Review

Vitamin D and Prevention of Colorectal Adenoma: A Meta-analysis

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Abstract

Background: **Vitamin D status is associated inversely with risk of colorectal cancer, but the association with adenoma risk is less clear. This meta-analysis examined the overall relationship between circulating (plasma or serum) 25-hydroxyvitamin D [25(OH)D], vitamin D intake (dietary, supplemental, or total), and colorectal adenoma incidence in published studies.**

Methods: **A meta-analysis composed of 17 epidemiologic studies [1 cross-sectional, 9 case-control, and 7 cohort or nested case-control studies; 7 on 25(OH)D and 12 on vitamin D intake] published before December 2007 was done to examine the association between circulating 25(OH)D, vitamin D intake, and colorectal adenomas. Summary Peto odds ratios (OR) were computed for overall and stratified analyses.**

Results: **Circulating 25(OH)D was inversely associated with risk of colorectal adenomas: the OR was 0.70 [95% confidence interval (95% CI), 0.56-0.87] for high versus low circulating 25(OH)D. The highest quintile of vitamin D intake was associated with an 11% marginally decreased risk of colorectal adenomas compared with low vitamin D intake (OR, 0.89; 95% CI, 0.78-1.02). For recurrent adenomas, there was a decreased risk of 12% (95% CI, 0.72-1.07) among individuals with high versus low vitamin D intake. The inverse associations appeared stronger for advanced adenoma [OR, 0.64; 95% CI, 0.45-0.90 for serum 25(OH)D and OR, 0.77; 95% CI, 0.63-0.95 for vitamin D intake], but the number of studies was small.**

Conclusions: **Both circulating 25(OH)D and vitamin D intake were inversely associated with colorectal adenoma incidence and recurrent adenomas. These results further support a role of vitamin D in prevention of colorectal adenoma incidence and recurrence.** (Cancer Epidemiol Biomarkers Prev 2008;17(11):2958–69)

Introduction

Colorectal cancer is one of the leading causes of cancer mortality in the United States and in many western countries. Adenomas are precursors to the majority of colorectal cancers. Because adenomas can be detected decades before development of cancer, they can serve as a predictive indicator for cancer (1, 2). The malignancy transformation rate for adenomas ranges from 5% for small adenomas to 50% for villous adenomas over 2 cm in diameter (3, 4). For some exposures, such as cigarette smoking, the latency period for colorectal cancer can be as long as 35 to 40 years, but a much shorter latency can be found for adenomas (2).

A role for vitamin D in prevention of colorectal cancer was first hypothesized in 1980 based on ecologic patterns of colorectal cancer mortality by latitude as an indication of regional variation in solar radiation, which is required for vitamin D synthesis (5). It is now known that the vitamin D receptor and the enzyme 1α-hydroxylase, which converts 25-hydroxyvitamin D [25(OH)D] to the active $1,25(OH)_2D$, are expressed in the colon, rectum, and nearly all tissues (6, 7). When activated by $1,25(OH)_2D$, the vitamin D receptor is a transcription factor that has been shown to decrease epithelial cell proliferation and to induce differentiation and apoptosis in colorectal neoplasia (8-10).

An inverse linear dose-response relation has been shown for both dietary intake of vitamin D and circulating levels of 25(OH)D with colorectal cancer risk (11). Recent studies including a meta-analysis of vitamin D exposure and colorectal cancer risk estimate a 50% decrease in colorectal cancer incidence for individuals with ≥1,000 IU/d vitamin D intake or ≥33 ng/mL circulating 25(OH)D (11, 12). Here, we conducted a meta-analysis to estimate the overall summary effect of vitamin D intake and circulating

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(plasma or serum) 25(OH)D status on adenoma risk and recurrence.

Materials and Methods

Study Inclusion. Studies were identified by searching PubMed and MEDLINE before December 2007 for the terms vitamin D, cholecalciferol, calcifediol, calcidiol, and calcitriol in combination with colorectal adenoma or adenomatous polyp. Other forms of vitamin D were identified and searched using the Medical Subject Heading feature in PubMed. References from relevant articles were crosschecked to identify any studies that were missed in the database search.

For inclusion in this analysis, studies must have provided information in quantiles, or at minimum, contrasted high versus low vitamin D, and included 95% confidence intervals (95% CI). Individual authors were contacted for further data when these criteria were not met. Three of five authors responded; data from these authors were included in this analysis, whereas nonrespondents were recontacted twice by E-mail before being excluded. Further, studies must have adjusted for age and sex or concluded no differential effect by sex before combining results (13). When available, odds ratios (OR) adjusted for additional factors were selected.

Calcium was an important covariable given its independent effect on colorectal cancer and adenomas and that calcium absorption is strongly influenced by vitamin D status. Most studies did not adjust or stratify by calcium. Thus, the modifying effect of calcium could only be analyzed in four studies that examined calcium through clinical supplementation (14) or stratification by calcium status (15, 16, 25).

Classification of Circulating 25(OH)D and Vitamin D Intake. Vitamin D intake was assessed through dietary intake and total intake. Dietary intake encompassed food sources captured by self-report. Total intake included dietary as well as supplementary sources such as multivitamins.

Circulating 25(OH)D, the stored form of vitamin D, was used as a marker of vitamin D status. The active form $1,25(OH)_2D$ is tightly regulated by the body, and circulating $1,25(OH)_2D$ does not reveal vitamin D status until extreme deficiency or excess ensues. Thus, we considered 25(OH)D as a marker of vitamin D status in this analysis.

Statistical Analysis. The OR and 95% CI for high versus low vitamin D exposure groups were extracted for each study. Peto's Assumption-Free Method was used to obtain the summary OR (17). If a study presented more than one OR for a result stratified by covariates, the stratified results were pooled into one summary OR before being entered into the analysis.

To establish the appropriate weighing of each study toward the summary OR, the 95% CI was used to compute the SE for each logarithm of the OR (equal to the difference between the upper and lower bounds of the 95% CI divided by 3.92). The square of the SE was the estimated variance of the log OR.

