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Worldwide Cutaneous Malignant Melanoma Incidences Analyzed by Sex, Age, and Skin Type Over Time (1955–2007): Is HPV Infection of Androgenic Hair Follicular Melanocytes a Risk Factor for Developing Melanoma Exclusively in People of European-Ancestry?

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Worldwide cutaneous malignant melanoma incidences analyzed by sex, age, and skin type over time (1955–2007): Is HPV infection of androgenic hair follicular melanocytes a risk factor for developing melanoma exclusively in people of European-ancestry?

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ABSTRACT

The cutaneous malignant melanoma (CMM) incidence has been increasing in an exponential manner in certain populations around the world for over 7 decades. To help illuminate the etiology, we performed worldwide temporal (1955–2007) CMM incidence analysis by sex, age (0–14, 15–29, 30–49, 50–69, 70–85+), and skin type on 6 continents using data from the International Agency for Research on Cancer. We observe an exponential increase in the CMM incidence over time and an increase of about 2 orders of magnitude between age groups 0–14 and 15–29 exclusively in European-ancestry populations around the world independent of skin type (I–III or III–IV). Other populations like the Chinese (III-IV) had much lower CMM incidences that either remained stable or temporally decreased but did not display a dramatic increase between the youngest age groups. The dramatic increase in the incidence between the youngest age groups found only in European-ancestry populations suggests one of the most important risk factors for CMM may be developing androgenic hair, the occurrence of which appears to correlate with the distribution of CMM over male and female body sites. Besides that potential new risk factor, the increasing CMM incidence with increasing age, known not to be from cumulative UV doses, may be associated with age-related changes to skin, i.e., thinning epidermis causing lower vitamin D_3 levels, and hair, i.e., whitening from higher reactive oxygen species. The temporal exponential increasing CMM incidence in European-ancestry populations may be due to Human Papilloma Virus infection of follicular hair melanocytes, found in CMM biopsies.

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Introduction

The incidence of cutaneous malignant melanoma (CMM) has been increasing in an exponential manner for over 7 decades in certain indoor-working populations around the world.[1-3] This increasing trend in CMM incidence over time has been attributed to a variety of risk factors: increasing terrestrial UVB radiation (290–315 nm) from ozone depletion increasing personal doses; increasing exposures to more body sites (less clothing and smaller swimsuits like bikinis) to erythemally-weighted UV radiation (UVR; 290–400 nm), which is primarily UVB radiation;[4] increasing tanning behaviors using the UVR from tanning devices or the sun during vacation holidays; increasing changes in diagnostic criteria and surveillance; increasing intermittent outdoor UVB exposures thought to increase the occurrence of sunburns.

These are popular explanations for the increasing trend in CMM over time; however, if true, they would create several paradoxes. The most intriguing paradox concerns UVR exposure. For example, higher doses from increasing terrestrial UVB radiation due to decreasing ozone levels cannot explain the increasing trends of CMM over time because atmospheric ozone levels stabilized during the 1990s.[5] More importantly, higher UVB doses cannot explain these increasing CMM incidence trends because outdoor workers get 3–10 times the annual UVB doses that indoor workers get,[6] yet they have lower incidences of CMM than indoor workers

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have.[7] Those findings also show cumulative UVB doses cannot be responsible for the higher CMM incidences observed with advancing age, so that another explanation is needed. Increasing body surface area exposure to UVB radiation does not explain this increasing trend in CMM because small bathing suits like bikinis were available since the 1960s so that people have been exposing as much of their surface body area as possible for over 5 decades. Moreover, epidemiology studies show that unlike non-melanoma skin cancer, which primarily occurs on chronically exposed body sites,[8] CMM primarily occurs on intermittently exposed body sites.[9] Paradoxically, Fitzpatrick skin type I-III[10] Europeans actually displayed a significant correlation between increasing incidences of CMM and decreasing UVB doses over time ($p < 10^{-6}$), most notably after 1960.[2] Increasing tanning behavior also does not explain this trend because, along with all the observations already mentioned, higher UVB exposures in the south steadily decreased CMM while lower UVB exposures in the north steadily increased CMM in the adolescent population of the United States (US) from 1988 to 2009.[11] Tanning indoors using devices along with tanning outdoors using the sun during holiday vacations to lower latitudes have also been blamed for the temporal increases; however, CMM has been gradually increasing in an exponential manner since 1936 with no change in the slope of the trendline throughout the time course (1936–2000),[1,3] which would be expected to occur sometime after 1960 if tanning significantly contributed toward the risk.[2] Although not a paradox, changes in diagnostic criteria over time was also not connected to the increasing incidence of CMM because several countries around the world (Australia, France, Italy, New Zealand, Norway, Sweden, the United Kingdom, the US, and the Union of Soviet Socialist Republics) were all found to have similar histological diagnostic criteria in 1930, 1955, and 1980.[12] Besides, it is not possible for all the physicians around the world to gradually change their CMM diagnostic criteria so that an exponential increase would occur for over 6 decades with no change in the trendline slope. Thus, scientists cannot explain the exponential temporal increase in CMM by increasing UVB doses, increasing body sites exposed, increasing tanning indoors or outdoors, or increasing changes in diagnostic criteria. The remaining risk factor is intermittent sun exposures.

