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Vitamin D and prevention of colorectal cancer

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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.

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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