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Exponentially Increasing Incidences of Cutaneous Malignant Melanoma in Europe Correlate with Low Personal Annual UV Doses and Suggests 2 Major Risk Factors

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Exponentially increasing incidences of cutaneous malignant melanoma in Europe correlate with low personal annual UV doses and suggests 2 major risk factors

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For several decades the incidence of cutaneous malignant melanoma (CMM) steadily increased in fair-skinned, indoor-working people around the world. Scientists think poor tanning ability resulting in sunburns initiate CMM, but they do not understand why the incidence continues to increase despite the increased use of sunscreens and formulations offering more protection. This paradox, along with lower incidences of CMM in outdoor workers, although they have significantly higher annual UV doses than indoor workers have, perplexes scientists. We found a temporal exponential increase in the CMM incidence indicating second-order reaction kinetics revealing the existence of 2 major risk factors. From epidemiology studies, we know one major risk factor for getting CMM is poor tanning ability and we now propose the other major risk factor may be the Human Papilloma Virus (HPV) because clinicians find β HPVs in over half the biopsies. Moreover, we uncovered yet another paradox; the increasing CMM incidences significantly correlate with decreasing personal annual UV dose, a proxy for low vitamin D_3 levels. We also discovered the incidence of CMM significantly increased with decreasing personal annual UV dose from 1960, when it was almost insignificant, to 2000. UV and other DNA-damaging agents can activate viruses, and UV-induced cytokines can hide HPV from immune surveillance, which may explain why CMM also occurs in anatomical locations where the sun does not shine. Thus, we propose the 2 major risk factors for getting CMM are intermittent UV exposures that result in low cutaneous levels of vitamin D_3 and possibly viral infection.

Introduction

For several decades the incidence of cutaneous malignant melanoma (CMM) has steadily increased in fair-skinned, indoor-working people around the world.[1-10] Scientists are not sure why CMM has steadily increased over time but from epidemiology studies, we know that the numbers of benign naevi, light skin and hair, and poor tanning ability are involved in the etiology.[11] We can find clues as to what may contribute toward CMM in the paradox between indoor and outdoor worker's CMM incidences and their personal annual UV (290–400 nm) doses. Outdoor workers get 3–10 times the annual UV dose that indoor workers get,[12] yet they have lower incidences of CMM and have half the odds ratio (OR of about 0.8) that indoor workers have (about 1.6) for getting CMM.[13-16] From this data, one can conclude that something other than cumulative UV dose is primarily involved in the etiology of CMM.

Most scientists believe intermittent UV exposures resulting in sunburns initiate CMM,[14] but the creation and use of sunscreens did not reduce the incidence. Sunscreens with primarily UVB (290–315 nm) protection were available from the early 1950s until 1988, and sunscreens with both UVB and UVA (316–400 nm) protection were available since 1988 with increasing SPF numbers over the years (http://en.wikipedia.org/wiki/Sunscreen). Some

scientists think strong UVA exposures allowed by older sunscreen formulations can also initiate CMM[17] with unique signature mutations,[18] while others believe the UVA passing through the glass of office[10] and car windows[19] promotes it. We now know that UVA can possibly also cause both initiation and promotion of CMM because like UVB it causes similar DNA damage, i.e., cyclobutane pyrimidine dimers.[20] Additionally, UVA causes oxidation of DNA bases in the cytosol prior to incorporation into the genomic DNA by polymerase eta[21,22] and causes DNA adduct formation in the presence of photosensitizers[23] that people can ingest from common foods.[24] Sunburns probably are not involved in the initiation or propagation of melanoma because a melanoma study using the opossum animal model, *Monodelphis domestica*, ironically showed intense sunburn doses of UVB gave significantly fewer melanomas than sub-erythemal doses.[25] UVB exposures of skin creates cutaneous vitamin D_3 production[26] that sunscreens dramatically reduce.[27] Furthermore, contrary to popular belief, outdoor workers get numerous sunburns[28–31] reviewed by Glanz.[32]

