

Incidence of Skin Cancers and Precancerous Lesions in Japanese – Risk Factors and Prevention –

Keishi Araki, Toru Nagano, Masato Ueda, Fumio Washio, Shaw Watanabe ¹,
Naohito Yamaguchi ², and Masamitsu Ichihashi

An examination of the occurrence of skin cancers and precancerous lesions among residents of Kasai City (34° 56' N) since 1992, and of Ie-island (25° 10' N) since 1993, has been conducted to characterize the prevalence and incidence of skin cancers in Japanese people and to evaluate risk and preventive factors.

The mean prevalence of actinic keratosis (AK) in residents of Kasai City and Ie-island was 203.33 and 756.26, respectively, indicating that twice the dose of UVB radiation causes a 3–4 fold higher incidence of AK, although life styles, including types of occupations, differ in these two locations.

Working outdoors, having skin type I and/or a history of severe sunburns during childhood were found to be important risk factors, while the use of cosmetics after 20 years of age was a protective factor, for AK and possibly for skin cancers. Further, sunscreen use among males over 60 years of age in Kasai City from 1994 through 1998 suggested that sunscreen use may reduce AK development in older people.

Four and 12 cases of skin cancers were found in residents of Kasai City (from 1992 to 1997) and on Ie-island (from 1993 to 1998), respectively. These numbers are too small to establish the prevalence of skin cancer in Japanese, but indicate that people living in areas of higher ambient solar radiation have a higher incidence of skin cancer.

This epidemiological study strongly indicates that sun protection is the major modality to reduce sun-induced cutaneous tumors in Japanese. *J Epidemiol*, 1999 ; 9 : S14-S21.

skin cancer, actinic keratosis, epidemiology, risk factors, sunscreen

Non-melanoma skin cancer (NMSC) is the most common type of malignant tumor found among light-skinned people. Epidemiological studies indicate that basal cell carcinoma (BCC), the most common type of NMSC, usually occurs on the head and neck. Exposure to the sun is thought to be the most important risk factor for NMSC and melanoma, although exact patterns of exposure (such as the duration, intensity, frequency and age at exposure) have not yet been clearly examined. Further, the relationship of solar radiation to BCC and melanoma is more complex ^{1,2}. Melanoma incidence generally increases near the equator and seems to be related with total accumulated exposure, but it also seems to be more related to intermittent exposures. Armstrong and Holman ³ reported that short-term intense exposures during weekends and vacations for light-skinned people are associated with an increased risk

of melanoma. Krickler et al ⁴ suggested that infrequent but intense sun exposure on vacation may be associated with increased risk of BCC development.

However, there is relatively little information in the United States, and even less information in Japan, about the incidence of NMSC. Population-based cancer registries, which are the main sources of cancer incidence statistics, generally do not include NMSC patients. Further, hospital cancer registries are of relatively little use in estimating NMSC incidence since these tumors are usually treated in out-patient private offices.

In Japan, Miyaji ⁵ performed a statistical survey of skin cancer rates between 1956 and 1960 in new patients attending dermatology clinics at University Hospitals in Japan. Tada and Miki ⁶ analyzed the rates of skin cancers between 1971 and 1975, and more recently, we ⁷ reported the rates of skin can-

Kobe University School of Medicine, ¹ Tokyo University of Agriculture, ² National Cancer Center Research Institute.
Address for correspondence : Department of Dermatology, Kobe University School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe-shi, Hyogo, 650-0017 Japan.

cers at 27 University Hospitals in Japan between 1976 and 1980, and between 1986 and 1990. The statistics showed an upward trend in rates of skin cancers in our studies and suggested an increase of skin cancer in Japan during the last decade. They showed that the BCC/SCC ratio was 2:1 from 1986 to 1990, much higher than the 1.14:1 ratio reported by Tada and Miki for 1971 to 1975.

Those studies however, did not allow a true population based cancer incidence rate to be determined. Therefore, we have now attempted to determine the prevalence and incidence of skin cancers and precancerous lesions on sun-exposed body sites of Japanese. These data were collected from health examinations in Kasai City^{8,9} (located in the middle of Japan with a population of about 50,000), and on Ie-island, Okinawa Prefecture¹⁰ (located at the southern end of Japan with a population of about 5,000).

