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Review

# Is prevention of cancer by sun exposure more than just the effect of vitamin D? A systematic review of epidemiological studies

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**Abstract** The number of studies reporting on the association between sunlight exposure, vitamin D and cancer risk is steadily increasing. We reviewed all published case–control and cohort studies concerning colorectal-, prostate-, breast cancer, non-Hodgkin's lymphoma (NHL) and both sunlight and vitamin D to update our previous review and to verify if the epidemiological evidence is in line with the hypothesis that the possible preventive effect of sunlight on cancer might be mediated not only by vitamin D but also by other pathways.
We found that almost all epidemiological studies suggest that chronic (not intermittent) sun exposure is associated with a reduced risk of colorectal-, breast-, prostate cancer and NHL. In colorectal- and to a lesser degree in breast cancer vitamin D levels were found to be inversely associated with cancer risk. In prostate cancer and NHL, however, no associations were found. These findings are discussed and it is concluded that the evidence that sunlight is a protective factor for colorectal-, prostate-, breast cancer and NHL is still accumulating. The same conclusion can be drawn concerning high vitamin D levels and the risk of colorectal cancer and possibly breast cancer. Particularly in prostate cancer and NHL other sunlight potentiated and vitamin D independent pathways, such as modulation of the immune system and the circadian rhythm, and the degradation of folic acid might play a role in reduced cancer risk as well.


## 1. Introduction

The inverse association between sunlight, vitamin D and various types of cancer has become an area of great scientific interest. The association between solar radiation and reduced cancer mortality in North America was identified more than 60 years ago.[1] In 1980, the Garland brothers proposed the hypothesis that vitamin D is a protective factor against colon cancer.[2] Subsequently, the inverse association between ambient solar radiation and cancer incidence and mortality rates has

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been described for many types of cancer in many countries. In 2006 and 2009, we reviewed all published studies concerning sun exposure, vitamin D and cancer, excluding those about skin cancer.[3,4] For many types of cancer only ecologic studies were available, the majority reporting inverse associations between sunlight and cancer incidence and/or mortality. For colorectal-, prostate-, breast cancer and non-Hodgkin's lymphoma (NHL), in addition to ecologic studies, case–control and prospective studies were performed as well. We concluded that there was accumulating evidence of sunlight as a protective factor for several types of cancer. With the exception of colorectal cancer, the epidemiological evidence of a risk-reducing effect of vitamin D on cancer was considered less convincing.

Recently the effects of ultraviolet (UV) radiation and vitamin D on immune function in immunopathological diseases such as psoriasis and multiple sclerosis (MS) were reviewed.[5] It was suggested that for immunomodulation other UV-induced mediators might be more important than vitamin D. Moreover animal experiments showed that UVB is more effective than vitamin D in the prevention of both MS and colon cancer.[6,7]

We performed a new systematic review on the association between the incidence and mortality of colorectal-, prostate-, breast cancer and non-Hodgkin's lymphoma and both sunlight and vitamin D in order to:

- update our previous reviews,
- verify if the epidemiological evidence is in line with the hypothesis that the possible preventive effect of sunlight on cancer is more than just the effect of vitamin D.

## 2. Methods

### 2.1. Search strategy

A search was performed in two electronic databases: EMBASE (1980 to 15th August 2012) and MEDLINE (1966 to 15th August 2012). Text words (or mesh terms) that were used included cancer (NOT skin cancer) and, separately colon, rectal, colorectal, prostate, breast cancer and non-Hodgkin's lymphoma (NHL) using combinations with text words (or mesh terms) for sunlight or ultraviolet rays and vitamin D. Citation lists of the found studies were used to identify other relevant studies.

## 3. Inclusion criteria and review of the studies

Studies concerning the influence of sunlight and vitamin D on the incidence and mortality of colorectal-, prostate-, breast cancer and NHL were evaluated. All identified titles and abstracts (written in English) were reviewed by one of the authors (van der Rhee).

Inclusion criteria were case–control studies and cohort studies, with original data that met the following demands:

Studying the effect of sunlight and/or vitamin D on cancer, with a clear description of methodology and containing effect estimates with *p*-value or confidence intervals.

Excluded were:

- ecologic studies, because they have well-known limitations: the most important are the so-called ecological fallacies (occurring when associations of groups of individuals are not the same as those for individuals), confounding and misclassification of exposure.[8] In addition they suffer from many potential methodological problems. Moreover, only a small number of new ecological studies were published after 2009 and findings of these studies were in line with those of previous studies.
- studies that report on the influence of the season of diagnosis on cancer survival, since we consider the season of diagnosis an unreliable surrogate for sun exposure on an individual level as it may be influenced by many factors that are not sun-related.
- vitamin D intake studies, when examining the relationship between vitamin D and cancer risk are of little value, particularly because the most important source of vitamin D, the sun, is disregarded in many of these studies. In addition meta-analyses[9,10] revealed that the low vitamin D intake in the studied populations might limit the possibility to detect a protective effect, which may require higher dosages.
- studies reporting on associations with vitamin D blood levels after cancer diagnosis.
- studies reporting on 1,25-hydroxyvitamin D levels only, since 25-dihydroxyvitamin D is considered to be a much better reflection of the vitamin D status.
- studies reporting on data from predictive models.

There are recent meta-analyses available on studies of vitamin D blood levels and the risk of colorectal-, prostate- and breast cancer. We will concentrate on describing the results of these analyses. In addition we will mention (generally very recent) studies that were not included in these analyses.

