

# **Vitamin D, Sun exposure and Cancer**

**A review prepared for the Cancer Society of New Zealand**

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## TABLE OF CONTENTS

<b>Executive Summary.....</b>	<b>3</b>
<b>Background.....</b>	<b>4</b>
<b>Vitamin D Sources and Metabolism.....</b>	<b>5</b>
<b>Determinants of Vitamin D Status.....</b>	<b>6</b>
<b>Vitamin D Status of New Zealanders.....</b>	<b>7</b>
<b>Methods.....</b>	<b>8</b>
<b>Ecological Studies.....</b>	<b>9</b>
<b>Analytical Studies.....</b>	<b>10</b>
<b>Colorectal Cancer.....</b>	<b>11</b>
<b>Prostate Cancer.....</b>	<b>15</b>
<b>Breast Cancer.....</b>	<b>17</b>
<b>Ovarian and Endometrial Cancer.....</b>	<b>18</b>
<b>Non-Hodgkin Lymphoma.....</b>	<b>19</b>
<b>Other Cancers.....</b>	<b>19</b>
<b>Cancer Survival.....</b>	<b>20</b>
<b>All Cancers.....</b>	<b>21</b>
<b>Summary.....</b>	<b>22</b>
<b>Conclusion.....</b>	<b>22</b>
<b>Implications for Policy on Sun Exposure.....</b>	<b>23</b>
<b>Summary Tables .....</b>	<b>25</b>
<i>1. Ecological studies of UV exposure &amp; cancer</i>	
<i>2. Studies of vitamin D &amp; Colorectal cancer</i>	
<i>3. Studies of vitamin D or UV exposure &amp; prostate cancer</i>	
<i>4. Studies of Vitamin D or UV exposure &amp; breast cancer</i>	
<i>5. Studies of vitamin D &amp; ovarian or endometrial cancer</i>	
<i>6. Studies of vitamin D or UV exposure &amp; Non-Hodgkin lymphoma</i>	
<i>7. Studies of vitamin D &amp; pancreatic or renal cancer</i>	
<i>8. Studies of vitamin D or season of diagnosis &amp; cancer survival</i>	

**Appendices: .....30**

- A – Ecological studies of UV radiation and cancer*
- B – Cohort studies investigating the relationship between colorectal cancer and dietary intake of vitamin D*
- C – Case control studies investigating the relationship between colorectal cancer and dietary intake of vitamin D*
- D – Nested case control studies investigating the relationship between colorectal cancer and blood 25-hydroxyvitamin D*
- E – Cohort studies investigating the relationship between prostate cancer and dietary vitamin D*
- F – Case control studies investigating the relationship between prostate cancer and dietary vitamin D*
- G – Studies investigating the relationship between prostate cancer and sun exposure*
- H – Nested case control studies investigating the relationship between prostate cancer and blood 25-hydroxyvitamin D*
- I – Observational studies investigating the relationship between breast cancer and sun exposure or dietary vitamin D*
- J – Observational studies investigating the relationship between breast cancer and blood 25-hydroxyvitamin D*
- K – Observational studies investigating the relationship between ovarian or endometrial cancer and dietary vitamin D or blood 25-hydroxyvitamin D*
- L – Observational studies (all case control) investigating the relationship between non-Hodgkin lymphoma and sun exposure or dietary vitamin D*
- M – Observational studies investigating the relationship between cancer of the pancreas or kidneys and vitamin D*
- N – Observational studies investigating the relationship between cancer survival and season of diagnosis*
- O – Observational studies investigating the relationship between cancer survival and vitamin D*

**References.....63**

## EXECUTIVE SUMMARY

### Background

The purpose of this report is to review the epidemiological evidence on sun exposure, vitamin D and non-skin cancers. This need for a review has been prompted by recent results from national studies showing low vitamin D levels in both New Zealand children and adults

### Methods

The search strategy for publications was based on a 2006 review by Garland *et al* in the *American Journal of Public Health* which searched PubMed in December 2004, supplemented by Medline searches in April and July 2007 for studies published in 2005-2007.

### Results

- ◇ *Colorectal cancer*: There is strong evidence that vitamin D, through sun exposure or dietary sources, protects against colorectal cancer. A recent meta-analysis shows a significant inverse association between blood 25-hydroxyvitamin D and colorectal cancer. The quality of this evidence is as strong as that for sun exposure and melanoma.
- ◇ *Prostate cancer*: a large number of studies have been published with inconsistent evidence, which does not support an association between vitamin D and prostate cancer.
- ◇ *Breast cancer*: the limited evidence suggests an inverse association between vitamin D and breast cancer, but more research is required to confirm this possibility.
- ◇ *Ovarian cancer*: the limited evidence suggests there is no association between vitamin D and ovarian cancer.
- ◇ *Non-Hodgkin lymphoma*: the limited evidence suggests an inverse association between vitamin D and risk of non-Hodgkin lymphoma, but more research is required.
- ◇ *Cancer survival*: the limited evidence suggests cancer survival is associated inversely with vitamin D and diagnosis during summer or autumn, but more research is required.
- ◇ *All cancers*: the limited evidence suggests there may be an inverse association between vitamin D and total cancer incidence, but more research is required.

### Conclusion

The strong evidence from studies showing an inverse association between vitamin D and colorectal cancer, when combined with similar (albeit limited) findings from studies of total cancer incidence and mortality, suggests that cancer incidence and mortality in New Zealanders should decline if levels of vitamin D in the population are increased.

## BACKGROUND

The public health policy on sun exposure in New Zealand (and most other countries) currently recommends against unnecessary sun exposure in order to minimise the risk of skin cancer.<sup>1,2</sup> This policy is increasingly being challenged by international research which suggests that sun exposure, by increasing body levels of vitamin D, may protect against a range of cancers. Research on sunlight, vitamin D and cancer was prompted by a landmark paper by Cedric and Frank Garland which was published in the *International Journal of Epidemiology* in 1980.<sup>3</sup> This paper was the focus of the April 2006 issue of the same journal,<sup>4</sup> indicating strong support by epidemiologists for the possible role that vitamin D has in protecting against cancer.

The idea that sun exposure may protect against cancer is not new, having been originally proposed by Apperly in 1941,<sup>5</sup> but then forgotten until interest in sunlight, vitamin D and cancer was stimulated in the 1980s by the epidemiological work of the Garland brothers and their colleague Gorham from San Diego, and by laboratory research showing that vitamin D encouraged cell differentiation and inhibited cell proliferation.<sup>6,7</sup> Since then, there has been a large international research effort into the possible protective effects of vitamin D against a range of cancers, but mostly with regard to colon, breast and prostate cancers,<sup>8</sup> and more recently extending to other types of cancer such as non-Hodgkin lymphoma.<sup>9</sup>

This research has created a dilemma for the Cancer Society of New Zealand, which has to balance the strongly established scientific evidence, that sun exposure increases the risk of skin cancer, against the emerging evidence that sunlight and vitamin D may protect against a wide range of other cancers. The purpose of this report is to review the epidemiological evidence on sun exposure, vitamin D and non-skin cancers since the 1980 Garland report. This need for a review has been made timelier by recent results from national studies showing low vitamin D levels in both New Zealand children and adults.<sup>10,11</sup> Studies of sun exposure, vitamin D and skin cancer have not been reviewed due to limited time and because there is consensus among health professionals that sun exposure is a cause of skin cancer.

## VITAMIN D SOURCES AND METABOLISM

Vitamin D occurs in our bodies in two forms: either as cholecalciferol (vitamin D<sub>3</sub>) from sun exposure or eating of animal foods, or as ergocalciferol (vitamin D<sub>2</sub>) from plant foods.<sup>12</sup> The sun is the major source of vitamin D in most land animals including humans. The sun emits ultraviolet (UV) radiation that is classified into three wavelength bands. UVC with wavelength 100-280 nm is filtered out by the ozone layer and does not reach the surface of the earth. UVA, with a longer wave length of 316-400 nm, reaches the earth in larger amounts than UVB which has a wavelength band of 290-315 nm.<sup>13</sup>

Vitamin D<sub>3</sub> is synthesised in the skin by UVB activating its precursor 7-dehydrocholesterol.<sup>12</sup> It then circulates in the blood to the liver where it is converted to its main metabolite, 25-hydroxyvitamin D (25OHD), which has blood levels about 1000 times higher than the active metabolite, 1,25-dihydroxyvitamin D (1,25-(OH)<sub>2</sub>D). Until recently, it was thought that the conversion to 1,25-(OH)<sub>2</sub>D occurred only in the kidneys, but there is increasing evidence, originally from laboratory cancer research,<sup>14</sup> that the cells of most organs have the vitamin D receptor, and along with this, the capacity to synthesize 1,25-(OH)<sub>2</sub>D locally – the so-called autocrine or paracrine synthesis of the active metabolite.<sup>15</sup> The autocrine synthesis of 1,25-(OH)<sub>2</sub>D is dependent on circulating levels of 25OHD.

Vitamin D status is determined by measurement of serum 25OHD level. Previously, the cut-point for vitamin D insufficiency was considered to be a serum 25OHD level of 50 nmol/L.<sup>16</sup> However, there is increasing evidence that serum 25OHD levels should be above 80-100 nmol/L for optimum health. Epidemiological studies have observed that risk of a range of diseases or markers – including bone mineral density, hip fracture, muscle strength, periodontal disease, diabetes, hypertension, coronary heart disease, lung function and colon and breast cancer – is lowest at high 25OHD levels.<sup>17-23</sup> This evidence is consistent with physiological studies which show that the proportion of calcium absorbed in the gut maximises at 40% when serum 25OHD levels are above 80 nmol/L;<sup>24</sup> while the ratio of serum 25OHD to serum vitamin D maximises at serum 25OHD levels of about 100 nmol/L.<sup>25</sup>

International studies which have measured both 25OHD<sub>3</sub> and 25OHD<sub>2</sub> during winter indicate that more than 80% of vitamin D is synthesised by the sun.<sup>26,27</sup> For example, it has been estimated that 10-15 minutes of whole-body exposure to the peak summer sun will generate

and release up to 20,000 IU (500 ug) of vitamin D<sub>3</sub> into the circulation.<sup>28</sup> New Zealanders are likely to get a higher percentage of their vitamin D from the sun because of the poor sources of oral vitamin D available in New Zealand. The main food sources of vitamin D are fatty fish - such as herrings, kippers, cod, and canned salmon and tuna – and eggs and butter.<sup>29</sup> In Australia, where there is mandatory fortification of margarine and low fat spreads, margarine is also an important source of vitamin D, contributing 50% of dietary intake, followed by 16% from canned fish and 10% from eggs.<sup>30</sup>

The last Australian adult dietary survey estimated dietary vitamin D intake of 2.0-2.2 ug/day in women and 2.6-3.0 ug/day in men.<sup>30</sup> This is considerably lower than in the United States, where vitamin D intake ranges from 5-10 ug/day, mainly due to vitamin D fortification of a wide range of foods including milk, cereal and fruit juices.<sup>29</sup> In comparison, sun exposure has been estimated to produce the equivalent of 70 ug/day, based on summer serum 25OHD levels of outdoor workers.<sup>31</sup> Oral vitamin D intake has not been assessed in recent New Zealand national surveys, such as the 1997 Adult Nutrition Survey and the 2002 Children's Nutrition Survey, because of incomplete data for the vitamin D content of food in the Crop & Food data base. It is likely to be lower than in Australia since there is no mandatory fortification of foods in New Zealand, while the most commonly available dietary supplement dose of 100 IU (2.5 ug) per tablet, if this dose is taken daily, will only increase serum 25OHD levels by 1-2 nmol/L.<sup>32</sup>

## **DETERMINANTS OF VITAMIN D STATUS**

Since the sun is the primary source of vitamin D in humans, vitamin D status is determined mainly by the timing, and amount, of outdoor sun exposure and the capacity of skin to synthesise vitamin D. Skin thickness, and hence vitamin D synthesis, decreases with age,<sup>33</sup> so that older people typically have lower serum 25OHD levels than younger. Melanin, by absorbing UVB radiation, blocks the skin synthesis of vitamin D,<sup>34</sup> so that people with dark skin typically have lower serum 25OHD levels than people with white skin. Serum 25OHD levels are higher in men, who generally spend more time outdoors, than women. Serum 25OHD levels follow a sinusoidal pattern throughout the year, being highest in late summer and lowest at the end of winter, because of seasonal variations in the strength of solar radiation due to the solar zenith angle, which is directly overhead at noon in summer, but

angled towards the equator in winter.<sup>35</sup> Solar radiation decreases with increasing latitude, and is not strong enough to synthesise vitamin D at anytime of the day from October to March at latitudes above 52<sup>0</sup> in the Northern Hemisphere.<sup>36</sup> Thus, populations living at high latitudes generally have lower serum 25OHD levels than those living near the equator.

## VITAMIN D STATUS OF NEW ZEALANDERS

Recent reports from national nutrition surveys indicate lower than expected serum 25OHD levels. Mean serum 25OHD level in the 2002 Children's Nutrition Survey was 50 nmol/L for children of all ethnicities aged 5-14 years.<sup>10</sup> By ethnicity, mean levels were 44 nmol/L for Maori, 38 nmol/L for Pacific, and 53 nmol/L for New Zealand and Other (NZEO) children. These levels are lower than those reported from national surveys in the United Kingdom - 60 nmol/L for ages 4-10 and 56 nmol/L for ages 11-14 years<sup>37</sup> - and in the United States - 79 nmol/L for boys and 65 nmol/L for girls aged 12-19 years.<sup>38</sup> The picture is the same for adults, with the mean serum 25OHD being 50 nmol/L for participants aged >15 years in the 1997 Adult Nutrition Survey.<sup>11</sup> The ethnic specific means were: Maori, females 38 nmol/L, males 43 nmol/L; Pacific, females 33 nmol/L, males 44 nmol/L; NZEO, females 49 nmol/L, males 53 nmol/L. By comparison, the mean adult level from a UK national survey was 50 nmol/L,<sup>39</sup> and 71 nmol/L for males and 62 nmol/L for females aged 40-59 years for winter in the 3<sup>rd</sup> National Health And Nutrition examination Survey (NHANES III).<sup>38</sup> There are no national Australian surveys with data on serum 25OHD available for comparison with the New Zealand results.

## METHODS

Because of limited time available to meet the deadline for the planned July 26 meeting of the *Roundtable on Vitamin D, UVR exposure & Health*, it was agreed with the Cancer Society that a rapid literature review would be carried out. The search strategy was based on the recent review by Garland et al who searched PubMed in December 2004 for epidemiological studies of vitamin D, sunlight, ultraviolet radiation and latitude in association with cancers of the colon, breast, prostate and ovary.<sup>8</sup> This was supplemented by a Medline search on 24 April 2007 with the key words 'cancer' and 'vitamin D' for human studies published in 2005-2007, which identified 450 publications. To ensure that no articles were missed with key words related to 'sun exposure' instead of 'vitamin D', a further Medline search was carried out on 11 July 2007 for human studies published in 2005-2007 that combined the key words 'cancer' or 'neoplasms' with any of the following: 'sunlight', 'sun exposure', 'ultraviolet rays', 'ultraviolet radiation', 'UVR' or 'sun protection'. This identified 597 articles, out of which there were several relevant papers that had not been detected by the earlier search on April 24. The abstracts of papers from both searches were read and all epidemiological studies identified. Additional reports of epidemiological studies were identified from the lists of references in the above studies.

## ECOLOGICAL STUDIES

Ecological studies examine associations between exposure and disease at the group level. Typically, comparisons of these measures are made for populations living in cities, counties, states or countries. These studies are typically used to generate rather than test hypotheses, since the association between exposure and disease is not made for individuals. Most studies on the topic of this report have reported measures of solar radiance, such as latitude or from satellites, rather than vitamin D intake. Ecological studies which have published on the relationship between sun exposure and cancer (mortality or incidence) are described in Appendix A.<sup>3 40-60</sup> Their results are summarised in Table 1.

Putting aside the early study of Apperly,<sup>5</sup> which lay unrecognised for a number of decades, the current research interest in vitamin D and cancer has been stimulated by several ecological studies that have examined the association between measures of solar radiation and cancers of the colon,<sup>3</sup> breast,<sup>40</sup> prostate<sup>41</sup> and ovary,<sup>45</sup> and lymphoma.<sup>46</sup> These studies have used both direct measures of UV exposure, and proxy measures estimated from latitude, and have reported both cancer mortality and incidence. Most studies report data from the United States, which provides the greatest opportunity for detecting associations between UV radiation and cancer because of its large geographical area and large population. Some studies report international comparisons, which have the potential to be confounded by national differences in other lifestyle causes of cancer.<sup>51 55 57</sup> Studies from within a single country minimise this problem. Recent reports have examined the full range of cancers, while attempting to control for confounding from other lifestyle variables.<sup>59 60</sup>

Studies have consistently reported inverse associations between cancers of the colon and rectum, breast, prostate and ovary (Table 1). The evidence for lymphoma is mixed, with inverse, positive and no associations being reported, as it is for some other types of cancer. Only one paper has reported on total cancer, and which found an inverse association between UVB irradiance and mortality from all cancers in a comparison of US states.<sup>59</sup> As mentioned above, these studies can only generate hypotheses, and their results are given no weight in this report, aside from any support they may provide for analytical studies. The latter are used to test these hypotheses because they link exposure and disease risk in individuals.

## ANALYTICAL STUDIES

Analytical studies measure individuals to determine whether exposure to a risk factor is associated with disease status. They are categorised into two main groups:

1. experimental studies, such as randomised controlled trials, where the exposure is actively changed by the researchers;
2. observational studies, where the researchers merely observe and measure exposure.

Observational studies are categorised into:

- ◇ cohort studies, where exposure is measured before disease onset, and are sometimes called prospective or follow-up studies;
- ◇ case control studies, where disease status is determined before measuring exposure;
- ◇ cross-sectional studies, where information on exposure and disease status is collected at the same point in time (from each individual).

Nested case control studies are a variant of the cohort design, where an exposure measurement collected at baseline is later extracted only for people who subsequently develop the disease (cases) and matched controls, not for the total cohort.

