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Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma

Running title: Meta-analysis of serum vitamin D and cancer

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Notes

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Abstract

Epidemiological studies have suggested a reduced risk of several cancers associated with high vitamin D status. We performed a systematic review with meta-analyses of observational studies of serum 25-hydroxyvitamin D level and colorectal, breast and prostate cancer, and colonic adenoma. The literature to December 2009 was searched without language restriction. The meta-regression analysis was done in order to compute dose-response effects. Because in case-control studies, serum 25-hydroxyvitamin D level is measured after the diagnosis of cancer, separate analyses for case-control and prospective studies were done. We identified 35 independent studies. The seven studies on colorectal adenomas were heterogeneous in terms of endpoint and control for major confounding factors, and we did not perform a meta-analysis of these data. The summary relative risk (SRR) and (95% confidence interval) for a 10 ng/mL increase in serum 25-hydroxyvitamin D was 0.85 (0.79; 0.91) for colorectal cancer (2630 cases in 9 studies); 0.89 (0.81;0.98) for breast cancer (6175 cases in 10 studies); and 0.99 (0.95;1.03) for prostate cancer (3956 cases in 11 studies). For breast cancer, case-control studies (3030 cases) had major limitations and obtained SRR of 0.83 (0.79; 0.87) while SRR of prospective studies (3145 cases) was 0.97 (0.92; 1.03). For colorectal and breast cancer, differences between cases and controls in the season of blood draw or in overweight/obesity or physical inactivity could not explain the results. In conclusion, a consistent inverse relationship between serum 25-hydroxyvitamin D levels and colorectal cancer was found. No association was found for breast and prostate cancer.

Introduction

Vitamin D can inhibit cell proliferation and promote apoptosis *in vitro*, and several tissues can locally produce the physiologically active form of vitamin D, 1α,25-dihydroxyvitamin D, which has anti-carcinogenic properties.[1] In addition, these tissues express the vitamin D receptor (VDR) that enables cellular action of the 1α,25-dihydroxyvitamin D. These basic research findings have strengthened the credibility of the hypothesis largely derived from ecological studies in the USA by which a higher vitamin D status would be associated with a lower risk of cancer.[2]

The 25-hydroxyvitamin D is the precursor of the physiologically active 1α,25-dihydroxyvitamin. The serum level of 25-hydroxyvitamin D is a result of skin exposure to sunlight, total vitamin D intake and other factors such as age and skin pigmentation. Serum levels vary with season, with the highest levels in summer and autumn. 25-hydroxyvitamin D has a half-life in the circulatory system of about 2-3 weeks.[3] In contrast, serum 1α,25-dihydroxyvitamin D is tightly biochemically regulated, except in situations of extreme deficiency, in keeping with its role in calcium homeostasis. It has a circulating half-time of 5-15 hours and exhibits little seasonal variability.[3,4] For these reasons, the serum 25-hydroxyvitamin D is considered as better reflecting the vitamin D status than the serum 1α,25-dihydroxyvitamin D.

The first report of an inverse association between serum 25-hydroxyvitamin D and cancer was published in 1989 for colorectal cancer in the USA.[5] Since then, a number of observational studies have examined plasma or serum 25-hydroxyvitamin D levels in relation to cancer risk.

In this paper, we performed a meta-analysis of observational studies that examined the association between measured serum 25-hydroxyvitamin D levels and risk of colorectal, breast, and prostate cancers.

Methods

Methodology for literature search

The literature search was conducted in the following databases: PubMed, ISI Web of Science (Science Citation Index Expanded) and Embase, up until December 2009, including articles ahead of publication. The following keywords were used in searching: "breast cancer", "breast neoplasm", "colon cancer", "colorectal cancer", "rectal cancer", "prostate cancer" and "colorectal adenoma". To define the exposure, the following key words were used: "vitamin", "vitamin D", "25-hydroxyvitamin D", "25(OH)D", "cholecalciferol", "calcidiol", "calcitriol" and "vitamin D receptors". We searched for the key words in the headers and in the abstract, when available. We also performed a manual search of references cited in the selected articles and published reviews.

Primary inclusion criteria were case-control and cohort studies published as an original article, which reported relative risk estimates or crude data for serum 25-hydroxyvitamin D levels. Studies reporting data from predictive models or serum 1α,25-dihydroxyvitamin D levels only were excluded. Ecological studies, case reports, reviews and editorials were not considered eligible. In a second step, we selected studies reporting the minimum information on relative risks necessary to perform adequate meta-analysis:

1. Sufficient information to estimate the relative risk and 95% confidence intervals for the different quantiles used to categorize serum 25-hydroxyvitamin D levels (odds ratios, relative risks or crude data and

corresponding standard errors, variance, confidence intervals or P-value of the significance of the estimates).

2. Studies had to be independent and not duplicate results published in another article. When several articles concerned the same subjects, results from the publication using the largest sample of subjects were used.

