EXHIBIT 1

Based on my review of the reliable and credible publicly available published peer-reviewed scientific literature regarding calcium nutrition, metabolism, and physiology, their interactions with colorectal carcinogenesis, mammary gland carcinogenesis and prostate carcinogenesis, I conclude that there is significant scientific agreement in support of the following health claims:

- Calcium may reduce the risk of colorectal cancer.
- Calcium may reduce the risk of colon cancer.
- Calcium may reduce the risk of rectal cancer.
- Calcium may reduce the risk of breast cancer.
- Calcium may reduce the risk of prostate cancer.
- Calcium may have anticarcinogenic effects in the colon, breast, and prostate.
- Calcium may reduce the risk of recurrent colon polyps.

Calcium

I. Intestinal Calcium Absorption and Retention of Ingested Calcium

A. Mechanisms of Calcium Absorption

Calcium in foods occurs as salts or in association with other dietary constituents in the form of complexes of calcium ions. Calcium must be released in a soluble, and probably ionized, form before it can be absorbed (i.e., transferred from the intestinal lumen to the circulatory system). Once in a soluble form, calcium is absorbed by two routes, transcellular and paracellular transport.[1]

The saturable, transcellular pathway is a multi-step process, involving the entry of luminal calcium ions across the microvillar membrane into the enterocyte, then movement through the cytosol (i.e., translocation to the basolateral membrane), followed by active extrusion from the enterocyte into the lamina propria and diffusion into the general circulation. The entry of calcium ions across the apical membrane of the enterocyte is favored electrochemically because the concentration of calcium ions within the cell (10^{-7} to 10^{-6} M) is considerably lower than that in the intestinal lumen (10^{-3} M), and the cell is electronegative relative to the intestinal lumen.[1] Therefore, the movement of calcium ions across the apical membrane does not require the expenditure of energy. However, because lipid membranes are impermeable to calcium ions, apical entry must involve the participation of a calcium ion channel or integral membrane transporter residing within the brush border membrane. Evidence suggests that the calcium transport protein, CaT1, may be the putative calcium ion transporter.[2,3]

The intracellular diffusion of calcium ions is thought to be facilitated by a cytosolic calcium-binding protein, calbindin D_{9K}, whose biosynthesis is dependent on the presence of vitamin D (in the form of 1,25-dihydroxycholecalciferol). Calbindin D_{9K} facilitates the diffusion of calcium ions across the cell by acting as an intracellular calcium ferry or chaperone. The active extrusion of calcium ions at the basolateral membrane takes place against an electrochemical gradient and is mediated primarily by a calcium-dependent ATPase. While each step in the transcellular movement of calcium ions has a vitamin D-dependent component, the intracellular concentration of active calbindin D_{9K} is believed to be rate-limiting in 1,25-dihydroxycholecalciferol-induced transcellular calcium transport.[1]

The paracellular route of calcium absorption involves passive calcium transport through the tight junctions between mucosal cells. Because it does not require a transporter and is driven by the large luminal:serosal calcium concentration gradient, this transport pathway is non-saturable and appears to be independent of nutritional or physiologic regulation (although some limited evidence suggests that it also may respond to 1,25-dihydroxycholecalciferol in an as yet unknown manner).[1,4]

Most calcium absorption in humans occurs in the lower small intestine, but there is some evidence for a colonic component that may increase total calcium absorption by as much as 10%.[5] However, the large intestine may represent a site of increased importance for calcium absorption when acidic fermentation takes place. Slightly acidic intracolonic pH increases the efficiency of colonic absorption of calcium.[6] For example, prebiotics acidify slightly the intracolonic pH (secondary to increased production of short-chain fatty acids as byproducts of increased fermentation) and have been shown to increase the fractional true absorption of ingested calcium in human adolescents, young adults and postmenopausal women.[6]

When dietary calcium is abundant, the paracellular pathway appears to be dominant.[7] When dietary calcium is limited, the active 1,25-dihydroxycholecalciferol-dependent transcellular pathway increases in importance.[7] Transmembrane calcium receptors (especially in renal tissues) mediate the conversion of 25-hydroxycholecalciferol to biologically-active 1,25-dihydroxycholecalciferol through regulation of the expression of 25-hydroxycholecalciferol-1α-hydroxylase and thereby indirectly regulate hormone-mediated up-regulation and down-regulation of calbindin D_{9K} activity in mucosal cells.[1] The beginning of a decline in plasma calcium ion concentration evokes an increase in serum 1,25-dihydroxycholecalciferol concentration, which in turn stimulates increased calbindin D_{9K} biosynthesis in the intestinal mucosa.[1]

B. Efficiency of Calcium Absorption

The efficiency of absorption of ingested calcium is inversely proportional to chronic calcium intake. However, this adaptive decrease in the fraction of ingested calcium that does not appear in the feces as calcium intake decreases is not sufficient to offset the

decrease in the amount of calcium that is absorbed as a result of a decrease in calcium intake.[8,9] Regardless of the efficiency of absorption, the amount of calcium that is absorbed is directly proportional to the amount ingested.[8,9] For example, despite the significantly greater efficiency of absorption when human calcium intake is less than 500 mg/day, the total amount of calcium absorbed from such a low-calcium diet is less than half the amount that is absorbed (even with significantly lower efficiency) from a diet providing 1000 mg/day.[10,11]

The efficiency of calcium absorption varies throughout the life cycle. It is greatest in infancy, when about 60% of consumed calcium is absorbed,[12] decreases during childhood, and increases again early in adolescence, when about 25% of consumed calcium is absorbed.[13] The efficiency of calcium absorption remains at about this level into middle adulthood.[13] As adults age beyond middle adulthood, the efficiency of calcium absorption declines gradually. For example, in postmenopausal women and older men, the efficiency of calcium absorption has been reported to decrease by an average of about 0.2 percentage points annually.[13,14]

Decreased production of estrogen results in decreased efficiency of calcium absorption in women at any age.[8,13] For example, the apparent absorption of dietary calcium by premenopausal and perimenopausal women ranges between 17% and 58% and decreases slightly with increasing calcium intake.[15] However, women over 65 years old respond to low calcium intakes with significantly smaller increases in fractional calcium absorption than occur in women 20 to 35 years old consuming the same inadequate amount of calcium.[16] Similarly, amenorrheic young women with hypoestrogenic anorexia nervosa have significantly less efficient calcium absorption than is enjoyed by healthy eumenorrheic young women.[17]

Racial differences affect the efficiency of calcium absorption. For example, African American girls exhibit significantly more efficient calcium absorption after menarche than do Caucasian girls.[18] Interestingly, African American adults later exhibit significantly lower rates of bone fractures than do Caucasian adults.[19,20]

C. Calcium Retention

The retention of ingested calcium within the body reflects the interplay among the amount of calcium consumed, the efficiency of calcium absorption, and urinary excretion of calcium. For example, when a group of healthy adult women reduced their calcium intake from 2000 mg/day to 300 mg/day, although their efficiency of calcium absorption increased significantly, their urinary excretion of calcium decreased significantly, and their efficiency of whole body retention of ingested calcium increased significantly (from 27% to 37%), the overall net result was a significant decrease in the net amount of calcium retained (from 540 mg/day to 111 mg/day).[21]

Amenorrheic young women with anorexia nervosa have significantly greater urinary excretion of calcium than healthy eumenorrheic women; coupled with the reduced absorption efficiency also exhibited by such women, these greater losses produce significantly reduced net calcium retention (evidenced by significantly reduced bone mass).[17] Similarly, in contrast to the generally beneficial effects of moderate exercise on calcium metabolism and skeletal physiology, exercise-induced amenorrhea also produces significantly decreased net calcium retention (and lower bone mass).[22,23]

Vegetarian diets produce metabolizable anions (such as acetate and bicarbonate) that may increase renal resorption of filtered calcium, decreasing urinary calcium excretion.[24,25] Consequently, vegetarians may be more efficient retainers of dietary calcium.

Racial differences may affect the efficiency of calcium resorption in the kidneys. For example, African American children aged 9 to 18 years have exhibited significantly less urinary excretion of calcium than similarly-aged Caucasian children.[26] In contrast, it was reported that less calcium was excreted in the urine of African American girls before menarche but that urinary calcium excretion was similar in African American and Caucasian girls after menarche.[18]

Data from 181 balance studies subjected to nonlinear regression analysis indicate that maximal calcium retention occurs in men and women when dietary calcium intake is 1200 mg/day.[27-29] Nonetheless, this level of intake may be inadequate for many individuals. For example, a daily intake of 1300 mg of calcium was insufficient to maximize calcium retention in all members of a group of adolescent females.[28]

II. Colorectal Cancer

Colorectal cancer is the third most common life-threatening cancer in the US and accounts for about 10% of total cancer incidence and total cancer deaths in the US and for about 2.5% of all deaths among adults in the US.[30-33] The incidence of colorectal cancer in the US is about 60 cases per 100,000 adults, with about 148,000 new diagnoses and about 57,000 deaths in the US in 2002.[31] Colorectal cancer occurs with nearly equal frequency in men and women.[31] Five-year survival following diagnosis is between 10% and 90%, depending on the stage of disease at first diagnosis.[31]

A. Maintenance of the Normal Colorectal Epithelium

The intestinal epithelium is in a constant state of renewal with a continuous high rate of cell proliferation, differentiation and apoptotic cell death.[34-36] Colonocytes turnover rapidly, with an average lifespan of only 2 to 3 days.[37,38] Undifferentiated precursor cells are produced from stem cell populations in the lower 40% to 60% of the crypts of the colonic mucosal villi and quickly begin to migrate toward the villar luminal epithelial surface where they reside briefly, die and are shed directly into the lumen.[35,36] During

migration along the crypt axis toward the luminal surface undifferentiated precursor cells lose their proliferative capability and differentiate into either enteroendocrine or mucus-secreting goblet cells, which tend to remain in the lower portion of the crypt, or absorptive cells, which move to the luminal surface.[39] Following 36 to 48 hours of mature differentiated function, senescent absorptive cells extrude into the lumen and die in a regulated manner by apoptosis.[34]

Short-lived mammalian cells such as colonocytes are capable of maintaining healthy populations of fully functional cells through a combination of continuous production of new replacement cells and initiation of the death of mature cells (programmed cell death) in response to signal transduction through specific receptors.[40] Condensation of the nuclear chromatin and mitochondria, blebbing of the cell membrane, characteristic swelling of the endoplasmic reticulum and fragmentation of the cells into membrane-bound apoptotic bodies are signs of total cell destruction.[41,42] The most important characteristic of this self-destruction is that apoptotic cells themselves actively provide the molecules necessary for the apoptotic mechanism to proceed.[43] In most cases, the apoptotic mechanism is diminished or delayed if an inadequate amount of extracellular calcium ion (Ca^{2+}) is present, implying that prolonged intracellular influx of Ca^{2+} is a basic requirement for programmed cell death.[44,45] It has been shown that the process of programmed cell death is critically dependent upon the ability of the cell to achieve and sustain a prolonged significant elevation in its intracellular free Ca^{2+} concentration.[46,47] Similarly, the ability of agents to inhibit the proliferation of human HCT-15 colon cancer cells is proportional to their ability to produce sustained increase in intracellular free Ca^{2+} concentration.[48]

The first step in apoptotic change is the opening of the permeability transition pores in the inner mitochondrial membrane.[49] The onset of the mitochondrial permeability transition (MPT; depolarization of the mitochondrial membrane) is the key event in apoptotic cell death.[50,51] Opening of the pores results in electrolyte movement and depolarization of the inner mitochondrial membrane, entry of water into the mitochondrial matrix, swelling of the matrix, and deformation of cristae.[50,52] Contortional change in cristae damages the outer mitochondrial membrane, resulting in the release of pro-apoptotic intermembrane proteins (including cytochrome c, procaspases and apoptosis-inducing factor (AIF)) into the cytosol.[50,52] AIF activates a nuclease which hydrolyzes nuclear DNA while cytochrome c activates caspase 9 which activates caspase 3 which performs pro-apoptotic proteolysis of intracellular proteins.[50,52]

B. Conversion of the Normal Colorectal Epithelium into a Neoplastic Epithelium

In a general model, cancer progresses through 4 stages: initiation (conversion of a normal cell to a cancer cell), promotion (the induction of cellular replication and shortening of the latency period, reducing the length of the cell cycle and accelerating proliferation), clonal expansion (unrestrained proliferation resulting in tumor formation)

and progression (the accumulation of defects in growth control and differentiation that produce metastasis).[53,54] Colorectal carcinogenesis is an even more complex, multistep process involving initiation, promotion, expansion and progression stages that are not necessarily discrete or well-defined events.[55,56]

During the initiation stage of colorectal cancer, carcinogen-triggered mutations accumulate in protooncogenes (such as c-*myc* and K-*ras*) and in tumor-suppressor genes (such as the MCC gene, the DCC cell adhesion protein gene and the p53 tumor suppressor gene).[56-58] In addition, hypomethylation of DNA is typical of neoplastic human colorectal cells[59,60] and contributes to overexpression of the c-*myc* protooncogene in the colon,[56] increases the incidence of K-*ras*, p53 and DCC mutations[56] and accelerates the progression of early polyps to more advanced adenomas.[61]

All of these mutations may contribute in varying degrees to the development of colorectal neoplasia. For example, increased expression of c-*myc* proteins is associated with increased intracellular DNA synthesis.[62] In human colon epithelium, the rate of cell proliferation is proportional to the extent of c-*myc* expression.[63] Conversely, in human colon carcinoma cells, the degree of cellular differentiation is inversely proportional to the extent of c-*myc* expression.[64] Therefore, increased expression of c-*myc* proteins may predispose the colorectal mucosa to preneoplastic hyperproliferation.

Mutations in the adenomatous polyposis coli (APC) gene (such as occur in individuals with familial adenomatous polyposis) increase the risk for colon cancer.[65-69] Mutations in this gene may be the initiating events in the development of most or all colorectal neoplasia.[70-72] It is estimated that 85% of colorectal cancers are associated with mutations in the APC gene that promote unrestrained hyperproliferation of the colorectal epithelium in response to a proliferation-inducing stimulus.[70,72]

In the normal colorectal mucosa, exposure to carcinogenic compounds is irritating and produces damage to the epithelium. In response, a temporary hyperproliferative phase, with increase in volume ("expansion") of the proliferative compartment of the colorectal mucosal crypt, restores damaged luminal epithelium in a compensatory healing process.[73-78] When cells carrying a mutation in the APC gene are stimulated to respond to a proliferation-inducing stimulus, unrestrained hyperproliferation produces preneoplastic structures of dysplastic tissue (aberrant crypt foci).[79] Aberrant crypt foci (ACF) are preneoplastic lesions predictive of increased risk for colon cancer.[80-89]

Carcinogenic receptor activation also can contribute to the initiation or promotion of colorectal cancer. For example, colorectal carcinoma cells express the $P2Y_2$ subtype of the P2Y receptor.[90,91] Activation of $P2Y_2$ receptors stimulates phospholipase C-catalyzed ATP-dependent production of inositol 1,4,5-triphosphate (IP_3) and diacylglycerols (DAG) from cellular membrane phosphatidylinositol 4,5-biphosphate.[92] In contrast to the pro-apoptotic sustained increase in intracellular free Ca^{2+}

concentration,[44-48] IP_3 stimulates rapid transient transmembrane calcium ion flux from intracellular stores into the cytoplasm,[93,94] a mildly proliferation-inducing response,[95,96] while DAG stimulates slower and prolonged activation of protein kinase C (PKC), with subsequent increase in cytoplasmic cAMP concentration.[94]

PKC stimulates tumor promotion and cell growth, as well as events related to tumor progression, such as invasion, metastasis and tumor cell adhesion to endothelium and extracellular matrix components.[97-100] Acting via cAMP, PKC induces the activation of transcriptional factors, such as activator protein-1 (AP-1) and nuclear factor-κB (NF-κB), and increases the expression of key enzymes, such as ornithine decarboxylase (ODC), inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2).[101-103]

The conversion of ornithine to putresine by ODC is the rate-limiting step in the polyamine biosynthetic pathway.[104] Increased biosynthesis of polyamines is required for increased cellular proliferation,[104,105] while depletion of intracellular polyamines slows proliferation.[106,107] Adenomas and carcinomas of the colon exhibit increased ODC activity.[108-110] In vitro, increasing the calcium ion concentration of the growth medium resulted in decreased ODC activity in mouse colon cancer cells.[111] In animal models, inhibition of ODC activity produces significantly reduced incidence of chemically-induced colorectal tumors.[112]

Activation of PKC also inhibits apoptosis.[113,114] Conversely, inhibition of PKC induces apoptosis via the generation of ceramide and activation of sphingomyelinase.[115,116] Ceramide stimulates the initiation of the mitochondrial permeability transition[116] which results in release of cytochrome c into the cytosol, where it induces the activation of caspase-3, a key protease involved in inducing apoptotic events.[117-119]

Human colon adenocarcinoma-derived Caco-2 colon cancer cells have responded to low medium Ca^{2+} concentration with activation of the PKC signaling pathway, resulting in upregulation of c-*myc* expression and progression of cells out of the S (stationary) phase and into the DNA synthetic phase.[120] In contrast, high medium Ca^{2+} concentration activated the Ca^{2+}–sensing receptor (CaSR) and produced deactivation of the PKC signaling pathway, resulting in downregulation of c-*myc* expression and return of cells to the S phase.[120,121] In contrast, PKS deactivates CaSR, preventing antiproliferative increases in intracellular Ca^{2+} concentrations.[122]

DAG normally are found in the human colonic contents and feces in a wide range of concentrations.[123] Luminal DAG can be taken up by the colonic mucosa[124] and have been postulated to stimulate colonic cellular proliferation;[125] DAG stimulates cellular proliferation in cultured human colon adenoma cells and colon carconima cells[125] and in the rat colon *in vivo*[126] and bacterial production of DAG in the human colon lumen stimulates colonocyte PKC activation and cellular proliferation.[123,124,127] In humans,

dietary calcium supplementation significantly decreased fecal DAG content,[128] significantly increased the conversion of fecal DAG to monoglyceride and fatty acids[128] and significantly decreased the rate of proliferation of the rectal mucosal epithelium.[129] However, these results were not confirmed in another study.[130]

Colorectal carcinogenesis may be most sensitive to calcium ions during the initiation and promotion stages. Noncancerous and cancerous human colon cells express a 25-hydroxycholecalciferol receptor as well as 25-hydroxycholecalciferol-1α-hydroxylase, enabling them to take up 25-hydroxycholecalciferol and convert it to 1,25-dihydroxycholecalciferol.[131-133] It has been suggested that supplemental dietary calcium supports circulating calcium homeostasis and may slow the rate of renal conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol, resulting in a higher serum 25-hydroxycholecalciferol concentration and thereby supplying the colonic mucosa with larger amounts of 25-hydroxycholecalciferol for intracolonocyte conversion to 1,25-dihydroxycholecalciferol.[134-137] In the presence of 1,25-dihydroxycholecalciferol, intracellular calcium ion concentration is significantly greater in luminal colon mucosal epithelial cells than it is in basal crypt cells.[135] In cell culture, the rate of cellular differentiation in cultures of noncancerous human colon cells was directly correlated with the concentration of 1,25-dihydroxycholecalciferol in the culture medium.[121,138-142] By inducing calcium ion-dependent cellular differentiation in migrating colonocytes, increased colonic conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol could inhibit abnormal colorectal cell development.[134,135,137]

Human colon cancer cells also express a high-affinity 1,25-dihydroxycholecalciferol receptor[138] and the rate of human colon cancer cell proliferation has been shown to be inversely proportional to the concentration of 1,25-dihydroxycholecalciferol in the culture medium.[138] Conversely, the rate of cellular differentiation in cultures of human noncancerous colon cells and of human colon carcinoma cells was directly correlated with the concentration of 1,25-dihydroxycholecalciferol in the culture medium.[121,138-142] On an animal model of metastatic colorectal carcinoma, injections of 1,25-dihydroxycholecalciferol significantly inhibited the growth of human colon cancer xenografts in immunosuppressed mice.[143]

However, the number of 1,25-dihydroxycholecalciferol receptors per cell in the colon epithelium decreases following the malignant transformation of colon cells.[144-148] Loss of 1,25-dihydroxycholecalciferol receptors may explain colon cancer cell escape from the chemopreventive actions of calcium ions.[149] For example, human colonic epithelial cells harvested from biopsy samples of normal-appearing colon mucosa obtained from patients with a history of previous neoplasm or of familial polyposis or with symptomatic familial polyposis responded to the same medium calcium ion concentration that terminates culture growth and induces terminal differentiation of noncancerous human colon epithelial cells in culture[150] with significantly decreased rates of cell proliferation.[151] In contrast, the rate of cell proliferation was not affected by medium calcium ion concentration in cell cultures of human colonic epithelial cells harvested from biopsy

samples of either adenomas or carcinomas.[151] Similarly, in three human colon carcinoma and two human colon adenoma cell lines, increasing medium Ca^{2+} concentration significantly suppressed the proliferation of well-differentiated cells but had no effect on poorly-differentiated cells.[151] In addition, noncancerous colonocytes harvested from patients with colon cancer responded to increasing medium Ca^{2+} concentrations with significantly decreased rates of cell proliferation while medium Ca^{2+} concentration had no effect on the rate of proliferation of cancerous colonocytes harvested from the same patients.[152] In cell culture, high intracellular Ca^{2+} concentrations suppress expression of the c-*myc* protooncogene in noncancerous colonocytes, while low intracellular Ca^{2+} concentrations stimulate expression of the c-*myc* protooncogene and hyperproliferation of colon cells.[153] The suppression of proliferation of human colon cancer cells requires 1,25-dihydroxycholecalciferol-dependent Ca^{2+} influx following receptor-ligand binding.[138]

These observations suggest that as colon cells progress from normal to adenomatous to carcinomatous cells, the importance of continuation of the initiating stimuli becomes negligible, as does the impact of calcium ions; adenomatous and carcinomatous colorectal cells lose "responsiveness" to the effects of calcium ions.[150,151,154] The antitumorigenic effects of calcium supplementation may not be universal and may affect only the prevention or early transformation and not the growth of existing tumors.[151,155] Therefore, dietary supplementation with calcium is most likely to be beneficial in the prevention of colon cancer if it occurs before hyperproliferation progresses to neoplasia.[150] Consequently, supplemental calcium may be ineffective in chemoprevention in individuals in whom carcinogenesis may have commenced, potentially confounding the results of studies that may fail to observe a chemopreventive effect of dietary supplementation with calcium.

Colorectal neoplasms also can arise from another distinct genetic pathway in which the frequent loss of expression of one of the DNA mismatch repair enzymes, usually hMLH1 or hMSH2, results in microsatellite instability[156,157] and produces predisposition to colorectal adenoma and carcinoma.[158] For example, hereditary nonpolyposis colorectal cancer is characterized by defective DNA mismatch repair enzymes.[157-161]

The progression from aberrant crypt foci to adenomatous polyp (adenoma) to carcinoma requires the ability of the abnormal tissue to remain undifferentiated, loosely associated and proliferative. The more tightly associated the new tissue becomes, the less undifferentiated and proliferative it becomes.[162,163] Tight association between colorectal epithelial cells requires interaction between calcium ions and cell surface receptors (calcium-sensing receptors; CaSR).[164] CaSR in human colonocytes are G protein-coupled receptors that transduce extracellular Ca^{2+} ion binding into intracellular responses.[165-169] Ligand-receptor binding of Ca^{2+} to CaSR promotes expression of E-cadherin,[164] a calcium-dependent cell adhesion molecule (one E-cadherin molecule binds to another in the extracellular space, linking cells at specialized intercellular "tight"

junctions).[154,170] By its nature, E-cadherin is antitumorigenic (in part) by stimulating cell adhesion-dependent cellular differentiation.[162,163] Most CaSR-containing cells are non-replicating and are found in the crypt epithelium of normal human colorectal mucosa and in the more differentiated non-replicating crypt cells in human colorectal adenocarcinomas.[165,167] Activation of CaSR inhibits the proliferation of cultured human colon cancer cells.[165] These observations suggest that calcium ions, via CaSR and E-cadherin, may inhibit the proliferation of colonic epithelial cells by inducing their terminal differentiation.[171-174]

Interestingly, a single nucleotide polymorphism (substitution) in the gene for the calcium-sensing receptor increases the survival of patients with rectal cancer by increasing CaSR activity.[175] In contrast, methylation of the promoter sequence of the E-cadherin gene results in reduced synthesis of E-cadherin,[176-178] a situation that is commonly found in human colon carcinomas.[179] Promoter sequence methylation may predict the future development of colorectal carcinoma; for example, in the human colon affected by ulcerative colitis, areas of dysplastic colon mucosa exhibit significantly greater methylation of the promoter sequence of the E-cadherin gene, with significantly less synthesis of E-cadherin, than do areas of nondysplastic colon mucosa.[180]

Although the adenoma-to-carcinoma sequence results primarily from a series of mutations affecting cell growth, differentiation and programmed cell death,[181-185] methylation disorders also contribute to the malignant transformation of adenomatous polyps.[186] Hypomethylation of DNA is associated with significantly increased expression of the intracellular cytoplasmic calcium-binding protein S100A4 (also known as p9Ka, CAPL and calvasculin).[187] Increased expression of S100A4 (as well as of the S100A6 "calcyclin,"[188] S100A8 and S100A9 (separately or as the "calprotectin" heterocomplex[189]) intracellular cytoplasmic calcium-binding proteins) is associated with significantly decreased intracellular calcium ion concentration and significantly increased cell motility and progression of nonmalignant colon adenoma cells to malignant colorectal carcinoma cells.[190-195] In human colon cancer tissue samples, the presence of the S100A4 protein was associated with a significantly decreased survival time for patients with colorectal cancer post-colonectomy.[196]

C. Dietary Fatty Acids, Fecal Excretion of Soluble Bile Acids and Colorectal Cancer

A high-fat diet has been recognized for some time as a major risk factor for colorectal cancer.[197,198] Excessive amounts of dietary fatty acids may promote colorectal cancer by increasing the amounts of long-chain fatty acids and bile acids present within the lumen of the colon.[198] Long-chain fatty acids and bile acids irritate and damage the epithelial cells of the colon and reduce the integrity of the mucosal barrier.[198,199] As a result of this cellular destruction, a compensatory ("healing") increase in the rate of cellular proliferation ("restitution"[137]) occurs.[77,78,198,200,201] Cholic acid,[200-204] deoxycholic

acid,[77,202-207] lithocholic acid,[208,209] linoleic acid[78,210,211] and oleic acid[77,78] have been shown to stimulate the proliferation of colonic epithelial cells. In addition to triggering local hyperproliferation, these fatty acids and bile acids increase the sensitivity of colonocytes to mutagens and carcinogens[212,213] and act as promoters of experimentally-induced colon carcinogenesis.[214,215] Rats perfused with deoxycholic acid have exhibited significantly increased rates of colon epithelial proliferation and colorectal cancer.[77,207]

D. Dietary Calcium and Fecal Excretion of Potentially Carcinogenic Soluble Bile Acids

Carcinogenic secondary bile acids are formed from primary bile acids in the colon by the action of microbial 7α-dehydroxylase.[216] This enzyme is most active when colon luminal pH is alkaline.[217,218] Consequently, an alkaline colon luminal pH promotes the development of colorectal cancer.[217,218] In a retrospective observational study of men with and without epithelial neoplasia of the colon, the feces from men with colon cancer were significantly more alkaline than were the feces from men without colon cancer.[219] Calcium gluconate and calcium lactate acidify colon pH,[220] inhibit the formation of secondary bile acids[217,218] and inhibit chemically-induced colon carcinogenesis in laboratory animals.[221-228]

In humans, calcium phosphate salts ($CaHPO_4$) buffer colonic protons and increasing calcium intake increases (alkalinizes) the pH of the colonic contents and the feces.[229,230] In a randomized placebo-controlled clinical trial, patients with previously-removed colorectal adenocarcinomas responded to 30 days of dietary supplementation with calcium (1200 mg/day) with significantly greater increases in fecal pH than those that accompanied placebo administration.[231] In healthy human men, compared to the consumption of calcium-deficient milk products, the consumption of calcium-replete milk products produced a significant increase in fecal pH and a significant decrease in the production of secondary bile acids.[232]

However, the chemoprotective effect of oral calcium salts cannot result solely from interactions with protons.[116] Calcium carbonate (which alkalinizes colon pH[233]) also inhibits chemically-induced colon carcinogenesis in laboratory animals.[224,225,234-247]

An alternative hypothesis is that dietary supplementation with calcium provides sufficient calcium ions to allow some to reach the colon where they reaggregate with phosphate ions and protons, forming calcium phosphate.[248] Human diets typically contain an excess of phosphate; therefore, only supplemental calcium is required in order to increase colonic calcium phosphate salt content.[249] Within the colon, calcium phosphate salts bind to noxious long-chain fatty acids and bile acids, forming insoluble soaps that are unavailable to act as substrates for microbial 7α-dehydroxylase and that are unable to diffuse through to the mucosal surface and exert procarcinogenic or carcinogenic effects on the colorectal mucosa.[74,75,77,78,249-258] Evidence obtained in experiments on

laboratory animals and from human clinical trials supports this hypothesis. For example, doubling (as calcium carbonate[259] or calcium lactate[260]), tripling (as calcium lactate[261]) or quadrupling (as calcium phosphate[251,262]) calcium intake has significantly decreased the fecal excretion of soluble bile acids and free long-chain fatty acids in rats, while increasing fatty acid intake has increased fecal excretion of calcium soaps in healthy humans.[263]