The major risk factors involved in CMM had to exist prior to the first documented increase in the incidence in 1936 (Connecticut, United States).[33] To understand how many major risk factors are responsible for the increasing incidence of CMM, we must know the temporal incidences as far back as possible to discern if the increase is linear (one major risk factor) or exponential (interaction between 2 major risk factors). For this reason, we analyzed the fair-skinned European countries' CMM incidences over time and personal annual UV dose for males and females from 1955 to 2000 using data from the International Agency for Research on Cancer (IARC). We found an exponential increase in the incidence of CMM, implicating 2 major risk factors. In addition, we found CMM increases with decreasing personal UV dose, implicating low cutaneous vitamin D_3 levels as one of the major risk factors. We suggest the other major risk factor, besides the germline incorporated Human Endogenous Retrovirus (HERV) that is already implicated in the etiology of CMM and other cancers,[34] may be HPV infection because clinicians found it in over half the CMM's biopsied.[35-38]

Materials and Methods

Temporal analysis

We analyzed the CMM incidences at 5-year interval midpoints from 1955 to 2000 for European countries using IARC's age-adjusted, world population normalized data.[1–9] We aggregated the regional registries for England, Germany, Poland, France, and Switzerland to estimate national incidence trends.

The temporal CMM data plotted in **Figure 1** for all European countries was from the averaged data in **Table 1A** and the western (<17 °E) and eastern (>17°E) countries were plotted from the averaged data in **Tables 1B and 1C**, respectively. Because we wanted to compare the European CMM incidences of white people (skin types I and II),[39] we excluded countries that had populations with primarily skin types III or darker (e.g., Italy, Spain, and Portugal). To show a lack of bias, we
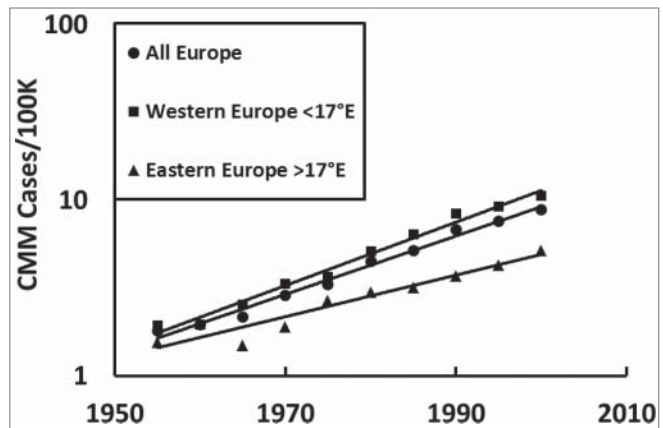

Figure 1. Temporal CMM incidences among fair-skinned people in Europe (plotted from the averaged data in **Table 1A**), western Europe <17°E (**Table 1B**), and eastern Europe >17°E (**Table 1C**). Note the exponential increase in CMM over the decades (semi-log plot). See statistical data in **Table 5A**.

also analyzed the data of all the countries listed in Table 1A and included Italy, Spain, and Portugal and found a similar exponential increase in the CMM incidences with a slightly reduced slope (results not shown). The temporal data in **Figure 2** was plotted from the averaged data in **Table 2** for countries located every 5°N from 46–50°N, 51–55°N, 56–60°N to over 60°N. In **Figure 3**, we compare female and males in the northern (averaged 46–55°N for ~50°N) and southern (averaged all countries above 55°N for ~60°N) regions of Europe from the averaged data in **Table 3**. In some of our analyses (**Fig. 2**

Table 1A. European countries with CMM incidence data (24 countries averaged in **Fig. 1**).

