

Journal of the American College of Nutrition, Vol. 18, No. 90005, 392S-397S  
(1999)

Published by the [American College of Nutrition](#)

# Vitamin D, Calcium and Prevention of Breast Cancer: A Review

**Martin Lipkin, MD and Harold L. Newmark, DSc**

Weill Medical College of Cornell University, Strang Cancer Research Laboratory  
at The Rockefeller University, New York (M.L.)  
Rutgers University, New Jersey (H.L.N.)

Address reprint requests to: Martin Lipkin, M.D., Strang Cancer Research  
Laboratory, Rockefeller University, 1230 York Ave., New York, NY 10021-6007.

## This Article

- ▶ [Abstract](#) **FREE**
- ▶ [Full Text \(PDF\)](#)

## Services

- ▶ [Similar articles in this journal](#)
- ▶ [Similar articles in PubMed](#)
- ▶ [Alert me to new issues of the journal](#)
- ▶ [Download to citation manager](#)
- ▶ [© Get Permissions](#)

## Citing Articles

- ▶ [Citing Articles via HighWire](#)
- ▶ [Citing Articles via Google Scholar](#)

## Google Scholar

- ▶ [Articles by Lipkin, M.](#)
- ▶ [Articles by Newmark, H. L.](#)
- ▶ [Search for Related Content](#)

## PubMed

- ▶ [PubMed Citation](#)
- ▶ [Articles by Lipkin, M.](#)
- ▶ [Articles by Newmark, H. L.](#)

## ▶ ABSTRACT

Several recent epidemiologic and experimental studies have suggested that decreased calcium and vitamin D intake and high dietary fat are associated with mammary gland carcinogenesis. Complete reduction or elimination of human exposure to environmental factors such as high-fat diets is inherently difficult to implement. Recent studies have begun to evaluate a possible role for increased dietary calcium and vitamin D in reducing the risk of colonic and mammary cancers, even in the presence of a high-fat diet. Studies from our laboratory recently found that decreased dietary calcium and vitamin D in a high-fat diet induced adverse changes in the mammary gland and several other organs, which were reversed by increasing dietary calcium and vitamin D; the findings further suggest a possible role for increased dietary calcium and vitamin D in the chemoprevention of these cancers.

**Key words:** breast cancer, calcium, vitamin D, chemoprevention, diet

### Key teaching points:

- Recent studies in animal models have suggested that increasing dietary calcium and vitamin D might

- ▲ [TOP](#)
- [ABSTRACT](#)
- ▼ [INTRODUCTION](#)
- ▼ [BASIC ASPECTS OF CALCIUM...](#)
- ▼ [GEOGRAPHIC DISTRIBUTION OF...](#)
- ▼ [MECHANISMS THROUGH WHICH VITAMIN...](#)
- ▼ [CONCLUSION](#)
- ▼ [REFERENCES](#)

inhibit the development of breast cancer.

- Epidemiologic studies of breast cancer and exposure to sunlight also have supported a role for vitamin D in the inhibition of breast cancer.
- Vitamin D induces differentiation of mammary gland cells.
- Humans with vitamin D receptor-positive tumors had longer disease-free survival than those with receptor-negative tumors.

## ▶ INTRODUCTION

Breast cancer is among the most frequently diagnosed cancers in the United States and West European countries [1–3]. Although an understanding of its cause is incomplete, several epidemiologic and experimental studies have now suggested that high dietary fat and decreased calcium and vitamin D intake have associations with mammary gland carcinogenesis [1,4–16].

▲ <a href="#">TOP</a>
▲ <a href="#">ABSTRACT</a>
▪ <a href="#">INTRODUCTION</a>
▼ <a href="#">BASIC ASPECTS OF CALCIUM...</a>
▼ <a href="#">GEOGRAPHIC DISTRIBUTION OF...</a>
▼ <a href="#">MECHANISMS THROUGH WHICH VITAMIN...</a>
▼ <a href="#">CONCLUSION</a>
▼ <a href="#">REFERENCES</a>

Complete reduction or elimination of human exposure to environmental factors such as high-fat diets is inherently difficult to implement. Recent studies [17–25,30] have begun to evaluate a possible role for increased dietary calcium and vitamin D in reducing the risk of colonic and mammary cancers, even in the presence of a high-fat diet. Studies from our laboratory recently found that decreased dietary calcium and vitamin D in a high-fat diet induced adverse changes in mammary gland and several other organs [24–29], which were decreased by increasing dietary calcium and vitamin D [30–32]; the findings further suggested a possible role for increased dietary calcium and Vitamin D in the chemoprevention of those cancers.

Specifically, in studies of short duration, a Western-style diet was given to mice; the Western-style diet had reduced levels of calcium and vitamin D and increased fat content with nutrient density levels of each comparable to those found in human Western diets. The mice developed hyperplasia and hyperproliferation, both in terminal ductules of mammary gland and in colonic epithelium, and developed hyperproliferation of ductular epithelium in prostate and pancreatic glands. We also completed a long-term study of mice on a Western-style diet and found in the colon development of the late-stage precancerous lesion of colonic whole-crypt dysplasia; long-term studies of breast and other organs are now in progress. Increasing dietary calcium and vitamin D decreased all of the organ-site changes noted above that were induced by the high fat content of the Western-style diet [30–32]. Thus, previous epidemiologic and laboratory studies, including some from our laboratory, have suggested that a high fat diet increases the risk of breast cancer as well as colon, prostate and pancreatic cancer and that carcinogenesis in those organs might be decreased by increasing dietary calcium and vitamin D. In this article we review current findings on relationships of dietary vitamin D and calcium and the development of breast cancer.

