Sex Differences in Numbers of Nevi on Body Sites of Young European Children: Implications for the Etiology of Cutaneous Melanoma

Philippe Autier,[1] Mathieu Boniol,[2] Gianluca Severi,[3] Remy Pedeux,[2] André-Robert Grivegnée,[1] Jean-François Doré,[2] and European Organisation for Research and Treatment of Cancer Melanoma Group

[1]Unit of Epidemiology, Prevention and Screening, Jules Bordet Institute, Brussels, Belgium; [2]Institut National de la Sante et de la Recherche Medicale, Centre Léon Bérard, Lyon, France; and [3]Cancer Epidemiology Centre, The Cancer Council Victoria, Carlton, Australia

Abstract

Background: **Since 1950, the greatest increase in cutaneous melanoma incidence in fair-skinned males took place on the trunk and on the head and neck, whereas in females, it took place on the limbs, mainly on the lower limbs. We examined the influence of sex on numbers and size of nevi on different body sites in white European schoolchildren.**

Methods: **Information about each holiday period since birth to interview was recorded from parents of six hundred twenty-eight 6- to 7-year-old children in four European cities (Brussels (Belgium), Bochum (Germany), Lyons (France), and Rome (Italy)). Number and anatomic location of small (2-4.9 mm) and large (≥5 mm) nevi and individual susceptibility to sunlight were independently assessed.**

Results: **After adjustment for host characteristics, sun exposure, and sun protection habits, males had 7% [95% confidence interval (95% CI), −7 to 19] more small nevi than females. However, compared to females, numbers of small nevi were increased by 17% (95% CI, 1-31) on the head and neck and by 16% (95% CI, 2-27) on the trunk and shoulders. In contrast, in males, the number of small nevi on upper limbs was decreased by −5% (95% CI, −26 to 13), and on lower limbs by −8% (95% CI, −34 to 13). The number of large nevi was 6% higher in males than in females (95% CI, −26 to 30).**

Conclusions: **The sex differences in small nevus distribution in schoolchildren reflect the sex differences in the anatomic distribution of melanoma in adults. Sex differences in sun exposure behaviors, dressing, and clothing would just add their effects to the sex-dependent inherited propensity to develop nevi on a given body site. These results reinforce the hypothesis by which childhood would be a decisive period for the occurrence of sun-induced biological events implicated in the genesis of cutaneous melanoma.** (Cancer Epidemiol Biomarkers Prev 2004;13(12):2003–5)

Introduction

In most fair skinned populations, the incidence of cutaneous malignant melanoma (melanoma) has considerably increased in the past 50 years, most probably because of the increase in intermittent sun exposure that took place after World War II (1). In many populations, the incidence of melanoma is slightly higher in females than in males. But gender differences in melanoma incidence are more pronounced when anatomic sites are considered: in males, the greatest increase in melanoma incidence over time took place on the trunk and the head and neck, whereas in females, the greatest increase in incidence over time took place on the limbs, mainly the lower limbs (2-4).

The number of nevi is the best predictor of melanoma occurrence in adults (5). The increase in nevus density (i.e., the number of nevi per unit of skin surface) is maximal before 15 years old (6-8). After nevus density stabilization at around 30 to 35 years old, nevus frequency steadily decreases with age. Nevus development is strongly genetically determined, but sun exposure would be necessary for complete phenotypic expression of the nevus genotype (9, 10).

Little is known of association between gender and nevus development. In this work, we examined the influence of sex on numbers and size of nevi on different body sites in white European 6- to 7-year-old children.

Methods

The study design has been described in a previous report (11). Briefly, 6- to 7-year-old Caucasian children were recruited between October 1995 and February 1997 in elementary schools of Brussels (Belgium), Bochum (Germany), Lyons (France), and Rome (Italy).

Received 3/17/04; revised 6/4/04; accepted 6/21/04.

