The Epidemiology of Nevi and Signs of Skin Aging in the Adult General Population: Results of the KORA-Survey 2000

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Nevi can approximate the melanoma risk and demographic changes will increase the meaning of signs of skin aging (SSA). However, little is known about the epidemiology of nevi and SSA in the general adult population. We aimed to estimate the prevalence and age distribution of common and atypical nevi and SSA as well as gender differences in a large population-based sample. Within the Cooperative Health Research in the Augsburg Region (KORA) in Germany, a population-based survey was performed. Data were gathered by interview and the number of pigmented lesions and presence of SSA were obtained by dermatological examination. A total of 2,823 adults (mean age 49 years, 50% women) participated (response 67%). Most subjects (60.3%) exhibited 11 to 50 common nevi and 5.2% had at least one atypical nevus. 51.9% were diagnosed with elastosis (Cutis rhomboidalis nuchae, 18.3%; Morbus Favre Racouchot 1.4%). Ephelides were seen in 16%, lentigines solaris in 62.4%, and lentigines seniles in 33.2%. All signs of skin aging increased significantly with age and so did lentigines solaris, seniles, and actinic keratoses. In contrast, common and atypical nevi and ephelides decreased significantly with age. Signs of skin aging are frequent and increase, in contrast to common and atypical nevi, with age.

Journal of Investigative Dermatology (2006) 126, 1490–1496. doi:10.1038/sj.jid.5700269; published online 27 April 2006

INTRODUCTION

The incidence of cutaneous malignant melanoma (MM) has increased significantly over the past decades. Today MM is the malignancy with the steepest increase in many countries. A high number of common nevi and the presence of atypical nevi have been identified as useful indicators for MM risk in several case-control studies (Garbe *et al.*, 1994b; Bauer and Garbe, 2003). However, little is known about the frequency of these entities and their risk factors in the general population.

In an earlier work from Australia, 1,518 individuals were examined and a peak of moles was determined for females aged 20–29 years with an average mole count of 27 and for males at age 15 with an average mole count of 43 (Nicholls, 1973). A British study of 432 individuals yielded the highest mole count in the third decade and a decline thereafter

(MacKie *et al.*, 1985). A decline of nevus counts after young adulthood was also reported in other studies (Armstrong *et al.*, 1986). The average mole count in 1,000 patients from an US outpatient service was 14.6 (Pack *et al.*, 1952). Common and dysplastic nevi were examined in 379 individuals from Sweden (aged 30–50 years), resulting in an average number of 67 moles/person and 18% of the group exhibiting at least one dysplastic nevus (Augustsson *et al.*, 1991). In a younger group of 508 students (aged 18–30 years) from the Netherlands, 5% were found to be affected with dysplastic nevi (Rampen *et al.*, 1988). Data from New Zealand claim that 9% of 380 individuals aged 30–39 and 50–59 years exhibit a dysplastic nevus.

Our aging population will face a corresponding increase of age- and UV-light-dependent skin changes. Two independent factors contribute to the increasing number of elderly. First, people born in years with a high birth rate (baby boomers) are growing into older age and secondly the life expectancy is increasing. However, data on the epidemiology of signs of skin aging in the general adult population are scarce. Most information today is derived from case-control studies (mostly on MM), which cannot be expected to yield results that can be applied to the general population. The aims of this cross-sectional study were to provide an estimate of the prevalence of common and atypical nevi in adults and to give the figures of age and sex distribution of the so-called skin aging sign in a large population-based sample.

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Abbreviations: CI, confidence interval; MM, malignant melanoma; SSA, signs of skin aging

Received 12 July 2005; revised 20 December 2005; accepted 10 January 2006; published online 27 April 2006

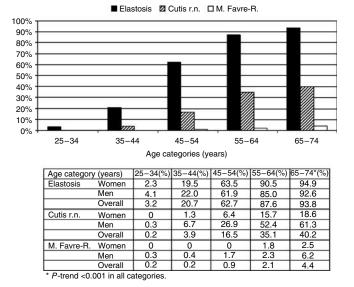


Figure 1. Prevalence of UV-light-related signs of skin aging in 2,823 adults of from Augsburg, Germany (1999–2001). Stratified by age groups (years) and gender (table).

