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On the roles of solar UV irradiance and smoking on the diagnosis of second cancers after diagnosis of melanoma

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Several recent papers have reported standardized incidence ratios (SIRs) for second cancers after diagnosis of cutaneous malignant melanoma. This review divides the types of cancer into five types: (1) those for which UV-B (UVB) irradiance and vitamin D reduces risk; (2) those for which UVB/vitamin D reduces risk and smoking increases risk; (3) smoking related; (4) unknown UVB/vitamin D and smoking sensitivity and (5) those for which UV irradiance increases risk. For those in category 1, SIRs were either significantly elevated or not significantly different from 1.0. For those in category 2, the SIR for kidney cancer was significantly elevated, whereas the SIRs for cervical, laryngeal and rectal cancer were significantly reduced. For those in category 3, all SIRs were significantly reduced. For those in categories 4 and 5, SIRs for all types except lip cancer were significantly elevated. A registry linkage study found significantly reduced SIRs for second cancers after diagnosis of nonmelanoma skin cancer in sunny countries but found increased SIRs in less sunny countries. The SIRs for second cancer for melanoma were elevated in both sunny and less sunny countries. This review concludes that sun exposure without sufficient vitamin D production may explain the elevated SIRs for vitamin D-sensitive cancers, whereas smoking—through production of skin elastosis, thereby reducing the risk of melanoma—probably explains the findings for smoking-related cancers. Thus, guidelines on UV irradiance should emphasize regular moderate UVB irradiance rather than avoidance for those who can tan.

Keywords: cancer risk factors, second cancer, melanoma, vitamin D, ultraviolet, sun burning, smoking

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Introduction

Since at least 1995, we have known that those diagnosed with melanoma have an increased risk of noncutaneous cancers,[1] and that those diagnosed with non-Hodgkin lymphoma (NHL) had an increased risk of melanoma.[2] Several papers have reported rates of second cancers after diagnosis of cutaneous malignant melanoma.[3-6] Rates for some types of cancers, such as breast, colorectal, prostate and NHL, are elevated after diagnosis of melanoma, whereas others, such as lung cancer, are reduced.

Evidence from ecological studies indicates that solar UV-B (UVB) irradiance is correlated with reduced risk of many types of cancer.[7-9] Thus, the increased incidence of types of cancer for which solar UVB irradiance and vitamin D are protective after diagnosis of melanoma is surprising. This paper addresses how to interpret the findings regarding second cancer after diagnosis of melanoma.

Results

Table 1 summarizes standardized incidence ratios (SIRs) for noncutaneous cancers after diagnosis of melanoma reported through 2008, whereas **Table 2** does the same for diagnosis of melanoma after diagnosis of noncutaneous cancers.

Table 3 presents results from several studies. One is a registry study for second cancers after diagnosis of melanoma.[3] That study grouped data into sunny countries (Australia, Singapore and Spain) and less sunny countries (Canada, Denmark, Finland, Iceland, Norway, Scotland, Slovenia and Sweden). Similar

Table 1. Cancers after diagnosis of melanoma—historical results

Cancer	Sex	SIR (95% CI)	Location	Reference
Bone		6.08*	Italy	10
Brain, nervous system		Increase	Denmark	1
Breast	F	1.02 (0.87–1.20)	Sweden	11
CLL		Increase	Denmark	1
CLL		2.3 (1.1–4.4)	Scotland	12
Colon		1.33 (1.00–1.74)	Sweden	11
Endometrial		1.41 (1.03–1.88)	Sweden	11
Kidney	M	2.14 (0.97–4.97)	Taiwan	13
Kidney		1.95*	Italy	10
Nervous system	M	1.73, (1.10–2.60)	Sweden	11
	F	2.03 (1.45–2.78)	Sweden	11
Noncutaneous	F	Not significant	Taiwan	13
NHL		2.0 (0.5–5.0)	Switzerland	14
NHL		1.42 (1.23–1.63)	Hong Kong	15
NHL		1.5 (0.0–2.4)	Scotland	12
NHL	M	1.91 (0.88–3.62)	Taiwan	13
Ovary	F	1.06 (0.75–1.46)	Sweden	11
Pancreatic		Not significant	Denmark	1
Prostate	M	1.7 (1.5–2.0)	Switzerland	15
Decreased				
Liver		0.46*	Italy	10
Lung		0.71*	Italy	10

*Statistically significant; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma

data are also given from three recent papers, each using similar data sets from the Surveillance, Epidemiology and End Results (SEER) database in the US. One used data from 1973–2006,[4] one from 1973–2003,[5] and one from 1992–2006.[6] Statistically significantly elevated SIRs of subsequent cancer were found follow-up times greater than two months for many cancers reported in these studies (see **Table 3**). Reference 5 reported results for 65 types of cancer; significantly elevated SIRs were found for 14 types and significantly reduced SIRs for 11 types.