The prevalence and incidence of NMSC could not be determined, since the numbers of BCC and SCC cases were too small for statistical analysis. The prevalence and incidence of actinic keratosis (AK), the precancerous lesion of SCC, however, was determined. Further, risk factors and preventive factors for AK, and possibly for NMSC, in Japanese were suggested by these studies at two distinct geographic locations.

MATERIALS AND METHODS

Kasai City (in the Hyogo Prefecture) and Ie-island (in the Okinawa Prefecture) in Japan are located at 34° 56' North and 25° 10' North, respectively. Since Kasai City is located near Kobe City, which is situated in the central part of Japan, the annual cumulative dose of solar UVB in Kasai City is similar to that of Kobe where rates of annual solar ultraviolet radiation have been measured since 1992.

Screening of skin cancers and precancerous lesions in these two locations were conducted as part of a program to screen for cancers, such as stomach, lung and uterus, and other common diseases of the aged. Residents aged 20 years and over were registered under the Health Science's Law for the Aged. Every year, a total of about 5,000 in Kasai City, and 1,000 on Ie-island, participated in the program. The study was carried out between May and December in Kasai City and between July and November on Ie-island. Trained dermatologists from Kasai Municipal Hospital and Kobe University, School of Medicine interviewed and examined the participants^{8,9}. The questionnaires requested information on the following topics: name, age, sex, address, telephone number, skin type, use of cosmetics and sunscreens, occupation, occupational sun exposure (outdoor or indoor), acute sunburns received during childhood, smoking habits, location of any skin tumors, past history and treatment for cutaneous disorders. Skin types were categorized on the basis of characteristics of sunburning and suntanning depending on the criteria of Satoh and Kawada¹¹, as fol-

lows: Type I, always burn, rarely tan; type II, moderately burn, moderately tan; or type III, never burn, always tan. Japanese skin type I may correspond to skin type II of Fitzpatrick's classification, Japanese skin type II to Fitzpatrick's skin type III and Japanese skin type III to Fitzpatrick's skin type IV, respectively. Participants were examined for skin cancers and precancerous lesions on the face, neck, extensor surface of forearms, and backs of the hands.

Age- and sex-standardized prevalence and incidence rates for actinic keratosis (AK), the precancerous state of squamous cell carcinoma (SCC), were calculated by the direct method, using the Japanese population in 1990 as the standard⁹. The incidence of AK was calculated for people who had participated in the screening consecutively for two years from 1992 through 1997. Sex- and age-specific prevalences and incidences were calculated with the SAS computer program (PC-SAS, 1987). Differences in AK prevalence and incidence rates were comparatively analyzed among the three skin types, with respect to working outdoors or indoors, experiencing or avoiding severe acute sunburn during childhood, and being a smoker or non-smoker. Numbers of seborrheic keratoses on the face and other sun-exposed sites were counted and participants were classified into two groups: subjects having 6 or more seborrheic keratoses or subjects having 5 or less. The differences in AK prevalence and incidence among people having different skin types, occupational exposure, cosmetic or sunscreen use, and severe acute sunburn at childhood, were estimated by the chi-square test. The statistical significance of multiple seborrheic keratoses in the development AK was also analyzed by the chi-square-test.

Sunscreen of SPF 46 (Kao Company, Tokyo, Japan) was supplied to male participants over 60 years of age and regular use of the sunscreen while outdoors was advised after their screening in 1994.

RESULTS

1. Prevalence and Incidence of AK in Kasai City

The numbers of participants were between 4867 (1609 males, 3258 females) in 1993 and 4225 (1461 males, 2764 females) in 1997 throughout the study period. Ages of the participants ranged between 20 and 97 years. A total of 110 cases of AK (71 males, 39 females), 3 BCC (all male) and one SCC (a male) were identified histopathologically during the 6 year period from 1992 through 1997 (Table 1). No melanomas were detected during the study. The total number of AK for each year is also listed in Table 1. The prevalence of AK in 1992⁹ was found to be 413.4 per 100,000 population, the highest value obtained during the study so far, and decreased to 86.8 (the lowest value) in 1995. The prevalence of AK in men was significantly higher than in women each year throughout the study period. The mean prevalence of AK per 100,000 popula-

tion, calculated from the total number of AK from 1992 to 1997, was 203.33 (281.55 for males, 120.5 for females) (Table 2). The incidences of AK per 100,000 Japanese residents were between 223.6 in 1993 and 99.9 in 1997, and the mean value was 148.2, as listed in Table 3.

