

A meta-analysis of nevus-associated melanoma: Prevalence and practical implications



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The reported prevalence of nevus-associated melanoma varies substantially. We performed a systematic review and meta-analysis to determine the incidence and prevalence of this disease; we also performed subanalyses considering age, tumor thickness, and nevus-type classification. In 38 observational cohort and case–control studies, 29.1% of melanomas likely arose from a preexisting nevus and 70.9% de novo. Any given melanoma was 64% less likely to be nevus-associated than de novo (risk ratio 0.36, 95% confidence interval [CI] 0.29–0.44; $P < .001$; $I^2 = 99\%$); nevus-associated melanomas had a lower mean Breslow thickness than de novo melanomas (mean difference -0.39 mm; 95% CI -0.60 to -0.18 ; $P = .0003$; $I^2 = 66\%$). No significant differences were noted regarding the association of nevus-associated melanomas with nondysplastic nevi or dysplastic nevi (risk ratio 0.77, 95% CI 0.49–1.20; $P = .24$; $I^2 = 98\%$). (J Am Acad Dermatol 2017;77:938–45.)

Key words: dysplastic nevus; melanoma; meta-analysis; nevus-associated; prevalence; thickness.

Nevus-associated melanoma (NAM) is defined by the coexistence of nevus components and melanoma features on histopathologic examination. Data in the literature suggests that NAM is commonly of the superficial spreading melanoma type and generally occurs on the trunk in younger patients.^{1–4} In contrast, de novo melanoma (DNM) is not associated with preexisting nevi and is thought to be more frequent than NAM; however, the prevalence and the biologic significance of NAM has not been clearly defined.

The scientific papers published since the late 1940s have indicated a wide range in prevalence of NAM, from 4%⁵ to 72%⁶; recently, Lin et al reviewed 25 studies and found 36% of melanomas were associated with a preexisting nevus.² However, the prevalence has not been fully analyzed because of the high heterogeneity of studies on this topic, in particular regarding the tumor thickness and nevus-type classification.

Abbreviations used:

CI:	confidence interval
DNM:	de novo melanoma
HR:	hazard ratio
NAM:	nevus-associated melanoma
RR:	risk ratio

It has been shown that the thicker the melanoma the higher the probability for nevus remnants to be obscured or destroyed by malignant proliferation.⁷ Thus, it is extremely difficult or even impossible to determine if the lesion had originally been associated with a nevus or not. Furthermore, information about the characteristics of NAMs (ie, whether the nevus is congenital or acquired or the cells have features of dysplasia) is often not provided or homogeneously reported.⁴

Despite the heterogeneity of the data, there is a global agreement that some melanomas develop in

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Funding sources: Supported by the Italian Ministry of Health (project code: NET-2011-02347213).

Conflicts of interest: None declared.

Accepted for publication June 28, 2017.

Reprints not available from the authors.

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Published online August 29, 2017.

0190-9622/\$36.00

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<http://dx.doi.org/10.1016/j.jaad.2017.06.149>

conjunction with a preexisting nevus. However, the biologic and prognostic significance of nevi in melanoma is still a highly controversial issue.^{2,8-13} In an attempt to better estimate the prevalence of NAM, we performed a systematic review and meta-analysis of published reports on the ratio of NAMs among melanoma patients. Furthermore, we aimed to control for heterogeneity performing subanalyses on age, tumor thickness, and nevus-type classification for dysplastic and nondysplastic nevi.

METHODS

The ethics committee of our institution waived the need for approval because the study did not affect routine diagnostic and therapeutic management. This report was written in accordance to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal where feasible.

Selection of relevant studies

All criteria for inclusion and exclusion of studies were specified before the literature search. Eligible studies for the systematic review were clinical trials, observational cohort studies, and case-control studies reporting the ratio of histologically confirmed NAMs in a given population of melanoma patients. The quality of included observational studies was evaluated using the Newcastle-Ottawa Scale.¹⁴ Case series and case reports were excluded, and reviews, abstracts, letters to the editor, and cross-sectional studies were eligible if the included information were not published in any other form.

Search strategy

To identify eligible studies, a search was conducted in the electronic databases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) for articles published January 1948–July 2016 with the following combination of terms: “melanoma” and (“mole” or “nevus” or “naevus” or “nevomelanocytic”) and (“remnant” or “arise” or “arose” or “association” or “associated”). The manual search was concluded by the perusal of the reference sections of all the relevant trials or reviews, and experts on the subject were contacted in an effort to identify relevant

unpublished data. Two authors (Drs Pampena and Kyrgidis) with expertise in conducting systematic reviews completed independently the search and screening of titles and abstracts. Studies of patients with melanoma that met the following criteria were included in the analysis: existence of 2 groups of patients with different types of melanoma, namely

NAM and DNM. Melanomas associated with medium (>1.5 cm in diameter) and large congenital nevi (>20 cm in diameter) were excluded, when indicated, because the risk of melanoma developing in this context has been estimated to be far higher (up to 10% in some reports) than those of small congenital nevi,¹⁵ in which the risk is comparable to acquired melanocytic nevi.¹⁶

CAPSULE SUMMARY

- The prevalence of nevus-associated melanoma varies across studies.
- Data from the present study highlight that most melanomas arise de novo; furthermore, the prevalence of nevus-associated melanoma does not seem to depend on whether or not the nevus had dysplastic features.
- Only one-third of melanomas arise in association with a preexisting nevus.

