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A meta-analysis of second cancers after a diagnosis of nonmelanoma skin cancer: Additional evidence that solar ultraviolet-B irradiance reduces the risk of internal cancers

William B. Grant *

Sunlight, Nutrition and Health Research Center (SUNARC), 2107 Van Ness Avenue, Suite 403B, San Francisco, CA 94109-2529, USA

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Abstract

Background: Nearly 20 types of cancer have been found to be inversely correlated with solar ultraviolet-B (UVB) levels determined geographically in ecologic studies, assuming that personal solar UVB irradiances were directly related to July solar UVB doses. This assumption has been questioned.
Methods: Rates of second cancer after diagnosis of nonmelanoma skin cancer (NMSC) from the literature were used in linear regression analyses. The risk modification of NMSC due to smoking was accounted for by comparing second cancer risk ratios (RRs) with lung cancer RRs in regression analysis for each cancer.
Results: For a diagnosis of squamous cell carcinoma, RRs for subsequent colon, gastric, and rectal cancers were significantly reduced, with that for renal cancer being marginally insignificant. For NMSC, RRs for cervical, esophageal, gastric, and rectal cancer were significantly reduced; those for colon and gallbladder cancer were marginally insignificant, while those for female breast, laryngeal, ovarian, renal, and uterine corpus cancers were insignificantly reduced; RRs for lip and salivary gland cancers and melanoma were significantly increased. Melanoma was inversely correlated with lung cancer.
Conclusion: These results provide nearly direct evidence that solar UVB irradiance reduces the risk of many internal cancers. The likely mechanism is production of Vitamin D.

1. Introduction

Solar ultraviolet-B (UVB; 290–315 nm) irradiance has been found to be inversely correlated with nearly 20 types of cancer in several observational studies [1,2]. The strongest evidence is for breast, colon, lung, and ovarian cancer, for which most of the studies are observational, generally ecologic in nature [3–10]. The hypothesis for the link between solar UVB irradiance and reduction of cancer risk is photoproduction of Vitamin D [3]. Evidence for this hypothesis extends back to 1941 [11]. Dietary Vitamin D and serum 25-hydroxyvitamin D [25(OH)D] studies support this link when sufficient levels of either are considered [12–14]. Case-control [15] and cohort [16] studies based on a Vitamin D index also support this hypothesis. However, since these studies are observational in nature, being primarily ecologic studies in which personal UVB irradiance was not determined, some other factors could explain the largely latitudinal or seasonal variations in cancer incidence and mortality rates.

Thus, a more direct measure of personal solar UVB irradiance is needed. To further investigate the links between solar UVB irradiance and risk of cancer, a meta-analysis of studies of second cancers following diagnosis of skin cancer of squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and nonmelanoma skin cancer (NMSC) was performed. UV irradiance is an important risk factor for skin cancer [17], so the population of those who developed either form of skin cancer can be generally assumed to have experienced greater UV irradiance than did the general population.

* Tel.: +1 415 776 5274; fax: +1 415 776 5270.
E-mail address: wgrant@sunarc.org.
URL: www.sunarc.org.

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Table 1
Diagnosis of SCC skin cancer and incidence of second cancers

Country	Years of SCC diagnosis	Number with SCC (males, females)	Number with second cancer other than skin cancer (males, females)	Controls	Ancillary information	Reference
Manitoba, Canada	1956–2000	4973, 2860	994, 323	Country		[26]
Denmark	1978–1989	3306, 1826	420, 142	Country		[20]
Sweden	1958–1992	16,252, 9695	2299, 946	Country		[32]
Sweden	1958–1996	11,409, 6,228	2739, 885	Country	Invasive SCC	[36]
Sweden	1958–1996	11,373, 10,920	1944, 1209	Country	In situ SCC	[36]
Switzerland	1974–1994	2592, 2110	384	Country		[29]
USA (CA, MN, NH)	1980–1986	11, 27				[32]
Northern California, USA	1974–1995	492, 330	144	Compared to 2204, 1458 patients		[38]

However, other factors also contribute to skin cancer risk. At the population level, smoking is perhaps the most important. Smoking has been linked to risk of BCC [18,19] and SCC [20–22]. The likely mechanism is reduction in antioxidant defenses since smoking generates free radicals leading to skin aging [23], and skin cancer is due largely to free radicals [24]. Smoking is also an important risk factor for many types of cancer [25]. Thus, this meta-analysis should have included consideration of the prevalence of smoking among each population as well as the history of skin cancer; however, such data are generally unavailable and unreliable, since they could not extend far enough back in time to be complete?