## BASIC ASPECTS OF CALCIUM AND VITAMIN D METABOLISM

Calcium is an essential structural and functional element in living cells. It is a key component in the maintenance of proper cell structure, and membrane viscosity or rigidity and its related permeability are partly dependent on local calcium concentration. Calcium is also a pivotal regulator of a wide variety of cell functions in its role as a major second messenger [33].

- ▲ [TOP](#)
- ▲ [ABSTRACT](#)
- ▲ [INTRODUCTION](#)
- [BASIC ASPECTS OF CALCIUM...](#)
- ▼ [GEOGRAPHIC DISTRIBUTION OF...](#)
- ▼ [MECHANISMS THROUGH WHICH VITAMIN...](#)
- ▼ [CONCLUSION](#)
- ▼ [REFERENCES](#)

Among the numerous cell functions modulated by calcium, its participation in cell division and the regulation of cell proliferation and differentiation are particularly important [34]. In cell and organ culture, increasing the concentration of calcium decreased cell proliferation, and cell differentiation was induced in mammary cells [35,36], esophageal epithelial cells [37], murine epidermal cells [34] and colon cells [38,39].

The absorption and metabolism of calcium are carefully regulated; 1,25 dihydroxyvitamin D<sub>3</sub> is an important modulator that can become deficient as a consequence of inappropriate diet or exposure to sunlight (see below). Therefore, vitamin D<sub>3</sub> has a role in the regulation of cell proliferation and differentiation with modulation of calcium metabolism, and it also has its own direct role in cell differentiation. Thus, vitamin D<sub>3</sub> has been shown to inhibit the proliferation of several malignant cell lines *in vitro* [40–42] and to induce the differentiation of human colonic cells [43], human myeloid leukemia cells [44] and other cell lines *in vitro* [45,46]. A role for vitamin D as a chemopreventive agent has also been studied in rodent models [47–50], indicating that the promotional stage of chemical carcinogenesis can be inhibited by vitamin D both in mouse skin [49] and in colon [50]. The effect of vitamin D<sub>3</sub> on polyamine metabolism also has been studied, and the induction of ODC activity by bile acids in the rat colon was inhibited by administration of 1 $\alpha$  hydroxyvitamin D<sub>3</sub> [51]. However, vitamin D<sub>3</sub> increased chemically-induced transformation of cultured cells *in vitro* [52,53] and promoted skin tumor formation in mice [54].

In studying interactions between vitamin D<sub>3</sub> and calcium, a synergistic effect was shown with vitamin D playing a permissive role for the expression of a calcium chemopreventive function [55]. However, the combination of both supplemental calcium and vitamin D<sub>3</sub> in high levels appeared to antagonize the inhibitory effect of each supplement alone on fat-promoted DMH-induced carcinogenesis in rodent colon [21].

## GEOGRAPHIC DISTRIBUTION OF BREAST CANCER AND VITAMIN D

▲ [TOP](#)

Studies of the geographic distribution of breast cancer and exposure to sunlight have provided useful support for a role of vitamin D intake and reduction of breast cancer. Thus, Garland and co-workers [[17,56–58](#)] have noted that breast cancer mortality rates follow a geographic distribution in the United States which is

similar to that of colon cancer, with the highest rates for both diseases occurring in the northeast. Breast cancer death rates in North America are thus highest in the northeast where ultraviolet B radiation levels allow decreased synthesis of vitamin D during a large part of the year. In that geographic region age-adjusted mortality rates from breast cancer tend to be about 40% higher than in Hawaii and considerably higher than in high sun-exposure regions of the southwest [[56](#)]. As occurs with colon cancer, higher than average stratospheric levels of air pollution also are associated with elevated breast cancer mortality rates [[57](#)].

A geographic association of latitude with breast cancer death rates is age-dependent with the strongest association occurring during postmenopause. Age-adjusted incidence rates and mortality from breast cancer in northern republics of the USSR also were approximately twice those in southern, with intermediate rates present at intermediate latitudes [[58](#)].

## ▶ MECHANISMS THROUGH WHICH VITAMIN D AND CALCIUM MAY INHIBIT CARCINOGENESIS

For many years an important question noted above has been the degree to which dietary fat may contribute to the etiology of breast cancer [[1,4,59](#)]. International studies have been carried out in which dietary fat intake has been studied in large populations over a large part of the subjects' lifetimes: those studies have

shown positive correlations of increased fat intake and breast cancer incidence and mortality [[4](#)] and migration [[60,61](#)]. By contrast, shorter-term prospective or case-control studies have generally not found positive correlations between fat intake and breast cancer risk in adults [[62–68](#)].

Many animal studies have demonstrated that dietary fat can function as a promoter rather than an initiator of chemically-induced mammary cancer [[69–72](#)] and colon cancer [[73](#)]. In studies of colon cancer, increased dietary fat has been shown to increase levels of free fatty acids and free unconjugated bile acids in the luminal contents of the colon. These substances have been shown to have irritant and proliferative-stimulating effects, inducing a wide variety of adverse cell damaging effects in the colon. A hypothesis [[74](#)] further suggested that this irritation-driven hyperproliferation could be reduced by increasing dietary calcium and vitamin D. Studies in animals, short-term interventions in humans and epidemiologic studies support the utility of the concept that increased dietary calcium and vitamin D can reduce the risk of colon cancer related to high dietary fat intake [[23,31,32,75](#)].