Data extraction

Two authors (Drs Pampena and Kyrgidis) independently extracted all information by using a standardized data extraction form. General characteristics of the study (author group, journal, year of publication, design, intervention and control group sample size, methodology, inclusion criteria, duration of follow-up, study quality, and limitations) and outcomes for both intervention and control groups were recorded when available and double-checked. Survival outcomes in the intervention and control groups of individual studies were calculated on the intention-to-treat basis. When appropriate, an attempt was made to complete the data set through communication with the authors.

Outcomes

The primary outcome was ratio of NAMs among all melanomas. Secondary outcomes included thickness of NAM, nevus-type associated with melanoma (particularly dysplastic or nondysplastic), and overall survival.

Statistical analysis

We expressed dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs), continuous outcomes as mean differences with 95% CIs, and continuous outcomes that were measured with different methodologies across studies as standardized mean differences with 95% CIs. For survival outcomes (and thus time-to-event data), we used the natural logarithm of the hazard ratio (HR)

and the corresponding 99% CI as data points for the meta-analysis. For studies not reporting HRs, we estimated HRs and the associated statistics for individual trials according to the information presented in the study report.¹⁷ Funnel plots were used to determine the likelihood of publication bias.¹⁸ The .01 level of significance was preferred over .05 to counteract type I error inflation. Meta-analysis was conducted using Review Manager 5 software (Cochrane Community, Oxford, England).

RESULTS

The initial literature search was completed in February 2016 and was subsequently updated in July 2016. A flowchart of search results is shown in Fig 1. After removal of duplicates, there was a total of 1832 papers to review; then 347 were excluded because they were case reports, and 1408 studies were excluded on the basis of the information in their title and abstract. Thus, 77 full-text original articles were evaluated; of these, 1 was a meta-analysis² and 1 a literature review.¹⁹ After reviewing these articles, we found that 38 studies fit our inclusion criteria and could be used in the quantitative analysis: 36 were original articles^{2-6,8,10,11,13,19-45} and 2 were letters to the editor.^{46,47} Supplemental Table I (available at <http://www.jaad.org>) summarizes data from the included studies.

Prevalence of nevus-associated melanoma

The 38 included studies accounted for 20,126 melanomas, of which 5852 (29.1%) were nevus-associated. For 31 cases, no clear association with nevus remnants could be interpreted. Any given melanoma was 64% less likely to be nevus-associated than de novo (RR 0.36, 95% CI 0.29-0.44; $P < .001$, random effects model), although a high heterogeneity was found ($I^2 = 99%$) (Fig 2). The funnel plot for the latter analysis demonstrated a uniform distribution of results, suggesting a low publication bias (Supplemental Fig 1, A; available at <http://www.jaad.org>).

Demographic and melanoma-related features

Regarding demographic and melanoma-related features, of the 9 studies reporting mean age, significant differences were found with age.^{3,11,13,20,24,29,31,43,47} Patients with NAMs were younger than patients with DNM ($P < .001$) by ~4.9 (95% CI 3.23-6.68) years. The heterogeneity associated with this outcome was moderate to large ($I^2 = 61%$) (Fig 3, A), but the funnel plot of this data showed a low publication bias (Supplementary Fig 1, B; available at <http://www.jaad.org>). Further, no

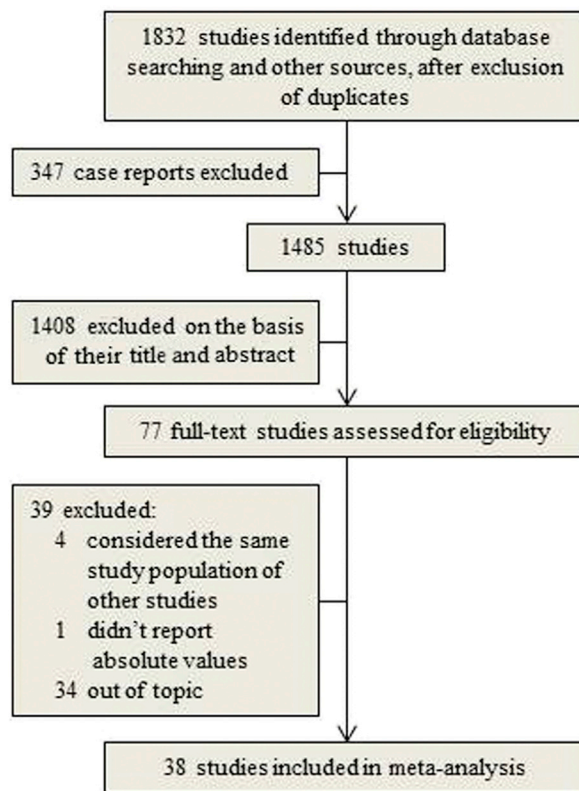


Fig 1. Flow chart of search and study selection process.

