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

Riccardo Pampena, MD,[a] Athanassios Kyrgidis, MD,[a] Aimilios Lallas, MD,[b] Elvira Moscarella, MD,[a] Giuseppe Argenziano, MD,[c] and Caterina Longo, MD, PhD[a,d]
Reggio Emilia, Italy; Thessaloniki, Greece; Naples, Italy; and Modena, Italy

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

From the Dermatology and Skin Cancer Unit, First Medical Department, Arcispedale Santa Maria Nuova, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Reggio Emilia[a]; First Department of Dermatology, Aristotle University of Thessaloniki[b]; Dermatology Unit, University of Campania, Naples[c]; and Dermatology Unit, University of Modena and Reggio Emilia.[d]

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Correspondence to: Caterina Longo, MD, PhD, Dermatology Unit, University of Modena and Reggio Emilia, Arcispedale Santa Maria Nuova-IRCCS, Viale Risorgimento 80, Reggio Emilia 42100, Italy. E-mail: longo.caterina@gmail.com.
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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.

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.

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]

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)