Research Article

Cancer Prevention Research

Estimating the Attributable Fraction for Cancer: A Meta-analysis of Nevi and Melanoma

Catherine M. Olsen, Heidi J. Carroll, and David C. Whiteman

Abstract

Epidemiologic research has shown convincingly that certain phenotypic attributes are associated with increased relative risks of melanoma. Although such findings have intrinsic utility, there have been few attempts to translate such knowledge into estimates of disease burden suitable for framing public health policy. We aimed to estimate the population attributable fraction (PAF) for melanoma associated with melanocytic nevi using relative risk estimates derived from a systematic review and meta-analysis. We identified eligible studies using citation databases, followed by manual review of retrieved references. Of 49 studies identified, 25 and 23, respectively, were included in meta-analyses of atypical and common nevi. For people with ≥1 atypical nevi, the summary relative risk was 3.63 (95% confidence interval, 2.85-4.62), with a PAF of 0.25. The relative risk increased by 1.017 (95% confidence interval, 1.014-1.020) for each common nevus; however, significant heterogeneity in risk estimates was observed. We estimated that 42% of melanomas were attributable to having ≥25 common nevi (PAF 25-49 nevi = 0.15; PAF ≥50 nevi = 0.27), whereas PAFs for low nevus counts were modest (PAF 0-10 nevi = 0.04; PAF 11-24 nevi = 0.07). We modeled PAF under scenarios of varying nevus prevalence; the highest melanoma burden was always among those with high nevus counts (PAF range of 0.31-0.62 for ≥25 common nevi). Patients with ≥25 common nevi and/or ≥1 atypical nevi are a high-risk group, which might be targeted for identification, screening, and education. This work is the necessary first step in designing targeted preventive strategies for melanoma, which must now be overlaid with information about cost and utility. *Cancer Prev Res; 3(2); 233–45. ©2010 AACR.*

Introduction

Cutaneous melanoma is an important public health problem; it is both increasing in incidence and as a cause of mortality in most Caucasian populations throughout the world (1). Considerable progress has been made in quantifying the relative risks (RR) of disease associated with a broad range of environmental factors including UV radiation, and genetic/host factors including family history, number and type of melanocytic nevi, and pigmentary characteristics such as skin, eye, and hair color (2). The RRs derived from epidemiologic research alone, however, do not provide enough information to guide policy makers in directing prevention and screening efforts.

Primary prevention efforts aimed at reducing UV exposure, the major modifiable risk factor for melanoma, are complicated because the relationship between UV and melanoma is not straightforward and is highly dependent on phenotype (3). It may also be important to identify individuals at higher than average risk who can be targeted for prevention and screening efforts. This will require an understanding not only of the magnitude of the risk associated with each factor, but also of the public health effect of each factor. One widely used measure is the population attributable fraction (PAF), which considers both the strength of association between risk factor and outcome, as well as the prevalence of the factor in the community. Thus, the PAF estimates the proportion of all cases of a given disease in a population that is attributable to a particular factor.

Common melanocytic and atypical nevi have been shown repeatedly to be independent risk factors for melanoma (4, 5), and of all the host susceptibility factors identified to date, the presence of large numbers of melanocytic nevi confers the highest risk of melanoma (6, 7). The aim of this work therefore was to systematically evaluate the most recent epidemiologic evidence describing the relationship between the number and type of melanocytic nevi and melanoma, and then to use these data to estimate the fraction of melanomas attributable to these phenotypic characteristics.

Materials and Methods

A systematic review and meta-analysis was done in accordance with the Meta-analysis of Observational Studies

Authors' Affiliation: Cancer Control Laboratory, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland, Australia

Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Corresponding Author: Catherine M. Olsen, Cancer Control Laboratory, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland 4029, Australia. Phone: 61-7-3362-0265; Fax: 61-7-3845-3502; E-mail: Catherine.Olsen@qimr.edu.au.

doi: 10.1158/1940-6207.CAPR-09-0108

in Epidemiology guidelines for reviews of observational studies (8).

Eligibility criteria

We included case-control, nested case-control, or population-based cohort studies in the meta-analysis provided that they permitted quantitative assessment of the association between common or atypical nevi (whole-body counts) and histologically confirmed melanoma. Only studies published as original articles were included. We included studies reporting various measures of RR because melanoma is a rare disease, and in such instances, odds ratios (OR) and standardized incidence ratios provide a valid estimate of the RR.

Literature search

Eligible studies up to September 2008 were identified by searching the following databases and by hand searching the reference lists of the retrieved articles.

- Medline 1950 (U.S. National Library of Medicine, Bethesda, MD) using PubMed software as the search interface
- Embase 1966 (Elsevier Science, Amsterdam, Holland) using the Embase search interface
- Conference Papers Index 1982 (CSA, Bethesda, MD) using the CSA Illumina search interface
- ISI Science Citation Index using the ISI Web of Science search interface

For computer searches, we used the following medical subject headings terms or text words (using both U.K. and U.S. spellings): melanoma, nevi, nevus, dysplastic nevus syndrome, pigmented nevus, pigmented lesion, skin lesion, melanocytic lesion, cutaneous factor, risk, etiologic, etiology, cohort studies, and case-control studies (Addendum). Studies that had been commonly cited in the literature were also included as citation search terms in the ISI Science Citation Index (1990 to present) to identify subsequent studies that had referenced them. Only studies of adult populations (>18 y) were included. The search was not limited to studies published in English. We read the abstracts of all identified studies to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine if they met the study inclusion criteria. Where multiple reports from one study were found, the most recent or most complete publication was used.

The primary computerized literature search identified 115 potentially eligible studies. After a review of the study abstracts, we retrieved 80 articles for further assessment, of which 2 reports of cohort studies (9, 10), and 47 from case-control studies (refs. 4, 5, 7, 11–54; total = 49) met the eligibility criteria (Fig. 1). The remaining 31 studies were excluded because they either did not present enough data to compute effect estimates of the association between nevus count and melanoma ($n = 6$), were not independent of other included studies ($n = 14$), or they represented an ineligible study design [e.g., case-series, nonpopulation-based cohort study (i.e., cohorts of people with atypical nevi; $n = 11$].

Data extraction

An abstraction form summarizing the study design, study population, and relevant raw and adjusted data were completed for each article by two independent reviewers, both investigators (CO, HC); inconsistencies were rereviewed until consensus was achieved. The following information was recorded for each study: study design, location, years of data collection (case-control studies), number of cases and controls or person-year duration of follow-up (cohort studies), age of study population, variables for which statistical adjustment was done, definitions and categories of nevus variables, point estimates (RR, OR, or standardized incidence ratio), and 95% confidence intervals (95% CI). Where several risk estimates were presented, we abstracted those adjusted for the greatest number of potential confounders. Studies that reported results separately by gender, body site, or histologic subtype with no combined data were treated as independent data sets in the meta-analysis.

We did not assess the methodologic quality of the primary studies and hence did not exclude studies on the basis of quality score (8), but instead performed subgroup and sensitivity analyses according to study features that could potentially affect the strength of the association between nevus counts and melanoma.