significant differences between men and women were reported in the 17 studies in which sex was indicated.^{2,8,11,13,20,21,24,25,27,29-31,33,38,41,43,47} In addition, no relevant differences were observed between the NAM and DNM groups regarding melanoma histologic subtype and body site. Superficial spreading melanoma was the most frequent histologic subtype, and the trunk and extremities were the most common locations reported in both groups (Supplemental Table II; available at <http://www.jaad.org>).

Thickness of nevus-associated melanoma. Of the 38 included studies, only 16 studies for DNM^{2,4,13,19,20,25-27,29,30,35,39,41,43,45,47} and 1 more study for NAM⁴⁴ classified melanomas according to Breslow thickness. A higher prevalence of invasive melanoma was reported for both the DNM and NAM groups; however, in situ tumors were slightly more prevalent in the NAM group (408/2057, 19.8%) than the DNM group (727/4995, 14.6%) (Supplemental Table II; available at <http://www.jaad.org>). Furthermore, 8 studies included detailed information on mean Breslow thickness (Fig 3, B).^{2,3,8,11,13,24,31,47} In these studies having moderate-to-substantial heterogeneity ($I^2 = 66%$), NAMs were found to be less thick than DNMs (mean difference -0.39 mm, 95% CI -0.60 to -0.18 mm; $P = .0003$, random effects

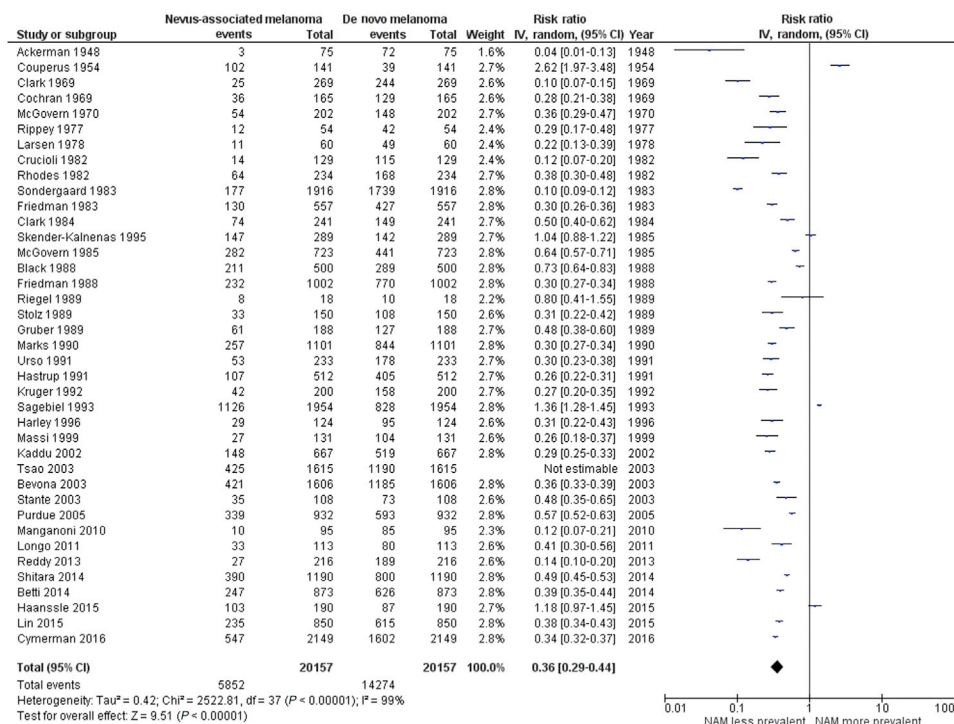


Fig 2. Forest plot of the prevalence of nevus-associated melanomas in 38 published studies. The mentioned studies reported the ratio of histologically confirmed nevus-associated melanomas in a given population of melanoma patients. *CI*, Confidence interval; *NAM*, nevus-associated melanoma.

model). However, a funnel plot of this data was not suggestive of publication bias (Supplemental Fig 1, C; available at <http://www.jaad.org>).