- ▲ [TOP](#)
- ▲ [ABSTRACT](#)
- ▲ [INTRODUCTION](#)
- ▲ [BASIC ASPECTS OF CALCIUM...](#)
- [GEOGRAPHIC DISTRIBUTION OF...](#)
- ▼ [MECHANISMS THROUGH WHICH VITAMIN...](#)
- ▼ [CONCLUSION](#)
- ▼ [REFERENCES](#)

- ▲ [TOP](#)
- ▲ [ABSTRACT](#)
- ▲ [INTRODUCTION](#)
- ▲ [BASIC ASPECTS OF CALCIUM...](#)
- ▲ [GEOGRAPHIC DISTRIBUTION OF...](#)
- [MECHANISMS THROUGH WHICH VITAMIN...](#)
- ▼ [CONCLUSION](#)
- ▼ [REFERENCES](#)

Since there are numerous epidemiological correlations of colonic and mammary cancer, animal studies have been carried out to evaluate the possibility that dietary calcium and vitamin D might influence the promotional effect of high-fat diets in chemically-induced mammary cancer. When rodents were maintained on low-fat diets, dietary calcium and vitamin D had little effect except when the dietary calcium was very low [76]; when rodents were fed high fat diets, however, a significant increase in mammary tumors resulted by decreasing the dietary calcium and vitamin D to nutrient density levels found in Western human adult populations.

Further studies [14,77] also suggested that vitamin D and phosphate interacted with dietary calcium in the presence of high-fat diet. Dietary vitamin D had the largest individual effect: in higher amounts it inhibited tumorigenesis in the presence of low ingested calcium and phosphate, but was less effective with a high-calcium diet. These dietary studies in rats are in general agreement with a mechanism postulated for the effect of high dietary fat in breast cancer promotion [74]. According to this concept, high dietary fat would produce an increased flux of circulating lipids into breast tissue, particularly during its rapid growth. These lipids could increase their presence in mammary cells, particularly small ductal epithelial cells, where tumors tend to appear, largely via the hydrolysis of circulating triglycerides to free fatty acids for transport across cell membranes of adjacent fat cells. As occurs in the colon, this could adversely effect calcium-dependent cell structures and very sensitive cell-signaling systems because of the strong binding of these free fatty acids to calcium [30,74].

Maintaining adequate intra-cellular calcium levels depends on adequate circulating calcium and the active hormonal form of vitamin D, calcitriol [1,25 dihydroxycholecalciferol or 1,25 di-OHD<sub>3</sub>) [33,34,78]. Calcium blood levels are sufficiently important physiologically to be tightly maintained within a narrow range by interactions of parathyroid hormone, calcitonin, 1,25 di-OHD<sub>3</sub>-controlled dietary absorption, loss due to reacting with ingested food components and losses in urine and sweat [79]. However, increasing blood levels of 1,25 di-OHD<sub>3</sub> also facilitates cellular uptake of calcium from circulating blood. Low dietary vitamin D could, therefore, be anticipated to increase the ability of circulating lipids to promote the development of breast cancer by limiting the individual's physiological capacity to elevate 1,25 di-OHD<sub>3</sub>, thus resulting in a reduced ability of cells to replenish calcium that was lost via binding to free fatty-acids. In the animal studies noted above [14,77], although the data are limited, the greatest single effect was due to dietary vitamin D.

Further, important studies carried out recently also support the likelihood that vitamin D and calcium may influence the development of breast cancer. Thus, biologically active hormone-like forms of vitamin D, such as 1,25 di-OHD<sub>3</sub> and 1- $\alpha$ -hydroxycholecalciferol (1  $\alpha$  OHD<sub>3</sub>), have shown potent differentiation-inducing properties on cancer cell lines from a variety of tissues [79]. Differentiation-inducing effects of 1,25 di-OHD<sub>3</sub> on human breast cancer cell lines have been noted that may involve the regulation of epidermal growth factor receptors [80] and morphologic changes in the cells [81]. In rats with mammary tumors induced by methylnitrosourea, treatment with the synthetic analogue 1- $\alpha$ -OHD<sub>3</sub> significantly inhibited tumor progression [79]. Further studies on human breast tumor and cancer cell lines have shown that over 80% of human breast tumors contain 1,25 di-OHD<sub>3</sub> receptors and that *in*

*in vitro* 1,25 di-OHD<sub>3</sub> inhibits proliferation and promotes differentiation in several types of cells.

Individuals with 1,25 di-OHD<sub>3</sub> receptor-positive tumors had significantly longer disease-free survival than those with receptor-negative tumors. The circulating levels of 1,25 di-OHD<sub>3</sub> occurring *in vivo* may therefore exert inhibiting effects on receptor-positive tumors [82,83].

## ► CONCLUSION

Thus, recent studies from our laboratory have shown that a Western-style diet containing decreased calcium and vitamin D and increased fat content induced hyperproliferation and hyperplasia in mammary gland and colonic epithelium in short-term studies; dietary calcium supplementation inhibited those changes. A

Western-style diet also induced colonic whole-crypt dysplasia (a late-stage preneoplastic lesion) in a long-term feeding study. We also demonstrated that feeding mice a Western-style diet for a short duration induced epithelial cell hyperproliferation in the exocrine pancreas and prostate glands, suggesting that a diet with low levels of calcium and vitamin D, together with increased fat content, might also enhance carcinogenesis in those organs. Low calcium and increased dietary fat have been associated with increased incidences of human cancers of the breast, prostate and pancreas, and previous animal studies have supported an association of fat intake, types of fatty acids and those cancers. Vitamin D and calcium are closely linked physiologically since the bioavailability of calcium via gastrointestinal tract absorption and transport into cells both depend on adequate vitamin D.