A standardized data-collection protocol was used for gathering the relevant data from each selected article. For each cancer site, data abstraction was performed independently by two readers (two by two combinations of JH, BC, MJS and GB) and then cross-checked. Information on serum 25-hydroxyvitamin D levels was extracted across all published categories in order to construct dose-response models. When data were reported by gender or by cancer sites, the estimates were extracted separately for the two factors.

Selection of data and methods of analysis

Estimates of risk

Since cancer is a relatively rare disease, we ignored the distinction between the various estimates of relative risk (i.e., odds ratio, rate ratio, risk ratio) and all measures were interpreted as relative risk. Every measure of association, adjusted for the maximum number of confounding variables, and corresponding confidence intervals were transformed into log relative risks and the corresponding variance was calculated using the formula proposed by Greenland (1987).[6] The European Prospective Investigation on Cancer and Nutrition (EPIC) study on vitamin D status and colorectal cancer[7] provided to this study the results in the format needed for this meta-analysis. When no estimates were given, crude estimates were calculated from tabular data. We used Woolf's formula to evaluate the standard error of the log relative risk.[6] A study identification number was set as a random effect, since some of these estimates came from the same study.

The homogeneity of the effects across studies was assessed using the large sample test based on the Chi-square statistic. Since the Chi-square test has limited power, we considered statistically significant heterogeneity at the P= 0.10 level of association. A further measure of heterogeneity I^2, a transformation of the square-root of the Chi-square divided by its degrees of freedom has been considered in order to compare between heterogeneities for different numbers of pooled studies. Larger values of I^2 indicate greater heterogeneity.[8]

Pooled estimates of the effect of 25-hydroxyvitamin D levels on the risk were based on a two-step procedure. First, a linear model was fitted within each study to estimate the relative risk per unit increase of serum 25-hydroxyvitamin D. When sufficient information was published (the number of subjects at each serum level category), the model was fitted according to the method proposed by Greenland and Longnecker (1992).[9] This method provides the natural logarithm of the relative risk, and an estimator of its standard error, taking into account the fact that the estimates for separate categories depend on the same reference group. When the number of subjects at each serum level category was not available from the publications, coefficients were calculated ignoring the correlation between the estimates of risk at the separate exposure levels.[9]

Second, the summary relative risk was estimated by pooling the study-specific estimates with the mixed effects models in order to be conservative and to generalize the results.[6] PROC MIXED in SAS (SAS Institute Inc. SAS Windows version (8.02), 1999, Cary, NC, USA), with maximum likelihood estimates, was used to take into account two sources of variations: between-study and within-study variability.[10] The final summary relative risks

expressed the risk of cancer associated with an increment of serum 25-hydroxyvitamin D by 1 ng/mL and 10 ng/mL.

Heterogeneity and sensitivity analyses

Several sensitivity analyses were conducted to evaluate the stability of the pooled estimates. We first examined pooled relative risks for case-control and prospective (cohort and nested case-control) studies separately. We also examined changes in results after exclusion of specific studies.

Meta-regressions and subgroup analyses were carried out to investigate between-study heterogeneity.[11] Heterogeneity was investigated by looking at all the possible factors that could influence the estimates (cancer sub-sites, type of study, adjustment for confounding factors, and categories used for exposure and features of the population). To investigate whether publication bias might affect the validity of the estimates, funnel plots of the regression of log relative risk on the sample size, weighted by the inverse of the pooled variance were constructed.[12]

Results

A total of 42 relevant studies were retrieved. Table 1 summarizes the 28 studies on colorectal breast and prostate cancer included in the meta-analysis. Table 2 summarizes the 7 studies on colorectal adenoma and Table 3 lists the 7 studies not included in the meta-analysis with the reasons for exclusion. All studies reported results for cancer incidence but one cohort study reported only mortality.[17] The age of subjects included in studies generally ranged from 50 to 74 years.

Studies and data selection

Colorectal cancer

Nine studies, one hospital-based case-control and eight nested case-control studies included a total of 2630 colorectal cancer cases.[5,8,13-19] The Women's Health Initiative (WHI) was a randomized trial testing the effect of calcium plus vitamin D supplementation in postmenopausal women.[19] The placebo group included women who were followed-up without receiving vitamin D supplements. This control group was thus considered equivalent to a cohort study and we calculated dose-response estimates using the crude data specific to this group. For Wu *et al.* (2007) [19] we abstracted estimates from the Health Professionals Follow-up Study and the Nurses Health Study separately.

Colorectal adenoma

Seven studies, 4 case-control and 3 cohort or nested case-control studies, included a total of at least 2029 patients with adenoma or of adenoma recurrences (Table 2).[39-45] We classified the study by Peeters et al., 2004 [43] as case-control study as the time from blood draw to colonoscopy examination was probably short and no follow-up time was provided. Four studies used as outcome patients diagnosed with one or more adenoma(s), [39-41,45] one used subjects diagnosed with advanced adenoma, [43] one used the total number of adenoma recurrences,[42] and one used numbers of subjects with adenoma recurrences.[44] In one study, endoscopic examinations were done in a fraction of subjects. [39]

Breast cancer

Ten studies, five case-control studies, one cohort, and four nested case-control studies, included a total of 6175 cases of mainly post-menopausal women.[17,20-28] As above, the placebo arm of the WHI trial on calcium plus vitamin D supplementation was considered equivalent to a cohort study on breast cancer and we calculated dose-response estimates from the crude data of the placebo group.[25] We classified the study by Renjmark et al [28] as a case-control study as the time from blood draw and mammography to breast cancer diagnosis was probably short and no follow-up time was provided.