Further details are described elsewhere.[3]

## 4. Results

### 4.1. Colorectal carcinoma

#### 4.1.1. Associations with sunlight

Seven studies meeting our inclusion criteria were identified: four case–control[11–14] and three prospective studies.[15–17] The case–control studies of Kampman et al.[11] and Slattery et al.[12] were performed with the

same cases. Kampman et al.[11] observed no statistically significant associations between sunshine exposure and colon cancer risk. Slattery et al.[12] stratified the same subjects by genetic variation in the androgen (AR) and vitamin D receptor (VDR). Men with low levels of sunlight exposure and more than 23 polyglutamine (CAG) repeats of AR had the greatest risk of colon cancer (OR = 1.51; 95% CI: 1.09–2.09). In women a comparable phenomenon was observed. In a case–control study with 750 cases of rectal cancer[13] high levels of sunshine exposure were associated with a borderline protective effect for p53 tumour mutations (OR = 0.78; 95% CI: 0.59–1.02).

Freedman et al.[14] found an inverse association between colon cancer mortality and exposure to sunlight.

In the prospective US Radiologic Technologist study[15] in never/past (not in current) users of Hormone Replacement Therapy an inverse association with higher ambient UV exposure was observed (RR for the highest versus lowest tertile = 0.40; 95% CI: 0.17–0.93). In the Swedish Women's Lifestyle and Health cohort[16] a (non-significant) lower risk for colorectal cancer was found (RR = 0.81; 95% CI: 0.47–1.39) for women who spent at least one week per year on sunbathing vacations between 10 and 39 years. In the NIH-AARP Diet and Health Study (450.934 white non-Hispanic subjects) an inverse association between ambient residential UV exposure and colon cancer risk (HR = 0.88; 95% CI: 0.82–0.96) was found[17]. Further details of the studies on colorectal cancer risk are given in Tables 1 and 2.

#### 4.1.2. Associations with vitamin D levels in serum

Twelve prospective studies on the association between blood 25(OH)D and colorectal cancer risk[18–27] or mortality[28,29] were included. With the exception of a Finnish study,[27] all showed inverse associations, a few not statistically significant.[19,23,28] Ma et al.[30] performed a meta-analysis with a total of 2767 cases and 3948 controls. The pooled RR's for colorectal cancer for the highest versus lowest blood 25(OH)D levels were 0.67 (95% CI, 0.54–0.89). A 10 ng/mL increment in blood 25(OH)D level conferred an RR of 0.74 (95% CI, 0.63–0.89). Two other meta-analyses gave more or less comparable results.[31,32]

Three recent studies were not included in these meta-analyses.[27–29] In a Finnish cohort[27] a significantly elevated risk for the highest versus lowest quartile of 25(OH)D levels was observed (OR = 1.88; 95% CI:1.07–3.22).

In the NHANESIII cohort, it was found that vitamin D serum levels $\geqslant$100 nmol/L versus $<$50 nmol/L were inversely associated with colorectal cancer mortality (RR = 0.35; 95% CI: 0.11–1.14).[28] Fedirko et al.[29] observed in the EPIC study that participants with prediagnostic 25(OH)D levels in the highest quintile had an adjusted HR of 0.69 (95% CI: 0.50–0.93) for colorectal cancer-specific mortality and 0.67 (95% CI: 0.50–0.88) for overall mortality, compared with the lowest quintile.

### 4.2. Prostate carcinoma

#### 4.2.1. Associations with sunlight

Nine studies were included: seven case–control studies and two prospective studies.

With one exception[33] the case–control[14,34–38] and prospective studies[17,39] showed negative associations between sunlight and the risk[17,34,35,37,38] or survival[14,36] of prostate cancer. These studies were mainly performed in relatively low solar UV environments, while the study showing positive associations was done in Australia in a high ambient solar UV environment. Further details of the studies on prostate cancer risk are shown in Tables 1 and 2.

#### 4.2.2. Associations with vitamin D

Sixteen prospective studies were identified. Fourteen on the relationship between 25(OH)D levels and the risk of prostate cancer[40–53] and two on the effect of vitamin D levels on mortality[28,54]. Eleven studies found no association between prostate cancer risk and the blood levels of vitamin D metabolites. The study of Ahn et al.[49] observed no statistically significant trend in overall prostate cancer risk with increasing season-standardised serum 25(OH)D level. However, serum concentrations greater than the lowest quintile (12.8–42.0 nmol/L) were associated with increased risk of aggressive disease. Two studies[40,48] found negative associations.

Two studies on the relationship between vitamin D blood levels and mortality could be included. For levels $\geqslant$80 25(OH)D nmol/L versus $<$50 nmol/L, Freedman et al.[28] found a RR of 1.23 (95% CI: 0.50–3.05). Fang et al.[54] found that men with the lowest 25(OH)D quartile were more likely to die of their cancer (HR = 1.59; 95% CI: 1.06–2.34) compared to those in the highest quartile.

The most recent meta-analysis, performed by Gilbert et al.[55] (in total 4353 cases), with one exception[53], comprising all studies on the relationship between vitamin D levels on prostate cancer risk,[40–52] studied the results of a total of 4353 cases. They found that the OR per 10 ng/mL increase in 25(OH)D was 1.04 (95% CI: 0.99–1.10) for total prostate cancer and 0.93 for aggressive prostate cancer. The meta-analysis of Gandini et al.[32] showed similar results.

### 4.3. Breast cancer

#### 4.3.1. Associations with sunlight

Thirteen studies were included (four case–control and nine prospective studies).

