Published in final edited form as:
Int J Cancer. 2010 April 15; 126(8): 1997–2001. doi:10.1002/ijc.24903.

Sunlight, Hormone Replacement Status and Colorectal Cancer Risk in Post-Menopausal Women

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Abstract

A reanalysis of the Women's Health Initiative (WHI) randomized clinical trial found a significant interaction between supplementation with vitamin D/calcium and estrogen therapy and the risk of colorectal cancer risk, with reduced risks from supplementation limited to the placebo arms of the estrogen trials. To explore whether the vitamin D effects are modified by estrogen therapy, we report a largely cross-sectional, analysis of the association between sun exposure, which is an important vitamin D source, and colorectal cancer risk among postmenopausal women in the U.S. Radiologic Technologists study. Among 21,695 participants, there were a total of 108 cases. Sun exposure was based on time outdoors and on ambient ultraviolet radiation (UV) exposure based on residence linked to erythemal exposures derived from the Total Ozone Mapping Spectrometer (TOMS) database. Although there was no relationship between outdoor time or ambient UV measure and colorectal cancer risk in current hormone replacement therapy (HRT) users, in never/past HRT users, there was an inverse association with higher ambient UV exposure, RR for highest vs. lowest tertile=0.40; 95% CI 017, 0.93; p for trend = 0.04. Non-significant lower risks were also associated with higher levels of outdoor time (≥3.5 hours/week) in never/past HRT users. The interaction between both indicators of sun exposure and HRT and CRC risk was not significant. These data, although exploratory, are consistent with evidence from the WHI suggesting a decrease in colorectal cancer risk may be associated with vitamin D exposure among postmenopausal women who are not taking HRT, but not among current HRT users.

Sunlight exposure has been linked to lower risk of colorectal cancer incidence and mortality in several ecologic and observational studies.1⁻4 The association is hypothesized to be mediated by vitamin D, specifically circulating 25-hydroxyvitamin D [25(OH)D], which is derived in large part from solar radiation.5 Several studies of prospective circulating 25(OH)D and colorectal cancer support the hypothesis.6⁻8

Among the supportive studies is a case-control study of circulating 25(OH)D, which was nested within the Women's Health Initiative (WHI) randomized clinical trial.9 The trial itself, however, found no benefit to colorectal cancer risk from the combined calcium and vitamin D-supplement intervention.9 To examine the seemingly inconsistent results, Ding et al.10 recently reanalyzed data from the Women's Health Initiative (WHI) randomized clinical trial, focusing on the potential interaction between estrogen therapy and the combination of calcium and vitamin D supplements on colorectal cancer risk. The reanalysis

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by Ding et al., however, observed no association with colorectal cancer risk related to supplementation in those randomly assigned to estrogen therapy and decreased risk associated with supplementation in the placebo group.10, 11 The interaction between estrogen/placebo groups was statistically significant. The authors concluded that estrogen therapy may modify the effect on colorectal cancer risk of either calcium and/or vitamin D.

To explore the relationships observed by Ding et al., we report here a preliminary, largely cross-sectional, analysis of the association between different measures of past sun exposure and colorectal cancer risk among postmenopausal women in the U.S. Radiologic Technologists (USRT) study who reported their status as either current or former and never users of hormone replacement therapy (HRT). By examining the associations with reported sun exposure, our analysis indirectly explores whether the effects of vitamin D, which is derived in large part from UV exposure,12 are modified by estrogen therapy.

Methods

The USRT Study comprises a cohort of radiological technologists who were residing in the United States and certified by the American Registry of Radiological Technologists for at least two years between 1926 and 1982.13 An initial questionnaire was mailed in 1983–1989, and a second, self-administered questionnaire (1994–1998) ascertained incident cancers and obtained information on a variety of demographic and lifestyle risk factors. The current study, however, is primarily cross-sectional, relying on data from a third questionnaire self-administered in 2003–2005 with questions on past (lifetime) sun exposure, residence, and cancers.