Prostate cancer

Eleven cohort or nested case-control studies included a total of 3956 cases.[17,29-38] One study,[31] presented relative risk using the highest category as the reference, so we calculated the relative risk from the crude data by quartiles. Three studies were nested within randomized trials on supplementation with selenium, [32] beta-carotene and α-tocopherol [34] or calcium supplements.[33] These interventions had no influence on the risk of prostate cancer [32,33,54] and we thus included in the meta-analysis results obtained from all men included in the trials.

Information about and adjustment for season of blood draw

Of the 35 studies in Table 1 and 2, three did not report how they dealt with the season of blood draw.[15,40,44] The 32 other studies opted for one or for two control strategies. Sixteen case-control studies matched cases and controls by month or season of blood draw and statistical adjustment for month or season of blood draw was done in eleven studies. Seven studies displayed results stratified by month or season of blood draw [17, 19,22,28,30, 39,41] and the overall and relative risks by season of blood draw were not materially different. The large

EPIC cohort studies [7,38] showed that the means of serum 25-hydroxyvitamin D concentration by month of blood draw were similar in prostate cancer cases and controls,[38] and always lower among colorectal cancer cases than controls.[7] Only two studies (both on colorectal cancer) elected to draw all blood samples during winter only.[5,13]

Information and adjustment for confounding factors

Several factors other than age are known to be associated with low levels of serum 25-hydroxyvitamin D and increased risk of colorectal cancer, breast cancer, and of colorectal adenoma such as being overweight or obese, and physical inactivity. Three studies of colorectal cancer occurrence [7,18,19] adjusted for body mass index and physical exercise. Three prospective studies of breast cancer occurrence adjusted for these two factors,[20,25,27] and one [24] adjusted for body mass index but not physical inactivity, presumably because this factor was equally distributed among cases and controls. The study of colorectal and breast cancer mortality [17] did not adjust for these two factors because they had no influence on relative risks.

For colorectal adenoma, not all studies did adjust for body mass index, physical activity or smoking status (Table 2), three factors known to be associated with both 25-hydroxyvitamin D levels and adenoma occurrence.[55] In addition, four studies did not take into account bowel examinations done in previous years [40,41,43,45] and none inquired on colorectal cancer screening history. A history of bowel examination or of screening was probably associated with lower probability of adenoma during the study and with greater health consciousness, which may be associated with higher vitamin D status.

Obesity and physical inactivity are not associated with prostate cancer, and therefore, adjustment on these to two factors was not likely to affect risks associated with serum 25-hydroxyvitamin D levels.

Results of the meta-analysis

Because of the heterogeneity of studies on colorectal adenomas, and the lack of appropriate control of major confounding factors, we decided that it was not appropriate to perform a meta-analysis of their results.

Pooled estimates

Results of the meta-analyses summarizing the change in cancer risk associated with 1.0 and 10 ng/mL increase in serum 25-hydroxyvitamin D level are displayed in the Figures and in Table 4. A significant inverse relationship was found between 25-hydroxyvitamin D levels and the risk of colorectal cancer with a summary relative risk (SRR) of 0.85 (Table 4). The three studies on colorectal cancer occurrence that controlled for body mass index and physical inactivity had results similar to other studies.

For breast cancer the pooled estimates of 0.89 reached statistical significance (Table 4). However, restricting the analysis to prospective studies (3145 cases) yielded a SRR of 0.97 for a 10 ng/mL increase (95% CI: 0.92; 1.03), while the SSR for the five case-control studies (3030 cases) was 0.83 (95% CI: 0.79; 0.87) ($P<0.001$ for the difference between SRRs, data not shown). These results suggest that the five case-control studies were responsible for the apparent decrease in risk associated with increasing serum 25-hydroxyvitamin D level.

For prostate cancer the results did not show any association with 25-hydroxyvitamin D levels (SRR = 0.99 for a 10 ng/mL increase; 95% CI: 0.95-1.03).