Epidemiologic investigations of breast cancer incidence and exposure to sunlight have further suggested vitamin D to have an important role in inhibiting breast cancer. Dietary vitamin D in North America is low in most segments of the population and is enhanced by skin exposure to sunlight; the latter varies considerably with latitude and air quality. The studies of Garland *et al.* suggest a strong inverse correlation between breast cancer occurrence and skin production of vitamin D.

Decreased solar radiation, particularly in urban areas where the greater part of the US population lives, thus results in reduced biologically available vitamin D from this source and creates an increased dependency on dietary intake. In the US recommended dietary intakes of vitamin D are 10 µg (=400 units) from 1 to 24 years of age for both males and females and 5 µg (=200 units) above 24 years of age, except for pregnant females. Daily dietary intakes, however, are far lower with females' consuming an average of 1.5 µg (60 units) and elderly females a median intake of 1.35 µg (54 units). This low average intake of dietary vitamin D, coupled with a reduced capacity to convert vitamin D to 25 OHD<sub>3</sub> and further to 1,25 di-OHD<sub>3</sub>, serves to explain documented low levels of active vitamin D metabolites in older populations; the low levels are partly correctable with dietary supplementation.

Interesting studies on osteoporosis resemble those on breast cancer in terms of dietary requirements and recommendations. Thus, the Subcommittee on the Tenth Edition of the RDAs emphasized the importance

▲	<a href="#">TOP</a>
▲	<a href="#">ABSTRACT</a>
▲	<a href="#">INTRODUCTION</a>
▲	<a href="#">BASIC ASPECTS OF CALCIUM...</a>
▲	<a href="#">GEOGRAPHIC DISTRIBUTION OF...</a>
▲	<a href="#">MECHANISMS THROUGH WHICH VITAMIN...</a>
▪	CONCLUSION
▼	<a href="#">REFERENCES</a>

of recommended intake levels of calcium and its biochemically associated vitamin D throughout childhood to age 25 years. There is little risk of intake of vitamin D at RDA levels, since risk of hypervitaminosis only occurs on prolonged intake of five times or more of the RDA (over 2000 units or 50 mcg daily).

Therefore, reduction of breast cancer risk, simultaneously with several other cancers and with osteoporosis, might be achieved by increasing the dietary intake of vitamin D and calcium to current recommended levels. This may be particularly applicable to females during puberty and adolescence when the proliferation of mammary epithelial cells and potential exposure to genotoxic agents increases, as well as to other age groups in the general population.

## ▶ FOOTNOTES

The preparation of this report was aided by NCI Grant P01 CA29502.

Received May 1, 1999.

## ▶ REFERENCES

▲ <a href="#">TOP</a>
▲ <a href="#">ABSTRACT</a>
▲ <a href="#">INTRODUCTION</a>
▲ <a href="#">BASIC ASPECTS OF CALCIUM...</a>
▲ <a href="#">GEOGRAPHIC DISTRIBUTION OF...</a>
▲ <a href="#">MECHANISMS THROUGH WHICH VITAMIN...</a>
▲ <a href="#">CONCLUSION</a>
▪ <a href="#">REFERENCES</a>

1. Carroll KK, Khor HT: Dietary fat in relation to tumorigenesis. *Prog Biochem Pharmacol* 10: 308–53, 1975. [\[Medline\]](#)
2. National Center for Health Statistics: US Department Health Human Services. 172: 4–60, 1990.
3. Boring CC, Squires TS, Tong T: Cancer statistics. *CA Cancer J Clin* 43: 7–26, 1993. [\[Medline\]](#)
4. Armstrong B, Doll R: Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 15: 617–631, 1975. [\[Medline\]](#)
5. Draser HS, Irving D: Environmental factors and cancer of the colon and breast. *Br J Cancer* 27: 167–172, 1973. [\[Medline\]](#)
6. Zhang L, Bird RP, Bruce WR: Proliferative activity of murine mammary epithelium as affected by dietary fat and calcium. *Cancer Res* 47: 4905–4908, 1987. [\[Abstract/Free Full Text\]](#)
7. Lok E, Ratnayake WMN, Scott FW, Monggeau R, Fernic S: Effect of varying the type of fat in a semi-purified AIN-76A diet on cellular proliferation in mammary gland and intestinal crypts in female Swiss Webster mice. *Carcinogenesis* 13: 1735–1741, 1992. [\[Abstract/Free Full Text\]](#)
8. Cohen LA, Thompson DO, Maenra Y, Choc K, Blank ME: Dietary fat and mammary cancer. 1. Promoting effects of different dietary fats on N-nitrosomethylurea-induced rat mammary tumorigenesis. *J Natl Cancer Inst* 77: 33–42, 1986.
9. Gammal EB, Carroll KK, Plunkett ER: Effects of dietary fat on mammary carcinogenesis by 7,12-dimethylbenz(a)anthracene in rats. *Cancer Res* 27: 1737–1742, 1967. [\[Medline\]](#)
10. DeWille JW, Waddell K, Steinmeyer C, Farmer SJ: Dietary fat promotes mammary tumorigenesis in MMTV/v-Ha-ras transgenic mice. *Cancer Lett* 69: 59–66, 1993. [\[Medline\]](#)
11. Welsch CW, House JL, Herr BL, Eliasberg SJ, Welsch MA: Enhancement of mammary carcinogenesis by high levels of dietary fat: A phenomenon dependent on ad libitum feeding. *J Natl Cancer Inst* 82: 1615–1620, 1990. [\[Abstract/Free Full Text\]](#)
12. Longcope C, Corbach B, Goldin M, Woods J, Dwyer J: The effect of a low fat diet on estrogen metabolism. *J Clin Endocrinol Metab* 64: 1246–1250, 1987. [\[Abstract\]](#)