Study population

Our evaluation of colorectal cancer risk was limited to post-menopausal women who were cancer-free (except for nonmelanoma skin cancer) as of the second questionnaire and who responded to the third questionnaire, n=21,695. Seventy-three percent of respondents to the second questionnaire in the current study answered the third questionnaire. Women were included as post-menopausal if they indicated on the second questionnaire that they had menopause (including surgical menopause) or were not still menstruating, even if they were unsure whether menstrual cessation was permanent. Participants ranged in age from 34 to 90 years at the time of the second questionnaire. Eligible cases were those who reported a diagnosis of colorectal cancer on the third questionnaire. Thus, all cases occurred after the second questionnaire (1994–1998) and before the third (2003–2005).

Pathology and other medical record information were requested to validate the self-reported colorectal cancers. Among the 128 post-menopausal female participants reporting colorectal cancer, medical record information was obtained for 78 (61%). Of these 78, medical records validated the colorectal diagnosis (ICD-10, C18, C20) for 62 (79%). We excluded nine (12%) incorrectly reported “colorectal cancers,” as well as seven (9%) who reported “nearby” cancers of the rectosigmoid junction, anus, and small intestine. Although not incorrectly reported, we also excluded four (5%) *in situ* colorectal cancers. Because a high proportion of self-reported colorectal cancers were validated and there was no significant difference by age, marital status, race and UV region of residence between those potentially eligible cases for whom medical information was and was not obtained, we included colorectal cancer cases for whom no medical record confirmation could be obtained (n=50). Thus, there were a total of 108 cases.

UV and other exposures

Although we relied on information on past sun exposure reported from the third questionnaire, which was provided at the same time cancers were reported, we used information on age, race, marital status, BMI, smoking and HRT use from the earlier questionnaire (1994–1998), to reduce recall bias and facilitate appropriate temporal relationships where possible. The questions on sun exposure covered five age periods (<13 years; 13–19 years; 20–39 years; 40–64 years; and ≥65 years), for which we obtained the city, state, and country in which the participant lived for the longest time. We also asked about amount of time spent outdoors (9am–3pm) in summer during weekdays (0, <1, 1–2, 3–4, 5–6 hours/day) and separately, during weekends (same hour categories) for each of the age periods. Our study used exposure information reported for ages 20–39 years, because that was the age group closest to, but preceding, the diagnoses in nearly all of the cases.

Personal UV exposures were based on summing the time subjects reported that they spent outdoors (9am–3pm) for weekdays and weekends and categorizing time in four groups: ≤3.5, >3.5–7.0, >7.0–14.0, and >14 hours/week. Residential or ambient UV exposures were based on linking the city/state/country locations reported with the Total Ozone Mapping Spectrometer (TOMS) database. (http://toms.gsfc.nasa.gov)

The TOMS database, which is maintained by NASA, provides daily information on a noon-time erythemal estimate (which incorporates UVA and mainly UVB, the part of the UV spectrum responsible for cutaneous vitamin D production12) on a global scale in a 1.25 degree by 1 degree (longitude x latitude) grid. Using the NASA website, we linked geographic location to the daily Version 8 Erythemal noon-time dose estimates (the units are considered arbitrary). After selecting mean values for June, July, and August for the period 1978–2003, we based UV ambient exposures on tertiles of erythemal exposures for the USRT study population (0<182.982; 182.982-≤211.400; > 211.400).

We also constructed a variable with three levels that combined both aspects of summer UV exposure: personal time outdoors and ambient UV levels. The referent (low) level included all those reporting both ≤ 7 hours/week outside and the lowest 50% of ambient UV. The highest category consisted of those reporting both > 7 hours/week outside and the highest 50% of ambient UV. The middle category consisted of the remaining exposure combinations.

Statistical analysis

Logistic regression analysis was used to estimate odds ratios (and 95% confidence intervals), while controlling categorically for age (<60, 60–64, 65–69, 70–74, ≥75 yrs.), race (white/nonwhite), BMI (<25, 25-<30, ≥30 kg/m^2) and HRT status (in the unstratified analysis). Personal and ambient exposures were also mutually adjusted for each other. Monotonic trends across categories were tested by modeling median values per category as a continuous variable in a logistic model. We also evaluated multiplicative interaction by creating product terms and treating the categorical variables as continuous, ordinal variables. All analyses were conducted using SAS (version 9.1; SAS Institute, Cary, NC), with two-sided tests of significance (α=0.05).