Table 1. Number of AK and skin cancer in Kasai City and Ie-island.

year	Kasai City ^a			Ie-island ^b		
	AK (M/F)	BCC	SCC	AK (M/F)	BCC	SCC
1992	36 (24/12)	2	0	(-)	(-)	(-)
1993	34 (16/18)	1	0	37 (13/24)	5	1
1994	25 (19/ 6)	0	0	18 (7/11)	3	1
1995	10 (9/ 1)	0	0	24 (11/13)	1	0
1996	12 (9/ 3)	0	0	31 (11/20)	0	0
1997	11 (9/ 2)	0	1	20 (8/12)	0	0
1998	(-)	(-)	(-)	20 (11/ 9)	1	0
total	128 (86/42)	3	1	150 (61/89)	10	2

AK; actinic keratosis, BCC; basal cell carcinoma, SCC; squamous cell carcinoma

^a Data of 1992; from reference 8, data of 1993-1995; from reference 9.

^b Data of 1993-1996; from reference 10.

Table 2. Comparative study on prevalence of actinic keratosis among people in Kasai City and Ie-island (per 100,000 population).

year	Kasai City ^a			Ie-island ^b		
	man	woman	total	man	woman	total
1992	466.1	321.3	413.4	(-)	(-)	(-)
1993	336.0	248.0	291.2	961.6	1387.0	1159.4
1994	334.1	77.9	203.7	522.6	615.7	572.8
1995	147.0	28.8	86.8	1072.6	968.2	1014.3
1996	223.6	26.1	123.1	862.0	1086.4	988.6
1997	181.9	20.7	101.8	737.4	491.1	612.1
1998	(-)	(-)	(-)	693.6	711.8	702.7
total	281.5	120.4	203.3 ^c	808.3	876.7	841.7 ^d

^{a, b, c, d} The prevalence between two places was statistically significant. (P<0.05)

Table 3. Incidence of actinic keratosis in Kasai City and Ie-island.

year	Kasai City ^a			Ie-island ^b		
	examined	case	incidence ^c	examined	case	incidence ^c
1993	2516	16	223.6	(-)	(-)	(-)
1994	2518	12	171.2	1118	14	734.4
1995	2622	10	145.0	1014	15	637.0
1996	2706	12	117.3	1035	20	625.5
1997	2562	11	99.9	996	20	641.3
1998	(-)	(-)	(-)	1199	20	656.8
total	12924	61	148.2	5362	89	659.0

^a Data of 1993 and 1994; from reference 9.

^b Data of 1994-1996; from reference 10.

^c After standardization to the Japanese population in 1990.

2. Prevalence and Incidence of AK in Ie-island

The numbers of people who participated in the study were approximately 1000 every year from 1993 through 1998. A total of 150 cases of AK (61 males, 89 females), 10 BCC and 2 SCC were diagnosed histopathologically during those 6 years (Table 1). No melanomas were detected. The number of AK patients each year are listed in Table 1. The prevalence of AK was between 1159.4 (the maximum value in 1993) and 572.8 (the lowest value in 1994). The mean AK prevalence on Ie-island was 841.7, about 4 times higher than that of Kasai City (Table 2). There was no significant difference between the prevalence of AK in men and in women. The incidences of AK per 100,000 Japanese in 1994 was 734.4, the highest value found during the study period (Table 3). The mean incidence of AK on Ie-island was approximately 4 times higher than in Kasai City. The standardized prevalence rate of NMSC per 100,000 Japanese was 50.0 for men and women, however, that value may not be reliable since the number of patients was low.