Intermittent sun exposures were identified by epidemiology studies as the major risk factor associated with initiating CMM and the consensus was that it was due to intense UVB-induced sunburns, especially during childhood, and that this somehow caused CMM to increase over time. This belief created yet another paradox for several reasons. First, sunscreens with primarily UVB protection or with both UVB and UVA (316–400 nm) protection and with increasing sun protection factors have not reduced the incidence of CMM since their creation over 5 decades ago. Second, animal studies revealed sunscreens did not reduce the growth of melanoma[13] and, counter intuitively, higher UVB doses including sunburn doses, actually gave decreasing numbers of animals with melanomas.[14] Third, human studies confirmed sunscreens only prevent sunburns not CMM[15] and some epidemiology studies actually found sunscreens increased the risk for getting CMM in a dose-dependent manner.[16] Fourth, the most sun-sensitive individuals are albinos who get severe sunburns and have numerous, early onset non-melanoma skin cancers, but they rarely get melanoma although they have the same number of melanocytes as pigmented people.[17] Note that almost all epidemiology studies that concluded intermittent sun exposures causing sunburns is a risk factor for CMM did not include questions concerning sun protective measures like avoidance behavior and sunscreen use (see examples in reference 7), which probably confounded the findings because fair-skinned, sun-sensitive individuals are more prone to protect themselves (see overview of studies in reference 18). Finally, the International Agency for Research on Cancer (IARC) published an official report concluding sunscreens do not protect against getting CMM.[19] Thus, the role of UVB-induced sunburns is questionable in human CMM, while the role of UVA[3] and visible light[20] exposures have not been fully elucidated.

The epidemiology studies that appeared to display correlations between sunburns and CMM may actually reflect the sun-sensitive individual's reluctance to go outdoors and be exposed to the burning UVB rays because they harbor painful childhood sunburn memories. This idea originated with epidemiology studies that found people's perception of having a tendency to sunburn,

rather than the actual number of sunburns, along with normally being untanned were risk factors associated with CMM.[21,22] Support for this idea came from a recent well-documented epidemiology study that revealed the risk for CMM was greatest in melanocortin-1-receptor variant individuals with protective phenotypes who got limited sun exposures, like those who tanned well after repeated sun exposures (odds ratio, OR 2.4; 95% CI, 1.6–3.6), had dark hair (OR 2.4; 95% CI 1.5–3.6), or had dark eyes (OR 3.2; 95% CI 1.8–5.9), and the same risk pattern was observed for persons who did not freckle, tanned after their first exposure to strong summer sun, reported little or average recreational or occupational sun exposure, or who reported no sun burning events compared to controls; meta-analysis of published studies supported those findings.[23] In fact, increased childhood sun exposures from outdoor activities were shown to be protective against CMM yielding a lower risk[24] while sun exposures in adulthood or occupational exposures were not related to the risk.[25] Moreover, outdoor workers with lower incidences of CMM actually get numerous sunburns every year (reviewed in reference 26). Thus, the belief that CMM is caused by sunburns at any age needs to be reevaluated because it also created a paradox.

In order to help illuminate our understanding on the etiology of CMM and possibly resolve some of these apparent paradoxes, we extended our earlier CMM studies[1-3] to examine the role of age and skin type. To do this we analyzed males and females in 5 age groups (0–14, 15–29, 30–49, 50–69, 70–85+ yr.) with Fitzpatrick skin types I-VI[10] in 57 countries on 6 continents around the world from 1955 to 2007.

Materials and methods

Analysis of CMM incidence by sex, age, and skin type over time (1955–2007)

We analyzed the age-standardized CMM (ICD-10, C43) incidence rates (ASR) per 100,000 world standard population at 5-year interval midpoints over time from 1955 to 2007 for males and females in 5 age groups (0–14, 15–29, 30–49, 50–69, 70–85+) with Fitzpatrick skin types I-III, III-IV, IV-V, and IV-VI.[10] White, non-Hispanic white or Caucasian skin is primarily represented by Fitzpatrick skin type I-III; Asian, Latino, Hispanic, and Polynesian skin is primarily represented by Fitzpatrick skin type III-IV; brown to black or African American skin is primarily represented by Fitzpatrick skin type IV-VI;[27] eastern Indian skin is primarily represented by Fitzpatrick skin type IV-V;[28] Mediterranean, olive tone skin is primarily represented by Fitzpatrick skin type III-IV.[29] One possible limitation to this study is that a Fitzpatrick skin type for the primary population of each country had to be assigned if the IARC data did not segregate the populations by skin type, e.g., white, non-Hispanic white, non-Maori, Maori, or black (African-American). We used data designated as white, other white, or non-Hispanic white for Fitzpatrick skin type I-III whenever available.

We used the national data or aggregated the regional population-based cancer registry data to obtain a national average from *Cancer Incidence in Five Continents (CI5) Volume I to X*.[30] For example, in Europe we aggregated the regional registries for CMM incidences in Austria, Belgium, England, France, Germany, Hungary, Poland, Romania, Scotland, Switzerland, and The Netherlands to estimate national incidence trends. Note that Denmark began collecting data in 1953 while all the other European countries began collecting data after 1955 so we excluded the 1953 data set. Iceland began collecting data in 1955 but their CMM incidence for the year 1960 actually included the years 1955 to 1963. We included and analyzed all available data for each country around the world whenever it began collecting data until 2007, but note that some countries did not collect data during certain time intervals between 1955 and 2007. In South America, after regional aggregation, we averaged the CMM incidence data of 6 countries: Argentina, Brazil, Chile, Columbia, Ecuador and Uruguay. In Africa, after regional aggregation, we averaged the CMM incidence data for 8 countries: Egypt, Libya, Algeria, Uganda, Malawi, Zimbabwe, South Africa, and Tunisia.

We analyzed 57 countries in total; the data shown here is for Australia, the US (white, other white, or non-Hispanic white), Europe (24 countries average shown), China, South America (6 countries average shown), Spain, Italy, Israel, New Zealand (Maoris), India, Africa (8 countries average shown), and the US African-American blacks. The data for the countries analyzed but not shown here are New Zealand (non-Maori whites), Canada, Japan, Cuba, Cyprus, Korea, Kuwait, Malta, Philippines, Portugal, and Thailand.