Epidemiologists typically use the following hierarchy, in descending order of importance, to decide on causation when comparing results from different study designs:

1. Experimental studies provide the strongest evidence, since the exposure is actively modified
2. cohort studies are next, since measurement of exposure precedes disease onset
3. case control and cross-sectional studies are lowest, since measurement of exposure may be affected by the disease process or biased after disease onset.

Nearly all studies on vitamin D, sun exposure and cancer are observational studies. The only intervention studies published to date – one from the Women’s Health Initiative<sup>61</sup> and the other a small study from Nebraska<sup>62</sup> – are both affected by design issues which are discussed below. Given this, the strongest body of evidence on vitamin D and cancer comes from nested case control studies comparing baseline measurements of blood 25-hydroxyvitamin D, the main marker of vitamin D status, with subsequent risk of cancer. These studies provide better assessments of vitamin D status than cohort studies of dietary vitamin D, since most vitamin D comes from sun exposure.<sup>26 27</sup> Moreover, laboratory measurements of blood vitamin D

levels are likely to be less biased than measurement of dietary vitamin D intake using questionnaire methods such as food frequency questionnaires (FFQ).

Studies have been grouped as follows based on the number of publications identified in the literature search:

- ◇ colorectal cancer: 27 reports summarised in Table 2,
- ◇ prostate cancer: 25 reports in Table 3
- ◇ breast cancer: 9 reports in Table 4
- ◇ ovarian and endometrial cancer: 7 reports in Table 5
- ◇ non-Hodgkin lymphoma: 5 reports in Table 6
- ◇ other cancers (pancreatic and renal): 3 reports in Table 7
- ◇ cancer survival: 8 reports in Table 8.

## COLORECTAL CANCER

Twenty-seven sets of results were identified (Table 2). These have been separated into the following groups:

- ◇ cohort studies of dietary vitamin D
- ◇ case control studies of dietary vitamin D
- ◇ nested case control studies of blood 25-hydroxyvitamin D
- ◇ a single randomised controlled trial (RCT).

### **Cohort studies of dietary vitamin D** (described in Appendix B).<sup>63-76</sup>

Fourteen cohort studies of dietary vitamin D and colon cancer were identified. These studies have been carried out mostly in the United States, but also in Finland,<sup>70 71</sup> Sweden<sup>72</sup> and France.<sup>74</sup> Six studies reported significant ( $p < 0.05$ ) inverse associations between vitamin D intake and risk of colon cancer;<sup>63 66-68 73 76</sup> while eight reported no association.<sup>64 65 69-72 74 75</sup>

### **Case control studies of dietary vitamin D** (Appendix C).<sup>77-82</sup>

Six case control studies of dietary vitamin D and colon cancer were identified. In contrast with the cohort studies, the case control studies were mostly carried out in Europe – in Majorca,<sup>77</sup> Italy<sup>79 81</sup> and Sweden<sup>80</sup> – with the remainder in the United States. Only one of these studies reported an inverse association between dietary vitamin D and colon cancer,<sup>79</sup>

while the remainder reported no association. Given the well recognised problem of dietary measurement error that is likely to arise in case control studies, particularly when recalling dietary patterns from 10 years or more prior to the diagnosis of cancer, when cancer is initiated, little importance is given to the results of these studies, particularly when they report on a dietary nutrient which is mainly synthesised in the body through sun exposure.

**Nested case control studies of blood 25-hydroxyvitamin D** (Appendix D).<sup>61 83-87</sup>

Five nested case control studies have been published comparing baseline blood 25-hydroxyvitamin D levels with subsequent risk of colorectal cancer;<sup>61 83-86</sup> plus one cohort study which estimated baseline plasma 25-hydroxyvitamin D levels from a sub-sample, and linked these with subsequent risk of colorectal cancer.<sup>87</sup> All studies have been carried out in the US, except for one study in Finland.<sup>85</sup> Two studies were carried out on the same cohort, although stored blood samples from different cases and matched controls were analysed in each report.<sup>83 84</sup> Two studies came from RCTs which combined participants in treatment and placebo arms to compare baseline 25-hydroxyvitamin D levels with follow-up cancer risk.<sup>61 85</sup>

Only two of the five nested case control studies reported significant inverse associations between baseline 25-hydroxyvitamin D and colorectal cancer risk.<sup>61 86</sup> However, recently all five studies have been combined in a meta-analysis by Gorham and colleagues which reported the following pooled relative risks (96% CI) compared to the lowest 25-hydroxyvitamin D quintile (Q1): Q2 = 0.82 (0.59, 1.14); Q3 = 0.66 (0.47, 0.92); Q4 = 0.59 (0.41, 0.82); Q5 = 0.46 (0.32, 0.64).<sup>22</sup> The p-value for trend was <0.01; and the blood level of 25-hydroxyvitamin D  $\geq$  33 ng/mL (82 nmol/L) was associated with a 50% reduction in risk, compared with the reference category of  $\leq$  12 ng/mL (30 nmol/L).

Blood samples may have been collected from some cases in the above studies after their cancer had started, and in these cases it is possible their measured blood 25-hydroxyvitamin D level was different to that prior to cancer onset. If such an error is present, it is probable that the blood tests either overestimated or underestimated long term blood 25-hydroxyvitamin D levels in a proportion of both cases and controls. Such a non-differential error is more likely than a differential error (such as recall bias) since blood samples were collected many years before diagnosis, and vitamin D measurements were carried out in laboratories. If present, this would have resulted in attenuation of effect such that the observed cancer relative risks associated with blood vitamin D are likely to have underestimated the true association.<sup>88</sup>

### **Randomised controlled trial of vitamin D supplementation<sup>61</sup>**

The single major RCT on vitamin D supplementation and colorectal cancer comes from the Women's Health Initiative.<sup>61</sup> This double blind study enrolled 36,282 cancer free women aged 50-79 years between 1993-1998, and randomised them to receive daily doses of either 400 IU of vitamin D combined with 1000 mg of calcium or placebo. By the end of follow-up in 2005, 168 new cases of colorectal cancer were confirmed in the supplemented group compared with 154 in the placebo group; giving a final relative risk (95% CI) was 1.08 (0.86, 1.34).

There are at least three possible reasons for the lack of an effect from vitamin D in this major study. Firstly, the daily dose of vitamin D, although considered sufficient when the study started, is now considered to be too low, and will have only increased serum 25-hydroxyvitamin D levels in the treated group by about 7 nmol/L.<sup>32</sup> Secondly, the already too-low dose of vitamin D was aggravated by low compliance with the daily supplementation regime, with only 70% of participants taking supplements 50% or more of the time. This approximates to 35% or more of the study target dose, or about 140 IU of vitamin D per day.<sup>89</sup> Thirdly, a significant proportion of participants were already taking calcium and vitamin D supplements on entry into the study, and continued using them throughout the trial, resulting in contamination of the placebo group.<sup>89</sup>

### **Summary for colorectal cancer**

Given the above concerns about the RCT from the Women's Health Initiative, the strongest evidence that vitamin D protects against colorectal cancer comes from the nested case control studies of blood 25-hydroxyvitamin D. The meta-analysis of these studies provides evidence which meets many of the Bradford-Hill criteria for causation.<sup>22</sup> These include:

- ◇ the temporal requirement of measuring exposure before disease onset;
- ◇ a dose-response relationship;
- ◇ a moderately strong odds ratio of about 2 when comparing the lowest and highest quintiles;
- ◇ consistency between the results of the nested case control studies which were homogeneous according to the DerSimonian-Laird test ( $p=0.90$ ). These studies are supported by inverse associations observed in several of the diet cohort studies (Table 2);
- ◇ biological plausibility based on a substantial body of laboratory work showing that vitamin D encourages cell differentiation and proliferation of colon cells.<sup>90</sup>

- ◇ consistency with the broad epidemiological evidence showing inverse associations between UV exposure and colorectal cancer mortality and morbidity in several countries (Table 1).

The quality of the evidence from nested case control studies showing an inverse association between baseline levels of blood 25-hydroxyvitamin D and subsequent risk of colorectal cancer is as good as, if not better than, the evidence that sun exposure increases the risk of melanoma which has recently been reviewed in a meta-analysis by Gandini and colleagues.<sup>91</sup> While this 2005 meta-analysis reviewed a large number of epidemiological studies published up to 2002 (n=57), aside from 5 cohort studies and 2 nested case control studies, most were case control studies (n=50) which collected information on sun exposure, using questionnaires, after cases had been diagnosed. The meta-analysis found evidence of recall bias for the measure of total sun exposure, since there was heterogeneity in the strength of the relative risks when comparing studies published before 1990 (pooled RR = 0.92, 95% confidence interval (CI): 0.59, 1.42) with those published after 1990 (pooled RR = 1.75, 95% CI: 1.31, 2.35). The authors concluded that increased public awareness over time of the link between sun exposure and malignant melanoma probably explains the rise in the pooled relative risk for total sun exposure after 1990.<sup>91</sup> Thus, this questionnaire information, mainly from case control studies, does not meet the Bradford-Hill criterion of temporality and is more prone to bias than the laboratory methods of blood vitamin D status used in the nested case control studies of colon cancer.

Further, the only measure of sun exposure in the meta-analysis that was associated with a melanoma relative risk of about 2 (similar in strength to that comparing the risk of colorectal cancer between the bottom and top quintiles of baseline blood 25-hydroxyvitamin D), was history of sunburn (pooled RR = 2.00, 95% CI: 1.71, 2.35). For intermittent sun exposure, the pooled relative risk of melanoma was 1.62 (95% CI: 1.31, 1.99), and for chronic sun exposure, the pooled relative risk of melanoma was 0.96 (95% CI: 0.87, 1.04).<sup>91</sup>

Overall, the quality of the evidence showing an inverse association between baseline blood 25-hydroxyvitamin D and subsequent risk of colorectal cancer is as good as the evidence that sunburn increases the risk of malignant melanoma. Is it logical to accept one but not the other? To be consistent, it is reasonable to conclude there is strong evidence that vitamin D, through sun exposure or dietary sources, protects against colorectal cancer.

## PROSTATE CANCER

Twenty-five studies were identified (Table 3). These have been separated into the following groups:

- ◇ cohort studies of dietary vitamin D
- ◇ case control studies of dietary vitamin D
- ◇ observational studies of sun exposure
- ◇ nested case control studies of blood 25-hydroxyvitamin D

### **Cohort studies of dietary vitamin D** (Appendix E).<sup>92-95</sup>

Four studies of dietary vitamin D and prostate cancer were identified. Three were from the US and one from Finland.<sup>93</sup> Two of the US studies used validated FFQs to measure vitamin D intake, and with 1792 and 3811 cases each, their statistical power to detect any association between vitamin D and prostate cancer was very high.<sup>92,94</sup> Despite this, none of the four cohort studies reported any association between baseline vitamin D intake and subsequent risk of prostate cancer (Table 3).

### **Case control studies of dietary vitamin D** (Appendix F).<sup>96-101</sup>

Six case control studies of dietary vitamin D and prostate cancer were identified. These studies mostly were carried out in Europe – in Serbia,<sup>96</sup> Sweden<sup>97</sup> or Italy<sup>101</sup> – with the remainder in Uruguay<sup>98</sup> or the United States.<sup>99,100</sup> None of these studies reported any association between dietary vitamin D and prostate cancer (Table 3). As discussed above for colon cancer, case control studies of diet and cancer are prone to dietary measurement error, which if random may have hidden any true association between dietary vitamin D and prostate cancer.

### **Studies of sun exposure** (Appendix G).<sup>102-105</sup>

Four studies of sun exposure and prostate cancer were identified. The first published was a case control study from the UK.<sup>103</sup> The cases were patients presenting to a urology clinic, and controls came from the same clinic and had prostatic hypertrophy. Lifetime UV exposure was measured using a validated questionnaire. Participants in the lowest quartile of UV exposure had a 3-fold increase in the risk of prostate cancer, compared to the highest quartile. This study was repeated from the same sampling frame and produced similar findings.<sup>105</sup> A further

case control study was published based on participants from the San Francisco bay Area.<sup>104</sup> In contrast with the above UK hospital-based study, the US study had a true population-based sampling strategy with cases coming from the regional cancer registry and controls selected by random digit dialling. A sun exposure index, based on the difference in skin colour between forehead and inside upper arm, measured with a spectrophotometer, was inversely associated with risk of prostate cancer. The other study was an analysis of data collected in the follow-up of the NHANES I cohort.<sup>102</sup> Sun exposure was estimated using solar radiation data from national weather services stations, based on the place of longest residence during the follow-up period for each participant. Participants in the highest tertile of solar radiation had a 38% reduced risk of prostate cancer compared to the lowest tertile.

The results of these three studies, which all used measures of sun exposure and reported inverse associations with prostate cancer risk, contrast with the cohort and case control studies of diet which found no association between vitamin D intake and prostate cancer. The reasons for this are unclear, but may due to the primary role of the sun as a source of vitamin D rather than diet.

#### **Nested case control studies of blood 25-hydroxyvitamin D** (Appendix H).<sup>87 106-114</sup>

Ten nested case control studies have been published comparing baseline blood 25-hydroxyvitamin D levels with subsequent risk of colorectal cancer;<sup>106-114</sup> plus one cohort study which estimated baseline plasma 25-hydroxyvitamin D levels from a sub-sample, and linked these with subsequent risk of colorectal cancer.<sup>87</sup> All studies were from the US, except for a Finnish sample,<sup>110</sup> which was included in a further meta-analysis of participants from Norway and Sweden.<sup>112</sup> The latter study found a U-shaped association between serum 25-hydroxyvitamin D and prostate cancer risk, and is reported twice in Table 3 to reflect this, while the former study found an inverse association. All the remaining (US) studies found no association between 25-hydroxyvitamin D and prostate cancer.

This contrasts greatly with the findings of a significant inverse association for the nested case control studies of 25-hydroxyvitamin D and colon cancer.<sup>22</sup> A similar meta-analysis of prostate cancer studies has not been done, but if and when it is, the results of individual studies reported in Appendix H show no clear pattern and suggest a meta-analysis will find no association. One possible explanation is that the US studies were carried out in cohorts that were vitamin D replete. In contrast with the Finnish study, which reported an inverse

association, and where the mean levels of 25-hydroxyvitamin D were 41 and 44 nmol/L in cases and controls, respectively,<sup>110</sup> some of the US studies had 25-hydroxyvitamin D levels above 75 nmol/L.<sup>107-109</sup> Alternatively, it maybe the case that vitamin D is unrelated to prostate cancer risk. Evidence for this comes from the cohort study by Giovannucci and colleagues who found in the same cohort that estimated serum 25-hydroxyvitamin D was inversely associated with colorectal cancer but not prostate cancer.<sup>87</sup> A full discussion of these studies has been published recently by Schwartz.<sup>115</sup>

### **Summary for prostate cancer**

Given the lack of consistency in the findings from studies of vitamin D and prostate cancer, particularly from the large number of nested case control studies, and despite the extensive laboratory research showing the anti-cancer properties of vitamin D in prostate cells,<sup>116</sup> the current evidence does not support an association between vitamin D and prostate cancer risk. This is the conclusion of recent reviews which call for more research on this topic.<sup>116 117</sup>

## **BREAST CANCER**

Nine studies were identified (Table 4). These have been separated into the following groups:

- ◇ observational studies of dietary vitamin D and sun exposure
- ◇ case control studies of blood 25-hydroxyvitamin D

### **Studies of dietary vitamin D and sun exposure** (Appendix I).<sup>118-122</sup>

Five observational studies of dietary vitamin D, sun exposure and breast cancer were identified. All studies were carried out in North America. Three were cohort studies from the US,<sup>118-120</sup> and the other two were case control studies from Canada.<sup>121 122</sup> Two studies measured both dietary vitamin D and sun exposure.<sup>118 122</sup> Three studies reported significant inverse associations between vitamin D intake or sun exposure and breast cancer risk,<sup>119 120 122</sup> while a further study reported an inverse association between sun exposure and breast cancer risk that just failed to reach statistical significance ( $p=0.06$ ).<sup>118</sup> The only study to report no association was a small case control study from Canada, which most likely had low statistical power because of its small sample size (only 108 cases).<sup>121</sup>

### **Case control studies of blood 25-hydroxyvitamin D (Appendix J).<sup>123-126</sup>**

Four studies were identified which measured blood levels of 25-hydroxyvitamin D. Only one of these was a nested case control study,<sup>123</sup> while the remainder were conventional case control studies which measured 25-hydroxyvitamin D after diagnosis in cases, by which time levels may not have reflected vitamin D status at the time cancer was initiated.<sup>124-126</sup> Only one of these four studies reported a significant inverse association,<sup>125</sup> which has been reported in a further publication,<sup>127</sup> although the nested case control study by Bertone-Johnson and colleagues also observed an inverse association which just failed to reach statistical significance (p=0.06).<sup>123</sup>

### **Summary for breast cancer**

The number of studies identified is too small to reach a firm conclusion about the association between vitamin D, sun exposure and risk of breast cancer. Four out of the nine studies reported significant inverse associations,<sup>119 120 122 125</sup> and a further two just failed to reach statistical significance.<sup>118 123</sup> Importantly, there are no reports yet of a positive association between vitamin D intake or sun exposure and breast cancer. If there was truly no association between vitamin D and breast cancer, the results in Table 4 should have been distributed across all three possible directions of association. At the moment, the research leans more towards an inverse association, but much further research is required confirm this possibility.

## **OVARIAN AND ENDOMETRIAL CANCER**

Six studies of vitamin D and ovarian cancer,<sup>128-133</sup> and one of endometrial cancer,<sup>134</sup> were identified (Table 5, Appendix K). One was a nested case control study, which reported an inverse association between plasma 25-hydroxyvitamin D and ovarian cancer risk in women with a BMI >25, but not in the total sample.<sup>128</sup> The remainder all measured dietary vitamin D, including a meta-analysis of 12 cohort studies which also reported no association with ovarian cancer.<sup>130</sup>

### **Summary of ovarian cancer**

The limited evidence suggests no association between vitamin D and risk of ovarian cancer.