Fixed- and random-effects models were considered. The random-effects measure was used because it enabled the individual studies to estimate a different effect (18) by assuming the effect within each study varies around an overall average effect. Funnel plots were analyzed to assess for publication bias.

Homogeneity among studies was assessed using DerSimonian-Laird (19) to determine the appropriateness of combining ORs from individual studies. In the case of heterogeneity, a sensitivity analysis was done. Heterogeneity was additionally assessed through the I^2 statistic. I^2 represents the proportion of total variation across study estimates due to heterogeneity. It is a transformation of the H statistic (square root of the χ^2 heterogeneity statistic divided by its degrees of freedom; ref. 20).

Calculations were done using Review Manager version 4.2 (RevMan; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003).

Results

Seventeen case-control, cohort, and cross-sectional studies that examined the relation between intake or circulating vitamin D and colorectal adenoma were identified and described in this analysis. A summary of included studies examining total and dietary vitamin D intake and risk of colorectal adenoma is included in Table 1 and those of circulating 25(OH)D in Table 2.

Vitamin D Intake. Twelve of 13 identified studies met criteria for inclusion in the analysis. One study was excluded because the results were stratified to the extent that selection of one subgroup would not be generalizable, and insufficient data were provided for the subgroups to be combined and a summary OR created (21). Correspondence was made with the first author, but the necessary stratification data for our analysis could not be obtained.

A statistically significant inverse association of high vitamin D intake versus low intake was reported in two studies (16, 22) and an additional six studies found inverse associations that were of marginal significance or nonsignificance (13, 15, 23-26). Four studies reported no association or possibly a slightly but nonsignificantly increased risk of colorectal adenoma with increased vitamin D intake (27-30).

The overall estimate using the random-effects model was a marginally significant 11% decreased risk of colorectal adenomas among individuals with high vitamin D intake compared with low vitamin D intake (OR, 0.89; 95% CI, 0.78-1.02; Fig. 1). The DerSimonian-Laird test for heterogeneity among the studies was not significant ($\chi^2 = 14.57$; $df = 11$; $P = 0.20$; $I^2 = 24.8\%$). Fixed-effects models yielded findings of the same magnitude (OR, 0.90; 95% CI, 0.81-1.00).

Included studies comprised seven cohort studies (16, 22, 25-28, 30) and five case-control studies (13, 15, 23, 24, 29). Results were similar for hospital- and population-based case-control studies. The overall suggestive decreased risk of colorectal adenomas among high versus low dietary vitamin D intake was shown with comparable magnitude by case-control studies (OR, 0.86; 95% CI, 0.67-1.09) and cohort studies (OR, 0.91; 95% CI, 0.76-1.08; Table 3). Both tested null for heterogeneity, although there was greater homogeneity among case-control studies (DerSimonian-Laird $\chi^2 = 2.58$; $df = 4$; $P = 0.63$; $I^2 = 0\%$) than cohort studies (DerSimonian-Laird $\chi^2 = 11.85$; $df = 6$; $P = 0.07$; $I^2 = 49.4\%$).

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Table 1. Included studies on high versus low quantiles of vitamin D intake and colorectal adenomas

First author, year	Location	Study period	No. cases	No. and type of controls	Source of vitamin D intake	Vitamin D quantile ranges, cut points, or median (IU/d)*	OR (95% CI)*	*P* for trend	Adjusted for
Case-control studies									
Boutron, 1996	France	1985-1990	154	427 Hospital-based	Total (dietary and supplements)	Cut points Men: 120, 156, 200, 212, ≥212 Women: 96, 128, 160, 256, ≥256	1.00 0.9 (0.5-1.5) 1.0 (0.5-1.7) 0.6 (0.3-1.2) 0.7 (0.4-1.3)	0.14	Age, sex, total energy intake
Whelan, 1999	New York, United States	1993-1997	29	395 Hospital-based	Supplements	Vitamin D supplement usage	0.85 (0.39-1.86)	Not given	Age, sex
Peters, 2001 †	Maryland, United States	1994-1996	239	228 Hospital-based	Dietary	Median 79 217 489 617	 1.00 1.29 (0.77-2.2) 1.09 (0.64-1.84) 0.83 (0.48-1.42)	Not given	Age, sex
Levine, 2001 †	California, United States	1991-1993	467	500 Hospital-based	Total	Range: 1.0-148 148-266 266-531 531-1870	 1.00 1.02 (0.69-1.51) 0.95 (0.63-1.43) 1.11 (0.67-1.55)	0.99	Age, sex, body mass index (BMI), race, clinic, sigmoidoscopy date, total fiber, saturated fat intake, multivitamin use
Boyapati, 2003	North Carolina, United States	1995-1997	177	228 Hospital-based	Total	Range: Men: 0-175 176-356 357-2302 Women: 0-158 159-433 434-1656	 1.00 1.10 (0.66-1.81) 0.69 (0.41-1.18)	0.19	Age, sex, total energy intake

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Table 1. Included studies on high versus low quantiles of vitamin D intake and colorectal adenomas (Cont'd)