Cancer risk was increased for both low and high levels of 25-hydroxyvitamin D in one study of colorectal cancer.[5] In the Nordic cohort study of prostate cancer, the Norwegian and Swedish cohorts, but not in the Finnish cohort found that cancer risk was increased for both low and high levels of 25-hydroxyvitamin (data not shown).[53] Risks increased above 41 ng/mL in the Garland study, and above 32 ng/mL in the Norwegian and Swedish cohort studies. For all three cancers, results did not vary with different methods used for controlling time of blood draw (data not shown). Detailed reporting of results by month of blood draw by the two EPIC studies showed that such bias could not explain the association found for colorectal cancer and the absence of association found for prostate cancer.[7,38]

Heterogeneity analysis

High between-study heterogeneity was found for all sites, especially when all case-control and prospective studies on breast cancer were considered together (Table 4). In order to investigate between-study heterogeneity and the robustness of the associations found, we carried out subgroup and meta-regression analyses for factors that might interfere with the association such as, age, body mass index, sex (for colorectal cancer), cancer sub-site (e.g., colon and rectum), study design, publication year, reference category for vitamin levels and highest categories of serum 25-hydroxyvitamin D levels. SRRs for colorectal cancer in men and women, or for rectal and colonic cancer were not different (p=0.69 and 0.86, respectively). The only factor significantly explaining the variability among estimates was the design of studies on breast cancer reflecting the discrepancy between the results of case-control compared to cohort or nested case-control studies. None of the other factors considered in the sub-group or meta-regression analyses affected the SRRs for any of the other four tumors (data not shown).

Sensitivity analyses and publication bias investigation

A series of further analyses were performed to test the stability and sensitivity of the analysis. Single studies with special features that could influence results were excluded. For colorectal cancer the following studies were excluded: the cohort study on cancer mortality [17]; the study conducted in Asia [21]; and the only case-control study on colorectal cancer that reported only one estimate for 25-hydroxyvitamin D level above the median.[15] The pooled relative risk, for the dose-response model, was not materially affected by exclusion of any one of these studies (Table 5).

For colorectal, breast and prostate cancers, the funnel plot regression of dose-response estimates did not indicate the presence of significant publication bias (P=0.19, 0.62, and 0.92 respectively). For colorectal cancer, the funnel plot regression on highest versus lowest relative risks did not suggest any significant publication bias (P=0.27, data not shown).

Discussion

Our results suggest that, in well fed populations, an inverse relationship between serum 25-hydroxyvitamin D levels and colorectal cancer exists. No association was found for breast and prostate cancer. A non-significant decreased risk of breast cancer risk was associated with higher serum 25-hydroxyvitamin D, but results from prospective studies only did not support an association between vitamin D status and breast cancer. No evidence was found for an association between serum 25-hydroxyvitamin D and prostate

cancer. Studies of colorectal adenomas were too heterogeneous and so a meta-analysis of their results was not appropriate.

The case-control design implies that the measurement of 25-hydroxyvitamin D is done in individuals already diagnosed with cancer. Therefore, results from this study design need to be interpreted cautiously because of the potential for reverse causation, that is, low vitamin D status being a consequence, rather than a cause of the disease. For example, when symptoms are severe or during the treatment of cancer, exposure to sunlight and dietary habits are likely to change (due to hospitalizations, disability or change in lifestyle). In the UK case-control study of breast cancer,[20] three quarters of cancer cases had been diagnosed well before blood was drawn, thus increasing the likelihood of reverse causation. In Crew et al (2009) [26] serum 25-hydroxyvitamin D level was measured in only 43% of controls approached, and thus the lower breast cancer risk may have been the consequence of selection bias. A similar issue could explain the lower breast cancer risk observed in the German case-control study [23] in which only 66% of cases and 43% of controls approached consented to have blood drawn.
The "nested case-control" study is a case-control study embedded within a prospective cohort study, and serum 25-hydroxyvitamin D level is measured in archived blood samples collected several years before disease diagnosis. Therefore, in cohort and nested-case-control studies, as the blood sample is taken well before the diagnosis of cancer, it is unlikely that any association observed is due to the effect of cancer on the blood level of 25-hydroxyvitamin D.

Summary relative risks found by the meta-analysis are not likely to be influenced by differences regarding season of blood draw or lack of control of major confounding factors such as overweight or obesity and lack of physical

activity. In most studies only one measurement of serum 25-hydroxyvitamin D level was usually made. Also, a variety of laboratory methods were used for measuring serum 25-hydroxyvitamin D concentrations (e.g., five different methods in studies of colorectal cancer) and it is notorious that these methods yield different results [56,57]. These sources of inaccuracies are expected to introduce noise in the data. Our results suggest that these sources of inaccuracies were not strong enough for concealing the relationship we found between 25-hydroxyvitamin D levels and colorectal cancer.

Analyses of specific subgroups reported by studies (i.e., for colon and rectal cancer separately) should be interpreted cautiously as the results were very heterogeneous results, and false positive findings may have occurred due to the multiple statistical testing used.

Contrary to two other meta-analyses,[58,59] we did not compute pooled risk estimates comparing groups with the highest to groups with the lowest serum 25-hydroxyvitamin D level. These comparisons are less meaningful than dose-response estimates as summary relative risk varies according to numbers of serum level categories reported by studies (i.e., quantiles or author's defined limits between categories). Differences in numbers of serum level groups across studies introduce distortion in the results and tend to spuriously increase the apparent protective effect associated with increasing serum 25-hydroxyvitamin D level. In addition, these two meta-analyses did not report separate results for case-control and cohort studies.

