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Vitamin D and prevention of colorectal cancer

Edward D. Gorham [a,b], Cedric F. Garland [b], Frank C. Garland [a,b,*], William B. Grant [c], Sharif B. Mohr [a], Martin Lipkin [d], Harold L. Newmark [e], Edward Giovannucci [f], Melissa Wei [f], Michael F. Holick [g]

[a] *Naval Health Research Center, San Diego, CA 92186, USA*
[b] *University of California, San Diego, School of Medicine, Department of Family and Preventive Medicine, La Jolla, CA 92093, USA*
[c] *SUNARC, San Francisco, CA 94109, USA*
[d] *Strang Cancer Prevention Center, New York, NY 10021, USA*
[e] *Susan Lehman Cullman Laboratory for Cancer Research, Rutgers, The State University of New Jersey, Piscataway, and The Cancer Institute of New Jersey, New Brunswick, NJ, USA*
[f] *Harvard School of Public Health, Departments of Nutrition and Epidemiology, Boston, MA 02115, USA*
[g] *Vitamin D Laboratory, Section of Endocrinology, Nutrition and Diabetes, Department of Medicine, Boston University School of Medicine, Boston, MA 02118, USA*

Abstract

Background: Inadequate photosynthesis or oral intake of Vitamin D are associated with high incidence rates of colorectal cancer, but the dose–response relationship has not been adequately studied.
Methods: Dose–response gradients from observational studies of Vitamin D intake and serum 25-hydroxyvitamin D were plotted as trend lines. The point on each linear trend line corresponding to an odds ratio of 0.50 provided the prediagnostic Vitamin D intake or 25-hydroxyvitamin D concentration associated with 50% lower risk compared to <100 IU/day Vitamin D or <13 ng/ml serum 25-hydroxyvitamin D. Medians of these values were determined.
Results: Overall, individuals with ≥1000 IU/day oral Vitamin D ($p < 0.0001$) or ≥33 ng/ml (82 nmol/l) serum 25-hydroxyvitamin D ($p < 0.01$) had 50% lower incidence of colorectal cancer compared to reference values.
Conclusions: Intake of 1000 IU/day of Vitamin D, half the safe upper intake established by the National Academy of Sciences, was associated with 50% lower risk. Serum 25-hydroxyvitamin D of 33 ng/ml, which is known to be safe, also was associated with 50% lower risk. Prompt public health action is needed to increase intake of Vitamin D_3 to 1000 IU/day, and to raise 25-hydroxyvitamin D by encouraging a modest duration of sunlight exposure.

Keywords: Vitamin D; Colorectal cancer; Calcifediol; Dose–response gradient; Serum; Diet; Incidence; Epidemiology; Methods; Prevention

1. Introduction

Markedly higher mortality rates from colon cancer in the northeast and lower rates in the south, southwest and west led to the development of a theory that Vitamin D and calcium reduce the risk of colon cancer [1]. Maps of the geographic epidemiology of colon cancer played a key role in making the discovery that Vitamin D reduced risk [1,2]. Since the theory was advanced, four observational studies [3–6] have provided data on the dose–response relationship between serum 25-hydroxyvitamin D (25(OH)D) and risk of colorectal cancer, and 14 observational studies [7–20] have provided data on the dose–response gradient of oral intake of Vitamin D with risk.

Despite findings that in general support the Vitamin D-cancer theory, and a powerful geographic gradient by latitude [2] the overall dose–response gradient for the effect of Vitamin D on incidence of colorectal cancer has not been determined. Understanding of the dose–response relationship is needed to enhance decision-making about the emerging role of Vitamin D as a tool for reducing incidence and mortality from colorectal cancer.

* Corresponding author.

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2. Materials and methods

A systematic review was conducted of published studies that provided sufficient data to calculate the dose–response relationship of serum 25(OH)D or oral intake of Vitamin D with risk of colorectal cancer.

2.1. Search strategy

A PUBMED search was conducted of the MEDLINE database for the period from January 1966 to December 2004 by entering ("Vitamin D" or "cholecalciferol" or "calcidiol" or "calcifediol" or "calcitriol") and ("colon cancer" or "colorectal cancer" or "colonic neoplasms") and ("cohort" or "case–control" or "epidemiology") as subject terms or words mentioned in the abstract. The search yielded 44 articles that were potentially observational studies. Two readers reviewed abstracts of these articles, and copies were obtained of those that met the criteria for inclusion (below). Reference lists of the articles that were retrieved also were reviewed in an effort to identify potentially relevant studies not identified by the MEDLINE search.

2.2. Criteria for inclusion

Observational studies were included in this systematic review if they were published in a medical journal indexed in MEDLINE, either of prospective (cohort) or retrospective (case–control) design, provided odds ratios or relative risks by quantiles, and provided a *p*-value for trend or sufficient data to allow calculation of the *p*-value, and had colon or colorectal cancer as the outcome. Studies of precursor lesions such as polyps were not included. However, they will be described in a separate research report.

Eighteen observational studies met these criteria, including four of serum 25(OH)D and 14 of oral intake of Vitamin D in association with risk of colon or colorectal cancer. For consistency, serum concentrations of 25(OH)D in nmol/l were converted to ng/ml using the conversion factor, 2.5 nmol/l = 1 ng/ml. Intakes of Vitamin D in micrograms were converted to international units (IU) using the conversion factor, 0.025 μg = 1 IU.

3. Results

3.1. Analysis of studies

A majority (10 of 18) studies found that inadequate Vitamin D status was significantly associated with higher risk of cancer of the colon [3,6–10,12,13,15] or distal colon and rectum [5], one found a borderline association of low Vitamin D intake with elevated risk of colorectal cancer after multivariate adjustment [11], one found an non-significant odds ratio of 0.4 for the highest quartile of 25(OH)D compared to the lowest and no significant dose–response gradient [4], three provided Vitamin D data that had been adjusted for intake of calcium and found no association [16,17,19] and three reported unadjusted data but no association [14,18,20]. Characteristics and results of each study are summarized below.

3.2. Serum 25(OH)D

The four observational studies of the association between prediagnostic 25(OH)D and risk of colorectal cancer are summarized in Table 1 and described below.

3.2.1. Study 1

A matched, nested case–control study of prediagnostic serum 25(OH)D was reported by Garland et al. [3]. It was based on a cohort of 25,620 healthy men and women residents of Washington County, MD, specifically, The Johns Hopkins University Operation Clue Cohort. The volunteers donated samples of blood in 1974–1975. Serum was separated into aliquots and frozen at −70 °C for use in future cancer research. Cases were ascertained from the cancer registry of the only general hospital in the rural county.

Thirty-four cases of colon cancer were ascertained during the first 8 years of follow-up (1975–1983). Sixty-seven matched controls were drawn from the same cohort, using a probability sampling procedure, and matched to the controls on age (±1 year), race, sex, county of residence, and date blood was drawn (±1 month). Frozen samples of serum from cases and controls were thawed and analyzed using HPLC and UV absorbance detection [21]. Specimens were identified only by individual code numbers, and the code was not broken until the results of the 25(OH)D assays were

Table 1
Serum 25-hydroxyvitamin D concentration associated with 50% reduction in risk of colorectal or distal colon and rectal cancer according to observational studies, 1989–2005

Authors, year, reference	Cancer site	Sex	Cases	Controls	25-Hydroxyvitamin D concentration associated with 50% reduction (ng/ml)	*p* for trend
Garland et al., 1989 [3]	Colon	Both	34	67	25	>0.20
Braun et al., 1995 [4]	Distal colon and rectum	Both	57	114	27	0.13
Tangrea et al., 1997 [5]	Distal colon and rectum	Both	103	204	67	0.03
Feskanich et al., 2004 [6]	Colorectal	Women	193	383	40	0.01
No. of subjects, median serum 25(OH)D			387	768	33	0.01

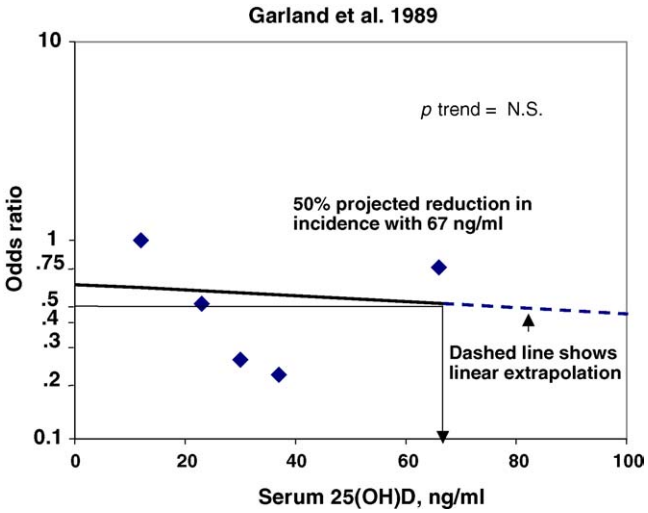

Fig. 1. Dose–response gradient of risk of colon cancer according to quintile of serum 25(OH)D, men and women, The Johns Hopkins Operation Clue Cohort, Washington County, MD, 1974–1983. *Source:* Garland et al. [3].