First author, year	Location	Study period	No. cases	No. and type of controls	Source of vitamin D intake	Vitamin D quantile ranges, cut points, or median (IU/d)*	OR (95% CI)*	*P* for trend	Adjusted for
Cohort and nested case-control studies									
Kampman, 1994[‡]	United States	1986-1990	331	9,159 Population-based	Total	Range: 4-175 175-264 264-402 402-648 648-5078	 1.00 0.96 0.83 0.68 1.29 (0.87-1.93)	0.32	Age, BMI, alcohol intake, family history of colon cancer, indications for endoscopy, history of previous endoscopy, total energy, fiber, saturated fat, and folate intake
Martinez, 2002	Arizona, United States	Cross-sectional	639	665 Population-based	Dietary supplements total	Range: <86 86-174 175-455 >455	 1.00 1.01 (0.72-1.43) 0.88 (0.62-1.25) 1.02 (0.71-1.47)	0.91	Age, sex, number of colonoscopies, number of polyps at baseline, history of prior polyps, aspirin use, fiber, calcium intake
Lieberman, 2003	United States	1994-1997	312 (97% men)	1,359 Hospital-based	Dietary	Range: <179.5 179.5-270.2 270.3-417.7 417.8-644.9 >644.9	 1.00 1.14 (0.77-1.69) 0.98 (0.65-1.47) 0.69 (0.45-1.07) 0.61 (0.39-0.97)	Not given	Age, medical history, total energy intake Not adjusted for sex but cohort (97% men)
Kesse, 2005[§]	France	1993-1997	516	4,804 population-based	Total	Range: <69.2 69.2-94.8 94.8-130.4 >130.4	 1.00 1.49, (1.16-1.91) 1.25 (0.96-1.62) 1.15 (0.88-1.49)	0.72	BMI, alcohol intake, education, current smoking status, family history of colon cancer, physical activity, total energy intake

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Table 1. Included studies on high versus low quantiles of vitamin D intake and colorectal adenomas (Cont'd)

First author, year	Location	Study period	No. cases	No. and type of controls	Source of vitamin D intake	Vitamin D quantile ranges, cut points, or median (IU/d)*	OR (95% CI)*	*P* for trend	Adjusted for
Hartman, 2005	United States 8 clinical centers	1991-1994	754	1,151 Hospital-based	Dietary supplements total	Range: <134 134.1-196 196.1-282 282.1-468 >468	 1.0 1.22 (0.91-1.65) 0.87 (0.65-1.18) 0.77 (0.56-1.02) 0.84 (0.62-1.13)	0.03	Age, sex, intervention group, site, interaction between sex and intervention group, nonsteroidal anti-inflammatory disease use, total energy intake
Jacobs, 2007 ‡	Arizona, United States	4 y	360	804 Hospital-based	Total	Median: 45.5 125.5 257.0	 1.00 0.95 (0.65-1.37) 0.95 (0.64-1.39)	0.78	Age, energy intake, number of colonoscopies, previous polyps
Jacobs, 2007§	Arizona, United States	4 y	144	388 Hospital-based	Total	Median: 30.5 107.6 234.2	 1.00 0.90 (0.51-1.60) 0.71 (0.38-1.32)	0.28	Age, energy intake, number of colonoscopies, previous polyps
Oh, 2007	United States	1980-2002	2,747 women	48,115 Population-based	Total	Median: 135 226 312 419 601	 1.00 0.81 (0.71, 0.92) 0.79 (0.68, 0.93) 0.75 (0.62-0.90) 0.79 (0.63-0.99)	0.07	Age, BMI, smoking, alcohol intake, family history of colon cancer, history of previous endoscopy, physical activity, menopausal status and hormone use, aspirin use, total energy, fiber, red meat, folate, phosphorous, calcium, and retinol intake

*Average of men and women unless otherwise noted.
†Data more detailed than published study available through personal contact.
‡Study subgroup of men.
§Study subgroup of women.

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Table 2. Included and excluded studies of high versus low quantities of circulating (plasma or serum) 25(OH)D and colorectal adenomas

Author, year	Location	Study period	No. cases	No. and type of controls	25(OH)D quantile cut points, means, or medians (ng/mL)	Relative risk or OR (95% CI)	*P* for trend	Adjusted for
Case-control studies								
Peters, 2001*	Maryland, United States	1994-1996	239	228 Hospital-based	Median:		Not given	Age, sex, season of blood draw
					15.2	1.0		
					21.4	0.40 (0.22-0,74)		
					26.5	0.67 (0.38-1.19)		
					31.3	0.47 (0.26-0.85)		
					39.4	0.43 (0.23-0.81)		
Levine, 2001	California, United States	1991-1993	473	507 Hospital-based	Range:		0.10	Age, sex, race, study site, date of sigmoidoscopy, total calories, BMI, intake of fat and fiber, multivitamin use, calcium:phosphorus ratio
					1-15.2	1.0		
					15.3-24.5	0.99 (0.68-1.44)		
					24.6-34.2	0.86 (0.59-1.26)		
					34.3-115	0.74 (0.51-1.09)		
Peters, 2004 †	United States, 10 centers	1993-1999	271	273 Population-based	Range:		0.85	Age, ethnicity, study center, month of blood draw
					6.8-19.2	1.0		
					>19.2-24.5	0.73 (0.41-1.32)		
					>24.5-30.6	1.08 (0.61-1.90)		
					>30.6-36.6	0.89 (0.49-1.64)		
					>36.6-72.8	1.10 (0.60-2.05)		
Peters, 2004 ‡	United States, 10 centers	1993-1999	123	124 Population-based	Range:		0.0002	Age, ethnicity, study center, month of blood draw
					6.8-19.2	1.0		
					>19.2-24.5	0.93 (0.39-2.22)		
					>24.5-30.6	0.56 (0.22-1.44)		
					>30.6-36.6	0.28 (0.11-0.75)		
					>36.6-72.8	0.27 (0.11-0.69)		

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Table 2. Included and excluded studies of high versus low quantities of circulating (plasma or serum) 25(OH)D and colorectal adenomas (Cont'd)