13. Hopkins GJ, Carroll KK: Relationship between amount and type of dietary fat in promotion of mammary carcinogenesis induced by 7,12-dimethylbenz(a)anthracene. *J Natl Cancer Inst* 62: 1009–1012, 1979.
14. Carroll KK, Jacobson EA, Eckel LA, Newmark HL: Calcium and carcinogenesis of the mammary gland. *Am J Clin Nutr* 54: 206–208s, 1991.
15. Welsch CW: Enhancement of mammary tumorigenesis by dietary fat: Review of potential mechanisms. *Am J Clin Nutr* 45: 192–202, 1987. [\[Free Full Text\]](#)
16. Newmark HL: Vitamin D adequacy: A possible relationship to breast cancer. In Weisburger EK (ed): "Conference on Diet and Cancer: Diet and Breast Cancer," 4th Conference, Washington, DC, 1993. New York: Plenum, pp 109–114, 1994.
17. Garland C, Shekelle RB, Barrett-Connor E, Criqui MH, Rossoff AH, Paul O: Dietary vitamin D and calcium and risk of colorectal cancer: A 19-year prospective study in men. *Lancet* 1: 307–309, 1985. [\[Medline\]](#)
18. Lipkin M, Newmark HL: Effect of added dietary calcium on colonic epithelial-cell proliferation in subjects at high risk for familial colonic cancer. *N Eng J Med* 313: 1381–1384, 1985. [\[Abstract\]](#)
19. Buset M, Lipkin M, Winawer S, Swaroop S, Friedman E: Inhibition of human colonic epithelial cell proliferation in vivo and in vitro by calcium. *Cancer Res* 46: 5426–5430, 1986. [\[Abstract/Free Full Text\]](#)
20. Buset M, Lipkin M, Winawer S, Friedman E: Direct and indirect protection of human colonic epithelial cells by calcium. *Gastroenterology* 92: 1334, 1987.
21. Pence BC, Buddingh F: Inhibition of dietary fat-promoted colon carcinogenesis in rats by supplemental calcium or vitamin D. *Carcinogenesis (London)* 9: 187–190, 1988. [\[Abstract/Free Full Text\]](#)
22. Lipkin M, Friedman E, Winawer SJ, Newmark H: Colonic epithelial cell proliferation in responders and nonresponders to supplemental dietary calcium. *Cancer Res* 49: 248–254, 1989. [\[Abstract/Free Full Text\]](#)
23. Scalmati A, Lipkin M, Newmark H: Calcium, vitamin D, and colon cancer. *Clinics in Applied Nutrition* 2: 67–74, 1992.
24. Khan M, Yang K, Newmark H, Wong G, Telang N, Rivlin R, Lipkin M: Mammary ductal epithelial cell hyperproliferation and hyperplasia induced by four components of a Western-style diet. *Carcinogenesis* 15: 2645–2648, 1994. [\[Abstract/Free Full Text\]](#)
25. Xue LX, Newmark HL, Yang K, Lipkin M: Model of mouse mammary gland hyperproliferation and hyperplasia induced by a Western-style diet. *Nutr Cancer* 26: 281–287, 1996. [\[Medline\]](#)
26. Xue LX, Lipkin M, Newmark HL: Induced hyperproliferation in epithelial cells of mouse prostate by a Western-style diet. *Carcinogenesis* 18: 995–999, 1997. [\[Abstract/Free Full Text\]](#)
27. Newmark HL, Lipkin M, Maheswari N: Colonic hyperplasia and hyperproliferation induced by a nutritional stress diet with four components of Western-style diet. *J Natl Cancer Inst* 82: 491–496, 1990. [\[Abstract/Free Full Text\]](#)
28. Newmark HL, Lipkin M, Maheswari N: Colonic hyperproliferation induced in rats and mice by nutritional stress diets containing four components of a human Western-style diet (Series 2). *Am J Clin Nutr* 54: 209–214S, 1991.
29. Xue LX, Yang K, Newmark HL, Leung D, Lipkin M: Epithelial cell hyperproliferation induced in the exocrine pancreas of mice by a Western-style diet. *J Natl Cancer Inst* 88: 1586–1590, 1996. [\[Abstract/Free Full Text\]](#)
30. 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 Can Inst* 91: 176–181, 1999. [\[Abstract/Free Full Text\]](#)
31. Richter F, Newmark H, Richter A, Leung D, Lipkin M: Inhibition of Western diet induced hyperproliferation and hyperplasia in mouse colon by two sources of calcium. *Carcinogenesis* 16: 2685–2689, 1995. [\[Abstract/Free Full Text\]](#)
32. Risio M, Lipkin M, Newmark H, Yang K, Rossini FP *et al.*: Apoptosis, cell replication, and

