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# Increasing Incidences of Cutaneous Malignant Melanoma by Region Around the World

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## 1. Introduction

For decades, cutaneous malignant melanoma (CMM) has been steadily increasing among indoor workers in industrialized countries around the world [Godar et al 2009; Godar submitted]. Scientists believe strong, intermittent UVB (290-320 nm) exposures, i.e., sunburn episodes, initiate CMM [Elwood et al 1985], and some believe the UVA (321-400 nm) passing through glass windows in offices and cars promotes it [Godar et al 2009]. In support of those possibilities exists the paradox between indoor and outdoor worker's UV exposures and their incidences of CMM. Although outdoor workers get three to ten times the annual UV doses that indoor workers get [Godar et al 2001; Godar 2005], they have similar or lower incidences of CMM [Gandini et al 2005; Kennedy et al 2003].

To understand what factor(s) may be responsible for the increasing incidence of CMM among indoor workers, we must know the temporal incidence by region around the world, especially by latitude [Godar, In press]. The causative agent of CMM is probably UVB-initiated sunburn episodes [Elwood et al 1985], but the promoting agent is unknown and may be UVA passing through office windows and cars [Godar et al 2009], and earlier (<1988) through UVB-absorbing sunscreens [Gorham et al 2007]. However, there could be a different promoting agent or an additional promoting agent; whatever the promoting agent(s) are, they must have entered and/or left our environment years before the first observed increase in Connecticut, USA in 1935 [EPA 1987; Rousch et al 1988].

We can analyze the CMM incidences of indoor working, industrialized populations over time and by latitudinal regions to get clues to the nature of the promoting agent(s). In this book chapter, we will explore the incidence of CMM all over the world during two decades, 1980 and 2000, by latitudinal regions of each fair-skinned continent: Europe, North America, and Australia (including New Zealand).

## 2. Analysis methods

We can obtain the CMM incidence data for Australia, New Zealand, USA, Canada, and Europe from the International Agency for Research on Cancer (IARC) [Doll et al 1966; Doll et al 1970; Waterhouse et al 1976; Waterhouse et al 1982; Muir et al 1987; Parkin et al 1992; Parkin et al 1997; Parkin et al 2002; Curado et al 2007].

We can average the CMM incidence data of IARC from the following regions for the years 1980 and 2000 to get mean latitudes or latitudinal ranges for each region in a country or continent:

1. Northern Europe (~65°N; range ~60-70°N) - Iceland, Norway, Sweden, and Finland,
2. Middle Europe (~55°N, <20°E; range ~50-60°N) - Ireland, Northern Ireland, Scotland, England, Denmark, the Netherlands, Belgium, and Germany, and either includes or excludes the following countries ≥20°E: Poland, Estonia, Latvia, Lithuania, and Belarus,
3. Southern Europe (~45°N; range 40-50°N) - France, Switzerland, Austria, Czech Republic, Slovakia, and Croatia, and either includes or excludes countries with predominately skin types ≥III: Portugal, Spain and Italy,
4. British Isles data from the year 2000 for the following regions (~53°N, range ~51-56°N): (~54.5°N) Scotland, Northern Ireland, Northern and Yorkshire, (~53.5°N) Ireland, North Western, Merseyside and Cheshire, Trent; (~52.5°N) West Midlands, East Anglia; (~51.5°N) South and Western, Oxford, and Thames,
5. Northernmost Canada and USA (~65°N; ~60-70°N) - Northwest Territories and Alaska,
6. Northern Canada (~55°N; range ~50-60°N) - British Columbia, Alberta, Saskatchewan, Manitoba, and Ontario,
7. Southern Canada (~45°N; range ~40-50°N)- Newfoundland and Quebec; Nova Scotia, New Brunswick, and Prince Edward's Island,
8. Northern USA (~45°N; range ~40-50°N) - Washington, Oregon, Idaho, Montana, Iowa, Wisconsin, Illinois, Indiana, Michigan, Ohio, Pennsylvania, District of Columbia, New Jersey, New York (excludes New York City), Vermont, Rhode Island, Massachusetts, and Maine (2000 yr data was not available for the other states: New Hampshire, Delaware, Maryland, North and South Dakota, Minnesota, Nebraska, Wyoming, and Nevada),
9. Southern USA (~35°N; range ~30-40°N) - California, Arizona, Utah, Colorado, New Mexico, Oklahoma, Texas, Missouri, Louisiana, Kentucky, Alabama, Georgia, South Carolina, Virginia, and Florida (2000 yr data was not available for the other states: Kansas, Arkansas, Mississippi, Tennessee, and North Carolina);
10. Southernmost USA (~20°N) - Hawaii,
11. Southern Hemisphere - Australia - (~19°S) Townsville, Queensland; (range ~20-29°S) Queensland, Western, (32°S) South; (range 30-39°S) New South Wales, Capital Territory, Victoria; (range <39°S) Tasmania and New Zealand
12. New Zealand 1980 regional plots - (~40.5°S; range 34.5-47°S) - (36°S) Northern, (38°S) Midland, (41°S) Central, and (44°S) Southern [regional values are from Bulliard et al 1994],