Statistical analysis

To pool the RR estimates for the presence of atypical nevi, a weighted average of the log RR was estimated, taking into account the random effects using the method of DerSimonian and Laird (55). Because for this exposure measure we were interested in an "any" versus "none" comparison, and some studies presented affect estimates for several categories of nevus count, we used the method of Greenland and Longnecker (56) to derive the relative effect and precision estimates for the required comparison. Statistical heterogeneity among studies was evaluated using the Cochrane Q test and I^2 statistics. The Cochrane Q test, which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, is widely known to have too much power to detect clinically unimportant heterogeneity if the number of studies is large (57). The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance (58), and does not inherently depend upon the number of studies considered ($I^2 = 100\% \times (Q - df)/Q$). We also conducted separate analyses by study type, geographic location, case family history of melanoma, definition of atypical nevi (standard or other), source of atypical nevus count (counted or self-report), year of publication (before and after 2000), and study size. Finally, we conducted sensitivity analyses, omitting each study in turn to determine whether the results could have been influenced excessively

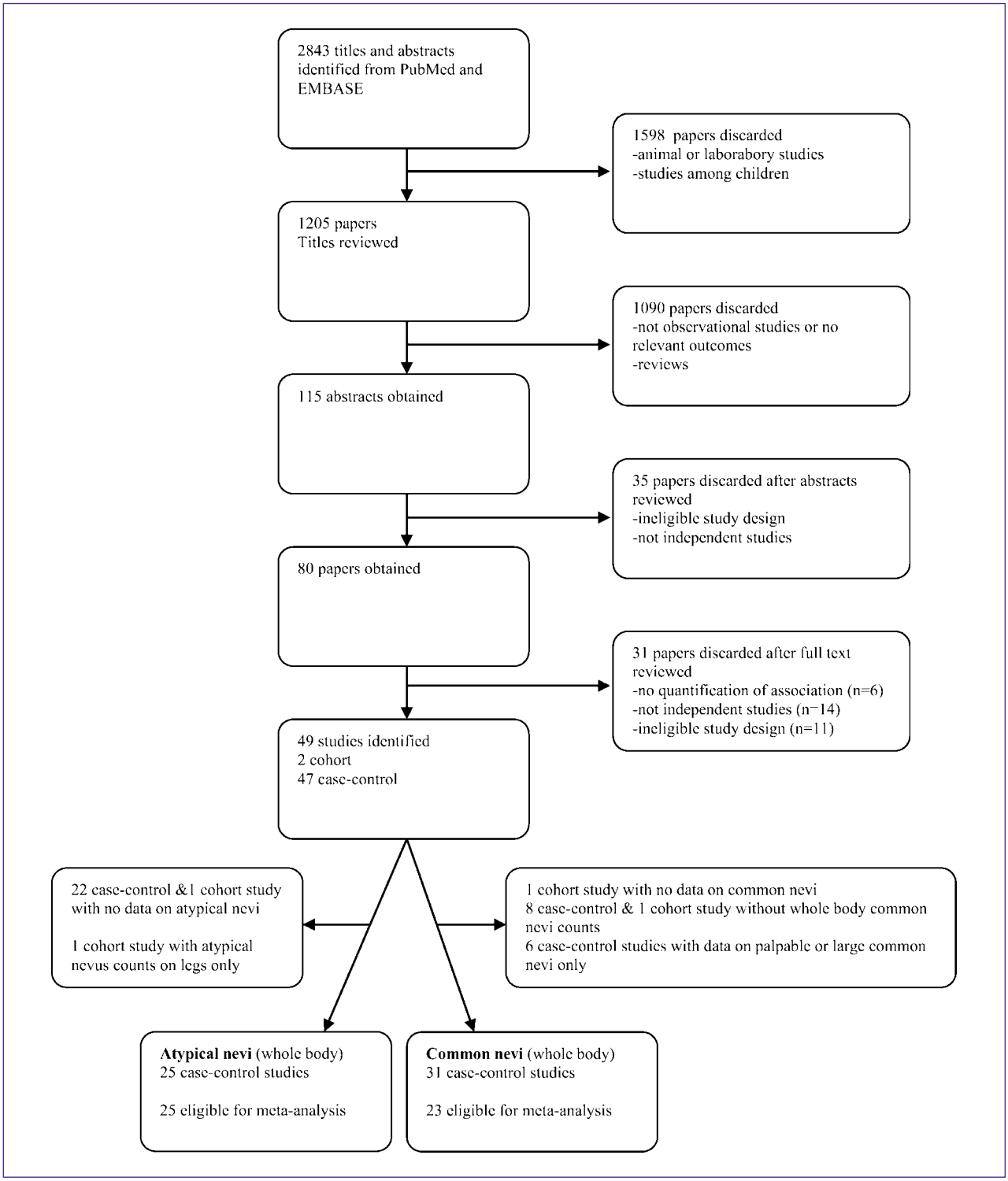

Fig. 1. Flow chart of literature search for studies on the association between common or atypical nevi and melanoma.

by a single study. We evaluated the publication bias by assessing the funnel-plot asymmetry (59, 60).

To pool RR estimates for common nevus counts, we conducted a dose-response meta-analysis using a method proposed by Greenland and Longnecker (56) and Orsini et al. (61), which estimated the study-specific slopes from the correlated natural log of the RR estimates across categories of nevus counts. Unlike other methods for pooling

estimates that assume independence of the estimates, this method accounts for the correlation between estimates that depend on the same reference group. The value assigned to each category of nevus count was the midpoint for closed categories, and we assigned a midpoint for open-ended top categories (120 where ≤120, 150 where >120, and 180 where >150). We conducted sensitivity analyses around the assignment of these midpoint values for the open-ended top categories. Moderate changes (i.e., from 80-120 nevi) did not materially alter the pooled effect estimates nor improve model fit. We conducted further analyses using the "pool first" (61) method, which requires pooling data from all of the studies before estimating the dose-response model. In addition, we checked for nonlinearity of the dose-response relationship by estimating polynomial models. Overall, the best-fitting model for these data was a linear model pooling the study-specific slopes (Supplementary Table S1). We performed subgroup analyses to examine heterogeneity by study characteristics including study type, study size, year of publication, geographic location, case family history of melanoma, and source of common nevus count, and again conducted sensitivity analyses to assess the effect of each study on the summary risk estimates.

PAFs for the presence of atypical nevi and common nevi in categories (0-10, 11-24, 25-49, and 50+) were estimated using Levin's formula (62), which requires only the RR estimate and the prevalence of the risk factor. CIs for the PAFs were derived using the substitution method described by Daly (63). For common nevi, we used the pooled RR for the number of nevi at the midpoint of each category for the PAF calculations (i.e., 5 for the 0-10 category, 18 for the 10-25 category, 37 for the 25-49 category, and 80 for the 50+ category). Because reporting of nevus counts varied across studies, we estimated the prevalence of the nevus exposures by calculating an average of the prevalence reported in study controls, which was weighted by the size of the control group. For common nevi, this was restricted to those studies that presented their nevus counts in similar categories. This approach to calculating PAFs has inherent limitations due to the underlying heterogeneity in prevalence estimates; however, reliable population-based data on nevus prevalence are scarce. We therefore conducted sensitivity analyses to evaluate the effect of different ranges of common and atypical nevus prevalence on the PAF estimates. For the 0 to 10 common nevi category, we calculated the PAF for a change in prevalence in increments of 0.025 from 0.3 to 0.5; the difference was distributed over the remaining three categories in a weighted fashion based on the original estimates. Similarly, for the 11 to 25 and 25 to 49 nevi categories, we calculated the PAF for prevalence ranging from 0.1 to 0.3, and calculated PAF for prevalence for the 50+ nevus category from 0 to 0.2. We modeled the PAF of atypical nevi based on prevalence ranging from 0.025 to 0.2, again in increments of 0.025.

All analyses were conducted using Stata 10.

Results

Measurement of nevus burden varied across studies; however, the nevus variables collected by the greatest number of studies were whole-body atypical nevus counts and whole-body common nevus counts, and thus, we used these two variables in our meta-analyses.