Author, year	Location	Study period	No. cases	No. and type of controls	25(OH)D quantile cut points, means, or medians (ng/mL)	Relative risk or OR (95% CI)	*P* for trend	Adjusted for
Nested case-control or cohort studies								
Platz, 2000	United States	1989-1996	326 Women	326 Population-based	Median 16.3 22.6 28.3 38.0	 1.0 0.64 (0.41-1.0) 0.58 (0.36-0.95) 1.04 (0.66-1.66)	1.0	Age, indication for endoscopy, BMI, smoking, alcohol intake, physical activity, aspirin, postmenopausal hormone use, red meat, folate, and methionine intake, date of blood draw
Grau, 2003*	United States, 6 centers	1992-1996	174	395 Hospital-based	Median: <29.1 >29.1	 1.05 (0.85-1.29) 0.71 (0.57-0.89)	0.12	Age, sex, study center, smoking status, alcohol intake, month of blood draw
Grau, 2003§	United States, 6 centers	1992-1996	376	422 Hospital-based	Mean 15.7 25.4 32.4 43.5	 1.0 0.82 (0.61-1.10) 1.03 (0.77-1.39) 1.03 (0.77-1.37)	0.454	Age, sex, study center, alcohol intake, smoking status, month of blood draw
Jacobs, 2007†	Arizona, United States	1995-1999	141	367 Hospital-based	Mean: 20.5 33.4	 1.0 0.97 (0.62-1.52)	Not given	Age, BMI, season of blood draw, previous polyps, number of colonoscopies
Jacobs, 2007‡	Arizona, United States	1995-1999	69	201 Hospital-based	Mean: 17.2 33.0	 1.0 0.49 (0.25-0.97)	Not given	Age, BMI, season of blood draw, previous polyps, number of colonoscopies
Cross-sectional studies								
Miller, 2007‖	North Carolina, United States	1998-2000	218	472 Hospital-based	Range: <20.8 20.8-33.8 >33.8	 1.0 1.06 (0.45-2.5) 0.80 (0.28-2.28)	0.27	Age, sex, race, month of blood draw
Miller, 2007¶	North Carolina, United States	1998-2000	218	472 Hospital-based	Range: <20.8 20.8-33.8 >33.8	 1.0 0.45 (0.19-1.10) 0.31 (0.13-0.74)	Not given	Age, sex, race, month of blood draw
Excluded studies								
Sieg, 2006	Germany	2002-2003	203	239	Mean 23.0	Data unavailable	Data unavailable	Multivariate adjustment data unavailable

* Calcium supplement group.
† Study subgroup of men.
‡ Study subgroup of women.
§ Control group; data from personal contact.
‖ Study subgroup of total calcium <711 mg/d.
¶ Study subgroup of total calcium >711 mg/d.

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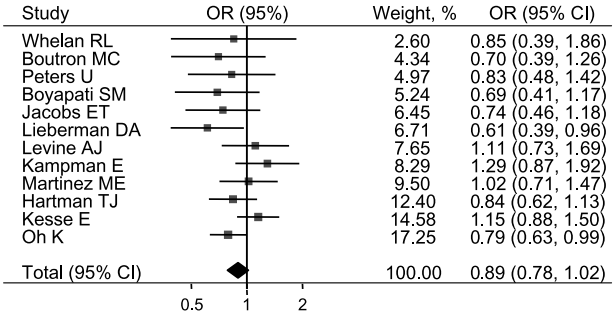

Figure 1. Vitamin D intake (dietary, supplemental, or total) and risk of colorectal adenoma for the highest compared with lowest quantile of vitamin D intake.

Of the vitamin D intake studies, six examined vitamin D from dietary sources (13, 15, 22, 25, 27, 30), four studies examined vitamin D supplements (15, 23, 25, 30), and eight studies examined dietary plus supplemental intake (total intake; refs. 15, 16, 24-26, 28-30). An inverse but not statistically significant association was observed among studies that examined dietary vitamin D intake alone (OR, 0.90; 95% CI, 0.79-1.03; Table 3). The dietary intake studies were consistent and homogenous (DerSimonian-Laird $\chi^2 = 8.07$; $df = 6$; $P = 0.23$; $I^2 = 25.7\%$). Supplemental intake had no relation with an OR of 1.00 (95% CI, 0.95-1.05), also with consistent and homogenous results (DerSimonian-Laird $\chi^2 = 1.94$; $df = 3$; $P = 0.58$; $I^2 = 0\%$). Total vitamin D intake was inversely but not significantly associated with adenomas (OR, 0.89; 95% CI, 0.79-1.01; DerSimonian-Laird $\chi^2 = 7.72$; $df = 8$; $P = 0.46$; $I^2 = 0\%$) at a similar magnitude of dietary vitamin D alone.

The inverse association of vitamin D intake was observed for a range of adenomatous outcomes including small adenomas (13), recurrent adenomas (23, 25, 26, 30), and advanced colorectal neoplasia (refs. 16, 22, 23, 27; Table 3). The inverse association on recurrent adenomas was highly consistent among the studies (DerSimonian-Laird $\chi^2 = 0.99$; $df = 3$; $P = 0.80$; $I^2 = 0\%$) but did not reach significance (OR, 0.88; 95% CI, 0.72-1.07). Advanced adenomas yielded significant inverse findings with OR of 0.77 (95% CI, 0.63-0.95).

Most of the vitamin D intake studies included men and women, whereas four studies drew from sex-specific cohorts. Kampman et al. presented separate results for men and women from two large cohorts, with the results for women updated by Oh et al. (16). Inverse relations were observed for women but not men, although neither result reached statistical significance (28). A recent analysis by Jacobs et al. stratified by sex and found a stronger inverse relation for women, although results for neither men nor women reached statistical significance (26). Kesse et al. also found a positive association in a cohort of French women, but results did not reach statistical significance (27). The study by Lieberman et al. was a predominately male (97%) cohort, and an inverse association was observed (22). Martinez et al. reported no difference in the relation when stratified by sex (30).

For the Health Professionals Follow-up Study cohort of men (28), the highest quintile did not confer an inverse association, although there was a linear inverse trend for total vitamin D intake through the fourth quintiles, suggesting the finding for quintile 5 may have been due to chance. In a sensitivity analysis in which we excluded Health Professionals Follow-up Study from the analysis, a significant inverse association was observed: OR of 0.87 (95% CI, 0.77-0.98) that was homogenous (DerSimonian-Laird $\chi^2 = 11.19$; $df = 10$; $P = 0.34$; $I^2 = 10.6\%$).