## NON-HODGKIN LYMPHOMA

Five studies, all case control studies, of sun exposure or vitamin D and non-Hodgkin lymphoma were identified (Table 6, Appendix L).<sup>135-139</sup> The studies have been carried out across the globe, starting with the Australian study by Hughes and colleagues in 2004,<sup>135</sup> which was followed by studies from Denmark,<sup>136</sup> the US<sup>137 139</sup> and Italy.<sup>138</sup> Three studies measured prior sun exposure,<sup>135 136 139</sup> one measured vitamin D intake,<sup>138</sup> and one measured both.<sup>137</sup> Three of the studies reported inverse associations between sun exposure or vitamin D and risk of non-Hodgkin lymphoma;<sup>135 136 138</sup> while a fourth study observed an inverse association for its measure of sun exposure that just failed to reach statistical significance ( $p=0.07$ ).<sup>137</sup> In contrast, the most recent study reported a positive association between sun exposure and risk of non-Hodgkin lymphoma.<sup>139</sup>

### Summary of non-Hodgkin lymphoma

The limited evidence suggests there may be an inverse association between vitamin D and risk of non-Hodgkin lymphoma, which is supported by some of the ecological studies (Table 1), but much further research is required confirm this possibility.

## OTHER CANCERS

Two studies of vitamin D and pancreatic cancer, and one of renal cancer, were identified (Table 7, Appendix M).<sup>140-142</sup> One was a nested case control study in Finland which observed a significant positive association between serum 25-hydroxyvitamin D and risk of pancreatic cancer,<sup>140</sup> in a cohort that previously has shown lower mean levels of 25-hydroxyvitamin D in cases of colorectal cancer compared with matched controls (see Appendix D).<sup>85</sup> In contrast, a meta-analysis of two large US cohorts has reported a significant inverse association between baseline vitamin D intake and risk of pancreatic cancer.<sup>141</sup> The only study identified of dietary vitamin D and renal cancer, a case control study, found no association.<sup>142</sup>

### Summary of other cancers

Further research is required.

## CANCER SURVIVAL

Eight studies were identified which examined cancer survival in relation to season of diagnosis and vitamin D (Table 8). These have been separated into the following groups:

- ◇ cancer survival by season of diagnosis
- ◇ cancer survival by vitamin D status

### **Season of diagnosis and cancer survival** (Appendix N).<sup>143-148</sup>

Six studies of cancer survival by season of diagnosis were identified. All have been carried on Norwegian cancer registry data by the same research group,<sup>143-147</sup> aside from a very large study which examined survival in over one million patients from South East England.<sup>148</sup> All studies have reported lower mortality for cancer patients diagnosed in autumn or summer, compared with those diagnosed in winter, in all patients, or subgroups. The cancers showing reduced mortality include breast, colon, prostate, lung and Hodgkin's lymphoma. The reductions in mortality vary from about 5% in the English study,<sup>148</sup> to over 20% in some of the Norwegian studies.<sup>143 145</sup>

### **Vitamin D and cancer survival** (Appendix O).<sup>149 150</sup>

Two studies of vitamin D and survival of lung cancer patients were identified. Both reports come from the same group of lung cancer patients in Boston. The first report examined dietary vitamin D, and found a significant inverse association with mortality for patients diagnosed in summer, but not for those diagnosed in winter.<sup>149</sup> The second report observed an inverse association between blood 25-hydroxyvitamin D and mortality, particularly in stage IB-IIIB cases.<sup>150</sup>

### **Summary of survival**

The number of studies identified is too small to reach a firm conclusion about the association between vitamin D, season of diagnosis and cancer survival. The limited evidence suggests there may be association between vitamin D status and cancer survival, but further research is required confirm this possibility.

## ALL CANCERS

Given the laboratory research showing that vitamin D has anti-cancer effects in a wide range of tissues,<sup>90</sup> and the evidence of autocrine synthesis of the active vitamin D metabolite (1,25-dihydroxyvitamin D) by many cell types,<sup>151</sup> vitamin D may reduce the incidence and mortality from all cancers. This possibility has been investigated by Giovannucci and colleagues in the US Health Professionals Follow-Up Study, where they estimated plasma 25-hydroxyvitamin D in the total cohort of 47,800 men based on regression coefficients from actual blood measures in a sub-sample of 1095 men.<sup>87</sup> This analysis found that an increment in 25-hydroxyvitamin D of 25 nmol/L was associated with a 17% reduction in total cancer incidence and 29% reduction in total cancer mortality. The reduction occurred mainly for digestive cancers (colorectum, stomach, pancreas, oesophagus and oral-pharynx), with a 43% reduction in incidence and 45% reduction in mortality, adjusting for a wide range of lifestyle covariates.

This finding is supported by a recent RCT of 1179 US women aged >55 years which found that taking daily doses of 1100 IU of vitamin D3 and 1500 mg of calcium reduced total cancer incidence by 60% compared with placebo.<sup>62</sup> However, a similar reduction also occurred in women who received calcium alone, so the effects may not be due to vitamin D. Moreover, it is surprising to see a significant reduction in cancer incidence in such a small sample, and the study needs to be confirmed by further RCTs.

## SUMMARY

- ◇ *Colorectal cancer*: There is strong evidence that vitamin D, through sun exposure or dietary sources, protects against colorectal cancer. Given the lost opportunity from the Women's Health Initiative RCT which gave too low a dose of vitamin D,<sup>61 89</sup> it is unlikely there will be a further RCT in the near future to test the effect of vitamin D on colon cancer risk. The best evidence will continue to come from nested case control studies of blood 25-hydroxyvitamin D. A recent meta-analysis shows a significant inverse association between 25-hydroxyvitamin D and colorectal cancer.<sup>22</sup> The quality of this evidence is as strong as the evidence for sun exposure and malignant melanoma.
- ◇ *Prostate cancer*: a large number of studies have been published with inconsistent evidence. Currently, it does not support an association between vitamin D and prostate cancer.
- ◇ *Breast cancer*: a limited number of studies have been published. Currently, the evidence supports an inverse association between vitamin D and breast cancer, but more research is required to confirm this possibility.
- ◇ *Ovarian cancer*: the limited evidence suggests there is no association between vitamin D and ovarian cancer.
- ◇ *Non-Hodgkin lymphoma*: the limited evidence suggests there may be an inverse association between vitamin D and risk of non-Hodgkin lymphoma, but more research is required confirm this possibility.
- ◇ *Cancer survival*: the limited evidence suggests cancer survival may be associated inversely with vitamin D and diagnosis during summer or autumn, but more research is required confirm this possibility.
- ◇ *All cancers*: the limited evidence suggests there may be an inverse association between vitamin D and total cancer incidence, but more research is required.

## CONCLUSION

The strong evidence from studies showing an inverse association between vitamin D and colorectal cancer, when combined with similar (albeit limited) findings from studies of total cancer incidence and mortality, suggest that cancer incidence and mortality in New Zealanders can be expected to decline if levels of vitamin D in the population are increased.

## IMPLICATIONS FOR POLICY ON SUN EXPOSURE

The above conclusion has implications for the policy on sun exposure currently supported by the NZ Cancer Society. This policy has been developed primarily from the need to limit the incidence of skin cancers, particularly malignant melanoma, in the general population.

However, the opposite effects of sun exposure and vitamin D on skin cancer and colorectal cancer need to be recognised by developing a sun exposure policy that minimises the risk of both types of cancer.

Further, since risk of skin cancer and vitamin D deficiency are inversely related, sun exposure policy needs to be developed so that people at low risk of skin cancer are able to increase their vitamin D status by increasing their sun exposure. The current NZ policy recognises this dilemma, but it needs to be progressed by developing more targeted messages that vary between population subgroups and minimise the risk of vitamin D deficiency in people with increased skin pigmentation.<sup>152</sup>

Three strategies are available for increasing the vitamin D status of the general population.

1. *Increasing sun exposure.* The sun is the primary source of vitamin D (>80%) and increasing sun exposure is the most effective strategy for increasing vitamin D levels.
2. *Fortification of foods with vitamin D.* There is a long regulatory pathway involved with the mandatory fortification of foods, and the recent experience with folic acid supplementation indicates that this will take a number of years to achieve.
3. *Vitamin D supplementation.* The doses of vitamin D supplements most commonly available in New Zealand are very low (about 100 IU per tablet), although higher doses (up to 1000 IU) are available. Equity issues are involved with supplementation since Maori and Pacific people, who have increased risk of vitamin D deficiency, are less likely to use supplements because of their poorer socioeconomic status. There are also safety issues with vitamin D as it is possible to overdose from excessive ingestion.<sup>153</sup>

A policy that combines all strategies is more likely to raise vitamin D levels than reliance on a single strategy.

Further research is required to assist policy development. There are few studies on the role of vitamin D and sun exposure for some cancers (eg. breast cancer, lymphoma) and further

epidemiological studies are required. However, New Zealand does not have the resources to carry out nested case control studies which compare baseline serum measurements of 25-hydroxyvitamin D with subsequent risk of cancer, since they cost many millions of dollars. In contrast, standard case control studies using objective measures of prior cumulative sun exposure, such as actinic damage which has been applied to multiple sclerosis,<sup>154</sup> are much less expensive and more fundable in New Zealand. Objective measures of prior sun exposure are preferable to questionnaire methods since they avoid the possibility of recall bias. Studies based on dietary vitamin D intake should be avoided, since diet contributes a very small part of total vitamin D sources and, thus, is not a valid measure of vitamin D status.

To date, policy has been based mainly on relative risk calculations from epidemiological studies which have had the main goal of determining whether sun exposure and vitamin D are risk factors for cancer. The next step requires the application of relative risk estimates into population attributable risk calculations which estimate the proportion of disease events that can be attributed to (explained by) a particular exposure. This has recently been done for international populations by the World Health Organisation.<sup>155</sup> The approach used in the WHO report needs to be updated with more recent results from epidemiological studies, particularly for melanoma and colon cancer and other non-communicable diseases such as hip-fracture and diabetes, where there is sufficient evidence, and applied to each of the main ethnic groups in the New Zealand population for whom there is available information. Given that much of the variation in skin-pigmentation in the NZ population is related to ethnicity, ethnic specific attributable risks should facilitate the decision making process around policy development. For example, Maori have about 80 registrations for colorectal cancer each year, much more than the approximate 15 annual registrations for melanoma,<sup>156</sup> of which between 8-13 (50-90%) can be attributed to sun exposure.<sup>155</sup> Attributable risk calculations need to be done for colorectal cancer, and other diseases such as diabetes and hypertension. While, the above numbers suggest it is likely that the overall health status of Maori may benefit from increased sun exposure, this process needs to be formally carried out using all available data sources, including the vitamin D data collected in the 1997 Adult Nutrition Survey funded by the Ministry of Health. If the required information is available, similar calculations also should be carried out for Pacific and Asian people as they are protected against skin cancer but have low vitamin D levels due to their increased skin pigmentation.

Table 1: Summary of *ecological studies* of UV exposure & cancer mortality and/or incidence (Appendix A).

Type of Study	Direction of Association		
	Inverse	None	Positive
Colon (and rectal) cancer	Garland 1980 <sup>3</sup> Emerson 1992* <sup>43</sup> Grant 2002b <sup>52</sup> Mizoue 2004 <sup>54</sup> Grant 2006a <sup>58</sup> Grant 2006b <sup>59</sup> Boscoe 2006* <sup>60</sup>		
Breast Cancer	Garland 1990 <sup>40</sup> Gorham 1990* <sup>42</sup> Grant 2002a <sup>51</sup> Grant 2002b <sup>52</sup> Grant 2006b <sup>59</sup> Boscoe 2006* <sup>60</sup>		
Prostate cancer	Schwartz 1990 <sup>41</sup> Hanchette 1992 <sup>44</sup> Grant 2002b <sup>52</sup> Grant 2004 <sup>55</sup> Boscoe 2006* <sup>60</sup>		
Ovarian Cancer	Lefkowitz 1994 <sup>45</sup> Grant 2002b <sup>52</sup> Garland 2006* <sup>57</sup> Grant 2006b <sup>59</sup> Boscoe 2006 <sup>60</sup>		
Lymphoma	Newton 1995* <sup>46</sup> Hartge 1996 <sup>48</sup> Grant 2002b <sup>52</sup> Grant 2006a <sup>58</sup> Grant 2006b <sup>59</sup> Boscoe 2006* <sup>60</sup>	Langford 1998 <sup>50</sup> Hu 2004* <sup>53</sup>	Bentham 1996* <sup>47</sup> McMichael 1996* <sup>49</sup>
Other Cancers	Grant 2002b <sup>52</sup> Mizoue 2004 <sup>54</sup> Grant 2006a <sup>58</sup> Grant 2006b <sup>59</sup> Boscoe 2006* <sup>60</sup>	Grant 2006b <sup>59</sup> Boscoe 2006* <sup>60</sup>	Grant 2006a <sup>58</sup> Boscoe 2006* <sup>60</sup>

\* Incidence

Table 2: Summary of studies of vitamin D & *colorectal* cancer.

Type of Study	Direction of Association			Total
	Inverse	None	Positive	
Cohort: dietary vitamin D (Appendix B)	Garland 1985 <sup>63</sup> Bostick 1993 <sup>66</sup> Kearney 1996 <sup>67</sup> Martinez 1996 <sup>68</sup> McCullough 2003 <sup>73</sup> Park 2007 <sup>76</sup>	Heilbrun 1985 <sup>64</sup> Willett 1990 <sup>65</sup> Zheng 1998 <sup>69</sup> Pietinen 1999 <sup>70</sup> Jarvinen 2001 <sup>71</sup> Terry 2002 <sup>72</sup> Kesse 2005 <sup>74</sup> Lin 2005 <sup>75</sup>		14
Case control: dietary vitamin D (Appendix C)	Ferraroni 1994 <sup>79</sup>	Benito 1991 <sup>77</sup> Peters 1992 <sup>78</sup> Pritchard 1996 <sup>80</sup> La Vecchia 1997 <sup>81</sup> Marcus 1998 <sup>82</sup>		6
Nested case control: blood 25-hydroxyvitamin D (Appendix D)	Feskanich 2004 <sup>86</sup> Wactawski-Wende 2006 <sup>61</sup> Giovannucci 2006* <sup>87</sup>	Garland 1989 <sup>83</sup> Braun 1995a <sup>84</sup> Tangrea 1997 <sup>85</sup>		6
Randomised trial (described in text)		Wactawski-Wende 2006 <sup>61</sup>		1
<b>Total</b>	10	17	0	27

\* estimated serum 25-hydroxyvitamin D

Table 3: Summary of studies of vitamin D or UV exposure & *prostate* cancer.

Type of Study	Direction of Association			Total
	Inverse	None	Positive	
Cohort: dietary vitamin D (Appendix E)		Giovannucci 1998 <sup>92</sup> Chan 2000 <sup>93</sup> Rodriguez 2003 <sup>94</sup> Tseng 2003 <sup>95</sup>		4
Case control: dietary vitamin D (Appendix F)		Vlajinac 1997 <sup>96</sup> Chan 1998 <sup>97</sup> Deneo-Pellegrini 1999 <sup>98</sup> Berndt 2002 <sup>99</sup> Kristal 2002 <sup>100</sup> Tavani 2005 <sup>101</sup>		6
Observational: sun exposure (Appendix G)	Luscombe 2001 <sup>103</sup> Bodiwala 2003 <sup>105</sup> John 2004 <sup>102</sup> John 2005 <sup>104</sup>			4
Nested case control: blood 25-hydroxyvitamin D (Appendix H)	Ahonen 2000 <sup>110</sup> Tuohimaa 2004 <sup>#112</sup>	Corder 1993 <sup>106</sup> Braun 1995b <sup>107</sup> Gann 1996 <sup>108</sup> Nomura 1998 <sup>109</sup> Platz 2004 <sup>111</sup> Jacobs 2004 <sup>113</sup> Baron 2005 <sup>114</sup> Giovannucci 2006* <sup>87</sup>	Tuohimaa 2004 <sup>#112</sup>	11
<b>Total</b>	6	18	1	25

\* estimated serum 25-hydroxyvitamin D

# U-shaped association

Table 4: Summary of studies of vitamin D or UV exposure & *breast* cancer.

Type of Study	Direction of Association			Total
	Inverse	None	Positive	
Observational: dietary vitamin D & sun exposure (Appendix I)	Shin 2002 <sup>119</sup> McCullough 2005 <sup>120</sup> Knight 2007 <sup>122</sup>	Simard 1991* <sup>121</sup> John 1999 <sup>118</sup>		5
Case control: blood 25-hydroxyvitamin D (Appendix J)	Lowe 2005 <sup>125</sup>	Janowsky 1999 <sup>124</sup> Bertone-Johnson 2005* <sup>123</sup> de Lyra 2006 <sup>126</sup>		4
<b>Total</b>	4	5	0	9

\* nested case control study.

Table 5: Summary of studies of vitamin D & *ovarian* or *endometrial*\* cancer (Appendix K).

Type of Study	Direction of Association			Total
	Inverse	None	Positive	
Cohort or nested case control of blood 25-hydroxyvitamin D		Koralek 2006 <sup>129</sup> Genkinger 2006 <sup>+130</sup> Tworoger 2007 <sup>#128</sup>		3
Case control		Bidoli 2001 <sup>131</sup> Goodman 2002 <sup>132</sup> Salazar-Martinez 2002 <sup>133</sup> Salazar-Martinez 2005* <sup>134</sup>		4
<b>Total</b>	0	7	0	7

<sup>+</sup> meta-analysis of 12 cohort studies

<sup>#</sup> nested case control study of plasma 25-hydroxyvitamin D

Table 6: Summary of studies (all case control) of vitamin D or UV exposure & *non-Hodgkin lymphoma* (Appendix L).

Type of Study	Direction of Association			Total
	Inverse	None	Positive	
All studies	Hughes 2004 <sup>135</sup> Smedby 2005 <sup>136</sup> Polesel 2006* <sup>138</sup>	Hartge 2006 <sup>137</sup>	Zhang 2007 <sup>139</sup>	5
<b>Total</b>	3	1	1	5

\* diet only.