- Western-style diet-induced tumorigenesis in mouse colon. *Cancer Research* 56: 4910–4916, 1996. [[Abstract/Free Full Text](#)]
33. Rasmussen H: The calcium messenger system (in 2 parts). *N Engl J Med* 314: 1094, 1164, 1986. [[Medline](#)]
  34. Whitfield JF, Boynton AL, MacManus JP, *et al.*: The regulation of cell proliferation by calcium and cyclic AMP. *Mol Cell Biochem* 27: 155, 1979. [[Medline](#)]
  35. McGrath CM, Soule HD: Calcium regulation of normal mammary epithelial cell growth in culture. *In Vitro* 20: 652, 1984. [[Medline](#)]
  36. Soule HD, McGrath CM: A simplified method for passage and long-term growth of human mammary epithelial cell. *In Vitro* 22: 6, 1985.
  37. Babcock MS, Marino MR, Gunning III WT, *et al.*: Clonal growth and serial propagation of rat esophageal epithelial cells. *In Vitro* 19: 403, 1983. [[Medline](#)]
  38. Friedman E, Lipkin M, Winawer S, Buset M, Newmark H: Heterogeneity in the response of familial polyposis cells and adenomas to increasing levels of calcium in vitro. *Cancer* 63: 2486–2491, 1989. [[Medline](#)]
  39. Boffa LC, Mariani MR, Newmark H, *et al.*: Calcium as modulator of nucleosomal histones acetylation in cultured cells. *Proc Am Assoc Cancer Res* 30: 8, 1989.
  40. Niendorf A, Arps H, Dietel M: Effect of 1,25-dihydroxyvitamin D<sub>3</sub> on human colon cancer in vitro. *J Steroid Biochem* 27: 825, 1987. [[Medline](#)]
  41. Colston K, Colston MJ, Feldman D: 1,25-dihydroxyvitamin D<sub>3</sub> and malignant melanoma: The presence of receptors and inhibition of cell growth in culture. *Endocrinology* 108: 1083, 1981. [[Abstract](#)]
  42. Lointier P, Wargovich JM, Saez S, *et al.*: The role of vitamin D<sub>3</sub> in the proliferation of a human colon cancer cell line in vitro. *Anticancer Res* 7: 817, 1987. [[Medline](#)]
  43. Higgins PJ, Tanaka Y: Cytoarchitectural response and expression of c-fos/p52 genes during enhancement of butyrate-initiated differentiation of human colon carcinoma cells by 1,25-dihydroxyvitamin D<sub>3</sub> and its analogs. In Lipkin M, Newmark HL, Kelloff G (eds): "Calcium, Vitamin D, and Prevention of Colon Cancer." Boca Raton, FL: CRC Press, p 113, 1991.
  44. Miyaura C, Abe E, Kuribayashi T, *et al.*: 1,25-dihydroxyvitamin D<sub>3</sub> induces differentiation of human myeloid leukemia cells. *Biochem Biophys Res Comm* 102: 937, 1981. [[Medline](#)]
  45. Kuroki T, Chida K, Hashiba H, *et al.*: Regulation of cell differentiation and tumor promotion by 1,25-dihydroxyvitamin D<sub>3</sub>. In Huberman E, Barr SH (eds): "Carcinogenesis." New York: Raven Press, p 275, 1985.
  46. Suda T, Miyaura C, Abe E, *et al.*: Modulation of cell differentiation, immune responses and tumor promotion by Vitamin D compounds. *Bone Min Res* 4: 1, 1986.
  47. Eisman JA, Barkla DH, Tutton PJM: Suppression of in vivo growth of human cancer solid tumor xenografts by 1,25-dihydroxyvitamin D<sub>3</sub>. *Cancer Res* 47: 21, 1987. [[Abstract/Free Full Text](#)]
  48. Honma Y, Hozumi M, Abe E, *et al.*: 1,25-dihydroxyvitamin D<sub>3</sub> and 1-hydroxyvitamin D<sub>3</sub> prolong survival time of mice inoculated with myeloid leukemia cells. *Cell Biol* 80: 201, 1983.
  49. Chida K, Hashiba H, Fukushima M, *et al.*: Inhibition of tumor promotion in mouse skin by 1,25-dihydroxyvitamin D<sub>3</sub>. *Cancer Res* 45: 5426, 1985. [[Medline](#)]
  50. Kawaura A, Tanida N, Sawada K, *et al.*: Supplemental administration of 1 alpha-hydroxyvitamin D<sub>3</sub> inhibits promotion by intrarectal instillation of lithocholic acid in N-methyl-N-nitrosourea-induced colonic tumorigenesis in rats. *Carcinogenesis* 10: 647–649, 1989. [[Abstract/Free Full Text](#)]
  51. Hashiba H, Fukushima M, Chida K, *et al.*: Systemic inhibition of tumor promoter-induced ornithine decarboxylase in 1alpha-hydroxyvitamin D<sub>3</sub>-treated animals. *Cancer Res* 47: 5031, 1987. [[Abstract/Free Full Text](#)]
  52. Kuroki T, Sasaki K, Chida K, *et al.*: 1,25-dihydroxy-vitamin D<sub>3</sub> markedly enhances chemically-induced transformation in BALB 3T3 cells. *GNN* 74: 611, 1983.

