Melanocytic nevi in a Brazilian community of predominantly Dutch descent (1999-2007)

Nevos melanocíticos numa comunidade de origem predominantemente holandesa no Brasil (1999-2007)

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Abstract: BACKGROUNDS - Epidemiological studies have shown a significant relationship between melanocytic nevi and cutaneous melanoma.

OBJECTIVE: To evaluate the development of melanocytic nevi in the pupils of a school composed primarily of children of Dutch descent and to assess the effect of environmental factors on these individuals whose phenotypic characteristics were similar to those of their ancestors.

METHODS: In 1999 a cohort study was initiated to count the number of melanocytic nevi in 282 pupils of 3 to 17 years of age, 53.9% of whom were boys. Five years later a repeat exam was conducted in 148 students of 8 to 22 years of age, 49.3% of whom were males. The association between the age, skin phototype, eye color, hair color and ethnic group of the pupils and their parents and the presence of melanocytic nevi was analyzed at the beginning and at the end of the study.

RESULTS: There was a significant increase in cases of melanocytic nevi and dysplastic nevi at the follow-up examination. The number of melanocytic nevi was greater in boys than in girls in both covered and exposed areas of skin. Likelihood analysis calculated using the odds ratio showed that boys were more likely to develop melanocytic nevi than girls and that the children of non-mixed and mixed race with lighter hair were more likely to develop melanocytic nevi than those of other ethnic groups and those with dark hair. Children with skin phototype I were more likely to develop melanocytic nevi in covered areas of skin compared to those with skin types II or III.

CONCLUSIONS: These data show that individuals of Dutch descent were more likely to develop melanocytic nevi than individuals of other ethnic origins.

Keywords: Epidemiology; Melanoma; Nevus, pigmented; Risk factors; Solar radiation

Resumo: FUNDAMENTOS - Estudos epidemiológicos têm demonstrado relação significativa entre nevos melanocíticos e melanoma cutâneo.

OBJETIVO: Acompanhar o desenvolvimento de nevos melanocíticos nos alunos de uma escola composta, majoritariamente, por descendentes de holandeses e a influência do meio ambiente sobre esses indivíduos com características fenotípicas semelhantes às de seus antepassados.

MÉTODOS: Em 1999, iniciou-se estudo coorte para contagem de nevos melanocíticos nos 282 alunos entre três e 17 anos, sendo 53,9% meninos. Após cinco anos, realizou-se novo exame em 148 alunos entre oito e 22 anos, dos quais 49,3% eram meninos. Analisou-se a relação da idade, sexo, fotótipo, cor dos olhos, cor dos cabelos e etnia dos alunos e dos pais com a presença de nevos melanocíticos no início e no final do estudo.

RESULTADOS: Houve aumento significativo de nevos melanocíticos e nevos displásicos no reexame. Os meninos tiveram mais nevos melanocíticos (áreas cobertas e expostas) do que as meninas. A análise de probabilidade para razão de risco revelou que os meninos têm mais chance de desenvolver nevos melanocíticos do que as meninas, assim como os de etnia não miscigenada e miscigenada e com cabelos claros têm mais que os alunos de outras etnias e com cabelos escuros. Os que apresentam fotótipo I são mais propensos a desenvolver nevos melanocíticos nas áreas cobertas do que os que têm fotótipos II e III.

CONCLUSÕES: Os dados demonstram que os indivíduos de etnia holandesa tiveram maior probabilidade de desenvolver nevos melanocíticos do que os outros grupos étnicos.

Palavras-chave: Epidemiologia; Fatores de risco; Melanoma; Nevo pigmentado; Radiação solar

Received on 10.06.2009.
Approved by the Advisory Board and accepted for publication on 17.05.2010.
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Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial funding: None / *Suporte financeiro: Nenhum*

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INTRODUCTION

The development of melanocytic nevi (MN) has been the object of numerous epidemiological studies. The results obtained from case-controlled studies have shown a significant association between the number of MN, principally dysplastic nevi (DN) and a greater likelihood of developing cutaneous melanoma. However, no consensus has yet been reached in this respect. [1-6]

Epidemiological studies to evaluate the development of MN generally involve a count of the nevi on the whole body or on a part of it. [7] The ideal model to evaluate the development of MN is histological confirmation, a difficult task to execute on a wide scale. Countable melanocytic lesions include compound, intradermal and junctional nevi and simple lentigo, which should not be counted separately. [7]

Individuals with light-colored eyes, blonde or red hair, and sunburn prone light-colored skin that fails to tan will be more likely to develop a large number of MN; however, this association has not been found to be statistically significant in all studies. [8-12]

Studies conducted in adults show a statistically significant association between a high number of MN and darker skin and hair. [13,14]