In humans, fecal excretion of soluble bile acids reflects colonic intraluminal soluble bile acid contents and increased fecal excretion of soluble bile acids is associated with increased risk for colorectal cancer.[264-270] In humans, dietary calcium supplementation has significantly reduced the proportion of secondary bile acids in the bile acid pool[198,254,271,272] and fecal soluble bile acid excretion.[198,231,252,254,271-274] In a randomized placebo-controlled cross-over clinical trial, 2 months of daily dietary supplementation with 1000 mg of elemental calcium (as calcium carbonate) significantly decreased the rate of conversion of primary bile acids to secondary bile acids.[275] In a randomized placebo-controlled clinical trial, daily dietary supplementation with 1500 mg of calcium for 9 months significantly reduced fecal excretion of free soluble bile acids.[271] In patients with adenomatous polyps of the colon, daily dietary supplementation with 1500 mg of calcium (as calcium carbonate) for 12 weeks significantly decreased the conversion of primary bile acids to secondary bile acids and significantly increased the fecal excretion of insoluble (mineral-chelated) bile acids.[256] Compared to pre-study, after 16 weeks of supplementation with either 2000 mg/day or 3000 mg/day of calcium, patients with a history of resected adenocarcinoma of the colon exhibited significant decreases in fecal excretion of soluble bile acids.[272] In a randomized placebo-controlled clinical trial, one week of daily dietary supplementation with 3 g calcium carbonate (providing 1200 mg of elemental calcium) produced significant increases in fecal excretion of insoluble bile acids and deoxycholic acid soaps in adult men 40 to 60 years old.[273]

The findings of a randomized placebo-controlled clinical trial of adult human subjects free of cancer are consistent with the hypothesis that dietary calcium supplementation decreases colorectal mucosal exposure to dietary irritants. In this study, fecal excretion of long-chain fatty acid soaps was significantly proportional to daily dietary elemental calcium intake ($r = 0.44$; $p = 0.03$).[276]

Not all available evidence is in agreement with the hypothesis that dietary calcium supplementation acts to decrease fecal excretion of soluble bile acids and increase fecal excretion of insoluble bile acids. The feces of patients with or without colon adenomas or carcinomas were not different in pH, calcium contents or bile acid composition in two studies.[277,278] In another group of healthy human volunteers, dietary calcium supplementation had no effect on fecal total bile acid content (although the relative proportions of soluble and insoluble bile acids were not reported).[257] In a randomized placebo-controlled clinical trial, patients with unremoved colorectal polyps whose diets were supplemented with calcium (1600 mg/day), vitamin C (150 mg/day), vitamin E (75

mg/day), β-carotene (15 mg/day) and selenium (101 mcg/day) for 3 years exhibited no effects of supplementation on fecal excretion of soluble bile acids.[279]

E. Dietary Calcium, the Cytotoxicity of Fecal Water and Colorectal Cancer

The extent of damage to the colorectal epithelium induced by long-chain fatty acids, bile acids, toxins or carcinogens is proportional to the cytolytic activity of fecal water.[251,280] In rats, oral calcium supplementation (equivalent to 4500 mg/day in humans) significantly decreased the cytolytic activity of fecal water.[251,262] When healthy men and women shifted from dairy product-rich to dairy product-free diets, they experienced a significant reduction in mean daily calcium intake (from 1488 mg/day to 372 mg/day) and a significant increase in the cytotoxicity and genotoxicity of fecal water.[232,281] In patients with adenomatous polyps of the colon, daily dietary supplementation with 1500 mg of calcium (as calcium carbonate) for 12 weeks significantly decreased the cytolytic activity of fecal water (by about 33%).[256] In other human studies, dietary calcium supplementation significantly reduced the cytotoxicity of fecal water.[198,254,271,272] However, in one study, healthy human volunteers consuming 1500 mg/day of calcium (as calcium triphosphate) for 1 week exhibited no significant changes in the cytolytic activity of fecal water.[248]

F. Dietary Calcium and Chemically-Induced Colorectal Cancer in Animal Models

Extensive research in animals has demonstrated the antineoplastic effect of calcium in the large bowel.[134,282] Dietary calcium deficiency (usually caused experimentally by artificially limiting the consumption of calcium to about half the typically-consumed amount) significantly accelerated the rate of colonic mucosal crypt cell proliferation in mice[283] and rats,[284] producing "hyperproliferation" of this tissue. Mucosal crypt cell hyperproliferation secondary to dietary calcium deficiency produces significant expansion of the proliferative compartment of the murine colon epithelium.[285]

Rodent colorectal tissue is sensitive to chemically-induced carcinogenesis. For example, injecting 1,2-dimethylhydrazine dihydrochloride (DMH) into rats and mice produces (compared to vehicle) significant increases in intracolonocyte ODC activity,[237,286] biosynthesis of polyamines in the colonic mucosa,[243] the rate of colorectal crypt cell proliferation,[213,236-238,240,286,287] colonocyte content of damaged DNA,[238] colonocyte content of K-*ras* mutations,[246] the formation of aberrant crypt foci,[213,238,240,287] the formation of adenomatous polyps,[213,226,286,288] the growth of adenomatous polyps[243] and the progression of adenomas to carcinomas.[213,226] DMH-induced rat colon carcinogenesis closely resembles human colon neoplasia in all of these characteristics.[289,290] In contrast, dietary supplementation with calcium inhibits chemically-induced colorectal carcinogenesis in laboratory rodents.[223,224,226,227,234,236-238,240,242,243,245,246,287] For example, DMH-injected rats whose diets were supplemented

with calcium carbonate,[224,234,236-238,240,242,243,245,246,287] calcium gluconate,[223,224] calcium lactate[224,226,227] or calcium phosphate ($CaHPO_4$)[227] in amounts providing a total daily calcium intake of 140% to 1000% of typical intakes experienced significant reductions in the extent and magnitude of all of the manifestations of DMH-induced colorectal carcinogenesis. In contrast, reduction of dietary calcium intake below typical amounts potentiates DMH-induction of adenocarcinoma production.[245,291]

In rats, DMH also significantly reduced the number of high-affinity 1,25-dihydroxycholecalciferol receptors in stem cells permanently resident in colonic crypts.[286,292] Conversely, supplemental 1,25-dihydroxycholecalciferol significantly inhibited DMH-induced increase in colonocyte cytosolic ODC activity, cell proliferation in colon crypts and the genesis of colon adenocarcinomas.[286] Dietary vitamin D deficiency has abolished the chemopreventive actions of supplemental calcium in DMH-injected rats.[243,246] In contrast, dietary supplementation with vitamin D alone (in the absence of dietary calcium in amounts greater than typical intakes) begun two weeks after DMH was injected into rats had no effect on subsequent tumor incidence or on the rate of colonocyte proliferation.[293] These findings have led to the suggestion that the chemopreventive actions of supplemental dietary calcium require the presence of at least facilitative amounts of 1,25-dihydroxycholecalciferol in the colorectal mucosa.[286]

In rats, hepatic conversion of ingested azoxymethane (AOM) to activated methyl-azoxymethane produces significant increases in the expression of c-*myc* proteins in the colonic mucosa,[294] intracolonocyte ornithine decarboxylase (ODC) activity,[235,295] the rate of colorectal crypt cell proliferation,[221,239,294] the formation of aberrant crypt foci,[239,241,244,296] the formation of adenomatous polyps,[222,225,247,295] the growth of adenomatous polyps,[255] and the progression of adenomas to carcinomas.[255] AOM-fed rats whose diets were supplemented with calcium carbonate,[225,235,239,241,244,247,295] calcium chloride,[225,294] calcium gluconate,[225] calcium glucurate[296,297] or calcium lactate[221,222] experienced significant reductions in the extent and magnitude of the manifestations of AOM-induced colorectal carcinogenesis. In a study examining the effect of the amount of supplemental calcium consumed on the relative effectiveness of chemoprevention of chemically-induced colorectal cancer, daily dietary calcium intake (as calcium lactate) equivalent to about 200 to 250 mg in humans was found to have no effect on AOM-induced colon carcinogenesis, while daily dietary calcium intake equivalent to about 1700 mg in humans significantly inhibited the formation of AOM-induced adenocarcinomas.[255]

The ingestion of *N*-methyl-*N*-nitrosourea (MNU) results in the induction of invasive carcinomas of the colon and rectum in laboratory rodents.[298-300] Diets providing 200% to 400% of the typical intakes of calcium (as supplemental calcium carbonate,[299] calcium gluconate[298] or calcium lactate[298]) have been reported to significantly decrease the number of MNU-induced invasive carcinomas of the colon and rectum. Similarly, doubling calcium intake (as calcium carbonate[301] or calcium lactate[301]) prevented *N*-

methyl-*N'*-nitro-*N*-nitrosoguanidine-induced hyperproliferation of the colorectal epithelium of rats. Ingestion of about 400% of the typical intakes of calcium (as supplemental calcium lactate) significantly reduced the number of aberrant crypts induced by oral exposure to the heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in rats.[302] In mice, doubling calcium intake by supplementation with calcium phosphate significantly decreased the magnitude of amine-induced increase in the rate of colonocyte cell proliferation.[303] In rats, dietary supplementation with calcium (as calcium phosphate, in amounts equivalent to about 4500 mg/day in humans) prevented the significant dietary heme-induced increases in cytolytic activity of fecal water and in the rate of epithelial cell proliferation in the colonic mucosa.[304]

G. The Rate of Colorectal Mucosal Crypt Cell Proliferation and Colorectal Cancer in Animal Models

A number of experimental manipulations produce increased cellular proliferation in the colonic crypts of laboratory animals, including small bowel resection,[305,306] jejunoileal bypass,[307-310] subtotal colectomy,[309] colostomy,[311] pancreatobiliary diversion,[312] exposure to bile acids[77,202-209,313,314] or long-chain fatty acids,[77,78,210,211] injection with 1,2-dimethylhydrazine dihydrochloride (DMH),[213,236-238,240,286,287] and ingestion of *N*-methyl-*N*-nitrosourea (MNU),[298,299] *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine[301] or azoxymethane (AOM).[221,239,294] In such animals, increased cellular proliferation in the colonic crypts is associated with colonic hyperplasia[305,308-313] and a statistically significantly increased incidence of tumorigenesis along the length of the large intestine.[213,222,225,226,238-241,243,244,248,255,286,287,296-299,312-315] These data from animal studies demonstrate that increased proliferative activity in the colonic mucosa ("hyperproliferation") is correlated with an increased risk of developing colon cancer.[213,238-240,287,316-318]

H. Dietary Calcium and the Rates of Colorectal Mucosal Crypt Cell Proliferation and Apoptosis in Animal Models

In normal healthy cancer-free rats, increasing dietary calcium intake by 50% over amounts typically consumed by the addition of either calcium carbonate or calcium phosphate to the diet significantly attenuated the rate of proliferation of the colonic epithelium.[74] Similarly, doubling the calcium intake of normal healthy cancer-free rats by the addition of calcium lactate to the diet significantly attenuated the rate of proliferation of colonic epithelial crypt cells.[236] In mice, the administration of an additional 50% of their typical daily intakes of calcium (as calcium carbonate) significantly decreased (by about 20%) the rate of proliferation of colonic epithelial cells within the proliferative compartment *in vivo* (sodium carbonate was ineffective).[78,319] In contrast to these reports, the normal noncancerous colonic mucosa of mice consuming twice their typical intakes of dietary calcium (as supplemental calcium carbonate) exhibited no change in the rate of proliferation of colonic epithelial cells within the

proliferative compartment; however, the rate of cellular apoptosis within the crypts was significantly increased, resulting in a net decrease in the size of the proliferative compartment of the crypts.[320] A similar change in the diet of rats also has been reported to produce a significant increase in the proportion of cells in colonic epithelial crypts undergoing apoptotic change, resulting in a net decrease in the size of the proliferative compartment of the crypts.[320]

I. The Rate of Colorectal Mucosal Crypt Cell Proliferation and Colorectal Cancer in Humans

Increased proliferation in the mucosa is an early step in the genesis of colorectal neoplasia; accelerated proliferation increases the rate of random mutations[321,322] and is procarcinogenic.[321-324] On the other hand, a decrease in the rate of colorectal epithelial cell proliferation significantly decreases the risk for colorectal cancer in humans.[325] Compared with cancer-free individuals and those at low risk for colon cancer, patients with current or previous colon cancer[274,321-324,326-330] and patients at high risk for colon cancer (patients with sporadic adenoma,[324,328-339] familial adenomatous polyposis,[198,322,340] ulcerative colitis,[328,341-344] or a family history of colon cancer[321,329,335,345] or following intestinal bypass surgery[117] and most elderly individuals[346,347]), on average, exhibit in their grossly normal-appearing colorectal mucosa both an increased epithelial cell proliferation rate and an extension ("expansion") of the colon crypt proliferative zone from the lower (basal) 60% of the crypt to include the upper (luminal) 40% of the crypt, including the most superficial portions of the crypts.[36,318,335,338,342,348] Expansion of the proliferative compartment of the colorectal mucosa into the areas of colonic crypts that normally are occupied by differentiated and nondividing cells, forming foci of aberrant crypt morphology ("aberrant crypt foci"), presages increased risk for colorectal cancer in humans.[80,83-89,274,330,347-352] In patients with previous colon cancer or sporadic adenomas, these changes also predict adenoma recurrence.[327,333]

All available evidence indicates that these two proliferation abnormalities (hyperproliferation and upward shift – "expansion" – of the proliferative zone) are reversible biomarkers or precursors for colon neoplasia.[206-209] In humans, the rectal mucosa provides an accessible tissue for examination of the anatomic, biochemical and physiologic status of the large intestine and the rate of epithelial cell proliferation and the width of the proliferative compartment in the rectal mucosa are reflective of those in the colonic mucosa.[332,335,353,354]

J. Dietary Calcium and the Rate of Colorectal Mucosal Crypt Cell Proliferation in Humans

The rate of crypt cell proliferation in rectal tissues obtained at biopsy has been shown to be significantly inversely proportional to dietary calcium intake in healthy human adults,[355] suggesting that daily dietary supplementation with calcium may reduce the risk

for colorectal cancer. Randomized placebo-controlled clinical trials of the effects of calcium supplementation (usually as calcium carbonate) on the rate of crypt cell proliferation in rectal tissues obtained at biopsy have confirmed this hypothesis.[137,229,340,356-360]

In randomized placebo-controlled clinical trials, compared to the effect of placebo, daily dietary supplementation with 1000 mg of calcium,[356] 1200 mg of calcium,[229,357] 1250 mg of calcium[340] or 2000 mg of calcium[356,358] produced significantly greater decreases in the rate of crypt cell proliferation in subjects with colorectal adenomas. Similarly, daily dietary supplementation with 1000 mg of calcium was more effective than placebo in decreasing the rate of crypt cell proliferation in subjects with familial adenomatous polyposis.[359] In a 12- month randomized placebo-controlled clinical trial examining patients with a history of polypectomy for colonic adenomatous polyps, dietary supplementation with either up to 1200 mg/day of calcium (as low-fat dairy products) or placebo, resulting in average daily calcium intakes of 1538 mg and 685 mg, respectively, dietary supplementation with calcium produced significantly greater decreases in colonic epithelial cell proliferative activity, size of the proliferative compartment, colonocyte nuclear size and cytokeratin AE1 content in cells in the lower portion of colon crypts and significantly greater increases in acidic mucin secretion by the colon.[137] These findings demonstrate that across a wide variety of disturbances in colorectal health, dietary supplementation with calcium normalizes colorectal mucosal epithelial proliferation.

The results of uncontrolled clinical trials also support this conclusion.[73,150,202,274,356,360-369] In an uncontrolled prospective clinical trial, daily dietary supplementation with 1300 to 1500 mg of calcium (as calcium carbonate) for 3 to 4 months produced significant decreases in the rate of proliferation of rectal crypt cells and in the size of the proliferative compartment in rectal tissues obtained via biopsy.[360,361] In another uncontrolled clinical trial, daily dietary supplementation with 900 mg of calcium (as either calcium carbonate or low-fat dairy foods) produced similar significant decreases in rectal epithelial crypt cell proliferation rates and in the numbers of proliferating cells in the upper portions of the crypts, without affecting the numbers of rectal cells undergoing apoptotic change, thereby reversing expansion of the proliferating compartment in patients with a history of polypectomy for colonic adenomatous polyps.[362] In other uncontrolled trials, investigators have observed significant decreases in the rates of rectal crypt cell proliferation when subjects were supplemented with 1000 mg of calcium daily[363] or 1250 or 1500 mg of calcium daily.[150,274,364] Daily dietary supplementation with 2000 mg of calcium returned the elevated rate of crypt cell proliferation in rectal tissues in patients with adenomatous polyps to the slower rate characteristic of cancer-free subjects.[365]

A cohort of patients with colorectal adenomas consuming 1500 mg of calcium (as calcium carbonate) daily for one year exhibited a significantly greater percentage of subjects with reduced numbers of proliferating cells in the proliferative compartment of their rectal mucosa.[366] In this trial, patients consuming supplemental calcium and self-

selected low-fat diets (providing less than 122 g of dietary fat daily) exhibited an even greater significant decrease in the mean number of proliferating cells in the proliferative compartment of their rectal mucosa.[366]

In a comparative study, although the rate of cell proliferation in the mucosal crypts of the rectum was not greater in patients with colorectal adenomas than in subjects who were adenoma-free, the rate of cell proliferation was inversely correlated with long-term dietary calcium intake.[367] Similarly, one week of dietary supplementation with calcium carbonate (providing 1000 mg of elemental calcium daily) significantly decreased intracolonocyte ODC activity in rectal mucosal tissues obtained via biopsy from patients with adenomatous polyps.[368] Consistent with these reports, calcium chloride protected normal-appearing human colon epithelial tissues in culture from deoxycholic acid-induced acceleration of colonic crypt cell proliferation.[73,369]

Human studies of the effects of calcium supplementation on the size of the rectal mucosal crypt proliferative compartment have observed significant decreases in the size of the rectal mucosal crypt proliferative compartment when the diets of study subjects were supplemented with 1000 mg of calcium daily,[356,363] 1500 mg of calcium daily[202] or 2000 mg of calcium daily.[363] These findings provide further evidence that dietary supplementation with calcium normalizes colorectal mucosal epithelial cell proliferation.

The results of cell culture studies are consistent with these human trials. In cell culture, mouse (MC-26) colon cancer cells and human (LoVo; WIDR; Caco-2) colon cancer cells responded to increased culture medium calcium ion concentration with growth inhibition.[319,370,371] In contrast, human colon adenocarcinoma-derived Caco-2 colon cancer cells responded to low medium concentration of Ca^{2+} with activation of the PKC signaling pathway, resulting in upregulation of c-*myc* expression and producing progression of cells out of the S (stationary) phase of the cell cycle and into the DNA synthetic phase.[371]

In contrast, no change in the rate of crypt cell proliferation in rectal or colorectal tissues obtained at biopsy was observed in several randomized placebo-controlled clinical trials in which the diets of patients with colorectal adenomas,[172,231,363,372-375] hereditary nonpolyposis colorectal cancer,[198] ulcerative colitis[376] or colorectal carcinoma[377] were supplemented with 1000 mg of calcium daily,[375] 1200 mg of calcium daily,[172,231,372] 1500 mg of calcium daily[374] or 2000 mg of calcium daily.[373,376,377] In uncontrolled studies, the rate of rectal crypt cell proliferation did not decrease when subjects were supplemented with 1000 mg of calcium daily,[363] or 1500 mg of calcium daily.[372] Similarly, several uncontrolled human studies of the effects of calcium supplementation on the size of the rectal mucosal crypt proliferative compartment have failed to observe a significant decrease in the size of the rectal mucosal crypt proliferative compartment when the diets of study subjects were supplemented with 1250 mg of calcium daily[364] or 1500 mg of calcium daily[364,367] In one study of men and women with a history of previous colorectal adenomas, the rate of rectal mucosal crypt cell proliferation was not

affected by the intake of dairy foods.[378] In one uncontrolled study, whose findings remain unconfirmed a decade later, patients with excised adenomatous polyps exhibited significantly increased rates of crypt cell proliferation in colon tissues obtained at biopsy one year after beginning daily dietary supplementation with 1500 mg of calcium (as calcium carbonate).[379]

Several of the studies that reported no decrease in the rate of crypt cell proliferation in rectal or colorectal tissues following daily dietary supplementation with calcium failed to control intersubject variability sufficiently to "allow" the decrease they did observe to be judged to be "statistically significant."[e.g., 376,378] The impact of this observation is to minimize the importance of the trials that failed to control intersubject variability adequately and to maximize the credibility of those trials that observed a significant decrease in the rate of crypt cell proliferation in rectal or colorectal tissues following daily dietary supplementation with calcium.

K. Dietary Calcium and Colorectal Cancer in Humans

Daily dietary supplementation with calcium has been investigated as a preventive dietary intervention for reducing the risk of colorectal cancer. In several randomized placebo-controlled clinical trials, dietary supplementation with calcium has significantly reduced the incidence of colorectal cancer.[134,380-383] In a randomized placebo-controlled clinical trial, 4 years of daily dietary supplementation with 1200 mg of calcium (as calcium carbonate) significantly reduced the relative risk for new carcinoma among patients with previously-removed colorectal adenoma (RR: 0.85; 95% CI: 0.74,0.98), independent of calcium intake at the beginning of the study.[134,382] Patients with adenomatous polyps consuming 800 mg/day of supplemental calcium (as calcium carbonate) for 3 years after polypectomy experienced significantly increased survival compared to patients with adenomatous polyps who did not consume supplemental calcium.[380] In a randomized placebo-controlled clinical trial, patients with unremoved colorectal polyps whose diets were supplemented with calcium (1600 mg/day), vitamin C (150 mg/day), vitamin E (75 mg/day), β-carotene (15 mg/day) and selenium (101 mcg/day) for 3 years exhibited a significantly reduced incidence of new polyps, although the rate of growth of the polyps present at baseline was not changed, confirming the effectiveness of dietary supplementation with calcium in reducing the risk for new polyp (new cancer) formation by preventing early preneoplastic hyperproliferation.[279,381,383]

The conclusion that dietary supplementation with calcium significantly reduces the incidence of colorectal cancer is supported by the results of a number of prospective observational studies.[384-393] In an epidemiologic study embedded within an 8-year randomized placebo-controlled clinical trial of 27,111 male smokers, over 70% of whom consumed at least 1200 mg of calcium daily, the multivariate-adjusted risk for colorectal cancer of men consuming the highest quintile of calcium daily (median intake: 1789 mg) was significantly less than that of men consuming the lowest quintile of calcium daily (median intake: 856 mg) (RR: 0.6; 95% CI: 0.4, 0.9).[384]

In a prospective observational study of 60,866 men and 66,883 women (the Cancer Prevention Study II Nutrition Cohort), the risk for colorectal cancer for individuals consuming more than 500 mg of calcium from supplements was significantly less than the risk of individuals not consuming calcium supplements (adjusted RR: 0.69; 95% CI: 0.49, 0.96), and the risk for colorectal cancer for individuals consuming less than 500 mg of calcium from supplements was significantly less than the risk of individuals not consuming any calcium supplements (RR: 0.71; 95% CI: 0.52, 0.96).[385] Therefore, calcium intake from supplements, the most reliable dietary intake recall data, significantly decreased the risk for colorectal cancer.

In a prospective observational study of 61,463 women, the risk for colorectal cancer for women over 54 years of age and consuming over 816 mg of calcium daily was significantly less than that of women over 54 years of age and consuming less than 568 mg daily (RR: 0.66; 95% CI: 0.49, 0.89).[386] Similarly, the risk for cancer localized to the colon for women over 54 years of age and consuming over 816 mg of calcium daily was significantly less than that of women over 54 years of age and consuming less than 568 mg daily (RR: 0.64; 95% CI: 0.44, 0.92).[386] The protective effect in the colon appeared to be primarily in the distal colon (RR: 0.33; 95% CI: 0.16, 0.67).[386] In a 9-year prospective observational study of 34,702 women who were postmenopausal at the beginning of the study, the risk for rectal cancer was significantly less in women with daily consumption of over 1278 mg of calcium than in women with daily consumption of less than 800 mg of calcium (RR: 0.59; 95% CI: 0.37, 0.94).[387] In a 7-year prospective observational study of 14,727 women 34 to 65 years old at the beginning of the study, the incidence of colorectal cancer among women consuming the highest quartile of daily calcium intake from fish and shellfish was significantly less than that among women consuming the lowest quartile of daily calcium intake from fish and shellfish (RR: 0.41; 95% CI: 0.22, 0.74).[388] In a 19-year prospective observational study of 1954 initially cancer-free men, the energy-adjusted risk for colon cancer for men consuming the highest quartile of calcium intake was significantly less than that of men consuming the lowest quartile of calcium intake (RR: 0.32; significantly different from RR = 1.0, $p < 0.05$).[389]

In the Iowa Women's Health Study cohort of 35,216 women, cancer-free and aged 55 to 69 years at the beginning of the study, the age-adjusted risk for colon cancer for women who consumed over 1547 mg of total calcium daily was significantly less than the risk for colon cancer for women who consumed less than 629 mg of total calcium daily (RR: 0.52; 95% CI: 0.33, 0.82).[390] In addition, the age-adjusted risk for colon cancer for women who consumed over 500 mg of calcium via dietary supplements daily was significantly less than the risk for colon cancer for women who never consumed dietary supplements containing calcium (RR: 0.57; 95% CI: 0.37, 0.88), confirming that dietary supplementation with significantly decreased the risk for colon cancer.[390]

The Iowa Women's Health Study also found that the risk for colon cancer was halved by long-term consumption of the current Institute of Medicine intake recommendations for calcium.[29,391] The relative risk for colon cancer among those women without a family history of colorectal cancer consuming more than 1296 mg of calcium from all sources

daily, compared to women consuming less than 821 mg from all sources daily, was 0.5 (95% CI: 0.3, 0.7).[391] The risk for colon cancer among those women without a family history of colorectal cancer consuming any dietary supplements containing calcium, compared to women never consuming dietary supplements containing calcium, was 0.7 (95% CI: 0.5, 0.9).[391] In contrast, the risk for colorectal cancer was independent of calcium or supplement intake in women with a family history of colorectal cancer.[391] In addition, the age-adjusted relative risk for colon cancer among those women with a family history of colorectal cancer, regardless of calcium intake, was significantly greater than the risk of women without a family history of colorectal cancer (RR: 1.8; 95% CI: 1.3, 2.4).[391] The results of a retrospective study conducted in France confirmed the importance of familial predisposition; the age-adjusted odds for colon cancer among men and women with a family history of colorectal cancer was significantly greater than the odds of men and women without a family history of colorectal cancer (OR: 1.9; significantly different from OR = 1.0, $p < 0.05$).[394] These findings suggest that a genetic predisposition to colorectal cancer biases the relative risks calculated from calcium intake data in favor of erroneously concluding that the incidence of colorectal cancer is independent of calcium intake (by artefactually inflating the variances of risk estimates).[391] They further imply that the conclusions drawn by epidemiologic studies reporting that the incidence of colorectal cancer is independent of calcium intake but that have not accounted for family history of colon adenomas or carcinomas may be unreliable.[391]

In another prospective observational study it was found that the risk for colon cancer for individuals consuming between 700 mg and 800 mg of calcium daily was significantly less than the risk for individuals consuming less than 500 mg daily (RR: 0.6; 95% CI: 0.4, 0.9).[392] There was no additional decrease in the risk for colon cancer when calcium intake exceeded 800 mg/day, suggesting that 800 mg/day may be the threshold intake required to enjoy the chemoprotective effect of calcium intake.[392] Alternatively, it has been estimated that the threshold intake for the chemoprotective effect of calcium intake on colorectal cancer for individuals consuming a "typical Western diet" is 900 to 1000 mg/day.[393] It has been suggested that these findings indicate that a population-wide increase in daily dietary consumption of calcium of 400 mg could prevent up to 16,000 deaths from colon cancer annually.[393]

Retrospective epidemiologic studies also have found that the risk for colorectal cancer was significantly decreased by routine consumption of adequate amounts of dietary calcium.[395-426] For example, in a case-control cross-sectional retrospective observational study, women with colon cancer had a significantly lower mean daily calcium intake than did cancer-free women.[395] In a cross-sectional observational study, the incidence of death from colon cancer was significantly inversely proportional to daily dietary calcium intake.[396] In a 15-year retrospective case-control study, patients with existing colorectal cancer reported significantly lower calcium intake (per unit of energy consumption) than did cancer-free subjects.[397] In a case-control study of women under 75 years old, the risk for colon cancer was significantly inversely proportional to daily calcium intake.[398] In

two case-control studies of adults with colorectal cancer, the risk for colorectal cancer was significantly inversely proportional to daily calcium intake.[399-401] In one such study, the inverse relationship between colorectal cancer risk and daily calcium intake was significant only in men (but not in women) over 66 years old but was statistically significant in both men and women less than 67 years old.[401]

The incidence of colorectal adenoma was significantly reduced by the routine consumption of adequate amounts of dietary calcium in the Health Professionals Follow-Up Study.[402] In that study, the risk for colon cancer was significantly decreased for men consuming more than 1213 mg of calcium daily, compared to men consuming less than 631 mg of calcium daily (RR: 0.58; 95% CI: 0.39, 0.87).[402] Furthermore, this effect also was apparent when consideration was limited to only calcium intake from foods (not supplements) (RR daily calcium intake from foods greater than 1051 mg compared to daily calcium intake from foods less than 605 mg: 0.61; 95% CI: 0.40, 0.91) or only calcium intake from dairy products (RR daily calcium intake from dairy products greater than 620 mg compared to daily calcium intake from dairy products less than 137 mg: 0.51; 95% CI: 0.32, 0.83).[402] However, the investigators also reported that the application of elaborate (and controversial) statistical modeling to these data successfully eliminated the statistical significance of these findings.[402,403]

In another case-control study, the risk for developing either colon cancer or rectal cancer was more than halved in subjects who consumed the highest quartile of dietary calcium intake, compared to the risk in those who consumed the lowest (OR: 0.41; 95% CI: 0.24, 0.69).[404] Similarly, the risk for developing only colon cancer was more than halved in subjects who consumed the highest quartile of dietary calcium intake, compared to the risk in those who consumed the lowest (OR: 0.46; 95% CI: 0.24, 0.89) and the risk for developing only rectal cancer was more than halved in subjects who consumed the highest quartile of dietary calcium intake, compared to the risk in those who consumed the lowest (OR: 0.36; 95% CI: 0.18, 0.72).[404] In a case-control study, the odds for developing either colon cancer or rectal cancer were significantly reduced by consumption of dietary calcium in amounts approximating or exceeding the current Institute of Medicine intake recommendations[29] (OR, daily calcium intake over 1030 mg compared to daily calcium intake less than 469 mg: 0.73; 95% CI: 0.54, 0.97).[405] In a case-control study of men and women, the risk for colon cancer of individuals consuming the highest quintile of daily calcium intake was significantly less than that of subjects consuming the lowest quintile of daily calcium intake (RR: 0.42; 95% CI: 0.25, 0.69); risk decreased 15% for every 295 mg of daily calcium intake.[406] In a case-control study of men and women, the risk for colon cancer of white individuals consuming the highest quintile of daily calcium intake was significantly less than that of white individuals consuming the lowest quintile of daily calcium intake (RR: 0.4; 95% CI: 0.3, 0.6).[407] In a case-control study of men and women, the risk for colon cancer of women consuming the highest quintile of daily calcium intake was significantly less than that of women consuming the lowest quintile of daily calcium intake, although there was no significant protective effect in men.[408] In a case-control study of men and women, the odds of

developing colorectal cancer by individuals consuming more than 1141 mg of calcium daily, compared to the odds of developing colorectal cancer by individuals consuming less than 593 mg of calcium daily, were, in men under 65 years old: 0.3 (95% CI: 0.1, 1.3); in men 65 years and older: 0.2 (95% CI: 0.1, 0.8); in women under 65 years old: 0.2 (95% CI: 0.1, 0.7); and in women 65 years and older: 1.4 (95% CI: 0.4, 5.5).[409]

In a case-control study, the odds for colon cancer (OR: 0.58; 95% CI: 0.47, 0.73[410]) and the odds for rectal cancer (OR: 0.63; 95% CI: 0.45, 0.87[411]) were significantly decreased by routine consumption of hard water (calcium concentration > 42 mg/L) compared to routine consumption of soft water (calcium concentration < 24 mg/L). These findings were confirmed in a follow-up study in which the odds for both colon cancer (OR: 0.68; 95% CI: 0.57, 0.82[412]) and rectal cancer (OR: 0.72; 95% CI: 0.58, 0.91[413]) were significantly decreased by routine consumption of hard water (calcium concentration > 150 mg/L) compared to routine consumption of softer water (calcium concentration < 75 mg/L).