Table 3 divides the various types of cancer into five categories: UVB/vitamin D sensitive (i.e., have reduced risk in ecological studies, due to vitamin D production), smoking and UVB sensitive, smoking related, UV sensitive (i.e., increased risk with UV irradiance) and unknown UVB/vitamin D and smoking sensitivity. Smoking is an important risk factor for many types of cancer, including lung, oropharynx, larynx, esophagus, pancreas, kidney, bladder and cervix.[17] Later studies added colorectal and liver cancer.[18] In an ecological study of several risk-modifying factors, bladder, cervical, colon, esophageal, laryngeal, pancreatic and rectal cancer directly correlated with lung cancer mortality rates.[7]

Table 2. Melanoma after diagnosis of cancer

Cancer	SIR (95% CI)	Location	Reference
CLL	3.1 (2.1–4.4)	Sweden	2
CLL	2.3 (0.0–2.4)	Scotland	12
NHL	2.4 (1.8–3.2)	Sweden	2
NHL	1.75 (1.48–2.07)	Hong Kong	15
NHL	2.1	Scotland	12
Ocular melanoma	2.38 (1.77–3.14)	International	16

CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma

For cancers with strong links to both UVB and smoking, results for melanoma were mixed. For cervical, esophageal, laryngeal, pancreatic and rectal cancer, SIRs were consistently below 1.0 but not always significantly so, suggesting that smoking was more important for these cancers than was UVB. For colorectal cancer, SIRs were significantly increased in sunny countries but reduced in the US. For kidney cancer, rates were significantly higher than 1.0 for both sunny countries and the US. For these two types of cancer, UVB appears to be more important.

For cancers more strongly linked to smoking than to UVB, significant inverse correlations emerge for melanoma.

Some cancers linked to higher UV irradiance, such as salivary gland cancer[19] and ocular melanoma,[20] have high SIRs after diagnosis of melanoma.

Discussion

Evidence is mounting from ecological and observational studies and randomized controlled trials that solar UVB and/or vitamin D reduce the risk of many types of cancer.[7-9,21-23] Solar UVB is the primary source of vitamin D,[24] and accounts for large annual variations in serum 25-hydroxyvitamin D [25(OH)D] concentrations.[25]

Although not detailed here, the findings for second cancers after diagnosis of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in Tuohimaa[3] offer further evidence regarding the role of solar UVB irradiance and risk of second cancers. In sunny countries, the SIRs for all solid cancers less skin and lip cancer were 0.79 [95% confidence interval (CI), 0.68–0.91] for SCC and 0.86 (95% CI, 0.80–0.92) for BCC. For less sunny countries, the corresponding values were 1.36 (95% CI, 1.33–1.38) and 1.35 (95% CI, 1.32–1.37). Integrated lifetime solar UVB irradiance[26] is an important risk factor for SCC, whereas integrated UV irradiance and sunburning appear to be risk factors for BCC.[27] In previous work, I explained the difference in SIRs between

Table 3. Standardized incidence ratios (SIRs) after diagnosis of melanoma from the literature