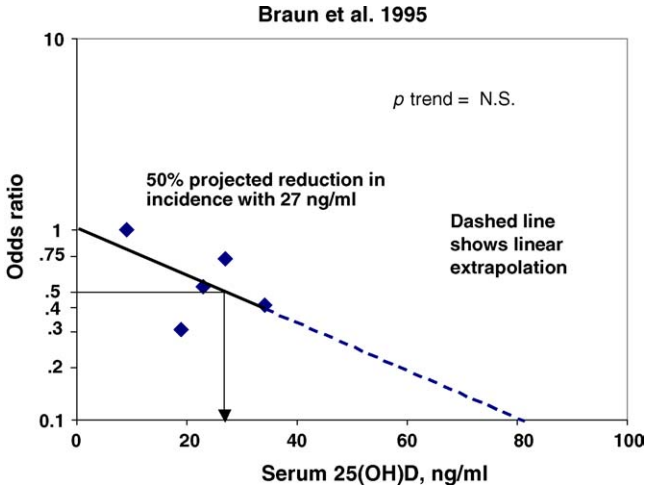

Fig. 2. Dose–response gradient of risk of colon cancer according to quintile of serum 25(OH)D, men and women, The Johns Hopkins Operation Clue Cohort, Washington County, MD, 1984–1991. *Source:* Braun et al. [4].

reported. The boundaries for the quintiles of serum 25(OH)D, from lowest to highest were, in ng/ml: 4–19, 20–26, 27–32, 33–41, and 42–91. The odds ratios for colon cancer, from lowest to highest quintile, were: 1.0, 0.48, 0.25, 0.21, and 0.73 (p trend = NS)(Fig. 1).

3.2.2. Study 2

A matched, nested case–control study of prediagnostic serum 25(OH)D was performed by Braun et al. of 57 cases of colon cancer of both sexes and 114 matched controls [4]. The cases were diagnosed in subsequent years in the same Johns Hopkins University Operation Clue Cohort, in which the Garland et al. study (above) was performed earlier. This study was conducted during 1984–1991 and was based solely on cases that were diagnosed after the first study was completed. The cases were matched to the controls on age (±1 year), race, sex, and date blood was drawn (±1 month). Serum was stored at −70 °C. The concentrations of 25(OH)D for the quintiles from lowest to highest were, in ng/ml: 0–17.2, 17.2–20.6, 20.7–24.6, 24.7–30.1, and ≥30.2. Odds ratios for colon cancer from lowest to highest quintile were: 1.0, 0.3, 0.5, 0.7, and 0.4 (Fig. 2). Although, the incidence rate of colon cancer was twice as high in the lowest quintile of 25(OH)D (<17.2 ng/ml) as in the highest, the p-value for trend was not statistically significant.

3.2.3. Study 3

Tangrea et al. performed a nested case–control study of prediagnostic serum 25(OH)D based on 146 incident cases of colorectal cancer including 103 of the distal colon and rectum that occurred in a cohort of 29,133 men aged 50–69 years [5]. Cases were obtained as part of routine surveillance of the cohort, which originally was established for the Alpha-Tocopherol and Beta Carotene Cancer Prevention Study. Cases were matched to controls on age, date of baseline blood draw, and study clinic. The study was performed in Finland during 1985–1993. The boundaries of serum 25(OH)D concentrations for quartiles from lowest to highest were, in ng/ml: 0–9.8, 9.9–13.8, 13.9–19.2, and ≥19.3. Relative risks for distal colon and rectal cancer were: 1.0, 0.8, 0.6, and 0.5 (p trend = 0.03) (Fig. 3). There was a similar but non-significant trend for distal colon cancer alone.

3.2.4. Study 4

The largest study to date was performed by Feskanich et al. and provided the clearest and most highly significant dose–response gradient [6]. It was a study of incidence of colorectal cancer in the Nurses Health Study cohort, based on 193 new cases of colorectal cancer that occurred in 32,826 female nurses aged 46–78 years during 1989–1991. Healthy controls from the cohort were matched to the cases on age and

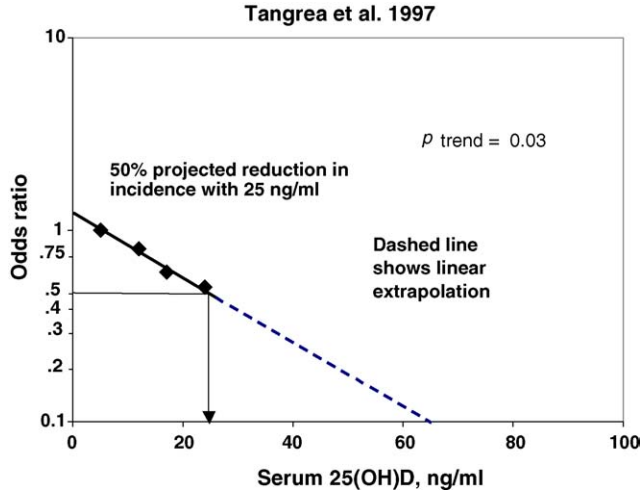

Fig. 3. Dose–response gradient of risk of distal colon and rectal cancer according to quartile of serum 25(OH)D, The Alpha Tocopherol and Beta Carotene Cancer Prevention Study Cohort, men, Finland, 1985–1993. *Source:* Tangrea et al. [5].

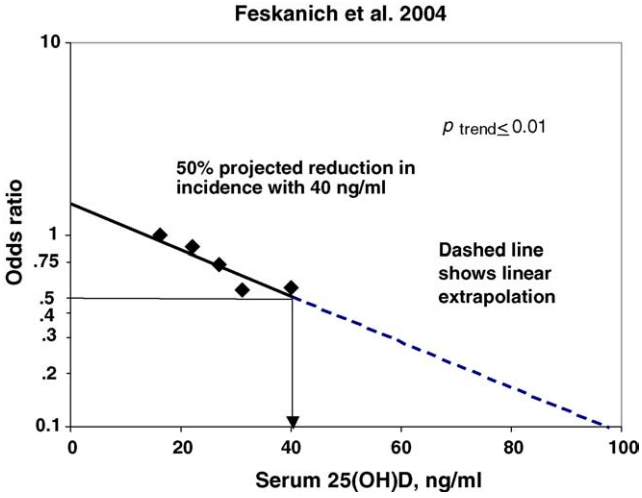

Fig. 4. Dose–response gradient of risk of colorectal cancer according to quintile of serum 25(OH)D, Harvard University Nurses Health Study Cohort, women, United States, 1989–1991. *Source:* Feskanich et al. [6].

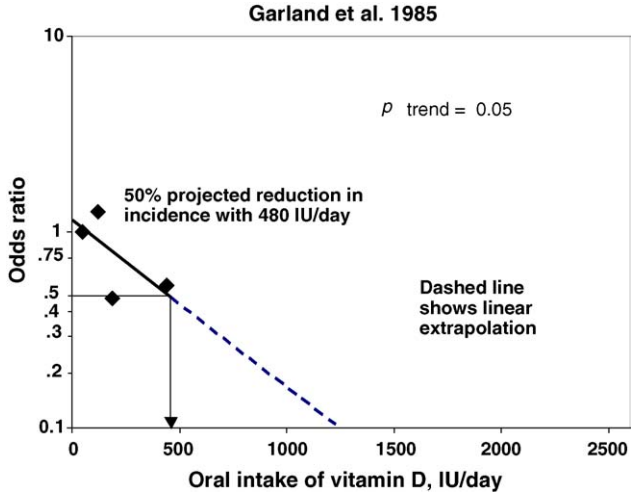

Fig. 5. Dose–response gradient of incidence of colon cancer according to quartile of oral Vitamin D intake, Western Electric Study Cohort, men, Chicago, 1959–1978. *Source:* Garland et al. [7].

month blood was drawn. The median serum 25(OH)D levels for quintiles from lowest to highest were, in ng/ml: 16.2, 22.2, 26.9, 31.2, and 39.9. (Cut points were not provided.) Odds ratios for colorectal cancer from lowest to highest quintile were: 1.0, 0.87, 0.70, 0.52, and 0.53 (p for trend $\leq$0.01). (Fig. 4). Although serum 1,25(OH)$_2$D was determined, it was not associated with risk of colorectal cancer (not shown).

3.3. Oral intake of Vitamin D

The 14 observational studies of the association between prediagnostic oral intake of Vitamin D and risk of colorectal cancer are summarized in Table 2 and described below.

3.3.1. Study 5

A prospective study of oral Vitamin D intake and risk of colon cancer was performed by Garland et al. of 49 cases of colon cancer that occurred in a cohort of 1954 men, the Western Electric Study Chicago Cohort [7]. The study was performed during 1959–1978. Unadjusted and multivariate adjusted relative risks were reported. The boundaries for quartiles of total oral intake of Vitamin D in IU/day were, from lowest to highest: 6–94, 95–147, 148–232, and 233–652. Relative risks from the lowest to the highest quartile were: 1.0, 1.26, 0.46, and 0.53 (p trend < 0.05) (Fig. 5).