Ultraviolet radiation is the most common environmental stimulus responsible for the proliferation of melanocytes and the development of MN, and plays an important role in the association between the number of MN and the likelihood of developing melanoma. [8,15,16]

Some MN may show a genetic predisposition for melanocytic proliferation or the development of melanocytes with a high risk of malignant transformation. The higher risk of melanomas in individuals with a large number of MN may reflect the increased likelihood of malignant transformation due to the overall increase in melanocytes in the skin. [17]

Epidemiological studies on the phenotype of individuals with less tanning capacity versus the development of MN are conflicting; consequently, there may be no relationship between skin type and the number of nevi. [3-6] Histological evaluation of skin that has been intensely exposed to sunlight in individuals with phototype I or II skin revealed abnormal melanocytes. [16,17]

There is a higher concentration of NM in exposed areas of the skin and a lower concentration in unexposed areas; however, a large concentration in areas that are not intensely exposed or that are only occasionally exposed to the sun may be explained by the "intermittent recreational exposure" theory. [17]

Episodes of severe sunburn in childhood are associated with a high risk of developing melanoma and basal cell carcinoma in adulthood. [12]

Children who live in areas with high-intensity solar radiation (close to the equator) have more NM. [9,10,18-21] Even moderate levels of ultraviolet radiation may be associated with a higher number of NM. [2,6,21] Fifty to eighty percent of the damage caused by sun exposure occurs in childhood and adolescence. Also at this time, intense, intermittent sun exposure that results in sunburn increases the probability of the appearance of skin melanoma. [21]

The natural histories of nevi and melanoma are relevant in general, since they represent the only visible model of the development of neoplasia. Due to their location on the skin and pigment synthesis, proliferative melanocytic lesions are perceptible while they are still small (0.1-0.2 cm in diameter), making them more easily recognizable than internal tumors.

Knowledge on the distribution and cause of MN advances slowly since there is still no agreement on uniform parameters. There is no consensus on the topographical distribution of nevi or on how to count them, and cohort studies, of which there are few, are more reliable than prevalence studies for the evaluation of the behavior of MN in children and adolescents. In Brazil, an important clinical study was conducted on congenital MN in children and adolescents and another on the frequency and body distribution of acquired MN. [22-23]

Future studies on the biology of MN may reveal the key to the genesis of melanoma and its prevention. [17]

Prospective studies should be conducted to evaluate the relationship between environmental factors and melanogenic mechanisms.

Knowledge on the origin and natural history of melanocytic nevi is important for the prevention of skin cancer, principally cutaneous melanoma. [16,17]

Migration led to important modifications in the genetic and anthropological structure of the autochthonous population. Migratory currents brought various population groups to Brazil, among them Europeans who established themselves principally in the south and southeast of the country. To evaluate the results of the mixture of races and the effects suffered by the native population, the genetic and anthropological composition of population groups would have to be systematically investigated and for this reason studies in Brazil are rare. As a consequence of many years of these migratory currents, few groups have remained isolated in closed communities. The population selected for this study is composed of Dutch individuals and their descendents, who have remained isolated in a closed community, marrying amongst themselves and having children within the same community, thus preserving the char-

acteristics of skin, hair and eye color, albeit in different environmental conditions to those prevailing in the Netherlands, their country of origin.

The initial objective of this study was to evaluate the development of MN in schoolchildren in a private school composed principally of Dutch descendents in the town of Holambra, and to reexamine them five years later. Between August 25, 1999 and May 30, 2001, a cohort study was performed to count MN in 282 schoolchildren of 3 to 17 years of age, 53.9% of whom were boys. A total of 148 children who agreed to participate in this second phase of the study were reexamined (52.43% of the original cohort) between September 27, 2006 and May 16, 2007.

MATERIAL AND METHODS

A cohort study of 282 schoolchildren of 3-17 years of age, 53.9% of whom were boys, was conducted between August 25, 1999 and May 30, 2001 in a school in which the population was composed predominantly of children of Dutch descent. The objective of the study was to describe MN and evaluate their association with gender, age, skin phototype, eye color, hair color and ethnic group. There were no exclusion criteria. The participants received no remuneration.

Of the 282 schoolchildren in the initial cohort study, 148 children (52.43% of the initial cohort) participated in a second examination to count MN. This sample consisted of 73 boys (49.32%) and 75 girls (50.67%) of 8 to 22 years of age. Of the original cohort, 110 failed to respond to the study invitation, one child died soon after the first investigation and 23 did not agree to be reexamined. Reexamination took place between September 27, 2006 and May 16, 2007.

