

## Prevention of malignant melanoma

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### Abstract

The results of Primary Prevention programs, aiming at the decrease of melanoma incidence, were less encouraging than those of Secondary prevention which aims at an early diagnosis of malignant melanoma. Australia was the country with the best results obtained in both Prevention strategies, especially in avoiding intense, though intermittent, UV exposure. The success of these programs encouraged health authorities to initiate their application to other disorders. New sunscreens containing substances correcting the UV-damaged DNA may offer a promising result in the decades to come. However, so far no one epidemiological study has proved the prevention of malignant melanoma with the use of sun protecting agents. A meta-analysis verified the connection between melanoma and "solarium" use. The protective role of vitamin D in the development of prostate, breast and colon cancer was shown in a meta-analysis. The authors, however, suggest that fair-skinned persons should take oral supplementation of vitamin D, instead of exposing themselves to the sun. The Hellenic Society of Dermatology and Venereology published the results of 5-year-prevention programs in Greece. Their favorable results in the early diagnosis of melanoma justify an intense continuation of these efforts. Hippokratia 2008; 12 (1): 17-21

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"The prognosis of malignant melanoma (MM) depends on its Prevention and Early Diagnosis"<sup>1</sup>. This motto, that is repeated in the Editorials of many English-language Medical Journals, is by no means a new statement. Since Primary Prevention includes every effort of the medical community to lower the disease prevalence and Secondary Prevention refers to the early detection of MM, the prognosis of the disease depends on its prevention.

The incidence of MM during the decades of 70s, 80s, 90s and the year 2000 was respectively 3, 7, 13 and 20 cases per 100,000 of population. This increase indicates that the measures of Primary Prevention that have been followed by the Medical Communities may be considered as failure<sup>2</sup>. On the contrary, Secondary Prevention seemed to be successful since disease-related mortality remained steady, mostly because of the early detection of MM<sup>2</sup>.

### Sun Protection and Malignant Melanoma

The review of the 20 most significant Web sites for the Prevention of MM discloses three simple suggestions for the public: a) Use sun protective agents with a factor of at least 15, b) Wear a hat with a wide rim, c) Do not forget eye protection with eye glasses<sup>3</sup>. Nevertheless, many non-blinded studies, published mainly during 2005, gave conflicting results concerning the usefulness of sun

protection. An observational comparison study among 1,812 children from Germany, suggested that the more sun protection used during holiday time outdoor the less likely of manifesting melanocytic nevi and consequently MM<sup>4</sup>. The use of educative hand-outs and distribution of free of charge sun protective creams, seemed not to change the habit of sunbathing among children<sup>5</sup>. Another 6-year program under the name of "Kidskin" concerning 639 children from Australia was unable to show any significant correlation between sun protection and decrease of nevus counts<sup>6</sup>. Yet, a clinicopathologic analysis of 932 MM, suggested that MMs histologically associated with a preexisting nevus were more rarely seen among patients staying outdoors under the sun, suggesting that ultraviolet radiation is probably not promoting the transformation of nevi to MM<sup>7</sup>.

On the contrary, randomized, comparative, prospective studies correlated sun protection with the decrease of nevus. The use of an SPF 30+ for three years in 309 children from Vancouver offered a skin with decreased number of nevi, especially on the intermittently exposed to the sun parts of the body<sup>8</sup>. One-week use of high sun protective factor (SPF) protection among 367 healthy volunteers in France offered a sun burn-free skin<sup>9</sup>. So far however, there is no one epidemiological study supporting the concept that sun protecting agents do prevent from the development of MM<sup>10</sup>.

The improvement of sun protecting creams which are expected to be four times more effective than those used a decade ago, may give a bright future according to a recent publication<sup>11</sup>. Their effect, however, will be obvious many decades later<sup>11</sup>. The possibility of creating a new generation of sun protecting creams incorporating enzymes that might restore the UV-damaged intracellular DNA, is exciting<sup>12</sup>.

#### UV-Light tanning as a type of substance – related disorder

Despite the general acceptance by the medical community that sun protection measures are useful against skin cancer, 96% of those participating studies for the significance of sun protection were using SPF creams to purposely gain a tanned skin<sup>9</sup>. This behavior had the characteristics of an addiction in some occasions<sup>13</sup>. So, a distinction was made among those visiting UV-Tanning Centers, known as “Solarium”, at least 100 times a year and those visiting these Centers less than 25 times a year. The first group was considered as “addicted” to Solarium and required a medical approach, the second group was eligible to follow Melanoma Prevention programs<sup>3</sup>.