The specific inclusion criterion was the availability of at least 9 consecutive years of data. The editorial process for quality control involves a detailed assessment of the validity, completeness, and comparability of the incidence data, the details of which are provided online (http://ci5.iarc.fr/CI5I-X/old/vol10/I_08.pdf).

This CMM data includes all tumor stages, thicknesses, histological subtypes, and body site locations. IARC data was obtained by the governments over the course of decades having consistent criteria. The data is more extensive than other databases because it covers a longer period of time (before 1975) and contains almost all the countries of the world, not just the US, using the same inclusion/exclusion criteria.

Skin type I-III continents and countries: Australia, US, and Europe

On the Australian continent, we analyzed all the available data for skin type I-III populations in each territory: Capital Territory (35.3°N), New South Wales (32.2°N), Northern Territory (20°N), Queensland (23°N), South (30°N), Tasmania (42°N), Victoria (37°N), and Western (26°N).

In New Zealand (40.9°N), we analyzed all the available data for skin type I-III populations separately from the native Polynesian Maori's with skin types III-V.

On the North American continent in the US, we analyzed skin type I-III populations separately from skin types IV-VI for all states with available data, but excluded Hawaii along with Alaska because they did not segregate their skin type populations for many years. The state's populations analyzed by sex and age for skin type I-III over time or UVR dose in the US were: Hawaii (21.31°N), Florida (27.8°N), Louisiana (30.7°N), Texas (30.9°N), Mississippi (32.6°N), Alabama (33°N), Georgia (33.3°N), Arizona (33.4°N), South Carolina (34°N), New Mexico (34.6°N), Arkansas (35.1°N), California (35.5°N), North Carolina (35.6°N), Oklahoma (35.6°N), Tennessee (35.8°N), Virginia (37.8°N), Kentucky (37.8°N), Missouri (38.4°N). West Virginia (38.8°N), Delaware (39.4°N), Colorado (39.5°N), Indiana (40.2°N), New Jersey (40.4°N), Utah (40.4°N), Pennsylvania (40.5°N), Ohio (40.5°N), Nebraska (41.2°N), Illinois (41.3°N), Connecticut (41.5°N), New York State (41.5°N; excluding New York City due to skin type mix), Rhode Island (41.8°N), Iowa (41.9°N), Massachusetts (42.3°N), Wyoming (42.7°N), Michigan (42.9°N), Wisconsin (43.7°N), South Dakota (44.1°N), Vermont (44.1°N), Idaho (44.2°N, only skin type I-III), Maine (44.3°N), Oregon (44.7°N), Montana (46.8°N), Washington State (47.3°N), and North Dakota (47.4°N). We also separately analyzed the native Hawaiians with primarily skin types III-IV residing in Hawaii.

On the North American continent in Canada (56.1°N), we analyzed all the available data for skin type I-III populations in each territory: Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland, Northwest Territories, Nova Scotia, Ontario, Prince Edward Island, and Quebec.

On the European continent, we separately analyzed countries with darker skin type III-IV from those having primarily lighter skin type I-III populations: Romania (46°N), Slovenia (46°N), Switzerland (47°N), France (47°N), Hungary (48°N), Austria (48°N), Slovakia (49°N), Czech (50°N), Poland (51°N), Germany (51°N), Belgium (51°N), The Netherlands (52°N), England (52°N), Ireland (53°N), Belarus (54°N), Lithuania (55°N), Denmark (56°N), Scotland (57°N), Latvia (57°N), Estonia (59°N), Sweden (62°N), Iceland (63°N), Norway (64°N), and Finland (65°N).

Skin type III-IV in countries and continents: China, Japan, Spain, and South America

On the Asian continent in China, we analyzed skin type III-IV populations in Beijing (39.9°N), Cixian (36.4°N), Haining County (30.5°N), Hong Kong (22.3°N), Jiashan (30.8°N), Macao (22.2°N), Nangang District, Harbin City (45.7°N), Qidong County (26.8°N), Shanghai (31.2°N), Wuhan (30.6°N), Yangcheng County (35.5°N), Yanting County (31.2°N), and Zhongshan (22.5°N).

In Japan, we analyzed skin type III-IV populations in Aichi Prefecture (38.2°N), Fukui Prefecture (37.5°N), Hiroshima 36°N), Miyagi Prefecture (35°N), Nagasaki (34.7°N), Niigata Prefecture (34.3°N), Osaka Prefecture (33.2°N), and Saga Prefecture (32.8°N).

On the European continent in Spain (40.5°N), we analyzed skin type III-IV Spanish populations in Albacete, Asturias, Basque Country, Canary Islands, Ciudad Real, Cuenca, Girona, Granada, La Rioja, Mallorca, Murcia, Navarra, and Tarragona.

On the continent of South America, we analyzed skin type III-IV populations in 6 countries: Argentina (Bahia Blanca 38.7°S, Cordoba 31.4°S, Mendoza 32.9°S, Tierra del Fuego 54°S), Brazil (Aracaju 10.9°S, Belo Horizonte 19.9°S, Cuiaba 15.6°S, Fortaleza 3.7°S, Goiania 16.7°S, Sao Paulo 23.6°S), Chile (Biobio Province 37.4°S, Region of Antofagasta 23.7°S, Valdivia 39.8°S), Columbia (Bucaramanga 7.1°N, Cali 3.4°N,

Manizales 5.1°N, Pasto 1.2°N), Ecuador (Cuenca 2.9°S, Quito 0.2°S), and Uruguay (34.9°S).

