19) or other sources (RR = 1.63, 95% CI: 1.17, 2.26). When we considered the six studies with both, cases and controls drawn from hospitals, the pooled RR was even lower (RR = 1.31, 95% CI: 1.25, 1.37).

The type of study was an important factor ($P < 0.001$) explaining much of the between-study variability with regard to atypical naevi (Table 5). In fact, Fig. 4 shows that RRs, for one atypical naevus, in

case-control studies were much lower and more precise than those in cohort studies.

When only case-control studies were considered, we could observe a considerable reduction in the risk estimates from the dose–response models (Table 6). In fact, the RR for the increase of five atypical naevi (RR = 6.36 95% CI: 3.80, 10.33) was twice as low as the RR calculated considering all types of studies together (RR = 10.49; 95% CI: 5.05, 21.76).

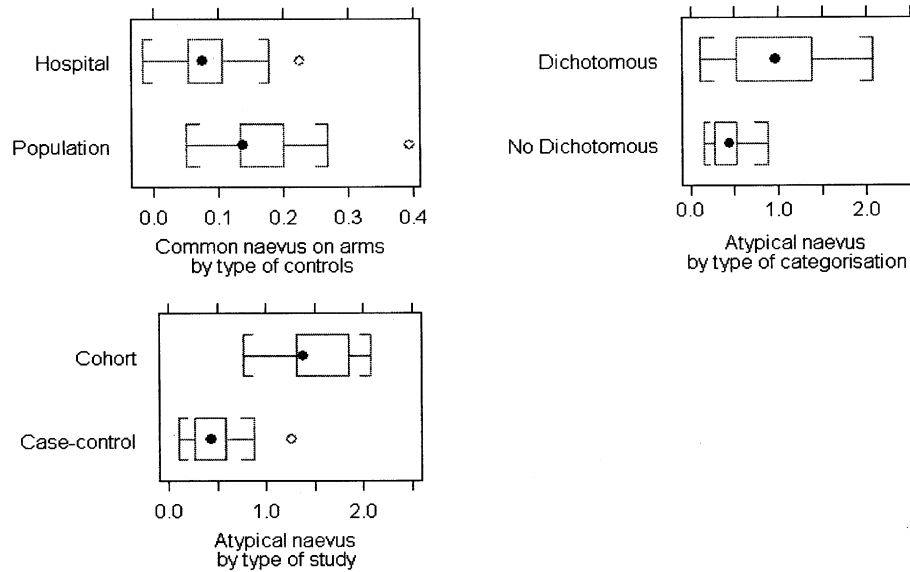


Fig. 4. Box and Whisker plots of log(RR) for the increase of one naevus by study features. The ends of the boxes are the upper and lower quartiles; the median is marked by a black dot inside the boxes.

Table 6

Estimates from meta-analysis for atypical naevi and melanoma from case-control studies

No. naevi	RR	Lower 95% CI	Upper 95% CI
0	1.00		
1	1.45	1.31	1.60
2	2.10	1.71	2.54
3	3.03	2.23	4.06
4	4.39	2.91	6.47
5	6.36	3.80	10.33

No. of studies = 13, Heterogeneity $\chi = 64.694$, $P < 0.001$.

It is highly likely that the type of study was related to the type of categorisation used for the estimates, because cohort studies used dichotomous categories to evaluate whether atypical naevi were present. In fact, cohort studies presented, in total, only 37 cases, whereas case-control studies had, in total, several thousand cases. Thirteen out of the twenty-eight studies, which investigated the association between atypical naevi and cutaneous melanoma, published the results for a dichotomous exposure, in terms of presence or absence of atypical naevus (Fig. 4). It was found that this type of categorisation was associated with the size of the estimates. The pooled estimate (RR = 2.86; 95% CI: 2.05, 3.99) that evaluated the risk for the increase of one atypical naevus from studies with dichotomous categorisation was significantly ($P = 0.010$) higher than in studies that considered more categories (RR = 1.60; 95% CI: 1.38, 1.85).