RESULTS

Finally, a total of 2,823 adults aged 25-74 years (mean age 49 years) were examined (response 67%). The gender ratio was balanced (1,412 women, 1,411 men) reflecting the stratified sampling procedure. Men were slightly older (mean 49.1 years, median 49) than women (48.5 years, 48) (NS).

Interview data

About three-quarters of the subjects (74.2%) reported that they use sunscreens or cosmetics with sun protection factor. For those who reported sunscreen use, the median sun protection factor was 12. 68.5% of the participants recalled at least one sunburn before the age of 16. Of those who reported at least one sunburn, the average number of reported sunburns was 7.2 (1-50). The use of a tanning booth was reported by 13.9%. Tanning booths were used during winter time most frequently between one and three times per month (46.4%) and almost equally once per week or less frequently than once a month (25.5%, that is, 24.5%). During summer time, the majority used tanning booths less frequently than once a month (55.1%), followed by an usage of one to three times per month (31.9%) and a weekly usage (10.1%). With respect to actual individual UV-light exposure, about onethird (31.3%) reported that they do not spend time in sunny areas during the year. Those who answered positively reported to spend an average of 3 weeks (median 2.0) per year in sunny areas. Roughly 30% (29.7%) reported that a dermatologist had checked their nevi at least once. In 42.6% of these cases, at least one nevus was removed as a consequence of these examinations. A positive personal history of skin cancer was given by 41 individuals (1.5%). The majority (80.5%, n=33) could recall the type of skin cancer, which was reported as basal cell carcinomas (n = 19, 57.6%) and MMs (n = 14, 42.4%). A family member with frequent common nevi (>50) was reported by 12.4% and a

Table 1. Gender differences in the UV-light-related behaviors for 1,412 women and 1,411men from Augsburg, Germany (1999-2001)

Women (%)	Men (%)	OR (for women), 95% CI, or <i>P</i> -value
19.2	8.6	2.5 (2.0–3.2)
79.1	69.2	1.7 (1.4–2.0)
33.0	26.4	1.4 (1.2–1.6)
1.4	1.5	1.0 (0.5–1.8)
61.9	75.1	0.5 (0.4-0.6)
6.3	7.9	< 0.001
1.9	2.2	< 0.001
	(%) 19.2 79.1 33.0 1.4 61.9 6.3	(%) (%) 19.2 8.6 79.1 69.2 33.0 26.4 1.4 1.5 61.9 75.1 6.3 7.9

family history of skin cancer was given by 2.9%. When comparing relevant data from the interview by gender (Table 1), it became clear that women use tanning booths significantly more often than men. Furthermore, women use sunscreens or cosmetics with sun protection factor significantly more often and also had their nevi checked by a dermatologist more frequently than men. On the other hand, men recalled sunburn before the age of 16 significantly more often and also recalled a higher number of sunburns. Furthermore, men spend more time in sunny areas than women.

Dermatological examination

Inter-observer variability. The agreement for the constitutional factors, skin type, eye color, and hair color, expressed by kappa values was 0.56, 0.72, and 0.84, respectively. The corresponding values for the presence of ephelides, lentigines solaris, lentigines seniles, and actinic keratosis were 0.63, 0.56, 0.86, and 0.73. The inter-observer variability, expressed by kappa, for the assessment of common nevi (four categories) was 0.66. Only the agreement for the grading of elastosis (four categories) was low with 0.31, whereas Cutis rhomboidalis nuchae was assessed in good accordance (0.66).