Table 7: Summary of studies of vitamin D & *pancreatic* or *renal*\* cancer (Appendix K).

Type of Study	Direction of Association			Total
	Inverse	None	Positive	
Cohort or nested case control of blood 25-hydroxyvitamin D	Skinner 2006 <sup>141</sup>		Stolzenberg-Solomon 2006 <sup>#140</sup>	2
Case control		Bosetti 2007* <sup>142</sup>		1
<b>Total</b>	1	1	1	3

# nested case control study of serum 25-hydroxyvitamin D

Table 8: Summary of studies of vitamin D or season of diagnosis & *cancer survival*.

Type of Study	Direction of Association			Total
	Inverse	None	Positive	
Season of diagnosis (Appendix N)	Robsahm 2004 <sup>143</sup> Moan 2005 <sup>144</sup> Porojnicu 2005 <sup>145</sup> Porojnicu 2007a <sup>146</sup> Lim 2006 <sup>148</sup>	Porojnicu 2007b* <sup>147</sup>		6
Vitamin D (Appendix O)	Zhou 2007 <sup>#150</sup>	Zhou 2005 <sup>149</sup>		2
<b>Total</b>	6	2	0	8

\* inverse association for men  $\leq$  50 years.

# nested case control study of blood 25-hydroxyvitamin D.

## Appendix A: Ecological studies of UV exposure and cancer

Paper	Population unit (number)	Measure of UV exposure	Measure of cancer occurrence	Main results
Garland 1980 <sup>3</sup>	US states (n=49).	Annual mean solar radiation from US Weather Bureau maps.	Colon cancer mortality (age-adjusted) for white males during 1959-61.	Inverse correlation for metropolitan (r = -0.9) and non-metropolitan (r = -0.6) states. Not explained by dietary consumption of meats, fruit & vegetables.
Garland 1990 <sup>40</sup>	US counties with UV measures (32 urban, 29 less urban)	Solar radiation measured by US National Oceanic & Atmospheric Administration.	Breast cancer mortality (age-adjusted) for white women during 1950-1969.	Inverse correlation: r = -0.80, p = 0.0001. No association between solar radiation and other cancers (p>0.05).
Schwartz 1990 <sup>41</sup> Anticancer Res	USA states (n=47)	Annual UV radiation estimated from latitude and cloud cover	Age-adjusted prostate cancer mortality for white & black men, 1950-1969.	Inverse correlation between UV radiation and prostate cancer mortality for whites (47 states, r = - 0.53, p < 0.001) and blacks (22 states, r = - 0.54, p < 0.01).
Gorham 1990 <sup>42</sup>	USSR Republics (n=15)	Average annual ambient solar energy	Breast cancer incidence for 1969-1971 (age-adjusted)	Inverse correlation with solar energy: r = -0.75, p = 0.001.
Emerson 1992 <sup>43</sup>	US states (n=9)	Average daily solar radiation from National Weather Service Stations	Colon and rectal cancer incidence for whites, 1973-1984 (age-adjusted)	Inverse correlation with solar radiation in men for colon cancer (p=0.03) and rectal cancer (p=0.01).
Hanchette 1992 <sup>44</sup>	Counties in the contiguous US (n=3073)	Epidemiologic index based on cloud cover & latitude. UV count based on altitude & latitude.	Prostate cancer mortality for white men, 1970-1979.	Positive correlation with latitude: r = 0.19, p = 0.0001. Significant association with epidemiological index (p=0.0002) and UV count (p=0.0001).
Lefkowitz 1994 <sup>45</sup>	USA: 100 largest cities	Solar radiation measured by pyranometers; and sulphur dioxide pollution	Ovarian cancer mortality (age-adjusted) for white women during 1979-1988.	Inverse correlation with solar radiation: r = - 0.42, p <0.0001. Remained significant when also adjusting for sulphur dioxide and ozone thickness.
Newton 1995 <sup>46</sup>	USA: 6 locations	Solar radiation	Incidence of non-Hodgkin lymphoma	Inverse association with solar radiation in men (p<0.05) and women, separately.
Bentham 1996 <sup>47</sup>	England and Wales: 59 counties	Annual erythemal UV radiation estimated from data and cloud cover.	Age and sex adjusted odds ratios of non-Hodgkin lymphoma incidence for 1968-85, for each county against all others combined.	Positive association with UV radiation (p=0.004), adjusting for social class and agricultural employment, plus age and sex.
Hartge 1996 <sup>48</sup>	USA: state economic areas	Annual solar UVB radiation from Robertson-Berger (RB) meters, adjusted for latitude, altitude and cloud cover.	Age-adjusted mortality from non-Hodgkin lymphoma for whites during 1970-1989.	Mortality decreased by 16% in men, and 17% in women, for each addition RB unit of UVB radiation (p<0.0001).
McMichael 1996 <sup>49</sup>	International: 49 cancer registries in Europe, North America & ANZ	Solar UVB estimated from latitude	Age-adjusted incidence of non-Hodgkin lymphoma in Caucasian populations.	Positive correlation with estimated solar radiation in men (r=0.50, p<0.001) and women (r=0.51, p<0.001).

Langford 1998 <sup>50</sup>	Europe (354 counties in 9 countries)	Solar UVB estimated from cloud cover & latitude	Non-Hodgkin lymphoma mortality for 1971-1980.	No association with UV after adjusting for per capita GDP (p=0.081).
Grant 2002a <sup>51</sup>	International from 34 countries	Latitude	Breast cancer mortality for 1994-96.	Positive correlation with latitude: r = 0.66, p < 0.001.
Grant 2002b <sup>52</sup>	US counties (combined into 506 state economic areas).	NASA Total Ozone Mapping Spectrometers (TOMS).	Cancer mortality (age-adjusted, ethnic specific) for 1970-1994.	Inverse association (p<0.001) with cancer of the breast, colon, ovary, prostate, non-Hodgkin lymphoma, bladder, oesophagus, kidney, lung, pancreas, rectum, stomach & uterus.
Hu 2004 <sup>53</sup>	US states (n=6)	UV index and latitude	Age-adjusted incidence of non-Hodgkin lymphoma for 1989-2000.	No association with UV index or latitude (p>0.05).
Mizoue 2004 <sup>54</sup>	Japanese prefectures (n=47).	Solar radiation averaged for 1961-1990.	Cancer mortality in 2000.	Inverse correlations (coefficient ranging from -0.6 to -0.3) for cancers of the oesophagus, stomach, colon, rectum, pancreas, and gall bladder and bile ducts, in both sexes.
Grant 2004 <sup>55</sup>	International from 32 countries (mostly developed)	UV estimated from latitude	Prostate cancer mortality for late 1990s.	Inverse correlation with estimated UV: r = -0.71, p < 0.001.
Schwartz 2006 <sup>56</sup> Cancer Causes Contr	US counties (>2500)	UV Index	Prostate cancer mortality for white males during 1950-94.	Inverse correlation with UV Index for counties above latitude 40°N: r = -0.16, p < 0.0001
Garland 2006 <sup>57</sup>	International (175 countries)	UVB irradiance estimated from latitude and stratospheric ozone column.	Ovarian cancer incidence (age-adjusted) for 2002.	Cancer incidence inversely correlated with UVB (p=0.002) and positively correlated with ozone (p=0.0008), adjusting for each other & fertility in women aged 15-19 years.
Grant 2006a <sup>58</sup>	Spanish provinces (n=48).	Latitude	Cancer mortality (age-adjusted) for 1978-1992.	In both sexes, latitude associated (p<0.05) <i>positively</i> with brain, gastric, pancreatic, rectal, and thyroid cancers; <i>negatively</i> with bladder, laryngeal (men only) and non-melanoma skin cancer. In women only, <i>positively</i> with non-Hodgkin's lymphoma and pleural cancer, <i>negatively</i> with uterine cancer.
Grant 2006b <sup>59</sup>	US States	UVB irradiance from NASA Total Ozone Mapping Spectrometers (TOMS).	Cancer mortality (age-adjusted) for 1950-69 and 1970-94.	UVB inversely associated with total cancer mortality in men and women separately, adjusting for smoking (via lung cancer), alcohol, urban/rural, Hispanic ethnicity and poverty. Same pattern for gastrointestinal, urogenital and breast cancers and lymphomas.
Boscoe 2006 <sup>60</sup>	US counties	UVB irradiance from NASA Total Ozone Mapping Spectrometers (TOMS).	Cancer incidence (1,499 counties) and mortality (3,108 counties) for whites during 1993-2002.	UVB inversely associated most strongly with incidence and mortality from cancers of the bladder, colon, Hodgkin lymphoma, myeloma, prostate, rectum, stomach, uterus and vulva; adjusted for age, poverty, income, smoking (via lung cancer), exercise, alcohol, outdoor occupation, urban/rural, and air quality.

## Appendix B: Cohort studies investigating the relationship between colorectal cancer and dietary intake of vitamin D.

Paper	Subjects	Methods	Measurement of vitamin D status	Confounders adjusted for	Main results
<i>Cohort</i>					
Garland 1985 <sup>63</sup>	<ul style="list-style-type: none"> <li>◇ 1954 men aged 40-55 years, from 2107 out of 3102 (67%) randomly selected in 1957 from 5397 men employed <math>\geq 2</math> years at electricity company in Chicago.</li> <li>◇ 153 men with cancer at baseline or missing information omitted from analyses.</li> </ul>	<ul style="list-style-type: none"> <li>◇ Baseline diet assessments in 1957 &amp; 1958.</li> <li>◇ Annual assessments until 1969; vital status determined in 99%.</li> <li>◇ 49 colorectal cancer cases over 19 year f/u, on death record or questionnaire, checked against medical records (88%).</li> </ul>	Average of vitamin D intake from 28-day diet histories collected by nutritionists at baseline & 1 year later.	Age & energy intake	Inverse association between quartile of vitamin D intake & 19 year risk of colorectal cancer: Q1 (lowest) = 30.7 /1000 Q2 = 38.9 /1000 Q3 = 14.3 /1000 Q4 = 16.4 /1000, (p-value for trend <0.05).
Heilbrun 1985 <sup>64</sup>	8006 Japanese men Hawaii	<ul style="list-style-type: none"> <li>◇ 100 colon cancer and 59 rectal cancer cases identified over 13-16 years of follow-up.</li> </ul>	Single 24-hour recall of food intake.	Age.	No association. Odds ratio (95% CI) of colon cancer, compared with the <i>highest</i> quartile (Q4) of vitamin D intake was: Q1 = 0.81 Q2 = 1.13 Q3 = 1.12, adjusting for all covariates (p-value for trend = 0.52).
Willett 1990 <sup>65</sup>	88,751 US female registered nurses aged 34-59 years in 1980, without cancer in 1980 (Nurses' Health Study).	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1980.</li> <li>◇ 150 colon cancer cases over 6 year f/u, from biennial questionnaires verified by pathology records or National Death Index.</li> </ul>	Self-administered validated 61-item FFQ of food intake.	Age, and intake of red-meat, chicken, fish and total energy.	No data reported, aside from text stating that vitamin D intake was not associated with colon cancer risk.
Bostick 1993 <sup>66</sup>	35,216 women aged 55-69 years in 1986, with valid 1985 Iowa driver's licence & without cancer.	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1986. Questionnaire mailed to home.</li> <li>◇ 212 cases of colon cancer over 5 year f/u, from state registry.</li> </ul>	Self-administered 127-item validated FFQ of food & supplements.	Age, height, parity, energy intake, low fat meat, vitamin E.	Inverse association. Relative risk (95% CI) of colon cancer, compared with the lowest quintile (Q1) was: Q2 = 0.71 (0.48, 1.07) Q3 = 0.76 (0.51, 1.13) Q4 = 0.78 (0.53, 1.17) Q5 = 0.54 (0.35, 0.84),

					adjusting for all covariates (p-value for trend = 0.02).  A stronger inverse association was observed for vitamin D from supplements than from food.
Kearney 1996 <sup>67</sup> (same sample as Giovannucci 1998 <sup>92</sup> & Platz 2004 <sup>111</sup> )	47,935 US male health professionals aged 40-75 years, without cancer in 1986.	◇ Baseline survey in 1986. Questionnaire mailed to home. ◇ 202 cases of colon cancer over 6 year f/u, from biennial questionnaires verified by pathology records or National Death Index.	Self-administered 131-item validated FFQ of food & supplements.	Age, family history of colon cancer, previous polyp, screening, smoking, alcohol, aspirin, physical activity, BMI, total energy, red meat, saturated fat, dietary fibre.	Inverse association. Relative risk (95% CI) of colon cancer, compared with the lowest quintile (Q1) was: Q2 = 1.06 (0.70, 1.60) Q3 = 0.85 (0.55, 1.31) Q4 = 0.68 (0.43, 1.08) Q5 = 0.66 (0.42, 1.05), adjusting for all covariates (p-value for trend = 0.02).  A stronger inverse association was observed for vitamin D from supplements than from food.
Martinez 1996 <sup>68</sup> (same survey as Willett 1990 <sup>65</sup> & Shin 2002 <sup>119</sup> )	89,448 US female registered nurses aged 34-59 years in 1980, without cancer in 1980 (Nurses' Health Study).	◇ Baseline survey in 1980. ◇ 501 cancer cases (396 colon, 105 rectal) over 12 year f/u, from biennial questionnaires verified by pathology records or National Death Index.	Self-administered validated FFQs of food & supplements: ◇ 1980 61 food items ◇ 1984 121 items ◇ 1986 136 items Analysis of vitamin D intake from 1980 FFQ, and from average of all 3 FFQs	Age, BMI, physical activity, family history of colorectal cancer, aspirin, smoking, red meat, alcohol.	Relative risk (95% CI) of colorectal cancer for highest 1980 quintile compared with the lowest was 0.67 (0.47, 0.95), p-value for trend = 0.02 adjusting for all covariates, in analyses restricted to unchanged milk intake in previous 10 years. Findings suggestive of inverse association between vitamin D and colorectal cancer, esp. rectal cancer.

Zheng 1998 <sup>69</sup>	34,702 women aged 55-69 years in 1986, with valid 1985 Iowa driver's licence & without cancer.	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1986. Questionnaire mailed to home.</li> <li>◇ 144 cases of rectal cancer over 9 year f/u, from state registry.</li> </ul>	Self-administered 127-item validated FFQ of food & supplements.	Age, smoking, hormone replacement therapy, total energy intake.	No association. Relative risk (95% CI) of colon cancer, compared with the lowest tertile (T1) was: T2 = 0.71 (0.47, 1.08) T3 = 0.76 (0.50, 1.16), adjusting for all covariates (p-value for trend = 0.20).
Pietinen 1999 <sup>70</sup> (same sample as Tangrea 1997 <sup>85</sup> & Chan 2000 <sup>93</sup> )	27,111 male smokers, aged 50-69 years, free of cancer, recruited from a population register of south-western Finland into an RCT of alpha-tocopherol and beta-carotene (ATBC Study).	<ul style="list-style-type: none"> <li>◇ Recruitment into the survey started in 1985.</li> <li>◇ 185 cases of colon &amp; rectal cancer, identified from the national cancer registry from 1985-1995.</li> </ul>	Self-administered 276-item validated FFQ of food.	Age, supplement group, smoking years, BMI, alcohol, education, physical activity at work, and calcium intake.	No association. Relative risk (95% CI) of colorectal cancer, compared with the lowest quartile (Q1) was: Q2 = 1.0 (0.6, 1.4) Q3 = 0.8 (0.5, 1.2) Q4 = 1.0 (0.7, 1.5), adjusting for all covariates (p-value for trend = 0.77).
Jarvinen 2001 <sup>71</sup>	9,959 cancer free men and women aged $\geq 15$ years with dietary measures (about 20% of the total sample) recruited in a health survey from the general population in Finland during 1966-72.	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1966-72.</li> <li>◇ 72 cases of colorectal cancer identified from the national cancer registry up to December 1991.</li> </ul>	Interviewer-administered 100 item quantitative FFQ.	Age, sex, BMI, occupation, smoking, geographical area & energy intake.	No association. Relative risk (95% CI) of colorectal cancer, compared with the lowest quartile (Q1) was: Q2 = 1.19 (0.59, 2.41) Q3 = 1.37 (0.67, 2.82) Q4 = 1.74 (0.82, 3.68), adjusting for all covariates (p-value for trend = 0.13).
Terry 2002 <sup>72</sup>	61,463 cancer free women, mean age 57 years at baseline, recruited through population-based mammography screening program in two Swedish counties.	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1987-1990.</li> <li>◇ 572 cases of colorectal cancer identified from the national cancer registry up to December 2000.</li> </ul>	Self-administered 67-item validated FFQ of food.	Age, BMI, education, red meat, alcohol, saturated fat, folic acid, vitamin C, & calcium.	No association. Relative risk (95% CI) of colorectal cancer, compared with the lowest quartile (Q1) was: Q2 = 0.96 (0.75, 1.22) Q3 = 0.95 (0.75, 1.21) Q4 = 1.05 (0.83, 1.33), adjusting for all covariates (p-value for trend = 0.73). Similar results for colon & rectal cancer.
McCullough 2003 <sup>73</sup> (same survey as Rodriguez 2003 <sup>94</sup> & McCullough	60,866 men & 66,883 women aged 50-74 years recruited from the Cancer Prevention Study (CPS II) in 21 US states in 1992-93.	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1992-93. Questionnaire mailed to home.</li> <li>◇ 683 cases of colorectal cancer (up to 31 Aug 1997), from CPS II survey and from state</li> </ul>	Self-administered 68-item validated FFQ of food & supplements.	Age, smoking, Gender, BMI, education, physical activity, family history of colorectal	Relative risk (95% CI) of colorectal cancer, compared with the lowest quintile (Q1) was: Q2 = 0.98 (0.78, 1.23) Q3 = 0.90 (0.72, 1.14) Q4 = 0.78 (0.61, 1.01)

