

# A Case-Control Study of Malignant Melanoma in Israeli Kibbutzim

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## Abstract

**Background:** Incidence rates for malignant melanoma in Israel are rising steadily, and the kibbutz population is at increased risk for this malignancy.

**Objectives:** To assess the risk factors for malignant melanoma among kibbutz members compared to matched healthy controls.

**Methods:** We conducted a case-control study of 168 malignant melanoma patients and 325 healthy controls, matched by age and gender. Data were collected on three categories of risk: demographic, personal (e.g., skin, eye and hair color), and environmental/behavioral (e.g., sun exposure, use of sunscreens).

**Results:** There were no differences between the groups regarding sociodemographic data. Significantly more patients than controls had fair, vulnerable skin ( $P < 0.001$ ), light eyes ( $P < 0.05$ ), and fair hair ( $P < 0.001$ ). There was no difference in family history of malignant melanoma or other cancers. Patients with malignant melanoma had significantly more additional skin lesions (e.g., keratoses) ( $P < 0.001$ ). More patients than controls recalled having been exposed to the sun for long periods when they were 6–13 years of age. A conditional logistic regression analysis showed that fair hair, fair vulnerable skin, and additional skin lesions were independently associated with malignant melanoma ( $P < 0.01$ ).

**Conclusions:** The main target population for interventions to reduce the incidence of malignant melanoma among kibbutz members should be individuals with these risk factors. A history of increased exposure to the sun from age 6 to 13 should also be taken into account as an independent risk factor.

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Morbidity and mortality rates for malignant melanoma have stabilized in Australia and England, probably due to the growing awareness of risk factors and the subsequent decreased exposure to the sun, as well as increased activities of early detection [1,2]. A similar trend, however, has not been seen in Israel [3]. The incidence of malignant melanoma in Israel has been rising steadily at a mean rate of 9.4% per year.

Jews who immigrated to Israel from Eastern Europe, or those born in Israel to parents who came from Eastern Europe, have the highest rates [4,5], with those born in Israel having double the risk of immigrants for at least three decades following the latter's arrival in Israel [6]. Also, malignant melanoma of the skin is significantly more prevalent among non-religious compared to ultra-orthodox Jews, presumably because the ultra-orthodox cover most of their body with clothing, thus avoiding exposure to the sun [7].

The 260 rural communal settlements in Israel (kibbutzim), with a population of 125,000 individuals, represent 2.2% of the general Israeli population [8]. Most are Israeli-born of Eastern European descent or are immigrants from Eastern Europe. A health survey conducted in the kibbutzim in 1992 showed that malignant melanoma is the second most prevalent cancer in that population, with an incidence of 60/100,000 in 1992 [9]. The incidence of malignant melanoma in the general population of Israel was 7.7/100,000 in 1989 and 10/100,000 in 1994 [3,10]. A previous study showed that the rate of malignant melanoma in the kibbutzim was twice that of the general Israeli population [11], while another study showed that malignant melanoma was the second most prevalent cancer in kibbutzim and that its incidence is increasing [12].

The aim of this case-control study was to assess specific risk factors among kibbutz members with malignant melanoma, compared to healthy matched controls.

## Materials and Methods

### Study design and population

The study was designed as a case-control study. The population included 168 malignant melanoma patients from 91 kibbutzim who were reported to have malignant melanoma in the 1992 study, and 325 healthy controls matched by gender and age ( $\pm 3$  years) residing in the kibbutzim during the study period. In all, 493 individuals participated in the study, with a patient-to-control ratio of close to 1:2. Two control subjects were enrolled for 157 of the patients, and one control for the other 11. The patients were recruited by the kibbutz nurses, who explained the objectives and methods of the study and obtained the subjects' informed consent to be interviewed. Medical charts were reviewed to confirm the diagnosis of malignant melanoma. Histological reports were requested from the pathological departments of the institutes that reached the pathological diagnoses. Level 1 non-invasive melanomas as well as all other histological forms of melanoma were included. Biopsies were not taken from other skin lesions reported by participants in the study.

### Instrument

All participants completed a structured questionnaire on demographic data; skin, hair and eye color; employment history; history of exposure to the sun (in childhood, during adolescence, during army service and in adulthood); family history of malignant melanoma; and use of sun protection (hats, clothing and sunscreens). Three categories of data were defined to characterize the patients and controls: a) demographic (ethnic origin, sex, age, number of years living on the kibbutz); b) "personal" (color of skin, hair and eyes, and family history of malignant melanoma); and c) environmental/behavioral (exposure to the sun over the years due to sun-tanning or work, and use of protective devices).

### Statistical analyses

Data were analyzed using the SPSS (Statistical Package for the Social Sciences) software. *T* tests, Chi-squared, and conditional logistic regression were used as appropriate. A *P* value of  $<0.05$  was used throughout to determine statistical significance.

## Results

The study population comprised 493 subjects from 91 kibbutzim, which included 168 melanoma patients and a control group of 325 subjects.