Circulating 25(OH)D. Eight studies that examined the relationship between circulating 25(OH)D and colorectal adenomas were identified, including four case-control

Table 3. Stratified summary ORs for the association between vitamin D and colorectal adenoma

	Vitamin D status, OR (95% CI)	
	Low	High
Vitamin D intake		
All adenomas ($n = 12$)	1.00	0.89 (0.78-1.02)
Recurrent adenomas ($n = 4$)	1.00	0.88 (0.72-1.07)
Advanced adenomas ($n = 4$)	1.00	0.77 (0.63-0.95)
Type of intake		
Dietary only ($n = 7$)	1.00	0.90 (0.79-1.03)
Supplements only ($n = 4$)	1.00	1.0 (0.95-1.05)
Total (dietary and supplements) ($n = 9$)	1.00	0.89 (0.79-1.01)
Type of study		
Case-control ($n = 5$)	1.00	0.86 (0.67-1.09)
Cohort ($n = 7$)	1.00	0.91 (0.76-1.08)
Sensitivity analysis		
Excluding Kampman men	1.00	0.87 (0.77-0.98)
Circulating 25(OH)D		
All adenomas ($n = 7$)	1.00	0.70 (0.56-0.87)
Advanced adenomas ($n = 2$)	1.00	0.64 (0.45-0.90)
Stratification by calcium		
Low calcium ($n = 4$)	1.00	0.78 (0.54-1.12)
High calcium ($n = 4$)	1.00	0.67 (0.46-0.97)
Sensitivity analysis		
Excluding Peters '01	1.00	0.79 (0.69-0.91)
Excluding Miller	1.00	0.72 (0.58-0.91)
Excluding Peters '01 and Miller	1.00	0.81 (0.70-0.93)

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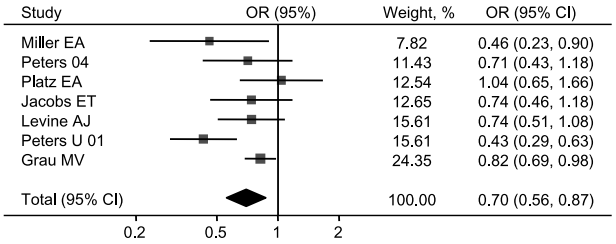

Figure 2. Circulating 25(OH)D and risk of colorectal adenoma for the highest compared with lowest quantile of 25(OH)D.

studies (15, 29, 31, 32), one nested case-control study (33), two cohort studies (14, 26), and one cross-sectional study (34). Seven of the eight studies identified were included in this analysis (Table 2). Data provided by Sieg et al. (30) did not include ORs and were excluded from this analysis.

Blood samples were drawn from individuals in multiple sites across the United States. Circulating 25(OH)D levels were presented as means, medians, or ranges. The highest value of 25(OH)D reported was 115 ng/mL in Levine et al. (29). Six studies accounted for season of blood draw: one study matched controls by date of blood draw (33), and five studies (14, 15, 26, 31, 34) adjusted for month of blood draw. One study did not adjust for seasonality (29). Studies that presented more than one OR for results stratified by calcium intake or sex were pooled into one summary OR for each study.

The Peto OR of primary colorectal adenoma risk for the overall combined studies using a random-effects model was 0.70 (95% CI, 0.56-0.87) for the highest versus lowest circulating 25(OH)D levels (Fig. 2). Fixed-effects models yielded similar findings (OR, 0.74; 95% CI, 0.65-0.84). The DerSimonian-Laird test suggested moderate heterogeneity among the pooled studies ($\chi^2 = 13.06$; $df = 6$; $P = 0.04$; $I^2 = 54.1\%$). Following a sensitivity analysis that excluded studies with the strongest inverse findings (34), the heterogeneity was no longer significant; both studies excluded $\chi^2 = 1.72$; $df = 4$; $P = 0.79$; $I^2 = 0\%$. The overall effect of the pooled studies remained inverse (OR, 0.81; 95% CI, 0.70-0.93). Results were stratified by sex in the Peters et al. study, and an inverse association between circulating vitamin D and colorectal adenomas was observed for women but not men (31).

The effect of including further adjusted models over more parsimonious models was examined within studies. The most adjusted models were selected when available. For the three studies where several multivariate models could have been selected, the effect of using the most adjusted model weakened the vitamin D and adenoma inverse relation by 8% (33) to 22% (35) or did not change the effect (29).

Four studies examined the vitamin D and adenoma relation in the context of calcium supplementation (14) or stratified by calcium levels (15, 29, 34). In the study by Grau et al. (14), subjects were randomized to 3 g calcium carbonate (1,200 mg elemental calcium) or placebo. In this study, an inverse association with circulating 25(OH)D was present for adenoma recurrence only among subjects receiving calcium supplements: relative risk = 0.88 (95% CI, 0.77-0.99) per 12 ng/mL increase of 25(OH)D, P for interaction = 0.006, but no effect of vitamin D was observed in the placebo group (14). In the three observational studies, subjects were stratified by calcium status above or below the median or mean total calcium intake (712, 711, and 744 mg/d, respectively). In the Peters et al. study, there was a 28% greater decreased risk of adenomas for each 10 ng/mL increase in 25(OH)D among subjects with calcium intake above the median (average 768 mg/d for cases and controls; ref. 15). Miller et al. also showed a 49% greater inverse relation of 25(OH)D among those in the high calcium group (34). These studies suggest that the risk of colorectal adenoma is lowest when both calcium intake and vitamin D status are optimized. Contrary to these results, Levine et al. found that individuals with high vitamin D but low calcium had a greater decreased risk of adenomas (OR, 0.40; 95% CI, 0.22-0.76) compared with those with calcium above the mean (OR, 1.17; 95% CI, 0.69-1.99; ref. 27). The overall compilation of the 25(OH)D studies stratifying for calcium yielded an inverse association for vitamin D and colorectal adenomas for both high and low calcium, with a stronger effect among those with high calcium intake (OR, 0.67; 95% CI, 0.46-0.97) compared with those with low calcium intake (OR, 0.78; 95% CI, 0.54-1.12). Of note, the Grau et al. study was a randomized trial of calcium while the others were observational (Table 3).