The analysis described here thus seeks to determine whether personal UV irradiance history as determined by skin cancer incidence, corrected for estimated smoking levels by each population, can be used as further evidence that solar UVB irradiance reduces the risk for several internal cancers.

2. Data and methods

All papers reporting second cancers after development of BCC and/or SCC skin cancer were found through the reference list in Nugent et al. [26] and by further search of the National Library of Medicine's PubMed database [27–40]. Characteristics of the studies are presented in Tables 1 and 2. Studies with fewer than 800 skin cancer cases were omitted. Earlier studies that were replaced by later studies, such as in Denmark and Sweden, were also omitted; however, some later studies did not include all the cancers included in the first study, as is the case for Sweden [33].

Because of the different relations of UVA and UVB to skin cancer and the different relative UV irradiances received by males and females, the data were considered in different combinations of skin cancer type and sex.

Previous work demonstrated that the higher the lung cancer risk ratios (RRs) were, the higher the RRs tended to be for other cancers. Lung cancer has been found to be highly correlated with other cancers for black American males [41], and lung cancer was used as the index of the adverse health effects of smoking in an ecologic study of the geographic variation of cancer mortality rates in the United States [2,10]. On the basis of this finding, RRs for each second cancer were plotted versus lung cancer RR for each population studied to account for the effect of smoking on risk of both skin cancer and many second cancers. The effect of solar UV irradiance on the risk of a particular cancer was thus taken as the regression value for lung cancer RR equal to unity. The index of lung cancer rate can be considered a measure of the non-UV irradiance contribution to skin cancer risk as well as a contribution to risk of the other cancer if smoking affects its risk.

Since the number of cases for each data point varied, the regression analysis was done in a manner that took the number of cases into account. The SAS statistical package (SAS Institute, Cary, NC) was used in the analysis.

Table 2
Same as in Table 1, but for BCC skin cancer

Country	Years of BCC diagnosis	Number with BCC (males, females)	Number with second cancer other than skin cancer (males, females)	Controls	Reference
Manitoba, Canada	1956–2000	15,586, 13,370	346, 178	Country	[26]
Denmark	1978–1989	18,968, 18,788	1878, 1240	Country	[28]
SW England	1981–1988		551, 238	Country	[34]
Finland	1953–1995	29,727, 42,197	4884, 4587	Country	[37]
Sweden	1958–1984	934, 1039	56, 76	Country	[27]
Switzerland	1974–1994	5947, 5931	586, 389	Country	[30]
Northern California, USA	1974–1989	1648, 1516	333, 223	1230, 820 from Northern California	[35]
USA (CA, MN, NH)	1980–1986	525, 269			[32]

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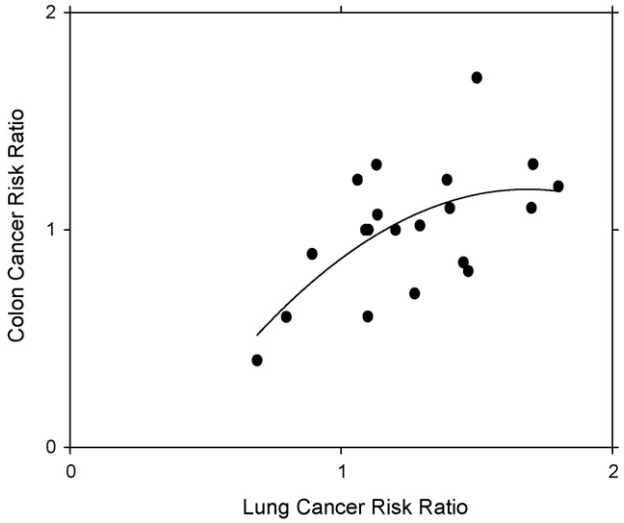

Fig. 1. Colon cancer risk ratio vs. lung cancer risk ratio after a diagnosis of nonmelanoma skin cancer. The regression fit to the data does not take into account the uncertainty of each data point and is intended merely to guide the eye.

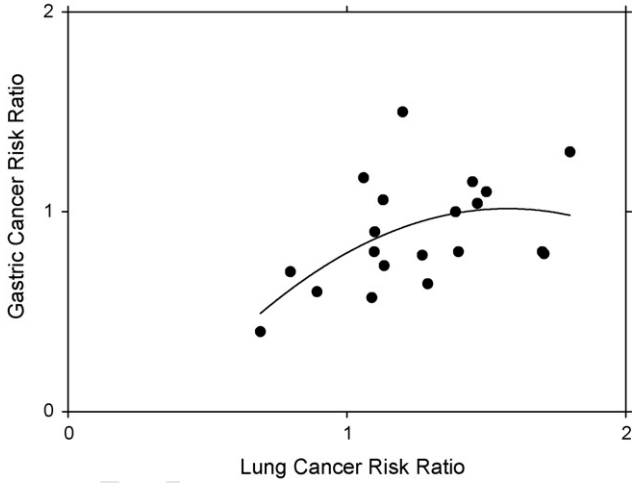

Fig. 2. As in Fig. 1 but for gastric cancer.