Common nevi, actinic keratosis, and atypical nevi (Table 2). Most subjects (60.3%) exhibited between 11 and 50 common nevi according to the dermatological examination. In 8.1% more than 50 nevi were recorded. The number of common nevi is significantly higher in men than women. At the date of examination, the prevalence of actinic keratosis was at 2.8% (confidence interval (CI) 2.2-3.4%). In accordance with the reported higher UV exposure, the prevalence in men was significantly higher than in women. In 5.2% (CI 4.4-6.0%), at least one atypical nevus was diagnosed and men were affected more frequently (NS).

Signs of UV-light-related skin aging (Table 3). Almost every second subject exhibited some degree of elastosis without marked gender differences (51.9%, CI 50.1-53.7%). Women, however, tended to show higher grades of elastosis. Cutis rhomboidalis nuchae was seen in 18.3% (Cl 16.9–19.7%) with a significant higher frequency and severity in men. Similarly, Morbus Favre Racouchot, which was seen in 1.4% (Cl 1.0–1.8%), was more frequent and more severe in men.

Ephelides, lentigines solaris, and lentigines seniles (Table 4). Ephelides were seen in 16% (Cl 14.7–17.4%) of the study population, with women exhibiting ephelides significantly

Table 2. Prevalence of common nevi, actinic kerato-sis, and atypical nevi in 2,823 adults from Augsburg,Germany (1999–2001) stratified by gender

	Overall (<i>n</i> = 2823)	Women (<i>n</i> = 1,412)	Men (<i>n</i> =1,411)	OR ¹ (for women), 95% Cl, or <i>P</i> -value
Number of com	nmon nevi			
0–10	31.6%	34.2%	28.9%	
11–50	60.3%	60.5%	60.1%	
51–100	6.6%	4.2%	9.0%	< 0.001
>100	1.5%	1.1%	2.0%	
Actinic keratoses present	2.8%	1.1%	4.5%	0.3 (0.1–0.4)
Atypical nevi present	5.2%	4.5%	6.0%	0.8 (0.5–1.1)

CI, confidence interval; OR, odds ratio.

¹Adjusted for observer.

more frequently than men. Men with ephelides, however, exhibited significantly more freckles than women. Lentigines solaris were present in 62.4% (Cl 60.6–64.2%) of the study population. In this case, men were affected more frequently and with a higher number of lentigines than women. Lentigines seniles were observed in one-third (33.2%, Cl 31.5–34.9%) of the subjects. Here, women were affected significantly more often and also exhibited a higher count of these lentigines.

Trends with age. Figure 1 shows the prevalence of elastosis, cutis rhomboidallis nuchae and Morbus Favre Racouchot in 5 age groups. For all 3 entities a significant increasing trend could be observed on different levels of frequency as expected. Similarly, there was a significant increasing trend of the prevalence of lentigines solaris and lentigines seniles with age in women and men (Figure 2). As expected, the increase of lentigines seniles is more pronounced later in life as compared to lentigines solaris, but in the highest age group, both entities reach an almost equal prevalence. In contrast, ephelides show a significant decreasing trend with age after 35 years.

The number of common nevi declines significantly after the age of 25 (Figure 3). This is expressed by a significantly increasing proportion of subjects with less than 11 nevi with increasing age group, and a corresponding decrease of persons with more than 50 nevi with increasing age category. The analysis for atypical nevi shows that, similar to common nevi, the proportion of subjects with atypical nevi also decreases significantly with age. In contrast and in accordance with other UV-light-related skin signs, the prevalence

Table 3. Prevalence of UV-light-related signs of skin aging in 2,823 adults from Augsburg, Germany (1999–2001)stratified by gender