Results

Table 1 presents the distribution for demographic and other factors for cases and non-cases. Cases were older than non-cases, and a similarly, large majority of both groups were white. Cases and non-cases were only slightly, and non-significantly, different with regard to BMI, marital status, smoking status, physical activity, and use of menopausal hormone therapy.

In table 2, we assessed colorectal cancer risk in relation to personal UV exposure (time outdoors), ambient UV, and a variable combining time outdoors and ambient UV levels, in all participants and in strata defined by HRT use at the time of the second questionnaire. There was no trend for risk associated with time outdoors in the total study population or in either of the two HRT strata. However, risks were non-significantly lower among those who were outdoors for each of the periods greater that 3.5 hours/week in the total population and among those formerly or never taking HRT, but there was no indication of decreased risk with greater time spent outdoors among those currently on HRT. There was no interaction by HRT status.

In the total population and in those currently on HRT, there was no association between ambient UV and colorectal cancer risk. There was, however, a statistically significant trend of inverse risk with residential UV exposure in those who had never used or were former users of HRT. The p-value for the Wald test for interaction between HRT status and ambient UV was 0.07.

Using the variable that combined both time outdoors and ambient UV levels, we found no association with colorectal cancer in the total population, and no association in current HRT users. In never/past HRT users, risks were lower in those categorized as exposed to medium or high exposures, although the trend was not significant. The test for interaction was also not significant.

We also compared six combinations consisting of two status categories of HRT (never/former and current users) and three categories of combined personal/ambient UV levels (low/medium/high). Compared to a referent group (OR=1.0) of never/former users with low UV exposures, we found that the risk for the three levels of UV in current HRT users were similar to each other (OR = 0.59, 0.38, and 0.58 respectively) and similar to former/never users with medium and high UV exposures (OR= 0.36 and 0.50 respectively).

Discussion

In this study of postmenopausal women, two indicators of UV exposure (time outdoors and ambient UV), and a variable combining the two factors, were evaluated in relation to colorectal cancer risk, to assess whether HRT status modifies disease risk. Although there was no relationship between outdoor time, ambient UV exposure and colorectal cancer risk in current HRT users, there was a statistically significant inverse trend with higher ambient exposure in never/past HRT users. The test for interaction by HRT status, however, was not significant. Non-significantly lower risks were also associated with levels of personal UV exposures ≥ 3.5 hours/week in never/past HRT users. Thus, these data, although limited, suggest that higher UV levels may offer protection against colorectal cancer in women, primarily to former/never HRT users.

In this study, the group with the highest risk was comprised of those who were neither current HRT users nor had medium or high UV exposure. Several studies have found current HRT protection against colorectal cancer risk. 14, 15 It is possible that HRT confers protection at least in part through biological mechanisms involving vitamin D (via UV and other sources) and/or components of the vitamin D signaling pathway. The mechanisms may include estrogen's established role in elevating levels of the hormonally active form of vitamin D (1,25 dihydroxyvitamin D, 1,25(OH)D)).16–18 This relationship may reflect an effect of estrogen on reducing levels of 25-hydroxyvitamin D-24-hydroxylase,17, 18 which is thought to degrade the active form of vitamin D; or on increasing vitamin D binding protein,19 which might in turn increase circulating levels of 25(OH)D. There is also some indication that estrogen may increase vitamin D receptor (VDR) expression.20, 21

As a largely cross-sectional study of prevalent colorectal cancer or colorectal cancer survivors with relatively small case numbers, our results are necessarily exploratory. Moreover, while recall of past sunlight exposures may introduce exposure misclassification, it is unlikely that past residential locations would be substantially affected by case status. In addition, although we were unable to validate all of the self-reported colorectal cancer cases, the relatively high validation rate for self-reported colorectal cases suggests that misclassification of case status is not substantial. In any case, it seems unlikely to be differential by both UV exposure and HRT status.

One key study weakness is that the USRT study findings involve risk associated with surrogates for UV exposure, and not vitamin D *per se*. Notably, we did not have information on multiple factors about outdoor time that may affect vitamin D production, including time of day, season, and protective behavior (e.g., sunscreen).