3. Skin Type and AK in Kasai City and Ie-island

The mean incidence of AK per 100,000 Japanese with skin type I, II or III was 444.6, 209.8, and 117.8, respectively in Kasai City (from 1993 to 97) and 1181.2, 409.1 and 388.4 on Ie-island (from 1994 to 1998) (Table 4). Patients with skin type I in Kasai City had a significantly higher incidence of AK compared with skin type III, but there was no statistical difference in AK incidence between skin type I and III on Ie-island.

4. Seborrheic Keratosis and AK

The number of seborrheic keratoses on sun-exposed areas and the prevalence of AK was examined in Kasai City and on Ie-island. Subjects were divided into two groups, one group with 5 or less seborrheic keratoses, and the other group with 6

or more. People having 6 or more seborrheic keratoses showed a statistically higher prevalence of AK than those who had 5 or less, both in Kasai City and on Ie-island (Table 5).

5. Severe Acute Sunburn with Blisters during Childhood and AK

Of 105 cases of AK detected in Kasai City between 1992 and 1995, 36 AK patients had severe sunburns in their childhood, and 69 did not. Of 3,013 participants who had experienced severe sunburns with blister formation during their childhood, 36 subjects were found to have AK. 69 AK patients were found among 15,537 participants who did not experience a severe sunburn during childhood. The prevalence of AK per 100,000 Japanese with severe sunburn was 256.2, significantly higher than that (78.0) of participants who had had no severe sunburn.

6. Tobacco Smoking and AK

Participants in the skin cancer study in Kasai City (from 1996 to 1997), and on Ie-island (from 1996 to 1998), were asked whether they smoked or not. Of 1802 participants in Kasai City who smoked, 5 had AK, and among 6621 participants who did not smoke, 18 AK cases were found. In 612 participants on Ie-island who smoked, 14 cases of AK were found, whereas of 2378 participants who did not smoke, 57 cases of AK were diagnosed. There was no significant difference between the prevalence of AK in smokers and non-smokers who live in Kasai City or on Ie-island (Table 6).

7. Effect of Sunscreen Use on AK in Men over 60 Years of Age in Kasai City

The number of male participants over 60 years of age who used sunscreen from 1995 to 1998 are shown in Table 7. One AK patient among 285 participants who used sunscreens, and

Table 4. Comparative study on incidence of actinic keratosis and skin type in Kasai City and Ie-island.

year	Kasai City			Ie-island		
	I	II	III	I	II	III
1993	842.4	158.8	0	(-)	(-)	(-)
1994	393.3	221.5	117.2	933.1	566.6	644.1
1995	362.2	182.4	121.0	1866.2	444.1	353.1
1996	280.6	288.3	117.3	1036.7	448.8	423.7
1997	344.4	198.1	115.5	937.8	263.3	164.3
1998	(-)	(-)	(-)	1132.2	322.5	356.9
total	444.6	209.8	117.8	1181.2	409.1	388.4

Incidence was age- and sex-standardized to the Japanese population in 1990.

Skin types; I, always burn, never tan; II, moderately burn, moderately tan; III, never burn, always tan.

Table 5. Relationship between prevalence of actinic keratosis and number of seborrheic keratoses.

(A); Kasai City					(B); Ie-island				
Year	No. of			Prevalence	Year	No. of			Prevalence
	SK	subjects	cases of AK			SK	subjects	cases of AK	
1994 #	0-5	2967	5	86.6	1994	0-5	798	5	163.1
	6 <	1031	19	396.0	1994	6 <	216	19	1266.1
1995 #	0-5	969	1	53.0	1995	0-5	721	7	207.4
	6 <	482	7	407.1	1995	6 <	314	24	1997.2
1996	0-5	2874	3	75.4	1996	0-5	694	8	223.7
	6 <	1015	9	197.1	1996	6 <	302	12	1019.1
1997	0-5	2812	3	80.5	1997	0-5	876	7	185.1
	6 <	1367	8	143.8	1997	6 <	323	13	1029.5
Total	0-5	9622	12	73.4 ^a	Total	0-5	2089	27	211.1 ^c
	6 <	3895	43	286.7 ^b		6 <	1155	68	1327.9 ^d

a vs b; c vs d; The prevalence between two groups in both places was statistically significant. ($P < 0.005$) #; from reference 9

Table 6. Relationship between prevalence of AK and smoking habit.

