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# The Familial Dysplastic Nevus Syndrome
## Natural History and the Impact of Screening on Prognosis
## A Study of Nine Families in the Netherlands

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**Abstract**—*Since* 1982, *nine families with the dysplastic nevus syndrome have been identified in the Leiden area (The Netherlands). A total of* 50 *primary melanomas were diagnosed in* 38 *persons. Nineteen of these melanomas had been diagnosed before the start of the screening programme (category I),* 11 *were detected at the initial examination of the families (category II), and* 20 *were found during the course of follow-up (category III).*

*To assess the effect of screening, we compared these categories with respect to the developmental stage of the melanomas. One of the* 19 *melanomas in category I, two of the* 11 *in category II and seven of the* 20 *in category III were melanoma* in situ. *The average thickness of the invasive melanomas in categories I, II and III was* 1.75, 0.80 *and* 0.54 mm *respectively. Sixteen of the* 19 *melanomas in category I* (84%) *were Clark III or IV, whereas* 15 *of the* 20 *melanomas in category III* (75%) *were Clark I or II.*

*From these findings it may be concluded that screening can lead to the detection of melanomas at an earlier stage, which in turn can permit curative treatment and improvement of both prognosis and life expectancy.*

*The need for supervision based on central registration of affected families to guarantee the continuity of screening is discussed.*

## INTRODUCTION

SINCE Cawley's initial description of familial malignant melanoma in 1952, there have been numerous similar reports [1–4]. The frequency of the familial variant of this disease among all melanoma cases ranges from 5 to 10% [4]. Familial malignant melanoma is characterized by a significantly earlier age at first diagnosis [2, 4–9], an increased frequency of multiple primary melanomas [2, 4–9], and a better survival rate [4, 6, 10] compared with sporadic melanoma.

In 1978 a syndrome was described in which clinically and histologically atypical nevi were associated with familial melanoma [11, 12]. This symptom complex has been named the FAMMM syndrome, the B-K mole syndrome or, more recently, the dysplastic nevus syndrome. The clinical features of the syndrome include multiple large melanocytic nevi with irregular outlines, variegated colours and the presence of a red (vascular) hue. Histologically, the major criteria are cellular atypia of the melanocytes, architectural atypia and a mesenchymal host response [11, 12]. The mode of genetic transmission is consistent with an autosomal dominant trait with a markedly variable expressivity and occasional non-penetrance [6, 10, 13–15].

Several studies have shown that the dysplastic nevus is the precursor lesion of the majority of familial melanomas [11, 12]. Periodic examination of patients with malignant melanoma and/or dysplastic nevi and their close relatives provides a basis for both primary prevention and earlier detection of this potentially lethal neoplasm. However, periodic screening may also have some disadvantages including not only the inconvenience of repeated check-ups, but also the violation of privacy and problems with insurance companies [16]. It may be difficult, for example, to obtain complete coverage of the cost of periodic examinations. Therefore, before screening programmes are undertaken on a larger scale, it must be certain that early diagnosis improves the prognosis and offers the prospect of a prolonged life expectancy. Although there is evidence in the literature [17] for a positive effect of screening, more studies are needed.

To investigate the effect of screening on the prognosis, we evaluated the data from nine families with malignant melanoma. The findings are presented, as well as some data on the natural course of the disease. In addition, the importance of central

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registration to guarantee the continuity of screening in families with hereditary tumours is discussed.

## PATIENTS AND METHODS

Nine families having at least three members with melanoma were selected for study. In all of these families dysplastic nevi were found in many melanoma patients and in many of their relatives. The total number of family members was 540. No relationship between the families has been found as yet. Individuals older than 10 years were screened in our out-patient department. Evaluation included examination and photography of all skin surfaces and biopsy of suspicious lesions. We also reviewed medical records and histological data of 16 patients with melanoma who had died before the study was started. All living patients and their relatives were examined initially between 1982 and 1984, and once or twice every year after that. The average length of follow-up was 57 months.

For the evaluation of the effect of screening, the melanomas were divided into three categories. Category I includes familial melanomas detected before the start of the screening programme, category II covers melanomas found in patients whose relatives were known to have familial melanoma and who were called up for examination; and category III comprises melanomas detected during the course of follow-up. The stages of development of the melanomas belonging to the three categories were compared. Differences in mean age at diagnosis of the melanomas and mean thickness were analysed for significance by an analysis of variance. For statistical analysis of differences in the occurrence of melanomas *in situ*, we used the chi-square test.