In a case-control study of adult men and women, daily calcium intakes equal to or greater than 1200 mg approximately halved the risk for the development of colorectal cancer in men.[414] The multivariate-adjusted odds ratio for the development of colorectal cancer among men with daily calcium intakes greater than 1400 mg, compared to men with daily calcium intakes less than 642 mg, was 0.46 (95% CI: 0.22, 0.96).[414] In contrast, the risk for the development of colorectal cancer among women was independent of daily calcium intake.[414] However, the multivariate-adjusted odds for the development of colorectal cancer of men with daily calcium intakes greater than 604 mg per 1000 kcal dietary energy intake were significantly less than those of men with daily calcium intakes less than 388 mg per 1000 kcal dietary energy intake (OR: 0.36; 95% CI: 0.19, 0.67) and the multivariate-adjusted odds for the development of colorectal cancer among women with daily calcium intakes greater than 667 mg per 1000 kcal dietary energy intake were significantly less than those of women with daily calcium intakes less than 410 mg per 1000 kcal dietary energy intake (OR: 0.47; 95% CI: 0.27, 0.83).[414]

In a retrospective observational study of patients with previous colorectal adenomatous polyps (the Wheat Bran Fiber Study), the risk for adenoma recurrence for patients consuming more than 1068 mg of calcium daily was significantly less than that of patients consuming less than 698 mg of calcium daily (adjusted OR: 0.56; 95% CI: 0.39, 0.80).[415] In a case-control study, the combination of low calcium intake and low fiber intake significantly increased the risk for colon cancer.[416] In a retrospective study of men and women with colorectal adenomatous polyps and matched control subjects without colorectal adenomatous polyps, the risk for colorectal adenomatous polyps of individuals consuming more than 1094 mg of calcium daily was significantly less than that of individuals consuming less than 558 mg of calcium daily (adjusted OR: 0.32; 95% CI: 0.11, 0.96).[417] In a case-control study of individuals with a history of previously-resected adenomatous polyps of the colon, any dietary supplementation with calcium significantly decreased (by about half) the odds of recurrence of adenoma (OR: 0.51; 95% CI: 0.27,

0.96).[418] In a case-control study of individuals with a history of previously-resected adenomatous polyps of the colon, risk for colorectal cancer was significantly inversely proportional to dietary calcium intake.[419] In a case-control study of men and women in China, the risk for colorectal cancer was reported to be inversely proportional to daily dietary calcium intake.[420]

In a case-control study of men and women, the incidence of colorectal cancer was significantly reduced among those subjects consuming over 1701 mg of calcium daily (men: OR, daily calcium intake greater than 1701 mg compared to daily calcium intake less than 681 mg: 0.7; 95% CI: 0.5, 0.9; women: OR, daily calcium intake greater than 1330 mg compared to daily calcium intake less than 546 mg: 0.6; 95% CI: 0.4, 0.9).[421] In another case-control study of men and women, the risk for colorectal cancer of subjects who consumed more than 1495 mg of calcium daily was significantly less than that of subjects who consumed less than 800 mg of calcium daily (OR: 0.7; 95% CI: 0.6, 0.9).[422] In another case-control study of men and women, the prevalence of colorectal cancer in subjects with osteoporosis who consumed an average of 2013 mg of calcium daily was significantly less than that of subjects without osteoporosis who consumed an average of 1002 mg of calcium daily (OR: 0.07; significantly different from OR = 1.0, $p < 0.05$).[423] The significant cancer-reducing effects of these high calcium intakes reinforces the conclusion that when daily calcium intake is below the current Institute of Medicine intake recommendations[29] (based on skeletal physiology), a gradation of calcium intakes is irrelevant to risk for colorectal cancer. It appears that only when daily calcium intakes equal or exceed the skeletal requirement is the chemopreventive property of dietary calcium expressed. However, in one case-control study, daily dietary supplementation with only 100 mg of calcium significantly reduced the risk for colon cancer.[424]

In studies of vitamin D receptor polymorphisms, daily calcium intakes greater than the study population median have eliminated the increased risk for colorectal cancer associated with low calcium intakes and the presence of a vitamin D receptor start codon polymorphism.[425] Similarly, individuals in the highest tertile of dietary calcium intake suppressed the expression of increased risk for colorectal adenoma associated with low calcium intakes and heterozygosity in the vitamin D receptor BsmI b allele.[426]

The results of other observational studies[385,427-434] support the conclusion that daily calcium intakes equal or exceeding the skeletal requirement are chemopreventive, even though those investigators failed to report a statistically significant association between dietary calcium intake and risk for colorectal cancer. Because the study populations in these reports[385,427-434] were largely calcium deficient (some severely so), the results of these studies[385,427-434] confirm that daily dietary calcium intakes less than current Institute of Medicine recommendations[29] deprive individuals of calcium's chemopreventive properties.

For example, in the 12-year Physicians' Health Study, a prospective observational study of 14,916 male physicians, the incidence of colorectal cancer was independent of calcium intake; however, none of these presumably well-informed professionals consumed more than 918 mg of calcium daily.[427] In another 12-year prospective observational study of 89,448 men, no relationship was observed between the incidence of colorectal cancer and calcium intake; however, less than 15% of these men consumed at least 1200 mg of calcium daily.[428] During 3.3 years of observation in a prospective observational study of 120,852 men and women aged 55 to 69 years at the beginning of the study (the Netherlands Cohort Study), the risk for colorectal cancer was not affected by calcium intake; however, fewer than 10% of study participants consumed at least 1200 mg of calcium daily.[429] In an 11-year prospective observational study of 50,535 men and women aged 20 to 54 years at the beginning of the study, the risk for colon cancer (after mathematical adjustments intended to account for differences in dietary energy intake) was not significantly affected by dietary calcium intake; however, fewer than 10% of the study participants consumed at least 1200 mg of dietary calcium daily.[430]

The results of other observational studies confirm that chronic dietary calcium deficiency is endemic in the study populations of most observational studies that have failed to observe a statistically significant chemopreventive effect of dietary calcium on risk for colorectal cancer. For example, 28 years after the beginning of a prospective observational study, the risk for colorectal cancer was found to be independent of calcium intake; however, about 80% of the subjects were chronically calcium deficient.[431] Similarly, in a 4-year prospective observational study of patients with a history of polypectomy for colonic adenomatous polyps, the risk for new carcinomas for patients whose energy-adjusted daily calcium intake was greater than 1044 mg was not different from the risk for patients whose energy-adjusted daily calcium intake was less than 610 mg; however, more than 80% of these patients were chronically calcium deficient.[432] Yet again, 22 years after the beginning of a prospective observational study, the risk for colorectal cancer was found to be independent of calcium intake in men; however, about 98% of the subjects were chronically calcium deficient and only about 16% consumed over 800 mg of calcium daily.[433] In the Nurses' Health Study, a prospective observational study of 88,751 women, the risk for colorectal cancer was found to be independent of calcium intake; however, more than 90% of these women were chronically calcium deficient.[434] In a prospective observational study of 60,866 men and 66,883 women (the Cancer Prevention Study II Nutrition Cohort), neither the risk for colorectal cancer for individuals consuming more than 988 mg of calcium from food sources daily compared to individuals consuming less than 504 mg of calcium from food sources daily nor the risk for colorectal cancer for individuals consuming more than 1255 mg of calcium from all sources daily compared to individuals consuming less than 561 mg of calcium from all sources daily were significantly affected by calcium intake; however, only 40% of these subjects consumed more than 925 mg of calcium daily and only 20% consumed more than 1255 mg of calcium daily.[385]

In contrast, in a single 24-year prospective observational study of 9959 men and women 15 years and older and cancer-free at the beginning of the study, the risk for colon cancer

was not related to the intakes of milk, milk products or calcium, with about 2/3 of these subjects consuming at least 1200 mg/day of calcium.[435]

In a subanalysis of the α–Tocopherol β–Carotene Cancer (ATBC) Prevention Study, calcium intake was not related to the incidence of colorectal cancer; however, an estimate of the percentage of study subjects consuming at least 1200 mg of calcium daily could not be determined from the data presented.[436]

Retrospective observational case-control studies provide additional support for the conclusion that dietary calcium adequacy is required in order to reduce colorectal cancer risk.[407,437-446] For example, in a 17-year retrospective observational case-control study, dietary calcium intake had no effect on the incidence of colon cancer; however, more than 95% of these subjects were chronically calcium deficient during this time.[437] In a case-control study of men and women aged 30 to 74 years, the risks for adenomatous or hyperplastic polyps were found to be independent of dietary calcium intake; however, only about 25% of subjects consumed at least 1200 mg of calcium daily.[438] In another case-control study, the risk for colon cancer and the risk for rectal cancer both were independent of dietary calcium intake; however, fewer than 20% of these subjects consumed at least 1200 mg of calcium daily.[439] In yet another case-control study, the multivariate-adjusted risk for colorectal cancer was independent of dietary calcium intake; however, virtually all of these subjects were chronically calcium deficient.[440] In a case-control study, the multivariate-adjusted risk for colorectal cancer was independent of dietary calcium intake; however, only about 25% of these subjects consumed over 1200 mg of calcium daily.[441] In one case-control study of men and women, the risk for colorectal cancer was independent of dietary calcium intake; however, only 25% of the men in this study consumed at least 1200 mg of calcium daily and only 25% of the women in this study consumed at least 1100 mg of calcium daily.[442] In a similar case-control study, the risk for colorectal adenomatous polyps was not affected by daily calcium intake; however, only about 20% to 25% of subjects consumed at least 1200 mg of calcium daily.[443] Likewise, the risk for colon cancer of African American men and women was independent of dietary calcium intake; however, only about 10% of these subjects consumed at least 1200 mg of calcium daily.[407] Similarly, in several other case-control studies of chronically calcium deficient men and women, the multivariate-adjusted odds for the development of colorectal adenomas or cancer were not affected by dietary calcium intake.[444-446]

In six other retrospective case-control studies of men and women, the risk for colorectal cancer was independent of dietary calcium intake; however, an estimate of the percentage of study subjects consuming at least 1200 mg of calcium daily could not be determined from the data presented.[447-452] In another case-control study, any dietary supplementation with calcium had no effect on the prevalence of first or recurrent adenomas, although an estimate of the percentage of study subjects consuming at least 1200 mg of calcium daily could not be determined from the data presented.[453]

However, it should be noted that in six retrospective observational studies, in which about 50% of the subjects consumed more than 1200 mg of calcium daily, the incidence of colorectal cancer was independent of calcium intake (usually because the 95% confidence interval for the odds ratio or relative risk ratio was large enough to include the value 1.0).[454-459] In addition, in a retrospective case-control study, voluntary consumption of calcium-containing dietary supplements appeared to have no effect on risk for colorectal adenoma, although a comparison of subjects consuming and not consuming such supplements was not made.[460] Furthermore, in a 3-year randomized placebo-controlled clinical trial, patients with a history of previously-removed colorectal adenomas receiving dietary supplementation with calcium (2000 mg daily) did not exhibit a significantly lower risk for colorectal cancer than was exhibited by similar patients whose diets were supplemented with placebo.[461]

It also should be noted that, as colon cells progress from normal to adenomatous to carcinomatous cells, the importance of continuation of the initiating stimuli becomes negligible, as does the impact of calcium ions; adenomatous and carcinomatous colorectal cells lose "responsiveness" to the effects of calcium ions.[150-152,154] The chemopreventive effects of calcium supplementation may not be universal and may affect only the prevention of early transformation or hyperproliferation and may not affect the growth of existing tumors.[151,152,155] Therefore, dietary supplementation with calcium is most likely to be beneficial in the prevention of colorectal cancer if supplementation occurs before hyperproliferation appears or progresses to neoplasia.[151,162,155] Consequently, supplemental calcium may be ineffective in chemoprevention in individuals in whom carcinogenesis may have commenced, potentially confounding the results of studies that may fail to observe a chemopreventive effect of dietary supplementation with calcium or of intakes of calcium equal to or exceeding the current Institute of Medicine recommendations[29] in broadly-defined study populations.

The interaction between physical activity and risk for colorectal cancer increases the impact of the findings of epidemiologic studies that reported a significant preventive or protective effect of calcium intakes equal to or exceeding the current Institute of Medicine recommendations. It has been reported that a low level of physical activity interferes with the chemopreventive actions of calcium intakes equal to or exceeding the current Institute of Medicine recommendations[29] in reducing the risk for colorectal cancer.[462,463] Therefore, the findings of epidemiologic studies of largely-sedentary populations that reported a significant preventive or protective effect of calcium intakes equal to or exceeding the current Institute of Medicine recommendations,[29] in spite of generally low levels of activity, are of increased importance while those that did not report such an effect may be confounded by lack of exercise and may therefore be irrelevant.

Investigators performing a quantitative meta-analysis of 24 epidemiologic studies published prior to 1996, comparing individuals consuming the highest quantile of calcium intake to those consuming the lowest and ignoring different definitions of "high" and "low" calcium intake, concluded that the risk for colorectal carcinoma was

significantly reduced by high daily intakes of dietary calcium (weighted pooled RR: 0.86; 95% CI: 0.74, 0.98).[464] Investigators performing a review of studies published prior to 1991 concluded that "increases in the daily intake of calcium in the diet may provide a means of colorectal cancer control."[465] Investigators performing a review of studies published prior to 1996 concluded that "a number of epidemiologic studies support the protective effect of calcium."[466] Investigators performing a review of studies published prior to 1999 concluded that the routine daily consumption of 1000 mg of calcium per 1000 kcal of dietary energy could prevent "most cases of colon cancer."[467] Investigators performing reviews of studies published prior to 1998 demonstrated that reduction in the risk for colorectal cancer generally requires daily calcium intakes of at least 800 mg.[468] The authors of a systematic review published in 2002 concluded that "Calcium supplementation reduces the risk of recurrent colorectal adenomas."[469] Other reviewers have concluded that "There is modest epidemiologic evidence for an inverse relationship between dietary calcium intake and risk for colorectal adenomas and carcinomas."[470] In their 2001 Consensus Opinion, the North American Menopause Society stated: "High calcium intake provides some chemoprotective properties against colorectal cancer."[471]

III. Breast Cancer

It was estimated that about 205,000 new cases of invasive breast cancer were diagnosed during 2002 in the US.[31] Over 99% of these cases occurred in women and about 20% will lead to premature death.[31] About 20% of these cases were diagnosed as ductal carcinoma in situ (DCIS), characterized by the proliferation of malignant mammary ductal epithelial cells within the confines of the basement membrane without evidence of invasion;[472] however, 5% to 10% of cases of DCIS are characterized by microinvasion of the ductal basement membrane.[473] Breast cancer ranks second (to lung cancer) among cancer deaths in women.[31] The 5-year relative survival rate for localized breast cancer is 96%, for regionally invasive breast cancer, 78%, and for metastatic breast cancer, 21%.[31,473] Lifetime risk for breast cancer in women is 12.5% and increases with age, estrogen use, the appearance of atypical hyperplasia, increased breast density, earlier age of menarche, later age of menopause, obesity after menopause, alcohol use, radiation exposure, never having had children and a positive family history of breast disorders.[31,474-476] Risk may be decreased by physical activity and maintenance of appropriate body weight.[31]

The pathogenesis of breast cancer is multifactorial and only incompletely understood.[477] However, continued biosynthesis of polyamines is required for cellular proliferation in the breast.[478] In particular, polyamines stimulate the proliferation of hormone-independent human breast cancer cells[479-481] and increase the sensitivity of estrogen-sensitive breast tissue to estrogens.[482,483] Human breast cancer tissue has been found to contain significantly greater activity of ornithine decarboxylase (ODC), the rate-limiting

enzyme in polyamine synthesis,[104] coincident with significantly greater concentrations of polyamines.[484-489] Overexpression of ODC is associated with increased malignant potential of human mammary epithelial cells,[490,491] progression of hormone-dependent human breast cancer to less differentiated, more metastatic and hormone-independent breast cancer,[479,492,493] and significantly reduced survivability of human breast cancer.[485,494] In contrast, inhibition of ODC has significantly reduced the rate of proliferation of both hormone-dependent and hormone-independent human and rodent breast cancer cells and the metastatic invasiveness of such cells *in vitro* and *in vivo*.[494-500] Dietary supplementation with calcium has significantly decreased ODC activity in the rectal epithelial mucosa of humans,[368] suggesting that calcium-induced inhibition of ODC-sensitive characteristics of epithelial cells also will be chemopreventive and chemoprotective in the breast. Consistent with this conclusion, although ODC activities were not measured, rats supplemented with dietary calcium exhibited significantly increased resistance to the breast cancer-promoting effects of a high-fat, low-calcium diet.[501]

A. Dietary Calcium and Breast Cancer

Evidence obtained from two large prospective epidemiologic studies supports the conclusion that adequate daily intakes of calcium may be chemopreventive against human breast cancer.[502,503] In the Nurses' Health Study cohort of 88,691 women (of whom only about 15% consumed the current Institute of Medicine recommendations for calcium[29]), the relative risk for breast cancer was found to be significantly decreased by intakes of calcium from dairy products in excess of 800 mg daily in premenopausal women (RR: 0.69; 95% CI: 0.48, 0.98).[502] There was an approximate 5% decrease in the risk for breast cancer for every 100 mg of calcium consumed as dairy products in excess of 200 mg daily.[502] In a 25-year prospective observational study of 4697 initially cancer-free women aged 15 years and older, the incidence of breast cancer was significantly reduced (by about half) by greater daily calcium intakes (RR for breast cancer, highest tertile of calcium intake compared to the lowest: 0.44; 95% CI: 0.24,0.80).[503] In addition, the results of one retrospective case-control study indicated that the multivariate-adjusted odds for breast cancer were significantly reduced by daily calcium intakes greater than 871 mg,[504] while the results of another indicated that the multivariate-adjusted odds for breast cancer were significantly reduced (by about 80%) in postmenopausal women who consumed the highest quartile of calcium daily (compared to women who consumed the lowest quartile of calcium daily).[505] Investigators conducting a retrospective case-control study in Shanghai, China, reported that although calcium intakes from milk, seafood, fruits or vegetables were not associated with risk for breast cancer, daily calcium intake from poultry sources was significantly inversely proportional to risk for breast cancer (OR, highest quintile of calcium intake from poultry foods compared to lowest quintile of calcium intake from poultry foods: 0.71; 95% CI: 0.55, 0.93).[506]

Although three retrospective case-control studies have reported that the incidence of breast cancer was independent of total daily calcium intake in their particular study populations,[474,507,508] there is no evidence that risk is increased by routine consumption of recommended amounts of calcium.

IV. Prostate Cancer

Prostate cancer is the second leading cause of cancer in males in the US.[31,509] About 189,000 new cases of prostate cancer were diagnosed in the US in 2002, while over 30,000 men in the US died from this disease that year.[31] The probability of a man in the US developing prostate cancer during his lifetime is 16.67%.[31] When all stages of prostate cancer are combined, the 5-year relative survival rate is 96%, relative 10-year survival is 75% and relative 15-year survival is 54%.[31]

Prostate cancer results from the proliferation of epithelial cells located predominantly in the peripheral zone of the prostate gland.[509] Carcinogenesis in the prostate occurs in a multistage process involving progression through a variety of pathways from a low-grade, small latent carcinoma to higher-grade metastatic disease.[510] Because carcinogenesis in the prostate resembles carcinogenesis in other calcium-responsive epithelial tissues (such as colorectal and breast), and because rats consuming supplemental dietary calcium have exhibited significantly increased resistance to the prostate cancer-promoting effects of a high-fat, low-calcium diet,[501] it is likely that adequate dietary calcium intake may reduce the risk for prostate cancer in men as well as reducing the risks for breast cancer in women and colorectal cancer in men and women.

A. Dietary Calcium and Prostate Cancer

The conclusion that adequate dietary calcium intake may reduce the risk for prostate cancer in men is supported by the results of a retrospective case-control epidemiologic study, in which the risk for histologically confirmed prostate cancer was found to be significantly decreased (by about 2/3) in men who consumed the most calcium on a routine daily basis (adjusted OR for prostate cancer, highest tertile of daily calcium intake compared to the lowest: 0.37; 95% CI: 0.14, 0.99).[511] This finding is of special interest because all of the men in the highest tertile of daily calcium intake consumed over 1200 mg of calcium daily.

In contrast, in a male subset (46 to 92 years old) of the case-control retrospective observational Baltimore Longitudinal Study of Aging, the energy-adjusted risk for prostate cancer was independent of calcium intake.[512] Several other prospective[513,514] and retrospective[515-520] observational studies have found the risk for prostate cancer to be independent of calcium intake. Similarly, in a 20-year observation of men who were free of prostate cancer when the study began (the Framingham Study), the incidence of prostate cancer was not associated with the bone density of the second metacarpal bone

(suggested by these investigators to be a surrogate marker of long-term calcium nutriture).[521]

The results of two prospective observational studies have been mistakenly interpreted as providing evidence that dietary calcium paradoxically increases risk for prostate cancer.[522,523] In the Physicians' Health Study, 20,885 men observed for 11 years demonstrated that, compared to men habitually consuming diets that were virtually devoid of calcium and dairy fats, men consuming moderately calcium-deficient diets and for whom calcium and dairy fat intakes were closely linked experienced a significantly increased incidence of prostate cancer,[522] confirming the cancer-promoting properties of dairy-type fats.[501] Similarly, the findings of a retrospective case-control observational study have confirmed that when calcium and dairy product intakes are correlated with a correlation coefficient (r) of 0.90, both will appear to increase risk for prostate cancer.[524,525] In the Health Professionals Follow-Up Study, in which 51,529 men were observed for about 8 years, excessive calcium intakes (over 2000 mg daily) were associated with significantly greater risks for advanced and metastatic prostate cancer than was chronic calcium deficiency (daily intake less than 500 mg).[523] However, risks were not increased in men consuming 500 to 1999 mg of total calcium daily, men consuming over 1000 mg of calcium daily from foods without supplementation or men consuming up to 1000 mg of calcium daily from foods plus over 900 mg of calcium daily from dietary supplements, confirming the safety of the current Institute of Medicine recommendations for calcium intakes.[29]

V. Bioavailability of Calcium from the Diet and from Dietary Supplements

Calcium absorption efficiency is fairly similar for most foods, including milk, dairy products and grains.[29] However, the efficiency of calcium absorption is reduced when the food sources include spinach, sweet potatoes, rhubarb, beans, unleavened bread, seeds, nuts, or soy isolates.[29] The fractional absorption of calcium from dietary supplements typically ranges from 25% to 35% (similar to range for calcium in milk).[29] In particular, men and women absorb calcium from calcium citrate and calcium carbonate with equivalent efficiency.[526,527] However, clinical achlorhydria may impair absorption of calcium from calcium carbonate while enhancing the absorption of calcium from calcium citrate.[528]

VI. Amounts of Supplemental Dietary Calcium that Are Effective in Reducing the Risks of Colorectal Cancer, Breast Cancer and Prostate Cancer

The reliable and credible scientific literature indicates that daily dietary supplementation with calcium-containing compounds in amounts that provide sufficient elemental calcium

to allow individuals to achieve daily total calcium intakes consistent with current Institute of Medicine recommendations for gender, age and reproductive status are effective in reducing the risks of colorectal cancer, breast cancer and prostate cancer.

Current recommended daily calcium intakes are 800 mg (4 through 8 years old), 1300 mg (9 through 18 years old), 1000 mg (19 through 50 years old) and 1200 mg (over 50 years old).[29] These intakes were chosen in order to ensure maximal skeletal development and duration.[29] Importantly, it appears that certain health benefits (particularly the chemopreventive property of dietary calcium) occur only at intakes at least equal to the skeletal requirement.