Nevus-type classification

The distinction between congenital and acquired nevi was reported in 13 of 38 studies,^{3,8,10,13,20,25,28,31,35,40,44,45,47} and in 1 study congenital nevi were excluded.¹¹ Considering this limitation, we found that most NAMs were associated with acquired nevi (acquired vs congenital, 1612 vs 471, 77.4% vs 22.6%). Moreover, when excluding congenital nevi, NAMs were much more frequently associated with intradermal nevi (n = 618, 54.0%) than with junctional (n = 249, 21.7%) or compound remnants (n = 176, 15.4%) (Table D).

Prevalence of dysplastic NAMs. A total of 15 studies indicated whether nevus remnants associated with melanoma were dysplastic or nondysplastic.^{3,4,10,13,20,23,25,28,29,32,35,39,40,44,47} A slight prevalence of nondysplastic remnants was reported (nondysplastic vs dysplastic, 1455 vs 1112, 56.7% vs 43.3%); data showed a slight nonsignificant trend for NAMs to be associated more frequently with nondysplastic nevi than dysplastic nevi (RR 0.77, 95% CI 0.49-1.20; P = .24, random effects model) (Fig 3, C). High heterogeneity (I² = 98%)

was associated with this result; however, the funnel plot showed a uniform distribution (Supplemental Fig 1, D; available at <http://www.jaad.com>).

Overall survival

From information available in 28 studies, the mean follow-up time was found to be 9.3 ± 8.8 years.^{2-4,8,10,11,20-25,27,29-36,38,39,41-43,45,47} However, only 2 studies^{8,11} reported deaths for both the NAM and DNM groups: Rhodes et al reported 10 deaths among 64 patients in the NAM group as opposed to 41 deaths among 168 patients in the other melanoma group,⁸ and Friedman et al reported 10 deaths among 130 patients in the NAM group as opposed to 78 deaths among 427 patients in the other melanoma group.¹¹ Both studies suggested a more favorable survival with NAM.¹¹

Lin et al,² Cochran et al,²² Friedman et al,¹¹ Kaddu et al,³ and Cymerman et al²¹ also investigated survival through Kaplan-Meier and multivariate analyses. Lin et al reported that the survival difference between NAM and DNM was not significant (P = .41).² Cochran et al reported that the 5-year survival was not statistically different among groups.²² Using life-table analysis, Friedman et al reported that the 5-year survival for NAM and DNM was 91% and 78%, respectively.¹¹ Kaddu et al

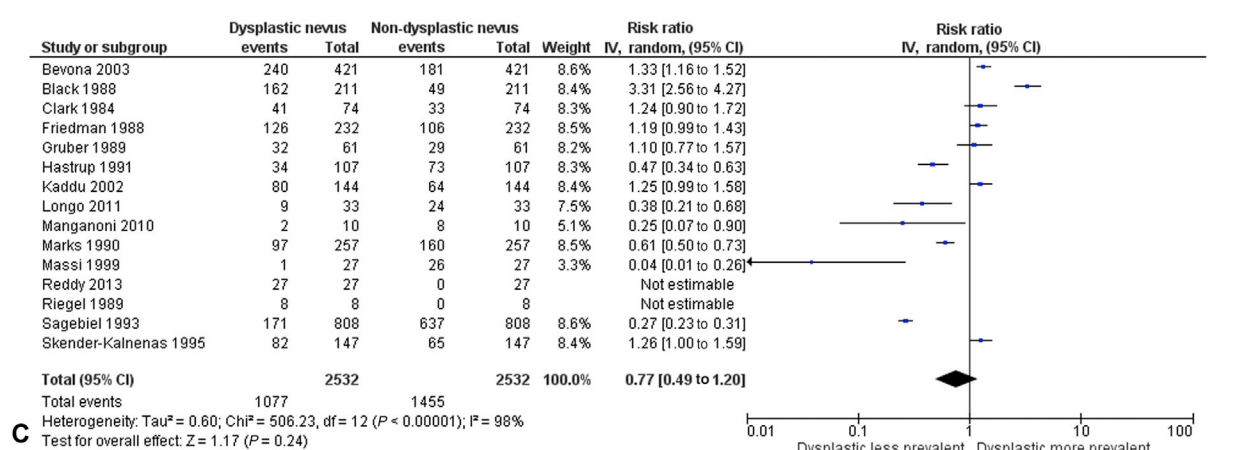
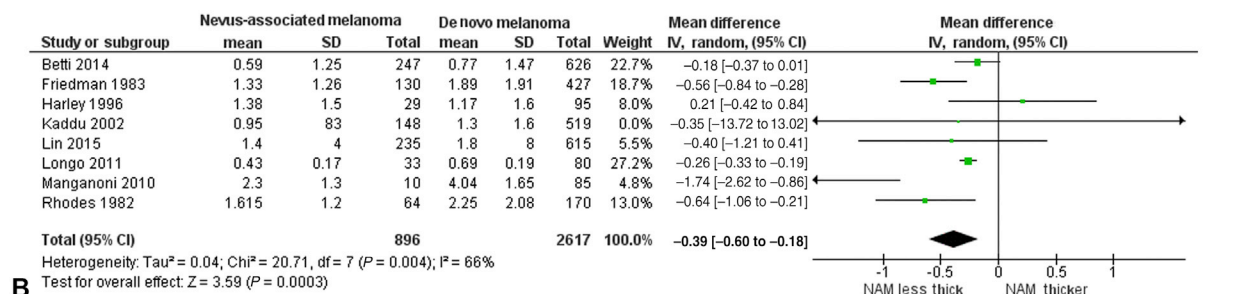
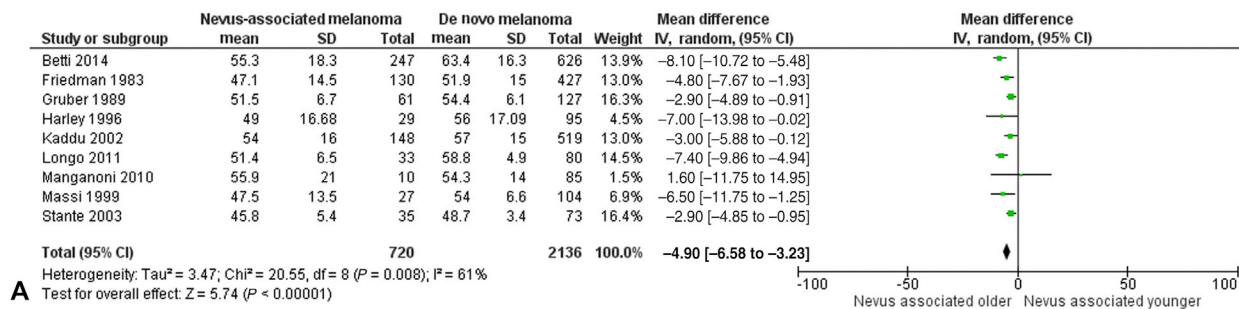