Grant support: Europe against Cancer Programme of the European Commission grants and Fondation de France fellowship (M. Boniol).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Philippe Autier, Unit of Epidemiology and Prevention, Jules Bordet Institute, 125 Boulevard of Waterloo, Brussels 1000. Fax: +32-2-538-65-51. E-mail: philippe.autier@bordet.be

Total Body Nevus Count. In each city, a physician trained for the recognition of skin pigmented lesions examined the entire skin of children in the primary schools. The scalp, the genital area, and the buttocks were not examined. Counting of nevi was done using transparent plastic slides pierced with 2- and 5-mm holes. We thus directly distinguished nevi with dimensions in the range 2 to 4.9 mm (hereafter referred as small nevi) from nevi with dimensions ≥5 mm (hereafter referred as large nevi).

Statistical Analysis. Examination of the influence of gender on nevus counts took into account the influence of other host and environmental factors that could be associated with gender. Details of the analysis procedures have been reported in previous article (12). In brief, two Poisson regression models were constructed, one having as end point the number of small nevi, and the other the number of large nevi. For small nevi, models were applied separately to four body sites (trunk and shoulders, upper limbs, lower limbs, and head and neck).

Poisson regression models for small nevi included variables related to host characteristics and sun exposure or sun protection habits. Models for large nevi were further adjusted for number of small nevi. A result was labelled as statistically significant if zero was not comprised in the 95% confidence interval.

Results

Parents who agreed to participate represented 682 (55%) out of the 1,234 apparently eligible children approached. Fifty-one children were excluded from the study because the child was not of Caucasian origin, or the skin examination was not done (e.g., the child was not willing to be examined), or the parents could not be reached for the interview. Three children were further excluded because of missing data in adjustment variables. The final sample for statistical analysis comprised 628 children (319 boys and 309 girls).

The median was 6 nevi ≥2 mm per child (range, 0-77). Detailed body distribution of nevi has been published elsewhere (13). In brief, of 5,933 nevi, 5,638 (95%) were small nevi (i.e., with one dimension between 2 and 4.9 mm), and 295 (5%) were large nevi (i.e., with one dimension ≥5 mm). Thirty-nine percent of small nevi were located on the trunk and shoulders, compared with 69% of large nevi, implying that large nevi are more likely than small nevi to develop on trunk and shoulders than on other body sites.

Table 1 shows that the total of small nevi was similar for boys and girls. In males, small nevi were somewhat more numerous on trunk and shoulders, and on head and neck, but less numerous on limbs. Large nevi were more numerous in males.

After multiple adjustments, small nevus numbers on trunk and shoulders and on the head and neck became significantly more associated with male than with female gender. A positive association (although not significant) with female gender was found in the upper limbs and in the lower limbs.

Apparently, males had more large nevi than females. But because (i) the number of small nevi is a strong predictor of the number of large nevi (12) and (ii) that most large nevi are located on the trunk and shoulders (13), adjusting for small nevi decreased the apparent association between male gender and the number of large nevi. No gender difference was apparent when the analysis of large nevus numbers was restricted to the trunk and shoulders (data not shown).

Discussion

Our study assessed the predictors of nevus counts in European young children according to body site, with multiple adjustments for host characteristics, sun exposure, and sun protection habits. Boys ages 5 to 6 years had significantly more small nevi (2-4.9 mm) on the back and shoulders, and on the head and neck than girls of same age. In contrast, in girls, there was a tendency for more small nevi on the limbs. Our results are comparable to those from studies in Australian adolescents and schoolchildren that found significantly larger numbers of small nevi on the back (14, 15) and on the head and neck (14) of males, whereas larger number numbers of small nevi were observed on female lower limbs (15). Alike the Australian study in schoolchildren (15), we found a larger number of large nevi in boys than in girls, but because the number of large nevi is strongly linked to the

Table 1. Numbers of nevi on body sites of 628 European children 6 to 7 years old

Body site	Males (n = 319)		Females (n = 309)		% Difference males/females		
	Mean	Range	Mean	Range	Unadjusted*	Adjusted†	95% Confidence interval
Nevi, 2 to 4.9 mm (n = 5,638)							
All sites	9.1	0-65	8.9	0-77	2	7	−7 to 19
Head and neck	1.5	0-16	1.3	0-9	14	17	1-31
Trunk and shoulders	3.7	0-25	3.2	0-29	13	16	2-27
Upper limb	1.9	0-3	2.1	0-3	−9	−5	−26 to 13
Lower limb	1.9	0-2	2.2	0-3	−16	−8	−34 to 13
Nevi, >5 mm (n = 295)	0.5	0-10	0.4	0-8	19	6‡	−26 to 30

NOTE: Buttocks, genital area, and scalp not included. Surface of selected body areas represent 86.5% of total body surface area.