	Overall (<i>n</i> =2,823)	Women (<i>n</i> = 1,412)	Men (<i>n</i> = 1,411)	OR ¹ (for women), 95% Cl, or <i>P</i> -value
Elastosis present severity of elastosis	51.9%	51.5%	52.2%	0.97 (0.84–1.13)
Mild	35.1%	32.7%	37.6%	
Moderate	14.9%	16.9%	12.9%	0.006
Severe	1.9%	2.0%	1.8%	
Cutis rhomb. nuchae present severity of Cutis rhomb. nuchae	18.3%	7.8%	28.8%	0.21 (0.16-0.26)
Mild	15.2%	6.7%	23.7%	
Moderate	2.6%	1.1%	4.1%	< 0.001
Severe	0.5%	0%	1.0%	
Morbus Favre Racouchot present severity of Morbus Favre Racouchot	1.4%	0.8%	2.1%	0.37 (0.19-0.75)
Mild	1.1%	0.7%	1.6%	
Moderate	0.2%	0.1%	0.4%	0.027
Severe	0.1%	0%	0.1%	

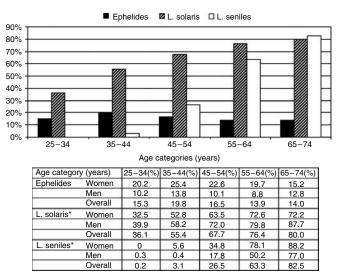
¹Adjusted for observer.

	Overall (<i>n</i> =2,823)	Women (<i>n</i> =1,412)	Men (<i>n</i> =1,411)	OR ¹ (for women) 95% CI, or <i>P</i> -value
Ephelides	16.0%	20.9%	11.1%	2.2 (1.7–2.7)
Frequency as proporti	ons of all ephelides			
1–10	2.9%	2.7%	3.2%	
11–50	35.9%	41.4%	25.6%	0.004
>50	61.2%	55.9%	71.2%	
Lentigines solaris	62.4%	57.8%	67.0%	0.7 (0.6–0.8)
Frequency as proporti	ons of all lentigines solaris			
1–10	8.2%	9.7%	6.9%	
11–50	51.3%	53.6%	49.3%	0.004
>50	40.5%	36.8%	43.8%	
Lentigines seniles	33.2%	38.5%	27.9%	1.6 (1.4–1.9)
Frequency as proporti	ons of all lentigines seniles			
1–10	30.5%	26.5%	36.0%	
11–50	60.7%	63.4%	57.1%	0.004
>50	8.8%	10.1%	6.9%	

Table 4. Prevalence of ephelides, lentigines solaris, and lentigines seniles in 2,823 adults from Augsburg, Germany(1999–2001) stratified by gender

CI, confidence interval; OR, odds ratio.

¹Adjusted for observer.



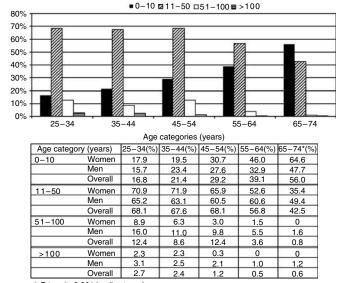
^{*} P-trend < 0.001.

Figure 2. Prevalence of ephelides, lentigines solaris, and lentigines seniles in 2,823 adults from Augsburg, Germany (1999–2001). Stratified by age groups (years) and gender (table).

of actinic keratosis increased markedly and significantly, especially after age 54 (Figure 4).

DISCUSSION

We here reported results of a large population-based survey on pigmented lesions and signs of skin aging. Reliable prevalence estimates could be derived from the dermato-



* P-trend <0.001 in all categories



logical examination of 2,823 men and women. The prevalence of lentigines solaris and seniles was found to be as high as 62.4 and 33.2%. Every second participants exhibited some degree of elastosis. Significant increasing trends with age were found for all UV-light-associated entities (Elastosis, Cutis rhomboidalis nuchae, Morbus Favre Racou-

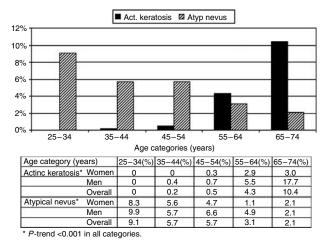


Figure 4. Prevalence of actinic keratosis and atypical nevi in 2,823 adults from Augsburg, Germany (1999–2001). Stratified by age groups (years) and gender (table).

chot, lentigines solaris, lentigines seniles, actinic keratosis), but not for ephelides. In contrast, common and atypical nevi decreased with age.