All Europe	°N	1955	1960	1965	1970	1975	1980	1985	1990	1995	2000
Romania	46			0.60	1.45	2.90	1.40	2.20			
Slovenia	46		1.35	1.85	2.35	1.95	2.55	3.80	5.05	6.80	8.85
Switzerland	47					4.89	6.85	8.83	10.30	12.10	15.21
France	47					2.53	3.32	4.07	5.31	7.23	8.41
Hungary	48			1.85	1.73	2.30	2.73	3.60			
Austria	48								14.00	10.90	11.02
Slovakia	49					2.50	3.70	3.80	4.40	5.05	6.35
Czech	50							5.45	6.30	8.00	9.35
Poland	51			1.30	1.55	1.90	2.34	2.49	3.24	3.91	4.67
Germany	51			2.00	2.20	2.25	3.83	4.45	5.55	6.20	8.77
Belgium	51									5.23	6.2
Netherlands	52		1.70			2.54	4.95	5.03	7.62	9.48	11.12
England	52		1.44	1.67	1.90	2.27	3.15	4.37	6.11	7.13	8.45
Ireland	53					4.50	6.30	8.55	8.50	9.20
Belarus	54						1.80	2.10	2.50	3.10
Lithuania	55							2.55	3.3	4.45
Denmark	56	1.9	2.7	3.9	5.4		7.15	8.75	10.3	12	13
Scotland	57			1.5	2.45	3	3.74	5.77	7.03	8.5	9.25
Latvia	57							2.45	2.55	3.35	3.7
Estonia	59						2.9	3.85	4.55	5.95
Sweden	62		2.60	3.20	4.50	5.45	7.70	9.55	11.05	11.85	12.00
Iceland	63		1.25		2.60		3.85	4.55	5.45	8.65	14.15
Norway	64	1.99	2.65	3.80	5.55	8.30	9.70	12.00	14.70	15.20	14.40
Finland	65	1.55	2.00	2.20	2.85	3.85	4.80	6.30	7.25	7.35	8.15
Average	53	1.81	1.96	2.17	2.88	3.33	4.48	5.16	6.82	7.62	8.9

Table 1B. Western European countries <17°E with CMM incidence data (15 countries averaged in **Fig. 1**).

West Europe <17°E	°N	1955	1960	1965	1970	1975	1980	1985	1990	1995	2000
Slovenia	46		1.35	1.85	2.35	1.95	2.55	3.80	5.05	6.80	8.85
Switzerland	47					4.89	6.85	8.83	10.30	12.10	15.21
France	47					2.53	3.32	4.07	5.31	7.23	8.41
Austria	48								14.00	10.90	11.02
Czech	50							5.45	6.30	8.00	9.35
Germany	51			2.00	2.20	2.25	3.83	4.45	5.55	6.20	8.77
Belgium	51									5.225	6.2
Netherlands	52		1.70			2.54	4.95	5.03	7.62	9.48	11.12
England	52		1.44	1.67	1.90	2.27	3.15	4.37	6.11	7.13	8.45
Ireland	53						4.50	6.30	8.55	8.50	9.20
Denmark	56	1.9	2.7	3.9	5.4		7.15	8.75	10.3	11.95	13
Scotland	57			1.5	2.45	3	3.74	5.77	7.03	8.5	9.25
Sweden	62		2.60	3.20	4.50	5.45	7.70	9.55	11.05	11.85	12.00
Iceland	63		1.25		2.60		3.85	4.55	5.45	8.65	14.15
Norway	64	1.99	2.65	3.80	5.55	8.30	9.70	12.00	14.70	15.20	14.40
Average	53	1.95	1.96	2.56	3.37	3.69	5.11	6.38	8.38	9.18	10.62

and **3**), we included a country only if it had more than 50% of the 5-year averaged CMM incidence data; countries excluded were Austria, Czech, Belarus, Belgium, Estonia, Hungary, Ireland, Latvia, Lithuania, and Romania.

Personal annual UV dose analysis

Latitude is a proxy for personal annual UV doses. For populations living in the regions analyzed and plotted in **Figure 4**, the average annual personal UV doses were calculated from the equation derived from the slope of the line ($R^2 = 0.99$) from several countries known population's UV doses after geometric conversion from planar to cylinder measurements, which represent the human body.[40] The countries that generated this equation with average annual personal UV doses were Sweden (60°N; 5,200 J/m^2), Denmark (55°N; 6,800 J/m^2), the Netherlands (52.5°N; 7,000 J/m^2), and the US (34°N, 10,000 J/m^2 and 44°N, 12,000 J/m^2):

$$UVdose = -280X + 22000$$

where X is the population centered latitude.[41] These average annual personal UV doses are erythemally-weighted UV doses in

J/m^2 that do not include vacations, which can be taken at any latitude.[12,42,43] Erythemally-weighted UV doses are obtained by multiplying the solar spectra in W/m^2, wavelength for wavelength from 290–400 nm, by the erythemal action spectrum,[44] and then multiplied by the number of seconds the person is exposed to that source to get the UV dose in J/m.[2,12]

Population weighting and statistical analysis

For all the temporal data, we conducted linear regression analysis using Minitab 16.2.4 (Minitab Inc.., State College, Pennsylvania) to evaluate the association between personal annual UV doses (independent variable) and log(CMM) incidence rate (dependent variable). We then performed multiple linear regressions to simultaneously assess the role of time and latitude in predicting log(CMM) incidence rate (**Table 5A**).