2005 <sup>70)</sup>		registries.		cancer, total energy, saturated fat, fruit, vegetables.	Q5 = 0.80 (0.62, 1.02), adjusting for all covariates (p-value for trend = 0.02). ◇ Inverse association seen in men not using multivitamins (Table 5). Stronger inverse association with colon cancer (Table 6).
Kesse 2005 <sup>74</sup>	67,312 cancer free women aged 40-65 years; French teachers who were members of a national insurance scheme.	◇ Baseline established in 1990. Dietary questionnaire mailed to home in 1993-95 and completed by 81%. ◇ 172 cases of colorectal cancer, identified up to June 2000 from biennial questionnaires, confirmed by histology.	Self-administered 208-item validated FFQ of food.	Age, education, smoking, family history of colon cancer, BMI, physical activity, energy & alcohol intake.	No association. Relative risk (95% CI) of colorectal cancer, compared with the lowest quartile (Q1) was: Q2 = 1.11 (0.74, 1.67) Q3 = 0.85 (0.55, 1.31) Q4 = 0.89 (0.58, 1.36), adjusting for all covariates (p-value for trend = 0.37).
Lin 2005 <sup>75</sup>	36,976 women, aged ≥45 years, free of cancer & cardiovascular disease, who were US health professionals recruited into an RCT of aspirin and vitamin E (Women's Health Study).	◇ Baseline recruitment began in 1993. ◇ 223 cases of colorectal cancer identified from annual questionnaires, confirmed by pathology, during 10 year f/u period.	Self-administered 131-item validated FFQ of food, including vitamin D supplements, collected at recruitment.	Age, randomised treatment, BMI, family history of colorectal cancer, history of colon polyps, activity, smoking, red meat, alcohol, total energy, saturated fat, multivitamins, menopause & post-menopausal hormones.	No association. Relative risk (95% CI) of colorectal cancer, compared with the lowest quintile (Q1) was: Q2 = 0.79 (0.50, 1.24) Q3 = 1.00 (0.65, 1.53) Q4 = 0.99 (0.64, 1.55) Q5 = 1.34 (0.84, 2.13), adjusting for all covariates (p-value for trend = 0.08).
Park 2007 <sup>76</sup>	85,903 men & 105,108 women, aged 45-75 years & cancer free, recruited from general population in Hawaii & Los Angeles to form a multi-ethnic sample.	◇ Baseline recruitment carried out during 1993-96. Questionnaire mailed to home. ◇ 2110 (1138 male, 972 female) cases of colorectal cancer, identified up to December 2001 by cancer registries in Hawaii & California	Self-administered 180-item validated FFQ of food, including vitamin D supplements, collected at recruitment.	Ethnicity, age, time in cohort, smoking, family history of colorectal cancer, activity, polyp history, NSAIDS, BMI, total energy, fibre, HRT.	Inverse association in men. Relative risk (95% CI) of colorectal cancer, compared with the lowest quintile (Q1) was: Q2 = 1.07 (0.89, 1.29) Q3 = 0.96 (0.79, 1.17) Q4 = 0.87 (0.66, 1.14) Q5 = 0.72 (0.51, 1.00), adjusting for all covariates (p-value for trend = 0.03). No association was observed in women. Compared with the lowest quintile (Q1):

					Q2 = 0.93 (0.74, 1.16) Q3 = 0.82 (0.65, 1.03) Q4 = 0.89 (0.67, 1.19) Q5 = 0.89 (0.63, 1.27), adjusting for all covariates (p-value for trend = 0.80).
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### Appendix C: Case control studies investigating the relationship between colorectal cancer and dietary intake of vitamin D.

Paper	Subjects	Methods	Measurement of vitamin D status	Confounders adjusted for	Main results
Benito 1991 <sup>77</sup>	<ul style="list-style-type: none"> <li>◇ 286 cases of colorectal cancer from the Majorca cancer registry during 1984-88 (72% response), aged ≤ 80 years, resident for 10 years and on electoral census.</li> <li>◇ 2956 controls from electoral census, group matched by sex and age. (89% response).</li> </ul>	◇ Home interviews for cases & controls over the same time period.	99-item FFQ of food intake during the previous year.	Age, sex, weight and total energy intake.	No association. Odds ratio (95% CI) of colorectal cancer, compared with the lowest quartile (Q1) was: Q2 = 1.27 Q3 = 1.30 Q4 = 0.74, adjusting for all covariates (p-value for trend > 0.05).
Peters 1992 <sup>78</sup>	<ul style="list-style-type: none"> <li>◇ 746 cases of colon cancer from Los Angeles, from California cancer registry during 1983-86 (72% response), aged 45-69 years, born in US, Canada or Western Europe.</li> <li>◇ 746 white controls from LA street addresses, individually matched by sex, age &amp; neighbourhood. (64% response).</li> </ul>	◇ Home interviews for cases & controls over the same time period.	Interviewer-administered 116-item validated FFQ of food over 15 years, including vitamin D supplements.	Fat, protein, carbohydrates, alcohol, calcium, family history, weight, activity and pregnancies (if female).	No association between vitamin D and presence of colon cancer. Odds ratio (95% CI) for each higher quintile of vitamin D = 1.08 (0.97, 1.20) adjusting for all covariates.
Ferraroni 1994 <sup>79</sup>	<ul style="list-style-type: none"> <li>◇ 828 cases of colon cancer and 498 of rectal cancer, from hospitals in Milan during 1985-92, median age 62 years.</li> <li>◇ 2,024 controls admitted to same hospitals, median age 55 years.</li> </ul>	◇ Participants interviewed in hospital.	Interviewer-administered 29-item FFQ of weekly food intake.	Age, sex, education, family history of colorectal cancer, BMI and total energy intake.	Inverse association. Odds ratio (95% CI) of colorectal cancer, compared with the lowest quintile (Q1) was: Q2 = 1.11 (0.89, 1.39) Q3 = 0.99 (0.78, 1.24) Q4 = 1.11 (0.88, 1.40) Q5 = 0.74 (0.58, 0.95), adjusting for all covariates (p-value for trend < 0.05).
Pritchard 1996 <sup>80</sup>	◇ 352 cases of colon cancer and 217 of rectal cancer,	◇ Questionnaires given to cases	Self-administered 55-item FFQ of food intake over	Age, sex, total energy and protein intake.	Odds ratio (95% CI) of colon cancer, compared with the lowest

	<p>from Stockholm cancer registry during 1986-88, mean age 67-68 years.</p> <p>◇ 512 controls from population register, grouped matched by age.</p>	<p>when in hospital or mailed to controls at home.</p>	<p>previous 5 years.</p>		<p>quartile (Q1) was:  Q2 = 0.8 (0.5, 1.2)  Q3 = 0.9 (0.6, 1.4)  Q4 = 0.6 (0.4, 1.0)  adjusting for all covariates (p-value for trend = 0.076).  Odds ratio (95% CI) of rectal cancer, compared with the lowest quartile (Q1):  Q2 = 0.7 (0.4, 1.3)  Q3 = 0.7 (0.4, 1.2)  Q4 = 0.5 (0.3, 0.9)  adjusting for all covariates (p-value for trend = 0.083).</p>
La Vecchia 1997 <sup>81</sup>	<p>◇ 1,225 cases of colon cancer and 728 of rectal cancer, from Italian hospitals in 6 areas during 1992-96, mean age 62 years.</p> <p>◇ 4,154 controls admitted to hospitals in the same areas as cases</p>	<p>◇ Participants interviewed in hospital.</p>	<p>Interviewer-administered 78-item validated FFQ of food intake over previous 2 years.</p>	<p>Age, region, sex, education, activity, total energy and fibre intake.</p>	<p>Odds ratio (95% CI) of cancer, highest quintile compared with the lowest was:  colon = 0.81 (0.7, 1.1);  rectal = 1.03 (0.9, 1.2).</p>
Marcus 1998 <sup>82</sup>	<p>◇ 348 female cases of colon cancer and 164 of rectal cancer, from Wisconsin cancer registry during 1990-91 (84% response), aged &lt; 75 years, with driver's licence (if &lt;65 years), telephone &amp; diagnosis within 3 years of interview.</p> <p>◇ 678 controls, group matched by age, from list of licensed Wisconsin drivers (&lt;65 years) or Medicare list (65-74 years), telephone &amp; living in Wisconsin (91% response).</p>	<p>◇ Telephone interview for cases &amp; controls over the same time period.</p> <p>◇ Followed by FFQ questionnaire mailed to home.</p>	<p>Self-administered 122-item validated FFQ of food intake over previous 2 years, including vitamin D supplements.</p>	<p>Age, and intake of energy and fibre.</p>	<p>Association for colon cancer not consistent in dose-response. Odds ratio (95% CI) of colorectal cancer, compared with the lowest quintile (Q1) was:  Q2 = 0.8 (0.5, 1.2)  Q3 = 0.8 (0.5, 1.3)  Q4 = 0.6 (0.4, 0.9)  Q5 = 0.7 (0.4, 1.1),  adjusting for all covariates (p-value for trend = 0.05).</p> <p>No association for rectal cancer. Compared with the lowest quintile (Q1):  Q2 = 0.7 (0.4, 1.3)  Q3 = 1.2 (0.7, 2.1)</p>

					Q4 = 0.6 (0.3, 1.1) Q5 = 0.8 (0.5, 1.5), adjusting for all covariates (p-value for trend = 0.42).
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### Appendix D: Nested case control studies investigating the relationship between colorectal cancer and blood 25-hydroxyvitamin D.

Paper	Subjects	Methods	Measurement of vitamin D status	Confounders adjusted for	Main results
Garland 1989 <sup>83</sup> (same study as Braun 1995a <sup>84</sup> & 1995b <sup>107</sup> )	25,620 cancer free community volunteers aged $\geq 35$ years at baseline, recruited from Washington County in Maryland, US.	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1974.</li> <li>◇ 34 cases of colon cancer identified from the university cancer registry up to December 1983.</li> <li>◇ 67 controls matched for age, sex, race and month of blood collection.</li> </ul>	Serum 25-hydroxyvitamin D measured on baseline blood sample.	None besides matching variables.	<p>No association between baseline serum 25OHD and colon cancer. Odds ratio of colon cancer compared with the lowest quintile (Q1):</p> <p>Q2 = 0.48 Q3 = 0.25 (p&lt;0.05) Q4 = 0.21 (p&lt;0.05) Q5 = 0.73.</p> <p>Odds ratio of colon cancer if serum 25OHD <math>\geq 20</math> ng/ml was 0.3 (one sided p=0.05).</p>
Braun 1995a <sup>84</sup> (same study as Garland 1989 <sup>83</sup> )	25,620 cancer free community volunteers aged $\geq 35$ years at baseline, recruited from Washington County in Maryland, US.	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1974. Same community sample as Garland (1989) above, but includes <i>different</i> cases and controls.</li> <li>◇ 57 out of 61 cases of colon cancer with serum, identified from the university cancer registry from 1984-1991.</li> <li>◇ 114 controls matched for age, sex, race and month of blood collection.</li> </ul>	Serum 25-hydroxyvitamin D measured on baseline blood sample.	None besides matching variables.	<p>No association between baseline serum 25OHD and colon cancer. Odds ratio (95% CI) of colon cancer compared with the lowest quintile (Q1):</p> <p>Q2 = 0.3 (0.1, 1.0) Q3 = 0.5 (0.2, 1.5) Q4 = 0.7 (0.2, 2.0) Q5 = 0.4 (0.1, 1.4), (p-value for trend = 0.5).</p>
Tangrea 1997 <sup>85</sup> (same sample as Chan 2000 <sup>93</sup> )	Male smokers, aged 50-69 years, free of cancer, recruited from a population register of south-western Finland into an RCT of alpha-tocopherol and beta-carotene (ATBC Study).	<ul style="list-style-type: none"> <li>◇ Recruitment into the survey started in 1985.</li> <li>◇ 146 cases of colon &amp; rectal cancer, identified from the national cancer registry from 1985-1993.</li> <li>◇ 290 controls matched for age, clinic and month of</li> </ul>	Serum 25-hydroxyvitamin D measured on blood sample collected at randomisation.	None besides matching variables.	<p>Mean serum 25OHD lower in colorectal cases compared with controls (12.2 v. 13.8 ug/l, p&lt;0.01).</p> <p>Odds ratio (95% CI) of colorectal cancer, compared with the lowest quartile (Q1) was:</p> <p>Q2 = 0.7 (0.4, 1.3)</p>

		blood collection.			Q3 = 0.8 (0.4, 1.3) Q4 = 0.6 (0.3, 1.1) (p-value for trend = 0.13).
Feskanich 2004 <sup>86</sup> (same study as Bertone-Johnson 2005 <sup>123</sup> )	32,826 cancer free female nurses, aged 43-70 years at baseline, from participants who provided blood sample in US Nurses Health Study.	<ul style="list-style-type: none"> <li>◇ Blood samples collected in 1989-90.</li> <li>◇ 193 cases of colon &amp; rectal cancer, self-reports up to 2000 confirmed by medical records.</li> <li>◇ 383 controls matched for age, and month of blood collection.</li> </ul>	Plasma 25-hydroxyvitamin D measured on baseline blood sample.	Matched variables plus BMI, activity, smoking, menopause, HRT, aspirin, family history of colorectal cancer, and intake of calcium, folate, methionine, retinol, red meat and alcohol.	Odds ratio (95% CI) of colorectal cancer, compared with the lowest quintile (Q1) was: Q2 = 0.93 (0.53, 1.63) Q3 = 0.79 (0.44, 1.40) Q4 = 0.58 (0.31, 1.07) Q5 = 0.53 (0.27, 1.04), (p-value for trend = 0.02), adjusted for confounders. Inverse association with 25OHD stronger for cancers of the distal colon and rectum.
Wactawski-Wende 2006 <sup>61</sup>	36,282 cancer free women, aged 50-79 years, who volunteered to take part in an RCT of calcium & vitamin D supplementation (Women's Health Initiative)	<ul style="list-style-type: none"> <li>◇ Blood samples collected at enrolment in 1993-1998.</li> <li>◇ 317 cases of colon &amp; rectal cancer, self-reports up to 2005 confirmed by medical records.</li> <li>◇ 317 controls matched for age, centre, race and date of blood collection.</li> </ul>	Serum 25-hydroxyvitamin D measured on blood sample collected at randomisation.	None besides matching variables.	Odds ratio (95% CI) of colorectal cancer, compared with the <i>highest</i> quartile (Q4) was: Q1 = 2.53 (1.49, 4.32) Q2 = 1.95 (1.18, 3.24) Q3 = 1.96 (1.18, 3.24) (p-value for trend = 0.02).
Giovannucci 2006 <sup>87</sup> (same sample as Kearney 1996 <sup>67</sup> )	47,800 US male health professionals aged 40-75 years, without cancer in 1986, followed to January 2000.	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1986. Questionnaire mailed to home.</li> <li>◇ 691 cases of colon &amp; rectal cancer up to January 2000, from biennial questionnaires verified by pathology records or National Death Index.</li> </ul>	Predicted plasma 25OHD calculated from following variables in sub-sample of 1095 men: race, place of residence, leisure physical activity, BMI, dietary and supplementary vitamin D; further adjusting for season of blood collection which was not used in predictive models.	Age, height, smoking, and intakes of total calories, alcohol, red meat, calcium, retinol, fruits & vegetables.	Relative risk (95% CI) of colorectal cancer associated with increment of 25 nmol/L in predicted serum 25OHD = 0.63 (0.48, 0.83).

## Appendix E: Cohort studies investigating the relationship between prostate cancer and dietary vitamin D

Paper	Subjects	Methods	Measurement of vitamin D	Confounders adjusted for	Main results
Giovannucci 1998 <sup>92</sup> (same sample as Kearney 1996 <sup>67</sup> & Platz 2004 <sup>111</sup> )	47,781 US male health professionals aged 40-75 years, without cancer in 1986 (Health Professionals Follow-Up Study).	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1986. Questionnaire mailed to home.</li> <li>◇ 1792 cases of prostate cancer, up to 1994, from biennial questionnaires verified by pathology records or National Death Index.</li> </ul>	Self-administered 131-item validated FFQ of food & supplements.	Age, BMI at age 21, tobacco, activity, vasectomy, total energy, fat, type of fat, vitamin E & lycopene.	Total dietary vitamin D intake (from food & supplements) was not associated with risk of total prostate cancer: relative risk 1.21 (95% CI: 0.92, 1.58) comparing $\geq 800$ IU/day versus $< 150$ IU/day (p for trend = 0.87).
Chan 2000 <sup>93</sup> (same sample as Tangrea 1997 <sup>85</sup> )	27,062 male smokers, aged 50-69 years, free of cancer, who completed a diet questionnaire, recruited from a population register of south-western Finland into an RCT of alpha-tocopherol and beta-carotene (ATBC Study).	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1985-1988.</li> <li>◇ 184 stage 2-4 cases of prostate cancer identified from the national cancer registry up to April 1993.</li> </ul>	Self-administered 276-item validated FFQ of food.	RCT allocation, education, age, BMI, & energy intake.	No association. Relative risk (95% CI) of prostate cancer, compared with the lowest quintile of vitamin D intake (Q1) was: Q2 = 0.8 (0.5, 1.3) Q3 = 0.7 (0.5, 1.2) Q4 = 0.9 (0.6, 1.4) Q5 = 0.8 (0.5, 1.3), adjusting for covariates (p = 0.86).
Rodriguez 2003 <sup>94</sup> (same sample as McCullough 2003 <sup>73</sup> )	65,321 cancer free men aged 50-74 years, who completed a diet questionnaire, recruited from the Cancer Prevention Study (CPS II) in 21 US states in 1992-93.	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1992-93. Questionnaire mailed to home.</li> <li>◇ 3811 cases of prostate cancer (up to 1999), from CPS II survey &amp; state registries.</li> </ul>	Self-administered 68-item validated FFQ of food & supplements.	Age, race, family history of prostate cancer, total energy, total fat, total calcium & education.	Actual results not reported, but statement in text that total vitamin D intake was not associated with incidence of prostate cancer.
Tseng 2005 <sup>95</sup> (same survey as John 1999 <sup>118</sup> & 2004 <sup>102</sup> )	3612 cancer free men, mean age 58 years, who completed a diet questionnaire at the initial interviews of the NHANES I follow-up study cohort.	<ul style="list-style-type: none"> <li>◇ Initial follow-up survey in 1982-84.</li> <li>◇ 131 cases of prostate cancer (up to 1992), from f/u interviews, confirmed by hospital records &amp; death certificates.</li> </ul>	Self-administered 105-item FFQ of food & supplements.	Age, race, energy intake, US region, urban/rural, education, recreational sun exposure, physical activity, smoking & alcohol.	No association. Relative risk (95% CI) of prostate cancer, compared with the lowest tertile of vitamin D intake (T1) was: T2 = 0.9 (0.6, 1.3) T3 = 1.3 (0.8, 2.1), adjusting for all covariates (p-value for trend = 0.24).