Figure 1 has averaged IARC data from numbers 1-3 above that either includes (circles) or excludes (squares) Eastern European and Southern European countries. Figure 2 has averaged IARC data from number 4 above. Figure 3 has averaged IARC data from numbers 5-10 above. Figure 4 has averaged IARC data from number 11 above. Figure 5 A and B have data from 12 above [Bulliard et al 1994].

### 3. Results

Figure 1 shows the incidences of CMM in the year 2000 for Europe. The values shown were averaged by latitudinal ranges ~40-50°N (~45°N), ~50-60°N (~55°N) and >60°N (~65°N). The lines with circles in the figure represent all the available European data. The lines with

squares represent the European data with excluded Eastern European ( $\geq 20^{\circ}\text{E}$ ) countries from latitudes  $50^{\circ}\text{N}$  to  $60^{\circ}\text{N}$ , i.e., Poland, Estonia, Lithuania, Belarus, Lithuania and Latvia, and excluded southern European countries from latitudes  $\sim 40^{\circ}\text{N}$  that have predominately people with skin type III or more, i.e., Spain, Portugal and Italy. Excluding the Eastern European countries and the Southern European countries did not change the trend. The data shows a flat incidence rate of CMM from about  $40^{\circ}\text{N}$  to  $55^{\circ}\text{N}$  and then an increasing incidence with increasing latitude above that.

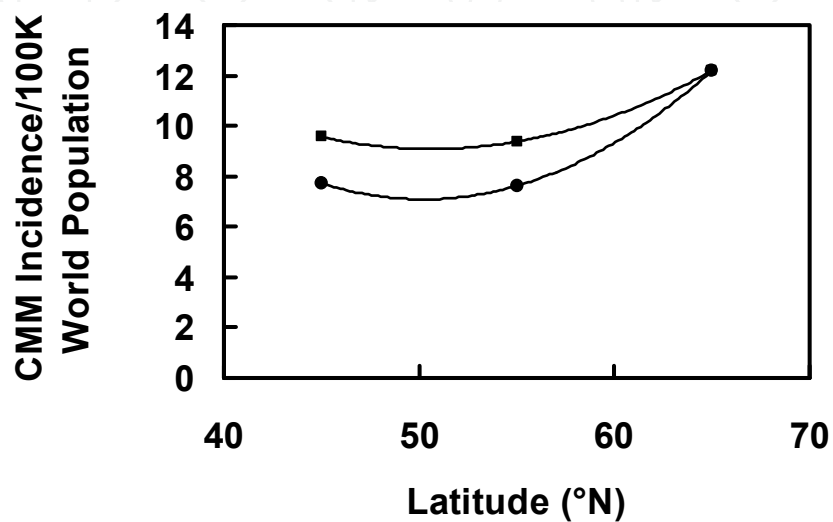


Fig. 1. The CMM incidences in the year 2000 for Europe averaged by latitudinal ranges  $\sim 40$ - $50^{\circ}\text{N}$  ( $\sim 45^{\circ}\text{N}$ ),  $\sim 50$ - $60^{\circ}\text{N}$  ( $\sim 55^{\circ}\text{N}$ ) and  $>60^{\circ}\text{N}$  ( $\sim 65^{\circ}\text{N}$ ). The circles include all the data (see the Analysis section), while the squares exclude the Eastern European countries from latitudes  $50^{\circ}\text{N}$  to  $60^{\circ}\text{N}$ , Poland, Estonia, Lithuania, Belarus, Lithuania and Latvia, and the countries with predominately skin types  $\geq \text{III}$ , i.e., Spain, Portugal and Italy.