Table 2
Vitamin D oral intake associated with 50% reduction in risk of colorectal cancer, according to observational studies, 1985–2005

Authors, year, references	Cancer site	Sex	Cases	Controls	Cohort	Person-years	Vitamin D intake associated with 50% reduction (IU/day)	p for trend
Garland et al., 1985 [7]	Colorectal	Men	49	1905	1954	31597	480	0.05
Bostick et al., 1993 [8]	Colon	Women	212	35004	35216	167447	1000	0.02
Kearney et al., 1996 [9]	Colon	Men	203	47732	47935	272681	770	0.02
Martinez et al., 1996 [10]	Colorectal	Women	501	88947	89448	1012280	800	0.04
Pritchard et al. 1996 [11]	Colorectal	Both	392	512	N/A	N/A	430	0.08
Marcus et al., 1998 [13]	Colorectal	Women	512	678	N/A	N/A	1000	0.05
Jarvinen et al., 2001 [14]	Colorectal	Both	72	9887	9959	195196	–	–
McCollough et al., 2003 [15]	Colorectal	Both	683	127,066	127,749	243464	600	0.02
Kampman et al., 2000[a] [16]	Colon	Both	1993	2410	N/A	N/A	–	–
Ferraroni et al., 1994[a] [18]	Colorectal	Both	828	2024	N/A	N/A	–	–
La Vecchia et al., 1997[a] [12]	Colorectal	Both	1953	4154	N/A	N/A	475	0.01
Terry et al., 2002[b] [17]	Colorectal	Women	572	60891	61463	184389	–	–
Peters et al., 1992[b] [19]	Colon	Men	746	746	N/A	N/A	[c]	[c]
Pietinen et al. 1999[b] [20]	Colorectal	Men	185	26926	27111	216888	–	–
No. of subjects, median Vitamin D intake			8816	342261	333952	2323943	1000	0.0001

Abbreviation: N/A, not applicable; dash (–) denotes no association reported.

[a] This study reported very low Vitamin D intake (lower limit of top quintile was approximately 80 IU/day).

[b] Study reported only calcium-adjusted data on Vitamin D intake.

[c] Dose–response could not be assessed since data were not reported for all quantiles. Favorable trend was described for Vitamin D.

3.3.2. Study 6

Bostick et al. performed a prospective study of oral Vitamin D intake and incidence of colon cancer [22]. There were 212 cases of colon cancer diagnosed in a cohort of 35,216 women, the Iowa Women's Health Study Cohort. Age-adjusted and multivariate adjusted relative risks were reported. Adjustment was performed for age, total energy intake, height, parity, total Vitamin E intake, a combined variable for intake of seafood and chicken, and the interaction of Vitamin E with age. The study was performed during 1986–1990. The total Vitamin D intake boundaries for the quintiles from lowest to highest were, in IU/day: 0–158, 159–266, 267–415, 416–618, and ≥619. Age-adjusted relative risks from lowest to highest quintile were: 1.0, 0.71, 0.76, 0.78, and 0.54 (p trend = 0.02) (Fig. 6). The results were similar after adjustment for the above multiple factors, but were no longer statistically significant.

3.3.3. Study 7

Kearney et al. conducted a prospective study of prediagnostic oral Vitamin D intake and incidence of colorectal cancer based on 203 new cases of colon cancer in the Male Health Professionals Study, a cohort of 47,935 allied health professionals including psychologists, veterinarians, optometrists, and other health professionals [9]. Adjustment was performed for age, intake of total calories, alcohol, aspirin, red meat, saturated fat, dietary fiber, family history of colon cancer, history of a previous polyp, history of endoscopic screening, body mass index, smoking history, and physical activity. The study was performed during 1986–1992. The total Vitamin D intake boundaries for the quintiles from lowest to highest were, in IU/day: 0–160, 161–246, 247–373, 374–612, and ≥613. Relative risks from lowest to highest quintile were: 1.0, 1.06, 0.85, 0.68, and 0.66 (p trend = 0.02) (Fig. 7).

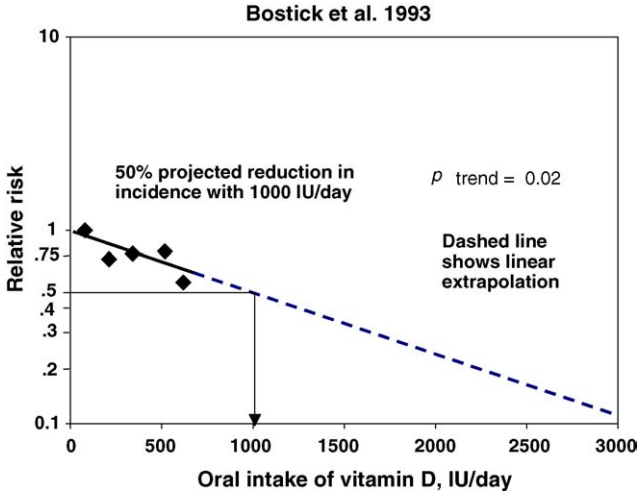

Fig. 6. Dose–response gradient of incidence of colon cancer according to quintile of oral Vitamin D intake, Iowa Women's Health Study Cohort, 1986–1990. *Source:* Bostick et al. [8].

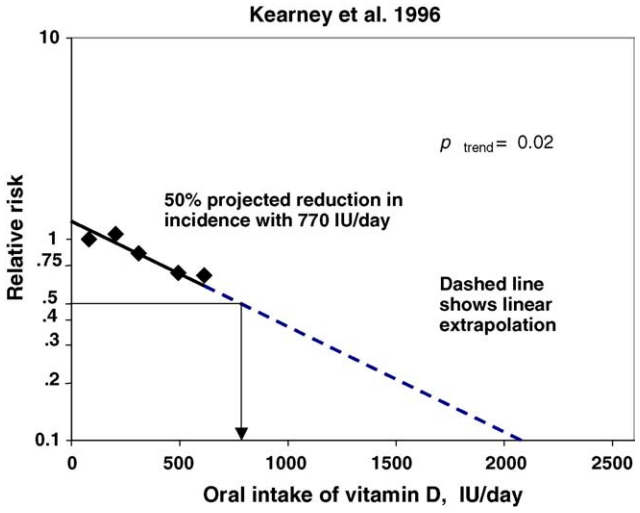

Fig. 7. Dose–response gradient of incidence of colorectal cancer according to quintile of oral Vitamin D intake, Harvard University Male Health Professionals Study Cohort, United States, 1986–1992. *Source:* Kearney et al. [9].

3.3.4. Study 8

A prospective study was performed by Martinez et al. of the association of prediagnostic Vitamin D intake with incidence of colorectal cancer in the Nurses Health Study Cohort, based on 501 new cases of colorectal cancer in the cohort of 89,448 female nurses [10]. This is the same cohort that was used for a study of 25(OH)D and colorectal cancer [6] (Section 3.2.4), although there was minimal overlap of cases as Study 4 included follow-up from 1980 to 1992 and Study 8 from 1989 to 2000. Adjustment was performed for age, body mass index, physical activity, family history of colon cancer, aspirin use, cigarette smoking, intake of red meat, and alcohol. The study was performed during 1980–1992. The boundaries of the quintiles for total oral intake of Vitamin D in IU/day were, from lowest to highest: 0–91, 92–156, 157–254, 255–477, and >478. Relative risks from lowest to highest quintile were: 1.0, 1.03, 0.84, 0.78, and 0.88 (p trend = 0.23). Relative risks for the same quintiles among those with unchanged milk intake during the 10 years prior to 1980 were 1.0, 0.92, 0.80, 0.71, and 0.67 (p trend = 0.02) (Fig. 8). For women with consistent intake of Vitamin D at all three times when intake was determined (in 1980, 1984, and 1986), the relative risks from lowest to highest tertile were 1.0, 0.75, and 0.33 (p trend = 0.003) (not shown).

3.3.5. Study 9

A matched case–control study of dietary Vitamin D intake was performed by Pritchard et al. of 352 cases of both sexes of colorectal cancer identified by the Stockholm Regional Cancer Registry during 1986–1988 [11]. Cases were matched on sex and age (±5 years) to 512 controls obtained by a random sampling procedure from a computerized population registry. Odds ratios were provided that were adjusted for age and sex and also for these covariates and total energy,

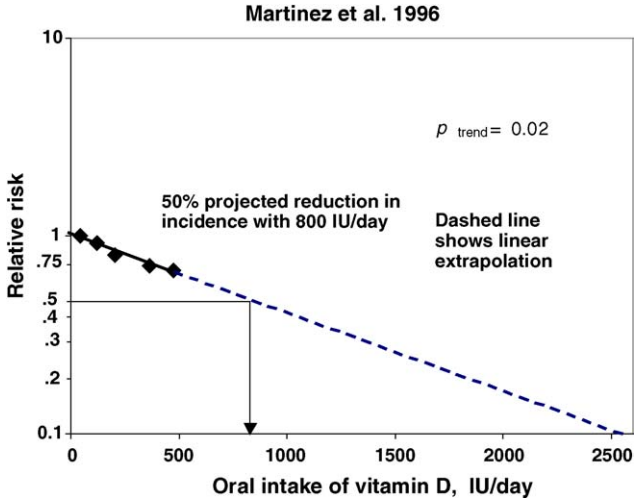

Fig. 8. Dose–response gradient of incidence of colorectal cancer according to quintile of oral Vitamin D intake, Harvard University Nurses Health Study Cohort, women, United States, 1980–1992. *Source:* Martinez et al. [10].