53. Jones CA, Callahan MF, Huberman E: Enhancement of chemical-carcinogen-induced cell transformation in hamster embryo cells by 1,25-dihydroxycholecalciferol, the biologically active metabolite of vitamin D<sub>3</sub>. *Carcinogenesis* 5: 1155, 1984. [[Abstract/Free Full Text](#)]
54. Wood AW, Chang RL, Huang M-T, *et al.*: Stimulatory effect of 1,25-dihydroxyvitamin D<sub>3</sub> on the formation of skin tumors in mice treated chronically with 7,12-dimethylbenz[a]anthracene. *Biochem Biophys Res Comm* 130: 924, 1985. [[Medline](#)]
55. Sitrin M, Halline A, Brasitus T: Effect of dietary calcium and vitamin D on colonocyte proliferation and dimethylhydrazine-induced colon cancer in rats. *Gastroenterology* 98: A311, 1990.
56. Garland F, Garland CF, Gorham ED, Young JF: Geographic variation in breast cancer mortality in the United States: a hypothesis involving solar radiation. *Prev Med* 19: 614–622, 1990. [[Medline](#)]
57. Gorham ED, Garland CF, Garland F: Acid haze air pollution and breast and colon cancer mortality in 20 Canadian cities. *Can J Public Health* 80: 96–100, 1989. [[Medline](#)]
58. Gorham ED, Garland F, Garland C: Sunlight and breast cancer incidence in the USSR. *Int J Epidemiol* 19: 820–824, 1990. [[Abstract/Free Full Text](#)]
59. Ingram DM: Trends in diet and breast cancer mortality in England and Wales 1908–1977. *Nutr Cancer* 3: 79–80, 1981.
60. Buell P: Changing incidence of breast cancer in Japanese-American women. *J Natl Cancer Inst* 51: 1479–1483, 1973.
61. Miller AB: Role of nutrition in the etiology of breast cancer. *Cancer* 39: 2704–2708, 1977. [[Medline](#)]
62. Miller AB, Kelly A, Choi NW, Matthews V, Morgan RW, Munan L, Burch JD, Feather I, Howe GR, Jain M: A study of diet and breast cancer. *Am J Epidemiol* 107: 499–509, 1978. [[Abstract/Free Full Text](#)]
63. Katsouyanni K, Trichopoulos D, Boyle P, Xirouchaki E, Trichopoulou A, Lisseos B, Vasilaros S, MacMahon B: Diet and breast cancer: a case-control study in Greece. *Int J Cancer* 38: 815–820, 1986. [[Medline](#)]
64. Lubin F, Wax Y, Modan B: Role of fat, animal protein, and dietary fiber in breast cancer etiology: a case-control study. *J Natl Cancer Inst* 77: 605–612, 1986.
65. Wynder EI, Rose DP, Cohen LA: Diet and breast cancer in causation and therapy. *Cancer* 58(Supp): 1804–1813, 1986. [[Medline](#)]
66. Hirohata T, Nomura AMY, Hankin JH, Kolonel LN, Lee J: An epidemiologic study on the association between diet and breast cancer. *J Natl Cancer Inst* 78: 595–600, 1987.
67. Jones DY, Schatzkin A, Green SB, Block C, Brinton LA, Ziegler RG, Hoover R, Taylor PR: Dietary fat and breast cancer in the National Health and Nutrition Examination Study I Followup Study. *J Natl Cancer Inst* 79: 465–471, 1987.
68. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE: Dietary fat and the risk of breast cancer. *N Engl J Med* 316: 22–28, 1987. [[Abstract](#)]
69. Rogers AE, Lee SY: Chemically-induced mammary gland tumors in rats: modulation by dietary fat. *Prog Clin Biol Res* 222: 255–282, 1986. [[Medline](#)]
70. Carroll KK, Hopkins GJ: Dietary polyunsaturated fat versus saturated fat in relation to mammary carcinogenesis. *Lipids* 14: 155–158, 1979. [[Medline](#)]
71. Ip C, Carter CA, Ip MM: Requirement of essential fatty acid for mammary tumorigenesis in the rat. *Cancer Res* 45: 1997–2001, 1985. [[Abstract/Free Full Text](#)]
72. Ip C: Fat and essential fatty acid in mammary carcinogenesis. *Am J Clin Nutr* 45 (Supp): 218–224, 1987. [[Free Full Text](#)]
73. Bull AW, Soulier BK, Wilson PS, Hayden MT, Nigro MD: Promotion of azoxymethane-induced intestinal cancer by high-fat diet in rats. *Cancer Res* 39: 4956–4959, 1979. [[Abstract/Free Full Text](#)]
74. Newmark HL, Wargovich MJ, Bruce WR: Colon cancer and dietary fat, phosphate, and calcium: A hypothesis. *J Natl Cancer Inst* 72: 1324–1325, 1984.

75. Lipkin M, Newmark HL: Calcium and the prevention of colon cancer. In *Cancer Chemopreventive Agents; Drug Development Status and Future Prospects*. J Cellular Biochem 22 (Supp): 65–73, 1995.
76. Jacobson EA, James KA, Newmark HL, Carroll KK: Effects of dietary fat, calcium, and vitamin D on growth and mammary tumorigenesis induced by 7,12-dimethylbenz(a)anthracene in female Sprague-Dawley rats. *Cancer Res* 49: 6300–6303, 1989. [[Abstract/Free Full Text](#)]
77. Carroll KK, Eckel LA, Fraher LJ, Frei JV, Newmark HL: Dietary calcium, phosphate and vitamin D in relation to mammary carcinogenesis. In "Calcium, Vitamin D, and Prevention of Colon Cancer." Lipkin M, Newmark HL, Kelloff G (eds) Boca Raton, FL: CRC Press, pp 229–239, 1991.
78. Newmark HL: Calcium in cellular function. *Triangle* 28(Suppl 1): 9–13, 1989.
79. DeLuca HF: The vitamin D story: a collaborative effort of basic science and clinical medicine. *FASEB J* 2: 224–236, 1988. [[Abstract](#)]
80. Koga M, Eisman JA, Sutherland RL: Regulation of epidermal growth factor receptor levels by 1,25 dihydroxy vitamin D<sub>3</sub> in human breast cancer cells. *Cancer Res* 48: 2734–2739, 1988. [[Abstract/Free Full Text](#)]
81. Frappart L, Falette N, Lefebvre MF, Bremond A, Vauzelle JL, Saez S: In vitro study of effects of 1,25 dihydroxy vitamin D<sub>3</sub> on the morphology of human breast cancer cell line BT.20. *Differentiation* 40: 63–69, 1989. [[Medline](#)]
82. Colston KW, Berger U, Coombes RC: Possible role for vitamin D in controlling breast cancer cell proliferation. *Lancet* 188–191, 1989.
83. Colston KW, Chander SK, MacKay AG, Coombes RC: Effects of synthetic vitamin D analogues on breast cancer cell proliferation in vivo and in vitro. *Biochem Pharmacol* 44: 693–702, 1992. [[Medline](#)]