## Appendix F: Case control studies investigating the relationship between prostate cancer and dietary vitamin D

Paper	Subjects	Methods	Measurement of vitamin D	Confounders adjusted for	Main results
Vlajinac 1997 <sup>96</sup>	<ul style="list-style-type: none"> <li>◇ 101 cases of prostate cancer, mean age 70.5 years, confirmed by histology at hospitals in two central Serbian towns, in 1990-94.</li> <li>◇ 202 hospital controls matched by age, hospital admittance, and residence.</li> </ul>	<ul style="list-style-type: none"> <li>◇ Interviews probably carried out in hospital (although not specifically stated).</li> </ul>	Interviewer-administered 150-item FFQ of food and supplement intake.	Total energy	No association. Odds ratio (95% CI) of prostate cancer, compared with the lowest tertile of vitamin D intake (T1) was: T2 = 0.97 (0.52, 1.84) T3 = 1.29 (0.91, 1.81), adjusting for all covariates (p-value for trend > 0.05).
Chan 1998 <sup>97</sup>	<ul style="list-style-type: none"> <li>◇ 526 cases of prostate cancer, aged &lt; 80 years (mean 70.7), from Örebro county, Sweden, confirmed by cancer registry during 1989-94.</li> <li>◇ 526 controls from county population register, group matched by age (mean age 70.6 yrs).</li> </ul>	<ul style="list-style-type: none"> <li>◇ Questionnaires mailed to home.</li> </ul>	Self-administered validated 68-item FFQ of food intake.	Age, family history of prostate cancer, smoking, total calories, calcium and phosphorus intake.	Adjusting for covariates, the continuous measure of vitamin D intake was not associated with risk of prostate cancer (p=0.55); while the relative risk of prostate cancer for the highest quartile (Q4) compared with the lowest (Q1) of vitamin D intake was 1.37 (95% CI 0.89, 1.81).
Deneo-Pellegrini 1999 <sup>98</sup>	<ul style="list-style-type: none"> <li>◇ 175 cases of prostate cancer, aged 40-89 years, from 4 major Montevideo hospitals, Uruguay, confirmed by cancer registry during 1994-97.</li> <li>◇ 233 controls from same hospitals, admitted with non-dietary conditions, aged &lt;90 years.</li> </ul>	<ul style="list-style-type: none"> <li>◇ Participants returned to hospital after discharge for interviews.</li> </ul>	Interviewer-administered 64-item FFQ of food intake.	Age, residence, urban/rural, education, family history of prostate cancer, BMI and total energy intake.	No association. Odds ratio (95% CI) of prostate cancer, compared with the lowest quartile of vitamin D intake (Q1) was: Q2 = 1.3 (0.7, 2.5) Q3 = 0.9 (0.5, 1.8) Q4 = 0.7 (0.4, 1.2), adjusting for all covariates (p-value for trend = 0.14).
Berndt 2002 <sup>99</sup>	457 men enrolled from community into a longitudinal study of aging in Baltimore continuously since 1958.	<ul style="list-style-type: none"> <li>◇ FFQ administered at clinic visit beginning 1994.</li> <li>◇ 69 cases of prostate cancer, confirmed by</li> </ul>	Food-frequency questionnaire. 47 (68%) cases completed FFQ after diagnosis, making it more like a case control study	Age, energy.	No association. Odds ratio (95% CI) of prostate cancer, compared with the lowest tertile of vitamin D intake (T1) was: T2 = 0.73 (0.37, 1.47)

		medical records.	than cohort.		T3 = 1.21 (0.64, 2.30), adjusting for all covariates (p-value for trend = 0.46).
Kristal 2002 <sup>100</sup>	<ul style="list-style-type: none"> <li>◇ 605 cases of prostate cancer with home telephone, aged 40-64 years, from King county, Washington State, confirmed by cancer registry during 1993-1996.</li> <li>◇ 592 controls from county population recruited by random-digit dialling, group matched by age.</li> </ul>	<ul style="list-style-type: none"> <li>◇ Home interviews.</li> <li>◇ FFQ left at end of interview for completion by participants before mailing it back to the researchers.</li> </ul>	Self-administered validated 99-item FFQ of food intake & supplements over the previous 3-5 years.	Age, race, family history of prostate cancer, education, BMI, PSA screening, vegetables, total energy & use of supplements (vitamins E & C, zinc).	No association. Odds ratio (95% CI) of prostate cancer, compared with the lowest quintile of vitamin D intake (Q1) was: Q2 = 0.80 (0.51, 1.28) Q3 = 1.10 (0.70, 1.72) Q4 = 0.70 (0.44, 1.12) Q5 = 1.06 (0.66, 1.70), adjusting for all covariates (p-value for trend = 0.98).
Tavani 2005 <sup>101</sup>	<ul style="list-style-type: none"> <li>◇ 1294 cases of prostate cancer, aged 46-74 years, from 4 Italian regions, confirmed by histology during 1991-2002.</li> <li>◇ 1451 controls, aged 46-74 years, admitted to hospitals in the same areas as cases.</li> </ul>	◇ Interviews carried out in hospital.	Interviewer-administered 78-item validated FFQ of food intake over previous 2 years.	Age, research centres education, BMI, smoking, activity, total energy, family history of prostate cancer.	No association. Odds ratio (95% CI) of prostate cancer, compared with the lowest quintile of vitamin D intake (Q1) was: Q2 = 1.22 (0.94, 1.59) Q3 = 1.05 (0.80, 1.38) Q4 = 1.27 (0.97, 1.66) Q5 = 1.32 (1.01, 1.75), adjusting for all covariates (p-value for trend = 0.06).

## Appendix G: Studies investigating the relationship between prostate cancer and sun exposure

Paper	Subjects	Methods	Measurement of sun exposure	Confounders adjusted for	Main results
<i>Cohort study</i>					
John 2004 <sup>102</sup> (same survey as John 1999 <sup>118</sup> & Tseng 2005 <sup>95</sup> )	3414 white cancer free men, aged 25-74 years, originally sampled from US population, followed by enrolment into the NHANES I follow-up study cohort.	<ul style="list-style-type: none"> <li>◇ Initial baseline interview &amp; dermatological examination in 1971-75.</li> <li>◇ 153 cases of prostate cancer (up to 1992), from f/u interviews, confirmed by hospital records &amp; death certificates.</li> </ul>	Solar radiation at longest place of residence, based on data from 235 national weather service stations.	Age, family history of prostate cancer, fat & calcium intake.	Relative risk (95% CI) of prostate cancer, compared with the lowest tertile of solar radiation (T1) was: T2 = 0.81 (0.55, 1.21) T3 = 0.62 (0.40, 0.95), adjusting for all covariates.
<i>Case control study</i>					
Luscombe 2001 <sup>103</sup>	<ul style="list-style-type: none"> <li>◇ 210 white cases of prostate cancer, mean age 70.6 years, from North Staffordshire Hospital, UK, confirmed by histology during 1999-2000.</li> <li>◇ 155 controls with prostatic hypertrophy from same hospital, mean age 67.0 yrs.</li> </ul>	◇ Participants interviewed (?) at hospital clinic.	Self-administered validated questionnaire of lifetime UV exposure (occupational and recreational), although 25% of participants needed help from an interviewer.	Age at diagnosis, vasectomy, diet, occupation.	Odds ratio (95% CI) of prostate cancer, compared with the <i>highest</i> quartile of UV exposure (Q4) was: Q1 = 3.03 (1.59, 5.78) Q2 = 1.51 (0.83, 2.76) Q3 = 1.18 (0.65, 2.16), adjusting for covariates.
Bodiwala 2003 <sup>105</sup>	<ul style="list-style-type: none"> <li>◇ 212 white cases of prostate cancer, mean age 70.4 years, from North Staffordshire Hospital, UK, confirmed by histology during 2001-2002.</li> <li>◇ 135 controls with prostatic hypertrophy from same hospital, mean age 67.2 yrs.</li> </ul>	◇ Participants interviewed (?) at hospital clinic.	Self-administered validated questionnaire of lifetime UV exposure (occupational and recreational).	Age at diagnosis.	Odds ratio (95% CI) of prostate cancer, compared with the <i>highest</i> quartile of UV exposure (Q4) was: Q1 = 3.21 (1.61, 6.40) Q2 = 1.68 (0.91, 3.09) Q3 = 1.40 (0.78, 2.52), adjusting for covariate.
John 2005 <sup>104</sup>	<ul style="list-style-type: none"> <li>◇ 450 white cases of prostate cancer, aged 40-79 years, from San Francisco regional cancer registry, during 1997-2000.</li> <li>◇ 455 controls aged 40-79 years recruited by random digit</li> </ul>	◇ Participants interviewed by trained interviewers (? at home or clinic).	Portable reflectometer used to measure skin pigmentation of inside of upper arm and forehead. Sun exposure index derived from difference of two measures.	Age, family history of prostate cancer, month of skin pigmentation measures.	Inverse association between sun exposure index and prostate cancer. Odds ratio (95% CI) of prostate cancer compared with the lowest quintile (Q1): Q2 = 0.87 (0.58, 1.30) Q3 = 0.80 (0.53, 1.20)

	dialling, with frequency matching by age .				Q4 = 0.95 (0.64, 1.42) Q5 = 0.51 (0.33, 0.80), (p-value for trend = 0.02)
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## Appendix H: Nested case control studies investigating the relationship between prostate cancer and blood 25-hydroxyvitamin D.

Paper	Subjects	Methods	Measurement of vitamin D status	Confounders adjusted for	Main results
Corder 1993 <sup>106</sup>	More than 250,000 members (?male and female) of the Kaiser Permanent Medical care Program of Northern California which started in 1964.	<ul style="list-style-type: none"> <li>◇ Blood sample collected during 1964-71.</li> <li>◇ 181 cases (90 black, 91 white) of prostate cancer up to end of 1987, confirmed by medical &amp; cancer registry records.</li> <li>◇ 181 controls matched for age, race and date of blood collection.</li> </ul>	Serum 25-hydroxyvitamin D measured on baseline blood samples.	None besides matching variables.	Cases and control had similar 25OHD levels (p=0.24).
Braun 1995b <sup>107</sup> (same sample as Garland 1989 <sup>83</sup> & Braun 1995a <sup>84</sup> )	25,620 cancer free community volunteers aged ≥35 years at baseline, recruited from Washington County in Maryland, US.	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1974.</li> <li>◇ 61 cases of prostate cancer with serum, identified from the County cancer registry from 1980-1992.</li> <li>◇ 114 controls matched for age and race.</li> </ul>	Serum 25-hydroxyvitamin D measured on baseline blood sample.	None besides matching variables.	<p>Cases and controls had similar distribution of month of blood collection. Mean serum 25OHD was similar for cases and controls (34.3 v. 33.2 ng/ml, p&gt;0.05).</p> <p>No association between baseline serum 25OHD and prostate cancer. Odds ratio (95% CI) of prostate cancer compared with the lowest quintile (Q1):            Q2 = 2.3 (0.7, 7.8)            Q3 = 2.3 (0.7, 7.7)            Q4 = 0.6 (0.1, 2.5)            Q5 = 2.4 (0.8, 8.2),            (p-value for trend = 0.60).</p>
Gann 1996 <sup>108</sup>	14,916 cancer free male doctors, aged 40-84 years, who volunteered to take part in an RCT of beta-carotene supplementation, & who provided a blood sample (Physicians' Health Study).	<ul style="list-style-type: none"> <li>◇ Blood samples collected at enrolment in 1982.</li> <li>◇ 232 (out of 520) cases of prostate cancer, self-reports up to 1992 confirmed by medical records.</li> <li>◇ 414 controls matched for</li> </ul>	Serum 25-hydroxyvitamin D measured on blood sample collected at randomisation.	Matching variables plus season of blood collection.	<p>Mean serum 25OHD was similar for cases and controls (29.3 v. 28.5 ng/ml) (p=0.80).</p> <p>No association between baseline serum 25OHD and prostate cancer. Odds ratio (95% CI if available) of prostate cancer, compared with the lowest quartile</p>

		age and smoking status.			(Q1) was: Q2 = 1.10 (NA) Q3 = 1.16 (NA) Q4 = 0.92 (0.56, 1.50) (p-value for trend = 0.82).
Nomura 1998 <sup>109</sup>	3,737 cancer free male Japanese-American, aged 45-68 years at baseline, recruited into the Honolulu Heart Program.	<ul style="list-style-type: none"> <li>◇ Blood samples collected in 1967-1970, 2 years after baseline interview</li> <li>◇ 136 cases of prostate cancer with stored serum, identified from the Hawaii cancer registry up to 1993 (excluding cases within 5 years of interview).</li> <li>◇ 136 male controls matched for age and month.</li> </ul>	Serum 25-hydroxyvitamin D measured on blood sample.	None besides matching variables.	Mean serum 25OHD was similar for cases and controls (41.0 v. 41.6 ng/ml) (p=0.66). No association between baseline serum 25OHD and prostate cancer. Odds ratio (95% CI) of prostate cancer, compared with the lowest quartile (Q1) was: Q2 = 0.8 (0.4, 1.8) Q3 = 0.8 (0.4, 1.7) Q4 = 0.8 (0.4, 1.8), (p-value for trend = 0.68).
Ahonen 2000 <sup>110</sup> (part of sample same as Tuohimaa 2004 <sup>112</sup> )	18,966 cancer free men, aged 40-55 years, recruited from workplaces in Finland, to take part in a lipid lowering RCT (Helsinki Heart Study).	<ul style="list-style-type: none"> <li>◇ Blood samples collected at enrolment in 1981-1982.</li> <li>◇ 149 (out of 158) cases of prostate cancer, up to end of 1995, confirmed by national cancer registry.</li> <li>◇ 566 controls matched for age, time of blood collection and residence.</li> </ul>	Serum 25-hydroxyvitamin D measured on blood sample collected at randomisation.	Matching variables plus RCT allocation, HDL-cholesterol, blood pressure & BMI.	Mean serum 25OHD was 41.4 nmol/L for cases and 44.0 nmol/L controls (p-value not stated).  Odds ratio of prostate cancer for participants with serum 25OHD below the median (40 nmol/L) was: 1.7 (95% CI: 1.2, 2.6) adjusting for confounders.
Platz 2004 <sup>111</sup> (same sample as Kearney 1996 <sup>67</sup> )	18,018 cancer free US male health professionals, aged 40-75 years at baseline in 1986, who provided a blood sample in 1993-1995.	<ul style="list-style-type: none"> <li>◇ Blood samples collected in 1993-1995.</li> <li>◇ 460 cases of prostate cancer (excluding microscopic T1a tumours), up to January 1998, verified by pathology records.</li> <li>◇ 460 controls matched by age, PSA test before blood draw, time of day &amp; season of blood draw.</li> </ul>	Serum 25-hydroxyvitamin D measured on blood sample.	Serum 1,25-(OH) <sub>2</sub> D, age, family history, height, physical activity, diabetes, vasectomy, smoking, intake of energy, red meat, fish, lycopene, fructose, and alpha-linolenic acid, and vitamin E & selenium supplements.	Mean serum 25OHD was similar for cases and controls (24.6 v. 23.9 ng/ml, p=0.20).  No association between serum 25OHD and prostate cancer. Odds ratio (95% CI) of prostate cancer, compared with the lowest quartile (Q1) was: Q2 = 1.00 (0.67, 1.49) Q3 = 0.77 (0.51, 1.15) Q4 = 1.19 (0.79, 1.79),

					(p-value for trend = 0.59).
Tuohimaa 2004 <sup>112</sup> (part of sample same as Ahonen 2000 <sup>110</sup> )	Sample from 3 Nordic countries: ◊ 18,966 cancer free men, aged 40-55 years, recruited from Finnish workplaces for a lipid lowering RCT (Helsinki Heart Study). ◊ About 160,000 men in the Janus Project in Norway. ◊ About 30,000 men in representative samples of 2 counties in Sweden.	◊ Blood samples collected in: - Finland 1981-1982; - Norway from 1973; - Sweden from 1985. ◊ 622 cases of prostate cancer, up to end of 1997, confirmed by national cancer registries. ◊ 1,451 controls matched for age, date of blood collection, region and country.	Serum 25-hydroxyvitamin D measured on blood sample.	None besides matching variables.	U-shaped association between baseline serum 25OHD and prostate cancer risk.  Odds ratio (95% CI) of prostate cancer, compared with the middle quintile (Q3) was: Q1 = 1.5 (0.8, 2.7) Q2 = 1.3 (0.98, 1.6) Q3 = 1 Q4 = 1.2 (0.9, 1.5) Q5 = 1.7 (1.1, 2.4).
Jacobs 2004 <sup>113</sup>	1312 men with non-melanoma skin cancer at 7 clinics in eastern US, enrolled in 2 waves into an RCT to determine if selenium supplements prevent recurrence of skin cancer.	◊ Blood samples collected at baseline of each wave (1983, 1989). ◊ 83 cases of prostate cancer in treatment and placebo arms of trial, up to 2002; mean age at baseline 67 years. ◊ 166 controls matched for age, treatment group and clinic site; mean age at baseline 67 years.	Plasma 25-hydroxyvitamin D measured on blood sample.	Age, clinic site, BMI and smoking.	Odds ratio (95% CI) of prostate cancer, compared with the lowest tertile (T1) was: T2 = 1.71 (0.68, 4.34) T3 = 0.75 (0.29, 1.91), (p-value for trend = 0.51), adjusted for covariates.
Baron 2005 <sup>114</sup>	672 cancer free men in the US, mean age 62 years, enrolled in an RCT to determine if calcium supplements prevent colorectal adenomas.	◊ Blood samples collected after 4 year treatment period (during 1992 - 1996). ◊ 70 cases of prostate cancer in treatment and placebo arms of trial, up to January 2003, confirmed by histopathology.	Serum 25-hydroxyvitamin D measured on blood sample from all participants; therefore, this is a <i>cohort</i> study, rather than nested case control study.	Age and RCT treatment.	Rate ratio (95% CI) of prostate cancer, compared with the lowest tertile (T1) was: T2 = 1.22 (0.66, 2.26) T3 = 1.32 (0.72, 2.43), (p-value for trend = 0.70), adjusted for covariates.
Giovannucci	47,800 US male health	◊ Baseline survey in 1986.	Predicted serum	Age, height, smoking,	Serum 25OHD not associated