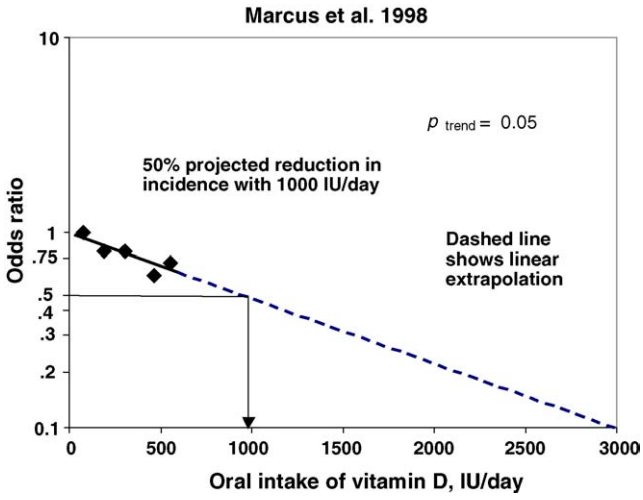

Fig. 10. Dose–response gradient of risk of colon cancer according to quintile of oral Vitamin D intake, Wisconsin Statewide Cancer Registry case–control study, women, 1990–1991. *Source:* Marcus et al. [13].

fat and protein intake. The boundaries of the quartiles for total oral intake of Vitamin D, from lowest to highest were, in IU/day: 0–115, 116–170, 171–279, and ≥280. Unadjusted odds ratios were not provided. Age- and sex-adjusted odds ratios revealed no dose–response relationship. However, odds ratios adjusted for age, sex, total energy and protein intake revealed a dose–response relationship with oral intake of Vitamin D, with odds ratios from lowest to highest quartile of: 1.0, 0.8, 0.9, and 0.6 (p trend = 0.08) (Fig. 9). Risk in the highest quartile of oral intake of Vitamin D compared to the lowest was 0.6 ($p \leq 0.05$) for colon cancer and 0.5 ($p \leq 0.05$) for rectal cancer. It was also noted in a subgroup analysis that individuals with >60 g/day intake of fat had an adjusted odds ratio 0.4 ($p \leq 0.05$) for the highest quartile of Vitamin D intake compared to the lowest, while no association was present in those who consumed ≤60 g/day of fat.

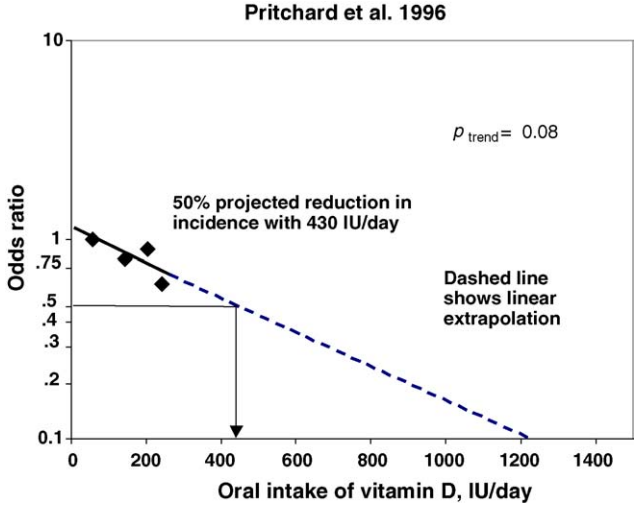

Fig. 9. Dose–response gradient of risk of colon cancer according to quartile of oral Vitamin D intake, Stockholm Regional Cancer Registry case–control study, men and women, 1986–1988. *Source:* Pritchard et al. [11].

3.3.6. Study 10

A matched case–control study was performed by Marcus et al. of 348 female cases of colon cancer identified through the Wisconsin statewide cancer incidence registry [13]. The cases were matched to 348 controls on sex and age. The study was performed during 1990–1991. The total oral Vitamin D intake boundaries for the quintiles from lowest to highest were, in IU/day: <148, 148–233, 234–372, 373–556, and ≥557. Odds ratios from lowest to highest quintile were: 1.0, 0.8, 0.8, 0.6, and 0.7 (p trend ≤0.05) (Fig. 10).

3.3.7. Study 11

A prospective study was performed by Jarvinen et al. based on 72 new cases of both sexes of colorectal cancer drawn from a cohort of 9959 persons, the Finnish Social Insurance Institution Health Survey Cohort [14]. The study was performed during 1966–1972. Adjustment was performed for age, sex, body mass index, smoking, occupation, energy intake, and area of residence. The total oral Vitamin D intake boundaries for quartiles from lowest to highest were, in IU/day: 0–102, 103–138, 139–195, and ≥196. Relative risks from lowest to highest quartile were: 1.0, 1.17, 1.40, and 1.18 (not significant) (Fig. 11). The authors noted that their inability to find an association of oral Vitamin D intake with risk of colorectal cancer may have been due to a carcinogenic effect of salted and smoked fish on the colon and rectum previously reported by the same investigators [23]. Most of the dietary intake of Vitamin D in this study was from fish, since milk in Finland was not fortified with Vitamin D at the time of the baseline study of this cohort.

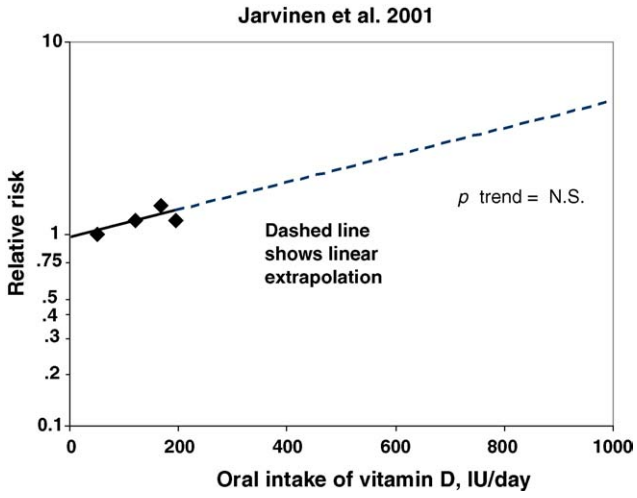

Fig. 11. Dose–response gradient of risk of colorectal cancer according to quartile of oral Vitamin D intake, Finnish Social Insurance Institution Health Survey Cohort, men and women, 1966–1972. *Source:* Jarvinen et al. [14].

3.3.8. Study 12

A prospective study was performed by McCullough et al. of prediagnostic oral intake of Vitamin D based on 683 cases of colorectal cancer in both sexes that occurred in the Cancer Prevention Study II Cohort of the American Cancer Society [15]. Adjustment was performed for age, body mass index, physical activity, family history of colon cancer, aspirin use, cigarette smoking, fruit intake, vegetable intake, and alcohol. The study was performed during 1992–1997. The total Vitamin D intake boundaries for the quintiles from lowest to highest were, in IU/day: 0–92, 93–156, 157–254, 255–477, and ≥478. Relative risks from lowest to highest quintile were: 1.0, 0.96, 0.89, 0.74, and 0.73 (p trend = 0.001) (Fig. 12).

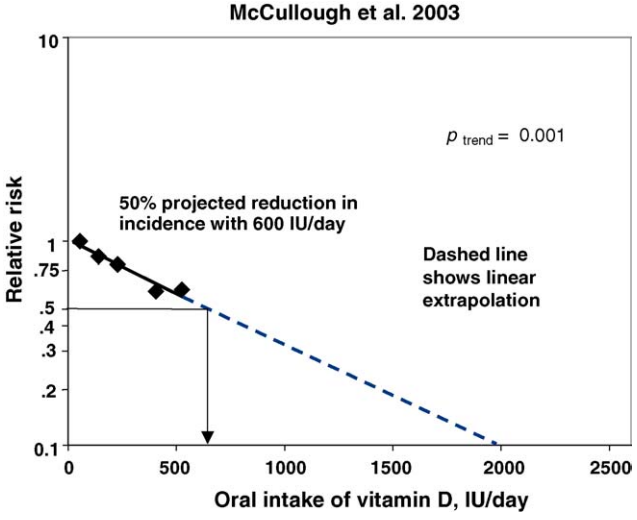

Fig. 12. Dose–response gradient of incidence of colon cancer according to quintile of oral Vitamin D intake, American Cancer Society Cancer Prevention Study II Cohort, United States, 1980–1992. *Source:* McCullough et al. [15].