Unfortunately, daily calcium consumption meets or exceeds these amounts in only a small fraction of the population.[29] For example, only half of children 4 to 8 years old consume at least 800 mg of calcium daily; less than 25% of boys 9 to 13 years old consume at least 1300 mg of calcium daily; less than 50% of boys 14 to 18 years old consume at least 1300 mg of calcium daily; only about 5% of adolescent girls consume at least 1300 mg of calcium daily; less than 50% of adult men and only about 10% of adult women consume at least 1000 mg of calcium daily; and less than 10% of the population over 50 years old consumes at least 1200 mg of calcium daily.[29] Recognizing the limitations of any recommendations that rely solely on the implementation of changes in life-long eating and dietary habits, the Institute of Medicine has suggested that "some seemingly healthy individuals may require higher calcium intakes"[529] and that for individuals at risk for dietary calcium intakes below recommendations, "use of calcium supplements may be desirable in order to meet [recommendations]."[530]

VII. Safety of Dietary Supplementation with Calcium in Amounts that Are Effective in Reducing the Risks of Colorectal Cancer, Breast Cancer and Prostate Cancer

The US Food and Drug Administration has published its finding that the following calcium-containing compounds are "safe": calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate and calcium sulfate.[531,532]

The Tolerable Upper Limit of Intake ("the maximal level of nutrient intake that is unlikely to pose risks of adverse health effects to almost individuals in the target group"[529]) for calcium has been set at 2500 mg daily for males and females over 1 year of age,[29] providing an ample margin of safety for individuals choosing to improve their health by supplementing their diets with calcium. This limit is not set lower during pregnancy or lactation and compares favorably with estimates of daily calcium consumption by modern hunter-gatherers.[13] The Food and Nutrition Board of the Institute of Medicine has stated that "for the majority of the general population, intakes of calcium from food substantially above the UL are probably safe."[29]

No adverse events have occurred when adults with chronic renal failure and receiving hemodialysis have consumed up to 8000 mg of calcium carbonate (providing up to 3200 mg of elemental calcium) daily for up to 48 months[533,534] or when adults with chronic renal failure and not yet receiving hemodialysis have consumed up to 3000 mg of calcium carbonate (providing up to 1200 mg of elemental calcium) daily for 6 months.[535] In these patients, daily dietary supplementation with calcium produced significant improvements in the clinical hyperphosphatemia caused by chronic renal failure.[533-535] In addition, both dialyzed[534] and nondialyzed patients[535] experienced attenuation of disease-induced secondary hyperparathyroidism and bone resorption. Similarly, adults with chronic renal failure and receiving hemodialysis have consumed an unspecified amount of calcium as calcium acetate for 8 weeks with significant improvements in clinical hyperphosphatemia.[536] Boys and girls aged 1 month to 16 years with chronic renal failure and undergoing hemodialysis regularly and consuming 10 to 340 mg of calcium carbonate per kg body weight daily (providing 4 to 136 mg of elemental calcium per kg body weight daily, equivalent to a daily intake of 400 to 13,600 mg of elemental calcium by a 100-kg adult) also have exhibited significantly attenuated hyperphosphatemia and secondary hyperparathyroidism without any adverse reactions.[537]

Increased risk for the development of symptomatic "milk alkali syndrome" (renal impairment, hypercalcemia, alkalosis) may accompany daily intakes of over 4,000 mg of elemental calcium, particularly if accompanied by equivalently large amounts (over 6,000 mg) of carbonate.[538] However, 4 days of daily supplementation with up to 5200 mg of elemental calcium and up to 7800 mg of carbonate was without adverse effect in young adult men and women[539] and 4 months of daily supplementation with 3240 mg of carbonate has been without adverse effect in healthy premenopausal women.[540] Individuals with uremia, hypothyroidism, adrenocortical insufficiency or PTH-secreting tumors may develop clinically relevant hypercalcemia after routine chronic daily consumption of 4,000 mg or more of elemental calcium.[541]

One investigator calculated a Lowest Observed Adverse Effect Level (LOAEL) for calcium for individuals with a history of nephrolithiasis of 1685 mg daily, an amount more than current Institute of Medicine recommendations.[542] The US Food and Drug Administration has concluded that daily intakes of elemental calcium up to at least 1800 mg pose no increased risk for kidney stones among the general population.[532]

A characteristic shared by all of the studies cited in this document is the absolute lack of any reports of any clinically-significant adverse reactions that could be attributed to dietary calcium. As noted by the North American Menopause Society in their 2001 Consensus Opinion, "The side effect profile from recommended levels of calcium intake is insignificant. No calcium intervention trials have reported any serious side effect associated with these levels."[471]

VIII. Additional Literature regarding Relationships between Dietary Supplementation with Calcium and Reduction of the Risks of Colorectal Cancer, Breast Cancer and Prostate Cancer

This literature review is by necessity brief and targeted to the requirements of the US Food and Drug Administration as concerns a balanced presentation of the published peer-reviewed scientific evidence relevant to the proposed health claims. However, it should be noted that the scientific literature upon which this review relies represents only a small fraction of the total available scientific literature base that may be relevant to the relationships between dietary supplementation with calcium and cancer. Literature searches performed on August 26, 2003, on the following topics obtained these numbers of citations:

Calcium and Cancer (17427 citations)
Calcium and Colon Cancer (351 citations)
Calcium and Colorectal Cancer (245 citations)
Calcium and Intestinal Cancer (4 citations)
Calcium and Breast Cancer (653 citations)
Calcium and Prostate Cancer (637 citations)
Calcium and Safety (1511 citations)

While there is some (undetermined) degree of repetition in the citations identified by these somewhat related searches, clearly there are at least 18000 unique citations that could be construed to be in some way relevant to this review. After examination of the 20828 citations listed above, 542 were found to be germane to the proposed health claims.

Conclusions

- The amount of ingested calcium that is absorbed increases with increasing daily dietary calcium intake.
- Daily dietary calcium intake of at least 1200 mg of elemental calcium is required in order to maximize the retention of absorbed calcium.
- The amount of dietary calcium required daily in order to maximize calcium retention is approximated by the current Institute of Medicine intake recommendations for this nutrient.
- Maximization of calcium retention is associated with reduced risk of colon cancer.
- Maximization of calcium retention is associated with reduced risk of rectal cancer.
- Maximization of calcium retention is associated with reduced risk of colorectal cancer.
- Maintenance of the normal healthy colorectal epithelium is dependent upon the ability of colonocytes to sustain elevated intracellular Ca^{2+} concentrations.
- The ability of colonocytes to sustain elevated intracellular Ca^{2+} concentrations reflects, at least in part, the local availability of sufficient amounts of Ca^{2+} ions.
- Colorectal carcinogenesis results from failure to maintain the normal healthy colorectal epithelium.
- The local availability of sufficient amounts of Ca^{2+} ions may inhibit or prevent colorectal carcinogenesis.
- Hyperproliferation of the colorectal mucosa presages colorectal cancer.
- Hyperproliferation of the colorectal mucosa produces expansion of its proliferative compartment and results in the formation of foci of aberrant crypt morphology ("aberrant crypt foci").
- The presence of aberrant crypt foci presages colorectal cancer.
- Attenuation of hyperproliferation of the colorectal mucosa reduces the risk for the development of aberrant crypt foci within the mucosa.

- Attenuation of hyperproliferation of the colorectal mucosa reduces the risk for the development of colorectal cancer.

- Locally available Ca^{2+} ions are most effective in the prevention of the early hyperproliferative phase of colorectal carcinogenesis.

- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient normalize the rate of colorectal mucosal epithelial proliferation.

- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient reduce the risk for and may prevent hyperproliferation of the colorectal mucosa.

- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient reduce the risk for and may prevent the formation of aberrant crypt foci.

- Secondary bile acids stimulate hyperproliferation of the colorectal mucosa and are endogenous colorectal carcinogens.

- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient decrease the exposure of the human colorectal epithelium to secondary bile acids.

- Risk for colorectal cancer is proportional to the cytotoxicity of fecal water.

- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient decrease the cytotoxicity of human fecal water.

- Extensive research in animals demonstrates the antineoplastic effect of calcium in colorectal tissues.

- Dietary supplementation with calcium is an effective chemopreventor in animal models of chemically-induced colorectal cancer.

- Dietary supplementation with calcium is an effective chemopreventor of chemically-induced colorectal cancer in humans.

- The risk for colorectal cancer is inversely correlated with daily dietary calcium intake.

- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient reduce the risk for colon cancer.

- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient reduce the risk for rectal cancer
- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient reduce the risk for colorectal cancer.
- The pathogenesis of breast cancer requires continued biosynthesis of polyamines within breast tissue.
- Calcium inhibits the biosynthesis of polyamines.
- Risk for breast cancer is inversely proportional to daily dietary calcium intake.
- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient reduce the risk for breast cancer.
- Carcinogenesis in the prostate gland is inhibited by adequate intake of dietary calcium.
- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient reduce the risk for prostate cancer.
- Routine chronic consumption of dietary and supplemental calcium in amounts consistent with the current Institute of Medicine recommendations for this nutrient is safe.

Summary Conclusions

In conclusion, I find that there is significant scientific agreement in support of the following health claims:

- Calcium may reduce the risk of colorectal cancer.
- Calcium may reduce the risk of colon cancer.
- Calcium may reduce the risk of rectal cancer.
- Calcium may reduce the risk of breast cancer.
- Calcium may reduce the risk of prostate cancer.
- Calcium may have anticarcinogenic effects in the colon, breast, and prostate.
- Calcium may reduce the risk of recurrent colon polyps.

/s/ Michael J. Glade[1]

Michael J. Glade, Ph.D., F.A.C.N., C.N.S.
(a copy of my CV is attached)

[1] The original signature page is on file with Emord & Associates, P.C., counsel to Marine Bio Inc. Dr. Glade requested that it not be submitted to FDA to avoid having it posted on the internet and available for nefarious use.

Michael John Glade, Ph.D.

8612 Kedvale Avenue, Skokie IL 60076

TEL: (847)-329-9818 e-mail: the_nutrition_doctor@yahoo.com

EDUCATION:

Ph.D., Animal Science - Nutrition — 1979
Cornell University, Ithaca, New York

Bachelor of Science, Molecular Biology — 1973
Massachusetts Institute of Technology, Cambridge, Massachusetts

PROFESSIONAL AND CAREER OBJECTIVES:

To contribute to the improvement of public health in the areas of nutrition and public health policy through an internationally recognized nutrition program

LICENSES, CERTIFICATIONS, HONORS:

Licensed Dietitian (L.D.), State of Illinois	1995 to present
Certified Nutrition Specialist (C.N.S.)	1993 to present
Fellow, American College of Nutrition (F.A.C.N.)	1992 to present
Honorary Member, Irish Veterinary Medical Association	1988 to present

EXPERIENCE:

Independent Consultant	May 1998 to present
Senior Research Analyst, ECRI, Plymouth Meeting, PA	1997 to 1998
Senior Scientist, American Medical Association, Chicago, IL	1990 to 1997
Visiting Scientist/Research Assistant Professor Northwestern University, Chicago, IL	1986 to 2002
Assistant Professor, University of Maryland, College Park, MD	1981 to 1986
Assistant Professor, Rutgers University, New Brunswick, NJ	1979 to 1981

Director and Nutritionist Adviser to the Board of Directors
International College of Advanced Longevity Medicine — 1998 to present

Member, Advisory Board
Society for Integrative Medicine — 1998 to present
National Graves' Disease Foundation — 1992 to 2001

Recorder
Nutrition Sciences Education and Research Fund — 1997 to present

Designated Representative of the C.B.N.S.
Intersociety Physician Nutrition Education Consortium — 1996 to present

Policy Paper Reviewer
Council for Agricultural Science and Technology (CAST). — 1996 to present

Lecturer
Capital University of Integrative Medicine, Washington, DC — 1999 to present
New York Chiropractic College (Diplomate in Nutrition program) — 1998 to present
Northwestern University Medical School, Chicago, IL — 1990 to 2002

Part-Time Faculty
Biostatistics, University of Bridgeport, Bridgeport, Connecticut — 1993 to present

Adjunct Faculty
Union Institute, Cincinnati, Ohio — 2000 to present

Book Review Editor
Nutrition: The International Journal of Applied and Basic Nutritional Sciences — 1992 to present

Manuscript Reviewer
The Journal of the American Medical Association, The Journal of the American College of Nutrition, Nutrition, and other peer-reviewed journals — 1980 to present

Council Coordinator
American College of Nutrition — 1994 to 1998

Certification Board for Nutrition Specialists
Director — 1992 to present
Director of Educational Programs — 2001 to present
President — 1996 to 1999
Vice-President — 1992 to 1996
Editor, Certifying Examination, Certification Board for Nutrition Specialists — 1992 to 2001
Editor/Author
1996 Study Guide for the Certifying Examination for Certified Nutrition Specialists — 1996
1996 Candidate's Guide for Licensure as a Nutrition Counselor, State of Illinois — 1996
1999 Study Guide for the Certifying Examination for Certified Nutrition Specialists — 1999
Study Guide for the Certifying Examination for Certified Nutrition Specialists, 3rd Edition — 2002
Lecturer, "Fundamentals of Human Nutrition" Review Course — 2002 to present

Complete Nutrition Expertise May 1998 to present

8612 Kedvale Avenue
Skokie IL 60076

- technical support
- educational/promotional materials
- seminars and symposia
- publications
- labeling
- regulatory affairs
- scientific product support
- policy development
- research protocol evaluation
- research design/implementation
- data analysis and interpretation
- product formulation

Product formulation and development projects have emphasized the rational combination of select vitamins, minerals, herbs, and phytonutrients and phytomedicines into formulas for individuals who are attempting to quit smoking or who are afflicted with alcoholism, caffeine dependency, colorectal cancer, breast cancer, cardiovascular disease, osteoporosis, arthritis or celiac disease. These projects have included the assembly of scientific substantiation for both product ingredients and product labeling.

Consulting Clinical Nutritionist September 1999 to present
North Shore Wellness and Cosmetic Surgery
281 Waukegan Road, Northfield, IL 60093

Patient care in the areas of nutritional support for cancer management, restoration of intestinal function, diabetes, chronic fatigue, multiple sclerosis, mental illness, skeletal function, heart disease, chronic fatigue syndrome, fibromyalgia, morbid obesity, yeast infection and smoking cessation.

Nutritionist/Medical Advisor September 2000 to present
Lake County Chapter, Celiac-Sprue Association

Past consulting projects:

Identification and substantiation of structure/function statements for dietary supplements containing ginseng (prepared for a commercial client).

Substantiation of new health claims for dietary supplements containing folic acid (prepared for a petition submitted to the FDA).

Substantiation of new health claims for dietary supplements containing antioxidant vitamins (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing selenium (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing antioxidant vitamins (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing selenium (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing phosphatidylserine (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing glucosamine (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing chondroitin sulfate (prepared for petitions submitted to the FDA).

Design of human trials to demonstrate the safety of a new dietary ingredient (prepared for a commercial client).

Preparation of the scientific background for petitions to FDA requesting approval to import new dietary ingredients (prepared for commercial clients).

Comparison of scientific manuscripts in several copyright infringement cases.

Substantiation of structure/function statements made for several dietary supplements (prepared for commercial clients).

Data analysis for the development of normal reference intervals for a series of new diagnostic tests.

Scientific substantiation and validation of a survey instrument for the assessment of overall health.

Scientific substantiation of a dietary supplement formulation for the support of cognitive functions (prepared for a commercial client).

Evaluation of the safety and effectiveness of a dietary supplement formulation for the chelation of heavy metals (prepared for a commercial client).

Evaluation of the safety and effectiveness of a dietary supplement formulation for enlargement of the human female breast (prepared for a commercial client).

Evaluation of the safety and effectiveness of dietary supplement formulations for enhancement of weight loss (prepared for commercial clients).

Evaluation of the safety and effectiveness of dietary supplement formulations for enhancement of sexual function (prepared for a commercial client).

Evaluation of the safety and effectiveness of dietary supplement formulations for enhancement of immune function (prepared for a commercial client).

Evaluation of the safety and effectiveness of dietary supplement formulations for enhancement of sleep (prepared for a commercial client).

Evaluation of the safety and effectiveness of a dietary supplement formulation for reduction of serum total cholesterol concentration (prepared for a commercial client).

Consultations with the Deputy Commissioner of the Food and Drug Administration concerning the scientific substantiation of proposed health claims for dietary supplements.

Presentations since May 1998:

Herbal management of diabetes. Natural Pharmacy East, Arlington, VA, October 1998.

Nutritional support for breaking nicotine addiction. International College for Advancement of Longevity Medicine Fall Symposium, Reno, NV, October, 1998.

Nutritional support for breaking nicotine addiction. Sixth International Congress of the American Academy of Anti-Aging Medicine, Las Vegas, NV, December, 1998.

Nutritional support for breaking nicotine addiction: A randomized, double-blind, placebo-controlled evaluation of a proprietary dietary supplement. American College of Nutrition Annual Symposium, Washington, DC, October, 1999

Efficacy of an enzyme product derived from *Aspergillus niger* and bromelain (AbsorbAid™) in improving protein absorption in nursing home patients on tube feeding. American College of Nutrition Annual Symposium, Las Vegas, NV, October, 2000.

Preventing cancer with nutrition. Prevention Plus, Oak Park, IL, October, 2000.

Celiac disease. Healthy Eating Seminar Series, Lake County Chapter, Celiac-Sprue Association, Waukegan, IL, October, 2000.

Gluten sensitivity and other digestive disorders. Healthy Eating Seminar Series, Lake County Chapter, Celiac-Sprue Association, Deerfield, IL, January, 2001.

Digestive disease; celiac disease; digestive ecology; using diagnostic technology to target trace elements and vitamin therapy. American Naprapathic Association, Countryside, IL, April 22, 2001.

Biomarkers of aging. Chicagoland Anti-Aging Conference, Wilmette, IL, May 19, 2001.

Restoration of digestive ecology. Designs for Health – Advanced Training in Clinical Nutrition, Designs for Health Institute, Boulder, CO, June 30, 2001.

The relationship between digestive tract function and autism. In-service training, Pfeiffer Foundation, Naperville, IL, July 2001.

Nutrition and brain function. Amer, Naprapathic Assoc., Countryside, IL, April 7,2002.

Fundamentals of Human Nutrition. Two-day Review Course in preparation for the certifying examination of the Certification Board for Nutrition Specialists. American College for the Advancement of Medicine, Ft. Lauderdale, FL, May 15-16, 2002.

Fundamentals of Human Nutrition. Two-day Review Course in preparation for the certifying examination of the Certification Board for Nutrition Specialists. American College of Nutrition, San Antonio, TX, October 2-3, 2002.

Fundamentals of Human Nutrition. Two-day Review Course in preparation for the certifying examination of the Certification Board for Nutrition Specialists. American College of Nutrition, New York, NY. April 5-6, 2003.

Fundamentals of Nutrition. Two-day Review Course in preparation for the certifying examination of the Certification Board for Nutrition Specialists. American College of Nutrition, Miami, FL, April 23-24, 2003.

Upcoming Presentations:

Fundamentals of Human Nutrition. Two-day Review Course in preparation for the certifying examination of the Certification Board for Nutrition Specialists. American College of Nutrition, New York, NY. April 5-6, 2003.

Teaching Lecture Topics since May 1998:

Environmental medicine and detoxification therapy.
Carbohydrate nutrition and nutritional therapy.
Protein nutrition and nutritional therapy.
Nutritional and herbal management of diabetes.
Nutritional therapeutics in cancer.
Nutrition and cancer prevention for consumers.
Celiac disease and its prevention and treatment.
Free radical and antioxidant biology.
Biostatistics for nutritionists (I designed and am teaching this course both in-class and over the internet)

ECRI

5200 Butler Pike, Plymouth Meeting, PA 19462 August 1997 to May 1998

SENIOR RESEARCH ANALYST
Technology Assessment

Evaluation of medical, nutritional, and technological therapies and diagnostic techniques for human endocrine, metabolic, musculoskeletal, and nutritional diseases.

Quality Assurance Manager, National Guidelines Clearinghouse (with AHCPR)

Participant in database design, National Guidelines Clearinghouse (with AHCPR)

Statistical expert, diagnostic technologies and meta-analysis

Provide in-house expertise to ECRI Management on food, device, drug, agriculture and nutrition-related health, policy, legal, and regulatory matters.

SUPERVISOR: Charles Turkelson, Ph.D.
Chief Research Analyst
Technology Assessment
ECRI

AMERICAN MEDICAL ASSOCIATION

515 N. State St. Chicago, IL 60610 1993 to 1997

SENIOR SCIENTIST, Technology Assessment & Nutrition
Department of Technology Assessment

Evaluation of medical, nutritional, and technological therapies and diagnostic techniques for human endocrine, metabolic, musculoskeletal, and nutritional diseases.

Development of Technology Assessments for the AMA *Diagnostic and Therapeutic Technology Assessment (DATTA)* project:

- Diagnostic Value of Plasma Lp(a) Concentrations
- Diagnostic Value of Plasma Apolipoproteins
- Diagnostic Value of Serum Thyroid-Stimulating Hormone (TSH)
- Diagnostic Value of Computerized Dynamic Posturography
- Diagnostic Value of 24-hour Esophageal pH Monitoring
- Therapeutic Value of Peripheral Parenteral Nutrition
- Therapeutic Value of Intraoperative Radiotherapy
- Therapeutic Value of Speech Therapy in Otitis Media
- Therapeutic Value of Recombinant Human Growth Hormone (rhGH) in Children with Short Stature
- Therapeutic Value of Mononuclear Leukocyte ("Buffy Coat") Infusions in Chronic Myelocytic Leukemia
- Therapeutic Value of Medicinal Leeches
- Therapeutic Value of Pedicle Screw Spinal Fixation Systems
- Therapeutic Value of Recombinant Human Growth Hormone (rhGH) in Children with Gonadal Dysgenesis

Related Duties:

Statistician; perform statistical analyses for all physician surveys administered by the *DATTA* project.

Co-Editor of the monthly AMA newsletter, *Technology News.*

Provide in-house expertise to AMA Senior Management on food, device, drug, agriculture and nutrition-related health, policy, legal, and regulatory matters.

Secretary, AMA House of Delegates Reference Committee E (advise AMA policy committees on medicine, nutrition, and public health).

Publications:

Published In:	No. of Publications:
DATTA Assessments:	13
peer-reviewed journals:	4
Proceedings chapters:	4
book reviews:	11
general public press:	16
peer-reviewed journals (submitted):	5

Original articles published in the monthly AMA newsletter, *Technology News*:

Risk Assessment in the Establishment of Upper Safe Limits for Nutrient Intakes	12/96
Dietary Fat and Cancer: Molecular Mechanisms	10/96
Clinical Significance of Melatonin (with B. Kendler)	9/96
Designing, Testing, and Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities	6/96
Dietary Phytochemicals in Cancer Prevention and Treatment	11/95
Electromagnetic Compatibility for Medical Devices: Issues and Solutions	9/95
FDA/NIH-Sponsored Conference: Comparing Treatments: Safety, Effectiveness, and Cost-Effectiveness	5/95
Clinical Significance of Oxidative Stress (with B. Kendler)	11/95
Diet and Cancer: Molecular Mechanisms of Interactions	1-2/95
Management of Disorders of Cholesterol, Triglyceride, and Lipoprotein Metabolism	11/94
AMA Annual Meeting Update (with S. Kalousdian)	7-8/94
Drug and Device-Induced Disease: Developing a Blueprint for the Future	/94
AMA Interim Meeting Update (with S. Kalousdian)	1-2/94
AMA Annual Meeting Update (with S. Kalousdian)	8/93
Breast Cancer Risk and Diet	1/93

Author of AMA policy statements on nutrition issues:

food irradiation;

lipoproteinemia;

bacterial contamination of meat;

dietary calcium requirements;

folic acid supplementation to prevent neural tube defects;

thiamin supplementation of alcoholic beverages to prevent polyneuropathy;

neonatal hyponatremia from hypo-osmolar bottled water

Speaking Invitations:

The Dietary Supplement and Health Education Act of 1994. Annual Meeting of the American College of Nutrition, Washington, DC, October, 1995.

Innovation in clinical nutrition. Harvard University, May 6, 1995.

Environmental medicine. New York Chiropractic College, April 29, 1995.

Environmental medicine. New York Chiropractic College, September 11, 1994.

Additional Responsibilities:

Meeting with representatives of the Food and Drug Administration, the US Department of Agriculture, and other federal agencies concerning:

food, device and drug regulation;
food safety;
direct to consumer advertising of medical therapies.

Collaboration with other AMA staff in the development of scripts for television programs aired on American Medical Television.

Represented AMA on "National Educational Forum on Food Safety Issues."

Book Review Editor, *Nutrition: The International Journal of Applied and Basic Nutritional Sciences.*

Reviewed manuscripts submitted to *the Journal of the American Medical Association*, *the Journal of the American College of Nutrition*, and other peer-reviewed journals.

Reviewed advertisements intended for use in AMA publications.

Policy paper reviewer for the Council for Agricultural Science and Technology (CAST).

Invitations to Chair National Meetings:

Invited to chair and organize a session on "Nutritional Controversies" at the 1996 Annual Meeting of the American College of Nutrition, San Francisco.

Invited to serve as co-chairman of a session of the 1994 Malnutrition and AIDS Symposium, Los Angeles.

Invited to serve as co-chairman of a session of the 1994 Annual Meeting of the American College of Nutrition, Atlanta.

SUPERVISOR: Sona Kalousdian, MD, MPH
Department Director, Department of Technology Assessment
American Medical Association
(773) 384-4915

AMERICAN MEDICAL ASSOCIATION

515 N. State St. Chicago, IL 60610 1990 to 1993

SENIOR SCIENTIST, Endocrinology, Metabolism & Nutrition
Department of Drugs

Evaluation of medical and nutritional therapies and diagnostic techniques for human endocrine, metabolic, musculoskeletal, and nutritional diseases.

Extensive revision of chapters in the Congressionally-recognized compendium of FDA-approved unlabeled drug use and nutritional therapy, *AMA Drug Evaluations*:

Fluid, Electrolyte, and Acid-Base Therapy (pp. 865-880*)
Drugs Used for Urolithiasis (pp. 907-924)
Drugs Used in Adrenocortical Dysfunction (pp. 1017-1036)
Drugs Used in Thyroid Disease (pp. 1037-1062)
Vitamins and Minerals (pp. 2283-2306)
Parenteral and Enteral Nutrition (pp. 2307-2362)
Drugs Used in Obesity (pp. 2439-2454)
Treatment of Disorders of Cholesterol and Lipoprotein Metabolism (pp. 2455-2500)

(* page numbers as in the 1995 edition)

Assistant Secretary, AMA House of Delegates Reference Committee E (advise AMA policy committees during development of policies concerning medicine, nutrition, and public health).

Collaboration with other AMA staff in the development of scripts for television programs aired on American Medical Television

Publications:

Published In:	No. of Publications:
AMA Drug Evaluations Chapters:	8
peer-reviewed journals:	12
Proceedings chapters:	6
book reviews:	1
general public press:	6

Speaking Invitations:

A review of hormonal regulation of cartilage growth in foals. Symposium on Equine Osteochondrosis, Cambridge University, United Kingdom, September, 1992.

Marginal copper deficiency as a cause of defective angiogenesis in chondrodysplasia. Symposium on Equine Osteochondrosis, Cambridge University, United Kingdom, September, 1992.

Endocrine regulation of equine growth plate chondrocytes. Symposium on Equine Osteochondrosis, Cambridge University, United Kingdom, September, 1992.

Equine osteochondrosis as a manifestation of induced episodic "pseudohypothyroidism." Symposium on Equine Osteochondrosis, Cambridge University, United Kingdom, September, 1992.

Insulin and thyroid hormones influence matrix production by chondrocytes. Seminars in Endocrinology, Northwestern University, Chicago, IL, April 2, 1991.

Additional Responsibilities:

Meetings with representatives of the Food and Drug Administration, the US Department of Agriculture, and other federal agencies concerning:

food, device and drug regulation;

food safety;

direct to consumer advertising of medical therapies

Collaboration with Centers for Disease Control in development of recommendations concerning folic acid and the prevention of neural tube defects (*Morbidity and Mortality Weekly*, August 2, 1991, and September 21, 1992).

Author of AMA policy statement on monosodium glutamate.

Provide in-house expertise to AMA Senior Management on food, device, drug, agriculture and nutrition-related health, policy, legal, and regulatory matters.

Represented AMA on "National Educational Forum on Food Safety Issues".

Book Review Editor, *Nutrition: The International Journal of Applied and Basic Nutritional Sciences.*

Review manuscripts submitted to *the Journal of the American Medical Association*, *the Journal of the American College of Nutrition*, and other peer-reviewed journals.

Review advertisements intended for use in AMA publications.

Coordinator, Council on Endocrinology, Bone, and Minerals; American College of Nutrition.

Advisory Board Member, National Graves' Disease Foundation

SUPERVISOR: Joseph Cranston, Ph.D.
Department Director
Department of Drugs
American Medical Association

NORTHWESTERN UNIVERSITY

303 E. Chicago Avenue, Chicago, IL 60610 1986 to 1990

RESEARCH ASSISTANT PROFESSOR
Department of Pharmacology

Funded originally as an NIH Senior Fellowship, this position - including both research and teaching - has been continued on a part-time, unpaid basis through the present time as a Visiting Scientist, Department of Molecular Pharmacology and Biological Chemistry

Laboratory and field research; presentation and publication of research findings; fund raising; maintenance of laboratory; practice of safe and proper animal housing and handling; practice of safe handling of hazardous substances.

Concentration on the effects of nutrients, hormones and growth factors on skeletal development and disease.

Guest lectures on pancreatic and thyroid disease and their prevention and medical and nutritional management.

Publications:

Published In:	No. of Publications:
peer-reviewed journals:	11
Proceedings chapters:	8
abstracts:	4
general public press:	98

Speaking Invitations:

Response of arthritic chondrocytes to polysulfated glycosaminoglycans. Skeletal Biology Program, Case Western Reserve University, Cleveland OH, May 14, 1990.

Flora and fauna of Africa and Europe. Department of Pharmacology, Northwestern University, Chicago, IL, February 9, 1989.

Influences of diet and endocrinology on equine developmental orthopedic disease. Department of Animal Sciences, University of Guelph, Ontario, Canada, January 18, 1989.

Diet and growth quality. Equine management class, University of Guelph, Ontario, Canada, January 18, 1989.

Fermentation enhancers. Department of Animal Sciences, University of Guelph, Ontario, Canada, January 17, 1989.

Nitrogen metabolism in the equine. Equine management class, University of Guelph, Ontario, Canada, January 16, 1989.