The same dermatologist performed the examinations in both phases of the study; hence the initial and final dermatological exams were comparable for the 148 children who underwent both evaluations. Data from the children who did not participate in the second part of the study were not included in the present analysis. The child's prior participation in the initial sample constituted the only inclusion criterion for participation in the present study.

This study, which was approved by the Postgraduate Subcommittee in Internal Medicine of the School of Medical Sciences and ratified by the University of Campinas (UNICAMP), was the subject of the author's Masters and Doctorate theses. The children were examined only after their parents or guardians had signed an informed consent form. The examination was then carried out at the school.

The school selected for the study is situated in Holambra, a town founded by the Dutch in 1948, situated in the northeast of the state of São Paulo (altitude 600 m; longitude 47.03^{O} west, latitude 22.37^{O} south; 64 square kilometers in size). The town has 9,111 inhabitants of whom approximately 1500 are Dutch immigrants or descendents of Dutch immigrants. The cultivation of flowers is the principal economic activity in the town.

The children were examined and photographed only after their parents or guardians had signed an informed consent form.

A clinical chart was filled out with the identification details of the child and his/her parents, as well as the independent variables: age, gender, skin phototype, eye color, hair color, ethnic group and presence of MN. Eye color was classified as light (blue or green) or dark (brown) and hair color as light (blonde or red) or dark (brown or black). Ethnic group was classified as follows:

Non-mixed: Caucasian or Dutch or the child of Dutch parents.
Mixed: individual with one Dutch parent married to a non-Dutch spouse.
Others: individuals of non-Dutch descent.

Countable lesions were defined as melanocytic nevi. No distinction was made between MN and lentigo simplex. [7] MN was defined as a pigmented, macular, flat, slightly raised, papulous, papillomatous, dome-shaped and pedunculated lesion with smooth, well-defined borders, a smooth or irregular surface and coloring that ranged from light brown to dark brown or black.

DN was defined as a macular or maculopapular lesion with uneven borders, poorly defined margins and irregular pigmentation with various tones of brown, pink or black.

The nevi were marked, photographed digitally and classified according to their size (≤ 6 mm or > 6 mm in diameter) and anatomical location on the skin (areas unexposed [*in*] to sunlight such as the scalp, submandibular region, chest, abdomen, back, axillae, internal surface of the arms and forearms, palms of the hands, gluteal region, thighs and soles of the feet, and exposed areas [*out*] such as the face, back of the neck, ears, area delimited by a V-cut neckline, exposed areas of the arms and forearms, back of the hands, legs and upper surface of the feet).

Ephelides, lentigo solar, seborrheic keratoses and café-au-lait spots were not considered countable lesions.[7]

The presence of ephelides, the dermatological manifestation indicative of a greater likelihood of an increased number of MN, was recorded. [11] Ephelides were defined as small, light-brown, dark brown or rust-colored marks with a tendency to agglomerate in

areas exposed to the sun such as the face, the upper portion of the back, the back of the neck, shoulders and the area delimited by a V-cut neckline. Ephelides had to be differentiated from lentigo simplex. [7]

Photographic documentation was made using a Nikon® D200 digital mirror reflex camera with a 55 mm, Auto-Micro-Nikkor lens and a 50 mm, f 1.8 Nikkor lens, with TTL metering system and circular flash.

The dermatological lesions were classified on clinical charts using the standard Microsoft Excel® program, 2002.

The variables studied were transformed into frequency tables of the categorical variables (gender, age, skin phototype, eye color, hair color and ethnic group) using absolute frequencies (n) and percentages (%), and descriptive statistics (with measures of position and dispersion) of the continuous variables (age, number of nevi). To compare the categorical variables between the lesions, the chi-square test and/or Fisher's exact test (for values < 5) were used. To compare the numerical values between the lesions, the Mann-Whitney test was used. To analyze the change in the variables between the beginning and the end of the study, McNemar's test for categorical variables and the Wilcoxon test for samples related to the continuous variables were used since distribution of the variables was not normal. Significance level for the statistical tests was defined as 5% ($p<0.05$).

Statistical analysis was performed using the Statistical Analysis System (SAS) software program for Windows, version 6.12 (SAS Institute Inc., 1989-1996, Cary, NC, USA).

RESULTS

Of the 282 schoolchildren in the initial study cohort, 148 underwent a recount of MN, 73 boys (49.32%) and 75 girls (50.67%).

Table 1 shows the distribution of the children according to their age at the second evaluation. Mean age was 13.32 ± 3.23 years (mean ± standard deviation) and median age was 13.00 years (range 8-16 years).

Classification of the students into the various ethnic groups is shown in Table 1. With respect to their fathers' ethnic group, 37 fathers (25.00%) were Dutch, 51 (34.46%) were of Dutch descent, 55 (37.16) were Brazilian and 5 (3.38%) belonged to other ethnic groups. With respect to their mothers' ethnic group, 21 (14.19%) were Dutch, 47 (31.76%) were of Dutch descent, 72 (48.64%) were Brazilians and 8 (5.41%) belonged to other ethnic groups.