Cancer	Melanoma, sunny countries, SIR (95% CI)[3]	Melanoma, less sunny SIR (95% CI)[3]	Melanoma (overall O:E), SIR (95% CI)[4]	Melanoma, SIR (95% CI)[5]	Melanoma, in situ SIR[6]	Melanoma, invasive SIR[6]
All sites			**1.28 (1.26–1.30)**	**1.32 (1.30–1.34)**	**1.32**	**1.57**
All solid, less skin, lip	1.03 (0.99–1.08)	**1.14 (1.11–1.17)**				
All solid less skin, lip, lung	**1.07**	**1.11**				
Vitamin D sensitive						
Brain, nervous system	1.10 (0.80–1.47)	**1.72 (1.45–2.02)**		**1.31 (1.13–1.51)**		
Breast, female	1.03 (0.92–1.15)	**1.26 (1.18–1.33)**	**1.10 (1.04–1.16)**	**1.07 (1.02–1.12)**		
Chronic lymphocytic leukemia			**1.20 (1.00–1.42)**	**1.29 (1.10–1.50)**	**1.44**	**1.57**
Corpus uteri	1.14 (0.85–1.51)	1.12 (0.97–1.29)		0.90 (0.79–1.01)		
Intestine, small			**1.46 (1.08–1.92)**	1.30 (0.98–1.69)		
Non-Hodgkin lymphoma			**1.25 (1.14–1.37)**	**1.25 (1.15–1.35)**	**1.21**	**1.56**
Other female genital	0.89 (0.43–1.64)	0.84 (0.57–1.19)				
Ovary	0.90 (0.62–1.26)	1.10 (0.95–1.27)		0.91 (0.77–1.07)		
Prostate	**1.20 (1.10–1.30)**	**1.31 (1.23–1.40)**	**1.15 (1.10–120)**	**1.13 (1.09–1.17)**	**1.24**	**1.15**
Stomach	0.94 (0.75–1.16)	0.94 (0.83–1.06)		1.01 (0.88–1.16)		
Thyroid			**1.75 (1.50–2.04)**	**1.90 (1.65–2.17)**	1.27	**2.67**
Smoking and vitamin D						
Bladder	0.83 (0.67–1.02)	1.05 (0.94–1.18)		1.01 (0.94–1.09)		
Cervix uteri				**0.57 (0.41–0.78)**		
Colon				0.99 (0.94–1.06)		
Colorectal	**1.13 (1.03–1.23)**	**1.13 (1.06–1.21)**			**0.87**	0.98
Esophagus	0.81 (0.54–1.15)	0.85 (0.64–1.11)		**0.78 (0.63–0.94)**		
Kidney	**1.35 (1.10–1.64)**	**1.25 (1.08–1.43)**	**1.28 (1.13–1.44)**	**1.29 (1.16–1.44)**	1.20	**1.47**
Larynx				**0.58 (0.45–0.73)**		
Pancreas	0.79 (0.60–1.03)	1.08 (0.94–1.24)		0.90 (0.79–1.01)		
Rectum				**0.91 (0.82–1.00)**		
Smoking related, little or unknown vitamin D						
Hypopharynx				**0.54 (0.29–0.90)**		
Leukemia, nonlymphocytic				**0.78 (0.66–0.93)**		
Liver				**0.77 (0.60–0.97)**		
Liver, gallbladder, bile ducts	**0.61 (0.41–0.89)**	**0.80 (0.65–0.97)**				
Lung, bronchus, trachea	**0.85 (0.76–0.95)**	**0.87 (0.80–0.95)**		**0.83 (0.79–0.88)**	0.68	**0.76**
Myeloid, monocytic leukemia				**0.82 (0.68–0.98)**		
Pharynx	0.86 (0.53–1.33)	0.67 (0.42–1.03)		**0.61 (0.40–0.88)**		
Unknown vitamin D sensitivity						
Bones and joints				**1.70 (1.05–2.59)**		
Soft tissue sarcoma			**2.00 (1.61–2.46)**	**2.80 (2.38–3.27)**		
UV sensitive						
Lip				1.26 (0.94–1.65)		
Melanoma			**8.61 (8.31–8.92)**	**8.99 (8.71–9.28)**	**8.43**	**12.50**
Ocular melanoma			**1.77 (1.13–1.44)**	**2.64 (1.93–3.54)**		
Salivary gland			**1.89 (1.38–2.52)**	**2.18 (1.69–2.77)**		
Nonepithelial skin				**2.31 (1.87–2.83)**		

Bold, statistically significant

the sunny and less sunny countries as being due to those living in sunny countries exposing more body surface area to the sun, thereby producing more vitamin D than those living in less sunny countries.[28]

Thus, the finding that SIRs for second cancers after diagnosis of melanoma are similar for sunny and less sunny countries but opposite for BCC and SCC is further evidence that solar UVB irradiance habits associated with continuous long-term vitamin D production may not be an important risk factor for melanoma.