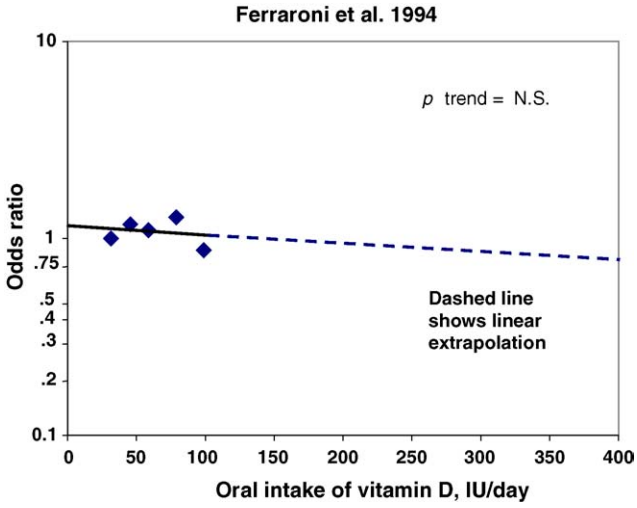

Fig. 13. Dose–response gradient of risk of colon cancer according to quintile of oral Vitamin D intake, Milan case–control study, 1985–1992. *Source:* Ferraroni et al. [18].

3.3.9. Study 13

An unmatched case–control study was performed by Ferraroni et al. of 828 male and female cases of colon cancer and 2024 hospital-based controls [18]. Adjustment was performed for age, sex, education, body mass index, family history of colorectal cancer, and total energy intake. The study was conducted in Milan during 1985–1992. The total Vitamin D intake boundaries for the quintiles from lowest to highest, for men were in IU/day: 0–32, 33–45, 46–59, 60–78, and ≥79. The study found no statistically significant association of variation in Vitamin D intake with risk of colon cancer within this low range of Vitamin D intakes, and no dose–response gradient. Odds ratios from lowest to highest quintile were: 1.0, 1.18, 1.10, 1.28, and 0.87 (Fig. 13). Oral intake of Vitamin D was extremely low in Italy due to lack of fortification of food or milk with Vitamin D, and little use of supplements containing it.

3.3.10. Study 14

A matched case–control study was performed by La Vecchia et al. of 1953 cases of colorectal cancer in seven Italian study areas [12]. The cases were matched to 4154 hospital controls with acute non-neoplastic diagnoses on hospital and area of residence. The study was performed during 1992–1996. The total oral Vitamin D intake boundaries for the quintiles from lowest to highest were, in IU/day: 0–79, 80–106, 107–133, 134–170, and ≥171. The odds ratios from lowest to highest quintiles were: 1.0, 0.98, 0.92, 0.80, and 0.77 (p trend <0.01) (Fig. 14). The Vitamin D intakes in this study were higher than in the study by Ferraroni et al. (Section 3.3.9), possibly due to the later time period of this study and apparently greater Vitamin D supplementation in the more recent period. These higher intakes of Vitamin D were associated with a significant dose–response gradient, unlike the lower intakes in the earlier Italian study.

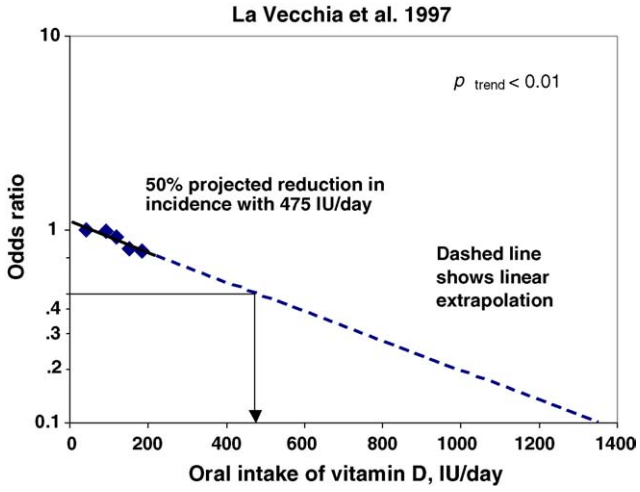

Fig. 14. Dose–response gradient of risk of colorectal cancer according to quintile of oral Vitamin D intake, 7 Italian study area case–control study, 1992–1996. *Source:* LaVecchia [12].

3.3.11. Study 15

A prospective cohort study was performed by Terry et al. of 572 cases of colorectal cancer drawn from a Swedish mammography screening cohort of 61,463 women during 1987–1989 [17]. All findings for quartiles of Vitamin D intake were adjusted for calcium intake, age, body mass index, education, red meat intake, alcohol consumption, and energy-adjusted intake of saturated fat, folic acid, and Vitamin C. The total Vitamin D intake boundaries for quartiles from lowest to highest were, in IU/day: 20–99, 100–129, 130–149, and 150–244. The study found no association between Vitamin D intake and risk of colon cancer. Relative risks from lowest to highest quartile were: 1.0, 0.96, 0.95, and 1.05 (not significant) (Fig. 15). In Sweden, as in Finland, the predominant source of Vitamin D was fish, including smoked and pickled fish that may be carcinogenic to the colon and rectum [23].

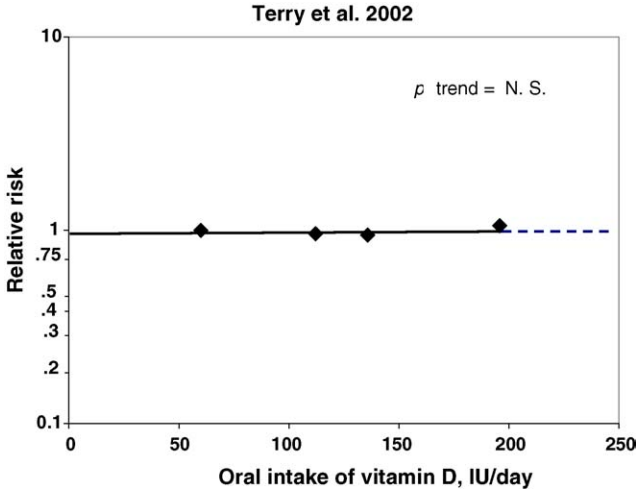

Fig. 15. Dose–response gradient of incidence of colorectal cancer according to quartile of oral Vitamin D intake, Swedish Mammography Screening Cohort, 1987–1989. *Source:* Terry et al. [17].

3.3.12. Study 16

An unmatched case–control study was performed by Kampman et al. of 1993 cases of colon cancer of both sexes and 2410 controls identified in three states [16]. Subjects from all three states were combined in the analyses. The study was performed during 1991–1994. Dose–response findings were not available from this study for total oral intake of Vitamin D, since the dose of Vitamin D contained in supplements was not ascertained. Findings presented by quintiles for dietary Vitamin D intake only were adjusted for intake of calcium, age, body mass index, family history of colon cancer, use of aspirin or non-steroidal anti-inflammatory drugs, total intake of energy and fiber, and long-term physical activity. The findings were not adjusted nor stratified according to latitude of residence.

Dietary Vitamin D intake boundaries for quintiles for men were, in IU/day: 0–144, 145–232, 233–319, 320–449, and ≥450. Odds ratios from lowest to highest quintile for men were: 1.0, 1.4, 1.1, 1.1, and 1.4 (not significant). Total intake boundaries for women were, in IU/day: 0–103, 104–164, 165–232, 233–343, and ≥344. Odds ratios from lowest to highest quintile for women were: 1.0, 0.9, 1.1, 1.0, and 1.1 (not significant). Although the effect of dietary Vitamin D was not significant, an analysis adjusted for calcium intake and other factors listed above revealed that users of Vitamin D supplements had approximately half the risk of colorectal cancer as non-users ($p = 0.01$ for both sexes combined).

3.3.13. Study 17

A matched case–control study was performed by Peters et al. of 746 male and female cases of colon cancer identified through the Los Angeles County Cancer Surveillance System [19]. The cases were matched to 746 neighborhood controls on age, sex, race, and neighborhood. All findings for Vitamin D intake that were presented by quantiles were adjusted for intake of calcium, fat, protein, carbohydrates, and alcohol; weight, physical activity, and family history of colon cancer. The study was performed during 1983–1986. The study did not describe risk for each individual quantile of Vitamin D intake, but reported no association between calcium-adjusted Vitamin D intake and risk of colon cancer. It was noted that when calcium was omitted from the adjusted models, a protective pattern for Vitamin D emerged in both men and women, but did not reach statistical significance.