Ninety-seven children (65.54%) had phototype I skin, while 48 (32.43%) had phototype II and 3 children had phototype III.

The majority of the children who attended the second evaluation had dark eyes (Table 1). With respect to hair color, in the cohort that initiated the study 84 children (56.75%) had light-colored hair (blonde or red) and 64 (43.25%) had dark hair (brown or black); however, at the second evaluation, the majority of the children in the cohort had dark hair (Table 1).

At the first evaluation, 64 children (43.24%) had MN ≤ 6 mm, while 84 (56.76%) did not. At the second evaluation, 146 children (98.65%) had MN and only two (1.35%) did not. The initial evaluation showed that 38.51% of the children had nevi on the covered areas of their body, while in the second evaluation, this percentage increased to 97.97%. At the first evaluation, 14.19% of children had nevi on the exposed areas of their skin, this percentage increasing to 94.59% at the second evaluation.

At the first examination, two children (1.35%) were found to have DN ≤ 6 mm, while at reevaluation, nine children (6.08%) had DN, seven of which were ≤ 6 mm in diameter while two were > 6 mm. All DN were situated on covered areas of the body.

Of the 148 children examined, 39 (26.35%; 20 boys and 19 girls), had ephelides at the first evaluation, while 92 (62.16%; 49 boys and 43 girls), were found to have ephelides at the follow-up examination.

The simultaneous presence of ephelides and MN was found in 14 children (9.45%), 11 boys (7.43%) and 3 girls (2.03%) at the first evaluation. At reevaluation, the simultaneous presence of ephelides and MN was found in 90 children (60.81%), 48 boys (32.43%) and 42 girls (28.37%).

DISCUSSION

In the present study, conducted with 148 of the schoolchildren who had been submitted to the initial examination, the same dermatologist performed the exams at the two different moments with a 5-year interval between them, providing an exact measurement of the dermatological lesions with image documentation. The results were obtained by comparing the findings of the 148 children at the initial and final evaluations, performed using the same evaluation criteria. This is a longitudinal, non-experimental, sectional, cohort study. Cohort studies are seldom performed and are more reliable than prevalence studies for the evaluation of the behavior of MN in children and adolescents. There are still no uniform parameters for counting nevi or for evaluating their topographical distribution. For this reason, and also to facilitate the reproducibility of this study, the protocol adopted for the present investigation was similar to that used in the majority of epidemiological studies. [7]

The Dutch ancestors of these children married

Table 1: Univariate logistic regression analysis for the total number of nevi, for in nevi and for out nevi at the end of the study

		Nevos (total) <30 (n=72) >30 (n=76)			Nevos in <15 (n=72) >15 (n=76)			Nevos out <15 (n=77) >15 (n=71)		
Variável	**N (%)**	**p-value**	**OR**	**95%CI***	**p-value**	**OR**	**95%CI***	**p-value**	**OR**	**95%CI***
Age (years)										
8-12	62 (41,9%)	–	1,00	–	–	1,00	–	–	1,00	–
13-17	70 (47,3%)	0,743	1,12	(0,57-2,22)	0,594	0,83	(0,42-1,65)	0,983	1,01	(0,51-2,00)
18-22	16 (10,8%)	0,999	1,00	(0,33-3,00)	0,829	1,13	(0,37-3,42)	0,741	0,83	(0,27-2,51
Sex										
Girls	75 (50,7%)	–	1,00	–	–	1,00	–	–	1,00	–
Boys	73 (49,3%)	<0,001	3,63	(1,84-7,16)	0,002	2,87	(1,47-5,59)	0,009	2,41	(1,24-4,66)
Phototype										
II+III	51 (34,5%)	–	1,00	–	–	1,00	–	–	1,00	–
I	97 (65,5%)	0,074	1,87	(0,94-3,72)	<0,001	4,07	(1,96-8,44)	0,394	1,35	(0,68-2,66)
Hair color										
Dark	101 (68,2%)	–	1,00	–	–	1,00	–	–	1,00	–
Light	47 (31,8%)	0,174	1,63	(0,81-3,28)	0,006	2,76	(1,33-5,73)	0,873	1,06	(0,53-2,12)
Eye color										
Dark	84 (56,8%)	–	1,00	–	–	1,00	–	–	1,00	–
Light	64 (43,2%)	0,089	1,77	(0,92-3,42)	<0,001	3,16	(1,60-6,25)	0,667	1,15	(0,60-2,21)
Ethnic group										
Others	42 (28,4%)	–	1,00	–	–	1,00	–	–	1,00	–
Mixed	56 (37,8%)	0,032	2,48	(1,08-5,69)	0,032	2,48	(1,08-5,69)	0,146	1,82	(0,81-4,10)
Non mixed	50 (33,8%)	0,007	3,26	(1,38-7,70)	0,007	3,26	(1,38-7,70)	0,595	1,25	(0,55-2,87)