This study has strengths and limitations. The large sample size and the random selection of a population-based sample should contribute to the quality and originality of the data. Several clinical outcomes were assessed in a standardized way and measures were taken to assure a valid and reliable assessment. Interview data contributed to the understanding of UV-light-related health behavior in the general population.

Studies like this are limited by the fact that no standardized and validated clinical diagnostic criteria exist for most dermatological signs and symptoms. Even for major dermatological disorders such as acne or psoriasis, no such criteria are available and this is also true for most parameters investigated here. Only few exemptions from this, like the UK refinement of the Hanifin and Rajka diagnostic criteria on atopic eczema, exist (Williams et al., 1994). This, however, is not a methodological problem restricted to Dermatology. We have tried to standardize the examination as far as possible and to make the diagnostic parameters explicit and reliable. However, it is likely that the diagnosis of pigmented lesions was affected by the age of subjects, which is to say that a macule was more likely to be called ephelide or nevi in adolescents, and senile lentigo in the elderly. Measures were taken to assess and control inter-observer variability. Recall bias is always a concern in nested case-control studies like that. There is certainly some concern about the validity of data on sunburns before the age of 16 when interviewing persons with a mean age of 49. It remains unclear whether this led to a systematic rather than a random error.

There is limited literature to compare our prevalence figures with. There is an increasing number of studies in children investigating common and atypical nevi and their risk factors, however, data in adults are scarce (Valiukeviciene *et al.*, 2005). In case adults were investigated, these studies were mostly case-control studies (Bauer and Garbe, 2003), which not necessarily allow to give population based estimates.

In a German survey of school beginners of the City of Hamburg, the number of common nevi was counted in 11.478 children aged 5–6 years during the compulsory school entrance examination. The median total nevus count was 11 and a significant increase of nevi with increasing number of holidays spent in the south was reported (Dulon *et al.*, 2002).

Researchers from central Italy have assessed dermatological outcomes in 5,837 men aged 18–19 during the military medical examination (Ballone *et al.*, 1999). Atypical nevi were seen in 37.2% and solar lentigines in 17.6%. Although this was a population-based large examination, this study population is hardly comparable with ours for several reasons (age group, gender restriction, geographical, and constitutional factors).

Another study from the UK has investigated 968 patients over 40 years of age who attended non-dermatological outpatient clinics (Memon *et al.*, 2000). Actinic keratosis was seen in 11.2%, with a strong predominance in men (15.4 *vs* 5.9%). This prevalence is much higher than in our population, which might in part be explained by the fact that the population from the UK was on average 10 years older than our study group. Furthermore, a clinic-based sample is not necessarily representative of the general population and there is some indication of selection in this study, as a considerable proportion volunteered for skin-related reasons. Also in the UK study group, a strong increase with age for moderate or severe elastosis and solar lentigines was noted.

Profound information on signs of skin aging, nevi, and their risk factors is provided by the Leiden Skin Cancer Study (Kennedy et al., 2003b). The published data so far are based on 580 patients (MM and nonmelanoma skin cancer (NMSC)) and 386 controls from the ophthalmology outpatient clinic. The counts for solar lentigines in the face (51.4%) and on the back (83.3%) were higher than in our population, whereas the frequency of ephelides in the face (12.4%) or on the back (19.6%) laid well in the range of our study (Bastiaens et al., 2004). Also in this case-control study, a strong increasing trend for solar lentigines and a decreasing trend for ephelides and nevi (>10 common nevi or atypical nevi) with age was reported (Bastiaens et al., 1999). The decrease of common nevi with age has been reported also by other studies before (Garbe et al., 1994a). For the control group of the Leiden Skin Cancer Study, the prevalence of actinic keratoses was reported to be 26%, which is much higher than in our group (Kennedy et al., 2003a). Atypical nevi were seen in 7% of the control patients, which corresponds well with our findings. An earlier case-control study from Germany including 513 melanoma patients and 498 age- and sex-matched controls from dermatology departments reported data on the prevalence and risk factors of frequent (>50) common and atypical nevi (Garbe et al., 1994a). The prevalence of both frequent common (17.8%) and atypical (26.4%) nevi was much higher in this case-control than in our study, which is not surprising when taking the composition of the casecontrol study population into account. For atypical nevi, associations with age and gender were reported similar to our findings.