Table 1C. Eastern European countries >17°E with CMM incidence data (9 countries averaged in **Fig. 1**).

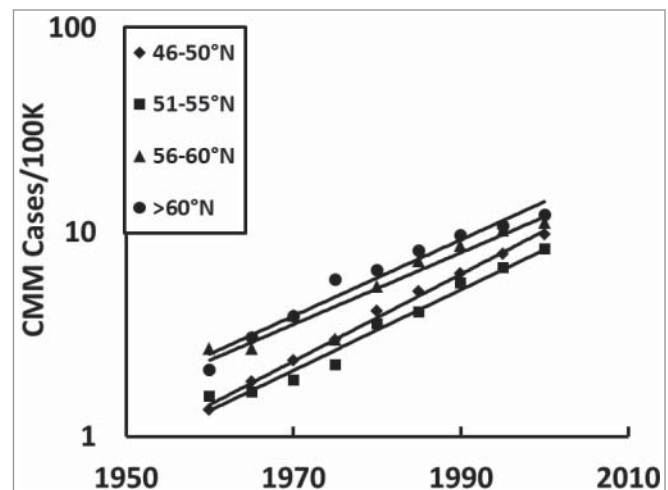| East Europe >17°E	°N	1955	1960	1965	1970	1975	1980	1985	1990	1995	2000
Romania	46			0.60	1.45	2.90	1.40	2.20			
Slovakia	49				2.50	3.70	3.80	4.40	5.05	6.35	
Hungary	48			1.85	1.73	2.30	2.73	3.60			
Poland	51			1.30	1.55	1.90	2.34	2.49	3.24	3.91	4.67
Belarus	54						1.80	2.10	2.50	3.10	
Lithuania	55							2.55	3.3	4.45	
Latvia	57							2.45	2.55	3.35	3.7
Estonia	59							2.9	3.85	4.55	5.95
Finland	65	1.55	2.00	2.20	2.85	3.85	4.80	6.30	7.25	7.35	8.15
Average	54	1.55	2.00	1.49	1.89	2.69	2.99	3.19	3.71	4.29	5.20

Figure 2. Temporal CMM incidences among fair-skinned people in Europe averaged every 5°N for only the European countries with more than 50% complete data sets; northern most (>60°N; mean ~64°N), northern (~51–55°N; mean ~52°N), middle (56–60°N; ~57°N), and southern Europe (~46–50°N; mean ~48°N) plotted from the averaged data in **Table 2**.

Table 2. Only European countries with more than 50% CMM incidence data averaged every 5°N (**Figure 2**).

46–50°N	°N	1955	1960	1965	1970	1975	1980	1985	1990	1995	2000
Slovenia	46		1.35	1.85	2.35	1.95	2.55	3.80	5.05	6.80	8.85
Switzerland	47					4.89	6.85	8.83	10.30	12.10	15.21
France	47					2.53	3.32	4.07	5.31	7.23	8.41
Slovakia	49					2.50	3.70	3.80	4.40	5.05	6.35
Average	**47**		**1.35**	**1.85**	**2.35**	**2.97**	**4.10**	**5.12**	**6.27**	**7.80**	**9.70**
51–55°N	°N	1955	1960	1965	1970	1975	1980	1985	1990	1995	2000
Poland	51			1.30	1.55	1.90	2.34	2.49	3.24	3.91	4.67
Germany	51			2.00	2.20	2.25	3.83	4.45	5.55	6.20	8.77
Netherlands	52		1.70			2.54	4.95	5.03	7.62	9.48	11.12
England	52		1.44	1.67	1.90	2.27	3.15	4.37	6.11	7.13	8.45
Average	**52**		**1.57**	**1.66**	**1.88**	**2.24**	**3.57**	**4.08**	**5.63**	**6.68**	**8.25**
56–60°N	°N	1955	1960	1965	1970	1975	1980	1985	1990	1995	2000
Denmark	56	1.9	2.7	3.9	5.4		7.15	8.75	10.3	12	13
Scotland	57			1.5	2.45	3	3.74	5.77	7.03	8.5	9.25
Average	**57**	**1.90**	**2.70**	**2.70**	**3.93**	**3.00**	**5.44**	**7.26**	**8.64**	**10.23**	**11.13**
>60°N	°N	1955	1960	1965	1970	1975	1980	1985	1990	1995	2000
Sweden	62		2.60	3.20	4.50	5.45	7.70	9.55	11.05	11.85	12.00
Iceland	63		1.25		2.60		3.85	4.55	5.45	8.65	14.15
Norway	64	1.99	2.65	3.80	5.55	8.30	9.70	12.00	14.70	15.20	14.40
Finland	65	1.55	2.00	2.20	2.85	3.85	4.80	6.30	7.25	7.35	8.15
Average	**64**	**1.77**	**2.13**	**3.07**	**3.88**	**5.87**	**6.51**	**8.10**	**9.61**	**10.76**	**12.18**