** OR= Odds ratio for the total number of nevi; in nevi and out nevi; 95%CI: 95% confidence interval.*

and had children within their own community, thus preserving the most common physical traits of the group such as light-colored skin, hair and eyes. They continued to live in the same place, with few moving away from the community to other geographical locations around the country. They also continued to practice the same professional activity, flower cultivation, which subjects them to long periods of exposure to ultraviolet light.

The town of Holambra, where the study was conducted, is situated at longitude 47.03º east and latitude 22.37º south. Various epidemiological studies have shown a significant relationship between the development of MN and exposure to the sun by population groups in regions located close to the equator. [10,12,18,19]

The miscegenation of Dutch immigrants with the Brazilian population only became significant from the third generation onwards.

In the group of schoolchildren evaluated, one-third consisted of individuals of non-mixed ethnicity (Dutch children or the children of Dutch parents), while one-third was of mixed ethnicity (children with one Dutch parent married to a non-Dutch spouse) and one-third was denominated "others" (children from origins other than those classified as non-mixed or mixed ethnic groups). In this latter group, there were children with Brazilian, Italian, Japanese, French and German ancestry.

The association of skin phototype I and II, the occurrence of nevi and an increased risk of skin cancer, more specifically melanoma, has been widely discussed in the literature. [8-12]

The occurrence of skin phototype I is not exclusive to the group of children of non-mixed ethnicity. Individuals with skin phototype I were also found among the Brazilians and individuals of mixed ethnicity, these children having the same likelihood of suffering damage from exposure to the sun. The individuals with phenotypes characterized by darker skin resulted from the miscegenation of ethnic groups. [24]

Ephelides occur more often in individuals with skin phototypes I and II: those with blonde or red hair, light-colored eyes, those of 6 to 18 years of age, and following sun exposure, principally after sunburn. This association has not been found to be significant in all studies. [8-12]

Of the 92 children with ephelides, these freckles were significantly more common in the non-mixed ethnicity group (42 children; 84.00%) and in the mixed ethnicity group (38 children; 67.86%) ($p<0.001$) but not in the group defined as "others" (12 children; 28.57%). Of the 56 children who did not have ephelides, 30 (71.43%) belonged to the ethnic group denominated "others" (chi-square test: $p<0.001$). At reevaluation, the incidence of ephelides was significantly higher in children with a Dutch father or a father of Dutch descent ($p<0.001$), in those with a Dutch mother or a mother of Dutch descent ($p<0.001$) and in those with skin phototype I ($p<0.001$), light-colored eyes ($p=0.005$) and light-colored hair ($p<0.001$). The association between the presence of ephelides and a greater likelihood of developing MN was statistically significant, in agreement with the findings of other studies. [11]

Few prospective studies have discussed the prevalence of nevi and the effect of environmental factors in their genesis. [2,3,6,11,25] There are reports on an increase in the number of nevi in the 8-15 year age-group, with a generally non-linear increase after this period. [2,3,8] The presence of a great number of nevi is associated with a risk of developing carcinoma and melanoma in adult life. [8,12]

A relationship between sun exposure and the genesis of MN is both defended and refuted. [6,8] A count of the nevi revealed a significant increase in the total number found in children and adolescents in this study sample between the first and second evaluation. There was a significant increase of 31.50 (range 0.00 – 174.00; $p<0.001$) in the median number of MN between the initial and final evaluations.

There was a significant increase in the number of children with nevi on covered and exposed areas of the body. The median number of MN (*in*) was 14 (range 2-74; $p<0.001$) and the median number of MN (*out*) was 12 (range 3-100; $p<0.001$).

Some studies have shown a greater occurrence of MN in individuals with light-colored hair. [4,5,12,17] In the present study, there was a difference, albeit not statistically significant, between the total number of nevi and hair color. Nevertheless, as shown in Table 2, the children with light-colored hair had a 2.2-fold greater likelihood of developing MN on covered areas of the body compared to those with dark hair.

Wiecker et al. showed a strong association between the development of MN in a group of 1,812 children of 2-7 years of age and the number of MN in the parents, reinforcing the hypothesis that there may be a hereditary factor in the genesis of nevi. These

Table 2: Multivariate logistic regression analysis for the total number of nevi, for in nevi and for out nevi at the end of the study (Stepwise criteria for the selection of variables).