All four case–control studies observed negative correlations between the risk of breast cancer[56–58] or

Table 1
Characteristics and outcomes of case–control studies investigating the association between sunlight and cancer risk.

| References | Country | Population | UV measure | Cancer | OR (95% CI) | Corrected for |
|---|---|---|---|---|---|---|
| Kampman et al.[11] | United States of America (USA), Northern California, Utah and Minnesota | 1993 ca (diagnosed between October 1991 and September 1994), 2410 co<br>Population based sampling procedures<br>91.3% White, 4.2% black and 4.4% Hispanic | Interview, recall hours spent outdoors per season | Colon | Highest versus lowest quintile<br>Men: 0.9 (0.7–1.1)<br>Women: 1.0 (0.8–1.4) | Age, BMI, family history of colorectal cancer, physical activity<br>energy intake, dietary fibre and<br>regular use of NSAID's |
| Slattery et al.[12] | USA, cancer registries Northern California, Utah and (colon cancer cases only) Minnesota | 1580 ca (diagnosed between October 1991 and September 1994), 1968 co, 797 ca, 1016 co<br>Population based sampling procedures<br>91.3% white, 4.2% black and 4.4% Hispanic | Interview, recall hours spent outdoors per season | Colon<br>Rectum | >23 CAG repeats (low versus high sun exp): Colon: 1.51 (1.09–2.09) Rectum: 1.06 (0.68–1.66) | Age, BMI, family history of colorectal<br>cancer, physical activity, energy intake,<br>smoking, dietary calcium and fibre and<br>regular use of NSAID's |
| Slattery et al.[13] | USA, cancer Registries Northern California and Utah | 951 ca (diagnosed between May 1997 and May 2001), 1205 co<br>Population based sampling procedures | Interview, recall hours spent outdoors per season | Rectum | Highest versus lowest tertile<br>All cases: 0.91 (0.73–1.13)<br>P53 mutations: 0.78 (0.58–1.03) | Age, BMI, family history of colorectal<br>cancer, physical activity, energy intake,<br>smoking, dietary calcium and fibre and<br>regular use of NSAID's |
| Bodiwala et al.[34] | United Kingdom | Hospital based 453 ca, 312 co (BPH)<br>Northern European Caucasians | Constructed from validated questionnaire | Prostate | Mean hours cumulative exposure/year highest versus lowest: 0.999 (0.999–1.000) Mean adult sunbathing score: 0.81 (0.77–0.86) History of regular foreign holidays: 0.50 (0.36–0.69) | Age |
| John et al.[35] | Greater San Fransisco Bay area, USA | 450 ca, 455 co<br>Non-hispanic white man.<br>Source: Population-based (random digit dialling) and Health Care Financing Administration | Residential solar radiation, sun exposure index based on pigmentation. Time spent outdoors constructed from questionnaire | Prostate | Sun exposure index (reflectometry)<br>highest versus lowest: 0.51 (0.33–0.80) | Age, family history of prostate cancer<br>and month of pigmentation measurement |
| Gilbert et al.[37] | UK, ProtecT study | Hospital based 1020 cases<br>5044 controls | Structured questionnaire on sun seeking behaviour during 2 years before diagnosis | Prostate | Intense sun exposure<br>Lowest versus highest tertile:<br>life course: 1.14 (0.92–1.42)<br>0–19 years: 1.08 (0.78–1.32)<br>20–49 years: 1.12 (0.90–1.38)<br>last 2 years: 1.24 (1.03–1.50)<br>Time spent outside<br>Lowest versus highest tertile:<br>life course: 0.98 (0.81–1.19)<br>5–19 years: 0.98 (0.82–1.17)<br>20–69 years: 0.96 (0.81–1.15) | Age, sunscreen use and pigmentation |

(*continued on next page*)

Table 1 (*continued*)

| References | Country | Population | UV measure | Cancer | OR (95% CI) | Corrected for |
|---|---|---|---|---|---|---|
| Kanaan et al.[38] | Washington DC area USA | Hospital based<br>91 cases<br>91 controls<br>African-American men, aged ⩾40 years | Constructed from validated questionnaire | Prostate | Outdoor UV exposure<br>0.31 (0.14–0.65)<br>Life course (highest versus lowest exp)<br>0–5 years: 0.17 (0.03–0.74)<br>6–11 years: 0.28 (0.08–1.06)<br>12–17 years: 0.41 (0.09–1.95)<br>18–29 years: 1.54 (0.39–6.03)<br>29–39 years: 1.05 (0.29–3.85)<br>⩾40 years: 1.33 (0.32–5.48) | Age |
| Nair-Shalliker et al.[33] | New South Wales, Australia | Population based<br>1084 cases<br>234 controls | Interview, hours spent outdoors during the day in a typical week in the warmer months of the year (October–March) | Prostate | Highest versus lowest quartile<br>2.07 (1.36–3.15) | Year of birth and sun sensitivity |
| John et al.[57] | Greater San Fransisco Bay area, USA | 1786 ca, 2127 co<br>Population-based: random digit dialing<br>Hispanic, African- American and non-Hispanic White women | Sun exposure index based on pigmentation. Time spent outdoors constructed from questionnaire | Advanced (=A) and Localised (=L) Breast cancer | Sun exposure index high versus low:<br>Light constitutive pigmentation<br>A: 0.53 (0.31–0.91)<br>L: 1.10 (0.74–1.63)<br>Medium constitutive pigmentation<br>A: 1.26 (0.74–2.15)<br>L: 1.06 (0.71–1.60)<br>Dark constitutive pigmentation<br>A: 1.28 (0.81–2.05)<br>L: 1.11 (0.74–1.67) | Age, race/ethnicity, education, family history of breast cancer, personal history of benign breast disease, number of full-term pregnancies, breastfeeding, height, alcohol consumption and a composite variable of body mass index, menopausal status and history of hormone therapy use |
| Knight et al.[56] | Ontario, Canada | 759 ca, 1135 co<br>Population-based<br>Population: partly European, partly mixed, partly non-European | Interview: outdoor activity episodes | Breast cancer ER+/PR+ | Highest versus lowest<br>Age 10–19 years: 0.65 (0.46–0.91)<br>Age 20–39 years: 0.67 (0.48–0.94)<br>Age 40–54 years: 1.00 (0.63–1.57) | Age, ethnicity, family history, ever breastfed, education, age at menarche and age at first birth |
| Lee et al.[58] | Tapei, Taiwan | 200 ca, 200 co<br>Hospital based | Interview: average daily sunlight exposure | Breast cancer | Daily exposure (⩾30 min versus <30 min): 0.60 (0.25–1.44) | Age, education, parity, HRT, BMI, energy intake and menopausal status |
| Petridou et al.[92] | Greece, children | 87 ca, 164 co<br>Hospital based, control children admitted for minor paediatric ailments | Interview, structured questionnaire. Time per year at seaside resort used as proxy for sun exposure | NHL | >15 days versus 0 days per year: 0.60 (0.43–0.83) | Socio-economic status, perinatal variables |