Using Minitab® 16.2.4 (Penn State, State College, Pennsylvania, US), we performed weighted regression of the cancer incidences on the different personal annual UV doses in the European countries by population (**Table 5B**).[45]

Results

We wanted to know how fast CMM is increasing in the white populations over time and how CMM correlates with personal annual UV dose in Europe.
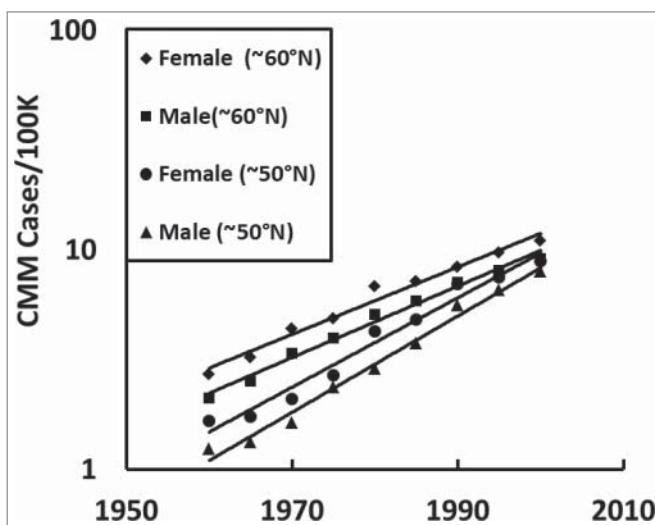

Figure 3. Temporal comparison of female and male CMM rates in northern (>55 °N; mean ~60°N) and southern (46–55°N; mean ~50°N) Europe (**Table 3**; statistical data in **Table 5B**).

Table 3. Males compared with females in northern (~60°N) and southern (~50°N) Europe.

Europe	°N	1960	1965	1970	1975	1980	1985	1990	1995	2000
Europe Female	~60	2.71	3.24	4.40	4.89	6.86	7.19	8.39	9.74	11.03
Europe Male	~60	2.11	2.53	3.40	3.98	5.10	5.88	7.14	8.11	9.13
Europe Female	~50	1.68	1.75	2.09	2.70	4.29	4.84	7.03	7.54	8.88
Europe Male	~50	1.25	1.34	1.63	2.38	2.89	3.77	5.63	6.59	7.98

First, we asked how the CMM incidences changed over time in all of Europe. **Figure 1** shows that CMM has been exponentially increasing over the decades in all of Europe (**Table 1A**). It also shows the western European countries (**Table 1B**) have a consistently higher incidence than the eastern European countries (**Table 1C**).

Next we asked how the southern (46–50°N), middle (51–55°N), northern (56–60°N), and northernmost (>60°N) European countries' CMM incidences changed over time to learn if the increase is linear or exponential in every latitudinal region. We only included countries with more than 50% of the available data (**Table 2**) in **Figure 2** so as not to skew the slopes of the trendlines by data that was only collected in the later years.

We then asked how females and males CMM rates compare in northern (~60°N) and southern (~50°N) Europe (**Table 3**). **Figure 3** shows females always have higher incidences of CMM than males in both northern (~60°N) and southern (~50°N) Europe and that both sexes have temporal exponential increases in CMM.