Skin type III-IV populations in Italy and Israel, skin type IV-V in India, skin type IV-VI in the US, and skin types III-VI in Africa

On the European continent in Italy, we analyzed the data for skin type III-IV populations in Alto Adige (46.4°N), Biella Province (45.6°N), Brescia Province (45.6°N), Catania and Messina (37.5°N), Catanzaro (38.9°N), Ferrara (44.8°N), Florence (43.8°N), Friuli-Venezia Giulia (46.1°N), Genoa (44.4°N), Latina Province (41.5°N), Lombardy Como Province (45.8°N), Lombardy Lecco Province (45.9°N), Lombardy Mantova Province (45.2°N), Milan (45.5°N), Modena (44.7°N), Naples (40.9°N), Nuoro (40.3°N), Palerme (38.1°N), Parma Province (44.8°N), Ragusa Province (36.9°N), Reggio Emilia Province (44.7°N), Romagna (44.5°N), Salerno (40.7°N), Sassari (40.7°N), Sondrio (46.4°N), South Lombardy (45.7°N), Syracuse Province (37.1°N), Torino (45.1°N), Trapani (38°N), Trento (46.1°N), Umbria (43°N), Varese Province (45.8°N), and Venetian Region (45.4°N).

In Israel (31.1°N), we analyzed the data for their skin type III-IV Jewish population.

In India, we analyzed skin type IV-V populations in Bangalore (13°N), Barshi (18.2°N), Bhopal (23.3°N), Chennai (Madras,13°N), Delhi (28.7°N), Dindigul, Ambillikai (10.4°N), Karunagappally (9°N), Mizoram (23.4°N), Mumbai (Bombay, 19°N), Poona (18.5°N), Sikkim State (27.3°N), and Trivandrum (8.5°N).

On the North American continent in the US, we analyzed skin type IV-VI populations separately for all states with available data. The state's populations analyzed by sex and age for type V-VI over time and UVR dose in the US were: Florida (27.8°N), Louisiana (30.7°N), Texas (30.9°N), Alabama (33°N), Georgia (33.3°N), Arizona (33.4°N), South Carolina (34°N), Arkansas (35.1°N), California (35.5°N), North Carolina (35.6°N), Oklahoma (35.6°N), Tennessee (35.8°N), Virginia (37.8°N), Missouri (38.4°N), Delaware (39.4°N), Colorado (39.5°N), Indiana (40.2°N), New Jersey (40.4°N), Pennsylvania (40.5°N), Ohio (40.5°N), Nebraska (41.2°N), Illinois (41.3°N), Connecticut (41.5°N), New York State (41.5°N; excluding New York City due to the mix of skin types), Rhode Island (41.8°N), Massachusetts (42.3°N), Michigan (42.9°N), Wisconsin (43.7°N), and Oregon (44.7°N).

On the African continent, we analyzed all the available data for countries with skin type III-VI populations: Egypt (Gharbiah; 26°N), Libya (Benghazi; 32.1°N), Algeria (Setif Wilaya; 36.2°N), Uganda (Kyadondo County; 1.07°N), Malawi (Blantyre; 15.8°N), Zimbabwe (Harare; 17.9°N), South Africa (PROMEC; 30°N), and Tunisia (North; 34°N).

Statistical analysis

For all the data, we conducted linear regression analysis using Minitab 16.2.4 (Minitab Inc., State College, Pennsylvania) to assess the role of time in predicting log (CMM) incidence rate in each age group studied and consider $p < 0.05$ significant. These predictions were also used to create Figure 5, where estimated incidence at 2010 at each of the 5 studied age groups was plotted for Australian males and South American males.

Results

We began by analyzing the CMM incidence of skin type I-III populations in Australia (New Zealand, results not shown), North America (in the US; Canada, results not shown), and Europe and found CMM increasing in an exponential manner over time for both males and females older than 14 y. (Fig. 1 left, middle, and right panels, respectively). Australian females were the only exception displaying no trend for ages 15–29 ($p > 0.9$, Figure 1 left lower panel). Note that all of these European-ancestry populations display a dramatic (about 2 log units) increase in the incidence of CMM between the 2 youngest age groups, i.e., 0–14 and 15–29.

In contrast to the skin type I-III populations around the world, the skin type III-IV populations with yellow skin tone have lower incidences and display either somewhat stable or downward trends over time for most age groups, except for the European-ancestry population in Spain (Fig. 2). On the Asian continent, the Chinese with skin type III-IV display decreasing temporal trends and do not have a dramatic increase in the CMM incidence between the 2 youngest age groups (Fig. 2 left panels), similar to the Japanese, Korean, and Thai populations (results not shown). Analysis of the continent of South America with skin type III-IV populations, reveals no increasing trend of CMM over time or a dramatic increase in the incidence between the youngest age groups for males but does show a slight increasing trend for females and a noticeable increase