A comparison of the sociodemographic data for the two study groups is presented in Table 1. There were no significant differences between the study groups in age, gender, family status, education, parents' country of origin, country of birth, place of birth, or place of residence. More than 90% were born in Israel, Europe or America; and 177 participants said they were born on a kibbutz (24.5% of the study group and 25.8% of the control group). Of the 330 participants who were not born on a kibbutz, 74%

**Table 1.** Sociodemographic data of patients and controls (none of the differences is statistically significant)

Variable	Melanoma [n (%)]		Controls [n (%)]	
Gender				
Male	75	(44.6)	144	(44.3)
Female	93	(55.4)	181	(55.7)
Mean age (yr)	53.5 $\pm$ 13.9		53.1 $\pm$ 13.6	
Education (yr)				
12	71	(42.5)	130	(40.4)
13 or more	96	(57.5)	192	(59.6)
Country of origin				
Israel	107	(64.5)	193	(59.8)
Europe/America	57	(34.3)	119	(36.8)
Asia/Africa	2	(1.2)	11	(3.4)
Father's country of origin				
Israel	11	(6.7)	22	(6.9)
Europe/America	151	(92.1)	266	(83.9)
Asia/Africa	2	(1.2)	29	(9.2)
Mother's country of origin				
Israel	17	(10.3)	28	(8.8)
Europe/America	147	(89.1)	262	(82.7)
Asia/Africa	1	(0.6)	27	(8.5)
Previous residence (not born on kibbutz)				
Rural	17	(15.2)	24	(10.9)
Urban	82	(73.2)	166	(75.1)
Both	13	(11.6)	31	(14.0)

**Table 2.** Comparison of skin, eye and hair color between the study groups

	Melanoma [n (%)]		Controls [n (%)]		OR	95% CI	<i>P</i>
Skin color							
Fair	91	(54.8)	102	(31.5)	2.9	(1.89, 4.42)	$<0.0001$
Dark	75		222	(68.5)			
Eye color							
Fair	140	(83.8)	250	(77.2)	1.9	(1.03, 3.34)	$<0.05$
Dark	27		74	(22.8)			
Hair color							
Fair	75	(44.9)	97	(29.8)	2.1	(1.36, 3.18)	$<0.001$
Dark	92		228	(70.2)			
Skin sensitivity							
Sensitive	151	(91.5)	242	(76.3)	3.9	(2.00, 7.42)	$<0.0001$
Not sensitive	14		75	(23.7)			

lived in an urban area before moving to the kibbutz. The mean number of years living on the kibbutz was  $38.5 \pm 14$  for both groups.

Table 2 shows a comparison of skin, eye and hair color, as well as the sensitivity of the skin to sun exposure. Significantly more patients had fair and sensitive skin compared to controls ( $P < 0.0001$ ); more had blue, light blue or green eyes ( $P < 0.05$ ); and more had fair hair (blonde, brunette or red) ( $P < 0.001$ ).

Participants were asked to recall the degree of sun exposure and their use of sun protection at the ages of 6–13, 14–18, 18–21, and above 21 years. The only significant difference in sun exposure between the study groups was that the melanoma group recalled more exposure of 3 hours or more per day without protection between the ages of 6 and 13 (20.0% in the melanoma group vs. 12.3%

**Table 3.** Factors independently associated with prevalence of malignant melanoma (conditional logistic regression)

Variable	OR	95% CI	P
Hair color	2.1	(1.21, 3.64)	<0.01
Skin sensitivity	3.2	(1.35, 7.34)	<0.01
Other skin lesions	2.1	(1.16, 3.89)	<0.015

in the control group;  $P < 0.05$ ). We defined a variable of exposure to sun at work from the age of 21 years, which comprised the product of the number of years at work and the number of hours per day exposed to the sun at work. There were no differences between the groups in this variable. However, 10% of the control group were not exposed to the sun at all during work compared to 5% in the melanoma group ( $P < 0.05$ , odds ratio = 2.44; 95% confidence interval 1.01, 5.91).

Significantly more melanoma patients reported other skin lesions, such as keratosis solaris, hyperpigmentation, skin growths and multiple freckles, than the controls (77.7% vs. 54.2%;  $P < 0.001$ , OR=2.7; 95% CI 1.55, 4.68). The results of a conditional logistic regression [Table 3] showed that fair hair, vulnerable skin and other skin lesions were independently associated with malignant melanoma ( $P < 0.01$  for each). The other variables that were entered into the model — including skin color, exposure to the sun at various ages and a family history of malignant melanoma or another malignancy — were not significantly associated with malignant melanoma in the patient. Fair skin interacted with skin sensitivity and thus was not included in the final model, but it was associated with malignant melanoma on univariate analysis.

There was no significant difference between the melanoma and control groups in the number of first-degree relatives with malignant melanoma (9.5% and 7.9%, respectively) or any other malignancy (47.1% vs. 40.9%, respectively).