			Total number of nevi <30 (n=72) >30 (n=76)			**"In" Nevi** <15 (n=72) >15 (n=76)			**"Out" Nevi** <15 (n=77) >15 (n=71)		
Variable	**N**	**(%)**	**p-value**	**OR**	**95%CI***	**p-value**	**OR**	**95%CI***	**p-value**	**OR**	**95%CI***
Sex											
Girls	75	50,7	–	1,00	–	–	1,00	–	–	1,00	–
Boys	73	49,3	<0,001	4,04	(1,98-8,25)	0,001	3,26	(1,59-6,70)	0,009	2,41	(1,24-4,66)
Phototype											
II+III	51	34,5	–	1,00	–	–	1,00	–	–	1,00	–
I	97	65,5	0,074	1,87	(0,94-3,72)	<0,001	4,56	(2,11-9,84)	0,394	1,35	(0,68-2,66)
Hair color											
Dark	84	56,8	–	1,00	–	–	1,00	–	–	1,00	–
Light	64	43,2	0,089	1,77	(0,92-3,42)	<0,001	2,23	(1,05-4,74)	0,667	1,15	(0,60-2,21)
Ethnic group											
Others	42	28,4	–	1,00	–	–	1,00	–	–	1,00	–
Mixed	56	37,8	0,024	2,77	(1,14-6,71)	0,032	2,48	(1,08-5,69)	0,146	1,82	(0,81-4,10)
Non mixed	50	33,8	0,004	3,88	(1,55-9,75)	0,007	3,26	(1,38-7,70)	0,595	1,25	(0,55-2,87)

** OR= Odds ratio for the total number of nevi; in nevi and out nevi; 95%CI: 95% confidence interval.*

authors concluded that even moderate sun exposure in the summer, even if no episodes of sunburn occur, is sufficient to induce the development of MN, and they believe that their findings have a direct effect on the concepts of prevention strategy. The present study shows that children of non-mixed ethnicity, Caucasian and Dutch children or the children of Dutch parents, were 3.9 times more likely to develop MN, whereas those with mixed ethnicity, one Dutch parent married to a non-Dutch spouse, were 2.8 times more likely (Table 2).

Analysis of the occurrence of MN between genders showed that boys had more MN, a median of 45 (range 1-174; $p<0.001$), which was significantly higher than that of the girls. The study showed that the boys were four times more likely to develop a large number of nevi compared to the girls ($p<0.001$; 95%CI: 1.98-8.25) (Table 2). The occurrence of MN on both covered and exposed areas of the body is also higher in males (Table 2). The reason for this significant difference between the sexes is unknown;[26] however, various authors have published similar results. [2,4,9,17,27]

There is no consensus with respect to the association between phenotypical characteristics, risk markers, particularly skin color, and the development of MN in children. [8-12] In the present study, children with phototype I skin were found to be 3.6 times more likely to develop MN ($p=0.002$; 95%CI: 1.55 – 6.67) compared to those with phototype II or III. Children with phototype I skin are 4.6 times more likely to develop a greater number of nevi on covered areas of the body ($p<0.001$; 95%CI: 2.11 – 9.84) compared to those with phototypes II or III. Individuals with less capacity to tan are more likely to develop a large number of MN. [11,14,26]

This study also found that there was a significant reduction in the number of children with blonde or red hair and an increase in the number of individuals with darker brown or black hair at the end of the study (Bowker's test for symmetry; $p=0.026$ and the McNemar test; $p<0.001$). This finding may be explained by the instability of phenotypical characteristics (hair and eye color) in the first years of life. The association between the number of MN and hair color has not been found to be significant; however, there have been reports of a greater occurrence of MN in individuals with light-colored hair. [2,8,14,18,26] Other investigators, however, have reported a greater occurrence of MN in individuals with dark hair. Some individuals with light skin, who are very sensitive to sunlight and more prone to sunburn, are more likely to develop acquired MN even if their hair is dark. [11,14] It was found that the children with red or blonde hair were 2.2 times more likely to develop a greater number of nevi on covered areas of the body ($p=0.036$; 95%CI: 1.05-4.74) compared to the children with dark hair (Table 2).

The association between eye color and the number of MN is not uniform and in general, more MN are found in individuals with light-colored eyes. [11,26] In the present study, there was no statistically significant association between eye color and the number of MN.

The number of MN has increased substantially by the end of adolescence, but does not increase linearly thereafter. [26] Various age-groups between 8 and 22 years were evaluated and no significant difference in the acquisition of MN was found between the groups. In the first cohort study, results showed a statistically greater number of MN in children of 13 to 17 years of age; however this was not confirmed at reevaluation. In the follow-up examination, a slight trend was found towards an increase in MN in the covered areas of the body in the ≥ 18 years age-group. In relation to the number of MN on exposed areas, a greater occurrence was found in the 13-17 years age-group; however, this association was not statistically significant.