Then we asked how the incidence of CMM varied with personal annual UV dose, starting at 1960 and assessing every 20 years, to see if CMM correlated with increasing or decreasing latitude. **Figure 4** shows all the countries with available data in 1960 that we followed every 20 y (**Table 4**). In 1980 and 2000, the CMM incidence significantly increased with decreasing personal annual UV dose.
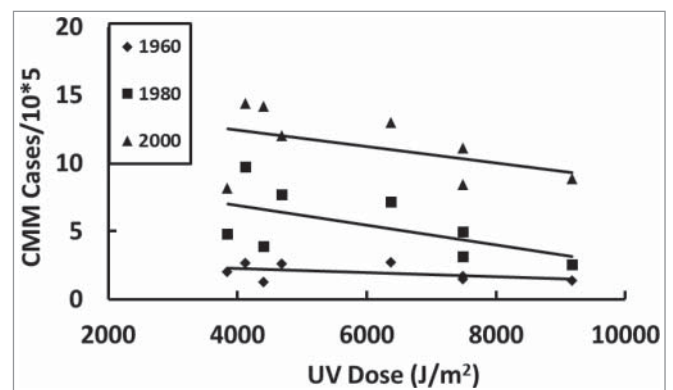

Figure 4. Average personal annual UV dose for populations of each country and CMM incidence trends in Europe over time. Eight European countries that had CMM incidence data in 1960 were followed every 20 y (**Table 4**; **Table 5A**).

Table 4. CMM incidences in 8 countries that had data in 1960 were followed every 20 y

Europe	°N	UV Dose	1960	1980	2000
Slovenia	46	9200	1.35	2.55	8.85
Netherlands	52	7500	1.70	4.95	11.12
England	52	7500	1.44	3.15	8.45
Denmark	56	6400	2.70	7.15	13.00
Sweden	62	4700	2.60	7.70	12.00
Iceland	63	4400	1.25	3.85	14.15
Norway	64	4100	2.65	9.70	14.40
Finland	65	3800	2.00	4.80	8.15

Because we found CMM incidence increases with decreasing UV dose in Europe, we plotted out Robinson et al.'s (1998) UVB-dose response data[25] for the marsupial animal model because the data was obtained in a controlled experimental environment (e.g., food intake and light/dark cycles, etc.). **Figure 5** shows the percentage of animals having CMM actually decreased with increasing UVB doses, including those producing sunburns, in a dose-dependent linear fashion ($R^2 = 0.96$).

Finally, we asked if our European CMM observations were significant or not. **Table 5A** shows that the significance of the exponential increase in CMM over time ($p < 10^{-30}$) and decreasing with UV dose ($p < 2.0 \times 10^{-7}$) have truly remarkably small P values. **Table 5B** shows that both females and males in northern ($\sim 60°N$) and southern ($\sim 50°N$) Europe have significantly lower CMM incidences with higher UV dose ($p < 10^{-6}$).

Discussion

We analyzed the CMM incidences in Europe to know how the rate increased over time and how it correlated with personal annual UV dose, which is a proxy for vitamin D status. We found the incidence of CMM increased at an exponential rate in Europe over time (**Fig. 1**; **Table 1A** and **5A**) with the western European countries having higher rates (**Table 1B**) than the eastern European countries (**Table 1C**), possibly due to cultural differences (e.g., more time indoors) or over diagnosis. However, because this exponential increase over time is seen in both western and eastern Europe it is unlikely to be from over diagnosis, as suggested by some scientists, because it is not possible to increasingly over diagnose at an increasing rate to that extent for more than 5 decades ($P < 10^{-7}$). Exponential increases occur every $5°N$ in Europe (**Fig. 2**; **Table 2**), which shows the increase is not specific to any particular latitudinal region. In addition, CMM is

Table 5A. Statistics for multiple linear regression of log(CMM incidence) data versus time and UV dose in all of Europe (N = 151).

Predictor	Coefficient	T	P
Year	0.02	20	$< 10^{-30}$
UV Dose	−0.000055	−5.4	$< 2.0 \times 10^{-7}$