| | | | | | | |
|---|---|---|---|---|---|---|
| Grandin et al.[93] | Six French cities | Hospital-based<br>395 ca, 698 co | Interview, outdoor leisure activities since leaving school | NHL | Outdoor activities<br>Highest versus lowest<br>0.9 (0.6–1.4) | Artificial UV use, sun exposure in past week |
| Soni et al.[89] | USA, Nebraska | 387 ca, 535 co<br>population-based: random digit dialing<br>Population: 95% white, 5% non-white | Telephone interviews aimed at determining sun exposure per season 2 years before interview | NHL | Total exposure (>30 h versus <14 h per week)<br>0.7 (0.5–1.1) | Age, sex and family history of cancer |
| Kricker et al.[83] | International (InterLymph consortium)<br>Meta-analysis | 8243 ca, 9697 co<br>Participants of European origin. Mixed group of controls (population-based, individually matched) | In-person or telephone interview | NHL | Recreational sun exposure (highest versus lowest): 0.76 (0.63–0.91) | Adjusted for covariates in the individual studies |
| Kane et al.[94] | North and Southwest England | Population based<br>267 ca, 486 co<br>204 ca, 486 co | Interview, recall hours spent outdoors | NHL<br>subtypes<br>DLBCL<br>FL | Hours spent outdoors: ⩾4 h versus <4 h per day<br>0.88 (0.63–1.22)<br>0.78 (0.54–1.11) | Age, sex and region |
| Kelly et al.[95] | USA, Rochester | 129 ca, 139 co<br>Hospital based | Standardised questionnaire on hours spent outdoors, sunbathing behaviour | NHL | Average hours outdoors/week: >8 h versus 0–2 h: 0.44 (0.11–1.84):<br>Sunbathing with the intention to tan/week<br>>1 versus 0: 0.27 (0.09–0.78) | Age, gender, race, family history of lymphoma or other cancer, medical history, smoking, alcohol, BMI and level of education |
| Wong et al.[96] | Singapore | Hospital based<br>465 cases<br>745 controls | Questionnaire on time spent outdoors daily and weekly | NHL | Time spent outdoors<br>*Daily*<br>(no versus >30 min)<br>Childhood: on schooldays 0.78 (0.59–1.04)<br>on non-schooldays 0.62 (0.47–0.81)<br>Adult on non-working days: 0.76 (0.57–1.02)<br>*Weekly*<br>(no versus >1 h)<br>Childhood: 0.73 (0.55–0.96)<br>Adult: 0.92 (0.69–1.21) | Age, gender, ethnicity, skin color, education, housing type, BMI and family history of cancer |
| Kelly et al.[97] | USA, Rochester | Hospital based<br>1009 cases<br>1233 controls | Questionnaire on hours of sun exposure per week | NHL | Average hours outdoors/week highest (⩾15) versus lowest (⩽3)<br>0–12 years: 0.88 (0.83–1.07) P*trend* 0.36<br>13–21 years: 0.68 (0.43–1.08) P*trend* 0.0025<br>22–40 years: 0.70 (0.48–1.01) P*trend* 0.23<br>⩾41 years: 0.75 (0.52–1.09) P*trend* 0.49 | Age, gender and family history of lymphoma |

BPH, benign prostatic hypertrophy; M, mortality; I, incidence; OR, odds ratio; ca, cases; co, controls; ER, oestrogen receptor; PR, progesterone receptor; DLBC, diffuse large B-cell lymphoma and FL, follicular lymphoma.