Figs. 1–3 show examples of these data. The regression line in these figures is not adjusted for the number of cases in each study.

3. Results

The results are given in Tables 3 and 4. Some results for cancers of the female organs are given for males and females combined because some studies combined the two sexes and because the lung cancer RRs were for males and females combined.

For SCC, the RRs for colon, gastric, and rectal cancers were found to be significantly reduced for males and females combined, with the RR for renal cancer being marginally insignificant. The RRs for melanoma and mouth cancer were found to be significantly greater than unity for males and for males plus females. The results for gastric and mouth cancer and melanoma were significant for males; only melanoma rates were significant for females. A marginally insignificant reduced RR was found for renal cancer. Insignificantly reduced RRs were found for males and females combined for female breast, colon, gallbladder, laryngeal, ovarian, and uterine corpus cancers.

For BCC, SCC, and NMSC, data for NMSC from [40] were included in some of the regressions. These cases are marked with an asterisk in the tables. The data in [40] were odds ratio (OR) rather than RR, and it is not clear whether they can be combined directly with the RR data. Inclusion of these data does not change the sign of the regression RR for the various cancers but does considerably reduce the 95% confidence intervals. For males and females combined, sig-

Table 3
Regression results for SCC and second cancer, adjusted for lung cancer incidence

Cancer	N, adjusted R^2, F, p, males	Ratio for lung cancer RR = 1, Males	N, adjusted R^2, F, p, females	Ratio for lung cancer RR = 1, females	N, adjusted R^2, F, p, males + females	Ratio for lung cancer RR = 1, males + females
Bladder					6, 0.10, 1.6, 0.28	0.62 (−0.80 to 2.04)
Breast, female					4, −0.43, 0.1, 0.78	1.04 (−0.62 to 2.71)
Colon	6, 0.59, 8.3, 0.04	0.76 (0.49–1.02)	6, 0.51, 6.1, 0.07	0.79 (0.52–1.06)	14, 0.46, 12, 0.005	0.78 (0.60–0.96)
Esophageal					6, 0.46, 5.3, 0.08	0.17 (−1.17 to 1.51)
Gastric	6, 0.39, 4.2, 0.11	0.72 (0.45–0.99)	6, 0.01, 1.1, 0.36	0.79 (0.30–1.27)	14, 0.23, 4.8, 0.05	0.76 (0.57–0.94)
HCC					3, 0.19, 1.5, 0.44	0.76 (−3.60 to 5.12)
Laryngeal					5, 0.15, 1.7, 0.28	0.59 (−2.78 to 3.96)
Melanoma	7, 0.61, 10, 0.02	5.6 (3.8–7.5)	7, 0.28, 3.3, 0.02	4.03 (2.32–5.74)	15, 0.45, 12, 0.004	4.7 (3.7–5.6)
Mouth	6, 0.22, 2.4, 0.19	3.15 (1.35–4.95)	4, 0.03, 0.06, 0.82	3.2 (−2.2 to 8.6)	10, 0.13, 2.3, 0.17	3.2 (1.9–4.4)
Multiple myeloma					5, −0.13, 0.5, 0.52	1.43 (−0.40 to 3.26)
NHL					7, −0.19, 0.02, 0.89	2.0 (0.7–3.3)
Pharyngeal					5, 0.32, 2.9, 0.19	0 (−4.5, 4.5)
Prostate	3, 0.90, 19, 0.14	1.16 (0.52–1.81)			4, −0.28, 0.3, 0.62	1.18 (0.20–2.15)
Rectal	3, 4.2, 0.61, 0.29	0.77 (−1.44 to 2.98)	3, 0.23, 1.6, 0.42	0.35 (−5.77 to 6.47)	7, 0.52, 7.5, 0.04	0.65 (0.31–0.99)
Renal	6, 0.56, 7.3, 0.05	0.61 (0.20–1.01)	6, −0.18, 0.2, 0.65	0.91 (0.78–1.04)	14, 0.15, 3.3, 0.09	0.83 (0.63–1.02)
Salivary glands					5, 0.18, 1.9, 0.26	7.5 (3.2–11.8)