Until 2005, no scientific correlation between Solarium and Skin cancer was proven. This was due to the relatively small number of persons who were included in the studies, with subsequent wide Confidence Intervals. During 2005 however, a meta-analysis of 13 studies disclosed the correlation of MM and Solarium with an Odds Ratio 1.69 (CI 1.32-2.18)<sup>14</sup>. Another meta-analysis from France suggested that aiming at the active cooperation, the repeated nature of behavioural programs and the long duration of efforts upon childhood may give effective prevention against skin cancer<sup>15</sup>.

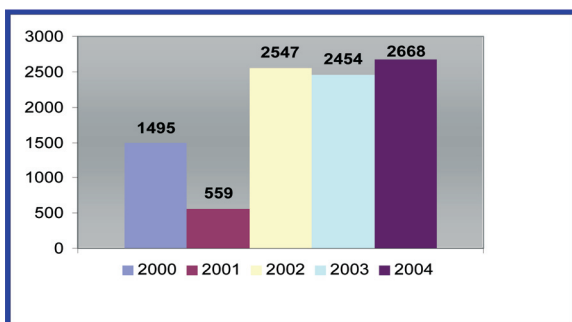
#### Prevention of MM in certain countries

The medical and political authorities of Australia, a country with a high prevalence of MM, have set up preventive programs since the early 80s. The results of these efforts are now coming up and seem very encouraging. The mortality from MM decreased at the ages under 55

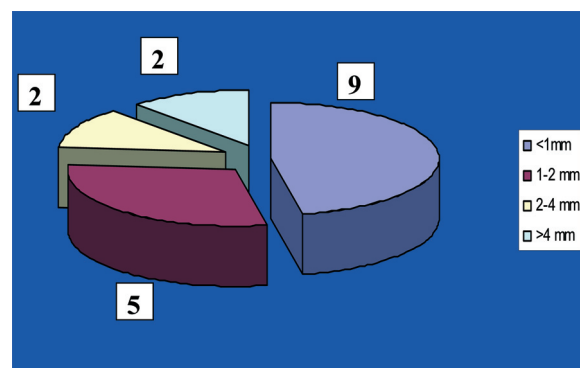
years, a fact that reflects the awareness of the young population about the dangers from the sun. It remained steady among patients aged 56-79, and showed a tendency of 3-4% annual increase among persons over 80 years of age<sup>16</sup>. Robin Marks, President of the International League of Dermatological Societies, has pointed out during 2004 that sun-behavioral attitudes of Australia citizens began to change. One year later, the same author underlined the belief that educational prevention programs will be more fruitful in the years to come<sup>16</sup>.

On the contrary, the 20-year prevention program at Central Texas did not influence either primary or secondary prevention<sup>17</sup>. The results of the campaign that the Hellenic Society of Dermatology and Venereology (HSDV) initiated since 2000 under the eponyms “European Melanoma Monday” and “Hellenic Week against Skin Cancer” were recently presented on an annual basis<sup>18</sup>. The actions being taken during this time, except from the free of charge public examination by Dermatologists all over Greece, were the following: an open MM information telephone line; brochures and TV broadcasting on the matter for a whole month; a media and press interview of HSDV board; educational programs delivered by experts and the help of teachers in elementary and high-schools. It is too early to evaluate the results of these efforts on Melanoma Primary Prevention in Greece. During the period 2000-2004, a total of almost 10,000 inhabitants of Greece were evaluated (Figure 1). A significant finding that is in favor of the success of Secondary Prevention Program, was the fact that 50% of the detected melanomas were thin ( $\leq 1$  mm), that is at an early stage of the disease (Figure 2)<sup>18</sup>.

Unfortunately, there are no registry data on the distribution of melanoma thickness before the campaign of HSDV to compare with later results. The data of SEER (Surveillance, Epidemiology and End Results) in Caucasians of USA, showed a stability in the percentage of thick (over 2 mm) MMs during the period 1988-1999<sup>19</sup>. Similar findings were observed in Scotland where the preventive strategies did not decrease the number of thick MM<sup>20</sup>.