Table 2
Characteristics and outcomes of cohort studies investigating the relation between sun exposure and cancer risk.

| References | Country | Population | UV and outcome measure | Cancer | RR (95% CI) | Corrected for |
|---|---|---|---|---|---|---|
| Freedman et al.[15] | USA, USRT study | 21.695 Post-menopausal women with no history of cancer. 108 cases in follow-up | Structured questionnaire for personal exposure. Highest (>14 h/week) versus lowest (⩽3.5 h/week) Residential exposure: highest versus lowest tertile | ♀: Colorectal | Total population: 0.77 (0.44–1.35) Former/never HRT: 0.64 (0.30–1.35) Total population: 0.64 (0.38–1.07) Former/never HRT: 0.40 (0.17–0.93) | Age, race, BMI and HRT status |
| Yang et al.[16**] | Sweden, Swedish Women's Lifestyle and Health cohort | 42.559 Women with no history of cancer. In follow-up: 133 case of colorectal ca | Structured questionnaire for sunseeking holidays and sunburns Annual number of weeks spent on sunbathing vacations | ♀: Colorectal | 1.14 (0.33–3.87) 1.40 (0.55–3.55) 0.81 (0.47–1.39) | Age, education, smoking, alcohol consumption, BMI and physical activity |
| | | 1053 cases of breast ca | Never = reference ⩾1: 10–19 years only ⩾1: 10–19 years and 20–29 years ⩾1: 10–19, 20–29 and 30–39 years | Breast | 0.81 (0.49–1.33) 0.56 (0.36–0.89) 0.88 (0.47–1.39) | |
| Lin et al.[17] | NIH-AARP Diet and Health Study | 450.934 White non-Hispanic subjects | Residential UV exposure Highest versus lowest quartile | | | Age |
| | | 5.133 cases of colon ca | | Colon | 0.88 (0.82–0.96) | |
| | | 1.912 cases of rectum ca | | Rectum | 0.90 (0.80–1.02) | |
| | | 21.439 cases of prostate ca | | Prostate | 0.91 (0.88–0.95) | |
| | | 8.681 cases of breast ca | | Breast | 1.03 (0.97–1.09) | |
| | | 2.731 cases of NHL | | NHL | 0.82 (0.74–0.92) | |
| | | 1.059 cases of DLBCL | | DLBCL | 0.80 (0.67–0.96) | |
| | | 577 cases of FL | | FL | 0.85 (0.68–1.07) | |
| John et al.[39] | USA, NHANES I | 3414 White men without history of prostate cancer who completed baseline questionnaire. 153 prostate cancer cases in follow-up | Solar radiation at place of birth (RR High versus Low) | ♂: Prostate | 0.49 (0.27–0.90) | Age, family history of prostate cancer and fat & calcium intake |
| | | | Solar radiation at longest residence (RR High versus Low) | | 0.80 (0.44–1.49) | |
| | | | Sun exposure determined by physician (RR considerable versus unimpressive) | | 0.78 (0.53–1.47) | |
| | | | Recreational exposure (frequent versus never/rare) | | 0.92 (0.55–1.52) | |
| Sturgeon et al. [61] | USA | 9778 White women, 1987 mortality rates. National Centre for Health Statistics | Residential region, age-and risk factor adjusted mortality ratios (South=reference). | Breast ♀ 20–49 years: | | Corrected for distribution of breast |
| | | | | West | 0.94 (0.76–1.16) | cancer risk factors and |
| | | | | Midwest | 1.05 (0.92–1.18) | mammography |
| | | | | Northeast | 0.99 (0.86–1.14) | use in residential region and recognised |
| | | | | Aged >50: | | |
| | | | | West | 1.13 (1.04–1.23) | risk and prognostic factors |
| | | | | Midwest | 1.08 (1.01–1.16) | |
| | | | | Northeast | 1.13 (1.04–1.23) | |

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| Laden et al.[62] | USA, Nurses Health Study Cohort | Nurses in 11 states, residing for at least 10 years in the same state. 3603 cases identified through 1992(white women) | Place of residence in 1976, stratified into 4 regions. Age-adjusted RR (region South is reference region)<br><br>Place of residence in 1976 Multivariate RR (region South is reference region)* | Breast<br>California<br>Northeast<br>Midwest<br>Breast<br>California<br>Northeast<br>Midwest | <br>1.16 (1.02–1.32)<br>1.02 (0.92–1.14)<br>1.02 (0.90–1.15)<br><br>1.13 (0.99–1.29)<br>1.05 (0.94–1.17)<br>1.03 (0.91–1.17) | Age in 5 categories, age at menarche, parity, age at first birth, use of OC, menopausal status, duration HRT use, fam history breast cancer, history of benign breast disease and BMI (5 cat) |
| John et al. [59] | USA, NHANES I | 5009 White women without history of cancer, with complete dietary and dermatological exams, 191 breast cancer cases in follow-up | Residential sun exposure at region of residence (RR South versus North-east)<br>Solar radiation at longest residence (RR High versus Low)<br>Solar radiation at place of birth (RR High versus Low)<br>Sun exposure determined by physician (RR considerable versus unimpressive)<br>Recreational exposure (frequent versus never/rare | ♀: Breast | 0.71 (0.47–1.09)<br>0.73 (0.50–1.08)<br>0.73 (0.49–1.09)<br>0.70 (0.43–1.14)<br>0.66 (0.44–0.99) | Age, education, age at menarche, age at menopause, BMI, frequency of alcohol consumption and physical activity |
| Millen et al. [60] | USA, Women's Health Initiative Observational Study | 71,662 Women free of breast cancer at baseline, 2,535 cases of postmenopausal breast cancer Mainly Caucasians | Solar radiation at longest residence (RR High versus Low) | | 0.73 (0.50–1.08) | Age, weight, family history of breast cancer, age at menarche, age at menopause, parity, age at first birth, hormone therapy duration, alcohol intake, education, race/ethnicity and physical activity |
| Kuper et al. [63**] | Sweden, Women's Lifestyle and Health cohort | 41.889 Women with no history of cancer 840 cases in follow-up | Solar radiation at place of birth (RR High versus Low) | Breast | 0.73 (0.49–1.09) | Parity, age at first birth, BMI, age at menarche, use of hormonal contraceptive, consumption of alcohol, breastfeeding, family history of breast cancer, physical activity and smoking |
| Engel et al. [65] | France, E3N cohort | 67.721 Particpants 2871 cases in follow-up | Residential sun exposure, highest versus lowest UV radiation | Breast | 0.90 (0.82–0.98) | BMI, physical activity, menopausal status, age at menopause, age at menarche, number of pregnancies, use of oral contraception, HRT, use of Ca, energy intake, alcohol consumption and smoking |

