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The natural history of common melanocytic naevi: a systematic review of longitudinal studies in the general population

Elseemieke I. Plasmeijer¹, Thi-My-Uyen Nguyen², Catherine M. Olsen³, Monika Janda², H. Peter Soyer⁵, ⁶, Adele C. Green¹,⁷

Author affiliations:
¹QIMR Berghofer Medical Research Institute, Cancer and Population studies, Brisbane, QLD, Australia; ²Queensland University of Technology, Institute of Health and Biomedical Innovation, Brisbane, QLD, Australia; ³QIMR Berghofer Medical Research Institute, Cancer Control Group, Brisbane, QLD, Australia; ⁴School of Public Health, The University of Queensland, Brisbane, Queensland, Australia; ⁵Dermatology Research Centre, The University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Queensland; ⁶Department of Dermatology, Princess Alexandra Hospital, Brisbane, Queensland, Australia; ⁷CRUK Manchester Institute and University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom

ORCID:
Adele C. Green: 0000-0002-2753-4841
Catherine M. Olsen: 0000-0003-4483-1888
H. Peter Soyer: 0000-0002-4770-561X

Corresponding author:
Elseemieke I. Plasmeijer, MD PhD
QIMR Berghofer Medical Research Institute, Cancer and Population studies, Brisbane, QLD, Australia; T: +61 7 38453578; F: +61 7 38453503
E-mail: elseemieke.plasmeijer@qimrberghofer.edu.au
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**Short title:** Review of longitudinal naevus studies

**Abbreviations:** CI: confidence intervals; SD: standard deviation; no.: number

**Limits:** 1000 words (Current 1011 but only 1 table, therefore 1,500 allowed), 2 Fig/Tables (Current 1, 1 supplemental), 15 Refs (Current 16)
To the Editor,

The risk of developing cutaneous melanoma increases with increasing numbers of common naevi on the skin (Olsen et al., 2010). It is estimated that around 50% of melanomas may develop from a naevus, 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 naevi, yet little is known about their natural history in the general population. Studies to date have shown a lower prevalence of naevi in older age-groups, but since these have been all cross-sectional in design, they do not address natural history which can only be 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 naevus 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 naevus counts in the general population.

Population-based longitudinal studies in adults (>18 y) that consisted of a baseline and at least one follow-up count of common naevi were included. The guidelines from the Preferred Reporting Items for systematic Reviews and Meta-Analyses (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 to 20 September 2016 were identified by searching Medline 1950 (U.S.
National Library of Medicine, Bethesda, MD; using PubMed software as the search interface) 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 2 review authors (EP and TN). Subsequently full-texts of potentially relevant articles were assessed for eligibility by the same 2 reviewers. Any discrepancy was resolved by consensus. No attempt was made to identify unpublished literature. Authors of one article were contacted per email for further information but did not respond.

708 studies were identified, of which two met the inclusion criteria (Table 1) (Flow chart as supplementary material). The first study (Tindall, 1976) examined 163 people reflecting the sex, race and socioeconomic status of the ambulatory population of Durham, North Carolina, USA, aged 64 years and over. Naevi 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 ten or more naevi decreased to 7%, compared to 15% at baseline (Table 1). Exact numbers of naevi were not provided and no information was given about changes in people with less than 10 naevi at baseline.

The second study (Koseoglu et al., 2015) conducted in Turkey included 60 healthy controls as part of a study examining naevus growth in patients receiving immunosuppressive treatment. Controls were matched to the cases by age, sex, race and Fitzpatrick skin type. Naevi were counted at baseline, 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 naevus count, size
of the naevi was dermoscopically measured and any dermoscopic changes were noted. In total 180 melanocytic lesions were counted. No changes in naevus counts were observed after 12 months (p= 0.564), nor were any dermoscopic changes noted, but the median size of the naevi 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 naevus 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 controls 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 naevus 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 is unable to be assessed.

Our review highlights a major gap in scientific knowledge regarding the natural history of common melanocytic naevi. While numerous reports from cross-sectional studies suggest that older populations generally have lower nevus counts, implying that common naevi involute over time (Green and Swerdlow, 1989), this evidence may merely reflect a cohort effect not a true age effect. The US study found a decline in the proportion of people aged 64 years and over with 10 or more naevi in a 10-year period (Tindall, 1976), while the Turkish study did not find changes in naevus 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 generalisation of the findings.
It is crucial to have longitudinal data on normal naevus development in all age groups in the general population as these are the strongest determinants of melanoma. Such knowledge will lead to better understanding of evolution of naevocytes or melanocytes if it occurs. Providing this missing link in naevus (and melanoma) aetiology would potentially help in tailoring secondary prevention strategies for melanoma. In conclusion, this review highlights the need for longitudinal naevus research in the general population to develop further knowledge on the natural history of naevi.

Conflict of interest: None of the authors have any conflict of interest to declare.

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References


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

<table>
<thead>
<tr>
<th>Study location</th>
<th>Tindall et al., 1976 (Tindall, 1976)</th>
<th>Koseoglu et al., 2015 (Koseoglu et al., 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort size</td>
<td>69</td>
<td>60</td>
</tr>
<tr>
<td>Cohort description</td>
<td>Reflection of the ambulant population of Durham, NC, aged 64 and over, survivors after 10 year follow up of original cohort of 163 persons</td>
<td>Healthy controls, matched by age, sex, race and Fitzpatrick skin type to 103 patients undergoing immunosuppressive therapy</td>
</tr>
<tr>
<td>Follow up</td>
<td>10 years</td>
<td>12 months</td>
</tr>
<tr>
<td>Mean age</td>
<td>Not stated</td>
<td>44 ±10.32 (SD)</td>
</tr>
<tr>
<td>Male, %</td>
<td>Not stated</td>
<td>40</td>
</tr>
<tr>
<td>Naevus count</td>
<td>Total body</td>
<td>Trunk, arms and legs</td>
</tr>
<tr>
<td>No. of naevi</td>
<td>% of people with 10 or more naevi</td>
<td>Mean no. of naevi (min-max)</td>
</tr>
<tr>
<td>At baseline</td>
<td>15%</td>
<td>4 (1-12)</td>
</tr>
<tr>
<td>At follow up</td>
<td>7%</td>
<td>4 (1-12)</td>
</tr>
<tr>
<td>Size of naevi: Median diameter in mm (min-max)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>N/A</td>
<td>3.01 (2.04-7.55)</td>
</tr>
<tr>
<td>At follow up</td>
<td>N/A</td>
<td>2.98 (2.00-7.77)</td>
</tr>
</tbody>
</table>