3.3.14. Study 18

A prospective study was reported by Pietinen et al. of 185 cases of colorectal cancer that occurred in a cohort of 27,111 Finnish male smokers aged 50–69 years, the ATBC study [20]. This is the same cohort that was used for a study of 25(OH)D and colorectal cancer [5] (Section 3.2.3). The study was conducted during 1985–1997. Multivariate adjustment was performed with covariates including calcium intake, age, sex, tertile of body mass index, number of years of smoking (<35 years versus ≥35 years), tertile of alcohol intake, education, physical activity at work, and alpha-tocopherol

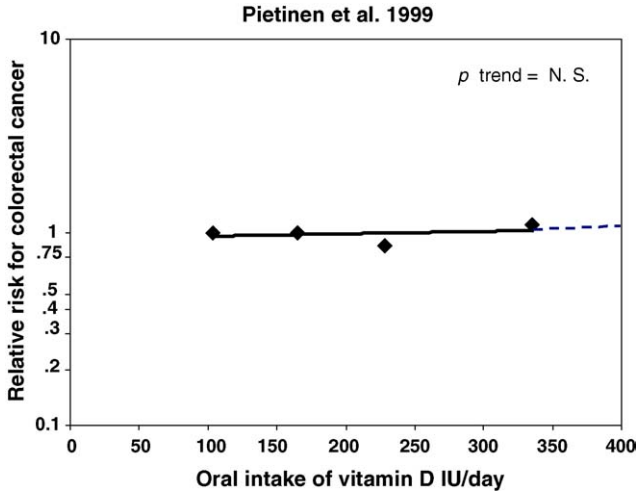

Fig. 16. Dose–response gradient of incidence of colon cancer according to quartile of oral Vitamin D intake, The Alpha Tocopherol and Beta Carotene Cancer Prevention Study Cohort, men, Finland, 1985–1997. *Source:* Pietinen et al. [20].

supplementation group (yes versus no). The median intake of Vitamin D intake by quartile from lowest to highest was, in IU/day: 103, 165, 228, and 345. Unadjusted relative risks and cut points of Vitamin D intake for quartiles were not reported. Age-adjusted relative risks from lowest to highest quartile, respectively, were: 1.0, 1.0, 0.9, and 1.1 (not significant) (Fig. 16). Multivariate-adjusted relative risks were: 1.0, 1.0, 0.8, and 1.0 (not significant). However, this study found a favorable dose–response relationship with calcium, with age-adjusted relative risks from lowest to highest quartile of 1.0, 0.7, 0.7, and 0.6 ($p = 0.04$). This population had an unusually high intake of calcium, with median intakes by quartile of 856, 1241, 1484, and 1789 mg/day. The dose–response relationship remained significant ($p = 0.04$) after further adjustment for smoking, body mass index, alcohol, education, and physical activity at work. There was a similar favorable dose–response relationship with intake of dairy products ($p = 0.02$) (not shown).

3.4. Summary of results

The intake of Vitamin D or the serum concentration of 25(OH)D that is effective in preventing 50% of the cases is the ED_{50} [24]. The median of the ED_{50} values from the four studies of prediagnostic serum was 33 ng/ml, compared to a reference level of 12 ng/ml (Table 1). The median of the ED_{50} values from the fourteen studies of oral intake of Vitamin D was 1000 IU/day, compared to a reference level of 100 IU/day (Table 2). The observational studies indicate that these concentrations and intakes would be associated with 50% lower incidence of colorectal cancer if they were introduced to a population with the reference levels of serum 25(OH)D during winter and the specified oral intake of Vitamin D. The reductions would be less in populations with better baseline Vitamin D status in winter.

4. Discussion

4.1. Strengths

This review was based on all studies that were identified through a MEDLINE search and it has a larger overall sample size than any study or review of this field. Many of the dose–response relationships that were used to identify the ED_{50} for Vitamin D or 25(OH)D were linear. The largest serum 25(OH)D study, that of the Nurses Health Study Cohort by Feskanich et al. [6] (Section 3.2.4; Fig. 4), had the clearest dose–response relationship, and it was linear. The same cohort, provided a clear linear dose–response relationship of oral Vitamin D intake with risk of colorectal cancer (Section 3.3.4; Fig. 8) [10]. Individuals with consistent intakes of Vitamin D over time had the clearest dose–response gradients, as would be expected [10]. The studies were for largely non-overlapping periods, another large cohort study, the Male Health Professionals Cohort, had a similarly clear linear dose–response relationship with a nearly identical ED_{50} [9] (Section 3.3.3; Fig. 7). There were reasonable explanations for studies that did not find the association or had mixed findings (see Sections 4.3–4.9).

4.2. Limitations

There are several limitations to the approach used in this study. While an effort was made to find relevant observational studies, the MEDLINE search may not have identified all. Some may have appeared in sources that were not indexed in MEDLINE, for example. Once the studies were assembled, and the results were plotted, it was assumed that the best approximation to the part of the dose–response curve of greatest interest was linear [24]. This was approximated with a least-squares trend line. This approach was consistent with most studies, including studies of oral intakes > 80 IU/day of Vitamin D that were not adjusted for calcium intake. While the estimation of the summary measure, the ED_{50} was based on linear trend lines similar to those in large studies [6,9,10], minor departures from linearity would tend to have minor effects. Only minor extrapolation was needed to determine the ED_{50} for serum 25(OH)D. Since oral intake of Vitamin D was quite low, extrapolation was needed to determine its estimated ED_{50}, except for one study of oral intake that required almost no extrapolation (Study 7) [9].

4.3. Characteristics of indeterminate, negative or mixed studies of oral Vitamin D

While the majority of studies reported a positive association of insufficient Vitamin D status with significantly increased risk of colorectal cancer [7,9,10,12,13,15] or a consistent trend of borderline significance [11,22], several studies of oral [14,18–20] or dietary [16,17] intake reported no association or mixed findings such as a statistically significant benefit of taking supplements containing Vitamin

D but not total oral Vitamin D intake [16]. Several design characteristics of the studies that did not detect associations or had mixed findings may have decreased their ability to detect the dose–response relationship: very low oral intake of Vitamin D [18], probable confounding by photosynthesized Vitamin D [19], lack of measurement of total oral Vitamin D intake [16,17], probable masking of an association with Vitamin D by overmatching on calcium [16,17,19], concealment of the effect of Vitamin D by intake of carcinogenic pickled and smoked fish [14,17,20], and possible non-differential misclassification of intake in case–control studies that would have required remote recall or high consistency of dietary intake for 20 years preceding diagnosis due to the long latency period thought to be characteristic of colorectal cancer [16,19].

4.4. Low intake of Vitamin D

Most dose–response curves in biology and medicine are sigmoid and have three distinct components: a nearly flat component on the left side of the curve at very low doses, a linear phase where the probability of the event of interest increases linearly with dose, and an asymptotic component on the right side, where increases in dose produce little or no further effect [25]. In general, the initial, roughly flat section of the curve inflects distinctly upward near a point where the probability of the event of interest is approximately 5–10%, and the linear component of the curve begins. The linear component generally extends diagonally across the range of doses producing from 10% to 90% of the effect [24]. At the top of the linear portion of the curve, there is another inflection and the curve becomes nearly horizontal near the point where the probability of the event is about 90–95% [24]. The combination of a flat section at the low end of the curve, a central linear portion, and an asymptotic flat section at the high end is characteristic of a classical dose–response curve [25]. Although, such curves are virtually horizontal at their asymptotic low and high ends, the largest segment of the curve is a straight diagonal line with a constant positive slope [25].

Dose or the outcome of interest may be in logarithmic units when plotting these curves. A few exceptions exist to the classical, mainly linear curve with asymptotic tails, such as biphasic or other complex curves, but the exceptions are uncommon [24]. The dose needed to produce 50% of the effect, or ED_{50} is log-normally distributed [24]. This is true along the entire linear portion of the dose–response curve.

Dose–response curves for preventive effects of compounds on incidence of a disease are, in general, plotted as a mirror image of the pharmacological dose–response curve, with incidence unaffected over an initial, virtually flat segment high on the left side of the curve, a linear decrease with dose over the downward sloping diagonal middle segment, and another virtually flat asymptotic segment low on the right side. The long, linear, segment of the curve tends to inflect toward the horizontal after the efficacy of the preventive compound in reducing incidence reaches about 90–95%, and the curve then generally becomes flat or has a slight downward slope to the right [24]. Throughout the linear portion of the range the slope is generally constant [24]. Although no extrapolation was needed for serum 25(OH)D, this linearity was the basis for extrapolation of the results from studies of oral intake.

According to data reported by Ferraroni et al. [18], whose study included only very low intakes of Vitamin D, the association of oral Vitamin D intake with risk of colorectal cancer had a horizontal trend through the lower limit of the top quintile, 80 IU/day. This was not surprising, since 80 IU is a very low intake compared to intakes at the low end of the top quantile of other study populations reviewed. Another study (Section 3.3.10) [12] also had relatively low intake of Vitamin D, although it had a statistically significant, downward trend in risk with increasing intake of Vitamin D.

4.5. Confounding by photosynthesized Vitamin D

In general, approximately 90–95% of circulating 25(OH)D at temperate latitudes is a result of photosynthesis [26]. In sunny areas in particular, the contribution of oral intake to serum 25-hydroxyvitamin D is but a few percent. Therefore, the role of solar UVB is critical, since 3000–5000 IU of cholecalciferol are metabolized daily [27]. The overwhelming predominance of photosynthesized Vitamin D probably accounted for the absence of a statistically significant association in the study by Peters et al. [19], which was conducted in Los Angeles, a sunny area with a Mediterranean subtropical climate. The Los Angeles area has a mean annual 2,007 h/year of sunlight that can be compared, for example, to 1,400 h/year in Boston. This climatic difference has important consequences for photosynthesis of Vitamin D. In Los Angeles, 3% of 7-dehydro-cholesterol was converted to pre-Vitamin D_3 in January, compared to no detectable photosynthesis in Boston during November through March [28]. A similar effect could also account for the lack of association in a study of oral intake that included mostly subjects from California and Utah [16]. Persons of various races should be included in future studies, since pigment cuts vitamin D photosynthesis [29–31].