Figure 2 shows the CMM incidences in the year 2000 for the British Isles: Ireland, Northern Ireland, Scotland and regions in England. A minimum appears to occur around  $53.5^{\circ}\text{N}$ .

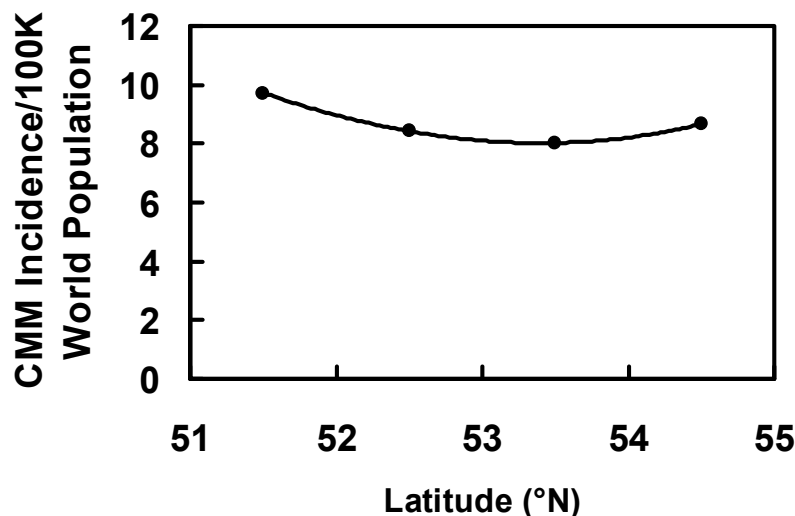


Fig. 2. The CMM incidences in the year 2000 for the British Isles: Ireland, Northern Ireland, Scotland and regions in England.

Figure 3 shows the CMM incidences in the year 2000 for North America: Canada and USA (includes Hawaii and Alaska). The CMM incidence decreases with increasing latitude and are unlike the Western European incidences that increase with increasing latitude above  $\sim 50^{\circ}\text{N}$ .

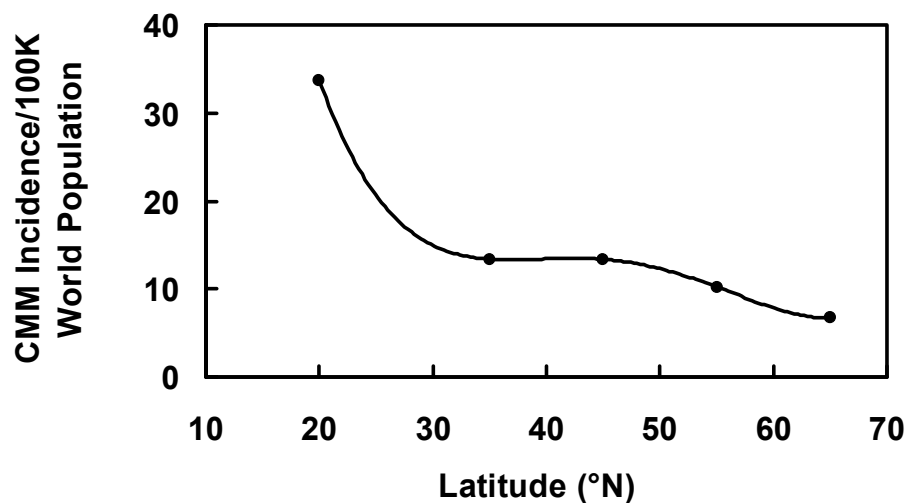


Fig. 3. The CMM incidences in the year 2000 for North America: Canada and USA (includes Hawaii and Alaska).

Figure 4 shows the CMM incidences in the years 1980 and 2000 for Australia by latitude. The CMM incidence decreases with increasing latitude until  $\sim 35^{\circ}\text{S}$  where it appears to increase somewhat with increasing latitude in 2000.