## Discussion

The objective of the present study was to assess risk factors for malignant melanoma among kibbutz members with the disease, compared to matched controls. Most kibbutz members are of European origin and reside in the same rural atmosphere with a similar degree of exposure to the sun. The results of this study are consistent with some of the results of other case-control studies on malignant melanoma, which showed that fair skin, hair and eyes, and increased exposure to the sun during adolescence are associated with a high risk for malignant melanoma [13–15]. These data indicate that the kibbutz population is at increased risk for malignant melanoma, compared to the general population in Israel. The known risk factors for malignant melanoma include fair skin and hair, overexposure to the sun especially at a young age, living in a rural area, and middle to high socioeconomic status [6,16–23]. The kibbutz population, on the whole, has these risk factors — most are of Eastern European descent and

thus have fair skin and hair, they are exposed to the sun from a young age, they live in a rural area, and they are of middle to high socioeconomic status. However, not all those at high risk develop malignant melanoma. A possible explanation for the finding that the rate of melanoma in kibbutzim has increased in contrast to the general population may stem from the fact that the kibbutz movement today has more Israel-born members of European-born parents compared to kibbutz members of earlier generations, most of whom were themselves born in Europe. According to Boyle et al. [6], the fair-skinned Israeli-born have higher rates of melanoma than their parents who immigrated to Israel from Europe. Additional possible explanations for the higher rates of melanoma in kibbutzim are a greater degree of awareness, which might lead to the removal of lesions that would not have become invasive if left untouched, and the fact that the kibbutzim are a very well-suited population for comprehensive and thorough data collection and are thus often involved in medical and epidemiological studies. However, since no reliable histological data were available for the lesions in the melanoma group, we can only speculate that they were removed at an early stage.

White et al. [13] reported that the constitutional factor most associated with malignant melanoma was sun sensitivity, measured as the reaction of the skin to chronic and acute sun exposure, while exposure to the sun in adulthood, including occupational exposure, was not associated with an increased risk for malignant melanoma. A study in nurses showed that increased exposure to the sun during adolescence (age 15–20) was a significant risk factor for malignant melanoma [14]. Elwood et al. [15] found that light-colored eyes, fair skin, light hair, and increased skin sensitivity to the sun were significant risk factors for malignant melanoma.

Our univariate analysis showed a significant association between malignant melanoma and fair sensitive skin, light hair and eyes, concomitant skin lesions and exposure to the sun for more than 3 hours per day between the age of 6 and 13 years. More control subjects reported no exposure whatsoever to the sun than did malignant melanoma patients ( $P < 0.05$ ).

Our conditional logistic regression showed that fair hair, sensitive skin and concomitant skin lesions are independently associated with malignant melanoma. Thus, skin and hair properties are the most significant risk factors for malignant melanoma among members of Israeli kibbutzim, most of whom are of European origin and have a similar pattern of sun exposure. Since all the study participants from both groups were exposed to the sun to a similar degree over the years, no significant differences were found in the extent of exposure to the sun or the use of sunscreens for protection. There is no definitive proof that sunscreens prevent the development of malignant melanoma, and they should not be relied upon [24].

Exposure to the sun for more than 3 hours per day between the ages of 6 and 13 years is probably a significant risk factor for malignant melanoma, but is less important than other factors. Since this study is retrospective in design and the degree of exposure to the sun is based on recall and therefore vulnerable to recall bias, we need to be cautious in drawing conclusions.

Many studies have reported that a family history of malignant melanoma is associated with an increased risk for malignant melanoma [19,25], but we did not find an increased prevalence of malignant melanoma in first-degree relatives of the malignant melanoma patients compared to the control group. This may stem from the relatively small sample size in this study compared to other published studies [1,25]. However, the lack of association may indicate that the participants in this study belong to a unique population group in which family history is not directly associated with an increased risk for malignant melanoma, and that the hereditary components are associated more with skin and hair characteristics. This finding provides additional evidence for skin and hair color being the most important risk factors for malignant melanoma, and is very similar to the findings reported by Elwood and colleagues [15] who reached similar conclusions. Inasmuch as several studies have reported similar findings and random phenomena usually do not replicate, it is reasonable to assume that these associations are true and not incidental. Thus, we have provided further evidence that individuals of European and American origin who have fair skin and hair, as well as concomitant skin lesions including freckles, are at increased risk for malignant melanoma and should avoid excessive exposure to the sun.

The study has methodological limitations. The definitions of skin and hair color and of skin sensitivity are based on the participants' self-assessments (in some cases with the help of the nurse). However, the study group consisted of intelligent lay persons whose self-estimation of these parameters should not be expected to introduce a serious bias into the study results. There is no mention of nevi — despite the importance of this entity in relation to melanomas — because the participants were not examined professionally. Nonetheless, the participants were asked about other skin lesions such as keratosis solaris, hyperpigmentation and freckles, and they were helped by the nurses in answering this item. A significantly higher proportion in the melanoma group than among the controls reported other skin lesions.

The results of the present study demonstrate that the principal target population for efforts to reduce the prevalence of malignant melanoma are individuals with fair skin and light hair who have particularly sensitive skin and additional skin lesions. To a far less extent was increased exposure to the sun in the 6–13 year age group an additional risk factor to be considered when planning

intervention programs. Since this variable is particularly vulnerable to recall bias, the results should be weighed accordingly.

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