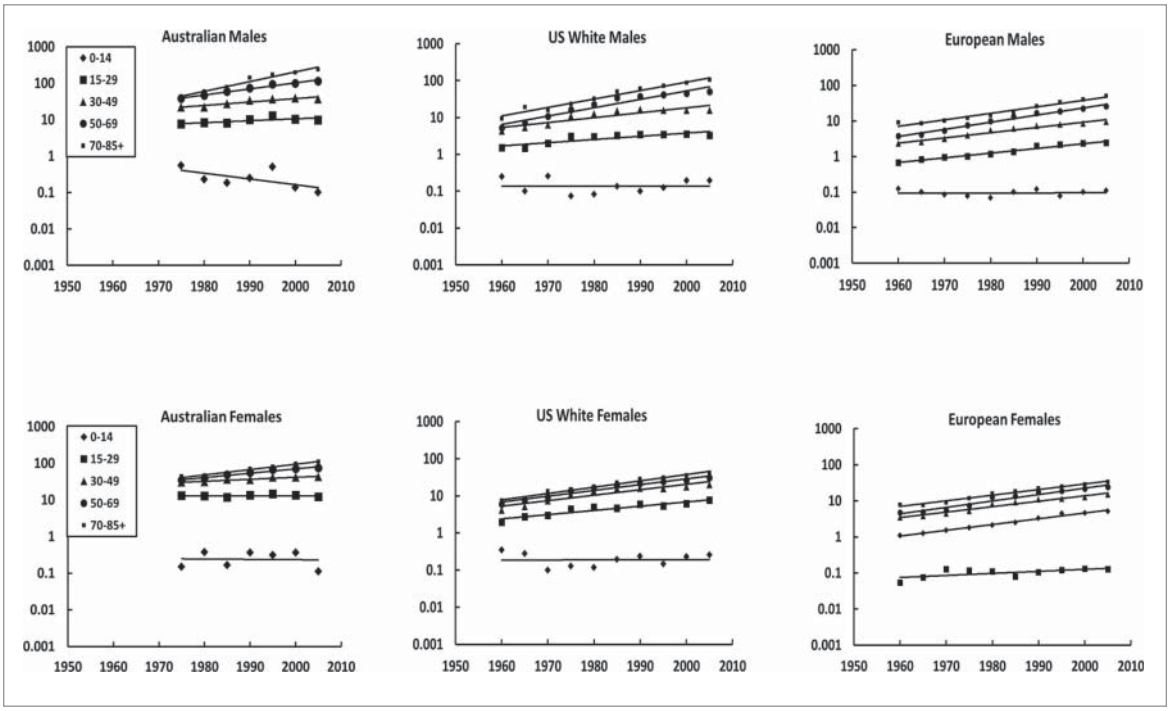

Figure 1. Age-standardized CMM cases per 100,000 people by year for males and females with Fitzpatrick skin type I–III.

in the incidence between the 2 youngest age groups, similar to, but not as pronounced as the skin type I-III population (Fig. 2 middle panels). The European-ancestry population in Spain is the only skin type III-IV population that exhibits an exponential increasing trend over time and appears to have a dramatic increase in the risk for CMM after age 14, similar to the skin type I-III European-ancestry population (Fig. 2 right panels).

The European-ancestry Italian (Fig. 3 left panels) and Israeli (Fig. 3 middle panels) skin type III-IV populations with olive skin tone also have increasing

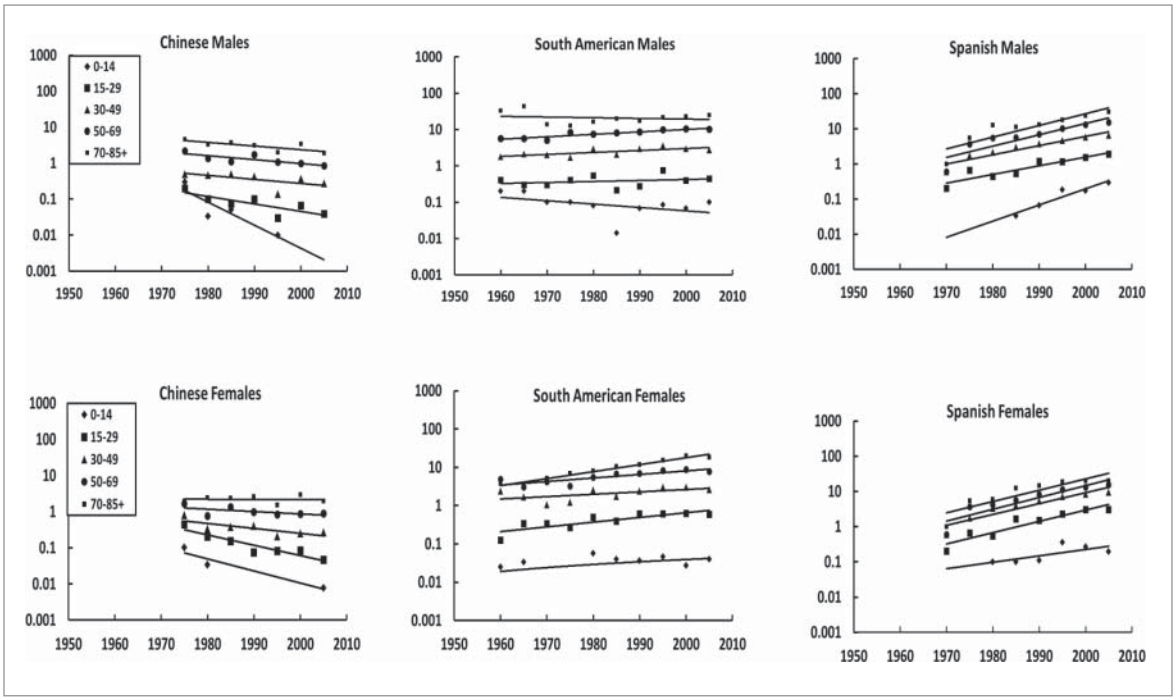

Figure 2. Age-standardized CMM cases per 100,000 people by year for males and females with Fitzpatrick skin type III–IV.