Fig 3. Forest plots of subanalyses. **A**, Mean age of patients with nevus-associated and de novo melanomas in 9 published studies. **B**, Thickness of nevus-associated melanomas in 8 published studies. The mentioned studies reported detailed information on mean Breslow thickness. **C**, Prevalence of dysplastic nevus-associated melanoma in 15 published studies. The mentioned studies indicated whether nevus remnants associated with melanoma were dysplastic or nondysplastic. *CI*, Confidence interval; *NAM*, nevus-associated melanoma; *SD*, standard deviation.

found no differences in survival ($P = .5$) between patients with NAM (n = 69, mean follow-up 78.22 months) and patients with DNM (n = 283, mean follow-up 84 months).³ Cymerman et al examined survival in 2 cohorts of melanoma patients; DNMs were associated with worse overall survival in univariate analysis, but this difference only remained significant in 1 cohort in their multivariate analysis (HR 1.27, 95% CI 0.93-1.75, $P = .14$; HR 1.70, 95% CI 1.19-2.44, $P = .004$).²¹

DISCUSSION

The main finding of the current systematic review and meta-analysis was that a minority of melanomas (29.1%) developed in conjunction with a preexisting nevus, and the majority (70.9%) developed de novo. This result provides further evidence that most melanomas do not originate from malignant transformation of nevus cells. The question of whether NAM is a result of a malignant transformation of nevus cells cannot be elucidated by the

Table I. Nevus-associated—related data of selected studies (n = 38)

Nevus type	Studies, n	Cases, n (%)
Congenital and acquired		
Congenital	13	471 (22.6)
Acquired	13	1612 (77.4)
Total		2083 (100.0)
Dysplastic and nondysplastic		
Dysplastic	15	1112 (43.3)
Nondysplastic	15	1455 (56.7)
Total		2567 (100.0)
Junctional, compound, and dermal*		
Junctional		
Dysplastic	12	135 (54.2)
Nondysplastic	13	114 (45.8)
Total	13	249 (21.7)
Compound		
Dysplastic	12	118 (67.0)
Nondysplastic	14	58 (33.0)
Total	14	176 (15.4)
Dermal		
Not specified	15	618 (54.0)
Total	18	102 (8.9)
Total		1145 (100.0)

*Congenital nevi were excluded.

findings of the present meta-analysis. Data in the literature suggest that NAM should not be considered an incidental collision phenomenon between a nevus and a melanoma because its incidence was shown to be higher than what would be expected by chance alone.⁴⁸ Furthermore, nevus and melanoma cells in NAMs have been recently demonstrated to share a similar mutational profile, which might indicate a common origin or even a malignant transformation of nevus melanocytes.⁴⁹ However, these findings are not substantial enough to justify the designation of nevi as precursor lesions, especially in light of evidence suggesting that the lifetime risk for an individual nevus to transform into melanoma is exceedingly low.⁵⁰