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Table 4
Regression results for BCC, SCC, and NMSC (females only for NMSC) adjusted for lung cancer incidence

Cancer	N, adjusted R^2, F, p, males	Ratio for lung cancer RR = 1, males	N, adjusted R^2, F, p, females	Ratio for lung cancer RR = 1, females	N, adjusted R^2, F, p, males + females	Ratio for lung cancer RR = 1, males + females
Bladder[a]			8, 0.32, 4.2, 0.09	1.20 (0.83–1.56)	18, 0.29, 7.8, 0.01	1.06 (0.87–1.25)
Breast, female[a]			9, 0.64, 15, 0.006	0.96 (0.73–1.18)	11, 0.53, 12, 0.007	0.96 (0.75–1.17)
Cervical[a]			2, 0.43, 5.5, 0.07	0.72 (0.41–1.03)	8, 0.48, 7.5, 0.03	0.71 (0.46–0.95)
Colon	9, 0.27, 4.0, 0.09	0.89 (0.65–1.12)	9, 0.24, 3.5, 0.10	0.85 (0.63–1.06)	21, 0.28, 8.6, 0.008	0.87 (0.73–1.02)
Esophageal	6, 0.59, 8.3, 0.05	0.58 (0.00–1.16)	5, −0.05, 0.8, 0.44	0.80 (−1.06 to 2.65)	13, 0.43, 10, 0.009	0.60 (0.21–0.99)
Gallbladder			3, 0.97, 61, 0.08	0.94 (0.24–1.65)	8, −0.09, 0.4, 0.54	0.72 (0.38–1.05)
Gastric	9, 0.28, 4.1, 0.08	0.74 (0.54–0.95)	10, 0.79, 35, 0.0004	0.74 (0.43–1.04)	22, 0.75, 63[a]	0.67 (0.52–0.82)
HCC[a]	4, −0.44, 0.09, 0.80	1.07 (0.13–2.02)	4, 0.96, 69, 0.01	0.34 (−1.14 to 1.81)	9, 0.88, 62, 0.0001	0.64 (0.11–1.17)
Laryngeal	7, 0.51, 7.3, 0.04	0.64 (−0.06 to 1.34)	5, 0.06, 1.2, 0.35	1.1 (−1.5 to 3.6)	13, 0.45, 11, 0.008	0.75 (0.18–1.32)
Lip			5, 0.49, 4.8, 0.12	1.3 (−5.4 to 7.9)	13, 0.25, 5.0, 0.05	1.66 (−0.46 to 3.78)
Melanoma[a]	11, 0.35, 6.3, 0.03	4.6 (3.0–6.3)	12, −0.07, 0.3, 0.58	3.16 (2.10–4.23)	25, 0.04, 2.1, 0.17	3.43 (2.62–4.24)
Mouth	9, 0.06, 1.5, 0.26	2.5 (1.3–3.8)	7, 0.12, 1.8, 0.23	2.7 (0.8–4.6)	17, 0.07, 2.2, 0.16	2.42 (1.53–3.30)
Multiple myeloma	6, 0.59, 8.2, 0.05	1.54 (1.25–1.83)	4, 0.04, 1.1, 0.40	1.20 (−0.70 to 3.11)	12, −0.04, 0.6, 0.47	1.18 (0.79–1.58)
NHL	8, 0.33, 4.5, 0.08	1.16 (0.57–1.75)	7, −0.04, 0.8, 0.42	1.38 (0.22–2.54)	16, 0.26, 6.3, 0.03	1.23 (0.80–1.66)
Ovarian[a]			6, 0.75, 12, 0.03	0.89 (0.52–1.26)	7, 0.69, 15, 0.01	0.92 (0.65–1.19)
Pharyngeal	5, 0.64, 8.2, 0.06	1.04 (−0.71 to 2.79)	4, −0.50, 0.0, 1.00	1.4 (−3.4 to 6.3)	10, 0.34, 5.7, 0.04	1.03 (0.02–2.03)
Prostate	8, 0.10, 1.8, 0.23	1.11 (0.93–1.29)			10, −0.10, 0.2, 0.69	1.09 (0.93–1.26)
Rectal	6, 0.11, 1.6, 0.27	0.83 (0.40–1.25)	6, −0.23, 0.08, 0.79	0.93 (0.53–1.34)	14, 0.18, 3.9, 0.07	0.83 (0.66–0.99)
Renal			10, −0.12, 0.03, 0.88	0.93 (0.72–1.14)	23, 0.03, 1.7, 0.20	0.93 (0.71–1.15)
Salivary glands					11, −0.05, 0.5, 0.48	4.9 (2.7–7.1)
Uterine corpus[a]			7, 0.41, 5.2, 0.07	0.77 (0.25–1.29)	10, 0.42, 7.6, 0.02	0.82 (0.51–1.12)

[a] Includes data for NMSC from [40].