## RESULTS

Fifty primary melanomas were diagnosed in 38 persons (14 males and 24 females) belonging to nine families. All cases were verified by pathologic review.

Ten of the 38 patients developed more than one primary melanoma. The highest number of primary melanomas seen in one patient was three. Sixteen patients were found to have died from melanoma before the time of the study; the average age at death was 47 (range 18–87 years). Nineteen melanomas had been diagnosed before the start of the screening programme (category I). The average age of our patients whose first melanoma was detected before the start of screening was 43 years (range 17–62). To date, 31 newly diagnosed melanomas have occurred in 24 family members. Eleven melanomas were detected at the initial examination of the families (category II), and 20 melanomas were found during the course of follow-up (category III). The average age of patients whose first melanoma was detected during follow-up ranged from 16 to 39 years (mean age 29). The age at diagnosis and the developmental stage of the melanomas in the three categories are shown in Tables 1 and 2. Melanomas *in situ* were found in one of the 19 melanomas in category I, in two of the 11 in category II and in seven of the 20 in category III. The average thickness of the invasive melanomas in the three categories was 1.75, 0.80 and 0.54 mm respectively. Sixteen of the 19 melanomas in category I (84%) were Clark III or IV, whereas 15 of the 20 melanomas in category III (75%) were Clark I or II. The mean age at diagnosis of the melanomas in these categories did not differ significantly ($P = 0.16$). The difference in mean thickness of the invasive melanomas was highly significant ($P = 0.001$), whereas the occurrence of melanomas *in situ* was of borderline significance ($P = 0.07$).

## DISCUSSION

Reports in the literature with data on the natural history of familial malignant melanoma are rare. It is well known that hereditary melanoma becomes manifest at an earlier age (43 years in the present study) than non-familial melanoma does [2, 4–9]. The age at diagnosis of melanoma due to the screening procedure is declining steadily. The average age of our patients whose first melanoma was detected during follow-up was 29 years.

Several authors have reported a better survival rate for familial malignant melanoma than for non-familial malignant melanoma [4, 6 10]. In a recent investigation performed by Kopf *et al.* [18], however, a similar prognosis was found for both groups. Exact data on the mortality rate and the age at death of patients with familial melanoma are not available. In the study done by Greene *et al.* [17], 28 out of 58 patients (45%), whose first melanoma had been diagnosed before the study, had died. In our study 16 patients died from melanoma before the study was started and the average age at death was 47 years (range 18–87).

Greene *et al.* [17] are the only authors to report a positive effect of screening on the prognosis of patients with familial malignant melanoma. In that study, 22 members of 14 families developed 39 new primary cutaneous melanomas. Almost all of these 39 lesions were in a biologically early stage of development; 35 were Clark II or less and 36 were less than 0.76 mm thick.

To assess the effect of screening on the prognosis of the disease we divided the melanomas into three categories: I for melanomas diagnosed before start of the screening procedures, II for melanomas detected at initial examination of the families, and III for melanomas found during the course of follow-up.

The stage of development of the melanomas

*Table 1. Age at diagnosis, thickness and Clark level of melanomas detected before the start of the screening programme (I), at initial examination of the families (II) and during follow-up (III)*