We plan to update the analysis prospectively when future cases are ascertained, but in the interim, the present analysis offers suggestive insights based on multiple indicators of UV exposure, which few observational studies of non-skin cancers have obtained. Moreover, the fact that the USRT study is nationwide, with participants in all 50 states, provides a particularly wide variation in ambient UV exposures.

These data from the USRT cohort study are consistent with evidence derived from the WHI10 suggesting a decrease in colorectal cancer risk may be associated with vitamin D exposure among postmenopausal women who are not taking HRT, but not among HRT users. They are also in line with findings from the Nurses' Health Study22 that found significantly reduced colorectal adenoma risk associated with vitamin D intake in past users of postmenopausal hormones, suggestively lower risks in never users, but no association in current users. When reviewed in the context of Ding et al., the UV associations support vitamin D as a factor affecting colorectal cancer risk in postmenopausal women who are not taking HRT. These results reinforce the importance of taking HRT status into account in analyses of vitamin D and colorectal cancer risk. Larger prospective studies of colorectal cancer risk with information on vitamin D status over time and HRT use would help elucidate whether the association reflects a true preventive effect.

Acknowledgments

This research was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, and the U.S. Public Health Service of the Department of Health and Human Services. We thank Li Cheung of Information Management Services, Inc. for biomedical computer assistance.

References

1. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol. 1980; 9:227–31. [PubMed: 7440046]
2. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer. 2002; 94:1867–75. [PubMed: 11920550]
3. Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). Cancer Causes Control. 2005; 16:83–95. [PubMed: 15868450]
4. Freedman DM, Dosemeci M, McGlynn K. Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. Occup Environ Med. 2002; 59:257–62. [PubMed: 11934953]
5. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr. 2004; 79:362–71. [PubMed: 14985208]

6. Feskanich D, Ma J, Fuchs CS, Kirkner GJ, Hankinson SE, Hollis BW, Giovannucci EL. Plasma vitamin D metabolites and risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev. 2004; 13:1502–8. [PubMed: 15342452]
7. Tangrea J, Helzlsouer K, Pietinen P, Taylor P, Hollis B, Virtamo J, Albanes D. Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. Cancer Causes Control. 1997; 8:615–25. [PubMed: 9242478]
8. Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK, Gorham ED. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. Lancet. 1989; 2:1176–8. [PubMed: 2572900]
9. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, Margolis KL, Ockene JK, Phillips L, Pottern L, Prentice RL, Robbins J, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006; 354:684–96. [PubMed: 16481636]
10. Ding EL, Mehta S, Fawzi WW, Giovannucci EL. Interaction of estrogen therapy with calcium and vitamin D supplementation on colorectal cancer risk: reanalysis of Women's Health Initiative randomized trial. Int J Cancer. 2008; 122:1690–4. [PubMed: 18092326]
11. Ding EL. Reply to Comment on: Interaction of hormone replacement therapy with calcium and Vitamin D supplementation on colorectal cancer risk. Int J Cancer. 2009; 124:1737–8.
12. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease 2. Am J Clin Nutr. 2004; 80:1678S–88S. [PubMed: 15585788]
13. Boice JD Jr, Mandel JS, Doody MM, Yoder RC, McGowan R. A health survey of radiologic technologists. Cancer. 1992; 69:586–98. [PubMed: 1728391]
14. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. The American journal of medicine. 1999; 106:574–82. [PubMed: 10335731]
15. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. Jama. 2002; 288:321–33. [PubMed: 12117397]
16. Gallagher JC, Riggs BL, DeLuca HF. Effect of estrogen on calcium absorption and serum vitamin D metabolites in postmenopausal osteoporosis. The Journal of clinical endocrinology and metabolism. 1980; 51:1359–64. [PubMed: 6255005]
17. Aarskog D, Aksnes L, Markestad T, Rodland O. Effect of estrogen on vitamin D metabolism in tall girls. The Journal of clinical endocrinology and metabolism. 1983; 57:1155–8. [PubMed: 6605356]
18. Buchanan JR, Santen R, Cauffman S, Cavaliere A, Greer RB, Demers LM. The effect of endogenous estrogen fluctuation on metabolism of 25-hydroxyvitamin D. Calcified tissue international. 1986; 39:139–44. [PubMed: 3093024]
19. Rejnmark L, Lauridsen AL, Brot C, Vestergaard P, Heickendorff L, Nexo E, Mosekilde L. Vitamin D and its binding protein Gc: long-term variability in peri- and postmenopausal women with and without hormone replacement therapy. Scandinavian journal of clinical and laboratory investigation. 2006; 66:227–38. [PubMed: 16714251]
20. Schwartz B, Smirnoff P, Shany S, Liel Y. Estrogen controls expression and bioresponse of 1,25-dihydroxyvitamin D receptors in the rat colon. Molecular and cellular biochemistry. 2000; 203:87–93. [PubMed: 10724336]
21. Protiva P, Cross HS, Hopkins ME, Kallay E, Bises G, Dreyhaupt E, Augenlicht L, Lipkin M, Lesser M, Livote E, Holt PR. Chemoprevention of colorectal neoplasia by estrogen: potential role of vitamin D activity. Cancer prevention research (Philadelphia, Pa). 2009; 2:43–51.
22. Oh K, Willett WC, Wu K, Fuchs CS, Giovannucci EL. Calcium and vitamin D intakes in relation to risk of distal colorectal adenoma in women. Am J Epidemiol. 2007; 165:1178–86. [PubMed: 17379616]