*No unadjusted ratio reached statistical significance.

†Mean adjusted difference between males and females, with females being the reference category, expressed in %, and 95% confidence interval. % differences are derived from coefficients of a Poisson regression models, including variables related to sun exposure, the skin phototype, the eye color, the average number of holiday periods, the average total duration of sun exposure, the average difference in latitude, the number of sunburn episodes, the study place, the average wearing of trousers and shirt, the average wearing of hat, and the average sunscreen use during holidays.

‡Same model as for nevi 2 to 4.9 mm, with inclusion of numbers of nevi 2 to 4.9 mm as a continuous variable.

number of small nevi, adjustment on small nevus numbers cancelled most of the gender influence on large nevus counts.

The gender difference we found in numbers of nevi 2 to 4.9 mm according to body site in school children is similar to the gender difference in body site distribution of melanoma found in adults (16-18). Studies with the Swedish Cancer Registry showed that before 20 years old, melanoma occurrence is more frequent on upper and lower limbs in females, whereas in males, it is more frequent on the trunk (19).

For explaining the gender difference in anatomic distribution of melanoma, gender differences in sun exposure behaviors and in dressing and clothing styles have been evoked (e.g., longer hair in females, or wearing of miniskirt by women versus pants by males; ref. 16). However, previous reports on data used in this study showed no significant gender difference in sun exposure, sunburn history (during and outside holiday periods), sun protection habits, sunscreen use, and wearing of clothes when in the sun (11, 12, 20). Moreover, that explanation cannot address the substantial gender differences observed on the trunk and shoulders.

A study done in Canadian Hutterite children found similar gender-specific differences in the body site distribution of nevi (21). The traditional religious costume of Hutterite children protects them from sun exposure, and thus in this population, gender difference in clothing or in sun exposure habits can hardly explain gender differences observed in body site nevus distribution.

Our results suggest that anatomic location of melanoma diagnosed during adult life would be already determined during the first years of life. Sex differences in sun exposure behaviors, dressing, and clothing would just add their effects to the inherited proneness to develop nevi on a given body site.

Studies on migrants have provided the most compelling evidence that childhood was a decisive period for sun-induced biological lesions involved in the genesis of melanoma (22). The results of this study reinforce the likelihood of the childhood hypothesis. The biological lesions acquired at these ages would survive during all life.

The numbers of small nevi and of large nevi are independent predictors of melanoma occurrence (23, 24). The fact that we found gender to be a predictor of the body site development of small, but not of large nevi, supports the hypothesis by which small nevi and large nevi would be related to different biological events involved in the genesis of melanoma.

The genetic information is identical in all melanocytes of an individual, and a nevus is a monoclonal expansion of a single melanocyte (25, 26). From a study on body site variations in benign melanocytic nevi adjacent to melanoma, Green (27) proposed the hypothesis of site-specific susceptibility to sunlight and to malignant transformation. Studies in European and in Australian children confirmed the site-specific differences in proliferation potential of melanocytes (13, 15). We further hypothesize that the likelihood for a melanocyte situated in a given anatomic site to develop into a small nevus is also influenced by gender. Thus, whatever happens in sun exposure in later life, sex-linked genetic factors acting during early life influence the likelihood that a melanoma would occur on a given body site.