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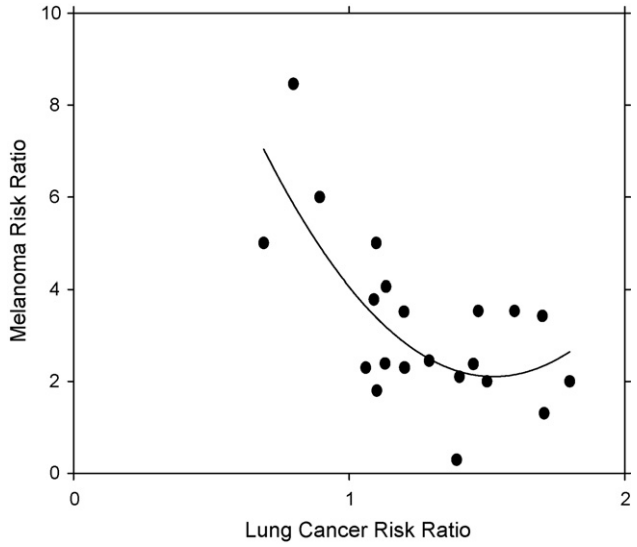

Fig. 3. As in Fig. 1 but for melanoma.

nificantly reduced RRs were found for cervical, esophageal, gastric, and rectal cancers; significantly increased RRs were found for melanoma and for mouth and salivary gland cancers. Marginally insignificant reduced RRs were found for colon and gallbladder cancers. Insignificant reduced RRs were found for female breast, laryngeal, ovarian, renal, and uterine corpus cancers. Also, a significantly increased RR was found for multiple myeloma for males.

4. Discussion

These results indicate that cancer RRs are often significantly reduced for those having a diagnosis of skin cancer prior to diagnosis of a second cancer when smoking history is taken into account. For some of the less common cancers, a significant risk reduction was not found, since the numbers of cases were often low.

Melanoma is, of course, linked to UV irradiance, especially UVA [42], but not to smoking. Vitamin D and UVB reduce the risk of melanoma [43–45]. However, due to the different effects of UVA and UVB, diagnosis of melanoma may not be a good indicator of reduced risk for internal cancer. However, one study in the U.K. did find reduced risk of internal cancers following a diagnosis of melanoma [46]. What is interesting here is that melanoma risk decreases with increasing lung cancer ratio; melanoma RRs are generally higher for lung cancer RRs less than 1.3 than for RRs greater than 1.3. This finding likely can be explained by lung cancer's being a risk for BCC and SCC but may indicate decreased risk for melanoma. A study in the literature reported a reduced risk of melanoma among smokers (RR = 0.6; 95% confidence interval [CI] = 0.3–1.3, >30 years, $p_{trend} = 0.03$) [47]. The agreement of the melanoma results here with those of that study increases confidence in my approach of comparing cancer RRs to lung cancer RRs.

The lips and pharynx, the organs in direct contact with smoke, had elevated ratios compared with lung cancer, although the mouth did not. The lips are also directly exposed to UV irradiance, and farmers often have elevated risks for lip cancer [48,49].

BCC and SCC appear to have different risks with respect to solar UV irradiance: BCC appears to be more related to intermittent UV irradiance and sunburning, whereas SCC appears to be more related to total lifetime UV irradiance [50]. Also, SCC seems to be linked more to UVB than UVA (315–400 nm) irradiance, whereas BCC is probably linked to both UVA and UVB irradiance, as suggested by studies of skin cancer incidence with respect to use of sunscreen [51]. Finally, males tend to spend more time in sunlight than do females. Thus, the general finding that SCC or NMSC was strongly associated with reduced risk of internal cancer whereas BCC was not is consistent with the spectral regions for risk of BCC and SCC: use of sunscreen could reduce the risk of SCC and production of Vitamin D while having little impact on risk of BCC.

5. Summary and conclusion

These results provide strong support for the finding in many ecologic and other observational studies that solar UVB, through production of Vitamin D, is an important risk reduction factor for cancer incidence and mortality and increased survival rates since these results are limited to those people in the populations who are very likely to have experienced greater lifetime solar UV irradiance.

A recent study found that the economic burden of foregone benefits of solar UVB irradiance and Vitamin D in the United States outweighed by a factor of 5–10 the economic burden of excess solar UV irradiance [52]. This study provides additional support for that finding.

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