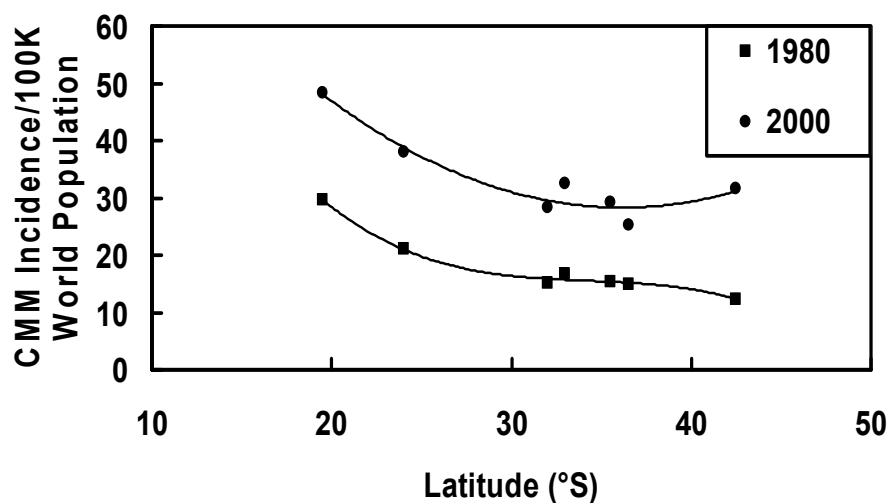


Fig. 4. The CMM incidences in the years 1980 and 2000 for Australia by latitude.

Figure 5A shows an exponential increasing incidence of CMM with latitude in the southern hemisphere. New Zealand by region (1980): Northern ( $36^{\circ}\text{S}$ ), Midland ( $38^{\circ}\text{S}$ ), Central ( $41^{\circ}\text{S}$ ), and Southern ( $44^{\circ}\text{S}$ ). Figure 5B shows the temporal exponential increase in the incidence of CMM from 1970 to 1985 in the different regions of New Zealand by latitude. There is an exponential increase in the incidence of CMM with increasing latitude and an exponential increase in the incidence of CMM over time as well.

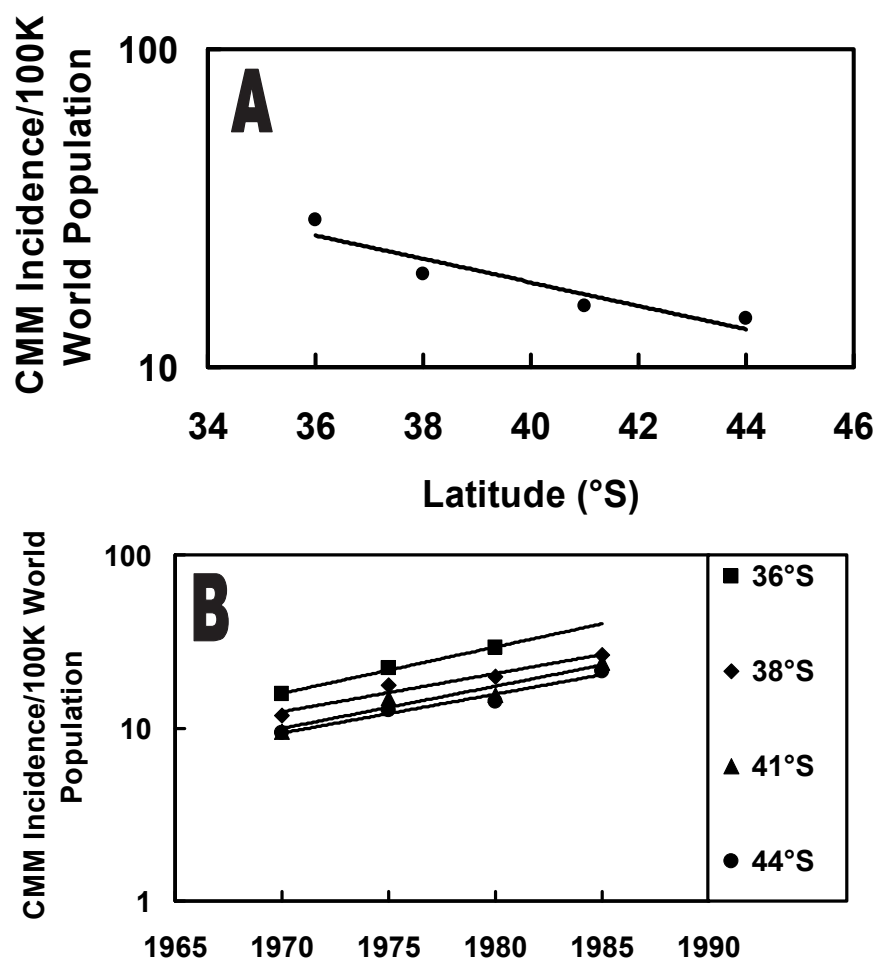


Fig. 5. **A)** Exponential increasing incidence of CMM with latitude in the southern hemisphere. New Zealand (1980) by region: Northern (36°S), Midland (38°S), Central (41°S), and Southern (44°N). **B)** The temporal exponential increase in the incidence of CMM from 1970 to 1985 in different regions of New Zealand by latitude.

