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Melanoma diagnosis during periodic surveillance of patients with multiple atypical naevi

Running head: Melanoma diagnosis in patients with multiple atypical naevi

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Although large observational studies demonstrate an association between presence of atypical naevi and melanoma risk, the actual benefit of dermatological surveillance for patients with multiple atypical naevi is less clear.[1,2] Therefore recommendations for surveillance of such patients vary between countries. The UK guideline for the management of cutaneous melanoma recommends that such patients should be taught how to self-examine for changing naevi.[3] A survey among dermatologists from the US revealed that 59% recommend annual screening for patients with atypical naevi.[4] In the Netherlands, patients with 5 or more atypical naevi commonly undergo long-term yearly surveillance by a dermatologist in addition to receiving skin self-examination instructions.[5] Here we examined the diagnosis of melanoma during periodic surveillance of Dutch patients with multiple atypical naevi and analyzed the clinical characteristics of the subset of patients with atypical naevi who developed melanoma. All patients with 5 or more clinically atypical naevi, based on ABCD-criteria, and patients with more than 100 common naevi (collectively referred to as AN patients here) are seen for yearly dermatological consultation and for unscheduled visits when patients would notice suspicious lesions at the dermatology department of Leiden University Medical Center. We performed a cohort analysis on 1131 AN patients (641 women, 493 men, mean age 41 years) who visited our department between 2011 and 2016 for periodic surveillance consisting of total skin examination with use of dermoscopy, and total body photography in a subset of patients. Patients with familial melanoma, recent melanoma diagnosis or other reasons for surveillance were excluded. During the follow-up period (total follow-up time 3268 years) melanoma was diagnosed in 39 patients, 17 women and 22 men at a mean age 48 years (range 22-58). The rate of incident melanoma was 1.1% per follow-up year. Nine patients developed multiple melanomas, resulting in a total of 56 melanoma cases. There were 46 invasive melanomas and 10 *in situ* melanomas. Median Breslow thickness of the invasive melanomas was 0.67 mm (range 0,2 – 2,7 mm). The majority of melanomas was of the superficial spreading type (87%). Melanoma was detected by the dermatologist during routine follow-up examination in 79%, had been noted by the patient first in 18% and had been discovered by the general practitioner in 4% of cases. During the surveillance period 1550 skin lesions were excised, but in a proportion of cases for other reasons such as cosmetic concerns and basal cell carcinoma. Based on total body photographs and histopathology, a reliable conclusion could be drawn if the melanoma had originated from a precursor nevus or *de novo* from normal appearing skin in 22 cases. In 72%

melanoma had developed from a atypical or common nevus, which is higher than reported for melanoma in the general population (29%).[6]

Study of the clinical characteristics of AN patients who develop melanoma might enable more precise delineation of the patient group for whom surveillance would be most beneficial. To identify additional risk factors for melanoma we performed a case-control study on a largely unrelated cohort of 410 AN patients who had their first visit between 2011 and 2016 and from whom we had collected detailed information on phenotypical risk factors for melanoma. The presence and absence of each clinical risk factor was compared among 85 AN patients who had developed melanoma previously, at first visit or during periodic surveillance (cases) and 325 AN patients who never had developed melanoma (controls). The age- and sex-adjusted risk of melanoma was highest among AN patients with red hair (OR 4.8) or blond hair (OR 1.9), more than 100 solar lentigines (OR 3.4) and blistering sunburn during childhood (OR 1.6) (Table 1).

Our results reinforce the notion that dermatological surveillance with periodic skin examination is beneficial and a justified strategy for early detection of melanoma in AN patients. Remarkably, most melanomas were diagnosed by the dermatologist during examination and had not been noticed by the patient in spite of skin self-examination instructions in the majority of cases. The modifying effects of skin phototype and ultraviolet radiation-induced damage on melanoma risk in AN patients point to the independence of pigmentation- and nevus-related factors in melanoma susceptibility. As AN patients with red or blond hair, solar lentigines or a history or sunburn during childhood are at highest risk of developing melanoma, regular surveillance of these patients seems of particular importance. Comprehensive assessment of the health benefits and costs of yearly follow-up of AN patients as compared to skin self-examination on a population-wide scale is required to formulate melanoma prevention strategies in this patient group at increased risk.

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Table. Clinical risk factors for melanoma in AN patients						
		Overall n= 410	**Melanoma** n= 85	**No Melanoma** n= 325	**OR (CI 95%)**	**OR (CI 95%) adjusted for age and gender**
Gender	Female	241	45	196	Reference	
	Male	168	40	128	1.4 (0.8 - 2.2)	
>100 common naevi	No	131	22	109	Reference	Reference
	Yes	258	57	201	1.3 (0.8 - 2.4)	1.2 (0.7 - 2.2)
≥5 atypical naevi	No	149	30	119	Reference	Reference
	Yes	225	46	179	1.0 (0.6 - 1.7)	1.0 (0.6 -1.8)
Skin type	I	47	9	38	1.3 (0.5 - 3.8)	1.9 (0.6 - 5.8)
	II	300	64	236	1.4 (0.6 - 3.1)	1.7 (0.7 - 3.9)
	III-V	54	8	46	Reference	Reference
Eye color	Blue	244	60	184	1.8 (1.1 - 3.1)	**1.7 (1.0-3.0)**
	Other	150	22	128	Reference	Reference
Hair color	Red or blond	20	6	14	2.2 (1.1-4.4)	**2.8 (1.3-6.1)**
	Brown or black	375	75	300	Reference	Reference
Sunbathing	Never	160	33	127	Reference	Reference
	Ever	117	31	86	1.1 (0.7 - 1.9)	1.5 (0.9 - 2.7)
Sunbed use	Never	302	72	230	Reference	Reference
	Ever	20	3	17	0.5 (0.2 - 1.3)	0.6 (0.3 - 1.3)
Blistering sunburn <20yr	No	318	59	259	Reference	Reference
	Yes	80	19	61	1.7 (1.1 - 2.7)	**1.6 (1.0 - 2.5)**
Solar lentigines	0-40	288	45	243	Reference	Reference
	40-100	77	29	72	2.0 (1.4-3.1)	**1.8 (1.2-2.8)**
	≥100	25	14	11	4.0 (1.7-9.7)	**3.1 (1.2-7.8)**
Actinic keratoses	0	353	64	289	Reference	Reference
	≥1	22	11	11	4.5 (1.8 - 10.7)	1.2 (0.4 - 3.5)