The second important finding of our study was a significantly lower mean Breslow thickness for NAMs than DNMs. This finding should be interpreted with caution because nevus remnants might possibly have been obstructed by malignant cells in thicker melanomas.⁷ This latter result is in-line with evidence suggesting a trend toward better overall survival of NAM patients than DNM patients. Several studies reported a survival benefit for NAM over DNM, but most of these comparisons failed to reach statistical significance.^{2,3,8,11,22} Recently, Cymerman et al confirmed NAM as an independent predictor of better survival through multivariate analysis.²¹

Furthermore, we attempted to investigate the characteristics of nevi involved in NAMs. However,

our analysis was limited by the significant heterogeneity among studies on reporting the nevus types. In particular, the differentiation between acquired and congenital nevi was omitted in several studies, and in 1 study only melanomas developing in association with acquired nevi were included. Thus, our finding that 77.4% of NAMs develop in conjunction with acquired nevi is associated with a significant bias. Furthermore, our analysis showed that the majority of these acquired nevi were intradermal, a type of nevi that usually develops in early childhood.⁵¹ Dermatologists should be aware that melanomas can arise in association with old and stable dermal nevi, and consequently, they should never forget to examine such nevi by dermoscopy during routine visits.

The current meta-analysis has some limitations. First, we considered a large number of uncontrolled studies and pooled data from different studies despite high heterogeneity; subanalysis was conducted to attempt and explain this heterogeneity. Second, the differentiation between congenital and acquired nevi and information about dysplastic features of associated nevi were often omitted and nonhomogeneously reported. The wide range of years of publication could explain the latter finding; the definition of dysplastic nevus has frequently changed during this time.⁵² Third, patients with NAMs were significantly younger than those with DNMs. One might speculate that this finding is related to a higher total nevus count in younger patients. In fact, it is known that the total nevus count decreased steadily in the age groups 60-69, 70-79, and 80-89 years, of which had 96 (47.3%), 68 (33.5%), and 39 (19.2%) nevi, respectively.⁵³ However, patients with NAMs and DNMs belonged to the same age group (mean age NAMs vs DNMs, 52 years vs 57 years), and thus, the younger age of NAMs is not likely to be related to differences in total nevus count.

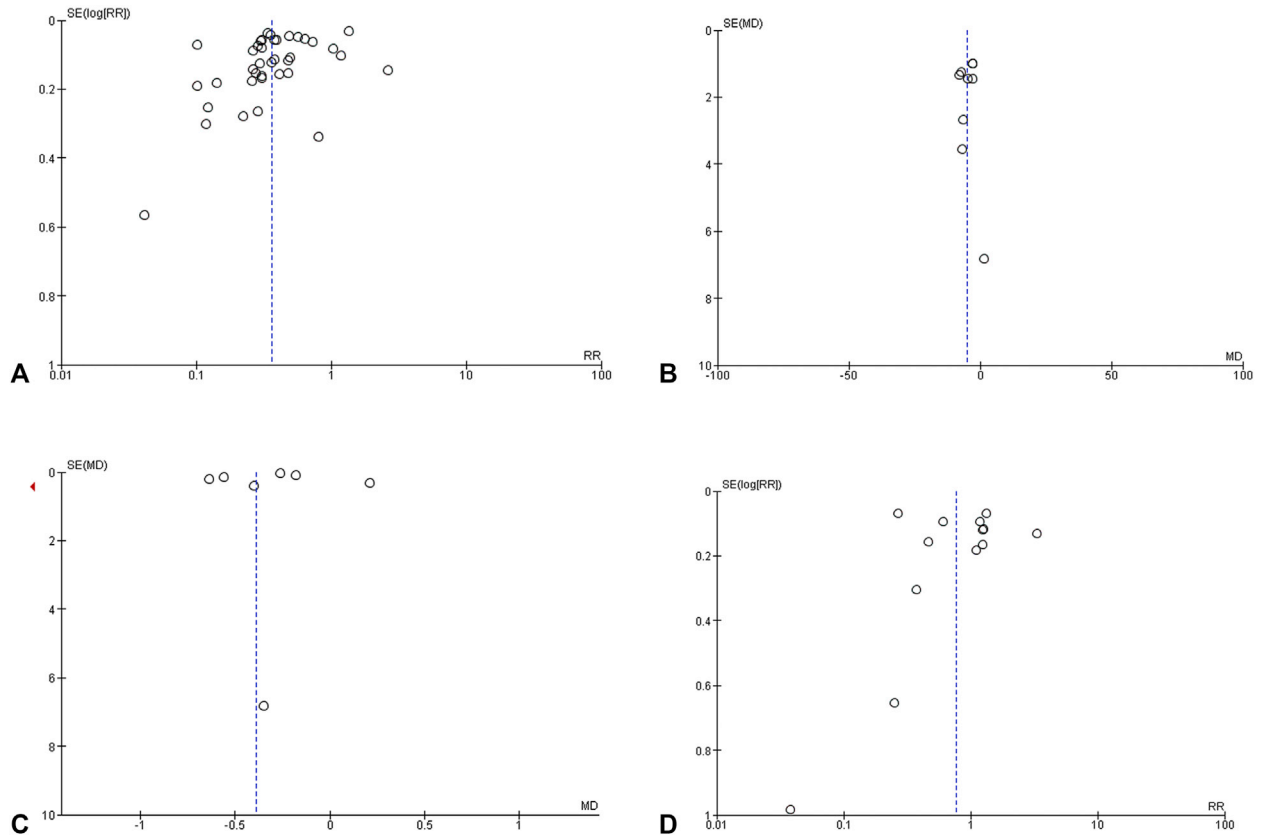
In conclusion, in this systematic review and meta-analysis we found that less than one-third of melanomas were nevus-associated and that NAMs were less thick than DNMs. Among NAMs, we found no significant differences in the distribution of dysplastic and nondysplastic remnants.