Two studies showed an overall 36% decreased risk of advanced adenoma for high versus low 25(OH)D (Table 3). Grau et al. reported a statistically significant 42% reduction in advanced adenomas (OR, 0.58; 95% CI, 0.36-0.94) among individuals with 25(OH)D levels above versus below the study median of 29.1 ng/mL and randomized to receive calcium supplementation (14). For subjects in the control group, there was a nonsignificant reduction in advanced adenomas among subjects in the highest quartile of circulating vitamin D (OR, 0.83; 95% CI, 0.39-1.79), no association in the second quartile (OR, 1.06; 95% CI, 0.52-2.17), and a marginally significant increased association in the third quartile (OR, 1.98; 95% CI, 1.01-3.88).[7] The combined result of advanced (distal colorectal) adenomas from Peters et al. pooling results of men and women (29) was an OR of 0.71 (95% CI, 0.43-1.19) for high compared with low 25(OH)D.

Discussion

Combining results from 12 studies of vitamin D intake and 7 studies of circulating 25(OH)D, high compared with low dietary vitamin D intake was associated with an 11% marginally decreased risk of colorectal adenomas and high versus low circulating 25(OH)D with a statistically significant 30% decreased risk.

The inverse association with colorectal adenomas was similar for dietary intake compared with total vitamin D intake (OR, 0.90 versus 0.89), whereas no association with supplemental vitamin D intake was found (OR, 1.0). That total intake did not have a stronger association compared with dietary sources alone was unexpected given that dietary sources of vitamin D are uncommon, and in some populations, supplements are an important source of

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total vitamin D intake. Furthermore, supplemental sources of vitamin D may contain folate and other micronutrients that could enhance an inverse relation between supplemental vitamin D and adenomas (36, 37).

The lack of association with supplemental vitamin D and absence of a stronger association between total versus dietary vitamin D suggest that supplemental sources of vitamin D may not be of maximum effectiveness. Of note, vitamin D present as ergocalciferol or vitamin D_2 may be less efficient than cholecalciferol or vitamin D_3 in raising 25(OH)D levels. Many multivitamins have used ergocalciferol, and supplemental vitamin D predicted 25(OH)D levels much less strongly than did dietary vitamin D in one study (38). Bioactivity may be further decreased by the presence of high levels of vitamin A in the form of retinol in multivitamins, which has been shown to bind and antagonize the vitamin D receptor by reducing the availability of the retinoid X receptor, which is required for the vitamin D receptor function (39). In the study by Oh et al., there was an inverse association of colorectal adenoma with higher total vitamin D intake, but this association was attenuated with increasing levels of retinol intake in a dose-response relation for increased tertiles of total vitamin D intake (16). No other studies of colorectal adenoma (or cancer) have examined this potential interaction with retinol, but high retinol intake appears to antagonize the positive influence of vitamin D on bone mass density (40) by inducing bone resorption (41) and decreasing the intestinal calcium absorption response to vitamin D in humans (42). Further, high retinol intake is associated with reduced bone mineral density (43) and increased risk of hip fractures (44, 45), although one study did not show any increase in hip or other fractures (46).

Dietary vitamin D may be an effective indicator of vitamin D status given its ability to reflect long-term exposure through multiple assessments of intake over several years. The food frequency questionnaires (47) used in the Oh et al. study (16), one of only two studies that showed a significant inverse association with vitamin D intake, captured almost two decades of intake.

However, vitamin D intake does not account for vitamin D produced by sun exposure or other potential confounding factors. Optimal daily UV-B sunlight exposure translates to an oral dose of 20,000 IU vitamin D and may be the main source (~90%) of vitamin D for most individuals. Physical activity has been used as a surrogate for outdoor sunlight exposure, with correlation between physical activity and 25(OH) D level corresponding to $r = 0.14$ (39). Where sunlight exposure is limited, at least 1,000 IU/d has been recommended to achieve 25(OH)D levels of 30 to 40 ng/mL (78-100 nmol/L) for optimal bone health (48). However, vitamin D is rare in food sources, mainly fish, fortified dairy products, and multivitamins and supplements.

Whether one should adjust for calcium intake when assessing the association between vitamin D and adenoma risk is questionable, especially given the suggestion of interaction between calcium intake and vitamin D status. In studies of dietary vitamin D, the correlation between calcium and vitamin D may be high given that fortified milk is an important source for both. Thus, a potential additional explanation for the stronger associations for dietary vitamin D than for supplemental vitamin D may be that most individuals high in dietary vitamin D will likely also have high dietary calcium intake, whereas the same assumption cannot be made for supplemental or solar sources of vitamin D. Two dietary studies that adjusted for calcium (16, 30) showed a weaker inverse association of dietary vitamin D among models further adjusted for calcium and other variables, although one cannot attribute this effect to calcium alone.

Potential effect modification by calcium for circulating 25(OH)D and adenoma incidence relation was suggested in three studies (14, 15, 34) but not in another (29). Effect modification by calcium was also shown for vitamin D intake in the study by Oh et al., which found that women with high vitamin D but low calcium did not have a decreased risk of adenoma (relative risk, 1.01; 95% CI, 0.79-1.30), but women with high calcium and vitamin D intakes had a decreased risk (relative risk, 0.75; 95% CI, 0.61-0.92) compared with women with both low vitamin D and low calcium intakes (16).