Feeding and management of pleasure and show horses. Potomac Horse Club, Silver Spring, MD, October, 1988.

Feeding and management of pleasure and show horses. Potomac Horse Club, Silver Spring, MD, October, 1988.

Homeorrhesis and the growing animal. Biological Sciences Seminar, University College, Dublin, Ireland, October 17, 1988.

Nutrition and developmental disorders of equidae. Department of Zoology, University College, Dublin, Ireland, October 17, 1988.

Nitrogen metabolism in horses. Veterinary College of Ireland, Dublin, Ireland, October 14, 1988.

The role of yeast culture in the nutritional management of young horses. 100th Irish Veterinary Congress, Dublin, Ireland, September 23, 1988.

The role of endocrine factors in equine developmental orthopedic disease. Developmental Orthopedic Disease Panel, American Association of Equine Practitioners Annual Meeting, New Orleans, LA, November 29, 1987.

Diet, chondrodysplasias and animals. Oral Biology Seminar, Northwestern University, Chicago, IL, October 29, 1987.

Effects of yeast culture on nitrogen metabolism in young horses. Alltech Biotechnology Symposium, Lexington, KY, April, 1987.

Bibliometric analysis of research activity in Brazil. Central Intelligence Agency, MacClean, VA, March, 1987.

Bibliometric analysis of research activity in Spain. Ministry of Science and Education, Madrid, Spain, March, 1987.

Cartilage disorders associated with changes in thyroid hormone metabolism. The Chicago Endocrine Society, Chicago, IL, December, 1986.

Dietary causes of osteochondrosis. Pathology Seminar, Northwestern University, Chicago, IL, April, 1986.

UNIVERSITY OF MARYLAND

College Park, Maryland 1981 to 1986

ASSISTANT PROFESSOR, Department of Animal Sciences
College of Agricultural Sciences

Teaching: (Class, laboratory, barn; lecture, hands-on formats)

Animal Husbandry (nutrition, diet formulation, diseases, management, genetics, physiology, functional morphology)

Animal Training (including principles of animal behavior and their application to training)

Safe Animal Handling (including principles of animal behavior and their application to safe practices in handling animals)

Protein Nutrition (graduate course)

Training:

How to Teach and Supervise Animal Training (undergraduate and graduate students; written materials; videotapes)

Laboratory Techniques (undergraduate and graduate students)

Field Research Techniques (undergraduates and graduates)

Dissertation and Scientific Writing

Grant Proposal Preparation

Research:

Animal Nutrition and Physiology Projects, including several in collaboration with the National Zoo, Washington, DC

Publications:

Published In:	No. of Publications:
peer-reviewed journals:	17
Proceedings chapters:	8
abstracts:	8
general public press:	73

Other projects: (in addition to those documented in publications)

hormone secretion rates in pigs

skeletal growth in monkeys

pharmacokinetics of ivermectin in bullfrogs

growth hormone concentrations in horses and zebras

Invitation to Chair National Meeting:

Invited to serve as co-chairman of a Non-Ruminant Nutrition session at the 1982 meeting of the American Society of Animal Science, Guelph, Ontario, Canada.

Speaking Invitations:

Quality feed management: tips for proper production and storage. Baltimore Horse Seminar, March, 1985.

Dietary carbohydrate induction of the multiple-messenger, inositol-calmodulin pathway. Animal Sciences Seminar, University of Maryland, February, 1985.

The use of ultrasound to monitor neonatal bone development. Invited seminar, Walter Reed Medical Center, Washington, DC, December, 1984.

Mechanisms of dietary induction of osteochondrosis. Invited seminar, Department of Animal Science, University of Alberta, Edmonton, Canada, August, 1984.

The Use of Self-Supervised Activity to Acquaint College Students with the Teacher-Student Dynamic. 10th International Conference, Improving University Teaching, College Park, MD, July, 1984.

Diagnostic ultrasound - a non-invasive method for examining bone. Pediatric Research Conference, University of Maryland School of Medicine, May, 1984.

Electrical stimulation of bone healing. Alice Deal Science Day, May, 1984.

Non-Traditional feeding practices for the performance horse. Maryland Nutrition Conference, Baltimore, MD, March, 1984.

The use of ultrasound. Nutritional Sciences Colloquium, University of Maryland, February, 1984.

Nutrient-hormone interactions and their impact on growth. Nutritional Sciences Colloquium, University of Maryland, February, 1984.

Feeding horses for a lot less money. Eastern Amateur Arabian Horse Show Circuit Fall Meeting, December, 1983.

Equine nutritional requirements. Baltimore Horse Seminar, November, 1983.

The costs of owning a horse, Maryland Society for the Prevention of Cruelty to Animals Field Day, May, 1983.

Ultrasonic measurement of bone strength. Alice Deal Science Day, April, 1983.

Nutritional manipulation of bone and joint development in growing horses. Maryland Nutrition Conference, Washington, DC, March, 1982.

Developmental origins of growth abnormalities. Animal Sciences Seminar, University of Maryland, October, 1981.

Additional Responsibilities:

Design of Animal Habitats:

Personally redesigned three multi-acre animal housing facilities, and assisted in their physical renovation

Animal Care:

Collaboration with veterinarians in prophylactic and interventive medical care, including personally:

administering medications by mouth
injection (intramuscular; intravenous)
nasogastric intubation; rectal gavage
bandaging; suturing
development of growth plate biopsy procedure for ungulates
necropsy

Animal Management:

Directly responsible for the management, breeding, and training of up to 120 horses residing at multi-building and multi-site facilities whose activities encompassed teaching, research, breeding, continuing adult education, veterinary care, demonstrations

Supervision of Personnel:

Supervision of up to two dozen permanent and temporary full and part time employees and volunteers engaged in animal husbandry

Record Keeping; Budgets:

Directly responsible for planning, developing, administering, and adhering to expense and revenue budgets, and for extensive and comprehensive record-keeping concerning all facets of a major university equine program

Fund-Raising:

Obtaining funds to support all programs and activities

Sources included federal agencies, state agencies, private foundations, private individuals, corporate entities, animal sales, animal rental

RUTGERS UNIVERSITY

New Brunswick, NJ 1979 to 1981

ASSISTANT PROFESSOR, Department of Animal Sciences

Teaching: (Class, laboratory, barn; lecture, hands-on formats):

Animal Husbandry (nutrition, diet formulation, diseases, management, genetics, physiology, functional morphology)

Animal Training (including principles of animal behavior and their application to training)

Safe Animal Handling (including principles of animal behavior and their application to safe practices in handling animals)

Training:

Field Research Techniques (undergraduates and graduates)

Grant Proposal Preparation

Research:

Animal Nutrition and Physiology Projects

Publications:

Published In:	No. of Publications:
Proceedings chapters	1
abstracts	1

Speaking Invitations:

Digestive physiology of the horse. Animal Sciences Seminar, University of Maryland, September, 1980.

Similarities between effects of dexamethasone on growing cartilage and osteochondrosis dissecans. Animal Science Seminar, University of California at Davis, April, 1980.

Osteochondrosis dissecans and growth suppression in dexamethasone treated horse foals. American Association of Equine Practitioners Annual Meeting, Miami Beach, December, 1979.

Effects of dexamethasone on calcium metabolism of pony foals. Animal Sciences Seminar, Rutgers University, May, 1979.

Additional Responsibilities:

Design of Animal Habitats:

Personally redesigned a multi-acre animal housing facility, and assisted in its physical renovation

Animal Care:

Collaboration with veterinarians in prophylactic and interventive medical care, including personally:

administering medications by mouth
injection (intramuscular; intravenous)
nasogastric intubation; rectal gavage
bandaging; suturing; necropsy

Animal Management:

Directly responsible for the management, breeding, and training of up to 11 horses residing at multi-building and multi-site facilities whose activities encompassed teaching, research, continuing adult education, veterinary care, demonstrations

Supervision of Personnel:

Directly responsible for the supervision of two permanent part time employees and a dozen or so volunteers engaged in animal husbandry

Record Keeping; Budgets:

Directly responsible for planning, developing, administering, and adhering to expense and revenue budgets, and for extensive and comprehensive record-keeping concerning all facets of a major university equine program

Fund-Raising:

Obtaining funds to support all programs and activities

Sources included federal agencies, state agencies, private foundations, private individuals, corporate entities, animal sales, animal rental

Refereed Journal Articles:

1. Glade, M.J. The effects of gestation, lactation, yeast culture and maternal calcium intake on the mechanical strength of equine bone. *Journal of Equine Veterinary Science*: submitted for publication.

2. Heimburger, D.C., and the Intersociety Professional Nutrition Education Consortium. 2002. Training and certifying gastroenterologists as Physician Nutrition Specialists. *Journal of Clinical Gastroenterology* 34:505-508.

3. Glade, M.J., D. Kendra and M.V. Kaminski, Jr. 2001. Improvement in protein utilization in nursing-home patients on tube feeding supplemented with an enzyme product derived from *Aspergillus niger* and bromelain. *Nutrition* 17:348-350.

4. Heimburger, D.C., and the Intersociety Professional Nutrition Education Consortium. 2000. Physician-nutrition-specialist track: If we build it, will they come? *American Journal of Clinical Nutrition* 71:1048-1053.

5. Glade, M.J. 1997. Intake of dietary calcium to reduce the incidence of osteoporosis. *Archives of Family Medicine* 6:491-494.

6. Glade, M.J. 1995. Management of disorders of cholesterol, triglyceride, and lipoprotein metabolism. *Archives of Family Medicine* 4:869-878.

7. Glade, M.J. 1995. Continuous ambulatory esophageal pH monitoring. *Journal of the American Medical Association* 274:662-668.

8. Glade, M.J., Y.S. Kanwar and P.H. Stern. 1994. Insulin and thyroid hormones alter chondrocyte metabolism in cell culture independently and in combination. *Connective Tissue Research* 31:37-44.

9. Glade, M.J. 1993. The effects of gestation, lactation, and maternal calcium intake on the mechanical strength of equine bone. *Journal of the American College of Nutrition* 12:372-377.

10. Glade, M.J. 1992. Effects of Yucca shidigera extract on feed utilization by equine weanlings. *Journal of Equine Veterinary Science* 12:93-98.

11. Letcher, J. and M.J. Glade. 1992. Efficacy of ivermectin as an anthelmintic in leopard frogs. *Journal of the American Veterinary Medical Association* 200:537-538.

12. Glade, M.J., Y.S Kanwar and T.J. Hefley. 1991. Enzymatic isolation of chondrocytes from immature rabbit articular cartilage and their maintenance of phenotypic expression in culture. *Journal of Bone and Mineral Research* 6:217-226.

13. Glade, M.J. 1991. Timed administration of leucine, isoleucine, valine, glutamine, and carnitine to enhance athletic performance. *Equine Athlete* 4:1-10.

14. Glade, M.J. 1991. Effects of dietary yeast culture supplementation of lactating mares on the digestibility and retention of the nutrients delivered to nursing foals via milk. *Journal of Equine Veterinary Science* 11:323-329.

15. Glade, M.J. 1991. Dietary yeast culture supplementation of mares during late gestation and early lactation. 3. Effects on mare and foal plasma metabolite, amino acid and endocrine profiles. *Journal of Equine Veterinary Science* 11:167-175.

16. Glade, M.J. 1991. Dietary yeast culture supplementation of mares during late gestation and early lactation. 2. Effects on milk production, milk composition, weight gain and linear growth of nursling foals. *Journal of Equine Veterinary Science* 11:89-95.

17. Glade, M.J. 1991. Dietary yeast culture supplementation of mares during late gestation and early lactation. 1. Effects on dietary nutrient digestibilities and fecal nitrogen partitioning. *Journal of Equine Veterinary Science* 11:10-16.

18. Glade, M.J. and M.D. Sist. 1990. Supplemental yeast culture alters the plasma amino acid profiles of nursling and weanling horses. *Journal of Equine Veterinary Science* 10:369-379.

19. Glade, M.J. and N.K. Luba. 1990. Benefits to foals of feeding soybean meal to lactating broodmares. *Journal of Equine Veterinary Science* 10:422-428.

20. Glade, M.J. and M. Campbell-Taylor. 1990. Effects of dietary yeast culture supplementation during the conditioning period on equine exercise physiology. *Journal of Equine Veterinary Science* 10:434-443.

21. Glade, M.J. 1990. Polysulfated glycosaminoglycan (PSGAG) accelerates the synthesis of collagen and glycosanminoglycans by arthritic equine cartilage tissues and chondrocytes. *American Journal of Veterinary Research* 51:779-785.

22. Sist, M.D., Youngblood, M.A., Williams, J.F. and Glade, M.J. 1988. Salivary and serum estrone sulfate levels in pregnant mares. *Journal of Equine Veterinary Science* 8: 164-167.

23. Glade, M.J. and M.D. Sist. 1988. Dietary yeast culture supplementation enhances urea recycling in the equine large intestine. *Nutrition Reports International* 37: 11-19.

24. Wright, L.L., M.J. Glade and J. Gopal. 1987. The use of transmission ultrasonics to assess bone status in the human newborn. *Pediatrics Research* 22:541-544.

25. Glade, M.J. and N.K. Luba. 1987. Serum triiodothyronine and thyroxine concentrations in weanling horses fed carbohydrate by direct gastric infusion. *American Journal of Veterinary Research* 48:578-582.

26. Glade, M.J., N.K. Luba, and H.F. Schryver. 1986. Effects of age and diet on the development of mechanical strength by the cannon bones of young horses. *Journal of Animal Science* 63:1432-1444.

27. Glade, M.J. and L.M. Biesik. 1986. Changes in serum hormone concentrations in weanling horses following gastric infusion of sucrose or casein. *Nutrition Reports International* 33:651-659.

28. Glade, M.J. and L.M. Biesik. 1986. Enhanced nitrogen retention in yearling horses supplemented with yeast culture. *Journal of Animal Science* 62:1633-1640.

29. Glade, M.J. 1986. Estimation of urine flow rate in weanling and yearling horses. *American Journal of Veterinary Research* 47:2151-2156.

30. Glade, M.J. and T.H. Belling. 1986. A dietary etiology for osteochondrotic cartilage. *Journal of Equine Veterinary Science* 6:151-154.

31. Glade, M.J. 1986. The control of cartilage growth in osteochondrosis. *Journal of Equine Veterinary Science* 6:175-187.

32. Glade, M.J. 1986. "Social Sleeping" among confined horses. *Journal of Equine Veterinary Science* 6:155-157.

33. Glade, M.J. and R.A. Salzman. 1985. Effects of hoof angulation on hoof growth and contraction in the horse. *Journal of Equine Veterinary Science* 5:45-50.

34. Glade, M.J. and T.J. Reimers. 1985. Effects of dietary energy supply on serum thyroxine, tri-iodothyronine and insulin concentrations in young horses. *Journal of Endocrinology* 104:93-98.

35. Glade, M.J., D. Beller, J. Bergen, D. Berry, E. Blonder, J. Bradley, M. Cupelo and J. Dallas. 1985. Dietary protein in excess of requirements inhibits renal calcium and phosphorus reabsorption in young horses. *Nutrition Reports International* 31:649-659.

36. Glade, M.J. 1985. Stimulation of electromagnetic osteogenesis in healthy growing yearlings. *Journal of Equine Veterinary Science* 5:149-153.

37. Glade, M.J. 1985. Overfeeding energy to horses. *Journal of Equine Veterinary Science* 5:95.

38. Glade, M.J., S. Gupta and T.J. Reimers. 1984. Hormonal responses to high and low planes of nutrition in weanling Thoroughbreds. *Journal of Animal Science* 59:658-665.

39. Glade, M.J. and T.H. Belling. 1984. Growth plate cartilage metabolism, morphology and biochemical composition in over- and underfed horses. *Growth* 48:473-482.

40. Glade, M.J. 1984. Feeding innovations for the performance horse. *Journal of Equine Veterinary Science* 4:165-168.

41. Glade, M.J. 1984. "Social sleeping" behavior in young horses. *Equine Practice* 6:10-14.

42. Glade, M.J. 1984. The influence of dietary fiber digestibility on the nitrogen requirements of mature horses. *Journal of Animal Science* 58:638-646.

43. Belling, T.H. and M.J. Glade. 1984. A non-destructive biopsy method allowing the rapid removal of live growth plate cartilage. *Veterinary Medicine/Small Animal Clinician* 79:528-531.

44. Glade, M.J. 1983. Nitrogen partitioning along the equine digestive tract. *Journal of Animal Science* 57:943-953.

45. Glade, M.J. 1983. Nutrition and performance of racing Thoroughbreds. *Equine Veterinary Journal* 15:31-36.

46. Glade, M.J., L. Krook, H.F. Schryver and H.F. Hintz. 1982. Morphologic and biochemical changes in cartilage of foals treated with dexamethasone. *Cornell Veterinarian* 73:170-192.

47. Glade, M.J., L. Krook, H.F. Schryver and H.F. Hintz. 1982. Calcium metabolism in glucocorticoid-treated foals. *Journal of Nutrition* 112:67-76.

48. Glade, M.J. and L. Krook. 1982. Glucocorticoid-induced inhibition of osteolysis and the development of osteopetrosis, osteonecrosis and osteoporosis. *Cornell Veterinarian* 72:76-91.

49. Glade, M.J., L. Krook, H.F. Schryver and H.F. Hintz. 1981. Growth inhibition induced by chronic dexamethasone treatment of foals. *Journal of Equine Veterinary Science* 1:198-201.

50. Matteo, C.M., M.J. Glade, A. Tanaka, J. Piret and A.L.Demain. 1975. Microbiological studies on the formation of gramicidin S synthetases. *Biotechnology and Bioengineering* 17:129-142.

Abstracts and Proceedings:

1. Glade, M.J., Kendra, D., Kaminsky, M.V., Jr. 2000. Efficacy of an enzyme product derived from *Aspergillus niger* and bromelain (AbsorbAid™) in improving protein absorption in nursing home patients on tube feeding. *Proceedings, Annual Meeting of the American College of Nutrition*, Las Vegas, NV, October.

2. Heimburger, D., and IPNEC. 2000. Training the Physician Nutrition Specialist (PNS). *Proceedings, Annual Meeting of the American College of Nutrition*, Las Vegas, NV, October.

3. Glade, M.J. 1998. Nutritional support for breaking nicotine addiction. *Proceedings, Sixth International Congress on Anti-Aging and Biomedical Technologies* (American Academy of Anti-Aging Medicine), Las Vegas, NV, December, p. unpaged.

4. Glade, M.J. 1998. Nutritional support for breaking nicotine addiction. *Proceedings, International College for Advancement of Longevity Medicine Fall Symposium,* Reno, NV, October, unpaged.

5. Glade, M.J. 1998. Herbal management of diabetes. *Proceedings, Second Annual Natural Pharmacy East Conference,* Arlington, VA, October, unpaged.

6. Glade, M.J., and M.E. Allen. 1996. Assessment of skeletal development in leopard geckos. II. Long bone morphometry and breaking strength. *Proceedings, Ninth Dr. Scholl Nutrition Conference,* Chicago, IL, October, unpaged.

7. Glade, M.J. 1995. The Dietary Supplement and Health Education Act of 1994. *Proceedings, Annual Meeting of the American College of Nutrition*, Washington, DC, October, p. 557.

8. Glade, M.J. 1993. $CuSO_4$ and chelated copper are bioequivalent when added to the diets of nursing foals. *Proceedings, Annual Meeting of the American College of Nutrition*, Chicago, October, p. 589.

9. Glade, M.J. 1993. $CuSO_4$ and chelated copper are bioequivalent when added to the culture medium of cartilage tissue and cells. *Proceedings, Annual Meeting of the American College of Nutrition*, Chicago, October, p. 589.

10. Glade, M.J. 1992. Equine osteochondrosis as a manifestation of induced episodic "pseudohypothyroidism." *Proceedings, Symposium on Equine Osteochondrosis*, Cambridge University, United Kingdom, September, p. 44.

11. Glade, M.J. 1992. Endocrine regulation of equine growth plate chondrocytes. *Proceedings, Symposium on Equine Osteochondrosis*, Cambridge University, United Kingdom, September, pp. 42-43.

12. Glade, M.J. 1992. Marginal copper deficiency as a cause of defective angiogenesis in chondrodysplasia. *Proceedings, Symposium on Equine Osteochondrosis*, Cambridge University, United Kingdom, September, pp. 30-31.

13. Glade, M.J. 1992. A review of hormonal regulation of cartilage growth in foals. *Proceedings, Symposium on Equine Osteochondrosis*, Cambridge University, United Kingdom, September, pp. 19-20.

14. Glade, M.J. 1992. The effects of gestation, lactation, and maternal calcium intake on the mechanical strength of equine bone. *Proceedings, Annual Meeting of the American College of Nutrition*, San Diego, October, p. 600.

15. Glade, M.J. 1992. Marginal copper deficiency as a cause of defective angiogenesis in chondrodysplasia. *Proceedings, Annual Meeting of the American College of Nutrition*, San Diego, October, p. 600.

16. Glade, M.J., C. Cahill and M. Campbell. 1989. Effect of exercise on plasma growth hormone concentrations in foals. *Proceedings, Equine Nutrition and Physiology Society*, pp. 63-64.

17. Glade, M.J. 1989. Effects of specific amino acid supplementation on lactic acid production by horses exercised on a treadmill. *Proceedings, Equine Nutrition and Physiology Society*, pp. 244-251.

18. Glade, M.J. 1989. Undergraduates and publishable equine research. *Proceedings, Equine Nutrition and Physiology Society*, pp. 233-235.

19. Glade, M.J. 1989. Supplemental yeast culture alters the plasma amino acid profiles of weanling Quarter horses. *Proceedings, Equine Nutrition and Physiology Society*, pp. 119-123.

20. Campbell, M. and M.J. Glade. 1989. Effects of dietary yeast culture supplementation during the conditioning period on heart rates and lactic acid production by horses exercised on a treadmill. *Proceedings, Equine Nutrition and Physiology Society*, pp. 72-78.

21. Glade, M.J. and P.H. Stern. 1988. Effect of polysulfated glycosaminoglycan (PSGAG) on monolayer cultures of articular chondrocytes. *Journal of Bone and Mineral Research*: 3: Suppl. 1:465.

22. Glade, M.J. 1988. The role of endocrine factors in equine developmental orthopedic disease. *American Association of Equine Practitioners* 33:171-189.

23. Wright, L.L., M.J. Glade and J. Gopal. 1987. Transmission ultrasonics to assess bone status in the human newborn. *Pediatrics Research*: 21:440A.

24. Glade, M.J. and N.K. Luba. 1987. Benefits to foals of feeding soybean meal to lactating broodmares. *Proceedings, Equine Nutrition and Physiology Society*, pp. 593-598.

25. Glade, M.J., T.J. Hefley and P.H. Stern. 1987. A cartilage digestion method maximizing digestion rates and cell yields. *Journal of Bone and Mineral Research*: 2: Suppl. 1: Abstr. 422.

26. Glade, M.J. 1987. The development of mechanical strength in the radius and ulna of the juvenile rhesus monkey. *Journal of Bone and Mineral Research*: 2: Suppl. 1: Abstr. 355.

27. Glade, M.J. 1987. Cross-sectional geometry of equine metacarpal bones: an initial biomechanical investigation. *Proceedings, Equine Nutrition and Physiology Society*, pp. 537-544.

28. Tutsch, L., M.J. Glade and A.O. Sager. 1985. Long bone growth in the limbs of miniature Hormel-Hanford swine. *Proceedings, Swine in Biomedical Research*, p. 73.

29. Glade, M.J. and L.M. Biesik. 1985. Effects of dietary yeast and urea supplementation of the nitrogen metabolism of yearling Thoroughbreds. *Proceedings, Equine Nutrition and Physiology Society*, pp. 26-31.

30. Glade, M.J. 1985. Electromagnetic induction of increased breaking strength in intact growing equine cannon bones. *Proceedings, Equine Nutrition and Physiology Society*, pp. 118-123.

31. Biesik, L.M., M.J. Glade and E.P. Young. 1985. Post-prandial hormone changes, hepatic T_4-5'-deiodinase activities and the incidence of osteochondrosis in growing swine. *Journal of Animal Science:* 61:Abstr. 101.

32. Biesik, L.M. and M.J. Glade. 1985. Changes in serum hormone concentrations in weanling horses following gastric infusion of specific nutrients. *Proceedings, Equine Nutrition and Physiology Society*, pp. 46-51.

33. Glade, M.J., E. Russek and N.K. Luba. 1984. Modeling the growth of young horses. *Journal of Animal Science*: 59:A23.

34. Glade, M.J. and N.K. Luba. 1984. Maximum cannon bone breaking strength is not increased by overfeeding young horses. *Journal of Animal Science*: 59:Abstr. 171.

35. Glade, M.J. and T.J. Belling, Jr. 1984. Alterations in the growth mechanism resulting from chronic overfeeding of young horses. *Journal of Animal Science*: 59:A13.

36. Glade, M.J. 1984. Insulin and thyroxine responses to high energy and protein feeding of weanling horses. *Journal of Animal Science*: 59:Abstr. 476.

37. Gupta, S. and M.J. Glade. 1983. Effects of high and low planes of nutrition on the endocrinology of growing horses. *Journal of Animal Science*: 57:(Suppl.) A2.

38. Gupta, S. and M.J. Glade. 1983. Hormonal responses to high and low planes of nutrition in weanling Thoroughbreds. *Proceedings, Equine Nutriton and Physiology Society*, pp. 45-49.

39. Glade, M.J., J.A. Seder and H.F. Schryver. 1983. Use of low frequency ultrasound in the measurement of the bone breaking strengths in live horses. *Proceedings, Equine Nutrition and Physiology Society*, pp. 33-38.

40. Glade, M.J. 1982. Nutriture and performance of racing Thoroughbreds. *Journal of Animal Science*: 55: (Suppl.) 381.

41. Glade, M.J. 1982. Nutritional manipulation of bone and joint development in growing horses. *Proceedings, Maryland Nutrition Conference*, pp. 65-68.

42. Glade, M.J. and P.I. Bell. 1981. Nitrogen partitioning along the equine digestive tract. *Journal of Animal Science*: 53:(Suppl.) 294.

43. Glade, M.J. and P.I. Bell. 1981. Lower digestive tract fermentation rates and nitrogen utilization in horses. *Proceedings, Equine Nutrition and Physiology Society*, pp. 26-29.

44. Nicoletti, J.M., J.E. Wohlt and M.J. Glade. 1980. Nitrogen utilization by ponies and steers as affected by dietary forage-grain ratios. *Journal of Animal Science*: 51: (Suppl.) 269.

45. Glade, M.J., J.E. Lowe, L. Krook, H.F. Hintz and P. Kenney. 1979. Osteochondrosis dissecans and growth suppression in dexamethasone-treated horse foals. *Proceedings, American Association of Equine Practitioners*: 25:361-365.

46. Glade, M.J., H. Hintz, L. Krook and H. Schryver. 1978. Skeletal metabolism in ponies on prolonged treatment with dexamethasone. *Federation Proceedings*: 37: Abstr.

47. Demain, A.L., C. Matteo, M. Glade, A. Tanaka, and J. Piret. 1974. Enzymatic synthesis of useful products. *First Intersectional Congress of the International Association of Microbiological Societies*, Tokyo, Japan.

LITERATURE CITED *for Calcium and Cancer Health Claims*

1. Bronner F. Intestinal calcium absorption: Mechanisms and applications. *J Nutr* 1987;117:1347-1352.
2. Peng JB, Chen XZ, Berger UV, Vassilev PM, Tsukaguchi H, Brown EM, Hediger MA. Molecular cloning and characterization of a channel-like transporter mediating intestinal calcium absorption. *J Biol Chem* 1999;274:22739-22746.
3. Zhuang L, Peng JB, Tou L, Takanaga H, Adam RM, Hediger MA, Freeman MR. Calcium-selective ion channel, CaT1, is apically localized in gastrointestinal tract epithelia and is aberrantly expressed in human malignancies. *Lab Invest* 2002;82:1755-1764.
4. Fleet JC, Wood RJ. Specific $1,25(OH)_2D_3$-mediated regulation of transcellular csalcium transport in Caco-2 cells. *Am J Physiol* 1999;276:G958-G964.
5. Barger-Lux MJ, Heaney RP, Recker RR. Time course of calcium absorption in humans: Evidence for a colonic component. *Calcif Tissue Int* 1989;44:308-311.
6. Cashman K. Prebiotics and calcium bioavailability. *Curr Issues Intest Microbiol* 2003;4:21-32.
7. Ireland P, Fordtran JS. Effect of dietary calcium and age on jejunal calcium absorption in humans studied by intestinal perfusion. *J Clin Invest* 1973;52:2672-2681.
8. Gallagher JC, Riggs BL, DeLuca HF. Effect of estrogen on calcium absorption and serum vitamin D metabolites in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 1980;51:1359-1364.
9. Heaney RP, Saville PD, Recker RR. Calcium absorption as a function of calcium intake. *J Lab Clin Med* 1975;85:881-890.
10. Heaney RP, Recker RR, Stegman MR, Moy AJ. Calcium absorption in women: Relationships to calcium intake, estrogen status, and age. *J Bone Min Res* 1989;4:469-475.
11. Heaney RP, Weaver CM, Fitzsimmons ML. Influence of calcium load on absorption fraction. *J Bone Min Res* 1990;5:1135-1138.
12. Abrams SA, Wen J, Stuff JE. Absorption of calcium, zinc and iron from breast milk by five-to seven-month-old infants. *Pediatr Res* 1996;39:384-390.
13. Heaney RP. Effect of calcium on skeletal development, bone loss, and risk of fractures. Am J Med. 1991 Nov 25;91(5B):23S-28S.
14. Bullamore JR, Wilkinson R, Gallagher JC, Nordin BEC, Marshall DH. Effects of age on calcium absorption. *Lancet* 1970;ii:535-537.
15. Wolf RL, Cauley JA, Baker CE, Ferrell RE, Charron M, Caggiula AW, Salamone LM, Heaney RP, Kuller LH. Factors associated with calcium absorption efficiency in pre- and perimenopausal women. *Am J Clin Nutr.* 2000;72):466-471.
16. Pattanaungkul S, Riggs BL, Yergey AL, Vieira NE, O'Fallon WM, Khosla S. Relationship of intestinal calcium absorption to 1,25-dihydroxyvitamin D $[1,25(OH)_2D]$ levels in young *versus* elderly women: Evidence for age-

related intestinal resistance to $1,25(OH)_2D$ action. *J Clin Endocrinol Metab* 2000;85:4023-4027.

