



The Natural History of Common Melanocytic Nevi: A Systematic Review of Longitudinal Studies in the General Population

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TO THE EDITOR

The risk of developing cutaneous melanoma increases with increasing numbers of common nevi on the skin (Olsen et al., 2010). It is estimated that around 50% of melanomas may develop from a nevus, especially melanomas in younger people and of the superficial spreading subtype (Cymerman et al., 2016), although the exact proportion is debated (Purdue et al., 2005; Shain and Bastian, 2016; Shitara et al., 2014; Tsao et al., 2003). Therefore, much can be learned from studying nevi, yet little is known about their natural history in the general population. Studies to date have shown a lower prevalence of nevi in older age groups, but because these have been all cross-sectional in design, they do not address natural history, which can be only loosely inferred from their findings (Green and Swerdlow, 1989; Piliouras et al., 2011; Stegmaier, 1959). For example, the lower prevalence in older age groups may be due to the generally lower sun exposure in earlier time periods (cohort effect) rather than an age effect (Bolanca et al., 2008). Almost all longitudinal studies have been undertaken in high-risk groups such as melanoma patients, their relatives, or atypical nevus patients (Abbott et al., 2015; Banky et al., 2005; Halpern et al., 1993), and their findings are unlikely to apply to the population at large. Therefore, we performed a systematic review of longitudinal studies of nevus counts in the general population.

Population-based longitudinal studies in adults (>18 years of age) that consisted of a baseline and at least one follow-up count of common nevi were included. The guidelines from the Preferred Reporting Items for systematic

Reviews and Meta-Analyses (i.e., PRISMA) statement were followed for reporting of the review (Moher et al., 2009). Inclusion criteria and methods of data analysis were specified in advance and documented (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016049474). Eligible studies through September 20, 2016, were identified by searching MEDLINE 1950 using PubMed software as the search interface (U.S. National Library of Medicine, Bethesda, MD) and hand-searching the reference lists of the retrieved articles. The following medical subject headings, terms, or text words were used: *naevus; naevi; nevus; nevi; melanocytic naevi; nevus, pigmented; cohort; longitudinal studies; and prospective*. First, titles and abstracts from retrieved articles were screened by two review authors (EP and TN). Subsequently, full texts of potentially relevant articles were assessed for eligibility by the same two reviewers. Any discrepancy was resolved by consensus. No attempt was made to identify unpublished literature. Authors of one article were contacted by e-mail for further information but did not respond.

708 studies were identified, of which two met the inclusion criteria (Table 1) (see Supplementary Figure S1 online). The first study (Tindall, 1976) examined 163 people reflecting the sex, race, and socioeconomic status of the ambulatory population of Durham, North Carolina, aged 64 years and older. Nevi were counted on the total body, among other skin conditions. After 10 years of follow-up, the counts were repeated on 69 living participants of the original 163 (42%). At follow-up, the percentage of people with 10 or more nevi

decreased to 7%, compared with 15% at baseline (Table 1). Exact numbers of nevi were not provided, and no information was given about changes in people with fewer than 10 nevi at baseline.

The second study (Koseoglu et al., 2015), conducted in Turkey, included 60 healthy control subjects as part of a study examining nevus growth in patients receiving immunosuppressive treatment. Control subjects were matched to the patients by age, sex, race, and Fitzpatrick skin type. Nevi were counted at baseline and at 3, 6, and 12 months on the trunk, arms, and legs; however, only the baseline and 12-month results were presented. In addition to the nevus count, size of the nevi was dermoscopically measured, and any dermoscopic changes were noted. In total, 180 melanocytic lesions were counted. No changes in nevus counts were observed after 12 months ($P = 0.564$), nor were any dermoscopic changes noted, but the median size of the nevi had decreased from 3.01 to 2.98 ($P < 0.001$) (Table 1).

Both studies have major limitations. In the US study (Tindall, 1976), age, sex, and race distributions of the study population were not provided, and no exact nevus counts were given overall or within demographic strata. The authors of the Turkish study (Koseoglu et al., 2015) did not specify from where or how the 60 matched control subjects were recruited and how representative they were of the general population. Neither did they note if there was any loss to follow up. Also, the significance of the decrease in median nevus size they report seems unlikely given the small difference and sample size. For both studies (Koseoglu et al., 2015; Tindall, 1976) no description was given of the examiners or the counting and size measurement procedure, and thus the accuracy of the data cannot be assessed.

Table 1. Longitudinal nevus counts: comparison of results from two cohorts

Study Characteristics	Tindall et al., 1976	Koseoglu et al., 2015
Study location	North Carolina, USA	Turkey
Cohort size	69	60
Cohort description	Reflection of the ambulant population of Durham, NC, aged 64 years and older; survivors after 10-year follow-up of original cohort of 163 persons	Healthy control subjects, matched by age, sex, race, and Fitzpatrick skin type to 103 patients undergoing immunosuppressive therapy
Follow-up	10 years	12 months
Age mean ± SD	Not stated	44 ± 10.32
Male, %	Not stated	40
Nevus count	Total body	Trunk, arms, and legs
No. of Nevi	People With 10 or More Nevi, %	Mean No. of Nevi (Min–Max)
At baseline	15%	4 (1–12)
At follow up	7%	4 (1–12)
Size of Nevi, Median Diameter in mm (Min–Max)		
At baseline	N/A	3.01 (2.04–7.55)
At follow up	N/A	2.98 (2.00–7.77)

Abbreviations: Max, maximum; Min, minimum; N/A, not applicable; SD, standard deviation.

Our review highlights a major gap in scientific knowledge regarding the natural history of common melanocytic nevi. Although numerous reports from cross-sectional studies suggest that older populations generally have lower nevus counts, implying that common nevi involute over time (Green and Swerdlow, 1989), this evidence may merely reflect a cohort effect and not a true age effect. The US study found a decline in the proportion of people aged 64 years and older with 10 or more nevi in a 10-year period (Tindall, 1976), whereas the Turkish study did not find changes in nevus counts over 12 months in their study population with a mean age of 44 years (Koseoglu et al., 2015). Both these studies have reported very limited longitudinal data, which hamper interpretation and generalization of the findings.

It is crucial to have longitudinal data on normal nevus development in all age groups in the general population because these are the strongest determinants of melanoma. Such knowledge will lead to better understanding of evolution of nevocytes or melanocytes if it occurs. Providing this missing link in nevus (and melanoma) etiology would potentially help in tailoring secondary prevention strategies for melanoma. In conclusion, this review highlights the need for longitudinal nevus research in the general population to develop further knowledge on the natural history of nevi.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at <http://dx.doi.org/10.1016/j.jid.2017.03.040>.

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