Some study features were investigated only for case-control studies, because it was not possible to extract much information from the papers on cohort studies.

The likelihood ratio test indicated that only a few two-factor interactions were statistically significant, and only

in the subgroup of case-control studies analysing atypical naevi. However, we dealt with only very sparse data and testing for interactions therefore had a low power.

3.5. Sensitivity analysis

Age was considered the most important confounding variable for the aetiology of melanoma. The estimates included in the analyses were adjusted for age or come from studies with matching for age, except for one [33] for common naevi and three [33,23,35] for atypical naevi. Excluding these studies, the pooled estimates for the increase of one common naevus (RR = 1.02; 95% CI: 1.01, 1.02) and one atypical naevus (RR = 1.98; 95% CI: 1.71, 2.29) did not significantly change. Twenty-one studies published the age ranges: two of them [76,66] presented a very low upper limit (50 and 54 years, respectively), whereas the others varied from 65 to 89 years. Meta-regression model indicated no relationships between the upper limits of the age ranges and the melanoma risk for common ($\beta = 0.004$ with $P = 0.167$) and atypical naevi ($\beta = -0.006$ with $P = 0.130$).

The choice of an upper limit for the highest category was necessary to obtain a mean value for the highest category in the dose-response analysis. The decision to assign a value of 125 common naevi to the upper category with an open end, for the count on the whole body, was investigated. Distributions of naevi, looking at the lower and upper limits of the categories for number of naevi, in all of the included studies, and corresponding rough variation of the number of controls and log(RR) were investigated. The analysis was not straightforward because the number of categories published varied from 2 to 6. The percentages of controls in classes with more

than 100 naevi were very low (from 2% to 7%). The studies with three categories, where the mean lowest limit for the highest category was 53 naevi, presented a mean percentage of controls in the upper categories of 18. The studies which consider four categories, and in which the mean lowest limit for the highest category was 87 naevi, showed that the mean percentage of controls in the upper category decreased to 8; in the two studies that published six categories, where the mean lowest limit for the highest category was 110 naevi, the percentages of controls in the upper categories was only 4.5. Thus, we noticed that by increasing the number of categories, the mean percentage of controls decreased in the upper category and its lower limit was augmented. This suggests that the distribution of naevi is not very different among the studies with a different number of categories. Moreover, eight studies in total, considered 100 naevi as the lowest limit for the upper category. Therefore, an upper limit of 125 was considered as a reasonable intermediate value because it includes all possible situations and it may be a reasonable choice for studies with a lower number of categories.

Pooled random effect estimates, obtained by assigning alternative upper limits for the open-end categories, were sensitive to changes in assignments (for an increase of one naevus the estimates were: RR = 1.022, 95% CI: 1.02, 1.03, for an upper limit of 100; RR = 1.019, 95% CI: 1.015, 1.023, for an upper limit of 125; RR = 1.017, 95% CI: 1.013, 1.020, for an upper limit of 150). As can be seen, there is a clear decreasing trend in the RR estimates with increasing numbers for the upper category.

The impact of the inclusion criteria was analysed (Table 7). Five studies were excluded for different reasons that were not related to dependence from other studies: Youl *et al.* [31] and Whiteman *et al.* [30] were excluded because they only published estimates for melanoma in children and adolescents, Cockburn *et al.* [48] was not considered because only the risk for large naevi (larger than a pencil eraser) in twins was estimated, while Green *et al.* [28] and Rolon *et al.* [27] were not included because mainly acral melanomas were considered in their studies. The pooled random effects estimate for the increase of one common naevus did not change when Green *et al.* [28], Youl *et al.* [31] and Whiteman *et al.* [30] were included in the analysis (RR = 1.020; 95% CI: 1.016, 1.023). Only a slight difference was observed in the RR, for an increase of one common naevus on the arms, when Rolon *et al.* [27] was included in the analysis (RR = 1.13 with 95% CI: 1.09, 1.17; and RR = 1.12 with 95% CI: 1.08; 1.16; with and without Rolon [27], respectively). When we considered large naevi (larger than a pencil eraser), defined in the Cockburn paper [48], as atypical naevi, and we included in the analysis the estimate published for dizygous twins together with estimates published for large naevi (≥ 5 mm) published by