The U-shaped association found in two cohort studies between 25-hydroxyvitamin D levels and colorectal or prostate cancer risk [5,53] could be considered as isolated observations because upper quantiles of 25-hydroxyvitamin D levels were not higher than in other studies (Table 1).

However, these results may also mean that, like for many agents that were proposed for cancer chemoprevention, a high vitamin D status could be associated with an increased risk of cancer or other serious adverse event.[60]

The inverse association between serum 25-hydroxyvitamin D levels and colorectal cancer risk appeared quite robust and consistent.
If low vitamin D status was a cause of colorectal cancer, then randomized trials should show a decrease in the risk of developing this cancer. However, the two randomized trials that examined the influence of vitamin D supplementation on colorectal cancer risk have not confirmed findings from observational studies.[16,61] The small size of the Trivedi trial [61] (2,686 subjects 65-84 years old) precluded the possibility of finding a statistically significant difference. The Women's Health Initiative (WHI) in the USA randomized 36,282 post-menopausal women to 10 μg of vitamin D per day and 1 g of elementary calcium, or to placebo.[16,25] After a mean of seven years' follow-up the intervention did not alter the risk of colorectal and breast cancers, or of all cancers. The negative findings of the WHI trial have been attributed to inadequate vitamin D doses, too low adherence to supplementation, too short a trial duration, or interactions between vitamin D and other substances, for example, menopausal hormone replacement therapy and calcium.[62-64]
Nonetheless, the discrepancy between observational and randomized trials points to the alternative hypothesis that vitamin D status would reflect an individual's propensity to develop colorectal cancer rather than be the cause of that cancer . This propensity would be associated with lifestyle, e.g., obesity, smoking, low physical activity, and other unknown risk factors that cannot be controlled by statistical analysis.

The randomized trial of vitamin D (27.5 μg vitamin D_3 per day) and calcium (1.4-1.5 g supplemental elemental calcium per day) in 1179 healthy post-

menopausal community-dwelling women in Nebraska (USA) reported a lower cancer incidence in women taking vitamin D and calcium than in women taking placebo.[65] However, this small-size trial reported only 50 cancer cases and its methodology and statistical analysis have been much criticized [66-69] and thus results should be considered cautiously.
Some authors have proposed that an "optimal vitamin D level" would exist below which the risk of cancer and other chronic diseases increases.[70,71] However, observational studies do not support an association between serum 25-hydroxyvitamin D levels and breast or prostate cancer. Before thinking that an optimal level would exist at least for colorectal cancer, a causal link between vitamin D status and occurrence of this cancer must first be demonstrated.

In conclusion, if additional observational studies of vitamin D and cancer are proposed, they should adopt different designs, such as assessment of serum 25-hydroxyvitamin D colorectal at different points in time, or longer follow-up of subjects. To assess whether vitamin D status is a risk factor or a risk marker for colorectal cancer, it is likely that new randomized trials will need to be organized to test whether increasing the 25-hydroxyvitamin D level changes the risk of colorectal cancer, and to determine how much of an increase is required to change the risk of cancer sufficiently to be useful as a public health measure.

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Figure caption

Figure – Forest plots of relative risks of cancer associated with 1 ng/mL increase in serum level of 25-hydroxyvitamin D. PY is publication year; CC is case-control study; Co is cohort study and NCC is case control study nested within a prospective cohort study. For colorectal cancer, there was only one case-control study [15] and for prostate cancer, there were no case-control studies.

Table 1 - Principal characteristics of studies * included in the meta-analysis.