Atypical nevi

A total of 25 studies presented data on the relationship between atypical nevi (whole-body counts) and melanoma (refs. 4, 5, 7, 11, 17, 18, 20–22, 25, 26, 29, 33, 36–38, 43, 45–49, 52–54; Fig. 1); these were all case-control studies (Table 1). One study presented data stratified by sex only (20); for that study, we included the data for men and women in the meta-analyses as two independent data sets. A single cohort study reported atypical nevus counts from the legs only (10), and this study was not included in the meta-analysis. For all studies, the pooled RR of melanoma for people with one or more atypical nevi compared with those with none was 3.63 (95% CI, 2.85-4.62) with evidence of significant heterogeneity ($P \leq 0.001$; Fig. 2). The results of subgroup analysis to examine the heterogeneity are provided in Table 2. Only two of the studies were population based; the pooled RR for these two studies was lower than for the nonpopulation-based case-control studies (2.63 versus 3.74; Table 2). No heterogeneity was observed for the two population-based case-control studies. When stratified by geographic location, the highest pooled RR was observed for the five studies conducted in North America (pooled RR, 5.86; 95% CI, 3.50-9.82), and the lowest was observed for those conducted in Central Europe (pooled RR 2.83; 95% CI, 1.41-5.69). There did not seem to be significant differences in the pooled RRs according to the definition of atypical nevus used, and only one study relied upon self-reported atypical nevus counts. For studies that included cases with a family history of melanoma ($n = 12$), the pooled RR was 3.92 (95% CI, 2.89-5.31) compared with 3.27 (95% CI, 1.77-6.04) for studies that did not ($n = 5$); the remaining eight studies did not state whether they included cases with a family history of melanoma. Studies published since 2000 were more homogeneous, and our most homogeneous estimate was derived by excluding the one study that relied on self-reported atypical nevus counts from this group; the pooled RR was 3.70 (95% CI, 2.76-4.96), which was very close to the pooled RR for all studies (3.63). Finally, the summary statistics were not influenced by sensitivity analysis excluding one study at a time, with the pooled RR ranging from 3.46 (2.74-4.38) with the omission of Rhodes et al. (11), to 3.79 (3.00-4.80) with the omission of Grulich et al. (33) The funnel plot of the effect estimates for the risk of melanoma related to atypical nevi was close to symmetrical and there was no evidence of publication bias using the Egger weighted regression method ($P_{bias} = 0.148$) or the Begg rank correlation method ($P_{bias} = 0.076$).

Table 1. Characteristics of the 25 case-control studies included in the meta-analysis of atypical nevi (whole body) and risk of melanoma

First author	Year of publication	Study location	Recruitment period	Age range	Source of cases	Source of controls	No. of cases	No. of controls	Source of count
Nikolaou	2008	Mediterranean Europe	2000 - 2004	19-84	Clinic/ hospital	Clinic/hospital	200	200	Counted
Li	2008	North America	1994 - 2006	18-75	Clinic/ hospital	Clinic/hospital	805	841	Self-report
Fortes	2007	Mediterranean Europe	2001 - 2003	>18	Clinic/ hospital	Clinic/hospital	287	299	Counted
Nijsten	2005	Central Europe	1998 - 2001	NS	Clinic/ hospital	Clinic/hospital	132	245	Counted
Titus-Ernstoff	2005	North America	1995 - 1998	20-69	Population	Population	323	424	Counted
Lasithiotakis	2004	Mediterranean Europe	1999 - 2003	19-88	Clinic/ hospital	Clinic/hospital	110	110	Counted
Fargnoli	2004	Mediterranean Europe	2000 - 2001	18-74	Clinic/ hospital	Clinic/hospital	100	200	Counted
Bakos	2002	South America	1995 - 1998	20-84	Clinic/ hospital	Clinic/hospital	103	206	Counted
Landi	2001	Mediterranean Europe	1994 - 1999	17-77	Clinic/ hospital	Clinic/hospital	183	179	Counted
Carli	1999	Mediterranean Europe	1990 - 1993	20-70	Clinic/ hospital	Population	131	174	Counted
Tucker	1997	North America	1991 - 1992	20-70	Clinic/ hospital	Clinic/hospital	716	1014	Counted
Rodenas	1996	Mediterranean Europe	1988 - 1993	20-79	Clinic/ hospital	Clinic/hospital	105	138	Counted
Bataille	1996	Northern Europe	1989 - 1993	16-75	Population	Clinic/hospital	426	416	Counted
Grulich	1996	Australia	1992 - 1993	15-84	Clinic/ hospital	Clinic/hospital	244	276	Counted
Garbe	1994	Central Europe	1990 - 1991	NS	Clinic/ hospital	Clinic/hospital	496	476	Counted
Weiss	1991	Central Europe	1984 - 1987	NS	Clinic/ hospital	Clinic/hospital	204	200	Counted
Halpern	1991	North America	1982 - 1983	NS	Clinic/ hospital	Population	105	181	Counted
Grob	1990	Central Europe	1986 - 1988	18-81	Clinic/ hospital	Population	207	295	Counted
Augustsson	1991	Mediterranean Europe	1964 - 1986	30-50	Population	Population	121	378	Counted
Garbe	1989	Central Europe	1987 - 1987	<89	Clinic/ hospital	Clinic/hospital	200	200	Counted
Mackie	1989	Northern Europe	1987 - 1987	NS	Population	Clinic/hospital	280	280	Counted
Roush	1988	Australia	NS	NS	Clinic/ hospital	Clinic/hospital	246	134	Counted
Cristofolini	1987	Mediterranean Europe	1983 - 1985	21-80	Clinic/ hospital	Clinic/hospital	103	205	Counted
Holly	1987	North America	1984 - 1985	20-74	Clinic/ hospital	Clinic/hospital	121	139	Counted
Rhodes	1980	North America	NS	NS	Clinic/ hospital	Not specified	138	217	Counted