#### 4. Discussion

The incidences of CMM in fair-skinned, indoor-working people have been steadily increasing in industrialized nations worldwide for decades (Godar et al 2009; Godar submitted). The regions of the world with the lowest CMM incidences are in Southern and Middle Europe ~40-60°N whether or not Eastern and Southern European countries are included or excluded from the analysis (Figure 1). However, regional data for the British Isles begins to show an increasing incidence with increasing latitude around 53.5°N (Figure 2).

That trend is counterintuitive because the amount of UVB present in the terrestrial spectrum decreases with increasing latitude, suggesting something else must be increasing the incidence of CMM with increasing latitude. Separate analysis of the data for the Eastern European countries, Poland, Estonia, Latvia, Lithuania including Saint Petersburg, Russia, gives an incidence of 4.73 (4.82 if Russia is excluded) half the value of Western European countries, which may be due to socio-economic status and/or vacation choices. In North America, there is clearly an increasing incidence of CMM with decreasing latitude (Figure

3); one does not observe the same trend as seen in Europe where an inversion in the incidence of CMM occurs near 53°N. Unlike Europe, the trend in North America continues to decrease with increasing latitude. This may be due to a cultural difference between Northern Europeans and Northern Canadians and Alaskans because we know Northern Europeans tend to take extended vacations at lower latitudes, e.g., Mediterranean. At lower latitudes, they can get sunburned to initiate CMM and then return to their country above 50°N, where there is more UVA relative to UVB, to promote CMM growth the rest of the year. We obtain a clue that vacation choice might be responsible by analyzing the southern Hemisphere data for the years 1980 and 2000 (Figure 4), where during 1980 we see a similar trend as observed in North America in the year 2000, but the trend changes to what we see in Europe in the year 2000. This upward change in the CMM trend for the lower latitudinal regions may be due to increased air travel over the decades leading to more people vacationing closer to the sunny equator. In 1980, New Zealanders displayed an exponential increasing incidence of CMM with increasing latitude (Figure 5A) that increased exponentially over time (Figure 5B). However, the temporal exponential increase with latitude is not only true of New Zealand but is also true for some other countries and regions around the world.

Whether the incidence of CMM is increasing exponentially or not does not change the fact that it is increasing at an alarming rate each year. In order to slow or stop this increasing trend, we must know what is causing it and, if possible, change it. We know whatever started the increasing incidence of CMM either entered or left our environment before 1935, because that is when we have documented data for the first increases in CMM in the USA (Godar et al 2009; Godar In Press). From that data, we know that nothing that came out after the increasing CMM trend began can be responsible for starting it. For example, fluorescent lights (~1938 ([http://wweu.wikipedia.org/wiki/Fluorescent\\_lamp](http://wweu.wikipedia.org/wiki/Fluorescent_lamp)), sunscreens (early 1950's for UVB absorbing and in 1988 for UVA and UVB absorbing; <http://en.wikipedia.org/wiki/Sunscreen>), and tanning devices (~1978; [http://en.wikipedia.org/wiki/Tanning\\_bed#History](http://en.wikipedia.org/wiki/Tanning_bed#History)) all entered our environment *after* the increasing incidence of CMM was first documented in the USA back in 1935 [EPA, 1987; Rousch et al 1988]. Thus, we should analyze what happened *before* 1935, during the early 20<sup>th</sup> century, in order to discover what might have affected the incidence of CMM.

During the early 20<sup>th</sup> century, people in industrialized countries went against evolution by working indoors during the day. That action alone drastically decreased their daily amount of cutaneous vitamin D<sub>3</sub> and simultaneously exposed them to only UVA radiation passing through glass windows in offices [Godar et al 2009] and cars [Moehrle et al 2003]. People created an artificial UV barrier with window glass that divides the UVB from the UVA, so that the vitamin D-making UVB wavelengths [MacLaughlin et al, 1982] were excluded while only the vitamin D-breaking [Webb et al 1989] and DNA-mutating UVA wavelengths [Peak and Peak 1991; Jones et al 1987; Halliday et al 2005] were included in our indoor-working environment. Possibly because this unnatural UV environment existed for decades in buildings and later in cars [Moehrle et al 2003], CMM was promoted by UVA, after being initiated by UVB sunburns, and began to steadily increase in the mid-1930's or before.