| Patient | Sex | Family | Diagnosis | Age category | Thickness | Clark level |
|---|---|---|---|---|---|---|
| 1 | f | A | 36 | II | 2.74 | IV |
| 2 | f | A | 50 | I | 1.20 | III |
| 3 | f | A | 43 | I | 2.80 | IV |
| | | | 44 | III | * | I |
| 4 | f | A | 23 | III | 0.55 | II |
| 5 | f | B | 16 | III | 0.43 | II |
| 6 | m | B | 37 | III | 1.01 | III |
| 7 | m | B | 66 | II | 0.50 | III |
| | | | 67 | III | 0.40 | II |
| 8 | f | B | 27 | III | * | I |
| 9 | m | C | 45 | II | 0.80 | IV |
| 10 | m | C | 29 | I | 0.60 | III |
| 11 | m | C | 17 | III | 0.48 | II |
| 12 | m | C | 43 | III | 0.35 | II |
| 13 | f | C | 72 | II | 0.88 | III |
| 14 | f | D | 15 | II | * | I |
| 15 | f | D | 27 | III | * | I |
| | | | 27 | III | 0.15 | II |
| 16 | f | D | 26 | III | * | I |
| | | | 24 | III | * | I |
| 17 | f | E | 42 | I | 2.28 | IV |
| | | | 44 | I | 1.12 | IV |
| 18 | f | E | 42 | II | 0.34 | II |
| 19 | f | E | 16 | II | * | I |
| 20 | f | F | 36 | I | 2.25 | III |
| | | | 38 | I | 2.40 | IV |
| | | | 40 | I | 0.45 | II |
| 21 | m | F | 51 | II | 0.71 | IV |
| | | | 52 | III | 0.91 | IV |
| | | | 55 | III | 0.68 | III |
| 22 | f | F | 51 | I | 0.50 | III |
| 23 | f | F | 60 | I | 0.69 | III |
| 24 | f | G | 62 | I | 2.30 | IV |
| 25 | f | G | 39 | II | 0.30 | II |
| | | | 39 | III | 0.59 | III |
| 26 | f | G | 33 | I | 0.55 | II |
| | | | 39 | III | 0.71 | III |
| 27 | f | G | 35 | I | 0.85 | III |
| 28 | m | H | 46 | I | 2.00 | IV |
| 29 | f | H | 41 | II | 0.60 | II |
| | | | 41 | II | 0.30 | II |
| 30 | m | H | 39 | III | * | I |
| 31 | f | H | 39 | III | 0.35 | II |
| 32 | m | H | 35 | I | 2.40 | IV |
| 33 | f | H | 34 | III | * | I |
| 34 | m | J | 60 | I | 5.00 | IV |
| 35 | m | J | 48 | I | 2.70 | IV |
| 36 | m | J | 17 | I | 1.40 | IV |
| 37 | f | J | 43 | I | * | I |
| 38 | m | J | 22 | III | 0.38 | II |

*Melanoma *in situ*.

varied widely between these categories as shown in Table 2. It was found that screening led to the detection of more melanomas *in situ* and less invasive melanomas at an earlier age. We consider this to be an indication of the effectiveness of our screening programme.

The responsibility for the continuity of periodic examination is a heavy burden on the dermatologist, and special administrative and out-patient facilities are needed. Experience with other hereditary tumours has shown that periodic control cannot be adequately guaranteed in this way [16]. The continuity was found to be interrupted (for example, by completion of short-term research programmes, loss of funds, departure of the coordinating physician or moving away of the patients), which led to

*Table 2. Developmental stage of melanomas detected before the start of the screening programme (I), at initial examination of the families (II) and during follow-up (III)*

| | I | II | III |
|---|---|---|---|
| Total number | 19 | 11 | 20 |
| Mean age at diagnosis (years)* | 43 | 42 | 35 |
| Range (years) | 17–62 | 15–72 | 16–67 |
| Melanoma *in situ*† | 1 | 2 | 7 |
| Invasive melanoma | 18 | 9 | 13 |
| Mean thickness (mm)‡ | 1.75 | 0.80 | 0.54 |
| Range (mm) | 0.45–2.80 | 0.30–2.74 | 0.15–1.01 |

*No differences between all categories (analysis of variance, $P = 0.15$).
†No differences between all categories (chi-square test, $P = 0.07$).
‡Differences between all categories (analysis of variance, $P = 0.0001$).
Differences between category I and II, respectively, I and III (Scheffe's test, $P < 0.05$).

unnecessary morbidity and mortality. One way to solve the practical problems involved might be to have the administrative work organized centrally and to have the physician perform the main screening work. For this purpose a registration centre (Foundation for the Detection of Hereditary Tumours) was set up in the Netherlands in 1983. Personal data, investigation results, diagnosis and treatment results are recorded for all patients as well as personal data and the screening results of all close relatives. The registration centre is responsible for maintaining the continuity of the investigation by periodic assessment of the screening results. At present, the activities of the centre are limited to familial adenomatosis polyposis and the multiple endocrine neoplasia syndrome type 2 (MEN-2 syndrome) [19], but because of the good results of screening the programme will now be extended to the familial dysplastic nevus syndrome.

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