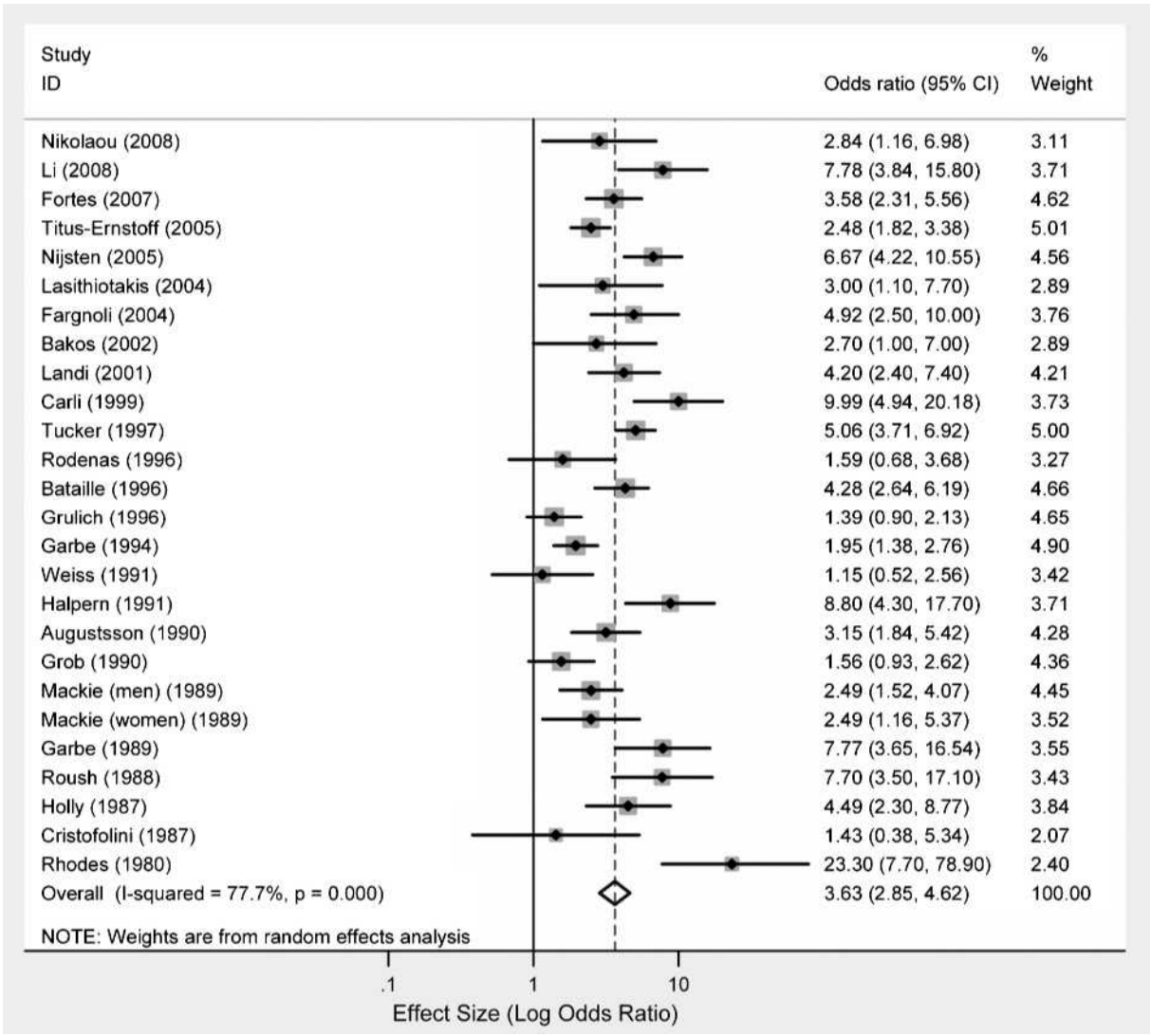

Fig. 2. Forest plot of the association between atypical nevi and melanoma using a random effects model. Each line represents an individual study result with the width of the horizontal line indicating 95% CI, the position of the box representing the point estimate, and the size of the box being proportional to the weight of the study.

Common nevi

A total of 31 studies provided data on the association between common nevi (whole-body count) and melanoma. An additional eight case-control studies (14, 24, 32, 34, 35, 39, 40, 49) and one cohort study (9) did not report on whole-body nevus counts, but rather specific body sites including the arms or legs. A further six studies presented data only for palpable and/or large common nevi (13, 19, 28, 30, 31, and 44) and one study did not use quantitative common nevus counts (27); these were also excluded from the analyses (Fig. 1).

For the dose-response meta-analysis, 23 case-control studies were eligible to be included in the meta-analyses of whole-body common nevus counts (Table 3; refs. 5, 7, 15, 17, 18, 21–23, 25, 29, 33, 36–38, 41, 43, 45–47, 50–53); seven studies that presented data in dichotomous categories only (4, 12, 16, 20, 26, 42, 54) were excluded because the analyses required three or more exposure categories. One study presented data stratified by sex only (50), and the data for men and women were included in the meta-analyses as two independent data sets.

Using a random effects model, the pooled RR for common nevi (whole body) for single-unit increase in nevus count for all studies was 1.017 (1.014-1.020; Fig. 3). Although there was evidence of significant heterogeneity ($P \leq 0.001$; Table 4), all RRs were in the same direction

and the heterogeneity was due to differences in the magnitude of the association. The results of subgroup analysis to examine the heterogeneity are provided in Table 5. Two of the studies were population based; the pooled RR for these studies was lower than that for the nonpopulation-based case-control studies (1.008 versus 1.018). As expected, the pooled RR for studies that included cases with a family history of melanoma was higher than for studies that did not (1.014 versus 1.012), and there was no evidence of heterogeneity among the four latter studies ($P = 0.41$). However, a large number of studies ($n = 10$) did not report information on inclusion/exclusion of cases with a family history. The pooled RR for studies conducted in Northern and Central Europe was higher than for studies from North America or Mediterranean Europe. Sensitivity analyses excluding one study at a time resulted in pooled RR ranging from 1.016 (95% CI, 1.013-1.019) when the study by Swerdlow et al. (15) was excluded, to 1.017 (95% CI, 1.015-1.020) when the study by Augustsson et al. (22) was excluded. Again, there was no evidence of publication bias using the Egger weighted regression method ($P_{bias} = 0.330$) or the Begg rank correlation method ($P_{bias} = 0.239$).

Population attributable fraction

Estimates of the PAF associated with the presence of atypical nevi and common nevus counts, calculated using the meta-analysis–derived summary RRs and the weighted average of the prevalence estimates from all studies, are presented in Table 6. There was a large degree of variation in prevalence of both atypical nevi and common nevus counts across studies, particularly for the lowest category of common nevi (0-10). The estimated PAF of melanoma associated with the presence of one or more atypical nevi was 0.25. Level-specific PAFs for common nevus counts ranged from 0.04 for 0-10 nevi to 0.27 for 50 or more nevi. Figure 4 presents an evaluation of the effect of different prevalence assumptions on the PAF of common nevi. We modeled the PAF under different scenarios of nevus prevalence. Varying the prevalence in the bottom two categories of nevus counts (0-10, 11-24) did not have a

Table 2. Meta-analysis results using a random effects model: Atypical nevi and risk of melanoma

	Number of studies	Pooled effect estimate (95%CI)	I^2 (%)	*P* heterogeneity
All studies	25	3.63 (2.85-4.62)	77.7	<0.001
By study design:				
Population-based	2	2.63 (2.01-3.44)	0	0.452
Clinic/hospital-based	23	3.74 (2.86-4.88)	78.6	<0.001
By study location:				
North America	6	5.86 (3.5-9.82)	92.1	<0.001
South America	1	2.70 (1.02-7.14)	-	-
Northern Europe	2	3.15 (2.13-4.65)	0	0.203
Central Europe	5	2.83 (1.41-5.69)	88.4	<0.001
Mediterranean Europe	9	3.60 (2.60-4.98)	47.4	0.055
Australia	2	3.16 (0.59-16.91	92.8	<0.001
By case family history of melanoma:				
Yes	12	3.92 (2.89-5.31)	72.7	<0.001
No	5	3.27 (1.77-6.04)	76.5	0.002
Not specified	8	3.45 (2.04-5.82)	84.5	<0.001
By definition used:				
Standard	16	3.56 (2.78-4.55)	70.7	<0.001
Other	8	3.69 (1.97-6.91)	85.6	<0.001
Not specified	1	7.78 (3.84-15.78)	-	-
By source of count:				
Counted	24	3.52 (2.76-4.49)	77.5	<0.001
Self-report	1	7.78 (3.84-15.78)		-
By study size:				
<200 cases	13	4.20 (3.03-5.83)	66.3	<0.001
≥200 cases	12	3.14 (2.24-4.41)	82.8	<0.001
By year of publication:				
Before 2000	16	3.48 (2.48-4.88)	82.5	<0.001
After 2000	9	3.98 (2.94-5.39)	57.4	0.016
Published after 2000 and excluding self-reported nevus count	8	3.70 (2.76-4.96)	51.0	0.046

substantial effect on the total PAF of common nevi with the PAF associated with these counts remaining under 0.14 under all scenarios. In contrast, under all prevalence scenarios examined, the highest burden was always associated with higher nevus counts (25-49, 50+), especially the 50+ category. We also modeled the PAF of atypical nevi based on prevalence ranging from 0.025 to 0.2; the PAF ranged from 0.06 to 0.34.