Some studies have found a statistically significant relationship between ethnic origin, some physical features and a greater likelihood of developing MN and melanoma. [28,29] A greater occurrence of MN was found in children of non-mixed (62%) and mixed ethnicity (55.36%) compared to the other groups. Nevertheless, there was no statistically significant association between the number of nevi and maternal or paternal ethnicity at the second evaluation. Comparison between the occurrence of nevi on covered or exposed areas of the body showed a higher frequency of nevi on covered areas of the body in boys (64.38%), in individuals with phototype I skin (62.89%), in individuals with light-colored eyes (68.89%) and in those of non-mixed ethnicity (62.00%). In the boys, there was a greater occurrence of nevi on unexposed areas. An anthropomorphic study previously carried out at the same school found that the children spend long periods of time exposed to the sun during curricular and extracurricular physical activities. The same study found that the boys tend to spend more time exposed to the sun than the girls. [30]

The progression of DN and the modifications that occur in nevi over the years may be explained by genotypical mechanisms involved in their genesis. A large number of the nevi found in this study measured 1 mm in diameter. Some authors suggest that melanocytes situated on the trunk would be less resistant to the effects of ultraviolet radiation compared to other areas such as the face. [26] Melanocytes less well adapted to intermittent exposure to ultravio-

let rays would tend to produce larger MN, characterized as atypical nevi. [26]

Digital image documentation was useful in recounting the nevi. Although the size of the MN was standardized into ≤ 6mm or > 6 mm, no MN larger than 4 mm were found, except for two DN found at reevaluation.

At the end of the study, no statistically significant association was found between the presence of dysplastic nevi and the variables of gender, age, ethnic group, maternal or paternal ethnic group, phototype, eye color or hair color.

CONCLUSION

The method selected to perform the MN count and evaluate their topographical distribution was found to be effective and easily reproducible.

The use of digital photographic equipment was fundamental in creating a database, enabling analysis of the dermatological images to be made at the two different evaluation moments and for possible use in future observations.

This study showed that the association between environmental and genetic factors determined the significant increase in the appearance of MN in the study group.

Individuals with phototype I skin should be informed with respect to the greater likelihood of the occurrence of MN and melanoma and the required protective measures.

The results of this study may be used as a platform for creating educational programs to prevent the development of MN and reduce the risks of melanoma in the future. ❑

REFERENCES

1. Augustsson A, Stierner U, Rosdahl, Suurküla M. Common and dysplastic naevi as risk factors for cutaneous malignant melanoma in a Swedish population. Acta Derm Venereol. 1991;71:518-24.
2. English DR, Armstrong BK. Melanocytic nevi in children. I. Anatomic sites and demographic and host factors. Am J Epidemiol. 1994;139:390-401.
3. English DR, Armstrong BK. Melanocytic nevi in children. II. Observer variation in counting nevi. Am J Epidemiol. 1994;139:402-7.
4. Green A, Siskind V, Green L. The incidence of melanocytic naevi in adolescent children in Queensland, Australia. Melanoma Res. 1995;5:155-60.
5. Harrison SL, Buettner PG, MacLennan R. The North Queensland "Sun-Safe" study: design and baseline results of a randomized Trial to determine the effectiveness of Sun-protective clothing in preventing melanocytic nevi. Am J Epidemiol. 2005:15;161:536-45.
6. Darlington S, Siskind V, Green L, Green A. Longitudinal study of melanocytic nevi in adolescents. J. Am Acad Dermatol. 2002;46:715-22.
7. English DR, MacLennan R, Rivers J, Kelly J, Armstrong BK. Epidemiological studies of melanocytic naevi: protocol for identifying and recording naevi. IARC internal report no 90/002, International Agency for Research on Cancer, Lyon, France, 1990.
8. Gallagher RP, McLean DI, Yang CP, Coldman AJ, Silver HK, Spinelli JJ, et al. Suntan, sunburn, and pigmentation factors and the frequency of acquired melanocytic nevi in children. Similarities to melanoma: the Vancouver Mole Study. Arch Dermatol. 1990;126:770-6.
9. Pope DJ, Sorahan T, Marsden JR, Ball PM, Grimley RP, Peck IM. Benign pigmented nevi in children. Prevalence and associated factors: the West Midlands, United Kingdom Mole study. Arch Dermatol. 1992;128:1201-6.
10. MacLean DI, Gallagher RP. "Sunburn" freckles, café-au-lait macules, and other pigmented lesions of school children: The Vancouver Mole Study. J Am Acad Dermatol. 1995;32:565-70.
11. Luther H, Altmeyer P, Garbe C, Ellwanger U, Jahn S, Hoffmann K, et al. Increase of melanocytic nevus counts in children during 5 years of follow-up and analysis of associated factors. Arch Dermatol. 1996;132:1473-8.
12. Harrison SL, Buettner PG, MacLennan R. Body - site distribution of melanocytic nevi in young Australian children. Arch Dermatol.1999;135:47-52.
13. English JS, Swerdlow AJ, MacKie RM, O'Doherty CJ, Hunter JÁ, Clark J, Hole DJ. Relation between phenotype and banal melanocytic naevi. Br Med J (Clin Res Ed). 1987;294:152-4.
14. Armstrong BK, de Klerk NH, Holman CD. Etiology of common acquired melanocytic nevi: constitutional variables, sun exposure, and diet. J Natl Cancer Inst. 1986;77:329-35.
15. Rivers JK, MacLennan R, Kelly JW, Lewis AE, Tate BJ, Harrison S, et al. The eastern Australian childhood nevus study: prevalence of atypical nevi, congenital