The increasing trend of signs of skin aging as seen in this study was expected and in some aspects also observed by others (Garbe et al., 1994a; Memon et al., 2000; Kennedy et al., 2003a; Bastiaens et al., 2004). Nevi, including atypical nevi, however, seem to follow an increasing trend until puberty and young adulthood followed by a steady decline afterwards. It was postulated that sunlight will contribute to both the increase and decrease of nevi by first encouraging proliferation via loss of growth control, followed by the induction of new antigens, which is eventually answered by an immune response, which then leads to the disappearance of the nevi (Armstrong et al., 1986). Cell-mediated immunity has also been suggested as mechanism of nevi elimination by others (Nicholls, 1973). There might also be a methodological explanation for the decline when the nevus prevalence is changing over birth cohorts (Kennedy et al., 2003a). With respect to the increase during the first and second decade, the role of hormones was also discussed (MacKie et al., 1985). Taking the age range of our population (25-74) into account, the observed decrease of nevi accords well with earlier observations. The increase of signs of skin aging in combination with the demographic changes will increase the demand not only for cosmetic but also for health services.

The results from a large survey in adults indicate that signs of skin aging are frequent and increase, in contrast to common and atypical nevi, with age.

MATERIALS AND METHODS

Study design and subjects

The KORA-Survey S4 (previously named KORA-Survey 2000) was performed within the framework of the research platform KORA (Cooperative Health Research in the Augsburg Region). The background and history of this platform was described elsewhere (Keil et al., 1996, 1998). The study base of this survey consisted of all registered residents of German nationality, aged 25-74 years, of the City of Augsburg (Bavaria, Germany) and two surrounding counties. A random cross-sectional sample stratified by age and gender of 6,640 subjects was drawn, representing approximately 1.5% of the eligible population. After excluding those who had died or moved out of the area (n=256), 6,384 subjects were invited by an informative letter to participate. Several attempts were made to approach non-responders by reminder letters, telephone calls, and personal home visits to those who were not accessible by phone. Finally, 4,261 subjects participated in this study between September 1999 and April 2001. Owing to logistic and financial reasons, the dermatological examination was offered in the main study center in the City of Augsburg only.

Ethical approval was granted by the Federal Ethics Committee (Landesaerztekammer Bavaria, Germany) and written informed consent was obtained from all participants before commencing the study. The study was conducted according to the Declaration of Helsinki Principles.

Outcome assessment

Personal interview. Standardized computer-assisted face-to-face interviews were performed by trained and certified interviewers. Several measures were taken to assure the validity of the interviews,

including the implementation of question-related instructions to the interviewer, supervision, and comparisons of tape-recordings and data entry. Basic socio-demographic information, as well as data on the general medical history and relevant lifestyle factors, was taken from this interview.

In addition, the physicians performing the dermatological examination conducted a separate personal interview focusing on the personal and family history of UV-light exposure and related dermatological disorders. In detail, we asked to recall the number of sunburns before the age of 16. Furthermore, we recorded how many of these sunburns were associated with blistering. Subjects were asked if and when they used sunscreens or cosmetics with a sun protection factor, and the duration of protected exposure was recorded. We were interested if subjects had ever seen a dermatologist for a nevus check, and if so, how often these checks were performed. The number of nevi, which were removed as a consequence of such a nevus check, was also assessed. As a measure of the personal UV-light exposure, we asked the subjects how many weeks a year they spent in sunny areas (e.g. during vacation). With respect to the family history, we asked whether the subjects can name a family member (parents, siblings, or children) having a lot (defined as >50) of nevi. Besides the individual history of skin cancer, we also inquired if there was any related incident known within the family (parents, siblings, or children).

