Melanoma arising from pre-existing naevus in carriers of a germline CDKN2A pathogenic variant

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Dear Editor, Most melanomas arise from melanocytes in normal-appearing skin with no discernible pigmented lesion. Approximately 30% of melanomas evolve from benign melanocytic naevi.[1] Individuals with a germline pathogenic *CDKN2A* variant, encoding the p16 and p14 tumour

suppressor proteins, have an estimated 70% risk of developing melanoma.[2,3] Carriers of a *CDKN2A* pathogenic variant are recommended to undergo periodic skin examinations to diagnose melanoma at an early stage.[4] Distinguishing melanoma from atypical naevus can be challenging in this patient group. At our department, total-body photography (TBP) is routinely used to surveil these patients, enabling the detection of alterations in existing naevi and the emergence of new lesions.[5]

In *CDKN2A* pathogenic variant carriers, it is unclear what proportion of melanomas develops from pre-existing naevi. To address this question, we studied established carriers of a *CDKN2A* pathogenic gene variant who developed melanoma or melanoma *in situ* from January 2009 to December 2023 and were observed at Leiden University Medical Center. Germline *CDKN2A* gene variants were detected using sequencing of all coding regions and multiplex ligation-dependent probe amplification. The diagnosis of melanoma was made based on pathological examination. Lentigo maligna (melanoma) was excluded. TBPs taken at least 6 months before melanoma development were examined to assess the presence of a pre-existing common naevus or atypical naevus. The pathology slides of the melanomas were reviewed for the presence or absence of a contiguous naevus component, blinded to the clinical data.

In total, 60 new melanomas were diagnosed in 44 patients with a *CDKN2A* pathogenic variant, including 47 cases of invasive melanoma (median Breslow thickness 0.5 mm) and 13 cases of melanoma *in situ* (Table 1). The median age at diagnosis was 49 years. TBPs demonstrated the presence of a pre-existing naevus in 47 of 60 cases (78%) at the exact anatomical location of melanoma development. The pre-existing lesion was found to be a common naevus in 31 cases and an atypical naevus in 16 cases, based on its morphology on earlier TBPs. Thirty-seven of 47 invasive melanomas (79%) and 10 of 13 *in situ* melanomas (77%) originated from a pre-existing naevus. Only 22% of melanomas in this cohort developed *de novo* from skin with no discernible pigmented skin lesion. When reviewing the histopathology slides, a contiguous naevus component was detected only in those cases with clinical evidence of a pre-existing naevus as shown by TBP. In the 47 melanomas arising from a pre-existing naevus clinically, pathological examination showed distinct naevus cell nests in 18 cases (38%). The lack of histological evidence of a naevus precursor in the remainder can be explained by sampling error in the histopathology slides or by overgrowing melanoma cells hindering the identification of naevus cell clusters.

The disease course in the patients with melanoma evolving from a naevus did not differ from that of patients with melanoma arising *de novo*. In this cohort of patients with hereditary melanoma, we found that melanoma developed in the context of a pre-existing naevus in the majority of cases (78%), making use of sequential TBP. This is a higher proportion than reported for sporadic melanoma (30%). We cannot exclude the possibility that the proportion of sporadic melanoma is underestimated as it was concluded solely from pathological examination.[1] In addition, our finding might be associated with the higher number of atypical naevi in carriers of a germline *CDKN2A* pathogenic variant. However, a sizeable proportion of melanomas in the patients arose from common naevi with no atypical features. Alternatively, the high frequency of melanoma emerging from a precursor naevus in these patients might be explained by the sequence of genetic alterations during tumorigenesis. In carriers of a germline inactivating *CDKN2A* gene variant, bi-allelic loss of *CDKN2A* occurs subclonally in the naevus stage, potentially conferring proliferative capacity.[6] In sporadic melanoma, this genetic alteration occurs later in melanoma evolution.[7] The frequent occurrence of naevus-associated melanoma in *CDKN2A* gene variant carriers is notable.

Table 1 Characteristics of 44 patients with a *CDKN2A* pathogenic variant and 60 melanomas

Characteristic	Value, *n* (%)[a]
Age, years (median, IQR)	49 (42–61)
Sex	
Male	25 (57)
Female	19 (43)
Skin type	
I	6 (14)
II	38 (86)
Naevus phenotype	
> 5 atypical naevi (AN)	9 (20)
> 100 common naevi or > 5 AN	19 (43)
Melanoma origin	
From naevus	
Common naevus	31 (52)
Clinically atypical naevus	16 (27)
From normal-appearing skin	13 (22)
Histopathology	
No distinct naevus nests	42 (70)
Residual naevus nests	18 (30)
Pre-existing lesion noticed by the patient	16 (27)
Melanoma subtype	
Invasive	47 (78)
Breslow thickness (median, mm)	0.5
In situ	13 (22)

IQR, interquartile range. [a]Unless otherwise noted.

A possible limitation of our study is the small number of incident melanomas in our cohort under surveillance. Additionally, our study included only patients with hereditary melanoma with fair skin type and sun exposure habits typical for northern Europeans. Although TBP is systematically performed in *CDKN2A* pathogenic variant carriers at our department, it is sometimes omitted in patients with few naevi. It should also be noted that the possibility of slow-growing melanomas mistakenly considered to represent naevi cannot be entirely excluded, despite the minimum interval of 6 months between photography and melanoma diagnosis. Our finding of frequent melanoma development from naevus precursor lesions is relevant in managing individuals with a *CDKN2A* pathogenic variant, supporting the routine use of TBP in this patient group to facilitate the detection of naevi that have changed in size, shape or colour. More than previously appreciated, the surgical removal of melanocytic naevi in these patients at high risk may prevent melanoma development.

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