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Supplemental Fig 1. Funnel plots assessing publication bias. **A**, Prevalence of nevus-associated melanomas in 38 published studies; **B**, Mean age of patients with nevus-associated and de novo melanomas in 9 published studies. **C**, Thickness of nevus-associated melanomas in 8 published studies. **D**, Prevalence of dysplastic nevus-associated melanoma in 15 published studies.

Supplemental Table I. Selected studies data (n = 38)^{2-8,10,11,13}

Study	Year	Study type	All melanomas	Nevus-associated melanomas	Time, y	Melanoma histotypes	Thickness categories	Nevus type	Dysplastic remnants specified	Congenital remnants specified
Haenssle et al ³⁰	2016	Prospective	190	103	15	All	All	NR	No	No
Rhodes et al ⁸	1982	Prospective	234	64	4.8	All	All	Dermal only	No	Yes
Friedman et al ¹¹	1983	Prospective	557	130	8	All	All	Dermal only	No	Congenital exclude
Rigel et al ²³	1989	Prospective	18	8	7.8	All	All	NR	Dysplastic only	No
Cymerman et al ²¹	2016	Prospective	2149	547	19	All	All	NR	No	No
Bevona et al ⁴	2003	Retrospective	1606	421	5	All	Invasive only	NR	Yes	No
Lin et al ²	2015	Retrospective	850	235	11	All	Invasive only	NR	No	No
Stolz et al ¹⁹	1989	Retrospective	150	33	NR	All	Thin only + in situ	NS	No	No
Black ²⁵	1988	Retrospective	500	211	6	SSM	Invasive only	NS	Yes	Yes
Manganoni et al ⁴⁷	2010	Retrospective*	95	10	27.8	NM	Invasive only	NR	Yes	Yes
Longo et al ¹³	2011	Retrospective	113	33	NR	All	All	NS	Yes	Yes
Betti et al ²⁴	2014	Retrospective	873	247	17.6	All	All	NR	No	No
Sagebiel ⁴⁰	1993	Retrospective	1954	1126	NR	SSM + NM	All	NR	Yes	Yes
Cochran et al ²²	1969	Retrospective	165	36	10	All	All	Dermal only	No	No
McGovern et al ³⁶	1985	Retrospective	723	282	33	SSM	All	NR	No	No
Gruber et al ²⁹	1989	Retrospective	188	61	2	All	All	NR	Yes	No
Skender-Kalnenas et al ⁴⁴	1995	Retrospective	289	147	NR	SSM + LMM + unclassified	Thin only + in situ	NS	Yes	Yes
Couperus et al ⁶	1954	Retrospective	141	102	NR	All	All	Junctional only	No	No
Clark et al ²⁶	1969	Retrospective	269	25	NR	SSM + NM + LMM	Invasive only	NR	No	No
Crucioli and Stilwell ²⁷	1982	Retrospective	129	14	11	All	All	NS	No	No
Reddy et al ³⁹	2013	Retrospective	216	27	11.5	All	All	NR	Dysplastic only	No
Stante et al ⁴³	2003	Retrospective	108	35	3.3	All	Thin only + in situ	NR	No	No
Clark et al ¹⁰	1984	Retrospective	241	74	3.8	All	All	NR	Yes	Yes
Friedman et al ²⁸	1988	Retrospective	1002	232	NR	All	All	NS	Yes	Yes
Marks et al ³⁵	1990	Retrospective	1101	257	4.8	SSM + NM	All	NR	Yes	Yes
Urso et al ⁴⁵	1991	Retrospective	233	53	4.3	All	All	NR	No	Yes
Hastrup et al ³²	1991	Retrospective	512	107	2.5	SSM + NM + unclassified	All	NS	Yes	No
Harley and Walsh ³¹	1996	Retrospective	124	29	1.3	All	All	NR	No	Yes
Massi et al ²⁰	1999	Retrospective	131	27	4	All	Invasive only	NR	Yes	Yes
Kaddu et al ³	2002	Retrospective	667	148	6	All	All	NR	Yes	Yes
Krüger et al ³³	1992	Retrospective	200	42	0.5	All	All	NR	No	No