Table 3. Characteristics of the 23 case-control studies included in the meta-analysis of common nevi (whole body) and risk of melanoma

First author	Year of publication	Study location	Recruitment period	Age range	Source of cases	Source of controls	No. of cases	No. of controls	Source of count
Nikolaou	2008	Mediterranean Europe	2000 - 2004	19-84	Clinic/ hospital	Clinic/hospital	200	200	Counted
Fortes	2007	Mediterranean Europe	2001 - 2003	>18	Clinic/ hospital	Clinic/hospital	287	299	Counted
Le Marchand	2006	North America	1986 - 1992	19-83	Population	Population	278	278	Self-report
Zanetti	2006	Other	2001 - 2002	20-75	Clinic/ hospital	Clinic/hospital	214	349	Self-report
Fargnoli	2004	Mediterranean Europe	2000 - 2001	18-74	Clinic/ hospital	Clinic/hospital	100	200	Counted
Lasithiotakis	2004	Mediterranean Europe	1999 - 2003	19-88	Clinic/ hospital	Clinic/hospital	110	110	Counted
Bakos	2002	South America	1995 - 1998	20-84	Clinic/ hospital	Clinic/hospital	103	206	Counted
Landi	2001	Mediterranean Europe	1994 - 1999	17-77	Clinic/ hospital	Clinic/hospital	183	179	Counted
Naldi	2000	Mediterranean Europe	1992 - 1994	NS	Clinic/ hospital	Clinic/hospital	542	538	Counted
Carli	1999	Mediterranean Europe	1990 - 1993	20-70	Clinic/ hospital	Population	131	174	Counted
Tucker	1997	North America	1991 - 1992	20-79	Clinic/ hospital	Clinic/hospital	716	1014	Counted
Grulich	1996	Australia	1992 - 1993	15-84	Clinic/ hospital	Clinic/hospital	244	276	Counted
Bataille	1996	Northern Europe	1989 - 1993	16-75	Population	Clinic/hospital	426	416	Counted
Rodenas	1996	Mediterranean Europe	1988 - 1993	20-79	Clinic/ hospital	Clinic/hospital	105	138	Counted
Garbe	1994	Central Europe	1990 - 1991	NS	Clinic/ hospital	Clinic/hospital	496	476	Counted
Weiss	1991	Central Europe	1984 - 1987	NS	Clinic/ hospital	Clinic/hospital	204	200	Counted
Grob	1990	Central Europe	1986 - 1988	18-81	Clinic/ hospital	Population	207	295	Counted
Dubin	1990	North America	1979 - 1982	>20	Clinic/ hospital	Clinic/hospital	289	527	Counted
Augustsson	1991	Mediterranean Europe	1964 - 1986	30-50	Population	Population	121	378	Counted
Garbe	1989	Central Europe	1987 - 1987	NS	Clinic/ hospital	Clinic/hospital	200	200	Counted
Cristofolini	1987	Mediterranean Europe	1983 - 1985	21-80	Clinic/ hospital	Clinic/hospital	103	205	Counted
Holly	1987	North America	1984 - 1985	20-74	Clinic/ hospital	Clinic/hospital	121	139	Counted
Swerdlow	1986	Northern Europe	1979 - 1984	15-84	Clinic/ hospital	Clinic/hospital	180	197	Counted

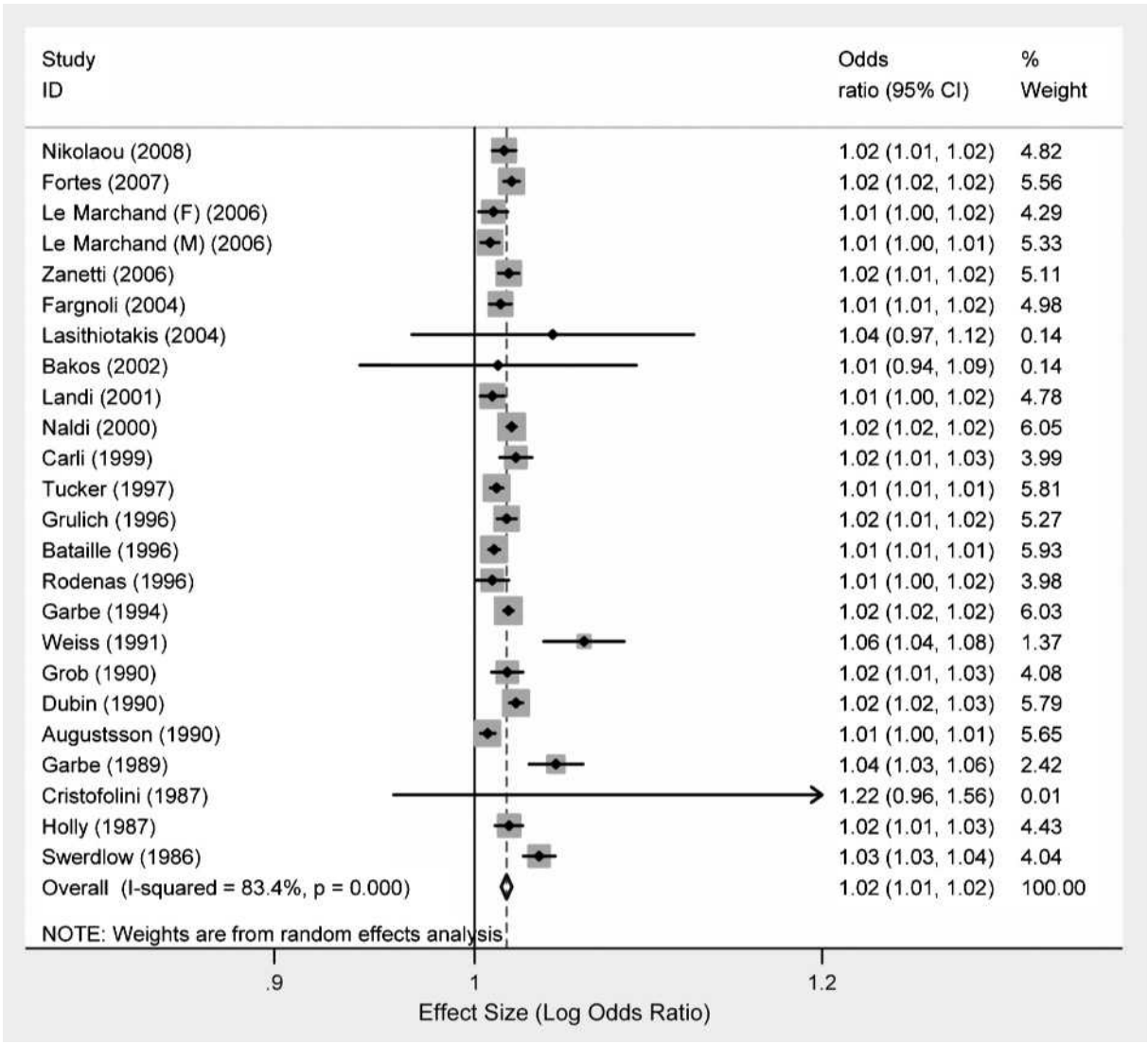

Fig. 3. Forest plot of the association between common nevi and melanoma using a random effects model. Each line represents an individual study result with the width of the horizontal line indicating 95% CI, the position of the box representing the point estimate, and the size of the box being proportional to the weight of the study.