17. Abrams SA, Silber TJ, Esteban NV, Vieira NE, Stuff JE, Meyers R, Majd M, Yergey AL. Mineral balance and bone turnover in adolescents with anorexia nervosa. *J Pediatr* 1993;123:326-331.
18. Abrams SA, O'Brien KO, Stuff JE. Changes in calcium kinetics associated with menarche. *J Clin Endocrinol Metab* 1996;81:2017-2020.
19. Farmer ME, White LR, Brody JA, Bailey KR. Race and sex differences in hip fracture incidence. *Am J Public Health* 1984;74:1374-1380.
20. Kellie SE, Brody JA. Sex-specific and race-specific hip fracture rates. *Am J Pub Health* 1990;80:326-328.
21. Dawson-Hughes B, Harris S, Kramich C, Dallal G, Rasmussen HM. Calcium retention and hormone levels in black and white women on high- and low-calcium diets. *J Bone Min Res* 1993;8:779-787.
22. Drinkwater B, Bruemner B, Chestnut C. Menstrual history as a determinant of current bone density in young athletes. *JAMA* 1990;263:545-548.
23. Marcus R, Cann C, Madvig P, Minkoff J, Goddard M, Bayer M, Martin M, Gaudiani L, Haskell W, Genant H. Menstrual function and bone mass in elite women distance runners. Endocrine and metabolic features. *Ann Intern Med* 1985;102:158-163.
24. Berkelhammer CH, Wood RJ, Sitrin MD. Acetate and hypercalciuria during total parenteral nutrition. *Am J Clin Nutr* 1988;48:1482-1489.
25. Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris RC Jr. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994;330:1776-1781.
26. Bell NH, Yergey AL, Vieira NE, Oexmann MJ, Shary JR. Demonstration of a difference in urinary calcium, not calcium absorption, in black and white adolescents. *J Bone Min Res* 1993;8:1111-1115.
27. Spencer H, Kramer L, Lensiak M, DeBartolo M, Norris C, Osis D. Calcium requirements in humans. Report of original data and a review. *Clin Orthop Related Res* 1984;184:270-280.
28. Jackman LA, Millane SS, Martin BR, Wood OB, McCabe GP, Peacock M, Weaver CM. Calcium retention in relation to calcium intake and postmenarcheal age in adolescent females. *Am J Clin Nutr* 1997;66:327-333.
29. Institute of Medicine. Calcium. In: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* National Academy Press, Washington, DC, 1997, chapter IV.
30. Miller K, Waye JD. Colorectal polyps in the elderly: What should be done? *Drugs Aging* 2002;19:393-404.
31. American Cancer Society. *Cancer Facts and Figures 2002.* (44 pages) http://www.cancer.org.
32. Turini ME, DuBois RN. Primary prevention: Phytoprevention and chemoprevention of colorectal cancer. *Hematol Oncol Clin North Am* 2002;16:811-840.
33. Potter JD. Nutrition and colorectal cancer. *Cancer Causes Control* 1996;7:127-146.

34. Marilley D, Vonlanthen S, Gioria A, Schwaller B. Calretinin and calretinin-22k increase resistance toward sodium butyrate-induced differentiation in CaCo-2 colon adenocarcinoma cells. *Exp Cell Res* 2001;268:93-103.
35. Gordon JI, Schmidt GH, Roth KA. Studies of intestinal stem cells using normal, chimeric and transgenic mice. *FASEB J* 1992;6:3039-3050.
36. Eastwood GL. A review of gastrointestinal epithelial renewal and its relevance to the development of adenocarcinomas of the gastrointestinal tract. *J Clin Gastroenterol* 1995;21(Suppl. 1):S1-S11.
37. Schmidt GH, Wilkinson MM, Ponder BA. Cell migration pathway in the intestinal epithelium: An in situ marker system using mouse aggregation chimeras. *Cell* 1985;40:425-429.
38. Wright NA, Irwin M. The kinetics of villus cell populations in the mouse small intestine. I. Normal villi: The steady state requirement. *Cell Tissue Kinet* 1982;15:595-609.
39. Whitfield JF, Bird RP, Chakravarthy BR, Isaacs RJ, Morley P. Calcium – Cell cycle regulator, differentiator, killer, chemopreventor, and maybe, tumor promoter. *J Cell Biochem Suppl* 1995;22:74-91.
40. Kerr JFR, Wyllie AH, Currie AR. Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer* 1972;26:239-257.
41. Arends MJ, Wyllie AH. Apoptosis: Mechanisms and roles in pathology. *Int Rev Exp Pathol* 1991;32:223-254.
42. Patel T, Gores GJ, Kaufmann SH. The role of proteases during apoptosis. *FASEB J* 1996;10:587-597.
43. Arends MJ, Morris RG, Wyllie AH. Apoptosis: The role of the endonuclease. *Am J Pathol* 1990;136:593-608.
44. Duke RC, Chervenak R, Cohen JJ. Endogenous endonuclease induced DNA fragmentation: An early event in cell mediated cytolysis. *Proc Natl Acad Sci USA* 1983;80:6361-6365.
45. Cohen JJ, Duke RC. Glucocorticoid activation of a calcium-dependent endonuclease in thymocyte nuclei leads to cell death. *J Immunol* 1984;132:38-42.
46. Furuya Y, Lundmo P, Short AD, Gill DL, Isaacs JT. The role of calcium, pH, and cell proliferation in the programmed (apoptotic) death of androgen-independent prostatic cancer cells induced by thapsigargin. *Cancer Res* 1994;54:6167-6175.
47. Trump BF, Berezesky IK. The role of altered $[Ca^{2+}]_i$ regulation in apoptosis, oncosis, and necrosis. *Biochim Biophys Acta* 1996;1313:173-178.
48. Sundaram SG, Milner JA. Diallyl disulfide induces apoptosis of human colon tumor cells. *Carcinogenesis* 1996;17:669-673.
49. Raff M. Cell suicide for beginners. *Nature* 1998;396:119-122.
50. Richter C. Pro-oxidants and mitochondrial Ca^{2+}: Their relationship to apoptosis and oncogenesis. *FEBS Lett* 1993;325:104-107.
51. Lemasters JJ, Nieminen AL, Qian T, Trost LC, Elmore SP, Nishimura Y, Crowe RA, Cascio WE, Bradham CA, Brenner DA, Herman B. The mitochondrial permeability transition in cell death: A common mechanism in

necrosis, apoptosis and autophagy. *Biochem Biophys Acta* 1998;1366:177-196.

52. Zamzami N, Kroemer G. The mitochondrion in apoptosis: How Pandora's box opens. *Nat Rev Mol Cell Biol* 2001;2:67-71.
53. Krishnan K, Brenner DE. Chemoprevention of colorectal cancer. *Gastroenterol Clin North Am* 1996;25:821-858.
54. Sporn MB. Approaches to prevention of epithelial cancer during the preneoplastic period. *Cancer Res* 1976;36:2699-2702.
55. Gwyn K, Sinicrope FA. Chemoprevention of colorectal cancer. *Am J Gastroenterol* 2002;97:13-21.
56. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990;61:759-767.
57. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, Nakamura Y, White R, Smits AMM, Bos JL. Genetic alterations during colorectal-tumor development. *N Engl J Med* 1988;319:525-532.
58. Fearon ER, Cho KR, Nigro JM, Kern SE, Simons JW, Ruppert JM, Hamilton SR, Preisinger AC, Thomas G, Kinzler K, Vogelstein B. Identification of a chromosome 18q gene that is altered in colorectal cancer. *Science* 1990;247:49-56.
59. Issa JPJ, Vertino PM, Wui J, Sazawal S, Celano P, Nelkin BD, Hamilton SR, Baylin SB. Increased cytosine DNA-methyltransferase activity during colon cancer progression. *JNCI* 1993;85:1235-1240.
60. Goelz SE, Vogelstein B, Hamilton SR, Feinberg AP. Hypomethylation of DNA from benign and malignant human human colon neoplasms. *Science* 1985;228:187-190.
61. Feinberg AP, Gehrke CW, Kuo KC, Ehrlich M. Reduced genomic 5-methylcytosine content in human colonic neoplasia. *Cancer Res* 1988;48:1159-1161.
62. Spencer CA, Groudine M. Control of c-*myc* regulation in normal and neoplastic cells. *Advanc Cancer Res* 1990;56:1-48.
63. Melhem MF, Meisler AI, Finley GG, Bryce WH, Jones MO, Tribby II, Pipas JM, Koski RA. Distribution of cells expressing myc proteins in human colorectal epithelium, polyps and malignant tumors. *Cancer Res* 1992;52:5853-5864.
64. Forgue-Lafitte M-E, Coudray A-M, Breant B, Mester J. Proliferation of the Caco-2 human colon-carcinoma cell line HT-29: Autocrine growth and deregulated expression of the c-*myc* oncogene. *Cancer Res* 1989;49:6566-6571.
65. Bodmer WF, Bailey CJ, Bodmer J, Bussey HJR, Ellis A, Gorman P, Lucibello FC, Murday VA, Rider SH, Scambler P, Sheer D, Solomon E, Spurr NK. Localization of the gene for familial adenomatous polyposis in chromosome 5. *Nature* 1987;328:614-616.
66. Leppert M, Dobbs M, Scambler P, O'Connell P, Nakamura Y, Stauffer D, Woodward S, Burt R, Hughes J, Gardner E, Lathrop M, Wasmuth J, Lalouel J-M, White R. The gene for familial polyposis coli maps to the long arm of chromosome 5. *Science* 1987;238:1411-1413.

67. Groden J, Thliveris A, Samowitz W, Carlson M, Gelbert L, Albertsen H, Joslyn G, Stevens J, Spirio L, Robertson M, Sargeant L, Krapcho K, Wolff E, Burt R, Hughes JP, Warrington J, McPherson J, Wasmuth J, Le Paslier D, Abderrahim H, Cohen D, Leppert M, White R. Identification and characterization of the familial adenomatous polyposis coli gene. *Cell* 1991;66:589-600.
68. Nathke IS, Adams CL, Polakis P, Sellin JH, Nelson WJ. The adenomatous polyposis coli tumor suppressor protein localizes to plasma membrane sites involved in active cell migration. *J Cell Biol* 1996;134:165-179.
69. Barth AI, Nathke IS, Nelson WJ. Cadherins, catenins and APC protein: Interplay between cytoskeletal complexes and signaling pathways. *Curr Opinions Cell Biol* 1997;9:683-690.
70. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell* 1996;87:159-170.
71. Potter JD. Colorectal cancer: Molecules and populations. *J Natl Cancer Inst* 1999;91:916-932.
72. Houlston RS. What we could do now: Molecular pathology of colorectal cancer. *J Clin Pathol Mol Pathol* 2001;54:206-214.
73. Bartram H-P, Scheppach W, Schmid H, Hofmann A, Dusel G, Richter F, Richter A, Kasper H. Proliferation of human colonic mucosa as an intermediate biomarker of carcinogenesis: Effects of butyrate, deoxycholate, calcium, ammonia, and pH. *Cancer Res* 1993;53:3283-3288.
74. Govers MJ, Termont DS, Van der Meer R. Mechanism of the antiproliferative effect of milk mineral and other calcium supplements on colonic epithelium. *Cancer Res* 1994;54:95-100.
75. Newmark HL, Lipkin M, Maheshwari 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* 1991;54:209s-214s.
76. Bird RP, Schneider R, Stamp D, Bruce WR. Effect of dietary calcium and cholic acid on the proliferative indices of murine colonic epithelium. *Carcinogenesis* 1986;7:1657-1661.
77. Wargovich MJ, Eng VWS, Newmark HL, Bruce WR. Calcium ameliorates the toxic effect of deoxycholic acid on colonic epithelium. *Carcinogenesis* 1983;4:1205-1207.
78. Wargovich MJ, Eng VWS, Newmark HL. Calcium inhibits the damaging and compensatory proliferative effects of fatty acids on mouse colon epithelium. *Cancer Lett* 1984;23:253-258.
79. McLellan EA, Bird RP. Aberrant crypts: Potential preneoplastic lesions in the murine colon. *Cancer Res* 1988;48:6187-6192.
80. Bird RP. Observations and quantification of aberrant crypts in the murine colon treated with a colon carcinogen: Preliminary findings. *Cancer Lett* 1987;37:147-151.
81. Correa P. Epidemiology of polyps and cancer. *Major Prob Pathol* 1978;10:126-152.
82. Hill MJ. Etiology of the adenoma-carcinoma sequence. *Major Prob Pathol* 1978;10:153-162.

83. Kendall CW, Janezic SA, Friday D, Venket Rao A. Dietary cholesterol enhances preneoplastic aberrant crypt formation and alters cell proliferation in the murine colon treated with azoxymethane. *Nutr Cancer* 1992;17:107-114.
84. Magnuson BA, Carr I, Bird RP. Ability of aberrant crypt characteristics to predict colonic tumour incidence in rats fed cholic acid. *Cancer Res* 1993;53:4499-4504.
85. Pretlow TP, Barrow BJ, Ashton WS, O'Riordan MA, Pretlow TG, Jurcisek JA, StellatoTA. Aberrant crypts: Putative preneoplastic foci in human colonic mucosa. *Cancer Res* 1991;51:1564-1567.
86. Pretlow TP, O'Riordan MA, Somich GA, Amini SB, Pretlow TG. Aberrant crypts correlate with tumour incidence in F344 rats treated with azoxymethane and phytate. *Carcinogenesis* 1992;13:1509-1512.
87. Rao CV, Desai D, Simi B, Kulkarni N, Amin S, Reddy BS. Inhibitory effect of caffeic acid esters on azoxymethane-induced biochemical changes and aberrant crypt foci formation in rat colon. *Cancer Res* 1993;53:4182-4188.
88. Shivapurkar N, Tang ZC, Frost A, Alabaster O. Inhibition of progression of aberrant crypt foci and colon tumour development by vitamin E and β-carotene in rats on a high-risk diet. *Cancer Lett* 1995;91:125-132.
89. Zarkovic M, Qin X, Nakatsuru Y, Oda H, Nakamura T, Shamsuddin AM, Ishikawa T. Tumour promotion by fecapentaene-12 in a rat colon carcinogenesis model. *Carcinogenesis* 1993;14:1261-1264.
90. Höpfner M, Lemmer K, Jansen A, Hanski C, Riecken E-O, Gavish M, Mann B, Buhr H, Glassmeier G, Scherübl H. Expression of functional P2-purinergic receptors in primary cells cultures of human colorectal carcinoma cells. *Biochem Biophys Res Commun* 1998;251:811-817.
91. Höpfner M, Maaser K, Barthel B, von Lampe B, Hanski C, Riecken E-O, Zeitz M, Scherubl H. Growth inhibition and apoptosis induced by $P2Y_2$ receptors in human colorectal carcinoma cells: Involvement of intracellular calcium and cyclic adenosine monophosphate. *Int J Colorectal Dis* 2001;16:154-166.
92. Harden TK, Boyer JL, Nicholas RA. P_2-purinergic receptors: Subtype-associated signaling responses and structure. *Annu Rev Pharmacol Toxicol* 1995;35:541-579.
93. Lustig KD, Conklin BR, Herzmark P, Taussig R, Bourne HR. Type II adenylylcyclase integrates coincident signals from G_s, G_i and G_q. *J Biol Chem* 1993;268:13900-13905.
94. Farese RV. Calcium as an intracellular mediator of hormone action: Intracellular phospholipid signaling systems. *Am J Med Sci* 1988;296:223:230.
95. Whitfield JF, Boynton AL, Macmanus JP, Sikorska M, Tsang BK. The regulation of cell proliferation by calcium and cyclic AMP. *Mol Cell Biochem* 1979;27:155-179.
96. Weiss H, Amberger A, Widschwendter M, Margreiter R, Ofner D, Dietl P. Inhibition of store-operated calcium entry contributes to the anti-proliferative effect of non-steroidal anti-inflammatory drugs in human colon cancer cells. *Int J Cancer* 2001;92:877-882.

97. Korczak B, Whale C, Kerbel RS. Possible involvement of Ca^{2+} mobilization and protein kinase C activation in the induction of spontaneous metastasis by mouse mammary adenocarcinoma. *Cancer Res* 1989;49:2597-2560.
98. Liu B, Renaud C, Nelson KK, Chen YQ, Bazaz R, Kowynia J, Timar J, Diglio CA, Honn KV. Protein kinase C inhibitor calphostin C reduces B16 amelanotic melanoma cell adhesion to endothelium and lung colonization. *Int J Cancer* 1992;52:147-152.
99. Amstad PA, Krupitza G, Cerutti PA. Mechanism of c-*fos* induction by active oxygen. *Cancer Res* 1992;52:3952-3960.
100. Kelloff GJ, Crowell JA, Steele VE, Lubet RA, Boone CW, Malone WA, Hawk ET, Lieberman R, Lawrence JA, Kopelovich L, Ali I, Viner JL, Sigman CC. Progress in cancer chemoprevention. *Ann N Y Acad Sci* 1999;889:1-13.
101. Fischer SM, Lee ML, Maldve RE, Morris RJ, Trono D, Burrow DL, Butler AP, Pavone A, Warren B. Association of protein kinase C activation with induction of ornithine decarboxylase in murine but not human keratinocytes cultures. *Mol Carcinog* 1993;7:228-237.
102. Klein IK, Ritland SR, Burgart LJ, Ziesmer SC, Roche PC, Gendler SJ, Karnes WE Jr. Adenoma-specific alterations of protein kinase C isozyme expression in APC^{min} mice. *Cancer Res* 2000;60:2077-2080.
103. Stauble B, Boscoboinik D, Tasinato A, Azzi A. Modulation of activator protein-1 (AP-1) transcription factor and protein kinase C by hydrogen peroxide and α–tocopherol in vascular smooth muscle cells. *Eur J Biochem* 1994;226:393-402.
104. Russell DH. Ornithine decarboxylase: A key regulatory enzyme in normal and neoplastic growth. *Drug Metab Rev* 1981;16:1-88.
105. Janne J, Poso H, Raina A. Polyamines in rapid growth and cancer. *Biochem Biophys Acta* 1978;473:241-293.
106. Williams-Ashman HG, Canellakis ZN. Polyamines in mammalian biology and medicine. *Perspect Biol Med* 1979;2:421-453.
107. Pegg AE. Polyamine metabolism and its importance in neoplastic growth and a target for chemotherapy. *Cancer Res* 1988;48:759-774.
108. Luk GD, Baylin SB. Ornithine decarboxylase as a biologic marker in familial colonic polyposis. *N Engl J Med* 1984;311:80-83.
109. Love RR, Verma AK, Surawicz TS, Morrissey JF. Absence of effect of supplemental oral calcium on ornithine decarboxylase (ODC) activity in colonic mucosae of healthy individuals with a family history of colorectal cancer. J Surg Oncol. 1990 Feb;43(2):79-82.
110. Hibshoosh H, Johnson M, Weistein IB. Effects of overexpression of ornithine decarboxylase (ODC) on growth control and oncogene-induced cell transformation. *Oncogene* 1991;6:739-743.
111. Ishizuka J, Bold RJ, Townsend CM Jr, Thompson JC. Role of calcium in the regulation of ornithine decarboxylase enzyme activity in mouse colon cancer cells. *Cancer Invest* 1995;13:181-187.
112. Steele VE, Moon RC, Lubet RA, Grubbs CJ, Reddy BS, Wargovich M, McCormick DL, Pereira MA, Crowell JA, Bagheri D, Sigman CC, Boone CW, Kelloff GJ. Preclinical efficacy evaluation of potential chemopreventive

agents in animal carcinogenesis models: Methods and results from the NCI Chemoprevention Drug Development Program. *J Cell Biochem Suppl* 1994;20:32-54.

113. Jarvis WD, Turner AJ, Povirk LF, Taylor RS, Grant S. Induction of apoptotic DNA fragmentation and cell death in HL-60 human promyelocytic leukemia cells by pharmacological inhibitors of protein kinase C. *Cancer Res* 1994;54:1707-1714.
114. Whelan RD, Parker PJ. Loss of protein kinase C function induces a proapoptotic response. *Oncogene* 1998;16:1939-1944.
115. Hannun YA. Functions of ceramide in coordinating cellular responses to stress. *Science* 1996;274:1855-1859.
116. Haimovitz-Friedman A, Kolesnick RN, Fuks Z. Ceramide signaling in apoptosis. *Br Med Bull* 1997;53:539-553.
117. Bradham C, Quian T, Streetz K, Trautwein C, Brenner DA, Lemasters JJ. The mitochondrial permeability transition is required for tumor necrosis factor α–mediated apoptosis and cytochrome *c* release. *Mol Cell Biol* 1998;18:6353-6364.
118. Chinnaiyan AM. The apoptosome: Heart and soul of the cell death machine. *Neoplasia* 1999;1:5-15.
119. Kluck RM, Bossy-Wetzel E, Green DR, Newmeyer DD. The release of cytochrome c from mitochondria: A primary site of Bcl-2 regulation of apoptosis. *Science* 1997;275:1132-1136.
120. Kallay E, Bajna E, Wrba F, Kriwanek S, Peterlik M, Cross HS. Dietary calcium and growth modulation of human colon cancer cells: Role of the extracellular calcium-sensing receptor. *Cancer Detect Prev* 2000;24:127-136.
121. Cross HS, Pavelka M, Slavik J, Peterlik M. Growth control of human colon cancer cells by vitamin D and calcium in vitro. *J Natl Cancer Inst* 1992;84:1355-1357.
122. Lamprecht SA, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin D and folate: Molecular mechanisms. *Nat Rev Cancer* 2003;3:601-614.
123. Morotomi M, Guillem JG, Weinstein IB. Production of diacylglycerol, an activator of protein kinase C, by human intestinal microflora. *Cancer Res* 1990;50:3595-3599.
124. Morotomi M, LoGerfo P, Weinstein IB. Fecal excretion, uptake and metabolism by colon mucosa of diacylglycerol in rats. *Biochem Biophys Res Commun* 1991;181:1028-1034.
125. Friedman E, Isaksson P, Rafter J, Marian B, Winawer S, Newmark H. Fecal diglycerides as selective endogenous mitogens for premalignant and malignant human colonic epithelial cells. *Cancer Res* 1989;49:544-548.
126. Craven PA, Pfanstiel J, DeRubertis, FR. Role of activation of protein kinase C in the stimulation of colonic epithelial proliferation and reactive oxygen formation by bile acids. *J Clin Invest* 1987;79:532-541.
127. Weinstein IB. Cancer prevention: Recent progress and future opportunities. *Cancer Res* 1991;51:5080-5085.

128. Atillasoy E, Fein B, Weinstein IB, Holt PR. Fecal diacylglycerol concentrations and calcium supplementation. *Cancer Epidemiol Biomarkers Prev* 1995;4:795-796.
129. Steinbach G, Lupton J, Reddy BS, Kral JG, Holt PR. Effect of calcium supplementation on rectal epithelial hyperproliferation in intestinal bypass subjects. *Gastroenterology* 1994;106:1162-1167.
130. Holt PR, Moss SF, Whelan R, Guss J, Gilman J, Lipkin M. Fecal and rectal mucosal diacylglycerol concentrations and epithelial proliferative kinetics. *Cancer Epidemiol Biomarkers Prev* 1996;5:937-940.
131. Tangpricha V, Flanagan JN, Whitlatch LW, Tseng CC, Chen TC, Holt PR, Lipkin MS, Holick MF. 25-hydroxyvitamin D-1α-hydroxylase in normal and malignant colon tissue. *Lancet* 2001;357:1673-1674.
132. Cross HS, Bareis P, Hofer H, Bischof MG, Bajna E, Kriwanek S, Bonner E, Peterlik M. 25-Hydroxyvitamin D_3-1α hydroxylase and vitamin D receptor gene expression in human colonic mucosa is elevated during early cancerogenesis. *Steroids* 2001;66:287-292.
133. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, Hewison M. Extrarenal expression of 25-hydroxyvitamin D_3-1α hydroxylase. *J Clin Endocrinol Metab* 2001;86:888-894.
134. Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, Rothstein R, Summers RW, Snover DC, Beck GJ, Frankl H, Bond JH, Greenberg ER. Calcium supplements and colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* 1999;340:101-107.
135. Brenner BM, Russell N, Albrecht S, Davies RJ. The effect of dietary vitamin D_3 on the intracellular calcium gradient in mammalian colonic crypts. *Cancer Lett* 1998;127:43-53.
136. Holt PR, Arber N, Halmos B, Forde K, Kissileff H, McGlynn KA, Moss SF, Kurihara N, Fan K, Yang K, Lipkin M. Colonic epithelial cell proliferation decreases with increasing levels of serum 25-hydroxy vitamin D. *Cancer Epidemiol Biomarkers Prev* 2002;11:113-119.
137. Holt PR, Atillasoy EO, Gilman J, Guss J, Moss SF, Newmark H, Fan K, Yang K, Lipkin M. Modulation of abnormal colonic epithelial cell proliferation and differentiation by low-fat dairy foods. A randomized controlled trial. *JAMA* 1998;280:1074-1079.
138. Lointier P, Wargovich MJ, Saez S, Levin B, Wildrick DM, Boman BM. The role of vitamin D_3 in the proliferation of a human colon cancer cell line *in vitro*. *Anticancer Res* 1987;7:817-821.
139. Giuliano AR, Franceschi RT, Wood RJ. Characterization of the vitamin D receptor from the Caco-2 human colon carcinoma cell line: Effect of cellular differentiation. *Arch Biochem Biophys* 1990;285:261-269.
140. Harper KD, Iozzo RV, Haddad JG. Receptors for and bioresponses to 1,25-dihydroxyvitamin D in a human colon carcinoma cell line (HT-29). *Metabolism* 1989;38:1062-1069.
141. Suda T, Shinki T, Takashashi N. The role of vitamin D in bone and intestinal cell differentiation. *Annu Rev Nutr* 1990;10:195-211.

142. Tanaka Y, Bush KK, Eguchi T, Ikekawa N, Taguchi T, Kobayashi Y, Higgins PJ. Effects of 1,25-dihydroxyvitamin D_3 and its analogs on butyrate-induced differentiation of HT029 human colonic carcinoma cells and on the reversal of the differentiated phenotype. *Arch Biochem Biophys* 1990;276:415-423.
143. Eisman JA, Barkla DH, Tutton PJM. Suppression of *in vivo* growth of human cancer solid tumor xenografts by 1,25-dihydroxyvitamin D_3. *Cancer Res* 1987;47:21-25.
144. Brehier A, Thomasset M. Human colon cell line HT-29: Characterization of 1,25-dihydroxyvitamin D_3 receptor and induction of differentiation by the hormone. *J Steroid Biochem* 1988;29:265-270.
145. Lointier P, Meggouh F, Dechelotte P, Pezet D, Ferrier C, Chipponi J, Saez S. 1,25-dihydroxyvitamin D_3 receptors and human colon adenocarcinoma. *Br J Surg* 1991;78:435-439.
146. Lointier P, Meggouh F, Pezet D, Dapoigny M, Dieng PND, Saez S, Chipponi J. Specific receptor for 1,25-dihydroxyvitamin D_3 (1,25-DR) and human colorectal carcinogenesis. *Anticancer Res* 1989;9:1921-1924.
147. Meggouh F, Lointier P, Saez S. Sex steroid and 1,25-dihydroxyvitamin D_3 receptors in human colorectal adenocarcinoma and normal mucosa. *Cancer Res* 1991;51:1227-1233.
148. Danes BS, De Angelis P, Traganos F, Melamed MR. Heritable colon cancer: Influence of increased calcium concentration on increased in vitro tetraploidy (IVT). *Med Hypotheses* 1991;36:69-72.
149. Danes BS. Effect of increased calcium concentration on *in vitro* growth of human colonic mucosal lines. *Dis Colon Rectum* 1991;34:552-556.
150. 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* 1986;46:5426-5430.
151. Friedman E, Lipkin M, Winawer S, Buset M, Newmark H. Heterogeneity in the response of familial polyposis epithelial cells and adenomas to increasing levels of calcium in vitro. *Cancer* 1989;63:2486-2491.
152. Buras RR, Shabahang M, Davoodi F, Schumaker LM, Cullen KJ, Byers S, Nauta RJ, Evans SRT. The effect of extracellular calcium on colonocytes: Evidence for differential responsiveness based upon degree of cell differentiation. *Cell Prolif* 1995;28:245-262.
153. Cross HS, Hulla W, Tong W-M, Peterlik M. Growth regulation of human colon adenocarcinoma-derived cells by calcium, vitamin D and epidermal growth factor. *J Nutr* 1995;125:2004S-2008S.
154. Wargovich MJ. Calcium and colon cancer. *J Am Coll Nutr* 1988;7:295-300.
155. Kelloff GJ, Crowell JA, Boone CW, Steele VE, Lubet RA, Greenwald P, Alberts DS, Covey JM, Doody LA, Knapp GG, Nayfield S, Parkinson DR, Prasad VK, Prorok PC, Sausville EA, Sigman CC. Clinical development plan: Calcium. Chemoprevention Branch and Agent Development Committee. National Cancer Institute. *J Cell Biochem Suppl* 1994;20:86-109.
156. Eshleman JR, Markowitz SD. Microsatellite instability in inherited and sporadic neoplasms. *Curr Opin Oncol* 1995;7:83-89.

157. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. *Science* 1993;260:816-819.
158. Tsao JL, Dudley S, Kwok B, Nickel AE, Laird PW, Siegmund KD, Liskay RM, Shibata D. Diet, cancer and aging in DNA mismatch repair deficient mice. *Carcinogenesis* 2002;23:1807-1810.
159. Aaltonen LA, Peltomaki P, Leach FS, Sistonen P, Pylkkanen L, Mecklin J-P, Jarvinen H, Powell SM, Jen J, Hamilton SR, Petersen GM, Kinzler KW, Vogelstein B, de la Chapelle A. Clues to the pathogenesis of familial colorectal cancer. *Science* 1993;260:812-816.
160. Marra G, Boland CR. Hereditary nonpolyposis colorectal cancer: The syndrome, the genes, and historical perspectives. *J Natl Cancer Inst* 1995;87:1114-1125.
161. Peltomaki P, Vasen HF. Mutations predisposing to hereditary nonpolyposis colorectal cancer: Database and results of a collaborative study. The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer. *Gastroenterology* 1997;113:1146-1158.
162. van Aken E, De Wever O, Correia da Rocha AS, Mareel M. Defective E-cadherin/catenin complexes in human cancer. *Virchows Arch* 2001;439:725-751.
163. Ilyas M, Tomlinson IPM. The interactions of APC, E-cadherin and β-catenin in tumour development and progression. *J Pathol* 1997;182:128-137.
164. Chakrabarty S, Radjendirane V, Appelman H, Varani J. Extracellular calcium and calcium sensing receptor function in human colon carcinomas: promotion of E-cadherin expression and suppression of beta-catenin/TCF activation. *Cancer Res* 2003;63:67-71.
165. Kallay E, Bonner E, Wrba F, Thakker RV, Peterlik M, Cross HS. Molecular and functional characterization of the extracellular calcium-sensing receptor in human colon cancer cells. *Oncol Res* 2003;13:551-559.
166. Chattopadhyay N, Yamaguchi T, Brown EM. Ca^{2+} receptor from brain to gut: Common stimulus, diverse actions. *Trends Endocrinol Metab* 1998;9:354-359.
167. Sheinin Y, Kallay E, Wrba F, Kriwanek S, Peterlik M, Cross HS. Immunocytochemical localization of the extracellular calcium-sensing receptor in normal and malignant human large intestinal mucosa. *J Histochem Cytochem* 2000;48:595-602.
168. Gama L, Baxendale-Cox LM, Breitwieser GE. Ca^{2+}-sensing receptors in intestinal epithelium. *Am J Physiol Cell Physiol* 1997;273:1168-1175.
169. De Luca F, Baron J. Molecular biology and clinical importance of the Ca^{2+}-sensing receptor. *Curr Opin Pediatr* 1998;10:435-440.
170. Takeichi M. Cadherin cell adhesion receptors as a morphogenetic regulator. *Science* 1991;251:1451-1455.
171. Bostick RM, Potter JD, Fosdick L, Grambsch P, Lampe JW, Wood JR, Louis TA, Ganz R, Grandits G. Calcium and colorectal epithelial cell proliferation: A preliminary randomized, double-blinded, placebo-controlled clinical trial. *J Natl Cancer Inst* 1993;85:132-141.

172. Newmark HL, Lipkin M. Calcium, vitamin D, and colon cancer. Cancer Res. 1992 Apr 1;52(7 Suppl):2067s-2070s.
173. Wargovich MJ, Baer AR. Basic and clinical investigations of dietary calcium in the prevention of colorectal cancer. *Prev Med* 1989;18:672-679.
174. Rozen P. An evaluation of rectal epithelial proliferation measurement as biomarker of risk for colorectal neoplasia and response in intervention studies. *Eur J Cancer Prev* 1992;1:215-224.
175. Speer G, Cseh K, Mucsi K, Takacs I, Dworak O, Winkler G, Szody R, Tisler A, Lakatos P. Calcium-sensing receptor A986S polymorphism in human rectal cancer. *Int J Colorectal Dis* 2002;17:20-24.
176. Berx G, Staes K, van Hengel J, Molemans F, Bussemakers MJ, van Bokhoven A, van Roy F. Cloning and characterization of the human invasion suppressor gene E-cadherin (CDH1). *Genomics* 1995;26:281-289.
177. Graff JR, Herman JG, Lapidus RG, Chopra H, Xu R, Jarrard DF, Isaacs WB, Pitha PM, Davidson NE, Baylin SB. E-cadherin expression is silenced by DNA hypermethylation in human breast and prostate carcinomas. *Cancer Res* 1995;55:5195-5199.
178. Hennig G, Behrens J, Truss M, Frisch S, Reichmann E, Birchmeier W. Progression of carcinoma cells is associated with alterations in chromatin structure and factor binding at the E-cadherin promoter in vivo. *Oncogene* 1995;11:475-484.
179. Dorudi S, Sheffield JP, Poulson R, Northover JM, Hart IR. E-cadherin expression in colorectal cancer: An immunochemical and *in situ* hybridization study. *Am J Pathol* 1993;142:981-986.
180. Azarschab P, Porschen R, Gregor M, Blin N, Holzmann K. Epigenetic control of the E-cadherin gene (CDH1) by CpG methylation in colectomy samples of patients with ulcerative colitis. *Genes Chromosomes Cancer* 2002;35:121-126.
181. Bedi A, Pasricha PJ, Akhtar AJ, Barber JP, Bedi GC, Giardello FM, Zehnbauer BA, Hamilton SR, Jones RJ. Inhibition of apoptosis during development of colorectal cancer. *Cancer Res* 1995;55:1811-1816.
182. Boland CR. The biology of colorectal cancer: Implications for pretreatment and follow-up management. *Cancer* 1993;71:4180-4186.
183. Fearon ER. Molecular genetic studies of the adenoma-carcinoma sequence. *Adv Intern Med* 1994;39:123-147.
184. Rustgi AK. Molecular genetics and colorectal cancer. *Gastroenterology* 1993;104:1223-1225.
185. Greenwald P, Kelloff GJ, Boone CW, McDonald SS. Genetic and cellular changes in colorectal cancer: Proposed targets of chemopreventive agents. *Cancer Epidemiol Biomarkers Prev* 1995;4:691-702.
186. Slattery ML, Schaffer D, Edwards SL, Ma K-N, Potter JD. Are dietary factors involved in DNA methylation associated with colon cancer? *Nutr Cancer* 1997;28:52-62.
187. Rosty C, Ueki T, Argani P, Jansen M, Yeo CJ, Cameron JL, Hruban RH, Goggins M. Overexpression of S100A4 in pancreatic ductal adenocarcinomas

is associated with poor differentiation and DNA hypomethylation. *Am J Pathol* 2002;160:45-50.

188. Bronckart Y, Decaestecker C, Nagy N, Harper L, Schafer BW, Salmon I, Pochet R, Kiss R, Heizman CW. Development and progression of malignancy in human colon tissues are correlated with expression of specific Ca^{2+}-binding S100 proteins. *Histol Histopathol* 2001;16:707-712.
189. Stulik J, Osterreicher J, Koupilova K, Knizek, Macela A, Bures J, Jandik P, Langr F, Dedic K, Jungblut PR. The analysis of S100A9 and S100A8 expression in matched sets of macroscopically normal colon mucosa and colorectal carcinoma: The S100A9 and S100A8 positive cells underlie and invade tumor mass. *Electrophoresis* 1999;20:1047-1054.
190. Kristinsson J, Armbruster CH, Ugstad M, Kriwanek S, Nygaard K, Ton H, Fuglerud P. Fecal excretion of calprotectin in colorectal cancer. Relationship to tumor characteristics. *Scand J Gastroenterol* 2001;36:202-207.
191. Takenaga K, Nakanishi H, Wada K, Suzuki M, Matsuzaki O, Matsuura A, Endo H. Increased expression of S100A4, a metastasis-associated gene, in human colorectal adenocarcinomas. *Clin Cancer Res* 1997;3:2309-2316.
192. Stulik J, Osterreicher J, Koupilova K, Knizek J, Bures J, Jandik P, Langr F, Dedic K, Schafer BW, Heizmann CW. Differential expression of the Ca^{2+} binding S100A6 protein in normal, preneoplastic and neoplastic colon mucosa. *Eur J Cancer* 2000;36:1050-1059.
193. Barraclough R. Calcium-binding protein S100A4 in health and disease. *Biochim Biophys Acta* 1998;1448:190-199.
194. Komatsu K, Andoh A, Ishiguro S, Suzuki N, Hunai H, Kobune-Fujiwara Y, Kameyama M, Miyoshi J, Akedo H, Nakamura H. Increased expression of S100A6 (Calcyclin), a calcium-binding protein of the S100 family, in human colorectal adenocarcinomas. *Clin Cancer Res* 2000;6:172-177.
195. Summerton CB, Longlands MG, Wiener K, Shreeve DR. Faecal calprotectin: A marker of inflammation throughout the intestinal tract. *Eur J Gastroenterol Hepatol* 2002;14:841-845.
196. Gongoll S, Peters G, Mengel M, Piso P, Klempnauer J, Kreipe H, von Wasielewski R. Prognostic significance of calcium-binding protein S100A4 in colorectal cancer. *Gastroenterology* 2002;123:1478-1484.
197. Steinbach G, Heymsfield S, Olansen NE, Tighe A, Holt PR. Effect of caloric restriction on colonic proliferation in obese persons: Implications for colon cancer prevention. *Cancer Res* 1994;54:1194-1197.
198. Cats A, Kleibeuker JH, van der Meer R, Kuipers F, Sluiter WJ, Hardonk MJ, Oremus ET, Mulder NH, de Vries EG. Randomized, double-blinded, placebo-controlled intervention study with supplemental calcium in families with hereditary nonpolyposis colorectal cancer. *J Natl Cancer Inst* 1995;87:598-603.
199. Chadwick VS, Gaginella TS, Carlson GL, Debognie JC, Phillips SF, Hofmann AF. Effect of molecular structure on bile acid-induced alterations in absorptive function, permeability and morphology in the perfused rabbit colon. *J Lab Clin Med* 1979;94:661-674.

200. Deschner EE, Cohen BI, Raicht RF. Acute and chronic effect of dietary cholic acid on colonic epithelial cell proliferation. *Digestion* 1981;21:290-296.
201. Deschner EE, Raicht RF. Influence of bile on kinetic behavior of colonic epithelial cells of the rat. *Digestion* 1981;19:322-327.
202. Koga S, Kaibara N, Takeda R. Effect of bile acids on 1,2-dimethylhydrazine-induced colon cancer in rats. *Cancer* 1982;50:543-547.
203. Cohen BI, Raicht RF. Effects of bile acids on colon carcinogenesis in rats treated with carcinogens. *Cancer Res* 1981;41:3759-3760.
204. Cruse JP, Lewin MR, Clark CG. The effects of cholic acid and bile salt binding agents on 1,2-dimehylhydrazine induced colon carcinogenesis in the rat. *Carcinogenesis* 1981;2:439-443.
205. Reddy BS, Narisawa T, Weisburger JH, Wynder EL. Effect of sodium deoxycholate on colon adenocarcinomas in germ free rats. *J Natl Cancer Inst* 1976;56:441-442.
206. Wargovich MJ. Phytic acid, a major calcium chelator from fiber-rich cereals stimulates colonic cellular proliferation (abstract). *Gastroenterology* 1986;90:1684.
207. Rafter JJ, Eng VWS, Furrer R, Bruce WR. Effects of calcium and pH on the mucosal damage produced by deoxycholic acid in the rat colon. *Gut* 1986;27:1320-1329.
208. Reddy BS, Watanabe K. Effect of cholesterol metabolism and promoting effect of lithocolic acid on colon carcinogenesis in germ-free and conventional F344 rats. *Cancer Res* 1979;39:1521-1524.
209. Glauert HP, Bennik MB. Influence of diet or intrarectal bile acid injections on colon epithelial cell proliferation in rats previously injected with 1,2-dimethylhydrazine. *J Nutr* 1983;113:475-482.
210. Sakaguchi M, Hiramatsu Y, Takada H, Yamamura M, Hioki K, Saito K, Yamamoto M. Effect of dietary unsaturated and saturated fats on azoxymethane-induced colon carcinogenesis in rats. *Cancer Res* 1984;44:1472-1477.
211. Bull AW, Nigro ND, Golembieski WA, Crissman JD, Marnett LJ. In vivo stimulation of DNA synthesis and induction of ornithine decarboxylase in rat colon by fatty acid hydroperoxides, autoxidation products of unsaturated fatty acids. *Cancer Res* 1984;44:4924-4928.
212. Silverman SJ, Andrews AW. Bile acids: Co-mutagenic activity in the Salmonella-mammalian-microsome mutagenicity test (Brief communication). *J Natl Cancer Inst* 1977;59:1557-1559.
213. Richards TC. Changes in crypt cell populations of mouse colon during recovery from treatment with 1,2-dimethylhydrazine. *J Natl Cancer Inst* 1981;66:907-912.
214. Cohen BI, Raicht RF, Deschner EE, Takahashi M, Sarwal AN, Fazzini E. Effect of cholic acid feeding on *N*-methyl-*N*-nitrosourea induced colon tumors and cell kinetics in rats. *J Natl Cancer Inst* 1980;64:573-578.
215. Nagengast FM, Grubben MJAL, van Munster IP. Role of bile acids in colorectal carcinogenesis. *Eur J Cancer* 1995;31A:1067-1070.

216. Lapre JA, de Vries HT, van der Meer R. Dietary calcium phosphate inhibits cytotoxicity of fecal water. *Am J Physiol* 1991;261:G907-G912.
217. Newmark HL, Lupton JR. Determinants and consequences of colonic luminal pH: Implications for colon cancer. *Nutr Cancer* 1990;14:161-173.
218. Reddy BS. Dietary fat and colon cancer: Animal model studies. *Lipids* 1992;27:807-813.
219. Kanazawa K, Konishi F, Mitsuoka T, Terada A, Itoh K, Narushima S, Kumemura M, Kimura H. Factors influencing the development of sigmoid colon cancer. Bacteriologic and biochemical studies. *Cancer* 1996;77(8 Suppl):1701-1706.
220. Samelson SL, Nelson RL, Nyhus LM. The protective effect of fecal pH on experimental colon carcinogenesis. *J R Soc Med* 1985;78:230-233.
221. Appleton GV, Bristol JB, Williamson RC. Increased dietary calcium and small bowel resection have opposite effects on colonic cell turnover. *Br J Surg* 1986;73:1018-1021.
222. Appleton GV, Davies PW, Bristol JB, Williamson RC. Inhibition of intestinal carcinogenesis by dietary supplementation with calcium. *Br J Surg.* 1987;74:523-525.
223. Beaty MM, Lee EY, Glauert HP. Influence of dietary calcium and vitamin D on colon epithelial cell proliferation and 1,2-dimethylhydrazine-induced colon carcinogenesis in rats fed high fat diets. *J Nutr* 1993;123:144-152.
224. Pence BC, Buddingh F. Inhibition of dietary fat-promoted colon carcinogenesis in rats by supplemental calcium or vitamin D3. *Carcinogenesis* 1988;9:187-190.
225. Pereira MA, Barnes LH, Rassman VL, Kelloff GV, Steele VE. Use of azoxymethane-induced foci of aberrant crypts in rat colon to identify potential cancer chemopreventive agents. *Carcinogenesis* 1994;15:1049-1054.
226. Vinas-Salas J, Biendicho-Palau P, Pinol-Felis C, Miguelsanz-Garcia S, Perez-Holanda S. Calcium inhibits colon carcinogenesis in an experimental model in the rat. *Eur J Cancer* 1998;34:1941-1945.
227. Wang A, Yoshimi N, Tanaka T, Mori H. The inhibitory effect of magnesium hydroxide on the bile acid-induced cell proliferation of colon epithelium in rats in comparison to the action of calcium lactate. *Carcinogenesis* 1994;15:2661-2663.
228. Wargovich MJ, Stephens LC, Gray K. Effect of two "human" nutrient density levels of calcium on the promotional phase of colon tumorigenesis in the F344 rat (abstract). *Proc Am Assoc Cancer Res* 1989;30:196.
229. Stern HS, Gregoire RC, Kashtan H, Stadler J, Bruce RW. Long-term effects of dietary calcium on risk markers for colon cancer in patients with familial polyposis. *Surgery* 1990;108:528-533.
230. van Faassen A, Hazen MJ, van den Brandt PA, van den Bogaard AE, Hermus RJ, Janknegt RA. Bile acids and pH values in total feces and in fecal water from habitually omnivorous and vegetarian subjects. *Am J Clin Nutr* 1993;58:917-922.

231. Gregoire RC, Stern HS, Yeung KS, Stadler J, Langley S, Furrer R, Bruce WR. Effect of calcium supplementation on mucosal cell proliferation in high risk patients for colon cancer. *Gut* 1989;30:376-382.
232. Govers MJAP, Termont DSML, Lapre JA, Kleibeuker JH, Vonk RJ, Van der Meer R. Calcium in milk products precipitates intestinal fatty acids and secondary bile acids and thus inhibits colonic cytotoxicity in humans. *Cancer Res* 1996;56:3270-3275.
233. Behling AR, Greger JL. Mineral metabolism of aging female rats fed various commercially available calcium supplements of yogurt. *Pharmacol Res* 1988;5:501-505.
234. Adell-Carceller R, Segarra-Soria M, Gibert-Jerez J, Salvador Sanchis JL, Lazaro-Santander R, Escrig-Sos J, Ruiz-Castillo J. Inhibitory effect of calcium on carcinogenesis at the site of colonic anastomosis: An experimental study. *Dis Colon Rectum* 1997;40:1376-1381.
235. Arlow FL, Walczak SM, Luk GD, Majumdar AP. Attenuation of azoxymethane-induced colonic mucosal ornithine decarboxylase and tyrosine kinase activity by calcium in rats. *Cancer Res* 1989;49:5884-5888.
236. Barsoum GH, Thompson H, Neoptolemos JP, Keighley MR. Dietary calcium does not reduce experimental colorectal carcinogenesis after small bowel resection despite reducing cellular proliferation. *Gut* 1992;33:1515-1520.
237. Behling AR, Kaup SM, Greger JL. Changes in intestinal function of rats initiated with DMH and fed varying levels of butterfat, calcium, and magnesium. *Nutr Cancer* 1990;13:189-199.
238. Hambly RJ, Rumney CJ, Cunninghame M, Fletcher JM, Rijken PJ, Rowland IR. Influence of diets containing high and low risk factors for colon cancer on early stages of carcinogenesis in human flora-associated (HFA) rats. *Carcinogenesis* 1997;18:1535-1539.
239. Li H, Kramer PM, Lubet RA, Steele VE, Kelloff GJ, Pereira MA. Effect of calcium on azoxymethane-induced aberrant crypt foci and cell proliferation in the colon of rats. *Cancer Lett* 1998;124:39-46.
240. Liu Z, Tomotake H, Wan G, Watanabe H, Kato N. Combined effect of dietary calcium and iron on colonic aberrant crypt foci, cell proliferation and apoptosis, and fecal bile acids in 1,2-dimethylhydrazine-treated rats. *Oncol Rep* 2001;8:893-897.
241. Molck A-M, Poulsen M, Meyer O. The combination of 1alpha,25(OH_2)-vitamin D_3, calcium and acetylsalicylic acid affects azoxymethane-induced aberrant crypt foci and colorectal tumours in rats. *Cancer Lett* 2002;186:19-28.
242. Nelson RL, Tanure JC, Andrianopoulos G. The effect of dietary milk and calcium on experimental colorectal carcinogenesis. *Dis Colon Rectum* 1987;30:947-949.
243. Sitrin MD, Halline AG, Abrahams C, Brasitus TA. Dietary calcium and vitamin D modulate 1,2-dimethylhydrazine-induced colonic carcinogenesis in the rat. *Cancer Res* 1991;51:5608-5613.

244. Thiagarajan DG, Bennink MR, Bourquin LD, Kavas FA. Prevention of precancerous colonic lesions in rats by soy flakes, soy flour, genistein, and calcium. *Am J Clin Nutr* 1998;68(6 Suppl):1394S-1399S.
245. Behling AR, Kaup SM, Choquette LL, Greger JL. Lipid absorption and intestinal tumor incidence in rats fed on varying levels of calcium and butterfat. *Br J Nutr* 1990;64:505-513.
246. Llor X, Jacoby RF, Teng B-B, Davidson NO, Sitrin MD, Brasitus TA. K-*ras* mutations in 1,2-dimethylhydrazine-induced colonic tumors: Effects of supplemental dietary calcium and vitamin D deficiency. *Cancer Res* 1991;51:4305-4309.
247. Skrypec DJ, Bursey RG. Effect of dietary calcium on azoxymethane-induced intestinal carcinogenesis in male F 344 rats fed high fat diets (abstract). *FASEB* 1988;2:A857.
248. Cats A, Mulder NH, de Vries EG, Oremus ET, Kreumer WM, Kleibeuker JH. Calcium phosphate: An alternative calcium compound for dietary prevention of colon cancer? A study on intestinal and faecal parameters in healthy volunteers. *Eur J Cancer Prev* 1993;2:409-415.
249. Van der Meer R, Termont DS, De Vries HT. Differential effects of calcium ions and calcium phosphate on cytotoxicity of bile acids. *Am J Physiol* 1991;260:G142-G147.
250. Govers MJAP, Van der Meer R. Effects of dietary calcium and phosphate on the intestinal interactions between calcium, phosphate, fatty acids, and bile acids. *Gut* 1993;34:365-370.
251. Lapre JA, De Vries HT, Koeman JH, Van der Meer R. The antiproliferative effect of dietary calcium on colonic epithelium is mediated by luminal surfactants and dependent on the type of dietary fat. *Cancer Res* 1993;53:784-789.
252. Newmark HL, Wargovich MJ, Bruce WR. Colon cancer and dietary fat, phosphate, and calcium: A hypothesis. *J Natl Cancer Inst* 1984;72:1323-1325.
253. Van der Meer R, Kleibeuker JH, Lapre JA. Calcium phosphate, bile acids and colorectal cancer. *Eur J Cancer Prev* 1991;1(Suppl 2):55-62.
254. Van der Meer R, Lapre JA, Govers MJ, Kleibeuker JH. Mechanisms of the intestinal effects of dietary fats and milk products on colon carcinogenesis. *Cancer Lett* 1997;114:75-83.
255. Wargovich MJ, Allnutt D, Palmer C, Anaya P, Stephens LC. Inhibition of the promotional phase of azoxymethane-induced colon carcinogenesis in the F344 rat by calcium lactate: Effect of simulating two human nutrient density levels. *Cancer Lett* 1990;53:17-25.
256. Welberg JW, Kleibeuker JH, Van der Meer R, Kuipers F, Cats A, Van Rijsbergen H, Termont DS, Boersma-van Ek W, Vonk RJ, Mulder NH, de Vries EGE. Effects of oral calcium supplementation on intestinal bile acids and cytolytic activity of fecal water in patients with adenomatous polyps of the colon. *Eur J Clin Invest* 1993;23:63-68.

257. Lapre JA, de Vries HT, Termont DSML, Kleibeuker JH, de Vries EGE, van der Meer R. Mechanism of the protective effect of supplemental dietary calcium on cytolytic activity of fecal water. *Cencer Res* 1993;53:248-253.
258. van der Meer R, Welberg JW, Kuipers F, Kleibeuker JH, Mulder NH, Termont DSML, Vonk RJ, de Vries HT, de Vries EGE. Effects of supplemental dietary calcium on the intestinal association of calcium phosphate and bile acids. *Gastroenterology* 1990;99:1653-1659.
259. Pence BC, Dunn DM, Zhao C, Patel V, Hunter S, Landers M. Protective effects of calcium from nonfat dried milk against colon carcinogenesis in rats. *Nutr Cancer* 1996;25:35-45.
260. Appleton GV, Owen RW, Williamson RC. The effect of dietary calcium supplementation on intestinal lipid metabolism. *J Steroid Biochem Mol Biol* 1992;42:383-387.
261. Appleton GV, Owen RW, Wheeler EE, Challacombe DN, Williamson RC. Effect of dietary calcium on the colonic luminal environment. *Gut* 1991;32:1374-1377.
262. Lapre JA, De Vries HT, Van der Meer R. Cytotoxicity of fecal water is dependent on the type of dietary fat and is reduced by supplemental calcium phosphate in rats. *J Nutr* 1993;123:578-585.
263. Suzuki K, Suzuki K, Mitsuoka T. Effect of low-fat, high-fat, and fiber-supplemented high-fat diets on colon cancer risk factors in feces of healthy subjects. *Nutr Cancer* 1992;18:63-71.
264. Haenszel W, Correa P, Cuella C. Social class differences among patients with large bowel cancer in Cali, Columbia. *J Natl Cancer Inst* 1975;54:1031-1035.
265. Hill MJ, Drasar BS, Aries V, Crowther JS, Hawksworth G, Williams REO. Bacteria and aetiology of cancer of the large bowel. *Lancet* 1971;i:95-100.
266. Hill MJ. Steroid nuclear dehydrogenation and colon cancer. *Am J Clin Nutr* 1974;27:1475-1480.
267. Jensen OM, MacLennan R, Wahrendorf J. Diet, bowel function, fecal characteristics, and large bowel cancer in Denmark and Finland. *Nutr Cancer* 1982;4:5-19.
268. Mower HF, Ray RM, Shoff R, Stemmermann GN, Nomura A, Glober GA, Kamiyama S, Shimada A, Yamakawa H. Fecal bile acids in two Japanese populations with different colon cancer risks. *Cancer Res* 1979;39:328-331.
269. Reddy BS, Hedges AR, Laakso K, Wynder EL. Metabolic epidemiology of large bowel cancer: Fecal bulk and constituents of high-risk North American and low-risk Finnish populations. *Cancer* 1978;42:2832-2838.
270. Turjman N, Goodman GT, Jacgar B, Nair PP. Diet, nutrition intake, and metabolism in populations at high and low risk for colon cancer: Metabolism of bile acids. *Am J Clin Nutr* 1984;40:937-941.
271. Alberts DS, Ritenbaugh C, Story JA, Aickin M, Rees-McGee S, Buller MK, Atwood J, Phelps J, Ramanujam PS, Bellapravalu S, Patel J, Bextinger L, Clark L. Randomized, double-blinded, placebo-controlled study of effect of wheat bran fiber and calcium on fecal bile acids in patients with resected adenomatous colon polyps. *J Natl Cancer Inst* 1996;88:81-92.