Table 7

List of papers excluded with reasons for exclusion

First author, Year [Ref.]	Main reasons for exclusion [Ref.]
Nordlung, 1985 [94]	Not independent from Roush, 1988 [71]
Dubin, 1986 [95]	Not independent from Dubin 1990 [74]
Green, 1986 [96]	Not independent from Green, 1985 [10]
Rigel, 1988 [97]	Not independent from Rigel, 1989 [73]
Weinstock, 1989 [98]	Not independent from Bain, 1988 [26]
Osterlind, 1990 [99]	Not independent from Osterlind, 1988 [70]
Augustsson, 1991 [100]	Not independent from Augustsson, 1991 [76]
Weiss, 1991 [78]	Not independent from Weiss, 1990 [35]
Kruger, 1992 [101]	Not independent from Garbe, 1989 [72]
Stierner, 1992 [62]	Not independent from Augustsson, 1991 [76]
Zaridze, 1992 [102]	Not independent from Zaridze, 1992 [79]
Schneider, 1994 [103]	Not independent from Moore, 1997 [34]
Carli, 1995 [104]	Not independent from Carli, 1999 [63]
Rieger, 1995 [105]	Not independent from Garbe, 1994 [82]
Carli, 1996 [106]	Not independent from Carli, 1999 [63]
Rodenas, 1997 [107]	Not independent from Rodenas, 1996 [25]
Rolon, 1997 [27]	Only plantar melanoma
Whiteman, 1997 [30]	Melanoma in children less than 15 years
Bataille, 1998 [15]	Not independent from Bataille, 1996 [86]
Green, 1999 [28]	Only melanoma of soles and palms
Masback, 1999 [108]	Not independent from Westerdahl, 1995 [85]
Cockburn, 2001 [48]	Estimates of risk only for large naevi in twins
Landi, 2002 [109]	Not independent from Landi, 2001 [92]
Youl, 2002 [31]	Melanoma in adolescents (15–19 years)

Youl *et al.* [31] and Whiteman *et al.* [30], a slight decrease was observed (RR = 1.86; 95% CI: 1.65, 2.09; whereas the overall estimate was RR = 1.96 with 95% CI: 1.71, 2.26 for each atypical naevus).

Following the observations of some authors [49,50], the method of assessment of naevi is an important aspect of the study design when considering the inclusion criteria. In fact, self-assessment of the number of melanocytic naevi is difficult to perform accurately, as this is severely underestimated [49]. However, from heterogeneity analysis (Table 4), we could observe that the pooled RR for common naevi on whole body (RR = 1.020; 95% CI: 1.015, 1.025), from the studies ($n = 5$) with self-assessment of the naevi count, was similar ($P = 0.434$) to the pooled estimate obtained from studies ($n = 20$) with an assessment of the naevi count by physician (RR = 1.018; 95% CI: 1.013, 1.023). For the naevi count on arms, similar results were found. The pooled estimate from the studies ($n = 4$) with self-assessment (RR = 1.081; 95% CI: 1.023, 1.143) was not significantly different ($P = 0.277$) from the pooled RR from the studies ($n = 13$) with assessment by the physician (RR = 1.144; 95% CI: 1.098, 1.193).