Circulating 25(OH)D is presumably the gold standard for assessing vitamin D status, although 25(OH)D has a half-life of only about 2 to 3 weeks and its levels tend to fluctuate throughout the year due to variation in solar radiation. Some heterogeneity in the summary OR was apparent for circulating 25(OH)D. Six of the seven studies reported a significant or suggestive inverse association, but for two of the studies, the inverse association appeared to be substantially stronger than for the others (15, 32). Following sensitivity analyses that excluded both of these two studies, the heterogeneity was no longer significant, whereas the overall effect of the pooled studies remained inverse for high versus low circulating 25(OH)D (OR, 0.81; 95% CI, 0.70-0.93). Thus, the heterogeneity was caused more by variation in the magnitude rather than in the direction of the association. The circulating 25(OH)D finding for adenomas (overall and for advanced adenomas) was larger in magnitude than the finding for intake but smaller in magnitude than the 50% reduction in incidence reported for colorectal cancer risk among individuals with high (33 ng/mL) compared with low circulating 25(OH)D (11, 12). One explanation for the weaker results for adenomas than for cancer is that vitamin D could have a role in preventing the formation of adenomas as well as their progression to cancer. Of note, although based on only a small fraction of the studies, an inverse association with vitamin D appeared to be stronger for advanced adenomas compared with the overall association.

Because the studies were observational, and the associations were moderate, residual confounding cannot be excluded. Potential sources for confounding include skin pigmentation, diet, age, and adiposity. Melanin in dark-pigmented individuals blocks effective UV-B radiation, and up to 10 times greater UV-B radiation exposure is required to produce vitamin D levels comparable with that in light-skinned individuals (39, 49). Hypovitaminosis D (≤15 ng/mL) is more prevalent among African Americans compared with White individuals (50). Elderly individuals have also been observed to be vitamin D insufficient year-round regardless of residency in sunny regions (51). Finally, obese individuals have decreased 25(OH)D and $1,25(OH)_2D$ possibly due to down-regulation of the vitamin D receptor and >50% decreased bioavailability

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of serum 25(OH)D secondary to deposition in adipose tissue (52). As indicated in Tables 1 and 2, cofactors were variably controlled across studies.

A limitation of this meta-analysis is that it examined only high versus low circulating 25(OH)D and vitamin D intake. The ability of this analysis to analyze characteristics of the adenomas such as size, location, and recurrence is also limited due to a small number of studies to quantify. Detection bias was reduced by using endoscopy screened controls or noncases.

In addition, all studies of circulating 25(OH)D had only a single measurement of 25(OH)D. Stronger associations between 25(OH)D and colorectal cancer and adenomas were found when measurements were made during winter months versus summer months in case-control and cohort studies (32, 53). Although adjustment or matching decreases some extraneous variability and potential measurement error, these do not entirely offset the limitations of using a single measurement to estimate long-term status.

All studies took place between 1980 and 2003, with two which were conducted in the 1980s (13, 28). The potential for publication bias was explored, and although funnel plot analysis indicated no substantial publication bias, this result was based on a limited number of studies and potential for bias cannot necessarily be excluded (54). The I^2 statistic was included with primary study results and sensitivity analyses were done when heterogeneity was suggested.

Subgroup analysis for sex was done, although a limited number of studies were stratified for these variables. Some of the studies suggested a more consistent inverse association in women, but overall more data would be necessary to ascertain a sex-specific role for vitamin D and colorectal adenomas.

The overall results of this meta-analysis indicate that vitamin D status, assessed through intake and circulating 25(OH)D, is associated with a decreased risk of colorectal adenoma, including advanced adenoma and recurrent adenoma. Some studies also suggest that the inverse association between vitamin D status and adenoma risk may be strongest when calcium intake is also high. These data add to the growing body of evidence supporting a potential benefit of improved vitamin D status and risk of colorectal neoplasia.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Lane N, Fenoglio CMI. Observations on the adenoma as precursor to ordinary large bowel carcinoma. Gastrointest Radiol 1976;1:111–9.
2. Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2001;10:725–31.
3. Morson B. Poyps and cancer of the large bowel. West J Med 1976;125:93–9.
4. Eide TJ. Risk of colorectal cancer in adenoma-bearing individuals within a defined population. Int J Cancer 1986;38:173–6.
5. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol 1980;9:227–31.
6. Holt PR, Arber N, Halmos B, et al. Colonic epithelial cell proliferation decreases with increasing levels of serum 25-hydroxy vitamin D. Cancer Epidemiol Biomarkers Prev 2002;11:113–9.
7. Cross HS, Peterlik M, Reddy GS, Schuster I. Vitamin D metabolism in human colon adenocarcinoma-derived Caco-2 cells: expression of 25-hydroxyvitamin D_3-1α-hydroxylase activity and regulation of side-chain metabolism. J Steroid Biochem Mol Biol 1997;62:21–8.
8. Xue L, Lipkin M, Newmark H, Wang J. Influence of dietary calcium and vitamin D on diet-induced epithelial cell hyperproliferation in mice. J Natl Cancer Inst 1999;91:176–81.
9. Miller EA, Keku TO, Satia JA, et al. Calcium, vitamin D, apoptosis in the rectal epithelium. Cancer Epidemiol Biomarkers Prev 2005;14:525–8.
10. Diaz GD, Paraskeva C, Thomas MG, Binderup L, Hague A. Apoptosis is induced by the active metabolite of vitamin D_3 and its analogue EB1089 in colorectal adenoma and carcinoma cells: possible implications for prevention and therapy. Cancer Res 2000;60:2304–12.
11. Gorham ED, Garland CF, Garland FC, et al. Vitamin D and prevention of colorectal cancer. J Steroid Biochem Mol Biol 2005;97:179–94.
12. Gorham ED, Garland CF, Garland FC, et al. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta-analysis. Am J Prev Med 2007;32:210–6.
13. Boutron MC, Faivre J, Marteau P, et al. Calcium, phosphorus, vitamin D, dairy products and colorectal carcinogenesis: a French case-control study. Br J Cancer 1996;74:145–51.
14. Grau MV, Baron JA, Sandler RS, et al. Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trail. J Natl Cancer Inst 2003;95:1765–71.
15. Peters U, McGlynn KA, Chatterjee N, et al. Vitamin D, calcium, and vitamin D receptor polymorphism in colorectal adenomas. Cancer Epidemiol Biomarkers Prev 2001;10:1267–74.
16. Oh K, Willett W, Wu K, Fuchs C, Giovannucci E. Calcium and vitamin D intakes in relation to risk of distal colorectal adenoma in women. Am J Epideimol 2007;165:1178–86.
17. Friedenreich CM. Methods for pooled analyses of epidemiologic studies. Epidemiology 1993;4:295–302.
18. Normand SL. Meta-analysis: formulating, evaluating, combining, and reporting. Stat Med 1999;18:321–59.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
20. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
21. Kim HS, Newcomb PA, Ulrich CM, et al. Vitamin D receptor polymorphism and the risk of colorectal adenomas. Cancer Epidemiol Biomarkers Prev 2001;10:869–74.
22. Lieberman DA, Prindiville S, Weiss DG, Willett W. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. VA Cooperative Study Group 380. JAMA 2003;290:2959–67.
23. Whelan RL, Horvath KD, Gleason NR, et al. Vitamin and calcium supplement use is associated with decreased adenoma recurrence in patients with a previous history of neoplasia. Dis Colon Rectum 1999;42:212–7.
24. Boyapati SM, Bostick RM, McGlynn KA, et al. Calcium, vitamin D, risk for colorectal adenoma: dependency on vitamin D receptor *Bsm*I polymorphism and nonsteroidal anti-inflammatory drug use? Cancer Epidemiol Biomarkers Prev 2003;12:631–7.
25. Hartman TJ, Albert PS, Snyder K, et al. The association of calcium and vitamin D with risk of colorectal adenomas. Polyp Prevention Study Group. J Nutr 2005;135:252–9.
26. Jacobs EADS, Benuzillo J, Hollis BW, Thompson PA, Martinez ME. Serum 25(OH)D levels, dietary intake of vitamin D, colorectal adenoma recurrence. J Steroid Biochem Mol Biol 2007;103:752–6.
27. Kesse E, Boutron-Ruault MC, Norat T, Riboli E, Clavel-Chapelon F. Dietary calcium, phosphorus, vitamin D, dairy products and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study. Int J Cancer 2005;117:137–44.
28. Kampman E, Giovannucci E, van't Veer P, et al. Calcium, vitamin D, dairy foods and the occurrence of colorectal adenomas among men and women in two prospective studies. Am J Epidemiol 1994;139:16–29.
29. Levine AJ, Harper JM, Ervin CM, et al. Serum 25-hydroxyvitamin D, dietary calcium in take, and distal colorectal adenoma risk. Nutr Cancer 2001;39:35–41.
30. Martinez ME, Marshall JR, Sampliner R, Wilkinson J, Alberts DS. Calcium, vitamin D, risk of adenoma recurrence (United States). Cancer Causes Control 2002;13:213–20.