We also know the ratio of UVA to UVB increases with increasing latitude and that CMM increases with latitude above ~53°N. Evidently, people who live above 50°N go to the beach during the summer and get sunburned at lower latitudes, where they are unfamiliar with the sun's intensity, to initiate CMM, and then they return home to northern latitudes that have primarily UVA for most of the year (inside as well as outside) to promote CMM. The

higher latitudes also allows the sun to aim more often at a perpendicular angle to the window glass where more UVA can pass through and directly expose people's skin during their workday [Pope and Godar 2010]. Furthermore, above  $\sim 50^\circ\text{N}$  there is little UVB to make cutaneous vitamin  $\text{D}_3$  most of the year [Webb et al 1988]. Above  $37^\circ\text{N}$ , a vitamin  $\text{D}_3$  "winter" occurs from at least November to February, which extends to October and March at higher latitudes, when the dose-rate of UVB is too low to make any previtamin  $\text{D}_3$ . In contrast, UVB exposure during peak hours occurs to some extent to outdoor workers during their workweek, so that they can maintain adequate levels of vitamin  $\text{D}_3$  in their skin and blood for most of the year. The blood levels of vitamin D (measured as 25-hydroxyvitamin D in serum) in outdoor workers who get about five times the solar UV dose that indoor workers get is about twice as high as indoor workers [Devgun et al 1981]. Increased cutaneous vitamin D levels, and natural exposure to UVA and UVB together, might explain why outdoor workers have a lower incidence of CMM compared to indoor workers, although they get 3-10 times more UV exposure.

The reason vitamin  $\text{D}_3$  is important for controlling CMM is because most melanoma cells can directly convert it to the hormone calcitriol [Reichrath et al 2007]. Calcitriol controls the growth rate [Eisman et al 1987; Colston et al 1981; Frampton et al 1983] and apoptotic cell death [Danielson et al 1998] of melanoma cells, while it also affects the immune system [Yang et al 1993a, b] and inhibits tumor promotion [Chida et al 1985]. Increased blood levels of vitamin D might be responsible for increasing the survival of melanoma patients who get regular, moderate sun exposures [Berwick et al 2005; Newton-Bishop et al 2011]. Thus, intermittent, strong UVB-induced sunburns may initiate CMM, while low cutaneous vitamin D levels and UVA-induced DNA damage may promote CMM.

## 5. Conclusions

The incidence of CMM is increasing at an alarming rate around the world in indoor working industrialized populations. In most regions of the world, the CMM incidence decreases with increasing latitude. However, in Europe the incidence appears flat up to  $\sim 50^\circ\text{N}$  where it begins to increase with increasing latitude. This may occur because there is more UVA relative to UVB for most of the year at higher latitudes. Windows that allow UVA to enter our vitamin D-deprived indoor-working environments and cars may be partly responsible for the increasing incidence of CMM. If this is true, we can lower the incidence or the rate of increase by simply placing UV filters on our office and car windows to help reduce CMM worldwide.

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## **Advances in Malignant Melanoma - Clinical and Research Perspectives**

Edited by Dr. April Armstrong

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This book titled *Advances in Malignant Melanoma - Clinical and Research Perspectives* represents an international effort to highlight advances in our understanding of malignant melanoma from both clinical and research perspectives. The authors for this book consist of an international group of recognized leaders in melanoma research and patient care, and they share their unique perspectives regarding melanoma epidemiology, risk factors, diagnostic and prognostic tools, phenotypes, treatment, and future research directions. The book is divided into four sections: (1) Epidemiology and Risk Factors of Melanoma, (2) Clinical Phenotypes of Melanoma, (3) Investigational Treatments for Melanoma and Pigmentary Disorders, and (4) Advances in Melanoma Translational Research. This book does not attempt to exhaustively cover all aspects of the aforementioned topics. Rather, it is a compilation of our authors'™ pearls and unique perspectives on the relevant advances in melanoma during the recent years.

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