Discussion

Risk factors for melanoma have been quantified in terms of RRs. From the perspectives of public health and health policy, however, the effect of any given risk factor depends not only on the magnitude of the association, but also on the distribution of the factor in the population. We have evaluated the most up-to-date available epidemiologic evidence about the magnitude of the relationship between atypical nevi and common nevus counts and melanoma risk by conducting a systematic review and meta-analysis. Our findings suggest that ~25% of melanoma cases are attributable to the presence of one or more atypical nevi. High common nevus counts (50 or more common nevi) account for ~27% of melanoma cases, whereas individuals with few common nevi (0-10) account for only ~4% of melanoma cases. To our knowledge, this is the first study to systematically evaluate the PAF of melanoma associated with atypical nevi and common nevus counts using estimates of RR derived through systematic review and meta-analysis.

Several limitations must be acknowledged when interpreting these findings, relating to the pooled RR estimates and to the nevus prevalence estimates. First, the studies contributing to the pooled RR estimates are prone to the usual biases associated with case-control studies, including selection bias, recall bias, and measurement error. It is unlikely that recall bias has unduly influenced the pooled RR

Table 4. Results of dose-response meta-analysis for risk of melanoma associated with an increase of one common nevi, and for numbers of common nevi (calculated from the linear model)

Number of common nevi (all studies, *n* = 24)	RR (95%CI)
Per increase of 1 nevus	1.017 (1.014-1.020)
10	1.18 (1.15-1.22)
20	1.40 (1.32-1.49)
30	1.66 (1.52-1.81)
40	1.96 (1.74-2.21)
50	2.32 (2.00-2.69)
80	3.85 (3.04-4.88)
120	7.56 (5.30-10.77)
150	12.54 (8.05-19.5)

estimates because in most studies, nevi were counted by independent personnel rather than by patients themselves. Nondifferential exposure misclassification would likely bias OR estimates toward the null, which would result in an underestimate of the true PAF (64). Selection bias due to control recruitment from dermatology clinics or hospitals in the majority of studies would also result in an attenuated effect if controls recruited in this way are more likely to have higher nevus counts than those recruited randomly from a population-based source. Second, there is uncertainty surrounding our calculations of the prevalence of common nevi in the study population due to a lack of data available from population-based sources. The studies contributing to the pooled estimates of RR represent diverse populations, and there was a large amount of between-study variation in the prevalence of common nevus counts. Our sensitivity analyses to examine the effect of changing prevalence of common nevi on the PAF were reassuring in this regard; the lowest total PAF was 0.31 based on a prevalence of 0 in the 50+ nevus category. However, even if the PAF estimates are based on imprecise assessments of the distribution of nevus counts in the population, our estimates are nevertheless useful in quantifying the potential for prevention by directing the level of screening surveillance at people with >25 common nevi and/or atypical nevi.

Another limitation to acknowledge in our estimation of the PAF associated with common and atypical nevi is our single risk factor approach, which does not take into account the potential interaction or confounding by other risk factors. For example, we know that common nevus counts are highly correlated with atypical nevus counts (65); however, from these analyses, we were unable to determine the degree of overlap between people with high nevus counts and atypical nevi. Multifactorial attributable fractions can only be estimated reliably when the data are presented and published in this way. We would encourage

Table 5. Subgroup analyses of risk of melanoma associated with common nevi

	No. of studies	RR (95%CI) per nevus	I^2 (%)	*P* heterogeneity
All studies	23	1.017 (1.014-1.020)	83.4	<0.001
Study design				
Population-based	2	1.008 (1.005-1.010)	0	0.777
Clinic/hospital-based	21	1.018 (1.015-1.021)	80.1	<0.001
Study location				
North America	4	1.014 (1.008-1.020)	86.4	<0.001
Northern Europe	2	1.022 (0.998-1.046)	96.4	<0.001
Central Europe	4	1.031 (1.017-1.044)	88.0	<0.001
Mediterranean Europe	10	1.014 (1.010-1.019)	79.3	<0.001
Other	3	1.017 (1.014-1.021)	0	0.95
Source of count				
Counted	21	1.018 (1.015-1.021)	84.0	<0.001
Self-report	2	1.012 (1.005-1.018)	73.1	0.024
Case family history of melanoma				
Yes	9	1.014 (1.011-1.017)	73.9	<0.001
No	4	1.012 (1.009-1.016)	0	0.41
Not specified	10	1.023 (1.017-1.028)	88.5	<0.001
By study size:				
<200 cases	10	1.016 (1.009-1.023)	80.1	<0.001
≥200 cases	13	1.017 (1.014-1.020)	84.9	<0.001
By year of publication:				
Before 2000	14	1.019 (1.015-1.023)	88.0	<0.001
After 2000	9	1.015 (1.011-1.018)	68.8	0.001

Table 6. Estimates of the population attributable fraction (PAF) of melanoma associated with atypical nevi and common nevus counts (whole body counts)

Nevus exposure	Prevalence ± SD*	PAF (95% CI)
Atypical nevi		
1 or more	0.126 ± 0.076	0.249 (0.189-0.313)
Common nevi		
0-10	0.434 ± 0.246	0.037 (0.030-0.043)
11-24	0.224 ± 0.074	0.074 (0.060-0.088)
25-49	0.208 ± 0.061	0.153 (0.123-0.183)
50+	0.129 ± 0.060	0.269 (0.209-0.334)

*Prevalence estimated by calculating the average for study controls where presented in similar nevus categories, weighted by the size of the control groups.

future publications to present the risk estimates for combinations of common risk factors so that additive effects can be explored. There are also challenges associated with the interpretation of PAFs, which have been discussed by others (66, 67).

An earlier systematic review and meta-analysis (68) included studies conducted up to 2002; however, a large number of relevant studies have entered the literature since that review was published in 2005. Indeed, we included 10 new studies in our meta-analysis (45–54) that were not published in time for the earlier analysis. Our study differs from that earlier review in that we have analyzed the effect of our pooled effect estimates on the disease at a population level by estimating the PAFs.

Although there is insufficient justification to recommend routine screening of all patients for melanoma (69, 70), there is some evidence that screening of patients at high risk of melanoma is cost effective (71) and likely to be associated with improved survival (72). The results of these analyses suggest that patients with 25 or more common nevi and/or one or more atypical nevi are a high-risk group for which identification, screening, and education may achieve disease prevention or early detection at low cost. A PAF of 0.42 for melanomas associated with 25 or more common nevi equates to 67,200 patients newly diagnosed with melanoma from an annual worldwide total of 160,000 new cases (73). Further work incorporating our findings with considerations of the cost and viability of alternative prevention strategies is required.