(A); Kasai City				
Year	Smoking	No. of		Prevalence ^a
		subjects	cases of AK	
1996	Yes	1019	3	142.0
	No	3185	9	164.1
1997	Yes	711	2	140.0
	No	3436	9	158.3
(B); Ie-island				
Year	Smoking	No. of		Prevalence ^a
		subjects	cases of AK	
1996	Yes	183	6	242.3
	No	832	25	263.9
1997	Yes	206	4	264.9
	No	761	16	305.0
1998	Yes	223	4	274.2
	No	785	16	304.9

^a There was no statistically significance between two groups in both places.

29 AK patients among 613 participants who did not use the sunscreen were found. The prevalence of AK in patients who use sunscreens was significantly lower than participants who did not use sunscreens (789.6). Our results strongly suggest that sunscreen use with age decreases new cases of AK among Japanese.

DISCUSSION

Sun exposure is virtually unavoidable over a lifetime and

dramatically differs in populations depending upon climate, geography, occupation, recreational and other daily activities. Consequent photoaging of the skin, including skin cancer, due to sun exposure may be greatly influenced by intrinsic factors such as DNA repair capacity and the degree of melanin pigmentation.

There is extensive epidemiological evidence that supports an important role for sunlight in human skin carcinogenesis ^{1,2}. Most epidemiologic studies on skin cancer were performed on Caucasians, and show that BCC is the most common skin can-

Table 7. Relationship between prevalence of AK and sunscreen use by male over 60 years of age in Kasai City (1995-1998).

(1995)	Sunscreen use	No. of male over 60 y.o.	AK	BCC	SCC	Prevalence ^a
	Yes	122	0	0	0	0
	No	738	9	0	0	183.5
	total	860	9	0	0	150.1
(1996)	Sunscreen use	No. of male over 60 y.o.	AK	BCC	SCC	Prevalence ^a
	Yes	115	1	0	0	115.6
	No	721	8	0	0	189.7
	total	836	9	0	0	163.2
(1997)	Sunscreen use	No. of male over 60 y.o.	AK	BCC	SCC	Prevalence ^a
	Yes	57	0	0	0	0
	No	770	3	1	0	61.3
	total	827	3	1	0	53.1
(1998)	Sunscreen use	No. of male patients	AK	BCC	SCC	Prevalence ^a of AK
	Yes	271	1	0	0	66.5
	No	971	20	1	0	315.9
	total	1242	21	1	0	263.6

AK; actinic keratosis, BCC; basal cell carcinoma, SCC; squamous cell carcinoma

^a The difference of prevalence between two groups was statistically significant. (P<0.05)

cer in light-skinned people. There is also strong evidence for the role of sunlight in SCC genesis. In experimental animal studies, UVB (290-320 nm) has been shown to be the causative wavelength of light for skin cancer, SCC in mice, and SCC and BCC in rats.

Japanese, who generally have darker skin than Caucasians, were believed about 40 years ago not to develop skin cancers on sun-exposed areas, but rather to develop skin cancers on legs and other covered areas due to burns and X-ray radiations.

The incidence of skin cancer however, is expected to increase among Japanese, since the mean life span in Japan is now nearly 76 years for males and 84 years for females, 20 years longer than 40 years ago. Further, ozone depletion by chlorofluorocarbons may be causing an increase in harmful UVB radiation at the earth's surface ¹². Recent changes in Japanese life-styles, such as exposing the skin more to sunlight to get tanned, may also contribute to an

increase of skin cancer.

To determine whether skin cancers and precancerous lesions in Japanese have increased, we conducted a study to analyze trends in the disease rate of skin cancers from 1976 to 1980 and from 1986 to 1990 at 27 University Hospitals in Japan ⁷. That study showed that rates of BCC and AK were higher in 1986-1990 than in 1976-1980, and also that rates of BCC, SCC and AK in southern parts of Japan were about five times higher than in northern Japan. Similar studies by Miyaji ⁵ from 1956 to 1960, and by Tada and Miki ⁶ from 1971 to 1975 provided additional information about skin cancer characteristics in Japan, but those studies did not report the prevalence or incidence of skin cancers in Japanese. IARC reports gave an estimated skin cancer incidence of 1.5~5.0 per 100,000 Japanese in Saga, Hiroshima, Osaka and Miyagai, but there is no report showing a reliable registry for skin cancer in those areas.