References

1. IARC. Solar and ultraviolet radiation. Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 55. Lyon: IARC; 1992.
2. Osterlind A, Hou-Jensen K, Moller Jensen O. Incidence of cutaneous malignant melanoma in Denmark 1978-82. Anatomic site distribution, histologic types, and comparison with non-melanoma skin cancer. Br J Cancer 1988;58:385–91.
3. MacKie R-M, Bray C-A, Hole D-J, et al. Incidence and survival from malignant melanoma in Scotland: an epidemiological study. Lancet 2002;360:587–91.
4. Chen Y-T, Zheng T, Holford T-R, Berwick M, Dubrow R. Malignant melanoma incidence in Connecticut (United States): time trends and age-period-cohort modeling by anatomic site. Cancer Causes Control 1994;5:341–50.
5. Berwick M, Halpern A. Melanoma epidemiology. Curr Opin Oncol 1997;9:178–82.
6. Harrison S, MaKie R-M, MacLennan R. Development of melanocytic nevi in the first three years of life. J Natl Cancer Inst 2000;92:1436–8.
7. English D-R, Armstrong B-K. Melanocytic nevi in children. I. Anatomic sites and demographic and host factors. Am J Epidemiol 1994;139:390–401.
8. Green A, Swerdlow T. Epidemiology of melanocytic nevi. Epidemiologic Rev 1989;11:204–21.
9. Bataille V, Snieder H, MacGregor AJ, Sasieni P, Spector TD. Genetics of risk factors for melanoma: an adult twin study of nevi and freckles. J Natl Cancer Inst 2000;92:457–63.
10. Wachsmuth R-C, Gaut R-M, Barret J-H, et al. Heritability and gene-environment interactions for melanocytic nevus density examined in a U.K. adolescent twin study. J Invest Dermatol 2001;117:348–52.
11. Autier P, Doré J-F, Cattaruzza M-S, Renard F, et al. Sunscreen use, wearing clothes and nevi number in 6- to 7-year-old European children. J Natl Cancer Inst 1998;90:1873–81.
12. Autier P, Severi G, Pedeux R, et al. Number and size of nevi are influenced by different sun exposure components: implications for the etiology of cutaneous melanoma (Belgium, Germany, France, Italy). Cancer Causes Control 2003;14:453–9.
13. Autier P, Boniol M, Severi G, et al. The body-site distribution of melanocytic nevi in 6 to 7 year old European children. Melanoma Res 2001;11:123–31.
14. Darlington S, Siskind V, Green L, Green A. Longitudinal study of melanocytic nevi in adolescents. J Am Acad Dermatol 2002;46:715–22.
15. MacLennan R, Kelly J-W, Rivers J-K, Harrison S-L. 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.
16. Bulliard J-L, Cox B, Elwood J-M. Comparison of the site distribution of melanoma in New Zealand and Canada. Int J Cancer 1997;72:231–5.
17. Elwood J-M, Gallagher R-P. Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. Int J Cancer 1998;78:276–80.
18. Green A, MacLennan R, Youl P, Martin N. Site distribution of cutaneous melanoma in Queensland. Int J Cancer 1993;53:232–6.
19. Berg P, Lindelof B. Differences in malignant melanoma between children and adolescents. A 35-year epidemiological study. Arch Dermatol 1997;133:295–7.
20. Severi G, Cattaruzza M-S, Baglietto L, et al. Sun exposure and sun protection in young European children. An EORTC multicentric study. Eur J Cancer 2002;38:820–6.
21. Kwan T-Y, Belke T-W, Enta T. Sex differences in the anatomical distribution of melanocytic nevi in Canadian Hutterite children. J Cutan Med Surg 2000;4:58–62.
22. Whiteman D-C, Whiteman C-A, Green A. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control 2001;12:69–82.
23. Bataille V, Newton-Bishop JA, Sasieni P, et al. Risk of cutaneous melanoma in relation to the numbers, types and sites of naevi: a case-control study. Br J Cancer 1996;73:1605–11.
24. Tucker M-A, Halpern A, Holly E-A, et al. Clinically recognized dysplastic nevi. A central risk factor for cutaneous melanoma. JAMA 1997;277:1439–44.
25. Robinson W-A, Lemon M, Elefanty A, et al. Human acquired nevi are clonal. Melanoma Res 1998;8:499–503.
26. Harada M, Suzuki M, Ikeda T, Kaneko T, Harada S, Fukuyama M. Clonality in nevocellular nevus and melanoma and expression-based clonality analysis at the X-linked genes by polymerase chain reaction. J Invest Dermatol 1997;109:656–60.
27. Green A. A theory of site distribution of melanomas: Queensland, Australia. Cancer Causes Controls 1992;3:513–6.