First Author, publication year [ref.]	Country	Study design	Study name	Study acronym	Mean years of follow-up	No. cases	No. controls or of total subjects if cohort	Type of quantile	Upper bound of lowest quantile or group †	Lower bound of upper quantile or group ‡
Colorectal cancer										
Garland et al, 1989 [5]	USA	NCC	Washington County, Maryland, for cases diagnosed between 1975 and 1983	-	9	34	67	Quintiles	19	42
Braun et al, 1995 [13]	USA	NCC	Washington County, Maryland, for cases diagnosed between 1984 and 1991.	-	17	57	114	Quintiles	17	30
Tangrea et al, 1997 [14]	Finland	NCC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	ATBC	8	146	290	Quartiles	10	19
Yaylim-Eraltan et al, 2006 [15]	Turkey	CC	-	-	-	26	52	Below/above median	20	20
Wactawski-Wende et al, 2006 [16]	USA	NCC	Women's Health Initiative	WHI	12	306	306	Quartiles	12	23
Freedman et al, 2007 [17]	USA	Cohort	Third National Health and Nutrition Examination Survey	NHANES III	12	66	16818	Tertiles	20	32
Otani, 2007 [18]	Japan	NCC	Japan Public Health Center	JPHC	14	375	750	Quartiles	20	30
Wu et al, 2007 [19]	USA	NCC	Health Professionals Follow-up Study and Nurses' Health Study	HPFS+NHS	9	372	739	Quintiles	16	40
Jenab et al, 2008 [7]	Europe	NCC	European Prospective Investigation into Cancer and Nutrition	EPIC	9	1248	1248	Quintiles	10	40
Breast cancer										
Bertone-Johnson, 2005 [20]	USA	NCC	Nurses' Health Study	NHS	7	701	724	Quintiles	22	42
Colston, 2006 [21]	UK	CC	-	-	-	179	179	Quartiles	20	60
Freedman, 2007 [17]	USA	Cohort	Third National Health and Nutrition Examination Survey	NHANES III	12	28	16818	Below/above median	25	25
Abbas, 2007 ‖ [22]	Germany	CC	Mamma Carcinoma Risk Factor Investigation	MARIE	-	1394	1365	Five groups, no quantiles	12	30
Abbas, 2009 ‖ [23]	Germany	CC	-	-	-	289	595	Four groups, no quantiles	12	24
Freedman, 2008 [24]	USA	NCC	Prostate, Lung, Colorectal and Ovarian Cancer Screening trial	PLCO	12	1005	1005	Quintiles	18	34
Chlebowski, 2009 [25]	USA	NCC	Women's Health Initiative	WHI	7	895	898	Quintiles	13	27
Crew, 2009 ‖ [26]	USA	CC	Long Island Breast Cancer Study Project	LIBCSP	-	1026	1075	Four groups, no quantiles	20	40
McCullough, 2009 ‖ [27]	USA	NCC	Cancer Prevention Study-II	CPS-II	6	516	516	Quintiles	15	29
Renjmark, 2009 ‖ [28]	Denmark	CC	-		-	142	420	Tertiles	24	34

Table 1, continued…..										
Prostate cancer										
Braun, 1995 [29]	USA	NCC	Washington County, Maryland	-	17	61	122	Quintiles	24	41
Nomura, 1998 [30]	USA	NCC	Honolulu	-	28	136	136	Quartiles	34	48
Ahonen, 2000 [31]	Finland	NCC	Helsinki Heart Study	HHS	14	149	566	Below/above median	12	22
Jacobs, 2004 [32]	USA	NCC	Nutritional Prevention of Cancer trial	NPC trial	19	83	166	Tertiles	25	33
Baron et al, 2005 [33]	USA	Cohort	Calcium Polyp Prevention Study	CPPS	10	33	672	Tertiles	25	34
Freedman, 2007 [17]	USA	Cohort	Third National Health and Nutrition Examination Survey	NHANES III	12	47	16818	Below/above median	25	25
Faupel-Badger et al, 2007 [34]	Finland	NCC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	ATBC	9	296	296	Quartiles	15	24
Li et al, 2007 [35]	USA	NCC	Physicians' Health Study	HPS	18	1066	1618	Quartiles	<18.3/24.4 §	>31.1/39.5 §
Mikhak, 2007 [36]	USA	NCC	Health Professionals Follow-up Study	HPFUS	14	684	692	Below/above median	15	15
Ahn, 2008 [37]	USA	NCC	Prostate, Lung, Colorectal and Ovarian Cancer Screening trial	PLCO	10	749	781	Quintiles	11	44
Travis, 2009 [38]	Europe	NCC	European Prospective Investigation into Cancer and Nutrition	EPIC	4	652	752	Quintiles	16	28

NR: not reported; NCC: nested case-control study; CC: case-control study; 25OHD: serum 25-hydroxyvitamin D level - *All studies had cancer incidence as endpoint, but Freedman et al, 2007 (ref.17) , that used cancer mortality as outcome. ; † Lower quantile was used as referent category; upper bound in ng/mL and mean values when upper level not available; ‡ Lower bound in ng/mL and mean values when lower level not available; § Median cutoff points for winter/spring-, and summer/fall-collected control samples; ‖ Also included *in situ* breast cancers.

Table 2 - Principal characteristics of studies on colorectal adenomas.

First Author, publication year [ref.]	Country	Study design	Study name	Study acronym	Mean years of follow-up	No. subjects with adenoma or No. of adenomas	No. controls or of total subjects if cohort	Endpoint	Adjustment for major potential confounding factors †	History of bowel examination taken into account
Platz et al, 2000 [39]	USA	NCC	Nurses' Health Study	NHS	7	326	326	Subjects with ≥1 adenoma	BMI, physical activity, smoking	Endoscopy examinations in previours years taken into acount
Levine et al, 2001 [40]	USA	CC	-	-		473	507	Subjects with ≥1 adenoma; adenomas <10 and ≥10 mm	BMI	Not explicit
Peters et al, 2001 [41]	USA	CC	-	-	-	236	218	Subjects with ≥1 adenoma	BMI, physical activity, smoking	Not explicit
Grau et al, 2003 [42]	USA	Cohort	Calcium Polyp Prevention Study	CPPS	4	279	803	Number of adenoma recurrences, small and advanced*	Smoking	All subjects had an initial colonoscopy before randomization
Peters et al, 2004 [43]	USA	CC	Prostate, Lung, Colorectal and Ovarian Cancer Screening trial	PLCO	-	394	397	Subjects with ≥1 advanced adenoma* in distal large bowel	BMI, physical activity, smoking	Not explicit
Jacobs et al, 2007 [44]	USA	NCC	Ursodeoxycholic Acid Trial	UDCA	3	210	568	Subjects with adenoma occurrence or recurrence	BMI	All subjects had an initial colonoscopy before randomization
Miller et al, 2007 [45]	USA	CC	Diet and Health Study III	-	-	111	238	Subjects with ≥1 adenoma	None	Not explicit

NCC: nested case-control study; CC: case-control study ; BMI: body mass index.