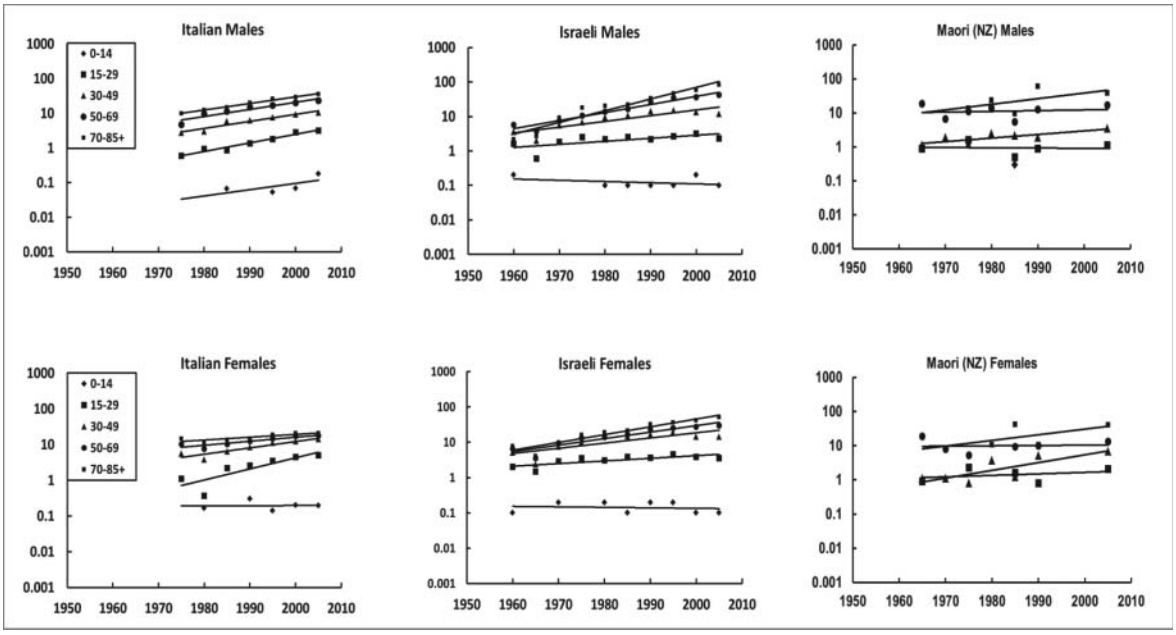

Figure 3. Age-standardized CMM cases per 100,000 people by year for males and females with Fitzpatrick skin type III–IV and IV–V.

temporal CMM incidence trends for both males and females over the age of 14 and also display the dramatic increase in the CMM incidence between the 2 youngest age groups. However, the native Maori Polynesian populations with skin type III-IV residing in New Zealand have CMM incidences that remained primarily unchanged over time for all male and female age groups (Fig. 3 right panels), similar to the native Hawaiian Polynesian population in Hawaii with skin type III-IV (results not shown). These Polynesian skin type III-IV populations, unlike the Italian or Jewish skin type III-IV populations, do not display this dramatic increase in the CMM incidence between the 2 youngest age groups.

The eastern Indian skin type IV-V (Fig. 4 left panels) and the African skin types III-VI (Fig. 4 middle

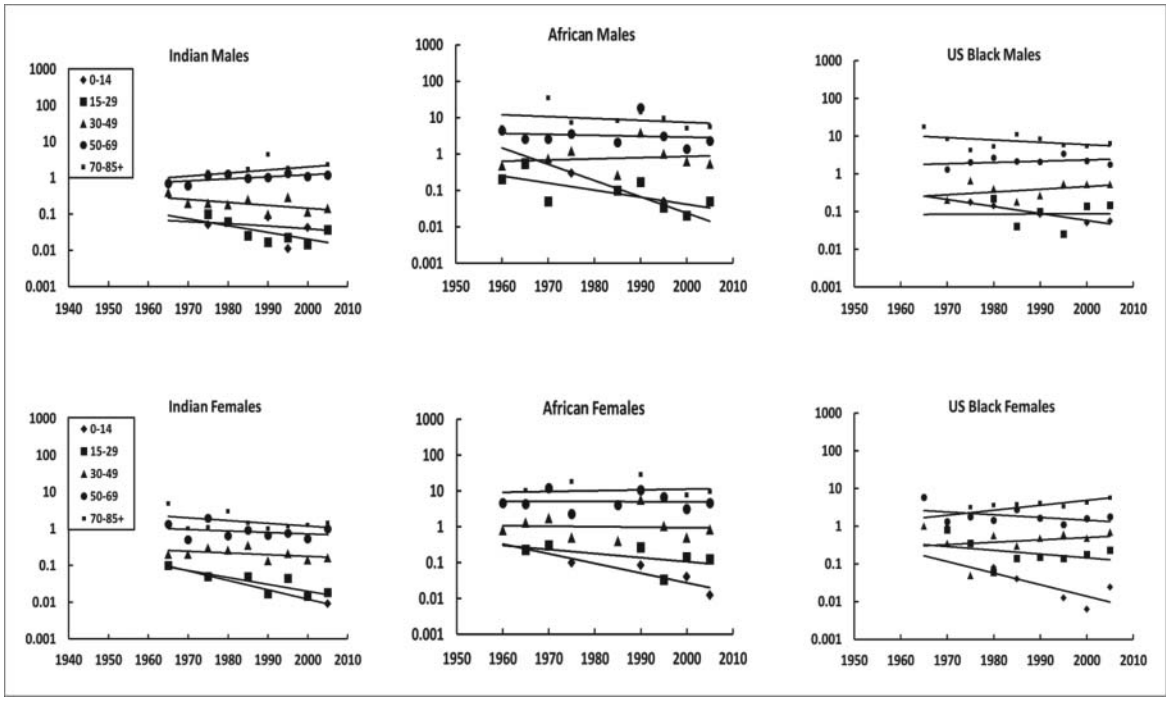

Figure 4. Age-standardized CMM cases per 100,000 people by year for males and females with Fitzpatrick skin type V–VI.