<p>2006<sup>87</sup> (same sample as Kearney 1996<sup>67</sup>)</p>	<p>professionals aged 40-75 years, without cancer in 1986, followed to January 2000.</p>	<p>Questionnaire mailed to home. ◇ 461 cases of prostate cancer up to January 2000, from biennial questionnaires verified by pathology records or National Death Index.</p>	<p>25OHD calculated from following variables in sub-sample of 1095 men: race, place of residence, leisure physical activity, BMI, dietary and supplementary vitamin D; further adjusting for season of blood collection which was not used in predictive models.</p>	<p>and intakes of total calories, alcohol, red meat, calcium, retinol, fruits &amp; vegetables.</p>	<p>significantly with risk of prostate cancer.  From figure 1, <i>estimated</i> relative risk (95% CI) of prostate cancer associated with increment of 25 nmol/L in predicted serum 25OHD about 0.8 (0.6, 1.2).</p>
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**Appendix I: Observational studies investigating the relationship between breast cancer and sun exposure or dietary vitamin D.**

Paper	Subjects	Methods	Measurement of vitamin D	Confounders adjusted for	Main results
<i>Cohort studies</i>					
John 1999 <sup>118</sup> (same survey as John 2004 <sup>102</sup> & Tseng 2005 <sup>95</sup> )	5009 white cancer free women, aged 25-74 years, originally sampled from US population, followed by enrolment into the NHANES I follow-up study cohort.	<ul style="list-style-type: none"> <li>◇ Initial baseline interview &amp; dermatological examination in 1971-75.</li> <li>◇ 191 cases of breast cancer (up to 1992), from f/u interviews, confirmed by hospital records &amp; death certificates.</li> </ul>	<ul style="list-style-type: none"> <li>◇ Usual sun exposure = time spent outdoors at work and during leisure time.</li> <li>◇ Total dietary vitamin D was calculated from foods (24-hour recall) and supplements.</li> </ul>	Age, education, menopause, BMI, alcohol intake, physical activity, & calcium intake (for models with oral vitamin D only).	Relative risk (95% CI) of breast cancer associated with: <ul style="list-style-type: none"> <li>◇ usual sun exposure: Low = 1.00 Medium = 0.81 (0.56, 1.17) High = 0.67 (0.42, 1.06), adjusting for all covariates (p-value for trend = 0.06).</li> <li>◇ total dietary vitamin D: &lt; 100 IU = 1.00 100-199IU: 1.01 (0.69, 1.49) ≥200 IU = 0.86 (0.61, 1.20), adjusting for all covariates (p-value for trend = 0.37).</li> </ul>
Shin 2002 <sup>119</sup> (same survey as Martinez 1996 <sup>68</sup> )	89,691 US female registered nurses aged 34-59 years in 1980, without cancer in 1980 (Nurses' Health Study).	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1980.</li> <li>◇ 3,482 breast cancer cases (827 pre-menopausal, 2345 post-menopausal) identified up until 1996, from biennial questionnaires verified by pathology records or National Death Index.</li> </ul>	Self-administered validated FFQs of food & supplements: <ul style="list-style-type: none"> <li>◇ 1980 61 food items</li> <li>◇ 1984-1996 about 130 items</li> </ul> Analysis of vitamin D intake from 1980 FFQ, and from average of all FFQs.	Age, physical activity, history of benign breast disease, family history of breast cancer, height, weight change since 18, BMI, age of menarche, parity, age of 1 <sup>st</sup> birth, alcohol, total energy, fat, glycaemic index, beta-carotene, & vitamin E.	Relative risk (95% CI) of breast cancer in pre-menopausal women, compared with the lowest quantile of vitamin D intake (Q1) was: <ul style="list-style-type: none"> <li>Q2 = 0.90 (0.72, 1.13)</li> <li>Q3 = 0.87 (0.68, 1.11)</li> <li>Q4 = 0.79 (0.60, 1.05)</li> <li>Q5 = 0.76 (0.56, 1.03)</li> <li>Q6 = 0.77 (0.60, 0.99)</li> <li>Q7 = 0.72 (0.55, 0.94), adjusting for all covariates (p-value for trend = 0.01).</li> </ul> Vitamin D not associated with risk of post-menopausal breast cancer.
McCullough 2005 <sup>120</sup> (same survey as McCullough 2003 <sup>73</sup> &	68,567 women aged 50-74 years recruited from the Cancer Prevention Study (CPS II) in 21 US states in 1992-93.	<ul style="list-style-type: none"> <li>◇ Baseline survey in 1992-93. Questionnaire mailed to home.</li> <li>◇ 2,855 cases of post-menopausal breast</li> </ul>	Self-administered 68-item validated FFQ of food & supplements.	Age, energy intake, history of breast cyst, family history of breast cancer, height, weight change from	Risk of breast cancer was not associated with dietary vitamin D or total vitamin D (including supplements) in all cases or in oestrogen receptor negative cases.

Rodriguez 2003 <sup>94</sup> )		cancer (up to 31 Aug 2001), from CPS II survey and from state cancer registries.		age 18, alcohol, parity & age of 1 <sup>st</sup> birth, education, HRT use & history of mammography.	However, relative risk (95% CI) of breast cancer in women with oestrogen receptors, compared with the lowest quantile of vitamin D intake (Q1) was: Q2 = 0.85 (0.75, 0.97) Q3 = 0.86 (0.73, 1.02) Q4 = 0.74 (0.59, 0.93), adjusting for all covariates (p-value for trend = 0.006).
<i>Case control study</i>					
Simard 1991 <sup>121</sup>	9,089 women aged 40-59 years, living in Montreal, enrolled in the Canadian National Breast Screening Study.	◇ Baseline interview in 1981-83. ◇ 40 cases of breast cancer identified over f/u (period not specified). ◇ 322 controls randomly sampled from cohort	24-hour diet record and 41-item FFQ	None.	No association. Mean daily intake of vitamin D was 1.65 IU/kg in cases and 1.34 IU/kg in controls.
Knight 2007 <sup>122</sup>	◇ 972 cases of invasive breast cancer, aged 20-69 years, from Ontario Cancer Registry, confirmed by histology, during 2003-2004. ◇ 1,135 controls randomly selected from residential telephone numbers in Ontario, frequency matched by age.	◇ Participants interviewed by phone.	Participants recalled sun exposure and oral vitamin D sources (milk, fish, cod liver and vitamin supplements) at ages: 10-19, 20-29 and 45-54 years, to cover period of breast development and breast involution.	Age, ethnicity, family history of breast cancer, breast feeding, education, age of menarche, age of 1 <sup>st</sup> birth.	Sun exposure & dietary vitamin D associated with decreased risk of breast cancer most strongly during ages 10-19 years, but not at ages 45-54 years.  At ages 10-19 years, odds ratio (95% CI) of breast cancer associated with: ◇ Outdoor activity Q1 = 1.00 Q2 = 0.87 (0.67, 1.12) Q3 = 0.74 (0.57, 0.96) Q4 = 0.65 (0.50, 0.85), (p-value for trend = 0.0006); ◇ Milk (glasses/week) None = 1.00 <5 = 0.95 (0.64, 1.41) 5-9 = 0.67 (0.48, 0.95) ≥10 = 0.62 (0.45, 0.86), (p-value for trend = 0.0004), adjusting for covariates.

## Appendix J: Observational studies investigating the relationship between breast cancer and blood 25-hydroxyvitamin D.

Paper	Subjects	Methods	Measurement of vitamin D	Confounders adjusted for	Main results
<i>Nested case control study</i>					
Bertone-Johnson 2005 <sup>123</sup> (same study as Feskanich 2004 <sup>86</sup> )	32,826 cancer free female nurses, aged 43-69 years at baseline, from participants who provided blood sample in US Nurses Health Study.	<ul style="list-style-type: none"> <li>◇ Blood samples collected in 1989-90.</li> <li>◇ 701 cases of breast cancer, self-reports up to 1996 confirmed by medical records.</li> <li>◇ 724 controls matched for age, menopausal status, use of HRT, and date &amp; time of blood collection.</li> </ul>	Serum 25-hydroxyvitamin D measured on baseline blood sample.	Matched variables plus BMI, parity, age of 1 <sup>st</sup> birth, family history of breast cancer, history of benign breast disease, HRT, age of menarche and menopause, alcohol & plasma alpha-carotene.	<p>Relative risk (95% CI) of breast cancer, compared with the lowest quintile of 25OHD (Q1) was:            Q2 = 0.95 (0.66, 1.36)            Q3 = 0.74 (0.51, 1.06)            Q4 = 0.77 (0.54, 1.11)            Q5 = 0.73 (0.49, 1.07),            (p-value for trend = 0.06),            adjusted for confounders.</p> <p>Inverse association with 25OHD stronger in women aged ≥60 years at blood collection (p=0.03) than in younger women (p=0.88).</p>
<i>Case control</i>					
Janowsky 1999 <sup>124</sup>	<ul style="list-style-type: none"> <li>◇ 156 cases of breast cancer, aged ≥21 years, from university breast clinics in North Carolina, during 1990-1991.</li> <li>◇ 184 controls from same clinics, frequency matched by age, race, clinic and month of blood collection.</li> <li>◇ 171 controls from general medical clinics, frequency matched on age &amp; race. Blood collected April-June 1991.</li> </ul>	<ul style="list-style-type: none"> <li>◇ Blood samples collected at the same time as interviews.</li> </ul>	25-hydroxyvitamin D measured on sample of whole blood.	None besides matching variables.	Mean blood 25OHD levels were similar for cases and hospital clinic controls of either race. Mean (95% CI) case control difference in: Blacks -2.57 (-5.35, 0.21), Whites 0.87 (-0.47, 2.21) nmol/L.
Lowe 2005 <sup>125</sup> (same sample as Colston 2006 <sup>127</sup> )	<ul style="list-style-type: none"> <li>◇ 179 cases of breast cancer, both incident and prevalent, aged 34-84 years, from a hospital</li> </ul>	<ul style="list-style-type: none"> <li>◇ Blood samples collected at the same time as interviews.</li> </ul>	Plasma 25-hydroxyvitamin D measured on blood sample.	None besides matching variables.	Odds ratio (95% CI) of breast cancer, compared with the <i>highest</i> quintile of 25OHD (Q4) was: Q1 = 5.83 (2.31, 14.7)

	<p>breast clinic in London, during 1998-2003.</p> <p>◊ total of 179 controls, 48 from same breast clinic, 131 from hospital mammo-graphy screening programme, frequency matched by age and season of blood collection.</p>				<p>Q2 = 1.83 (0.83, 4.03)</p> <p>Q3 = 1.61 (0.71, 3.64).</p>
de Lyra 2006 <sup>126</sup>	<p>◊ 60 cases of breast cancer, aged 29-70 years, from a hospital breast clinic in Brazil, during 2001-2005.</p> <p>◊ total of 34 controls, aged 32-70 years, from hospital clinic.</p>	◊ Blood samples collected at surgery.	Serum 25-hydroxyvitamin D measured on blood sample.	None.	Mean blood 25OHD levels were similar for cases and hospital clinic controls (results shown in figure without numerical values given).

**Appendix K: Observational studies investigating the relationship between ovarian or endometrial cancer and dietary vitamin D or blood 25-hydroxyvitamin D.**

Paper	Subjects	Methods	Measurement of vitamin D	Confounders adjusted for	Main results
<i>Nested case control study</i>					
Two Roger 2007 <sup>128</sup>	<ul style="list-style-type: none"> <li>◇ US Nurses Health Study (NHS): 32,826 cancer free female nurses, aged 43-69 years at baseline, from participants who provided blood sample in 1989-90.</li> <li>◇ 2<sup>nd</sup> US NHSII: 29,611 cancer free female nurses, aged 32-54 years at baseline, who provided a blood sample in 1996-99.</li> <li>◇ Women's Health Study (WHS): 28,345 cancer free female professionals, aged &gt;45 years at baseline, who provided a blood sample from 1992.</li> </ul>	<p>Cases of ovarian cancer: self-reports confirmed by medical records.</p> <ul style="list-style-type: none"> <li>◇ NHS: 141 to 2004.</li> <li>◇ NHSII: 20 to 2003.</li> <li>◇ WHS: 63 to 2004.</li> </ul> <p>Controls: with intact ovaries, matched for age, menopausal status, use of HRT, fasting status and date &amp; time of blood collection.</p> <ul style="list-style-type: none"> <li>◇ NHS/NHSII: 3 controls per case (n=481).</li> <li>◇ WHS: 2 controls per case (n=122).</li> </ul>	Plasma 25-hydroxyvitamin D measured on baseline blood sample.	Matched variables plus HRT use, BMI, parity, lactose intake, oral contraceptive use, season of blood draw.	<p>No association. Relative risk (95% CI) of ovarian cancer, compared with the lowest quartile of 25OHD (Q1) was:</p> <p>Q2 = 0.97 (0.61, 1.52)            Q3 = 1.20 (0.75, 1.93)            Q4 = 0.83 (0.49, 1.39),            (p-value for trend = 0.57),            adjusted for confounders;            p-value for heterogeneity between studies = 0.66).</p> <p>Inverse association with 25OHD observed in women with BMI <math>\geq 25</math> at blood collection (p-value for trend = 0.04).</p>
<i>Cohort</i>					
Koralek 2006 <sup>129</sup>	31,925 cancer free women, mean age about 61 years at baseline, enrolling in a breast cancer screening programme in 27 US cities (Breast Cancer Detection Demonstration Project).	<ul style="list-style-type: none"> <li>◇ Baseline dietary survey in 1987-89 (phase 2) using an FFQ.</li> <li>◇ 146 ovarian cancer cases identified up until 1995-98 (phase 4), from two phases of follow-up questionnaires verified by pathology records or National Death Index.</li> </ul>	Self-administered validated 62-item FFQ of food & vitamin use.	Age, menopause type, parity, age of menarche, oral contraceptive use, HRT use, dietary calcium and lactose.	<p>No association. Relative risk (95% CI) of ovarian cancer, compared with the lowest quartile (Q1) of total vitamin D intake including supplements was:</p> <p>Q2 = 0.95 (0.55, 1.62)            Q3 = 0.97 (0.53, 1.79)            Q4 = 1.08 (0.63, 1.87),            (p-value for trend = 0.65),            adjusted for confounders.</p>

Genkinger 2006 <sup>130</sup> (includes same cohorts as Tworoger <sup>128</sup> 2007 and Koralek 2006 <sup>129</sup> )	Meta-analysis of 8 cohort studies from North America (7) and Holland (1) with vitamin D data; studies included if $\geq 50$ cases and used validated FFQ. Cohorts had 408,824 cancer free women.	<ul style="list-style-type: none"> <li>◇ Baseline dietary surveys from 1976 to 1993.</li> <li>◇ 1296 ovarian cancer cases identified up to 2004, verified from medical, cancer registry or mortality records.</li> </ul>	Self-administered validated FFQs of food & vitamin use.	Age, BMI, smoking, activity, age of menarche, menopause, oral contraceptive use, HRT use, and energy intake.	No association. Relative risk (95% CI) of ovarian cancer, compared with the lowest quantile (Q1) of total vitamin D intake including supplements was: Q2 = 1.20 (0.97, 1.48) Q3 = 1.26 (1.00, 1.57) Q4 = 1.09 (0.79, 1.51) Q5 = 1.27 (0.98, 1.64) Q6 = 1.12 (0.90, 1.38), (p-value for trend = 0.60), adjusted for confounders.
<i>Case control</i>					
Bidoli 2001 <sup>131</sup>	<ul style="list-style-type: none"> <li>◇ 1031 cases of ovarian cancer, median age 56 years, from Italian hospitals in five, during 1992-1999.</li> <li>◇ 2411 controls, admitted to hospitals with acute non-neoplastic diseases in same 5 areas, median age 57 years.</li> </ul>	◇ Participants interviewed in hospital.	Interviewer-administered validated 78-item FFQ of food intake over previous 2 years.	Age, study centre, year of interview, education, BMI, parity, oral contraceptive use, work physical activity, and energy intake.	No association. Odds ratio (95% CI) of ovarian cancer, compared with the lowest quintile (Q1) of vitamin D intake was: Q2 = 0.8 (0.6, 1.1) Q3 = 0.9 (0.7, 1.2) Q4 = 0.9 (0.7, 1.2) Q5 = 0.7 (0.6, 1.0), (p-value for trend = 0.13), adjusted for confounders.
Goodman 2002 <sup>132</sup>	<ul style="list-style-type: none"> <li>◇ 558 cases of ovarian cancer, mean age 55 years, from cancer registries in Los Angeles (n=338) and Hawaii (n=220), during 1995-1997.</li> <li>◇ 607 controls, with <math>\geq 1</math> ovary, mean age 55 years, randomly selected from neighbourhoods in Los Angeles (n=324) and from health surveillance programme in Hawaii (n=283), group matched</li> </ul>	◇ Questionnaires administered by interviewers in homes (>95%).	Interviewer-administered validated 256-item FFQ of food and supplement intake.	Age, ethnicity, study centre, education, oral contraceptives, parity, tubal ligation, and intake of energy and calcium.	No association. Odds ratio (95% CI) of ovarian cancer, compared with the lowest quartile (Q1) of vitamin D intake was: Q2 = 1.19 (0.83, 1.71) Q3 = 1.14 (0.75, 1.71) Q4 = 1.49 (0.90, 2.47), (p-value for trend = 0.16), adjusted for confounders.

	by age and ethnicity.				
Salazar-Martinez 2002 <sup>133</sup>	<p>◇ 84 cases of ovarian cancer, median age 53 years, referred to specialist cancer hospital from clinics in Mexico City, during 1995-1997.</p> <p>◇ 629 controls, with uteri, randomly selected from women presenting with acute disease at same clinics as cases, median age 54 years.</p>	◇ Questionnaires administered by interviewers in hospital (cases) or at community clinics (controls) by same interviewers.	Self-administered validated 116-item FFQ of food intake.	Age, total energy intake, parity, recent change in weight, physical activity and diabetes.	Inverse association. Odds ratio (95% CI) of ovarian cancer, compared with the lowest tertile (T1) of vitamin D intake was: T2 = 0.70 (0.40, 1.24) T3 = 0.43 (0.23, 0.80), (p-value for trend = 0.01), adjusted for confounders.
Salazar-Martinez 2005 <sup>134</sup>	<p>◇ 85 cases of <i>endometrial</i> cancer, mean age 57 years, referred to specialist cancer hospital from clinics in Mexico City, during 1995-1997.</p> <p>◇ 629 controls, with uteri, randomly selected from women presenting with acute disease at same clinics as cases, mean age 52 years.</p>	◇ Questionnaires administered by interviewers in hospital (cases) or at community clinics (controls) by same interviewers.	Self-administered validated 116-item FFQ of food intake.	Age, total energy intake, parity, recent change in weight, physical activity and diabetes.	Inverse association. Odds ratio (95% CI) of <i>endometrial</i> cancer, compared with the lowest tertile (T1) of vitamin D intake was: T2 = 0.83 (0.46, 1.50) T3 = 0.38 (0.18, 0.82), (p-value for trend = 0.003), adjusted for confounders.