*Advanced distal adenoma: adenoma ≥ 10 mm or containing high-grade dysplasia or villous elements.

† Factors known to be associated with both serum 25-hydroxyvitamin D level and colorectal adenoma.

Table 3 - Studies excluded for the meta-analysis.

Study [ref.]	Country	Type of study	Reason for exclusion
Colorectal cancer			
Niv et al, 1999 [46]	Israel	Cross-sectional	Small study that examined serum 25OHD according to stage of CRC; no risk estimate was reported
Sieg et al, 2006 [47]	Germany	Cross-sectional	Comparison of mean serum 25OHD between CRC cases and controls; no risk estimate was reported
Feskanich et al, 2004 [48]	USA	Nested case-control	Nurses' Health Study, Redundant with Wu et al, 2007 [19]
Colonic adenoma			
No study was excluded			
Breast cancer			
Lowe et al, 2005 [49]	UK	Case-control	Redundant with Colston et al, 2006 [21]
Prostate cancer			
Gann et al, 1996 [50]	USA (Physicians' Health Study)	Nested case-control	Redundant with Li et al, 2007 [35]
Platz et al, 2000, 2004 [51,52]	USA (Health Professional Follow-up Study)	Nested case-control	Redundant with Mikhak et al, 2007 [36]
Tuohimaa et al, 2004 [53]	Sweden, Norway, Finland	Nested case-control	Reference category was the third quintile and no crude data allowing calculation of dose-response; replaced by Ahonen et al, 2000 [31]

Table 4 - Dose-response pooled estimates for a 10 ng/mL increase in levels of serum 25-hydroxyvitamin D, and between-study heterogeneity in results.

Disease	Units of increase	Summary relative risk	95% CI	Heterogeneity chi-square P-value	I^2
Colorectal cancer					
All studies	10 ng/mL	0.85	0.79; 0.91	0.004	55
NCC and cohort studies *	10 ng/mL	0.85	0.79;0.92	0.002	59
Breast cancer					
All studies	10 ng/mL	0.89	0.81;0.98	<0.001	88
NCC and cohort studies	10 ng/mL	0.97	0.92; 1.03	0.07	54
Prostate cancer					
All studies †	10 ng/mL	0.99	0.95; 1.03	0.11	37

NCC: nested case-control study

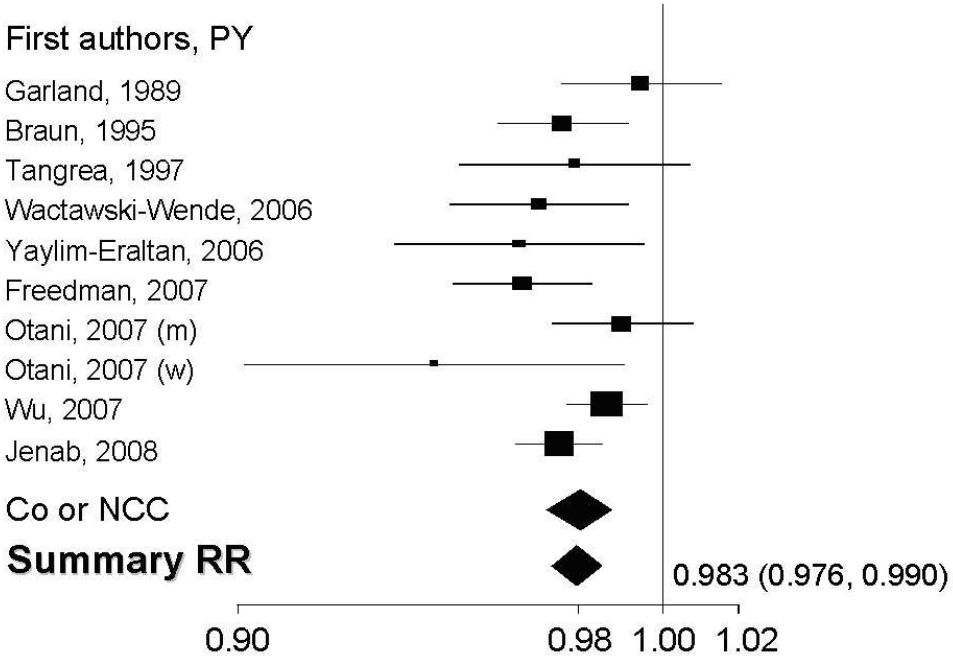
* All studies were prospective cohorts, but Yaylim-Eraltan et al, 2006 (ref.15).