We therefore initiated this study on the incidence of skin

cancers and precancerous lesions in Japanese in Kasai City (populated about 50,000 residents) since 1992, and on Ie-island (located in the far south of Japan) since 1993. The prevalence of AK per 100,000 Japanese in Kasai City has decreased every year, from 414.3 in 1992 to 86.8 in 1995. The incidence of AK in Kasai City also decreased from 1990 to 1997, suggesting that our educational campaign for residents informing them of the adverse effects of sunlight and the efficacy of sunscreens in protection against skin cancers, has contributed to the reduction of AK in Kasai City. We were unable to determine the prevalence or incidence of skin cancers, since the number of skin cancer patients was so limited. Occupational exposure to the sun is suggested to be a causative factor of AK, according to the prevalence and incidence of AK in Kasai City, which shows a higher ratio in people working outdoors, compared to people working indoors. However, there was no significant difference in the prevalence of AK in people working outdoors in Kasai City from 1995 to 1997 and on Ie-island throughout the study period.

Skin type I subjects of Kasai City had a significantly higher prevalence of AK in 1992, 1994, 1996 and 1997, but not in 1993 or in 1995, compared with skin type III subjects. However, no difference in AK prevalence among various skin types on Ie-island was observed, possibly because we had few skin type I patients on Ie-island for statistical analysis.

Xeroderma pigmentosum (XP) patients¹³, who have defective DNA repair and who have an early onset of skin cancers on skin exposed to the sun in childhood, exhibit multiple common benign skin tumors (termed seborrheic keratoses) as early as one year of age on sun-exposed sites, such as the face, the backs of the hands and the extensor surfaces of the forearms. That observation on XP patients prompted us to examine the relationship between seborrheic keratosis and AK. People with 6 or more seborrheic keratoses may belong to a high risk group for AK, and possibly for skin cancer, since the prevalence of AK on patients with 5 or less seborrheic keratoses was significantly lower than patients having 6 or more. Taken together, patients who have 6 or more seborrheic keratoses may have less efficient DNA repair than patients with 5 or less seborrheic keratoses, and defective repair of DNA damage may play a pivotal role in AK genesis.

The risk of BCC decreased significantly in Australians who migrated after they were 10 years of age compared with people who were born there or who migrated before they were 10 years old. The relative risk of SCC is also statistically smaller in Australians who immigrated after they were 20 years old compared with people born in Australia or who moved there after 10 years of age.

In our questionnaires, we asked whether the number of AK in Japanese correlated with severe acute sunburns during childhood. A higher prevalence of AK was observed among people who had severe acute sunburns during childhood compared

with those without such severe sunburns. In our XP (type A) siblings, first diagnosed at 4 and 2 years of age, the older sister had her first skin cancer (BCC) at 13 years of age, whereas the younger sister had her first skin cancer (BCC) at 23 years of age. This suggests an important role for sun-exposure during childhood in UV carcinogenesis¹⁴, possibly by shortening the incubation time of skin cancer development in Caucasians and in Japanese.

Reduction of AK by regular sunscreen use has been demonstrated by two research groups^{15,16}. Further, we have found that the prevalence of AK in females using cosmetics since their early 20s was significantly lower than female residents of Kasai City who did not use cosmetics. To further evaluate the effect of sunscreens with an SPF of 46 on the occurrence of AK, men over 60 years of age in Kasai City were asked to use sunscreens after their skin cancer examinations in 1994. The prevalence of AK in men who used sunscreens since 1995, was significantly lower than in men who did not use sunscreens, suggesting that sunscreen use is an efficient way to reduce AK in Japanese.

Our results thus indicate that people who work outdoors, have skin type I and have 6 or more seborrheic keratosis on sun-exposed areas, are at high risk for AK and possibly for NMSC. Further, protection of the skin from solar UV radiation since childhood may significantly reduce the risk of seborrheic keratoses, AK, BCC and SCC.