The finding that sunscreen use generally does not reduce the risk of melanoma unless used at latitudes below about 40° by fair-skinned individuals[29,30] also supports this hypothesis. The reason is that sunscreen apparently reduces the risk of sunburning in regions of higher solar UVB doses. The most important risk factors for melanoma include pale skin pigmentation[31] sunburning from recreational UV irradiance,[27] and recreational sun exposure.[32]

Thus, these results suggest that before and at the time of melanoma diagnosis, serum 25(OH)D concentrations were low. This hypothesis is consistent with sunburning's being a strong risk factor for melanoma, whereas chronic solar UV irradiance is not.[33] However, solar elastosis rather than vitamin D production may explain why chronic solar UV irradiance is not a significant risk factor in the meta-analysis by Chang et al.[33] A study in Sweden found "melanomas of the trunk and lower limbs dominate among patients $<$ 70 years, whereas tumors of the head are most common among patients $\geq$ 70 years."[34] Other evidence also indicates that oral vitamin D intake is associated with reduced risk of melanoma,[35] An observational study found "the hazard ratio for relapse-free survival (RFS) was 0.79 (95% CI, 0.64 to 0.96; p = 0.01) for a 20 nmol/L increase in serum level."[36] However, the association may be a confounding factor related to elastosis. A recent review mentioned that vitamin D has antiproliferative effects on cancer cells, which should apply to melanoma.[37] Also, that solar UVB irradiance is associated with reduced risk of melanoma.

In an ecological study of cancer mortality rates in Spain, melanoma mortality rates were inversely correlated with non-melanoma skin cancer mortality rates for women but not for men.[8] In a case–control study in the UK, "Overall the clearest relationship between reported sun exposure and risk was for average weekend sun exposure in warmer months, which was protective (OR 0.67, 95% CI, 0.50–0.89) for highest versus lowest tertile of exposure. Serum vitamin D concentrations were strongly associated with increased weekend and holiday sun exposure."[38]

Smokers have a reduced risk of melanoma.[39-43] Because both UV irradiance and smoking increase skin wrinkling through elastosis,[44] it was suggested that elastosis is the mechanism whereby smoking reduces the risk of melanoma.[22] In a study in Connecticut, "solar elastosis (present versus absent, HR = 0.4, 95% CI = 0.2 to 0.8, p = 0.009) w[as] strongly and independently associated with melanoma death after adjusting" for several factors.[45] The finding that those diagnosed with melanoma have reduced SIRs for cancers linked strongly to smoking is consistent with the role of smoking in reducing the risk of melanoma.[39-43]

Several studies have reported increased risk of NHL with respect to solar UV irradiance such as in the United States as a whole,[46] but also reduced risk in California.[47] A pooled analysis of ten studies found "Risk of NHL fell significantly with the composite measure of increasing recreational sun exposure, pooled OR = 0.76 (95% CI 0.63–0.91) for the highest exposure category (p for trend 0.01)."[48] The mechanism for increased risk may be immunosuppression.[49] Supporting evidence is that those receiving organ transplants have increased risk of NHL due to suppressing the immune system to prevent organ rejection.[50] A study in Minnesota found 25(OH)D insufficiency was associated with inferior event free survival and overall survival in diffuse large B-cell lymphoma and T-cell lymphoma.[51] Thus, there is observational evidence that UV may both increase and decrease risk of NHL.

This review has several implications. One is that those diagnosed with melanoma should have serum 25(OH)D concentrations tested and advised to keep serum 25(OH)D concentrations above 75–100 nmol/l to reduce the risk of other cancers.[52] Those who develop melanoma may want to avoid UV irradiance. Doing so may or may not affect the risk of additional melanomas. Those who cannot tan should limit UV irradiance.[33] Advice regarding solar UV irradiance should emphasize time of day when UVB doses are highest (near solar noon) and length of exposure as a function of location, season, skin pigmentation and so on.[53,54] It is interesting that despite 30 y of admonishing people in Australia to avoid the sun through the *Slip!, Slap!, Slop!* program,[55] melanoma rates, especially for thick melanoma, continue to increase.[56] Unfortunately, serum 25(OH)D concentrations have decreased significantly over the past two decades in the United States[57] and are lower than expected in Australia[58] and the UK.[59] Several factors might explain these trends, including fewer people living in rural locations, increasing rate of obesity and sun avoidance due to fear of melanoma and skin cancer.[60]

Methods

This is a review of the literature on second cancer after diagnosis of melanoma, as well as of melanoma after diagnosis of other types of non-skin cancer. Papers included in the review came from searches of PubMed.gov.

Disclosure of Potential Conflicts of Interest

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