† All studies were prospective cohort.

Table 5 - Overall Pooled estimates for colorectal cancer excluding single studies

Excluded studies [ref]	Pooled RR* and 95%C.I.	I^2
Freedman et al, 2007 [17]	0.985 (0.978, 0.991)	52
Yalim-Eraltan et al, 2006 [15]	0.984 (0.977, 0.991)	48
Otani et al, 2007 [18]	0.980 (0.975, 0.986)	37

* for 1 mg/mL unit increase of serum 25-hydroxyvitamin D



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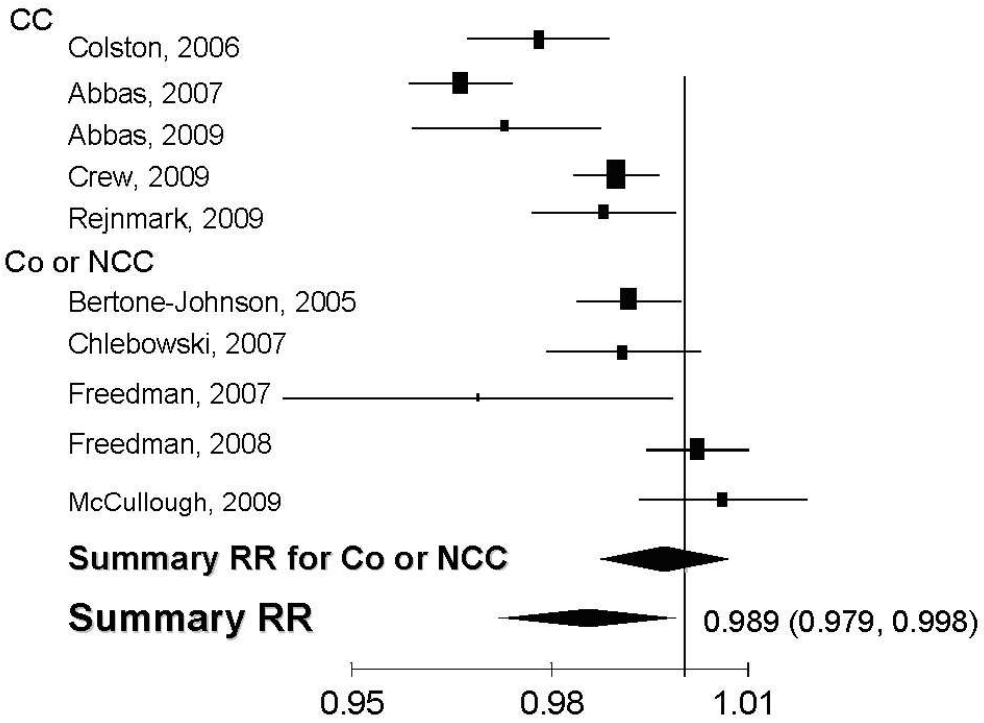

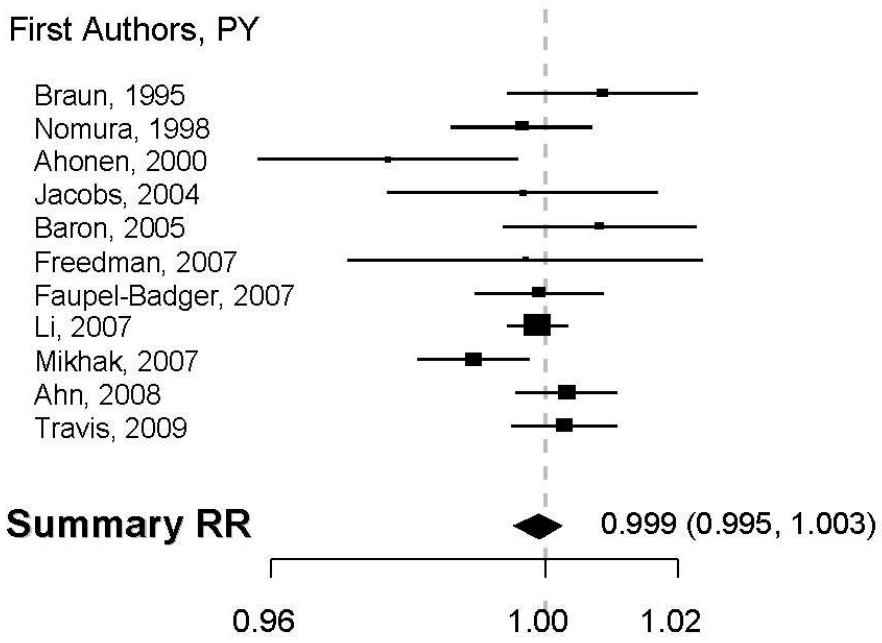

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