(*continued on next page*)

Table 2 (*continued*)

| References | Country | Population | UV and outcome measure | Cancer | RR (95% CI) | Corrected for |
|---|---|---|---|---|---|---|
| Edvardsen et al.[64] | Norway, Norwegian Women and Career Study | 41.188 Women with no history of cancer. 948 cases in follow-up | Recreational exposure (frequent versus never/rare) | Breast | 0.66 (0.44–0.99) | Age, BMI, height, menopausal status, hormone therapy use, use of oral contraceptives, mother's history of breast cancer, frequency of mammography, combined parity, age at first birth and daily intake of alcohol |
| Adami et al.[101] | Sweden | Swedish Cancer Registry 4.171.175 individuals were included in the analyses.10.381 cases of NHL were identified | Latitude of residence – lower south versus upper north. RR | ♂: NHL<br>♀: NHL | 1.21 (1.08–1.35)<br>1.26 (1.08–1.40) | Age |
| Freedman et al.[98] | USA, USRT study | 64.103 Participants, 137 cases in follow-up | Questionnaire for personal sun exposure: hours/wk spent outdoors during summer<br>Highest (>21 h/week) versus lowest (⩽7 h/week) quartile<br>Age: <13<br>Age: 13–19<br>Age: 20–29<br>Annual residential exposure (highest versus lowest quartile):<br>Age: <13<br>Age: 13–19<br>Age: 20–29 | NHL | <br><br>0.91 (0.48–1.74)<br>0.82 (0.46–1.49)<br>0.71 (0.41–1.22)<br><br>0.70 (0.41–1.20)<br>0.71 (0.42–1.22)<br>0.71 (0.40–1.33) | Age, gender and ethnicity |
| Veierod et al.[102] | Norway and Sweden, Norwegian-Swedish Women's Lifestyle and Health cohort | 104.953 Participants, 158 cases in follow-up | Questionnaire for sun seeking holidays ⩾1 week/year versus none | ♀: NHL | 1.00 (0.64–1.54) | Age, region of residence |
| Chang et al.[99] | USA, California Teachers Study cohort | 121.216 Participants, 629 cases in follow-up | Residential exposure<br>Highest versus lowest quartile | NHL | 0.58 (0.42–0.80) | Age, race, BMI and socioeconomic status |
| Bertrand et al.[100] | USA, Nurses Health Study | 115.482 participants, 1064 cases in follow-up | Residential exposure<br>Highest versus lowest tertile | ♀: NHL | 1.10 (0.94–1.29) | Age, height, BMI, physical activity and smoking |

M, mortality; I, incidence; OR, odds ratio; ♂, male; ♀, female; RR, relative risk; 95% CI, 95% confidence interval; HRT, hormone replacement therapy; DLBC, diffuse large B-cell lymphoma and FL, follicular lymphoma.

* Remarks: prevalence of breast cancer risk factors was higher in south compared with Northeast and Midwest, but lower then California. California: highest breast cancer mortality rates in the region, San Francisco has highest incidence rate of all registries in nation.

** These publications study the same cohort.

breast cancer mortality[14] and one or more aspects of sun exposure. Knight et al.[56] found that the risk reduction was particularly associated with ER+/PR + tumours (ER = oestrogen receptor; PR = progesterone receptor).

The prospective studies on breast cancer gave mixed results. Five of them were performed in the United States of America (USA). John et al.[59] found inverse associations both for residential exposure as well as recreational exposure and exposure determined by physicians. Millen et al.[60] found no consistent relation between breast cancer risk and the region of residence. However, women who reported less than 30 min outside had significantly higher risks than women who spent more than 2 h outside in daylight. Sturgeon et al.[61] using ecological data and not individual exposure data, found that the mortality rates of breast cancer among older women were 1.13 (95% CI: 1.04–1.23), 1.08 (95% CI: 1.01–1.16) and 1.13 (95% CI: 1.04–1.23) in the West, Midwest and Northeast, respectively, compared with the South. Laden et al.[62] also using ecological exposure data only, found no regional differences in the risk of breast cancer. In the NIH-AARP Diet and Health Study[17] no association between residential UV exposure and breast cancer risk was found. Three Scandinavian studies[16,63,64] gave mixed results as well. Kuper et al.[63] and Yang et al.[16] studying the same cohort partly reported different results. Kuper et al.[63] found no associations between personal sun exposure and breast cancer risk, while Yang et al.[16] showed reduced risks for women who, between the age of 10 and 30 years, spent at least 1 week every year on a sunbathing vacation. In the Norwegian Women and Career Study[64] no association was found between the risk of breast cancer and sun seeking vacations. Remarkably, the questionnaires of these Scandinavian studies only concern surrogates of intermittent sun exposure (sunburn and sun seeking vacations) and not chronic exposure (hours spent outside per day or per week). A French cohort study[65] found significantly inverse associations between residential exposure and breast cancer risk.

Details of the case–control and prospective studies on breast cancer risk are given in Tables 1 and 2.