Continued

Supplemental Table I. Cont'd

Study	Year	Study type	All melanomas	Nevus-associated melanomas	Time, y	Melanoma histotypes	Thickness categories	Nevus type	Dysplastic remnants specified	Congenital remnants specified
Rippey et al ⁴⁶	1977	Retrospective*	54	12	NR	SSM + NM + unclassified	All	Dermal only	No	No
Larsen ³⁴	1978	Retrospective	60	11	2	SSM + NM + unclassified	All	NR	No	No
Ackerman ⁵	1948	Retrospective	75	3	NR	All	All	Junctional only	No	No
Purdue et al ³⁸	2005	Retrospective	932	339	0.6	SSM + NM + LMM + unclassified	All	NR	No	No
Shitara et al ⁴¹	2014	Retrospective	1190	390	10	All	All	NR	No	No
McGovern ³⁷	1970	Retrospective	202	54	NR	All	All	Dermal only	No	No
Søndergaard ⁴²	1983	Retrospective	1916	177	29.3	SSM + NM + LMM + unclassified	All	NR	No	No

LMM, Lentigo maligna melanoma; NM, nodular melanoma; NR, not reported; NS, not specified; SSM, superficial spreading melanoma.

*Letter to the editor.

Supplemental Table II. Demographic and melanoma-related data of selected studies (n = 38)

Category	Nevus-associated melanoma		De novo melanoma		Total
	Studies, n	Cases, n (%)	Studies, n	Cases, n (%)	Cases, n (%)
Sex					
Male	17	1366 (54.3)	17	2966 (49.3)	4332 (50.8)
Female	17	1149 (45.7)	17	3046 (50.7)	4195 (49.2)
Total		2515 (100.0)		6012 (100.0)	8527 (100.0)
Histotype					
SSM	19	2685 (84.4)	16	5946 (64.0)	8631 (69.2)
NM	17	227 (7.1)	16	1613 (17.4)	1840 (14.7)
LMM	14	72 (2.3)	14	859 (9.2)	931 (7.5)
ALM	9	18 (0.6)	10	147 (1.6)	165 (1.3)
Desmoplastic	1	0 (0)	2	16 (0.2)	16 (0.1)
Others	5	53 (1.7)	5	175 (1.9)	228 (1.8)
Unclassified	9	128 (4.0)	9	533 (5.7)	661 (5.3)
Intermediate	0	0 (0)	0	0 (0)	0 (0)
Polypoid	0	0 (0)	1	2 (0.1)	2 (0.1)
Amelanotic	0	0 (0)	1	2 (0.1)	2 (0.1)
Total		3183 (100.0)		9293 (100.0)	12476 (100.0)
Body site					
Head and neck	16	266 (10.1)	14	1051 (17.3)	1317 (15.1)
Trunk	20	1515 (57.5)	16	2165 (35.6)	3680 (42.2)
Extremities	18	791 (30.0)	16	2682 (44.0)	3473 (39.8)
Upper extremities	14	223 (8.5)	13	663 (10.9)	886 (10.2)
Lower extremities	14	263 (10.0)	13	979 (16.1)	1242 (14.2)
Acral	2	19 (0.7)	3	92 (1.5)	111 (1.3)
Anogenital	1	2 (0.1)	2	2 (0.1)	4 (0.1)
Special sites	1	5 (0.2)	1	12 (0.2)	17 (0.2)
Others	2	22 (0.8)	2	61 (1.0)	83 (1.0)
Missing	2	13 (0.5)	2	25 (0.4)	38 (0.4)
Ocular	0	0 (0)	0	0 (0)	0 (0)
Mucosal		0 (0)	0	0 (0)	0 (0)
Occult	0	0 (0)	0	0 (0)	0 (0)
Total		2633 (100.0)		6090 (100.0)	8723 (100.0)
Thickness					
In situ	17	408 (19.8)	16	727 (14.6)	1135 (16.1)
Invasive	17	1649 (80.2)	16	4268 (85.4)	5917 (83.9)
Total		2057 (100.0)		4995 (100.0)	7052 (100.0)
Clark level					
I	17	408 (39.3)	16	727 (35.1)	1135 (36.5)
II	7	304 (29.3)	5	546 (26.3)	850 (27.3)
III	6	240 (23.1)	5	449 (21.6)	689 (22.1)
IV	6	84 (8.1)	5	315 (15.2)	399 (12.8)
V	2	3 (0.3)	4	37 (1.8)	40 (1.3)
Total		1039 (100.0)		2074 (100.0)	3113 (100.0)

ALM, Acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.