**Appendix L: Observational studies (all case control) investigating the relationship between non-Hodgkin lymphoma and sun exposure or dietary vitamin D.**

Paper	Subjects	Methods	Measurement of sun exposure or vitamin D	Confounders adjusted for	Main results
Hughes 2004 <sup>135</sup>	<p>◇ 704 cases of non-Hodgkin lymphoma, aged 20-74 years, in New South Wales and Aust. Capital Territory, from cancer registry, during 2000-2001.</p> <p>◇ 694 controls, randomly sampled from state electoral rolls, frequency matched by age, sex and state.</p>	◇ Participants interviewed by phone (restricted to English speakers).	Outdoor sun exposure hours on working and nonworking days, and vacations, during decade years of age (10, 20, 30, 40, 50, 60 years).	Age, sex, state, ethnicity, skin colour and ability to tan.	<p>Inverse association. Odds ratio (95% CI) of non-Hodgkin lymphoma, compared with the lowest quartile (Q1) of total sun exposure was:</p> <p>Q2 = 0.72 (0.53, 0.98)            Q3 = 0.66 (0.48, 0.91)            Q4 = 0.65 (0.46, 0.91),            (p-value for trend = 0.01),            adjusted for confounders.            Mainly due to inverse association for non-working days (p-value for trend = 0.0001).</p>
Smedby 2005 <sup>136</sup>	<p>◇ 3055 cases of non-Hodgkin lymphoma, median age 61 years, from all hospital lymphoma clinics in Denmark and Sweden, during 1999-2002.</p> <p>◇ 3187 controls, randomly sampled from population registers, frequency matched by age, sex and country, median age 59 years.</p>	◇ Participants interviewed by phone (restricted to Danish & Swedish speakers).	Sun exposure, and frequency of sunburns, during summer 5-10 years before interview and at age 20 years.	Age, sex, country, skin reaction to sun, hair and eye colour, education, smoking, BMI, autoimmune diseases, and history of blood transfusions.	<p>Inverse association. Odds ratio (95% CI) of non-Hodgkin lymphoma, compared with the lowest quartile (Q1) of total sun exposure was:</p> <p>Q2 = 0.8 (0.7, 0.9)            Q3 = 0.7 (0.6, 0.9)            Q4 = 0.7 (0.6, 0.9),            (p-value for trend = 0.001),            adjusted for confounders.</p>
Hartge 2006 <sup>137</sup>	<p>◇ 551 cases of non-Hodgkin lymphoma, aged 20-74 years, from SEER registries in Iowa, Los Angeles, Detroit and Seattle, during 1998-2000.</p> <p>◇ 462 controls, randomly</p>	◇ Participants interviewed at home (restricted to mostly non-African-Americans).	<p>Midday sun exposure during summer during teenage years, twenties, thirties and most recent decade.</p> <p>Self-administered 107-</p>	Age, sex, ethnicity and study area.	<p>No association. Odds ratio (95% CI) of non-Hodgkin lymphoma, compared with the lowest quartile (Q1) of total sun exposure was:</p> <p>Q2 = 0.85 (0.62, 1.18)            Q3 = 0.75 (0.54, 1.05)            Q4 = 0.73 (0.46, 1.15),</p>

	sampled by random digit telephone dialling (<65 years) or from Medicare population rosters (age 65-74 years), frequency matched by study area, age, sex and race.		item validated FFQ of food and supplement intake.		(p-value for trend = 0.07), adjusted for confounders.  No association with total dietary vitamin D. Odds ratio compared with the lowest quartile (Q1) of vitamin D was: Q2 = 0.99 (0.66, 1.49) Q3 = 1.10 (0.74, 1.63) Q4 = 1.10 (0.72, 1.67), (p-value for trend = 0.55).
Polesel 2006 <sup>138</sup>	<p>◇ 190 cases of non-Hodgkin lymphoma, aged 18-84 years, (out of 240) admitted to hospitals in 2 Italian provinces, during 1999-2002.</p> <p>◇ 484 controls, aged 18-84 years admitted to hospitals with acute non-neoplastic diseases in same 2 areas, median age 57 years.</p>	◇ Participants interviewed in hospital.	Interviewer-administered validated 78-item FFQ of food intake over previous 2 years.	Gender, age, centre, education, place of birth, hepatitis C virus test and total energy intake..	Inverse association. Odds ratio (95% CI) of non-Hodgkin lymphoma, compared with the lowest tertile (T1) of vitamin D intake was: T2 = 0.8 (0.5, 1.2) T3 = 0.6 (0.4, 0.9), (p-value for trend < 0.05), adjusted for confounders.
Zhang 2007 <sup>139</sup>	<p>◇ 601 female cases of non-Hodgkin lymphoma, aged 21-84 years, from cancer centre in Connecticut, during 1996-2000.</p> <p>◇ 717 female controls, randomly sampled by random digit telephone dialling (&lt;65 years) or from Medicare population rosters (age ≥65 years), frequency matched by age.</p>	◇ Information collected at in-person interviews.	Recreational sun exposure at 4 age periods: <18 yrs, 18-40, 41-60, >60 yrs.	Race, age, family history of non-Hodgkin's lymphoma, education, eye colour, skin type.	Positive association. Odds ratio (95% CI) of non-Hodgkin lymphoma, compared with the lowest tertile (T1) of summer sun exposure was: T2 = 1.3 (1.0, 1.7) T3 = 1.7 (1.2, 2.4), (p-value for trend 0.0051), adjusted for confounders.

### Appendix M: Observational studies investigating the relationship between cancer of the pancreas or kidneys and vitamin D.

Paper	Subjects	Methods	Measurement of vitamin D	Confounders adjusted for	Main results
<i>Cohort or nested case control studies</i>					
Stolzenberg-Solomon 2006 <sup>140</sup>	29,133 male smokers in southwestern Finland, aged 50-69 years, enrolled in into an RCT, to determine if anti-oxidant supplements prevent cancer.	<ul style="list-style-type: none"> <li>◇ Blood samples collected at baseline during 1985-1988.</li> <li>◇ 200 cases of pancreatic cancer in treatment and placebo arms of trial, up to 2001.</li> <li>◇ 400 controls matched for age and month of blood collection.</li> </ul>	Serum 25-hydroxyvitamin D measured on blood sample.	Years smoked, cigarettes per day, smoking cessation during trial, occupational physical activity, education and serum retinol.	Positive association. Odds ratio (95% CI) of pancreatic cancer, compared with the lowest quintile (Q1) of serum 25OHD was: Q2 = 1.30 (0.70, 2.40) Q3 = 2.12 (1.15, 3.90) Q4 = 1.50 (0.81, 2.76) Q5 = 2.92 (1.56, 5.48), (p-value for trend = 0.001), adjusted for covariates.
Skinner 2006 <sup>141</sup>	75,427 US female registered nurses, aged 34-59 years in 1980, without cancer in 1984 (Nurses' Health Study).  46,771 US male health professionals aged 40-75 years, without cancer in 1986.	<ul style="list-style-type: none"> <li>◇ Baseline dietary survey in 1984 for Nurses' Health Study and in 1986 for male health professionals.</li> <li>◇ 365 pancreatic cancer cases (178 female, 187 male) over 16 year f/u, from biennial questionnaires verified by pathology records or National Death Index.</li> </ul>	Self-administered validated 131-item FFQ of food & supplements.	Study, age, time period, total energy intake, smoking, diabetes, BMI, region of residence, parity (women) and use of multivitamins.	Inverse association. Relative risk (95% CI) of pancreatic cancer, compared with the lowest quintile (Q1) of total vitamin D intake was: Q2 = 0.78 (0.59, 1.01) Q3 = 0.57 (0.40, 0.83) Q4 = 0.56 (0.36, 0.87) Q5 = 0.59 (0.40, 0.88), (p-value for trend = 0.01), adjusted for confounders.
<i>Case control</i>					
Bosetti 2007 <sup>142</sup>	<ul style="list-style-type: none"> <li>◇ 767 cases of renal cell cancer, aged 24-79 years, admitted to hospitals in 4 Italian provinces, during 1992-2004.</li> <li>◇ 1534 controls, aged 22-79 years, admitted to hospitals with acute non-neoplastic diseases in same areas, matched by study centre, sex and age.</li> </ul>	◇ Participants interviewed in hospital.	Interviewer-administered validated 78-item FFQ of food intake over previous 2 years.	Gender, age, study centre, period of interview, education, BMI, smoking, alcohol, family history of kidney cancer and total energy intake.	No association. Odds ratio (95% CI) of renal cancer, compared with the lowest quintile (Q1) of vitamin D intake was: Q2 = 0.76 (0.58, 1.01) Q3 = 0.76 (0.58, 1.01) Q4 = 0.86 (0.65, 1.13) Q5 = 0.76 (0.57, 1.01), (p-value for trend = 0.16), adjusted for confounders.

## Appendix N: Observational studies investigating the relationship between cancer survival and season of diagnosis.

Paper	Subjects	Methods	Definition of season	Confounders adjusted for	Main results
Robsahm 2004 <sup>143</sup>	115,096 cases of breast, colon or prostate cancer, diagnosed during 1964-1992 in people born between 1900-1966 in Norway.	<ul style="list-style-type: none"> <li>◇ Cases identified by Cancer Registry of Norway.</li> <li>◇ 45,667 deaths in cohort, from cancer as underlying cause, identified up to end of 1992 from national population register.</li> </ul>	Winter: December-February; Spring: March-May; Summer: June-August; Autumn: September-November.	Age at diagnosis, birth cohort, period of diagnosis, stage of cancer at diagnosis, education, child-bearing pattern, and residential and occupational sun exposure.	Relative risk of mortality (95% CI) for diagnosis in summer (S) and autumn (A), compared with winter was: <i>Breast</i> cancer (women): S = 0.90 (0.86, 0.95) A = 0.85 (0.82, 0.90); <i>Colon</i> cancer (women): S = 0.84 (0.79, 0.90) A = 0.75 (0.70, 0.79); <i>Prostate</i> cancer (men): S = 0.88 (0.84, 0.86) A = 0.80 (0.77, 0.84); adjusted for confounders.
Moan 2005 <sup>144</sup>	27,745 cases of <i>colon</i> cancer, diagnosed during 1964-1992, aged <68 years at diagnosis, in people born between 1900-1966 in Norway.	<ul style="list-style-type: none"> <li>◇ Colon cancer cases identified by Cancer Registry of Norway.</li> <li>◇ Deaths in cohort, identified up to end of 1992 from national population register.</li> </ul>	Winter: December-February; Spring: March-May; Summer: June-August; Autumn: September-November.	None stated.	Relative risk of mortality was reduced (>20%) for diagnosis in autumn compared with winter, for both women and men, particularly within 18 months of diagnosis. No data provided on statistical significance
Porojnicu 2005 <sup>145</sup>	3,139 cases of <i>Hodgkin's lymphoma</i> , diagnosed during 1964-2000, in people born between 1900-1966 in Norway.	<ul style="list-style-type: none"> <li>◇ Colon cancer cases identified by Cancer Registry of Norway.</li> <li>◇ Deaths in cohort, identified up to end of 2000 from national population register.</li> </ul>	Winter: December-February; Spring: March-May; Summer: June-August; Autumn: September-November.	Age at diagnosis, birth cohort, decade of diagnosis, region of residence & sex.	Relative risk of mortality (95% CI) in 1 <sup>st</sup> 36 months after diagnosis, for autumn diagnosis compared with winter, was: All ages = 0.78 (0.62, 0.99), p=0.04; Age < 30 years = 0.36 (0.15, 0.87), p=0.025.
Porojnicu 2007a <sup>146</sup>	49,821 cases of <i>breast</i> cancer, diagnosed during 1964-1992, 11,866 aged ≤50 years and 37,955 aged >50 years at diagnosis, in women born between 1900-	<ul style="list-style-type: none"> <li>◇ Cases identified by Cancer Registry of Norway.</li> <li>◇ 6,615 deaths in cohort, from breast cancer as underlying cause,</li> </ul>	Summer: June-November; Winter: December-May.	Age at diagnosis, period of diagnosis, stage of cancer at diagnosis, education, and occupation.	Mortality reduced for cases diagnosed in summer, compared to those in winter, in women aged below and above 50 years.

	1966 in Norway.	identified up to end of 2001 from national population register.			
Porojnicu 2007b <sup>147</sup>	45,681 cases of <i>lung</i> cancer, diagnosed during 1960-2001, aged <68 years at diagnosis, in people born between 1900-1966 in Norway.	<ul style="list-style-type: none"> <li>◇ Lung cancer cases identified by Cancer Registry of Norway.</li> <li>◇ Deaths in cohort, in 1<sup>st</sup> 18 months of follow-up, identified up to end of 2001 from national population register.</li> </ul>	Winter: December-February; Spring: March-May; Summer: June-August; Autumn: September-November.	Age of diagnosis, stage of disease at diagnosis, and histology, sex, period of diagnosis, birth cohort and region.	Mortality did not vary with season of diagnosis in women or men, except for men aged ≤50 years, for whom it was 15% lower for diagnosis in Autumn compared with Winter – RR (95% CI) = 0.85 (0.73, 0.99), p=0.04.
Lim 2006 <sup>148</sup>	1,194,562 cancer cases in men and women (colon: 71,723 men, 76,266 women; lung 131,770 men, 60,353 women; breast: 182,895 women; prostate: 92,312 men), diagnosed during 1971-2002 in residents in South East England..	◇ Cases identified by regional cancer registry and vital status followed to June 2005.	Winter: December-February; Spring: March-May; Summer: June-August; Autumn: September-November.	Age at diagnosis, period of diagnosis.	Relative risk of mortality (95% CI) in 1 <sup>st</sup> 18 months after diagnosis, for summer diagnosis compared with winter, was: <i>Breast</i> cancer: women 0.86 (0.83, 0.89); <i>Prostate</i> cancer: men 0.96 (0.92, 1.00); <i>Colorectal</i> cancer: women 0.94 (0.91, 0.97) men 0.99 (0.95, 1.02); <i>Lung</i> cancer: women 0.95 (0.92, 0.97) men 0.94 (0.92, 0.95); <i>All cancer</i> : women 0.94 (0.93, 0.95) men 0.99 (0.98, 1.00); adjusted for confounders.

### Appendix O: Observational studies investigating the relationship between cancer survival and vitamin D.

Paper	Subjects	Methods	Measurement of vitamin D	Confounders adjusted for	Main results
Zhou 2005 <sup>149</sup>	456 early-stage non-small cell lung cancer patients, aged >18 years, recruited during 1992-2000 at a major Boston hospital.	<ul style="list-style-type: none"> <li>◇ Baseline interview, including dietary questionnaire, at the time of recruitment.</li> <li>◇ Data on cancer recurrence and survival collected from hospital records and Social Security Death Index.</li> </ul>	Self-administered validated 126-item FFQ of food & supplements.	Age, gender and clinical stage.	<p>No association in total sample between either recurrence free survival (p=0.66) or overall survival (p=0.44) and dietary vitamin D.</p> <p>Both measures of survival significantly increased for highest vitamin D quartile, compared with lowest quartile, among patients diagnosed in summer (p-trend &lt;0.01), but not for those diagnosed in winter.</p>
Zhou 2007 <sup>150</sup>	447 early-stage non-small cell lung cancer patients, aged >18 years, recruited during 1992-2002 at a major Boston hospital.	<ul style="list-style-type: none"> <li>◇ Baseline interview, including dietary questionnaire, at the time of recruitment.</li> <li>◇ Data on cancer recurrence and survival collected from hospital records and Social Security Death Index.</li> </ul>	<p>25-hydroxyvitamin D measured on blood sample collected at diagnosis.</p> <p>Self-administered validated 126-item FFQ of food &amp; supplements (collected from 309 patients).</p>	Age, stage, pack-years of smoking, lung cancer therapy, and surgery season.	<p>Inverse association. Hazard ratio (95% CI) of mortality for all cases, compared with the lowest quartile (Q1) of blood 25OHD, was:</p> <p>Q2 = 1.07 (0.74, 1.53)            Q3 = 0.80 (0.55, 1.18)            Q4 = 0.74 (0.50, 1.10),            (p-value for trend = 0.07),            adjusted for confounders; particularly for stage IB-IIIB cases (p-value for trend = 0.002).</p>

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