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31. Peters U, Hayes RB, Chatterjee N, et al. Circulating vitamin D metabolites, polymorphism in vitamin D receptor, and colorectal adenoma risk. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Project Team. Cancer Epidemiol Biomarkers Prev 2004;13:546–52.
32. Sieg J, Sieg A, Dreyhaupt J, Schmidt-Gayk H. Insufficient vitamin D supply as a possible co-factor in colorectal carcinogenesis. Anticancer Res 2006;26:2729–33.
33. Platz EA, Hankinson SE, Hollis BW, et al. Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and adenomatous polyps of the distal colorectum. Cancer Epidemiol Biomarkers Prev 2000;9:1059–65.
34. Miller EA, Keku TO, Satia JA, Martin CF, Galanko JA, Sandler RS. Calcium, dietary, and lifestyle factors in the prevention of colorectal adenomas. Cancer 2007;109:510–7.
35. Martinez ME, Giovannucci EL, Colditz GA, et al. Calcium, vitamin D, the occurrence of colorectal cancer among women. J Natl Cancer Inst 1996;88:1375–82.
36. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. The Calcium Polyp Prevention Study Group. N Engl J Med 1999;340:101–7.
37. Martinez ME, Giovannucci E, Jiang R, et al. Folate fortification, plasma folate, homocysteine and colorectal adenoma recurrence. Int J Cancer 2006;119:1440–6.
38. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst 2006;98:451–9.
39. Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). Cancer Causes Control 2005;16:83–95.
40. Michaelsson K, Wolk A, Jacobsson A, et al. The positive effect of dietary vitamin D intake on bone mineral density in men is modulated by the polyadenosine repeat polymorphism of the vitamin D receptor. Bone 2006;39:1343–51.
41. Jacobson A, Johansson S, Branting M, Melhus H. Vitamin A differentially regulates RANKL and OPG expression in human osteoblasts. Biochem Biophys Res Commun 2004;322:162–7.
42. Johansson S, Melhus H. Vitamin A antagonizes calcium response to vitamin D in man. J Bone Miner Res 2001;16:1899–905.
43. Melhus H, Michaelsson K, Kindmark A, et al. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. Ann Intern Med 1998;129:770–8.
44. Crandall C. Vitamin A intake and osteoporosis: a clinical review. J Womens Health Larchmt 2004;13:939–53.
45. Feskanich D, Singh V, Willett WC, Colditz GA. Vitamin A intake and hip fractures among postmenopausal women. JAMA 2002;287:47–54.
46. Lim LS, Harnack LJ, Lazovich D, Folsom AR. Vitamin A intake and the risk of hip fracture in postmenopausal women: the Iowa Women's Health Study. Osteoporos Int 2004;15:552–9.
47. Willett WC, Sampson L, Browne ML, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988;127:188–99.
48. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr 2004;79:362–71.
49. Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise vitamin D_3. Lancet 1982;1:74–6.
50. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and White women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. Am J Clin Nutr 2002;76:187–92.
51. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr 2003;89:552–72.
52. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690–3.
53. Wu K, Feskanich D, Fuchs C, et al. A nested case-control study on plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. J Natl Cancer Inst 2007;99:1120–9.
54. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. BMJ 2006;333:597–600.

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