#### 4.3.2. Vitamin D levels in serum

Sixteen studies were included: five case–control studies[66–70] and 10 prospective studies[71–80] on the relationship between 25(OH)D levels and the risk of breast cancer and one on the effect of vitamin D levels on mortality[28]. All case–control studies showed inverse associations between the vitamin D blood levels and breast cancer risk[66–70]. The prospective studies gave mixed results: four showed inverse associations[71,72,74,78] and six found no association[73,75–77,79,80]. Studying the relationship between breast cancer mortality and vitamin D levels ($\geqslant$80 25(OH)D nmol/L versus $<$50 nmol/L), Freedman et al.[28] found a RR of 0.65 (95% CI: 0.18–2.38).

According to the meta-analysis of Gandini et al.[32] the pooled estimates for a 10 ng/mg increase of 25(OH)D levels were 0.89 (95% CI: 0.82–0.98). Restricting the analysis to prospective studies only, yielded a SRR (summary relative risk) of 0.97 increase (95% CI: 0.92–1.03), whereas the SSR for the case–control studies was 0.83 (95% CI: 0.79–0.87). The authors suggest therefore that the case–control studies were responsible for the apparent decrease in risk. Two other meta-analyses[81,82] estimated that, compared with the lowest quantile, the highest quantile of circulating 25(OH)D was associated with a RR of 0.55 (95% CI: 0.38–0.80) and 0.61 (95% CI: 0.47–0.80), respectively. However, all these meta-analyses did not include the most recent studies[70,76–80], of which only two[70,78] found negative associations and four[76,77,79,80] no association.

### 4.4. Non-Hodgkin's lymphoma

#### 4.4.1. Associations with sunlight

Twenty-two studies on non-Hodgkin's lymphoma (NHL) were included: 17 case–control studies[83–97] and six prospective studies[17,98–102]. Twelve of the case–control studies showed inverse associations between sunlight exposure and the risk of NHL, one of them statistically not significant; four did not reveal an association and one showed a (non-significant) positive association. Ten of these case–control studies were described in a meta-analysis[83]: a pooled analysis of 10 independent studies of participants in the Interlymph Consortium, seven of them published elsewhere[84–90] and three additional studies. This meta-analysis, covering 8243 cases and 9697 controls in the USA, Europe and Australia concluded that the protective effect of recreational sun exposure was statistically significant at 18–40 years of age and in the 10 years before diagnosis, for B cell, but not T cell, lymphomas.

Not included in this meta-analysis were the studies of Freedman et al.[91] and six more recent studies[92–97]. Using data of 33.407 cases and 65.843 controls from mortality databases in 24 states of the USA, Freedman et al.[91] observed that, in comparison with regions with the lowest residential exposure, those residing in US states with the highest sunlight exposure (OR = 0.83; 95% CI: 0.81–0.86) and occupational sunlight exposure (OR = 0.88; 95% CI: 0.81–0.96) were negatively associated with non-Hodgkin's lymphoma mortality. The other studies not included in the analysis of Kricker et al.[83] found with one exception[93] that the highest versus lowest quantile of time spent outdoors was associated with a decreased risk of NHL[92,94–97].

The prospective studies gave less conclusive results. Freedman et al.[98] found that, both using residential and personal exposure data, high sun exposure was associated with a decreased risk. Three other US studies showed a decreased risk[17,99] and no association[100]

respectively. Two Scandinavian studies[101,102] found no decreased risk. A prospective Swedish study of Adami et al.[101] found a significantly positive relation between NHL incidence and latitude. Veierod et al.[102] using personal exposure data found no association.

Details of the case–control and prospective studies on NHL risk are shown in Tables 1 and 2. The individual studies included in the meta-analysis of Kricker et al.[83] are not shown.

#### 4.4.2. Associations with vitamin D

Four studies could be identified, one case–control study[95] and 3 prospective studies[28,103,104]. One case–control study[95] and a prospective study[103] found no associations between 25(OH)D levels and the risk of NHL. In the Finnish Alpha-Tocopherol Beta-Carotene Cancer Prevention Study cohort[104] an inverse association was found for NHL cases diagnosed less than 7 years from baseline (not for later diagnoses): the OR for the highest versus lowest tertile was 0.43 (95% CI: 0.23–0.83).

In the prospective study of Freedman et al. [28] no relations were found between 25(OH)D levels and the mortality of NHL.

## 5. Discussion

This review sums up the present epidemiological knowledge on the influence of sunlight exposure and circulating vitamin D levels on the risk of colorectal-, prostate, breast cancer and NHL. The results suggest that there is an inverse association between sunlight exposure and the risk of these malignancies. Initially we planned to perform a meta-analysis of the included studies, but we found out that their designs and their methods used to assess sun exposure and the timing of that exposure in terms of age at exposure and time between exposure and cancer incidence varied considerably. Consequently it was difficult to pool them in a reliable way. Although all studies on the association between sunlight exposure, vitamin D and cancer mortality showed a negative association their number was too low to draw definite conclusions.

In 1992, after reviewing epidemiological, experimental and other relevant evidence, the International Agency for Research on Cancer (IARC) concluded that solar UV is the main environmental cause of skin cancer[105]. Although the relation between sun exposure and the risk of skin cancer was obvious at that time, the different effects of different patterns of exposure on the three main types of skin cancer melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) were less clear. At present it is known that the risk of melanoma is significantly increased by intermittent exposure: particularly irregular and intense exposure (with sunburn), while more regular (chronic) exposure is to some degree inversely associated with melanoma.[106] Intermittent exposure appeared to be a risk factor independent of latitude, whereas the effect of total sun exposure, chronic and occupational exposure is different in low latitudes compared with high latitudes.[107] Most studies performed in European countries with a moderate climate found inverse associations between melanoma risk and chronic and occupational exposure.[108–111]

Basal cell carcinoma of the skin is also associated with acute and intense sun exposure. Recently a systematic review of the literature on the association between occupational sun exposure and BCC risk was published.[112] The pooled analysis of 23 studies revealed that the OR for the association between outdoor work and BCC risk was 1.43 (95% CI: 1.23–1.66). However, all included studies performed in European countries with a latitude of 50° NB or higher found a risk close to 1.0 or a negative association. In Scandinavian countries outdoor work is inversely associated with BCC risk.[111] Individuals with a high socioeconomic status, generally having an intermittent sun exposure attitude, were found to have a high risk of BCC, both in the United Kingdom[113] and the Netherlands,[114] suggesting that BCC is changing from a disease of the poor to a disease of the rich.