Table 5B. Statistics for females and males in northern and southern Europe

Europe	Slope	R^2	P
Europe Female ($\sim 60°N$)	0.035	0.98	2.7×10^{-7}
Europe Male ($\sim 60°N$)	0.016	0.99	3.1×10^{-8}
Europe Female ($\sim 50°N$)	0.020	0.97	4.2×10^{-7}
Europe Male ($\sim 50°N$)	0.022	0.99	3.5×10^{-8}

significantly higher for females than for males in both northern ($\sim 60°N$) and southern Europe ($\sim 50°N$; **Figure 3**, **Table 3** and **5B**). Counterintuitively, the increasing incidences of CMM significantly correlate with decreasing personal annual UV dose, a proxy for decreasing personal vitamin D_3, which is most notable after 1960 when it was not significant (**Fig. 4**; **Table 4**). The significant increasing slope in the incidence of CMM with decreasing UV dose over time, especially from 1980 to 2000, reveals that the gradation of lighter skin color with increasing latitude in Europe is not a reasonable explanation because it remained fairly constant. Furthermore, although the ratio of UVA to UVB increases with increasing latitude, which affects mortality of CMM,[46] this is not a reasonable explanation for temporal incidence increases from 1960 to 2000 because the ratio of UVA to UVB does not change very much over time. Finally, some investigators have suggested that increasing people's skin surface area from wearing smaller bathing suits over time is responsible, but this is also not a reasonable explanation because people did not expose more skin in an exponential fashion over time. Moreover, exposing more skin only increases the UV dose to those areas of the body, which is irrelevant because CMM also occurs where the sun does not shine. Instead, the temporal exponential increase shows second order reaction kinetics in the CMM incidence rates (**Fig. 1** and **2**), which reveals 2 major risk factors and suggests an infectious agent or agents are involved in the etiology.
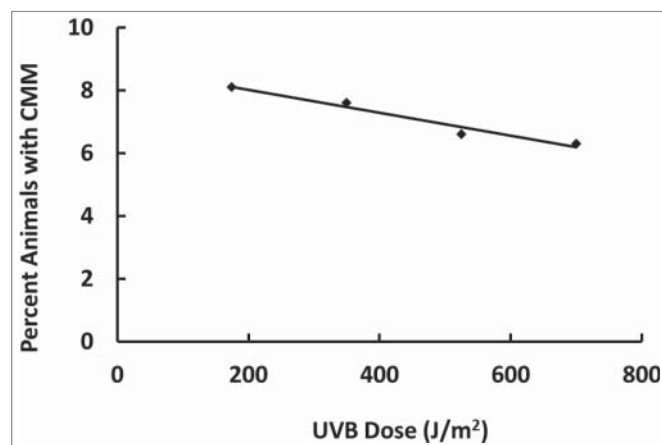
Figure 5. Percentage of animals with CMM decreases with increasing UVB dose in a linear dose-dependent manner ($R^2 = 0.96$). Plotted from the data of Robinson et al.[25]

From epidemiology studies, we know one major risk factor for indoor workers' getting CMM is intermittent UV exposures that were believed to involve sunburn episodes based on long-term memory recall surveys.[47] Scientists believed outdoor workers did not get sunburns, especially blistering sunburns, like indoor workers get because outdoor workers were found to have lower incidences of CMM and half the odds ratio (about 0.8) that indoor workers have for getting it (about 1.6).[13-16] This belief arose because outdoor workers are exposed to UV every day, unlike indoor workers, so that their skin acclimates by thickening the stratum corneum and by producing the pigment melanin (tan). However, contrary to this popular belief, outdoor workers can get numerous sunburns and can also experience blistering events[28-31] reviewed by Glanz.[32] For example, the study by Buller et al.[30] found 45% of the ski area employees got sunburned and 8% received blistering sunburns. Another study measured alpine skiers who got 0.5–7.6 times the minimum erythemal dose (MED), or the minimum amount of UV dose needed to produce a mild sunburn, for white individuals with skin type II and 10% got more than 1 MED/h during peak exposure times.[48] Furthermore, Robinson et al.[25] found that sunburn doses of UVB yielded fewer animals with melanoma than suberythemal UVB doses (175 J/m^2), which yielded the greatest percentage of opossums with melanomas. In fact, the percentage of animals with melanomas decreased with increasing UVB dose in a linear dose-dependent manner (see **Fig. 5**, $R^2 = 0.96$). However, the decisive factor was published by Vainio et al.[49] concerning an official IARC report that declared sunscreens significantly reduce the incidence of sunburns but that they do not reduce the OR for getting melanoma below 1.0 like outdoor workers' continual UV exposures do (OR~0.8), as shown by multiple independent studies.[13-16] So how can sunburns be responsible for initiating melanoma?