Dermatological examination

A dermatological examination of the entire skin, except the region of the underpants was performed in a standardized way. Two residents of the Department of Dermatology and Allergy of the Technical University Munich (J.M., E.K.) performed the examinations during the study period with an individual examination period of approximately 9 months each.

Quality assurance

Both residents were trained in assessing the dermatological parameters in a standardized way as defined below before the study. During a pilot phase of 2 weeks, the examination, interview, and the sequence of the elements of the study protocol were trained using volunteers. The pilot phase, as well as the first week of each resident's examination period, was supervised by the principal investigator (T.S.). Furthermore, the principal investigator visited the study center regularly. In order to train the categorical frequency assessment, total counts for different outcomes (nevi, lentigines, etc.) were performed and results were compared with the prior categorical estimates.

Inter-observer variability

In order to assess the inter-observer variability, a total of 59 consecutive subjects were examined independently by both residents. The agreement was expressed by κ -values.

Constitutional factors

During the dermatological examination, the skin type as defined by Fitzpatrick, as well as the eye color (blue, green, brown, blue-grey) and hair color (blond, brown, black, red-blond), was recorded.

Assessment of ephelides, lentigines solaris, and lentigines seniles

Ephelides were recorded with respect to the entire integument. They were defined as rather small (<3 mm), pale, brown, or red brown

macular lesions. Solar lentigines (sunburn freckles) were assessed in the shoulder region. They were defined as brown to black-brown macular or slightly raised lesions with a diameter up to 1 cm. Lentigines seniles were assessed on the outer forearms and the dorsum of the hands. They were defined as yellowish-brown or dark brown macular demarked lesions.

These lesions were recorded as either present/absent. If present, their frequency was categorized as either 1–10, 11-50, or >50.

Common and atypical nevi. Common nevi, which usually had a defined border, regular margin, uniform color, and macular or papular surface, were recorded with respect to the entire skin surface and without restriction to size. Frequency was assessed by four categories (1–10, 11–50, 51–100, and >100).

Atypical nevi fulfilled at least two of the following criteria: diameter $\ge 5 \text{ mm}$, ill-defined border, irregular margin, or varying color. The exact number of such atypical nevi was recorded.

Signs of skin aging. Elastosis defined as skin thickening combined with wrinkling and a yellowish color was assessed mainly with respect to the skin of the face. In addition, associated entities such as Cutis rhomboidalis nuchae and Morbus Favre Racouchot were recorded. For all three benign signs of skin aging, a four-point scale was used (absent, mild, moderate, and severe).

Skin cancer and precursors. Actinic keratosis as well as lesions suspicious of basal or squamous cell carcinoma or MM were also recorded with respect to their frequency and location.

Each subject received a one-sheet report of the dermatological examination. Here, the skin type, number of common nevi, degree of UV-light-induced skin damage, and any suspicious lesion were stated. The report was accompanied by appropriate advice for skin protection and the advice to consult a dermatologist in due time, in case a suspicious lesion needed further clarification. We proceeded this way, because the survey was designed to screen for suspicious lesions in the study center, but not to treat the participants at the same time.

Statistical analyses. In the descriptive statistics, prevalence estimates for major outcomes are given together with the 95% Cls. Associations of dichotomous variables were expressed by odds ratios and corresponding 95% Cls as measures of association and stability. χ^2 trend tests were used to investigate prevalence trends over age categories. All statistical analyses were performed with the software SPSS 12.0.

CONFLICT OF INTEREST

These authors state no conflict of interest.

ACKNOWLEDGMENTS

This study was supported by a governmental funding source: German Ministry of Education, Science, Research, and Technology (Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie, 01ER9502) and a grant of the P.G. Unna foundation. We highly appreciate the beautiful editorial assistance of Ann-Katrin Otto.

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