**Figure 1.** Citizens examined yearly by Greek Dermatologists, during the campaign of “Euromelanoma Screening Day” and “Hellenic Week against Skin Cancer”, promoted by Hellenic Society of Dermatology and Venereology



**Figure 2.** Percentage of identified Malignant Melanomas according to their thickness, after the Campaign of Hellenic Society of Dermatology and Venereology

### Secondary Prevention

An effective self-examination for the detection of MM is a prerequisite for a successful secondary prevention. Aiming at a better public education, the procedures followed by dermatologists for the recognition of MM among 4,032 melanocytic lesions were prospectively examined<sup>21</sup>. The following clinical signs were considered as crucial for the detection of MM, at increasing order of significance: the clinical "impression" of an irregular lesion; the "ugly duck" sign, that is the dissimilar appearance of MM to the rest of melanocytic lesions; the significant change of the inspected lesion and the history of recent change<sup>21</sup>. Eighty-eight percent of 696 patients with superficial spreading Melanoma and 71% of patients with Nodular Melanoma, did mention recent change of the lesion. The latter sign of evolution, change or elevation of the lesion, was the main diagnostic element in the Group of New-York, under Rigel et al<sup>22</sup>. These authors had installed the basis of Clinical Diagnosis of Melanoma, almost 20 years ago, under the mnemonic of ABCD. Nowadays, the addition of E (Evolution) is necessary and the new mnemonic is called ABCDE: A, for the asymmetry in one or two dimensions; B, for the irregular border; C, for the existence of more than two different colours; E, for the recent evolution or elevation of the lesion. It also seems that the ability of doctors to listen to their patients may save their lives. Almost 2% of 535 lesions, that were removed in order to calm the inquietude of the patients, were indeed MMs<sup>21</sup>.

### Prognosis in high – risk patients

Patients who are at high-risk for developing MM (Table 1) will probably suffer from Melanoma when they manifest a new lesion or a change in a preexisting one and their age is over 50 years<sup>23</sup>. In a survey of 309 persons, three of the ten who manifested melanocytic lesions for the first time at this age range and 5 of 23 who had noticed a change of these lesions were proved to suffer from true melanomas. The combination of Photography and Dermoscopy in high-risk patients may also help in the early diagnosis of MMs and decrease the number of unnecessary biopsies. Taking into consideration the total number of lesions that had been sent for histology under the clinical suspicion of MM, the percentage of benign to malignant lesions that were surgically removed dropped from 9:1 to 3:1 in a six-year period<sup>23</sup>.

Regarding the risk of melanoma among children with giant or multiple melanocytic nevi, interesting data were extracted from the observation of 1,008 patients at the "Nevus Network" in Ohio<sup>24</sup>. Two independent factors which are male gender and the presence of satellite lesions seemed to be associated with an increased risk. Almost 7% of children carrying more than three nevi suffered from MM. In addition, the management of giant nevi with surgical debridement did not offer a 100% protection from a future appearance of MM<sup>24</sup>. Similar data was derived from New York network registries where 5% of children with giant nevi manifested a MM. After a

mean follow-up of 4 years, the percentage of large congenital nevi that transformed into MM was 2.3% among 179 children. An increased incidence of MM and/or Neurocutaneous Melanosis was noticed in patients with nevi measuring at least 40 cm and/or a significant number of satellite nevi<sup>25</sup>.

### Dermoscopy in secondary prevention of MM

Dermoscopy has a significant impact on the secondary prevention<sup>1</sup>. Since physicians and especially Dermatologists, are responsible for the diagnosis, only experts can recognize when and how to use the new techniques of diagnosis. An algorithmic automated dermoscopy examination of 2.430 lesions from 9 centers in three Continents, suggested that the method offered results at least equal to those of Clinicians. Nevertheless, even the best laboratory may not contribute, but only to a second degree, to the final decision of the clinician and specialized doctor<sup>26</sup>.

### Peculiarities in sun protection and MM

The survival in 528 MM patients after 5 years of follow-up was better among those who had an increased exposition to sun damage<sup>27</sup>. This may probably reflect a kind of skin "hardening", like that of the management of photodermatitis with Ultraviolet A and B. The prophylac-

**Table 1:** Risk Factors for the Development of Malignant Melanoma

<u>Genetic</u>
Personal or Family history of Melanoma (FAMM Syndrome)
Type I skin Phototype (always burns, never tans)
<u>Phenotypical</u>
Blond or red hair
Noticeable freckling on the upper back
Solar lentigines (2 fold risk)*
Three or more atypical nevi (10 fold risk)**
Palpable nevi on the upper extremities (2 fold risk)*
<u>Environmental/Life style exposures</u>
More than three blistering sunburns before 20 years of age***
Previous residence in sunny area
<u>HARMM assessment model****</u>
History of previous melanoma
Age over 50 years
Regular dermatologist absent
Mole changing
Male gender