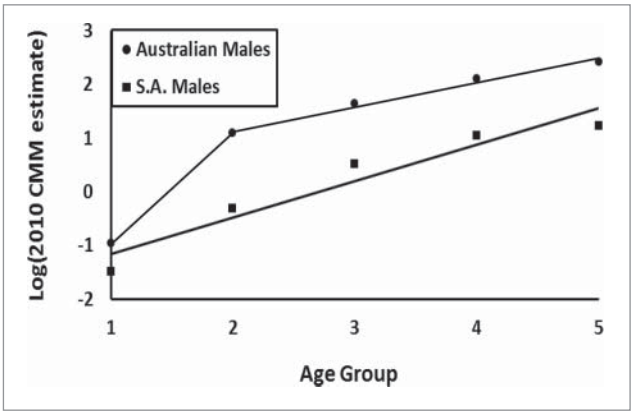

Figure 5. Vertical y-axis is the estimated log(CMM) at 2010 for either Australian (●) or South American (■) males and the horizontal x-axis has the 5 age groups in increasing order, i.e., age group 1 is the youngest 0–14 y. and age group 5 is the oldest, 70–85+.

panels) and US African-American (black) skin type IV-VI populations (Fig. 4 right panels) also do not have increasing temporal CMM incidence trends but rather appear to either remain stable or decrease over time depending on the age group. Note that these skin type III-VI populations also do not display the dramatic increase in the incidence between the 2 youngest age groups.

Curiously, regardless of skin type (I–IV) only the European-ancestry populations display a dramatic increase in the incidence of CMM between the 2 youngest age groups, i.e., 0–14 y. and 15–29 y., compared with the other age groups that have gradual increases. In Figure 5, we demonstrate the intensity (about 2 log units) of this change in the CMM incidence between the 2 youngest age groups using Australian males as an example of European-ancestry and contrast that result using South America males as an example of all other populations that do not display this dramatic increase.

Finally, we asked if the CMM increases in the incidences of males and females of different ages were significant over time for the skin type I-III populations and analyzed the US as an example (Table 1). The trends over time were significant for both males and females in all age groups over 14.

Table 1. Statistical analysis of CMM over time (1955–2007) for US males and females. Significance of regression for log(CMM incidence) versus time.

Age Group	Male R^2	Female R^2	Male p values	Female p values
0–14	0.01	0.02	0.78	0.73
15–29	0.77	0.93	1.0×10^{-3}	7.6×10^{-6}
30–49	0.68	0.94	3.0×10^{-3}	3.9×10^{-6}
50–69	0.98	0.99	4.1×10^{-8}	2.9×10^{-9}
70–85+	0.94	0.98	2.0×10^{-6}	4.1×10^{-8}

Discussion

For the first time, the CMM incidences over 5 decades (1955–2007) have been analyzed for males and females in all age groups (0–14, 15–29, 30–49, 50–69, 70–85+ yr.) with all Fitzpatrick skin types (I-VI) in 57 countries on 6 continents around the world. Previous studies ignored the youngest age groups (either below the age of 15 or 30), but we analyzed all age groups to obtain more clues into the etiology of CMM. We observe steady temporal exponential increases of CMM incidence exclusively in European-ancestry populations around the world regardless of skin type, I-III (Fig. 1; and in New Zealand and Canada, results not shown), III-IV with yellow skin tone (only in Spain, Figure 2 right panels) and III-IV with olive skin tone (both in Italy, Figure 3 left panels, and in Israel, Figure 3 middle panels). All other non-European-ancestry skin type III-VI populations around the world like the Chinese or South Americans, or the skin type IV-V populations in eastern Indian, or the skin type III-VI populations in Africa or the skin type IV-VI in the US have much lower CMM incidences that are either stable or slightly decrease over time (Figs. 2–4). Using the US as an example of the European-ancestry skin type I-III populations, we calculated p values that show significant trends over time in the CMM incidence for all age groups over 14 y. (Table 1). Surprisingly, we discovered a dramatic increase in the CMM incidence exists between the 2 youngest age groups, i.e., 0–14 and 15–29 yrs., in only the European-ancestry populations regardless of skin type (I-III or III-IV). We analyzed this dramatic increase in the CMM incidence by comparing Australian males with South American males to represent each scenario (i.e., European-ancestry versus non-European-ancestry) and found about a 2-unit log increase, or factor of about 100, exists only between the youngest Australian age groups (Fig. 5 top curve). Note here that the next 2-unit log increase requires the remainder of a person's entire lifetime to achieve. In contrast, the non-European-ancestry populations represented by the males in South America display a gradual increase in the CMM incidence for all the age groups (Fig. 5 bottom line).