3.6. Publication bias

Investigation of publication bias, for common naevi counted on the whole body, gave us some indications

that some studies without significant results were not published. The standard errors decreased as the size of the study increased and the plot showed a trend for smaller studies to report more positive results than the larger studies. The basic idea of the funnel plot approaches is that there should be no relationship between the study outcome and study size; the relationship that we observed was probably simply an artefact of the process of selecting these studies (publication bias). Rank correlation analysis of the funnel plot by Begg's method [51], suggested a highly significant effect of publication bias ($P = 0.008$). Similarly, linear regression analysis by Egger's method [43] indicated a general trend towards asymmetry of the funnel plot ($P = 0.004$). Sensitivity analysis proposed by Copas and Shy [45] showed that, if the likely number of unpublished studies increased, the estimates of the RR should decrease quite sharply. Thus, the "Trim and fill" analysis [44] indicated that the number of missing studies may be five and their inclusion would lead to a lower pooled estimate (RR = 1.016; 95% CI: 1.012, 1.020).

Exploration among studies on atypical naevi also showed that smaller studies tended to report a greater RR than results in general ($P = 0.019$). Similarly, a linear regression analysis (Egger's method) indicated a trend towards asymmetry of the funnel plot ($P < 0.001$). Using the "Trim and fill" analysis, four studies were identified in order to achieve symmetry of the funnel plot. When the analysis was restricted to case-control studies, no missing studies were identified. The method proposed by Copas and Shi gave an indication of a continuous estimate of less than 2, as being reasonably consistent with the data. For example, with a RR = 1.54 (95% CI: 1.29, 1.84), we got a P -value for publication bias of 0.09.

Finally, no asymmetry on the funnel plot was observed for common naevi counted on arms with Begg's method ($P = 0.39$) and linear regression analysis on the funnel plot (Egger's method) ($P = 0.241$). Sensitivity analysis proposed by Copas and Shy indicated a possible missing study, but adding this new study did not change the pooled RR significantly (RR = 1.12; 95% CI: 1.07, 1.17).

4. Discussion

One of the main problems with studies on naevi is that of ensuring valid counts. In 1990, IARC proposed a detailed protocol to standardise the methodologies in studies on naevi. However, even with a greater degree of standardisation, problems arise in the inter-observer variation: up to approximately 10% of the variation in the full body counts may be due to this [52]. We observed great heterogeneity in the methods of counting naevi: self-assessment, the interviewer counting raised

naevi on the arms and full body examinations conducted by trained clinicians. In our analysis, self-assessment of the number of common melanocytic naevi did not seem to have significantly affected the estimates. The pooled estimate from the studies with self-assessment of naevi count was found to be very similar to the estimate obtained from studies with assessment of naevi count by physicians. Moreover, as long as the error rates in counting are similar in the different phenotype or sun exposure groups, this will not represent a source of error in determining the aetiology of naevi.

In the heterogeneity analysis, it was seen that studies with hospital-based controls presented lower estimates, especially the ones with cases drawn from hospitals. It is likely that these studies published more reliable estimates because the assessment of naevi was usually much more precise in the hospital-based studies. Population-based studies used weak and over-simplified measures of the naevus count, such as self-assessment by the subjects or a very limited examination, and, overall, the data may be deficient in terms of details provided by a skilled examination.

R Rs extracted from cohort studies were much higher than ORs published in case-control studies. The populations of the two types of studies were probably different. Several characteristics were analysed and it was noted that mean age of cases in the case-control studies and in the cohort studies was significantly ($P < 0.001$) different: 50.9 and 34.9, respectively (fifteen case-control studies and seven cohort studies published information on the age of subjects). Three [53–55] out of eight cohort studies included high-risk patients and the younger age of cases can be explained by predominantly genetic factors.