The relationship between sunlight and the risk of colon cancer was initially proposed in 1980.[2] Since then this has been confirmed in many ecologic studies in different populations both for colorectal cancer as well as breast-, prostate cancer and NHL.[3,4] And now a substantial body of literature with case–control and cohort studies addresses this subject: we could include 26 case–control and 19 cohort studies. These studies generally contain individual data, although some show residential exposure data only. For colorectal- and prostate cancer the results are more or less unequivocal, but NHL and particularly breast cancer showed more divergent results. However, if studies with residential exposure and studies that investigated intermittent sun exposure only (mainly Scandinavian studies) were excluded, they were more or less unequivocal too.

It is not unlikely that the effect of sunlight exposure, not only in its role as a causal factor for skin cancer, but also when preventing cancer, is dependent on the pattern of exposure and on the latitude. For sustained vitamin D production chronic (continuous) sun exposure is probably more effective than intermittent bouts of intense exposure, particularly when it is considered that vitamin D production is self limiting: after about 30–60 min of sunlight the production quickly declines and after prolonged sun exposure the photochemical conversion of previtamin $D_3$ into biologically inert compounds is starting.[115,116] Moreover sunlight is more effective in inducing vitamin D production in sunny countries in a lower latitude than in Nordic countries. These considerations might explain that in several Scandinavian studies[16,63,64,101,102] no association or no significant association was found. The epidemiological evidence

of an inverse association between chronic sun exposure and colorectal-, breast-, prostate cancer and NHL and for an inverse association between serum vitamin D and colorectal cancer is consistent and persuasive. However the evidence of a causal link is not conclusive yet. Although in many of the included studies the results were corrected for other known risk factors, the possibility of confounding with other dietary and lifestyle factors cannot be excluded completely.

Vitamin D can inhibit cell proliferation and promote apoptosis in vitro in many types of cancer. Therefore the preventive effect of sunlight is usually ascribed to its role in the photosynthesis of vitamin D in the skin. However, there are several reasons to assume that other mechanisms could play a role as well. In multiple sclerosis it was found both in experimental[6] and in epidemiological studies[117] that the preventive role of continuous sunlight is independent of vitamin D production. Rebel et al.[7] observed in their animal experiments that UVB was more effective in preventing colon cancer than vitamin D intake. In their case–control study, Kelly et al.[95] found a reduction of lymphoma risk of 72% (OR: 0.28; 95% CI: 0.10–0.79) for frequent (>once per week versus never) sun exposure, but no association between lymphoma risk and vitamin D intake or 25(OH)D blood levels. The results of this systematic review are well in line with the hypothesis that sunlight is also effective independent of vitamin D as well, since no evidence was found for an association between vitamin D levels and the risk of prostate cancer and NHL. In colorectal cancer, however, with one exception (a Finnish study on a cohort of male smokers[27]) all studies show an inverse association between the level of 25(OH)D and the risk of this cancer. Data from randomised controlled trials could more definitively establish that this association is causal, but the current data are sparse.[4] In breast cancer most studies and meta-analyses show inverse associations. Prospective studies, however, give mixed results. In colorectal- and to a lesser degree breast cancer it is therefore likely that the observed protective effect of sunlight might (at least partly) be mediated by vitamin D, although an additional role for other pathways cannot be excluded. Particularly in NHL, such pathways may involve subclinical immunosuppression.[118]

Other pathways mentioned in the literature are the influence of sunlight on circadian rhythm and degradation of folic acid. Recent genetic association studies support the relation between circadian rhythm and the risk of several types of cancer, particularly breast cancer, prostate cancer and NHL.[119–121] Several studies suggest that circadian-related environmental influences such as light may influence cancer susceptibility[121,122] and disruption of the circadian rhythm is considered as "probably carcinogenic" by the IARC.[123]

Light exposure during the day can increase melatonin peak levels at night and these nocturnal melatonin peaks possibly have antiproliferative effects.[121,122] In a breast cancer cell line melatonin has been found to increase the sensitivity of these cells to the inhibitory effect of vitamin D.[124]

Since sunlight can play a role in the degradation of folic acid and since in animal experiments folate deficiency was shown to delay tumour progression a role for this pathway has been hypothesised.[125]

The evidence that chronic (not intermittent) sun exposure decreases the risk of colorectal-, breast-, prostate cancer and NHL is accumulating and gradually getting stronger. We therefore think that, particularly in countries with a moderate climate, intermitted sun exposure (and sunburn) should on the one hand be discouraged, because of skin cancer prevention, while on the other hand (moderate) chronic exposure possibly should be advised.

In colorectal- and breast cancer it is likely that the risk-reducing effect is mediated by vitamin D, since vitamin D levels were found to be inversely associated with cancer risk. In prostate cancer and NHL no such associations were found. Other sunlight potentiated and vitamin D independent pathways, such as immunosuppression and the influence on circadian rhythm, could play a role as well.

## Conflict of interest statement

None declared.

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