Rather than sunburns, we propose that intermittent UV exposures result in low levels of cutaneous vitamin D_3 because only UVB radiation can make vitamin D_3[26] and UVB decreases with increasing latitude[12] while the incidence of CMM increases with increasing latitude (**Fig. 4**; **Table 5A**). Because outdoor workers are chronically exposed to noontime UVB radiation (~11 a.m. to 3 pm), they make plenty of vitamin D_3 in their skin and have healthy blood levels. In contrast, indoor workers get intermittently exposed to UVB radiation (weekends and vacations) so that they do not have high levels of vitamin D_3 in their skin or blood. Outdoor workers (gardeners) who get about 5 times the solar UV dose that indoor workers get have about twice the vitamin D blood levels that indoor workers have.[50] Additionally, indoor workers get exposed to only UVA radiation that passes through glass windows while they work in their offices[10] and drive in their cars.[19] UVA cannot make vitamin D_3[26] but rather breaks it down in the skin, capillaries, and when bound to the vitamin D-binding protein.[51] Recently, the UVA passing through airplane windows has been implicated as the cause for pilots and flight attendants having twice the incidence of CMM as the general population.[52]

Vitamin D_3 is important in the etiology of CMM because melanoma cells can convert it to the hormone, 1,25 dihydroxyvitamin D_3, or calcitriol,[53] and initiate an apoptotic cell death mechanism[54] via the nuclear vitamin D receptor (VDR).[55] We can find evidence of vitamin D-induced suicidal death of melanoma cells from VDR polymorphisms that result in an increased risk for CMM, reviewed by Denzer et al.[56] and decreased survival of patients.[57] Moreover, melanoma patients, who get regular, moderate sun exposures live longer than those who do not[58] and CMM patients were found to have deficient vitamin D levels when compared with patients who did not have CMM.[59] Furthermore, calcitriol controls the growth of melanoma cells,[60-62] inhibits tumor promotion[63] and angiogenesis,[64] and boosts the immune system.[65–67] Recently, the importance of vitamin D in T cell activation has been revealed; they cannot kill virally infected cells or cancer cells unless they have enough vitamin D.[65]

Other than our data suggesting low vitamin D_3 levels as one of 2 major risk factors for getting CMM, we believe the other major risk factor is HPV infection. Although we do not present any data to support our belief, we think HPV is involved because HPV-38 is found in over half the CMM biopsies[35–38] and HPV infection is increasing at an exponential rate in Europe.[68] Clinicians found different strains of type b HPV, primarily HPV-38 and 16/18, in CMM and they found other strains of HPV, primarily HPV-77, in non-melanoma skin cancers.[69] The presence of HPV shortens the latency period of squamous cell carcinoma from ~15–20 y to ~2–5 y[69] and it might also shorten the latency period of CMM, which could explain why clinicians observe a seasonal diagnostic pattern.[70–72] HPV incorporates into the host's genomic DNA during the DNA damage repair processes[73–75] and once incorporated deploys its carcinogenic regime of E6 and E7 proteins that inactivate p53[76] and Bak,[77] respectively, so that the cell cannot die via either the DNA-damage or receptor-initiated apoptotic pathways.[78] However, vitamin D_3/calcitriol can initiate a p53-independent apoptotic cell death pathway[79] circumventing HPV's plan for cellular immortalization[80] by destroying the infected cell. Note that one of HPV's survival strategies is the production of E2 protein that causes the infected cell to release IL-10[81] helping to conceal HPV from immune surveillance.[82] Moreover, the opossums that got melanomas in the Robinson et al. 1998 study[25] were infected with PV, as demonstrated by UVB-induced papillomas.[83] In addition, it now appears that HPV can establish a latent infection[84] that may also have consequence both in the UV interaction and in the disruption of normal skin, which has been implicated in melanoma.[85] HPV may represent the first step in the transformation process because it's E6 and E7 proteins immortalize the melanocyte[80] setting it up for accumulating DNA mutations over time and possibly activating HERV, as other viruses are known to do.

Herein we present plausible explanations for the paradoxes observed over the decades from the second order reaction kinetics that reveals the existence of 2 major risk factors in the etiology of CMM. From epidemiology studies, we know intermittent UV exposures are a risk factor for getting CMM; we propose low cutaneous levels of vitamin D_3, rather than sunburns are a risk factor for getting CMM and we suggest the other major risk factor, along with HERV, may be HPV infection.

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