\*: the measurement of risk factor is according to Nijsten et al<sup>32</sup>

\*\*: Atypical nevi are defined as acquired nevi that satisfy at least three of the following five criteria:  $\geq 5$  mm in diameter, asymmetrical shape, irregular pigmentation, irregular or hazy border, erythema

\*\*\*possibly geographically dependent

\*\*\*\*Especially helpful in identifying higher risk groups of the skin cancer screening population<sup>33</sup>

tic use of cyclooxygenase inhibitors might probably help in the avoiding of MM in high-risk people, according to a recent paper<sup>28</sup>. Similarly, hypolipidemic agents may protect from Melanoma, a finding that reached statistical significance among patients receiving Lovastatin<sup>29</sup>.

### Primary prevention, vitamin D and internal cancer

A recent meta-analysis from San Diego, incorporating 63 studies brought under consideration the connection of sun protection and low vitamin D production in the skin and their association with solid tumors, especially of breast, colon, prostate and ovaries<sup>30</sup>. The protective action of vitamin D was shown in many studies. Those who used to consume less than 100 IU vitamin D and reached hydroxyvitamin D serum levels below 13 ng/ml, had a 50% greater chance to manifest colon cancer<sup>30,31</sup>.

It seemed that most Melanoma Primary Prevention Programs had to change because of these observations. Nevertheless, the authors suggested that daily ingestion of 1000 IU vitamin D and/or sun exposition of 40% of body surface area for 15 minutes is adequate for the production of the required vitamin D quantity to protect from cancer. Dark-skinned persons may be exposed to the sun for longer time periods. Following the consideration of light-skinned persons to acquire MM or other skin tumor, the authors proposed this population group better receive adequate quantities of vitamin D by a proper diet, instead of sun exposition<sup>31</sup>.

### Conclusions

Prevention of MM is the most powerful weapon the medical community can handle in its war against this deadly tumor. Data showing the results of primary prevention measures that aim at reducing the incidence of MM, were unsuccessful. This may partly be due to the perplexity of factors promoting disease initiation. Contrary to the study of other skin tumors, sun protecting agents were not decisively associated with the appearance of MM. The finding that sun protection during childhood may protect from the future appearance of melanocytic lesions like common moles, and the knowledge that sun damage is responsible for the development of skin cancer in general, did not significantly alter the behavior of people to the sun. The steadily increasing industry of Tanning "solar"Booths and the presence of a significant number of "addicted" people, requiring more than 100 "solarium" visits annually, is only a part of the problem. Ninety-six per cent of those participating studies for the significance of sun protection were using SPF creams only to gain a tanned appearance.

Actions against unprotected sun exposure were vigorously taken by Hellenic Society of Dermatology and Venereology, such as educational programs delivered by experts; informative material handed out in children of elementary and first classes of high schools; TV broadcasting and free of charge examination of people during the first complete week of every May. Analogous mea-

asures, apparently more intensive and supported by Authorities, were undertaken by Australians 20 years ago and offered a measurable decrease in morbidity of MM at the ages less than 55 years. Educational programs at Central Texas which also started 20 years ago were not helpful, probably because of the increase of nodular melanoma cases. The latter behaves in a distinctive manner compared to superficial spreading melanoma (SSM) which involves the main bulk of MM. During the 5 years of HSDV campaign (2000-2004), 18 cases of SSM were detected among 9,723 people examined. Fifty per cent of these melanomas were less than 1 mm thick, indicating an early stage of the disease. The screening of MM at an early and curable stage is the aim of the secondary prevention programs.

The rule of clinical ABCDE, where A is for Asymmetry, B for irregular Border, C for Color variation, D for Diameter  $\geq 6$  mm, E for recent Elevation or Evolution continues to be valid among dermatologists. However, this may not apply for self examination of those at high-risk of developing MM. Instead, recent data suggest that the following clinical signs may be useful for primary care physicians and people of high-risk group in acquiring MM: The clinical "impression" of an irregular lesion; the "ugly duck" sign, that is the dissimilar appearance of MM to the rest of melanocytic lesions; the significant change of the inspected lesion and the history of recent change.

Meta-analysis disclosed the prophylactic effect of vitamin D, generally being provided by skin under the sun influence, in preventing from solid tumors. However, the authors suggest that light-skinned people better be taken oral supplementary vitamin D instead of exposing themselves under the sun.

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