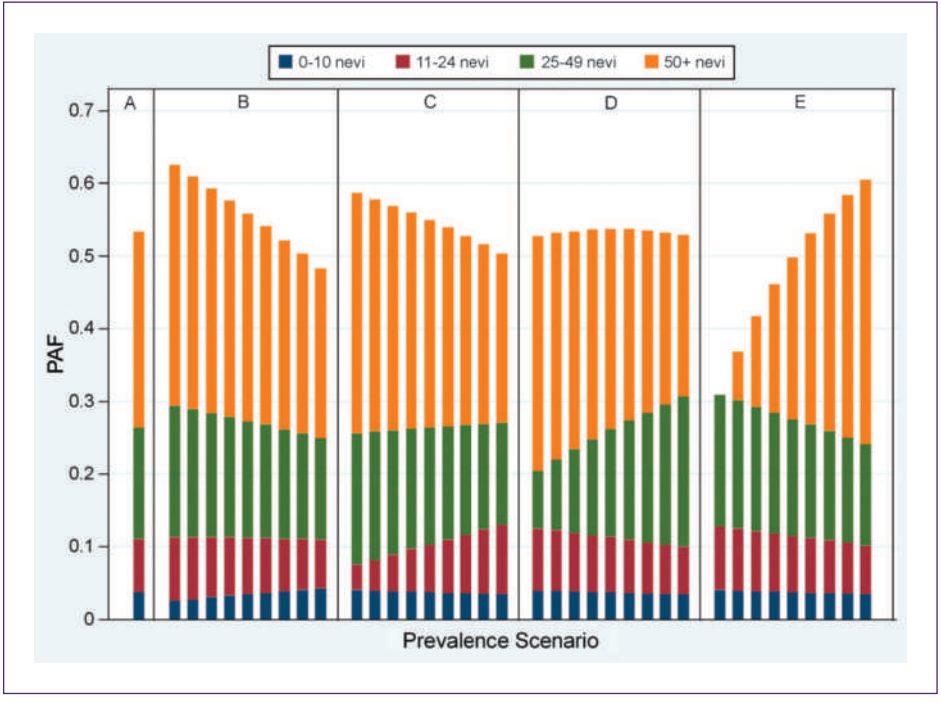

Fig. 4. PAF of melanoma associated with common nevus counts taking into account different prevalence scenarios. The graph is divided into five panels. A, an estimate of PAF calculated using the weighted average of nevus prevalence for studies that presented their data in like categories. B to E, the effect of changing nevus prevalence on the PAF; B, changing the prevalence in the 0 to 10 nevus count category from 0.3 to 0.5 by increments of 0.025; C and D, changing prevalence in the 11 to 24 and 25 to 49 nevus count categories, respectively, from 0.1 to 0.3 by increments of 0.025; and E, changing prevalence in the 50+ nevus count category from 0 to 0.2 by increments of 0.025.

Appendix

Search strategy to identify observational studies on the association of common or atypical nevi and cutaneous melanoma

PubMed
Medical subject headings terms
1. "melanoma"
2. "risk" or "cohort studies" or "case-control studies"
3. "nevus" or "nevus, pigmented" or "dysplastic nevus syndrome"
4. "case reports" (publication type) or "editorial" (publication type) or "letter" (publication type) or "comment" (publication type)
Text terms
1. "melanoma"
2. "aetiological*" or "etiology" or "aetiology" or "group*" or "risk"*
3. "nevi" or "nevus" or "naevi" or "nevu*" or "naevu*" or "moles" or "pigmented lesion*" or "skin lesion*" or "melanocytic lesion*" or "cutaneous factor*"
4. "treatment*"[Title/Abstract]
Search string
1 AND 2 AND 3 NOT 4

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This research was supported by a grant from the Xstrata Community Partnership Program Queensland. The researchers are independent of the funding source. D. Whiteman is a Principal Research Fellow of the National Health and Medical Research Council of Australia.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 6/3/09; revised 8/4/09; accepted 8/24/09; published OnlineFirst 1/19/10.

References

1. Giblin AV, Thomas JM. Incidence, mortality and survival in cutaneous melanoma. J Plast Reconstr Aesthet Surg 2007;60:32–40.
2. Tucker MA, Goldstein AM. Melanoma etiology: where are we? Oncogene 2003;22:3042–52.
3. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B 2001;63:8–18.
4. Roush GC, Nordlund JJ, Forget B, Gruber SB, Kirkwood JM. Independence of dysplastic nevi from total nevi in determining risk for nonfamilial melanoma. Prev Med 1988;17:273–9.
5. Bataille V, Bishop JA, Sasieni P, et al. Risk of cutaneous melanoma in relation to the numbers, types and sites of naevi: a case-control study. Br J Cancer 1996;73:1605–11.
6. Berwick M, Halpern A. Melanoma epidemiology. Curr Opin Oncol 1997;9:178–82.
7. Garbe C, Kruger S, Stadler R, Guggenmoos-Holzmann I, Orfanos CE. Markers and relative risk in a German population for developing malignant melanoma. Int J Dermatol 1989;28:517–23.
8. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama 2000; 283:2008–12.
9. Cho E, Rosner BA, Colditz GA. Risk factors for melanoma by body site. Cancer Epidemiol Biomarkers Prev 2005;14:1241–4.
10. Veierod MB, Weiderpass E, Thorn M, et al. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst 2003;95:1530–8.
11. Rhodes AR, Sober AJ, Mihm MC, Fitzpatrick TB. Possible risk factors for primary cutaneous malignant melanoma. Clin Res 1980;28:252.
12. Beral V, Evans S, Shaw H, Milton G. Cutaneous factors related to the risk of malignant melanoma. Br J Dermatol 1983;109:165–72.
13. Holman CD, Armstrong BK. Pigmentary traits, ethnic origin, benign nevi, and family history as risk factors for cutaneous malignant melanoma. J Natl Cancer Inst 1984;72:257–66.
14. Green A, Bain C. Hormonal factors and melanoma in women. Med J Aust 1985;142:446–8.
15. Swerdlow AJ, English J, MacKie RM, et al. Benign melanocytic naevi as a risk factor for malignant melanoma. Br Med J (Clin Res Ed) 1986; 292:1555–9.
16. Elwood JM, Williamson C, Stapleton PJ. Malignant melanoma in relation to moles, pigmentation, and exposure to fluorescent and other lighting sources. Br J Cancer 1986;53:65–74.
17. Holly EA, Kelly JW, Shpall SN, Chiu SH. Number of melanocytic nevi as a major risk factor for malignant melanoma. J Am Acad Dermatol 1987;17:459–68.
18. Cristofolini M, Franceschi S, Tasin L, et al. Risk factors for cutaneous malignant melanoma in a northern Italian population. Int J Cancer 1987;39:150–4.
19. Osterlind A, Tucker MA, Hou-Jensen K, Stone BJ, Engholm G, Jensen OM. The Danish case-control study of cutaneous malignant melanoma. I. Importance of host factors. Int J Cancer 1988;42:200–6.
20. MacKie RM, Freudenberger T, Aitchison TC. Personal risk-factor chart for cutaneous melanoma. Lancet 1989;2:487–90.
21. Grob JJ, Gouvernet J, Aymar D, et al. Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading melanoma. Cancer 1990;66:387–95.
22. Augustsson A, Stierner U, Rosdahl I, Suurkula M. Common and dysplastic naevi as risk factors for cutaneous malignant melanoma in a Swedish population. Acta Derm Venereol 1991;71:518–24.
23. Dubin N, Pasternack BS, Moseson M. Simultaneous assessment of risk factors for malignant melanoma and non-melanoma skin lesions, with emphasis on sun exposure and related variables. Int J Epidemiol 1990;19:811–9.
24. Elwood JM, Whitehead SM, Davison J, Stewart M, Galt M. Malignant melanoma in England: risks associated with naevi, freckles, social class, hair colour, and sunburn. Int J Epidemiol 1990;19:801–10.
25. Weiss J, Bertz J, Jung EG. Malignant melanoma in southern Germany: different predictive value of risk factors for melanoma subtypes. Dermatologica 1991;183:109–13.
26. Halpern AC, Guerry Dt, Elder DE, et al. Dysplastic nevi as risk markers of sporadic (nonfamilial) melanoma. A case-control study. Arch Dermatol 1991;127:995–9.
27. Marrett LD, King WD, Walter SD, From L. Use of host factors to identify people at high risk for cutaneous malignant melanoma. Cmaj 1992;147:445–53.
28. Zaridze D, Mukeria A, Duffy S. Risk factors for skin melanoma in Moscow. Int J Cancer 1992;52:159–61.
29. Garbe C, Buttner P, Weiss J, et al. Risk factors for developing cutaneous melanoma and criteria for identifying persons at risk: multicenter case-control study of the Central Malignant Melanoma Registry of the German Dermatological Society. J Invest Dermatol 1994;102:695–9.
30. White E, Kirkpatrick CS, Lee JA. Case-control study of malignant melanoma in Washington State. I. Constitutional factors and sun exposure. Am J Epidemiol 1994;139:857–68.
31. Holly EA, Aston DA, Cress RD, Ahn DK, Kristiansen JJ. Cutaneous