In many epidemiological studies, the naevus density was consistently correlated with pigmented traits, and with intense sun exposure and a history of sunburns [56–59]. In the heterogeneity analysis of this work, adjustment for sunlight indicators and other phenotypic factors did not seem to play an important role in explaining the variability in the estimates. However, the relationship between naevi, sun exposure and phenotypic factors is certainly complex. In fact, individuals who are prone to burning (red hair, dense freckling, very sensitive skin) may avoid sun exposure and develop fewer naevi than might be expected [52]. Moreover, it was suggested that the relationship between sun exposure and melanocytic naevi might have a parabolic dose–response curve [38].

In this meta-analysis, as in Ford's overview [60], which analysed the association of melanoma with a family history of the disease, the familial risk appeared to be essentially independent of the total naevus count. This result in the case-control studies may be explained by the low prevalence of a family history of melanoma among controls (the percentage in controls, calculated

on the nine studies that published this information, was 3.7%).

The results obtained from the meta-analysis confirmed that, the number of common naevi and atypical naevi are very important independent risk factors for the occurrence of melanoma. The risk for people with a very high number of naevi (“101–120” naevi) was found to be highly significant, almost seven times greater (pooled RR = 6.89; 95% CI: 4.63, 10.25) than for people with very few naevi (“0–15” naevi). Subjects with five atypical naevi presented a risk that was six times higher than people with no atypical naevi (RR = 6.52; 95% CI: 3.78, 11.25). Several possible mechanisms were suggested for this increased risk [61].

Numerous moles might indicate a greater genetic tendency to form melanoma. Although no major gene conferring an increasing risk has been identified, except for CDKN2A and CDK4 in melanoma-prone families, the possibility that some of the genes associated with naevi may play a direct role in melanoma progression cannot be excluded.

In addition, multiple naevi might indicate that previous exposure to environmental agents, such as increased sun exposure, has occurred, thereby independently causing both a large number of moles and an increased risk of melanoma formations. Analysis of two case-control studies showed evidence of a role for sun exposure in the development of naevus and atypical naevus [62]. However, we did not find any significant difference in the naevi count risk by country, even if the incidence varied 10-fold between study areas, and this may suggest that number of naevi and sun exposure act multiplicatively on the melanoma risk.

Finally, the hypothesis that melanocytes in naevi are particularly prone to undergo malignant transformation is supported by pathological studies in which two-thirds to three-quarters of patients with melanomas reported previous lesions and 25–50% had histological confirmation of an associated naevus. Thus, at least some naevi, if not all, are likely to be precursors of melanoma [63].

A recent study [64] suggested an interesting hypothesis on sun exposure and naevi, based on a “divergent pathway” model for melanoma occurring on different body sites. It was found that melanomas on the head and neck were more likely to arise in people with few naevi, many solar keratoses, and who presented high levels of occupational sun exposure. In contrast, melanomas of the same histological type arising on the trunk tended to occur among people with many naevi, few solar keratoses, and lower levels of occupational sun exposure. They suggested that after initiation by sunlight, melanocytes of naevus-prone individuals are induced to proliferate and become neoplastic with little (if any) further requirement for sun exposure. In contrast, people with a low tendency to develop naevi require ongoing exposure to sunlight to drive the development of

melanoma, beyond that required for initiation. Among these people, melanomas will tend to be on sun-exposed body sites and will be associated with chronic sun exposure.

It is not yet clear if the sun exposure pattern plays a pertinent role, independent of the body sites involved. However, the role of sun exposure was analysed in a separate meta-analysis of all publications on melanoma [110], which also investigated all heterogeneity factors that may have influenced the estimates.

The aetiology of naevi is complex. It varies by naevus type, and is probably due to the interaction of multiple genes and environmental factors. Understanding the aetiology of naevi, and the changes in naevi during tumour progression, may be the next important advance in gaining an understanding of the aetiology of melanoma.

The number of common naevi and atypical naevi were shown to be very important risk factors for the occurrence of the melanoma. The efficacy of periodic surveillance, combined with total cutaneous photography, could be verified on subjects at high-risk, defined considering these features [23,65].

Conflict of interest statement

The authors have no conflict of interest to disclose.

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