4.6. Lack of measurement of total oral Vitamin D intake

The study by Kampman et al. [16] reported only intake from dietary sources. Use of supplements containing Vitamin D was ascertained, but not the dosage of Vitamin D consumed from supplements. Terry et al. [17] also did not ascertain baseline intake of Vitamin D from supplements.

4.7. Masking of Vitamin D association by overmatching on calcium

Four studies provided only Vitamin D intake data that had been adjusted for oral intake of calcium [16,17,19,20]. There is a high correlation of dietary Vitamin D with calcium intake

in the United States ($r = +0.87$) [32], although the correlation of total oral intake of calcium with total intake of Vitamin D is somewhat lower ($r = +0.33$). Due to these correlations, statistical adjustment for dietary or total calcium could unintentionally mask an association of dietary Vitamin D with risk of colorectal cancer. Such an unintended masking effect occurred in the study by Peters et al. [19] that reported that omission of calcium from the adjustment model resulted in a protective trend for Vitamin D. A similar phenomenon may have occurred in another study with mixed findings [16]. It found that use of supplements containing Vitamin D was associated with reduction by half in incidence of colorectal cancer in both sexes combined ($p < 0.05$) [16]. This finding may have emerged because intake of Vitamin D from supplements alone was less strongly correlated with intake of calcium than intake of Vitamin D from food [32].

4.8. Masking of the association with Vitamin D by intake of carcinogenic preserved fish

Three of the studies that found no association with oral intake of Vitamin D were from Scandinavian countries, including the studies by Pietinen et al. [20] and Jarvinen et al. [14] in Finland, and Terry et al. in Sweden [17]. Jarvinen et al. provided an alternative explanation for the inability of studies in Scandinavian countries to detect an association of oral Vitamin D intake with risk. The predominant dietary source of Vitamin D in these countries is fish, since ordinary milk generally is not fortified with Vitamin D in these countries [14]. A large proportion of the fish consumed in Scandinavian countries is either preserved with sodium nitrate and nitrite, or is smoked. Consumption of such fish was associated with increased risk of colorectal cancer in Finland, according to a 24-year cohort study (relative risk = 2.6, $p < 0.01$) [23]. Preserved fish are rich in n-nitrosoamines that are carcinogenic to the colon and rectum [33]. Consistent findings were reported in Japan, where intake of fresh or raw fish was associated with reduced risk of colorectal cancer while salted or pickled fish was associated with increased risk [34].

4.9. Non-differential misclassification of oral Vitamin D intake

When exposures are randomly misclassified due to forgetting or inaccurate memory, there is a tendency for the relative risks to be closer to 1.0 than is true [35]. Such misclassification could mask or attenuate an association of Vitamin D with risk. Terry et al. found a correlation of $r = +0.5$ for dairy products or calcium ascertained by questionnaire compared to four 7-day food diaries completed by a subset of the participants. This suggests that a considerable degree of non-differential misclassification may have been present, making it harder to find an association of intake with risk. Non-differential misclassification also probably influenced the results of a case–control study with mixed results that depended on recall of dietary intake 2 years preceding the diagnosis, itself difficult, notwithstanding that the latency period of colorectal cancer is thought to be approximately 20 years [15].

4.10. Reference value of 25(OH)D

The reference value for 25(OH)D was based on the upper limit of the lowest quantile of the studies reviewed (<13 ng/ml). This value is similar to low 25(OH)D values commonly encountered toward the end of winter at all ages in many parts of North America [36,37] and, in general, in elderly adults at temperate latitudes [38], in people with osteoporosis [39], and those with dark skin pigmentation living at temperate latitudes [40–42].

The colon can synthesize $1,25(OH)_2D$ from 25(OH)D [43], helping to account for the geographic epidemiology that revealed an association of low sunlight levels with high rates of cancer colon [1]. The carcinogenic processes [44–48] that are inhibited by Vitamin D metabolites probably occur at the highest rates in winter, when serum 25(OH)D is lowest [28], and therefore the substrate for local synthesis of $1,25(OH)_2D$ in the colon [43] also is lowest.

4.11. Absence of toxicity

In analysis of 30 known studies reporting any adverse effect of high serum 25(OH)D in adults, 197 ng/ml was the median level for toxicity, and no reproducible toxicity was present below 100 ng/ml [49]. The proposed serum 25(OH)D level of approximately 33 ng/ml was associated with 50% lower colorectal cancer incidence, an ED_{50}, that is far below the threshold of toxicity. The daily intake of 1000 IU/day needed for an anticipated 50% reduction in incidence is also far below the safe (no adverse effect level, NOEL) of 2400 IU/day established by the National Academy of Sciences, which includes a safety factor [50].

4.12. Vitamin D in health care education

Advice on improving Vitamin D status and monitoring serum 25(OH)D at least annually during winter should become a routine part of care by physicians, dieticians and other medical care professionals. An analysis of data from international comparisons [51,52] and observational studies [53,54] has revealed that high intake of red meat also is associated with increased risk of colorectal cancer. Therefore, optimal nutritional advice for prevention of colorectal cancer also should include limiting the intake of animal protein, particularly red meat. A possible exception is fresh or frozen fatty fish (such as unprocessed salmon, tuna, herring, and sardines) that may be a useful source of Vitamin D in cultures living at high latitudes with minimal opportunities for sunlight exposure or supplementation.

4.13. The role of calcium

The observational studies of Vitamin D and colorectal cancer in the present review have revealed that considerably higher serum levels of 25(OH)D are needed to prevent colorectal cancer than to prevent or cure rickets or osteomalacia [55]. Otherwise, the etiology of colorectal cancer has several similarities with rickets and osteomalacia [56]. These similarities are consistent with a hypothesis that Vitamin D could reduce the incidence of colorectal cancer by a mechanism involving calcium [1]. Support for the Vitamin D–calcium hypothesis for preventing colorectal cancer was obtained from a 19-year prospective study that found a linear inverse dose–response relationship between dietary intake of calcium and incidence of colon cancer (Section 3.2.1) [7] and numerous other studies.

A subsequent study that analyzed prediagnostic serum helped to determine that the effect of Vitamin D deficiency was independent of the effect of oral calcium intake, since serum deficiency of 25(OH)D was associated with markedly increased risk of colon cancer (Section 3.3.1) [3]. Since 90–95% of circulating 25(OH)D is a product of photosynthesis rather than of oral intake [26], this study established that the beneficial effect of Vitamin D on colon cancer risk was not due solely to its occurrence in foods that contained both calcium and Vitamin D.

A complementary mechanism for a role of calcium emerged from research by Newmark et al. that involved the neutralization of bile acids by calcium [57,58], and a study by Lipkin et al. that demonstrated that intake of 1250 mg/day of calcium in humans was associated with a markedly reduced rate of proliferation of the colonic epithelium of persons at high risk of colorectal cancer [59,60]. In another study, by Holt et al., individuals with higher than average serum 25(OH)D had similarly lower rates of proliferation of the colonic epithelium [61].

Efforts to improve Vitamin D status are more likely to succeed in preventing colorectal cancer if they include long-term measures that ensure appropriate intake of calcium similar to levels recommended to ensure bone health. The recommended daily intake of calcium established by the National Academy of Sciences (NAS-RDI), is 800 mg at age 4–8 years, 1300 mg at 9–18 years, 1000 mg at 19–50 years, and 1200 mg at >51 years [50]. The National Institutes of Health Osteoporosis Consensus Conference recommended a slightly higher intake for postmenopausal women who are not taking hormone therapy [62].

An increase in the recommended daily intake of Vitamin D_3 to 1000 IU/day for adults and children aged 1 year and older would help tremendously as a public health measure, since it could influence manufacturers of multivitamins to include adequate amounts of Vitamin D_3 in their formulations. Adequacy of calcium and Vitamin D nutritional status could be advanced substantially by a proposal advanced to add moderate amounts of calcium and Vitamin D to current fortification of bread and grain [63]. Other recommendations for research and action on Vitamin D for prevention of colorectal cancer are outlined in Appendix A.

The observational studies reviewed here provide evidence that half the incidence of colorectal cancer could be prevented with a modest intake of 1000 IU/day of Vitamin D.

A similar reduction could be expected if serum 25(OH)D were maintained at ≥33 ng/ml year-around in the population. Further benefit is likely if dietary intake of calcium is maintained at the levels specified by the NAS-RDI.