nevus-like nevi, and other pigmented lesions. J Am Acad Dermatol. 1995;32:957-63.
16. English DR, Milne E, Jacoby P, Giles-Corti B, Cross D, Johnston R. The effect of school-based sun protection intervention on the development of melanocytic nevi in children: 6-year follow-up. Cancer Epidemiol Biomarkers Prev. 2005;14:977-80.
17. Green A, Swerdlow AJ. Epidemiology of melanocytic nevi. Epidemiol Rev. 1989; 11:204-21.
18. Coombs BD, Sharples KJ, CooKe KR, Skegg DC, Elwood JM. Variation and covariates of the number of benign nevi in adolescents. Am J Epidemiol. 1992;136:344-55.
19. Gallagher RP, McLean DI, Yang CP, Coldman AJ, Silver HK, Spinelli JJ, et al. Anatomic distribution of acquired melanocytic nevi in white children. A comparison with melanoma: the Vancouver Mole Study. Arch Dermatol. 1990;126:466-71.
20. MacLennan R, Kelly JW, Rivers JK, Harrison SL. The Eastern Australian Childhood Nevus Study: site differences in density and size of melanocytic nevi in relation to latitude and phenotype. J Am Acad Dermatol. 2003;48:367-75.
21. Robinson JK, Rigel DS, Amonette RA. Summertime sun protection used by adults for their children. J Am Acad Dermatol. 2000;42:746-53.
22. Fernandes NC, Machado JLR. Estudo clínico dos nevos melanocíticos congênitos na criança e adolescente. An Bras Dermatol. 2009;84:129-35.
23. Yarak S. Frequencia e distribuição corpórea dos nevos melanocíticos adquiridos na população de 2 a 18 anos que freqüenta creches ou escolas públicas, residentes em Votuporanga (SP) [Dissertação]. São Paulo: Universidade Federal de São Paulo; 2003.
24. Czarnecki D, Meehan CJ. Is the incidence of malignant melanoma decreasing in young Australians? J Am Acad Dermatol. 2000;42: 672-4.
25. Bauer J, Büttner P, Wiecker TS, Luther H, Garbe C. Risk factors of incident melanocytic nevi: a longitudinal study in cohort of 1.232 young German children. Int J Cancer. 2005;115:121-6.
26. Autier P. Epidemilogy of nevus. Ann Dermatol Venereol. 1997;124:735-9.
27. Milne E, Simpson JA, English DR. Appearance of melanocytic nevi on the backs of young Australian children: a 7-year longitudinal study. Melanoma Res. 2008;18:22-8.
28. Wiecker TS, Luther H, Buettner P, Bauer J, Garbe C. Moderate sun exposure and nevus counts in parents are associated with development of melanocytic nevi in childhood: a risk factor study in 1,812 Kindergarten children. Cancer. 2003;97:628-38.
29. Bakos L, Wagner M, Bakos RM, Leite CS, Sperhacke CL, Dzekaniak KS, et al. Sunburn, sunscreens, and phenotypes: some risk factors for cutaneous melanoma in southern Brazil. Int J Dermatol. 2002;41:557-62.
30. Eilert CA. Crescimento físico e performance motora: um estudo em descendentes de holandeses - Holambra. [Dissertação]. Campinas (SP): Faculdade de Ciências Médicas da Universidade Estadual de Campinas; 1997.

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How to cite this article/*Como citar este artigo*: Vallarelli AFA, Harrison SL, Souza EM. Nevos melanocíticos numa comunidade de origem predominantemente holandesa no Brasil (1999-2007). An Bras Dermatol. 2010;85(4):469-77.