What might explain the exponential increase in the incidence of CMM over the last 5 decades? One possible explanation is a contagious disease, e.g., viral infection. One viral infection found in CMM that has been increasing at an exponential rate in recent decades in at least Europe and the US is the Human Papilloma Virus (HPV).[31,32] Clinicians find both the cutaneous β HPV strains (e.g., HPV-38) and the high-risk mucosal α HPV strains (HPV-16 and 18) in acquired dysplastic nevi and in over half the CMM biopsies.[33,34] The high-risk mucosal α HPV strains immortalize melanocytes via their E6 and E7 proteins that inactivate 2 major apoptotic pathways (p53 and Bak, respectively), setting the scenario for expedient transformation.[35] In addition to HPV infection increasing exponentially over the last few decades, vitamin D levels have decreased dramatically from 1965 to 2010, as demonstrated by the inversely related parathyroid hormone levels that increased almost 10-fold during that period.[36] Vitamin D_3 levels have decreased over time due to less UVB exposure because people have been wearing more protective sunscreens[37] and have been spending more time indoors, further decreasing their exposure to UVB radiation while increasing their exposure to UVA radiation passing through glass windows in office buildings and cars.[3] Only UVA radiation can pass through glass, but rather than making vitamin D_3 like UVB radiation doses,[38] UVA only destroys it. The importance of vitamin D in CMM is demonstrated by the prediagnostic deficient and insufficient blood levels of melanoma patients[39] and by the fact that indoor workers have about half the vitamin D levels that outdoor workers have[40] and have a significantly higher risk (OR of about 1.6) for getting CMM than outdoor workers have (OR of about 0.8).[7] Mechanistically, vitamin D_3 can induce apoptotic cell death of melanoma cells[41] and enables their killing by activated T cells.[42] Interestingly, upon integration into the host genome, HPV can delete a large section of the DNA on chromosome 12q (12q13–15)[43] where the vitamin D receptor is located (12q13.11) removing yet another major apoptotic cell death pathway. Curiously, this section of the chromosome also includes CDK4, MDM2 and SAS and is found as an amplicon in many soft tissue tumors.[44] In addition, the seasonal fluctuations in vitamin D levels together with HPV infection expediting transformation may explain the noted seasonality of CMM diagnosis.[45] A recent study found the OR of vaccine-type HPV infections were increased to 2.19 for women who had insufficient (20–29 ng/ml) or deficient (12–19 ng/ml) vitamin D levels and increased to an OR of 2.9 for women with severe vitamin D deficiency (<12 ng/ml).[46] HPV infection occurs when vitamin D levels are low during the winter and spring months and promotion toward the cancerous state occurs during the summer months when UVB radiation is maximized[47] presumably because it causes immune suppression via soluble factors produced by skin cells. In an earlier study, we found a significant correlation between cervical and pharyngeal cancers - known to be caused by HPV infection - with increasing personal UVB dose (or decreasing latitude) in the US supporting a role for immunosuppressive soluble factors such as IL-10.[48] In support of a combined role for low vitamin D levels and HPV infection, we found the incidence of CMM increased significantly with lower personal UVB dose (or increasing latitude) *only* after 1960 in Europe.[49] If people wear sunscreens during the summer, they will make little vitamin D_3[37] and still produce immunosuppressive soluble factors from the UVA radiation increasing the risk for HPV-related cancers. Thus, it appears that deficient and even insufficient levels of vitamin D along with immune suppression increases the likelihood of having a prevalent HPV infection, which may increase the risk for getting CMM.

What might explain the 2 orders of magnitude dramatic increase in the CMM incidence between the 2 youngest age groups (0–14 and 15–29) that occurs exclusively in the European-ancestry populations around the world? The common explanation of lighter skin color does not explain this dramatic increase because, besides our findings, others found no significant difference exists in the CMM incidence between skin type I/II and III/IV Europeans ($p = 0.79$)[50] or Americans.[23] One plausible explanation is the hormonal changes that occur during puberty associated with growing androgenic body hair, the distribution of which[51] aligns well with the distribution of CMM.[9,52] Both androgenic body hair and CMM occur most frequently on the face, neck, and torso of males and the lower limbs of females. In addition to CMM and nevi,[32,33] HPV is also found in hair follicles that are reservoirs for persistent HPV infection[3] because they are immune-privileged sites.[54] Androgenic body hair may explain the dramatic increase in CMM incidence observed exclusively in people of European-ancestry over the age of 14 regardless of skin type because they

apparently have the most androgenic body hair of all the worlds' populations. For ages 14 and under, vellus hair appears to play a role in CMM.[55]

But why does the CMM incidence continue to increase with advancing age if it is not dependent on the cumulative UVB dose? One possible explanation is the aging process itself, which results in several body changes including increasing amounts of reactive oxygen species producing more oxidative DNA mutations and white hair along with thinning of the epidermis of skin producing less vitamin D_3.[56] Human white hair may be important in the etiology of CMM for 2 reasons; it represents increased production of reactive oxygen species[57] and it may allow transmission of UV down the hair shaft delivering higher doses of UVA along with some UVB to the melanocytes in the follicular bulge.[58] Although white hair does not technically act like a fiber optic cable, it does allow transmission of UVA and UVB down the hair shaft (Fig. 3 in reference 58), which may explain why people over the age of 50 get CMM on body sites that received continual sun exposure.[52] People of European-ancestry with red hair may be at the highest risk for getting CMM because their hair begins to turn white at the youngest age (in their 20s) compared with other skin type I-III people who have darker hair that begins to turn gray in their 30s; people of Asian-ancestry with brown/black hair begin to turn gray in their late 30s; people of African-ancestry with brown/black hair begin to turn gray in their 40s.[57] More importantly, redheads change directly from red to white hair without passing through the gray hair stage, as all other people do. Some evidence for the idea that white hair allows transmission of UVA (and visible light) and UVB to irradiate follicular melanocytes can be found in the gray horse model that has protective black skin and only gets melanoma after its gray hair turns white.[59]

Conclusions

The incidence of CMM has been gradually increasing in an exponential manner over the past several decades and increases dramatically after the age of 14, implicating androgenic melanocytes may be involved, but only in people of European-ancestry. In addition, CMM may develop through 2 major pathways; one observed in the younger populations (<50) that may be primarily affected by vitamin D_3 and may be UVA and Visible light-driven through skin to follicular vellus and androgenic melanocytes and the other observed in the older populations (>50) that may be partially affected by vitamin D_3 and may be UVA&UVB-driven through thinner skin and possibly through white hair to androgenic follicular melanocytes. Note that both pathways may be accelerated by HPV infection. If our hypothesis is true, we would expect to see a decrease in the incidence of CMM over the next few decades if everyone gets the HPV vaccination.

Abbreviations

CMM	cutaneous malignant melanoma
HPV	Human Papilloma Virus
OR	odds ratio
US	United States
UVR	Ultraviolet Radiation (290–400 nm)
UVA	Ultraviolet-A (316–400 nm)
UVB	Ultraviolet-B (290–315 nm)

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No potential conflicts of interest were disclosed.

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