melanoma in women. II. Phenotypic characteristics and other host-related factors. Am J Epidemiol 1995;141:934–42.
32. Westerdahl J, Olsson H, Masback A, Ingvar C, Jonsson N. Is the use of sunscreens a risk factor for malignant melanoma? Melanoma Res 1995;5:59–65.
33. Grulich AE, Bataille V, Swerdlow AJ, et al. Naevi and pigmentary characteristics as risk factors for melanoma in a high-risk population: a case-control study in New South Wales, Australia. Int J Cancer 1996;67:485–91.
34. Chen YT, Dubrow R, Holford TR, et al. Malignant melanoma risk factors by anatomic site: a case-control study and polychotomous logistic regression analysis. Int J Cancer 1996;67:636–43.
35. Berwick M, Begg CB, Fine JA, Roush GC, Barnhill RL. Screening for cutaneous melanoma by skin self-examination. J Natl Cancer Inst 1996;88:17–23.
36. Rodenas JM, Delgado-Rodriguez M, Herranz MT, Tercedor J, Serrano S. Sun exposure, pigmentary traits, and risk of cutaneous malignant melanoma: a case-control study in a Mediterranean population. Cancer Causes Control 1996;7:275–83.
37. Tucker MA, Halpern A, Holly EA, et al. Clinically recognized dysplastic nevi. A central risk factor for cutaneous melanoma. Jama 1997; 277:1439–44.
38. Carli P, Massi D, Santucci M, Biggeri A, Giannotti B. Cutaneous melanoma histologically associated with a nevus and melanoma *de novo* have a different profile of risk: Results from a case-control study. Journal of the American Academy of Dermatology 1999;40:549–557.
39. Langholz B, Richardson J, Rappaport E, Waisman J, Cockburn M, Mack T. Skin characteristics and risk of superficial spreading and nodular melanoma (United States). Cancer Causes Control 2000;11:741–50.
40. Mastrangelo G, Rossi CR, Pfahlberg A, et al. Is there a relationship between influenza vaccinations and risk of melanoma? A population-based case-control study. Eur J Epidemiol 2000;16:777–82.
41. Naldi L, Lorenzo Imberti G, Parazzini F, Gallus S, La Vecchia C. Pigmentary traits, modalities of sun reaction, history of sunburns, and melanocytic nevi as risk factors for cutaneous malignant melanoma in the Italian population: results of a collaborative case-control study. Cancer 2000;88:2703–10.
42. Loria D, Matos E. Risk factors for cutaneous melanoma: a case-control study in Argentina. Int J Dermatol 2001;40:108–14.
43. Landi MT, Baccarelli A, Calista D, et al. Combined risk factors for melanoma in a Mediterranean population. Br J Cancer 2001;85:1304–10.
44. Shors AR, Solomon C, McTiernan A, White E. Melanoma risk in relation to height, weight, and exercise (United States). Cancer Causes Control 2001;12:599–606.
45. Bakos L, Wagner M, Bakos RM, et al. Sunburn, sunscreens, and phenotypes: some risk factors for cutaneous melanoma in southern Brazil. Int J Dermatol 2002;41:557–62.
46. Fargnoli MC, Piccolo D, Altobelli E, Formicone F, Chimenti S, Peris K. Constitutional and environmental risk factors for cutaneous melanoma in an Italian population. A case-control study. Melanoma Res 2004;14:151–7.
47. Lasithiotakis K, Kruger-Krasagakis S, Ioannidou D, Pediaditis I, Tosca A. Epidemiological differences for cutaneous melanoma in a relatively dark-skinned Caucasian population with chronic sun exposure. Eur J Cancer 2004;40:2502–7.
48. Titus-Ernstoff L, Perry AE, Spencer SK, Gibson JJ, Cole BF, Ernstoff MS. Pigmentary characteristics and moles in relation to melanoma risk. Int J Cancer 2005;116:144–9.
49. Nijsten T, Leys C, Verbruggen K, et al. Case-control study to identify melanoma risk factors in the Belgian population: the significance of clinical examination. J Eur Acad Dermatol Venereol 2005;19:332–9.
50. Le Marchand L, Saltzman BS, Hankin JH, et al. Sun exposure, diet, and melanoma in Hawaii Caucasians. Am J Epidemiol 2006;164: 232–45.
51. Zanetti R, Rosso S, Martinez C, et al. Comparison of risk patterns in carcinoma and melanoma of the skin in men: a multi-centre case-case-control study. Br J Cancer 2006;94:743–51.
52. Fortes C, Mastroeni S, Melchi F, et al. The association between residential pesticide use and cutaneous melanoma. Eur J Cancer 2007; 43:1066–75.
53. Nikolaou VA, Sypsa V, Stefanaki I, et al. Risk associations of melanoma in a Southern European population: results of a case/control study. Cancer Causes Control 2008;19:671–9.
54. Li C, Liu Z, Wang LE, et al. Haplotype and genotypes of the VDR gene and cutaneous melanoma risk in non-Hispanic whites in Texas: a case-control study. Int J Cancer 2008;122:2077–84.
55. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
56. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135:1301–9.
57. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. Stat Med 1998;17:841–56.
58. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
59. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
60. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315:629–34.
61. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. The Stata Journal 2006;6:40–57.
62. Levin ML. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum 1953;9:531–41.
63. Daly LE. Confidence limits made easy: interval estimation using a substitution method. Am J Epidemiol 1998;147:783–90.
64. Hsieh CC, Walter SD. The effect of non-differential exposure misclassification on estimates of the attributable and prevented fraction. Stat Med 1988;7:1073–85.
65. Olsen CM, Zens MS, Stukel TA, et al. Nevus density and melanoma risk in women: a pooled analysis to test the divergent pathway hypothesis. Int J Cancer 2009;124:937–44.
66. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88:15–9.
67. Levine B. What does the population attributable fraction mean? Prev Chronic Dis 2007;4:A14.
68. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer 2005;41:28–44.
69. Geller AC. Screening for melanoma. Dermatol Clin 2002;20:629–40, viii.
70. Wolff T, Tai E, Miller T. Screening for skin cancer: an update of the evidence for the U S. Preventive Services Task Force. Ann Intern Med 2009;150:194–8.
71. Freedberg KA, Geller AC, Miller DR, Lew RA, Koh HK. Screening for malignant melanoma: a cost-effectiveness analysis. J Am Acad Dermatol 1999;41:738–45.
72. MacKie RM, McHenry P, Hole D. Accelerated detection with prospective surveillance for cutaneous malignant melanoma in high-risk groups. Lancet 1993;341:1618–20.
73. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.