Table 1

Distribution of colorectal cancer cases and non-cases according to selected factors

Characteristic	Cases (n=108)	Non-cases (n=21,587)	Test of signficance, p-value
Mean			
Age at baseline (years) *	57.5	53.5	<0.0001
Body mass index (kg/m^2)	26.2	25.8	0.45
Percent of group			
Caucasian	95.4	95.3	0.96
Currently married	65.4	72.4	0.11
Current smoker	16.7	13.7	0.37
Physical activity, walking/hiking >1 hour/week	52.0	55.5	0.48
Menopausal hormone therapy, current use	49.5	51.7	0.66

Table 2

Risk of colorectal cancer due to UV exposures by HRT status[1]

	Combined population			Never/Past HRT			Current HRT		
	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)	No. cases	No. controls	OR (95% CI)
Personal UV exposure									
≤3.5 h/wk	19	2865	1.0	12	1453	1.0	6	1343	1.0
>3.5–7.0	11	2831	0.67 (0.32–1.41)	6	1287	0.66 (0.25–1.76)	5	1479	0.87 (0.27–2.89)
>7.0–14.0	28	5679	0.81 (0.45–1.46)	13	2646	0.67 (0.30–1.47)	15	2893	1.25 (0.48–3.25)
>14.0	37	8392	0.77 (0.44–1.35)	17	3884	0.64 (0.30–1.34)	19	4293	1.13 (0.45–2.85)
P-trend			0.52			0.29			0.71
P-Interaction			0.34						
Ambient exposure (TOMS Summer UV) (tertiles)			(kj/m^2)						
0–182.982	38	6535	1.0	24	3315	1.0	12	3063	1.0
182.982 -<211.400	36	6898	0.92 (0.58–1.46)	19	3365	0.81 (0.44–1.49)	17	3368	1.31 (0.62–2.75)
>211.400	23	6601	0.64 (0.38–1.07)	7	2712	0.40 (0.17–0.93)	16	3717	1.11 (0.52–2.35)
P-trend			0.11			0.035			0.85
P-Interaction			0.07						
Combined personal and ambient exposure[2]									
Low	24	2622	1.0	16	1375	1.0	7	1181	1.0
Medium	35	9471	0.44 (0.26–0.74)	17	4563	0.36 (0.18–0.71)	17	4683	0.64 (0.26–1.55)
High	34	6795	0.63 (0.37– 1.06)	14	2917	0.50 (0.24–1.03)	20	3706	0.96 (0.40–2.28)
p-Trend			0.24			0.09			0.70
P-Interaction			0.26						

[1] Adusted for age, race, BMI, and HRT (in unstratified analysis; and personal and ambient exposures mutually adjusted for each other. Missing values are included as separate categories.

[2] High= >7 h/week outdoors and ≥50 percentile ambient UV (TOMS summer); low= <=7 h/week outdoors and <50 percentile ambient UV; medium = all others.