There are approximately 145,000 new cases of colorectal cancer per year in the US [64]. The results of observational studies reviewed here revealed that probably half, or 72,500 cases could be prevented using Vitamin D (Table 2), ideally in combination with calcium, assuming that most cases have deficient Vitamin D status. This assumption is reasonable given the age and geographic distribution of colorectal cancer cases. If Vitamin D deficiency is less than universal among cases, the fraction prevented by Vitamin D would be less, but still substantial. This reduction in incidence would be likely to prevent at least half the approximately 56,000 deaths from colorectal cancer each year [64], or 28,000 deaths. Now is the time to take definitive public health action on Vitamin D to prevent these completely needless cases and deaths.

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Appendix A

Suggested plan of action for research on cancer prevention using Vitamin D. Authors: Cedric F. Garland, Dr. P.H., Edward D. Gorham, Ph.D., M.P.H., and Frank C. Garland, Ph.D.

The following actions are suggested based on the results of this review:

1. *Recommendation*. The National Cancer Institute (NCI) or one of its committees should take action to officially recommend intake of 1000 IU/day of Vitamin D_3 and adequate calcium for cancer prevention, as an improvement of the Five-A-Day program for dietary prevention of cancer that was developed jointly by the NCI and grocery industry and is being disseminated through the news media and Internet. More than 25 years of research in six major population cohorts have provided an overall combined estimate that intake of 1000 IU/day of Vitamin D_3 would lead to the prevention of approximately half the incidence of colorectal cancer in the US. The results of this review suggest that approximately 72,500 new cases and 28,000 deaths would be prevented with such intake of Vitamin D_3 and adequate intake of calcium (800 mg/day for children and most adults, 1200 mg/day for postmenopausal women taking replacement hormones, and 1500 mg/day for those not taking replacement hormones). These intakes are safe according to the Food and Nutrition Board of the National Academy of Sciences and an NIH consensus conference that recommended optimal calcium intake. Special efforts should be made to communicate this recommendation to African-Americans, who are the sub-population greatest risk of Vitamin D insufficiency due to inadequate cutaneous synthesis. The cost of such a recommendation would be minimal, since the NIH regularly releases recommendations for cancer prevention on the Internet and in news releases. The main cost of adopting a recommendation would be that of adding new wording to existing materials and issuing a few news releases. The reduction in the number of new cases and loss of life from colorectal cancer would provide a tangible return on public investment in funding of cancer research.
2. *Consensus conference*. The National Cancer Institute should convene a consensus development conference on optimal intake of Vitamin D and calcium for prevention of colorectal cancer. A structure exists for convening such conferences and for dissemination of consensus statements through the Internet and publications. Such a conference would provide guidance for health professionals who rely on the NCI for information on cancer prevention. It would provide a consensual basis for advancing the goal of primary prevention of colon cancer, filling a vacuum left by recent research suggesting that traditional measures, such as increasing intake of fruits, vegetables and fiber, or reducing intake of fat, while potentially advantageous, are unlikely to provide major inroads toward primary prevention of colorectal cancer.
3. *Research program on Vitamin D and colorectal cancer prevention*. There is no national research program devoted to primary prevention of colorectal cancer. The NCI should develop and disseminate a request for applications (RFA) for research on of the role of Vitamin D in cancer prevention and in support of basic science in the field of Vitamin D. The RFA should be issued on an annual or semiannual basis. NIH leadership and Congress should allocate adequate funding to support such a program of research. An appropriate initial annual amount of extramural funding would be in the range of US$ 90 M for population-based studies, US$ 90 M for laboratory-based studies, and US$ 40 M for intervention studies, with support for NCI intramural research at an additional 10% of these levels.

   Such targeted support for a program of research on the role of Vitamin D in prevention of colorectal cancer would accelerate the pace of progress in using Vitamin D or its metabolites for prevention of colorectal cancer would help to recruit investigators to study the role of Vitamin D in cancer prevention. According to NCI professional staff, less than 3% of the current NCI budget is allocated to cancer chemoprevention. The needs of a Vitamin D and cancer research program could be addressed by increasing the proportion of the NCI budget devoted to chemoprevention. If funding were reallocated from existing programs, there would be no additional cost. If this were found to be infeasible, an appropriate initial annual allocation to develop a research program on Vitamin D and colorectal cancer prevention would be US$ 220 M. Such an allocation should be sustained for at least 5 years. The benefit:cost ratio would be highly favorable.
4. *Serum 25(OH)D atlas*. Offer a Request for Applications for development of an Internet-based atlas of serum 25(OH)D for US and Canadian cities and selected countries of the world. The serum 25(OH)D level of the population is known for relatively few locations in the world. An atlas of serum 25-hydroxyvitamin D measurements would be an invaluable resource for epidemiological research on cancer and many diseases that are related to Vitamin D insufficiency. The proposed atlas would provide the distribution of serum 25(OH)D levels in a probability sample of the general population. All serum samples would be analyzed in a central laboratory with precise calibration of measurements to National Institute of Standards and Technology (NIST) standards for 25-hydroxyvitamin D. Most of the benefit of such an atlas would result from collection of serum samples in the 50 largest urban areas of the US and Canada, and in a sample of the 174 countries reporting cancer incidence or mortality rates to the International Agency for Research on Cancer. For the US and Canada, separate measurements would be performed for whites, Hispanics, Asian Americans and African-Americans. The cost of development of this valuable epidemiological research resource would be approximately US$ 3 M annually for 5 years. The benefit:cost ratio would be high since the information would be useful to researchers and health planners across a wide range of diseases.
5. *Expand UVB network*. Offer a request for applications to update and expand the existing limited network of spectrophotometers to provide accurate measurement of ultraviolet B radiation at ground level, to include coverage of urban areas in the US and Canada. The Spectrophotometer

programs that are operated by the Department of Agriculture (USDA) and Environmental Protection Agency (EPA) are mainly located in rural areas, with minimal data available on UVB in urban areas, where most of the population is concentrated. Such a data resource would be of considerable value for population-based research on all diseases related to Vitamin D deficiency. Expansion of this program could be accomplished with an estimated US$ 4 M annually for installation of spectrophotometers in urban areas, maintenance and reporting. A substantial research resource for studies of all disease related to ultraviolet B and Vitamin D insufficiency would be created for numerous studies at modest cost.

6. *Calibration improvement*. Offer a request for applications to enhance the existing but underutilized national calibration program for 25(OH)D that provides a standards for use by all laboratories of serum 25(OH)D concentrations. The National Institute of Standards and Technology (NIST) has a standard for a few specified low concentrations of 25-hydroxyvitamin D, but analytical methods from different laboratories often are not calibrated to these standards and adequate standards do not exist for high concentrations. This program should be expanded to include standards for higher concentrations and support for NIST to disseminate information on the value of calibration at national Vitamin D research meetings and workshops, and provide the necessary samples. Greater standardization of 25(OH)D measurements could be achieved by enhanced support of existing facilities and the provision of standards without cost to all laboratories requesting them. The standards program for 25(OH)D could be expanded at an estimated cost of US$ 100 K/year for 2 years. The small cost is reasonable considering the high scientific value of standardization of measurements, making data on serum 25(OH)D comparable among all laboratories worldwide and across a wide range of diverse analytic methods.
7. Recommend performance of research supporting development and dissemination of a recommendation to oncologists and other clinicians that all individuals with a new diagnosis of colorectal cancer be evaluated for 25(OH)D deficiency, and, when indicated, provided adequate Vitamin D_3 to achieve Vitamin D sufficiency. Estimated cost of development of educational materials and dissemination of the information would be approximately US$ 1 M/year for 3 years. The cost–benefit ratio would be high, as existing surveys of age-specific 25(OH)D concentrations suggest that most colorectal cancer patients have relatively low serum levels of Vitamin D due in part to age and lifestyle.
8. Recommend performance of research supporting advanced technology for inexpensive routine measurement of 25(OH)D in populations at high risk of Vitamin D deficiency, including African-Americans, residence of the colorectal cancer belt in the northeastern US, advanced age, and existence of chronic disease institutionalization. Measurement of serum 25(OH)D currently costs in excess of US$ 100 per sample in research laboratories. Much lower cost could probably be achieved with advances in technology and economy of scale. Research should be supported on making measurement of 25(OH)D part of the routine capabilities of standard multichannel automated biochemical clinical laboratory test equipment. This research could be performed as a joint government–industry collaboration. Estimated cost would be US$ 2 M/year for 5 years, with sharing of the cost of development by industry.
9. Recommend performance of economic studies to evaluate the benefit:cost ratio of using Vitamin D for prevention of colorectal cancer. Preliminary data suggest that such analyses would be promising. The annual cost of colorectal cancer in the United States is approximately US$ 40 B including US$ 15 B for treatment and US$ 25 B in lost productivity.

Preventing approximately half of colorectal cancer incidence by a program that would ensure Vitamin D adequacy could save an estimated US$ 20 B/year. Annual supplementation of all Americans with 1000 IU/day Vitamin D_3 would cost approximately US$ 5 B. Although, further economic investigation would be desirable, a gross estimate of the annual return on investment considering the cost of supplementation would be US$ 20–5 B, or US$ 15 B/year, amounting to nearly a 40% per annum return on investment.

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