ACKNOWLEDGMENTS

Parts of this work were supported by a Grant-in-Aid from the Ministry of Education, Science and Culture of Japan, by the research fund for the Effects of Ultraviolet Ray Influence on Human Health from the Global Environmental Research, Environmental Agency, and by a grant from Shinryokukai, Kobe University School of Medicine, Japan. Further, this work is supported in part by a grant from the Japanese Committee for Sunlight Protection, Kyoto, Japan.

We are very grateful to Emiko Miki in Kasai City and Masako Namisato on Ie-island for their great help in the health examinations, and to Miss Mari Iwao for editorial assistance.

REFERENCES

1. Hunter DJ, Colditz GA, Stampfer MJ, Rosner B, Willett WC, Speizer FE: Risk factors for basal cell carcinoma in a prospective cohort of women. *Ann Epidemiol* 1990;1:13-23.
2. Elwood JM, Gallagher RP, Hill GB, Pearson JC: Cutaneous melanoma in relation to intermittent and constant sun exposure—the Western Canada Melanoma Study. *Int J Cancer* 1985;35:427-433.
3. Armstrong BK, Holman CDJ: Malignant melanoma of

- the skin. *Bull World Health Organ* 1987;2:245-252.
4. Krickler A, Armstrong BK, English DR, Heenan PJ: Does intermittent sun exposure cause basal cell carcinoma? A case-control study in Western Australia. *Int J Cancer* 1990;46:356-361.
 5. Miyaji T: Skin cancers in Japan: a nationwide 5-year survey, 1956-1960. In: National Cancer Institute Monograph, No.10. NCI, Conference on Biology of Cutaneous Cancer 1963:55-70.
 6. Tada M, Miki Y: Malignant skin tumors among dermatology patients in university hospitals of Japan. A statistical survey 1971-1975. *J Dermatol* 1984;11:313-321.
 7. Suzuki T, Ueda M, Ogata K, Horikoshi T, Munakata N and Ichihashi M: Doses of solar ultraviolet radiation correlate with skin cancer rates in Japan. *Kobe J Med Sci* 1996;42:375-388.
 8. Naruse K, Ueda M, Nagano T, Suzuki T, Harada S, Imaizumi K, Watanabe S, Ichihashi M: Prevalence of actinic keratosis in Japan. *J Dermatol Sci* 1997;15:183-187.
 9. Suzuki T, Ueda M, Naruse K, Nagano T, Harada S, Imaizumi K, Watanabe S, Ichihashi M: Incidence of actinic keratosis of Japanese in Kasai City, Hyogo. *J Dermatol Sci* 1997;16:74-78.
 10. Nagano T, Ueda M, Suzuki T, Naruse K, Nakamura T, Taguchi M, Araki K, Nakagawa K, Nagai H, Hayashi K, Watanabe S, Ichihashi M: Skin cancer screening in Okinawa, Japan. *J Dermatol Sci* 1999. (in press)
 11. Satoh Y, Kawada A: Action spectrum for melanin pigmentation to ultraviolet light, and Japanese skin typing. In *Brown Melanoderma: Biology and Disease of Epidermal Pigmentation*. Edited by TB Fitzpatrick, MM Wick, K Tada. University of Tokyo, Tokyo 1986:87-95.
 12. Slaper H, Velders GJM, Daniel JS, de Gruijl FR, van der Leun JC: Estimates of ozone depletion and skin cancer incidence to examine the Vienna Convention achievements. *Nature* 1996;384:256-258.
 13. English DR, Armstrong BK, Krickler A and Flency C: Sunlight and Cancer. *Cancer Causes & Control* 1997;8:271-280.
 14. Kondoh M, Ueda M, Nakagawa K, Ichihashi M: Siblings with xeroderma pigmentosum complementation group A with different skin cancer development: Importance of sun protection at an early age. *J Am Acad Dermatol* 1994;31:993-996.
 15. Thompson SC, Jolley D, Marks R: Reduction of solar keratoses by regular sunscreen use. *N Engl J Med* 1993;329:1147-1151.
 16. Naylor MF, Boyd A, Smith DW, Cameron GS, Hubbard D, Neldner KH: High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol* 1995;131:170-175.