## This article has been cited by other articles:



### ARCHIVES OF INTERNAL MEDICINE

[▶ HOME](#)

J. Lin, J. E. Manson, I-M. Lee, N. R. Cook, J. E. Buring, and S. M. Zhang  
**Intakes of Calcium and Vitamin D and Breast Cancer Risk in Women**  
*Arch Intern Med*, May 28, 2007; 167(10): 1050 - 1059.

[[Abstract](#)] [[Full Text](#)] [[PDF](#)]



### Carcinogenesis

[▶ HOME](#)

E. A. Hussain-Hakimjee, X. Peng, R. R. Mehta, and R. G. Mehta  
**Growth inhibition of carcinogen-transformed MCF-12F breast epithelial cells and hormone-sensitive BT-474 breast cancer cells by 1{alpha}-hydroxyvitamin D5**  
*Carcinogenesis*, March 1, 2006; 27(3): 551 - 559.

[[Abstract](#)] [[Full Text](#)] [[PDF](#)]



### American Journal of PUBLIC HEALTH

[▶ HOME](#)

C. F. Garland, F. C. Garland, E. D. Gorham, M. Lipkin, H. Newmark, S. B. Mohr, and M. F. Holick  
**The Role of Vitamin D in Cancer Prevention**

*Am J Public Health*, February 1, 2006; 96(2): 252 - 261.

[[Abstract](#)] [[Full Text](#)] [[PDF](#)]



JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION

▶ HOME

P. W. Parodi

**Dairy Product Consumption and the Risk of Breast Cancer**

J. Am. Coll. Nutr., December 1, 2005; 24(suppl\_6): 556S - 568S.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)



The American Journal of CLINICAL NUTRITION

▶ HOME

P. G Moorman and P. D Terry

**Consumption of dairy products and the risk of breast cancer: a review of the literature**

Am. J. Clinical Nutrition, July 1, 2004; 80(1): 5 - 14.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)



JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION

▶ HOME

M. L. Storey, R. A. Forshee, and P. A. Anderson

**Associations of Adequate Intake of Calcium with Diet, Beverage Consumption, and Demographic Characteristics among Children and Adolescents**

J. Am. Coll. Nutr., February 1, 2004; 23(1): 18 - 33.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)



Journal of Nutrition

▶ HOME

H. A. Norman, R. R. Butrum, E. Feldman, D. Heber, D. Nixon, M. F. Picciano, R. Rivlin, A. Simopoulos, M. J. Wargovich, E. K. Weisburger, *et al.*

**The Role of Dietary Supplements during Cancer Therapy**

J. Nutr., November 1, 2003; 133(11): 3794S - 3799.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)



JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION

▶ HOME

T. A. Nicklas

**Calcium Intake Trends and Health Consequences from Childhood through Adulthood**

J. Am. Coll. Nutr., October 1, 2003; 22(5): 340 - 356.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)



Cancer Epidemiology Biomarkers & Prevention

▶ HOME

P. A. Newcomb, H. Kim, A. Trentham-Dietz, F. Farin, D. Hunter, and K. M. Egan

**Vitamin D Receptor Polymorphism and Breast Cancer Risk**

Cancer Epidemiol. Biomarkers Prev., November 1, 2002; 11(11): 1503 - 1504.

[\[Full Text\]](#) [\[PDF\]](#)



JOURNAL OF THE NATIONAL CANCER INSTITUTE

▶ HOME

M.-H. Shin, M. D. Holmes, S. E. Hankinson, K. Wu, G. A. Colditz, and W. C. Willett

**Intake of Dairy Products, Calcium, and Vitamin D and Risk of Breast Cancer**

J Natl Cancer Inst, September 4, 2002; 94(17): 1301 - 1310.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)



G. D. Miller and J. J.B. Anderson

## The Role of Calcium In Prevention of Chronic Diseases

J. Am. Coll. Nutr., October 1, 1999; 18(90005): 371S - 372.

[\[Full Text\]](#) [\[PDF\]](#)

### *This Article*

▶ [Abstract](#) **FREE**

▶ [Full Text \(PDF\)](#)

### *Services*

▶ [Similar articles in this journal](#)

▶ [Similar articles in PubMed](#)

▶ [Alert me to new issues of the journal](#)

▶ [Download to citation manager](#)

▶ [© Get Permissions](#)

### *Citing Articles*

▶ [Citing Articles via HighWire](#)

▶ [Citing Articles via Google Scholar](#)

### *Google Scholar*

▶ [Articles by Lipkin, M.](#)

▶ [Articles by Newmark, H. L.](#)

▶ [Search for Related Content](#)

### *PubMed*

▶ [PubMed Citation](#)

▶ [Articles by Lipkin, M.](#)

▶ [Articles by Newmark, H. L.](#)