272. Lupton JR, Steinbach G, Chang WC, O'Brien BC, Wiese S, Stoltzfus CL, Glober GA, Wargovich MJ, McPherson RS, Winn RJ. Calcium supplementation modifies the relative amounts of bile acids in bile and affects key aspects of human colon physiology. *J Nutr* 1996;126:1421-1428.
273. Alder RJ, McKeown-Eyssen G, Bright-See E. Randomized trial of the effect of calcium supplementation on fecal risk factors for colorectal cancer. *Am J Epidemiol* 1993;138:804-814.
274. Lipkin M, Newmark H. Effect of added dietary calcium on colonic epithelial-cell proliferation in subjects at high risk for familial colonic cancer. *N Engl J Med* 1985;313:1381-1384.
275. van Gorkom BA, van der Meer R, Karrenbeld A, van der Sluis T, Zwart N, Termont DS, Boersma-van Ek W, de Vries EG, Kleibeuker JH. Calcium affects biomarkers of colon carcinogenesis after right hemicolectomy. *Eur J Clin Invest* 2002;32:693-699.
276. Welberg JW, Monkelbaan JF, de Vries EG, Muskiet FA, Cats A, Oremus ET, Boersma-van Ek W, van Rijsbergen H, van der Meer R, Mulder NH, Kleibeuker JH. Effects of supplemental dietary calcium on quantitative and qualitative fecal fat excretion in man. *Ann Nutr Metab* 1994;38:185-191.
277. Little J, Owen RW, Fernandez F, Hawtin PG, Hill MJ, Logan RF, Thompson MH, Hardcastle JD. Asymptomatic colorectal neoplasia and fecal characteristics: A case-control study of subjects participating in the Nottingham fecal occult blood screening trial. *Dis Colon Rectum* 2002;45:1233-1241.
278. Geltner-Allinger U, Brismar B, Reinholt FP, Andersson G, Rafter JJ. Soluble fecal acidic lipids and colorectal epithelial cell proliferation in normal subjects and in patients with colon cancer. *Scand J Gastroenterol* 1991;26:1069-1074.
279. Hofstad B, Vatn MH, Andersen SN, Owen RW, Larsen S, Osnes M. The relationship between faecal bile acid profile with or without supplementation with calcium and antioxidants on recurrence and growth of colorectal polyps. *Eur J Cancer Prev* 1998;7:287-294.
280. van Munster IP, Tangerman A, de Haan AF, Nagengast FM. A new method for the determination of the cytotoxicity of bile acids and aqueous phase of stool: The effect of calcium. *Eur J Clin Invest* 1993;23:773-777.
281. Glinghammar B, Venturi M, Rowland IR, Rafter JJ. Shift from a dairy product-rich to a dairy product-free diet: Influence on cytotoxicity and genotoxicity of fecal water - potential risk factors for colon cancer. *Am J Clin Nutr* 1997;66:1277-1282.
282. Pence BC. Role of calcium in colon cancer prevention: Experimental and clinical studies. *Mutat Res* 1993;290:87-95.
283. Richter F, Newmark HL, Richter A, Leung D, Lipkin M. Inhibition of Western-diet induced hyperproliferation and hyperplasia in mouse colon by two sources of calcium. *Carcinogenesis* 1995;16:2685-2689.
284. Rozen P, Liberman V, Lubin F, Angel S, Owen R, Trostler N, Shkolnik T, Kritchevsky D. A new dietary model to study colorectal carcinogenesis: Experimental design, food preparation, and experimental findings. *Nutr Cancer* 1996;25:79-100.

285. Nobre-Leitao C, Chaves P, Fidalgo P, Cravo M, Gouveia-Oliveira A, Ferra MA, Mira FC. Calcium regulation of colonic crypt cell kinetics: Evidence for a direct effect in mice. *Gastroenterology* 1995;109:498-504.
286. Belleli A, Shany S, Levy J, Guberman R, Lamprecht SA. A protective role of 1,25-dihydroxyvitamin D_3 in chemically induced rat colon carcinogenesis. *Carcinogenesis* 1992;13:2293-2298.
287. Barthold SW, Beck D. Modification of early dimethylhydrazine carcinogenesis by colonic mucosa hyperplasia. *Cancer Res* 1980;40:4451-4455.
288. Yu B, Wu J, Zhou X. [Interference of selenium germanium and calcium in carcinogenesis of colon cancer.] *Zhonghua Wai Ke Za Zhi* 1995;33:167-169.
289. Ahnen J. Are animal models of colon cancer relevant to human diseases? *Dig Dis Sci* 1985;30:103S-106S.
290. Chang WWL. Histogenesis of colon cancer in experimental animals. *Scand J Gastroenterol* 1984;19(Suppl. 104):27-43.
291. Ranhotra GS, Gelroth JA, Glaser BK, Schoening P, Brown SE. Cellulose and calcium lower the incidence of chemically-induced colon tumors in rats. *Plant Foods Hum Nutr* 1999;54:295-303.
292. Potten CS, Loeffler M. Stem cells: Attributes, cycles, spirals, pitfalls and uncertainties. Lessons for and from the crypt. *Development* 1990;110:1001-1020.
293. Comer PF, Clark TD, Glauert HP. Effect of dietary vitamin D_3 (cholecalciferol) on colon carcinogenesis induced by 1,2-dimethylhydrazine in male Fischer 344 rats. *Nutr Cancer* 1993;19:113-124.
294. Tao L, Kramer PM, Wang W, Yang S, Lubet RA, Steele VE, Pereira MA. Altered expression of *c-myc*, p16 and p27 in rat colon tumors and its reversal by short-term treatment with chemopreventive agents. *Carcinogenesis* 2002;23:1447-1454.
295. Pence BC, Dunn DM, Zhao C, Landers M, Wargovich MJ. Chemopreventive effects of calcium but not aspirin supplementation in cholic acid-promoted colon carcinogenesis: Correlation with intermediate endpoints. *Carcinogenesis* 1995;16:757-765.
296. Wargovich MJ, Jimenez A, McKee K, Steele VE, Velasco M, Woods J, Price R, Gray K, Kelloff GJ. Efficacy of potential chemopreventive agents on rat colon aberrant crypt formation and progression. *Carcinogenesis* 2000;21:1149-1155.
297. Wargovich MJ, Chen CD, Jimenez A, Steele VE, Velasco M, Stephens LC, Price R, Gray K, Kelloff GJ. Aberrant crypts as a biomarker for colon cancer: Evaluation of potential chemopreventive agents in the rat. *Cancer Epidemiol Biomarkers Prev* 1996;5:355-360.
298. Belbraouet S, Felden F, Pelletier X, Gastin I, Lambert D, Floquet J, Gueant JL, Debry G. Dietary calcium salts as protective agents and laminin P1 as a biochemical marker in chemically induced colon carcinogenesis in rats. *Cancer Detect Prev* 1996;20:294-299.

299. McSherry CK, Cohen BI, Bokkenheuser VD, Mosbach EH, Winter J, Matoba N, Scholes J. Effects of calcium and bile acid feeding on colon tumors in the rat. *Cancer Res* 1989;49:6039-6043.
300. Quilliot D, Belbraouet S, Pelletier X, Gueant JL, Floquet J, Debry G. Influence of a high-calcium carbonate diet on the incidence of experimental colon cancer in rats. *Nutr Cancer* 1999;34:213-219.
301. Reshef R, Rozen P, Fireman Z, Fine N, Barzilai M, Shasha SM, Shkolnik T. Effect of a calcium-enriched diet on the colonic epithelial hyperproliferation induced by *N*-methyl-*N'*-nitro-*N*-nitroso-guanidine in rats on a low calcium and fat diet. *Cancer Res* 1990;50:1764-1767.
302. Weisburger JH, Rivenson A, Hard GC, Zang E, Nagao M, Sugimura T. Role of fat and calcium in cancer causation by food mutagens, heterocyclic amines. *Proc Soc Exp Biol Med* 1994;205:347-352.
303. Bird RP. Effect of dietary components on the pathobiology of colonic epithelium: Possible relationship with colon tumorigenesis. *Lipids* 1986;21:289-291.
304. Sesink AL, Termont DS, Kleibeuker JH, Van der Meer R. Red meat and colon cancer: Dietary haem-induced colonic cytotoxicity and epithelial hyperproliferation are inhibited by calcium. *Carcinogenesis* 2001;22:1653-1659.
305. Nundy S, Malamud D, Obeertrop H, Sczerban J, Malt RA. Onset of cell proliferation in the shortened gut: Colonic hyperplasia after ileal resection. *Gastroenterology* 1977;72:263-266.
306. Williamson RCN, Bauer FLR, Ross JS, Malt RA. Proximal enterectomy stimulates distal hyperplasia more than bypass or pancreato-biliary diversion. *Gastroenterology* 1978;74:16-23.
307. Rainey JB, Davies PW, Williamson RCN. Relative effects of ileal resection and bypass on intestinal adaptation and carcinogenesis. *Br J Surg* 1984;71:197-202.
308. Scudamore CH, Freeman HJ. Effects of small bowel transection, or bypass in 1,2-dimethylhydrazine induced rat intestinal neoplasia. *Gastroenterology* 1983;84:725-731.
309. Williamson RCN, Bauer FLR, Terpstra OT, Ross JS, Malt RA. Contrasting effects of subtotal enteric bypass, enterectomy, and colectomy on azoxymethane-induced intestinal carcinogenesis. *Cancer Res* 1980;40:538-543.
310. Bristol JB, Wells M, Williamson RCN. Adaptation to jejunoileal bypass promotes experimental colorectal carcinogenesis. *Br J Surg* 1984;71:123-126.
311. Terpstra OT, Dahl EP, Williamson RCN, Ross JS, Malt RA. Colostomy closure promotes cell proliferation and dimethylhydrazine-induced carcinogenesis in rat distal colon. *Gastroenterology* 1981;81:475-480.
312. Williamson RCN, Bauer FLR, Ross JS, Watkins JB, Malt RA. Enhanced colonic carcinogenesis with azoxymethane in rat after pancreatobiliary diversion in mid small bowel. *Gastroenterology* 1979;76:1386-1392.

313. Rainey JB, Maeda M, Williamson RCN. The tropic effect of intrarectal deoxycholate on rat colorectum is unaffected by oral metronidazole. *Cell Tissue Kinet* 1986;19:485-490.
314. Williamson RCN, Rainey JB. The relationship between intestinal hyperplasia and carcinogenesis. *Scand J Gastroenterol* 1984;19(Suppl. 104):57-76.
315. Harte PJ, Steele G Jr, Rayner AA, Munroe AE, King VP, Wilson RE. Effect of major small bowel resection on dimethylhydrazine-induced bowel carcinogenesis. *J Surg Oncol* 1981;18:87-93.
316. Williamson RCN, Bauer FLR, Oscarson JEA, Ross JS, Malt RA. Promotion of azoxymethane-induced colonic neoplasia by resection of the proximal small bowel. *Cancer Res* 1978;38:3212-3217.
317. Lipkin M. Biomarkers of increased susceptibility to gastrointestinal cancer: New applications to studies of cancer prevention in human subjects. *Cancer Res* 1988;48:235-245.
318. Wargovich MJ, Lointier PH. Calcium and vitamin D modulate mouse colon epithelial proliferation and growth characteristics of a human colon tumor cell line. *Can J Physiol Pharmacol* 1987;65:472-477.
319. Penman ID, Liang QL, Bode J, Eastwood MA, Arends MJ. Dietary calcium supplementation increases apoptosis in the distal murine colonic epithelium. *J Clin Pathol* 2000;53:302-307.
320. Hambly RJ, Saunders M, Rijken PJ, Rowland IR. Influence of dietary components associated with high or low risk of colon cancer on apoptosis in the rat colon. *Food Chem Toxicol* 2002;40:801-808.
321. Preston-Martin S, Pike MC, Ross RK, Jones PA, Henderson BE. Increased cell division as a cause of human cancer. *Cancer Res* 1990;50:7415-7421.
322. Ames BN, Gold LS, Willett WC. The causes and prevention of cancer. *PNAS USA* 1995;92:5258-5265.
323. Lipkin M, Blattner WE, Fraumeni JF Jr, Lynch HT, Deschner E, Winawer S. Tritiated thymidine ($\varnothing_p$, $\varnothing_h$) labeling distribution as a marker for hereditary predisposition to colon cancer. *Cancer Res* 1983;43:1899-1904.
324. Ponz de Leon M, Roncucci L, Di Donato P, Tassi L, Smerieri O, Grazia M, Malagoli AG, De Maria D, Antonioli A, Chahin N, Perini M, Rigo G, Barberini G, Manenti A, Biasco G, Barbara L. Pattern of epithelial cell proliferation in colorectal mucosa of normal subjects and of patients with adenomatous polyps or cancer of the large bowel. *Cancer Res* 1988;48:4121-4126.
325. Scalmati A, Lipkin M. Intermediate biomarkers of increased risk for colorectal cancer: Comparison of different methods of analysis and modifications by chemopreventive interventions. *J Cell Biochem Suppl* 1992;16G:65-71.
326. Palmieri GMA. Dietary calcium and colonic cancer (letter). *N Engl J Med* 1986;314:1388.
327. Anti M, Marra G, Armelao F, Percesepe A, Ficarelli R, Ricciuto GM, Valenti A, Rapaccini GL, de Vitis I, D'Agostino G, Brighi S, Vecchio FM. Rectal epithelial cell proliferation patterns as predictors of adenomatous colorectal polyp recurrence. *Gut* 1993;34:525-530.

328. Bleiberg H, Buyse M, Galand P. Cell kinetic indicators of premalignant stages of colorectal cancer. *Cancer* 1985;56:124-129.
329. Lipkin M, Blattner WA, Gardner EJ, Burt RW, Lynch H, Deschner E, Winawer S, Fraumeni JF Jr. Classification and risk assessment of individuals with familial polyposis, Gardner's syndrome and familial non-polyposis colon cancer from [^{3}H]thymidine labeling patterns in colonic epithelial cells. *Cancer Res* 1984;44:4201-4207.
330. Lipkin M, Enker WE, Winawer SJ. Tritiated-thymidine labeling of rectal epithelial cells in "non-prep" biopsies of individuals at increased risk for colonic neoplasia. *Cancer Lett* 1987;37:153-161.
331. Lipkin M, Uehara K, Winawer S, Sanchez A, Bauer C, Phillips R, Lynch HT, Blattner WA, Fraumeni JF Jr. Seventh-Day Adventist vegetarians have quiescent proliferative activity in colonic mucosa. *Cancer Lett* 1985;26:139-144.
332. Paganelli GM, Biasco G, Santucci R, Brandi G, Lalli AA, Miglioli M, Barbara L. Rectal cell proliferation and colorectal cancer risk level in patients with nonfamilial adenomatous polyps of the large bowel. *Cancer* 1991;68:2451-2454.
333. Risio M, Lipkin M, Candelaresi G, Bertone A, Coverlizza S, Rossini FP. Correlations between rectal mucosa cell proliferation and the clinical and pathological features of nonfamilial neoplasia of the large intestine. *Cancer Res* 1991;51:1917-1921.
334. Rooney PS, Clarke PA, Gifford KA, Hardcastle JD, Armitage NC. Identification of high and low risk groups of colorectal cancer using rectal mucosal crypt cell production rate (CCPR). *Br J Cancer* 1993;68:172-175.
335. Scalmati A, Roncucci L, Ghidini G, Biasco G, Ponz de Leon M. Epithelial cell kinetics in the remaining colorectal mucosa after surgery for cancer of the large bowel. *Cancer Res* 1990;50:7937-7941.
336. Stadler J, Yeung KS, Furrer R, Marcon N, Himal HS, Bruce WR. Proliferative activity of rectal mucosa and soluble fecal bile acids in patients with normal colons and in patients with colonic polyps or cancer. *Cancer Lett* 1988;38:315-320.
337. Terpstra OT, van Blankenstein M, Dees J, Eilers GAM. Abnormal pattern of cell proliferation in the entire colonic mucosa of patients with colon adenoma or cancer. *Gastroenterology* 1987;92:704-708.
338. Welberg JW, de Vries EG, Hardonk MJ, Mulder NH, Harms G, Grond J, Zwart N, Koudstaal J, de Ley L, Kleibeuker JH. Proliferation rate of colonic mucosa in normal subjects and patients with colonic neoplasms: A refined immunohistochemical method. *J Clin Pathol* 1990;43:453-456.
339. Barsoum GH, Hendrickse C, Winslet MC, Youngs D, Donovan IA, Neoptolemos JP, Keighley MR. Reduction of mucosal crypt cell proliferation in patients with colorectal adenomatous polyps by dietary calcium supplementation. *Br J Surg* 1992;79:581-583.
340. Deschner EE, Lewis DM, Lipkin M. *In vitro* study of human rectal epithelial cells. 1. Atypical zone of H^3 thymidine incorporation in mucosa of multiple polyposis. *J Clin Invest* 1963;42:1922-1928.

341. Riddell RH. Dysplasia and cancer in ulcerative colitis: A soluble problem? *Scand J Gastroenterol* 1984;19 (Suppl. 104):137-149.
342. Biasco G, Lipkin M, Minarini A, Higgins P, Miglioli M, Barbara L. Proliferative and antigenic properties of rectal cells in patients with chronic ulcerative colitis. *Cancer Res* 1984;44:5450-5454.
343. Bleiberg H, Mainguet P, Galand P, Chretien J, Dupont-Mairesse M. Cell renewal in the human rectum: *In vitro* autoradiographic study on active ulcerative colitis. *Gastroenterology* 1970;58:851-855.
344. Deschner EE, Winawer SJ, Katz S, Katzka I, Kahn E. Proliferation defects in ulcerative colitis patients. *Cancer Invest* 1983;1:41-47.
345. Gerdes H, Gillin JS, Zimbalist E, Urmacher C, Lipkin M, Winawer SJ. Expansion of the epithelial proliferative compartment and frequency of adenomatous polyps in the colon correlate with strength of family history of colorectal cancer. *Cancer Res* 1993;53:279-282.
346. Paganelli GM, Santucci R, Biasco G, Miglioli M, Barbara L. Effect of sex and age on rectal cell renewal in humans. *Cancer Lett* 1990;53:117-121.
347. Roncucci L, Ponz de Leon M, Scalmati A, Malgoli G, Pratissoli S, Perini M, Chalin NJ. The influence of age on colonic epithelial cell proliferation. *Cancer* 1988;62:2373-2377.
348. Risio M, Coverlizza M, Ferrari A, Candelaresi G, Rossini F. Immunohistochemical study of epithelial cell proliferation in hyperplastic polyps, adenomas, and adenocarcinomas of the large bowel. *Gastroenterology* 1988;94:899-906.
349. Anti M, Marra G, Armelao F, Bartoli GM, Ficarelli R, Percesepe A, de Vitis I, Maria G, Sofo L, Rapaccini GL, Gentiloni N, Piccioni E, Miggiano G. Effect of Ω–3 fatty acids on rectal mucosal cell proliferation in subjects at risk for colon cancer. *Gastroenterology* 1992;103:883-891.
350. Biasco G, Zannoni U, Paganelli GM, Santucci R, Gionchetti P, Rivolta G, Miniero R, Pironi L, Calabrese C, Di Febo G, Miglioli M. Folic acid supplementation and cell kinetics of rectal mucosa in patients with ulcerative colitis. *Cancer Epidemiol Biomarkers Prev* 1997;6:469-471.
351. Cascinu S, Del Ferro E, Grianti C, Foglietti GP, Olivieri Q, Bartolucci M, Saba V, Lungarotti F, Catalano G. Hyperproliferative status of the epithelium in the remaining colorectal mucosa after surgery for cancer of the large bowel: Its implications in the prediction of adenomatous polyps recurrence. *GI Cancer* 1995;1:119-122.
352. Nakamura S, Kino I, Baba S. Nuclear DNA content of isolated crypts of background colonic mucosa from patients with familial adenomatous polyposis and sporadic colorectal cancer. *Gut* 1993;34:1240-1244.
353. Wargovich MJ, Harris C, Chen D, Palmer C, Steele VE, Kelloff GJ. Growth kinetics and chemoprevention of aberrant crypts in the rat colon. *J Cell Biochem* 1992;(Suppl. 16G):51-54.
354. Potten CS, Kellett M, Roberts SA, Rew DA, Wilson GD. Measurement of *in vivo* proliferation in human colorectal mucosa using bromodeoxyuridine. *Gut* 1992;33:71-81.

355. Morgan JW, Singh PN. Diet, body mass index and colonic epithelial cell proliferation in a healthy population. *Nutr Cancer* 1995;23:247-257.
356. Sandler RS, Baron JA, Tosteson TD, Mandel JS, Haile RW. Rectal mucosal proliferation and risk of colorectal adenomas: Results from a randomized controlled trial. *Cancer Epidemiol Biomarkers Prev* 2000;9:653-656.
357. Armitage NC, Rooney PS, Gifford K-A, Clarke PA, Hardcastle JD. The effect of calcium supplements on rectal mucosal proliferation. *Br J Cancer* 1995;71:186-190.
358. Bostick RM, Fosdick L, Wood JR, Grambsch P, Grandits GA, Lillemoe TJ, Louis TA, Potter JD. Calcium and colorectal epithelial cell proliferation in sporadic adenoma patients: A randomized, double-blinded, placebo-controlled clinical trial. *J Natl Cancer Inst* 1995;87:1307-1315.
359. Thomas MG, Thomason JPS, Williamson RCN. Oral calcium inhibits rectal epithelial cell proliferation in familial adenomatous polyposis. *Br J Surg* 1993;80:499-501.
360. Lipkin M, Friedman E, Winawer SJ, Newmark H. Colonic epithelial cell proliferation in responders and nonresponders to supplemental dietary calcium. *Cancer Res* 1989;49:248-254.
361. Lipkin M, Newmark H. Application of intermediate biomarkers and the prevention of cancer of the large intestine. *Prog Clin Biol Res* 1988;279:135-150.
362. Holt PR, Wolper C, Moss SF, Yang K, Lipkin M. Comparison of calcium supplementation or low-fat dairy foods on epithelial cell proliferation and differentiation. *Nutr Cancer* 2001;41:150-155.
363. O'Sullivan KR, Mathias PM, Beattie S, O'Morain C. Effect of oral calcium supplementation on colonic crypt cell proliferation in patients with adenomatous polyps of the large bowel. *Eur J Gastroenterol Hepatol* 1993;5:85-89.
364. Rozen P, Fireman Z, Fine N, Wax Y, Ron E. Oral calcium suppresses increased rectal epithelial proliferation of persons at risk of colorectal cancer. *Gut* 1989;30:650-655.
365. Wargovich MJ, Isbell G, Shabot M, Winn R, Lanza F, Hochman L, Larson E, Lynch P, Roubein L, Levin B. Calcium supplementation decreases rectal epithelial cell proliferation in subjects with sporadic adenoma. *Gastroenterology* 1992;103:92-97.
366. Rozen P, Lubin F, Papo N, Knaani J, Farbstein H, Farbstein M, Zajicek G. Calcium supplements interact significantly with long-term diet while suppressing rectal epithelial proliferation of adenoma patients. *Cancer* 2001;91:833-840.
367. Rozen P, Lubin F, Papo N, Zajicek G. Rectal epithelial proliferation in persons with or without a history of adenoma and its association with diet and lifestyle habits. *Cancer* 1998;83:1319-1327.
368. Lans JI, Jaszewski R, Arlow FL, Tureaud J, Luk GD, Majumdar AP. Supplemental calcium suppresses colonic mucosal ornithine decarboxylase activity in elderly patients with adenomatous polyps. *Cancer Res* 1991;51:3416-3419.

369. Bartram H-P, Kasper K, Dusel G, Liebscher E, Gostner A, Loges C, Scheppach W. Effects of calcium and deoxycholic acid on human colonic cell proliferation in vitro. *Ann Nutr Metab* 1997;41:315-323.
370. Guo Y-S, Draviam E, Townsend CM Jr, Singh P. Differential effects of Ca^{2+} on proliferation of stomach, colonic, and pancreatic cancer cell lines in vitro. *Nutr Cancer* 1990;14:149-157.
371. Hulla W, Kallay E, Krugluger W, Peterlik M, Cross HS. Growth control of human colon-adenocarcinoma-derived Caco-2 cells by vitamin-D compounds and extracellular calcium *in vitro*: Relation to c-*myc*-oncogene and vitamin-D-receptor expression. *Int J Cancer* 1995;62:711-716.
372. Baron JA, Tosteson TD, Wargovich MJ, Sandler R, Mandel J, Bond J, Haile R, Summers R, van Stolk R, Rothstein R, Weiss J. Calcium supplementation and rectal mucosal proliferation: A randomized controlled trial. *J Natl Cancer Inst* 1995;87:1303-1307.
373. Weisgerber UM, Boeing H, Owen RW, Waldherr R, Raedsch R, Wahrendorf J. Effect of longterm placebo controlled calcium supplementation on sigmoidal cell proliferation in patients with sporadic adenomatous polyps. *Gut* 1996;38:396-402.
374. Alberts DS, Einspahr J, Ritenbaugh C, Aickin M, Rees-McGee S, Atwood J, Emerson S, Mason-Liddil N, Bettinger L, Patel J, Bellapravalu S, Ramanujam PS, Phelps J, Clark L. The effect of wheat bran fiber and calcium supplementation on rectal mucosal proliferation rates in patients with resected adenomatous colorectal polyps. *Cancer Epidemiol Biomarkers Prev* 1997;6:161-169.
375. van Gorkom BAP, Karrenbeld A, van der Sluis T, Zwart N, van der Meer R, de Vries EGE, Kleibeuker JH. Calcium or resistant starch does not affect colonic epithelial cell proliferation throughout the colon in adenoma patients: A randomized controlled trial. *Nutr Cancer* 2002;43:31-38.
376. Bostick RM, Boldt M, Darif M, Wood JR, Overn P, Potter JD. Calcium and colorectal epithelial cell proliferation in ulcerative colitis. *Cancer Epidemiol Biomarkers Prev* 1997;6:1021-1027.
377. Cascinu S, Ligi M, Del Ferro E, Foglietti G, Cioccolini P, Staccioli MP, Carnevali A, Luigi Rocchi MB, Alessandroni P, Giordani P, Catalano V, Polizzi V, Agostinelli R, Muretto P, Catalano G. Effects of calcium and vitamin supplementation on colon cell proliferation in colorectal cancer. *Cancer Invest* 2000;18:411-416.
378. Karagas MR, Tosteson TD, Greenberg ER, Rothstein RI, Roebuck BD, Herrin M, Ahnen D. Effects of milk and milk products on rectal mucosal cell proliferation in humans. *Cancer Epidemiol Biomarkers Prev* 1998;7:757-766.
379. Kleibeuker JH, Welberg JW, Mulder NH, van der Meer R, Cats A, Limburg AJ, Kreumer WMT, Hardonk MJ, de Vries EGE. Epithelial cell proliferation in the human sigmoid colon of patients with adenomatous polyps increases during oral calcium supplementation. *Br J Cancer* 1993;67:500-503.
380. Duris I, Hruby D, Pekarkova B, Huorka M, Cernakova E, Bezayova T, Ondrejka P. Calcium chemoprevention in colorectal cancer. *Hepatogastroenterology* 1996;43:152-154.

381. Almendingen K, Hofstad B, Vatn MH. Lifestyle-related factors and colorectal polyps: Preliminary results from a Norwegian follow-up and intervention study. *Eur J Cancer Prev* 2002;11:153-158.
382. Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, Rothstein R, Summers RW, Snover DC, Beck GJ, Frankl H, Pearson L, Bond JH, Greenberg ER. Calcium supplements and colorectal adenomas. Polyp Prevention Study Group. *Ann N Y Acad Sci* 1999;889:138-145.
383. Hofstad B, Almendingen K, Vatn M, Andersen SN, Owen RW, Larsen S, Osnes M. Growth and recurrence of colorectal polyps: A double-blind 3-year intervention with calcium and antioxidants. *Digestion* 1998;59:148-156.
384. Pietinen P, Malila N, Virtanen M, Hartman TJ, Tangrea JA, Albanes D, Virtamo J. Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* 1999;10:387-396.
385. McCullough ML, Robertson AS, Rodriguez C, Jacobs EJ, Chao A, Carolyn J, Calle EE, Willett WC, Thun MJ. Calcium, vitamin D, dairy products, and risk of colorectal cancer in the cancer prevention study II nutrition cohort (United States). *Cancer Causes Control* 2003;14:1-12.
386. Terry P, Baron JA, Bergkvist L, Holmberg L, Wolk A. Dietary calcium and vitamin D intake and risk of colorectal cancer: A prospective cohort study in women. *Nutr Cancer* 2002;43:39-46.
387. Zheng W, Anderson KE, Kushi LH, Sellers TA, Greenstein J, Hong CP, Cerhan JR, Bostick RM, Folsom AR. A prospective cohort study of intake of calcium, vitamin D, and other micronutrients in relation to incidence of rectal cancer among postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 1998;7:221-225.
388. Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE, Riboli E. Prospective study of diet and female colorectal cancer: The New York University Women's Health Study. *Nutr Cancer* 1997;28:276-281.
389. Garland C, Shekelle RB, Barrett-Connor E, Criqui MH, Rossof AH, Paul O. Dietary vitamin D and calcium and risk of colorectal cancer: A 19-year prospective study in men. *Lancet* 1985;1:307-309.
390. Bostick RM, Potter JD, Sellers TA, McKenzie DR, Kushi LH, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women. The Iowa Women's Health Study. *Am J Epidemiol* 1993;137:1302-1317.
391. Sellers TA, Bazyk AE, Bostick RM, Kushi LH, Olson JE, Anderson KE, Lazovich D, Folsom AR. Diet and risk of colon cancer in a large prospective study of older women: An analysis stratified on family history (Iowa, United States). *Cancer Causes Control* 1998;9:357-367.
392. Faivre J, Boutron MC, Senesse P, Couillault C, Belighiti C, Meny B. Environmental and familial risk factors in relation to the colorectal adenoma--carcinoma sequence: Results of a case-control study in Burgundy (France). *Eur J Cancer Prev* 1997;6:127-131.
393. Wu K, Willett WC, Fuchs CS, Colditz GA, Giovannucci EL. Calcium intake and risk of colon cancer in women and men. *J Natl Cancer Inst* 2002;94:437-446.

394. Newmark HL, Shiff SJ. Re: Calcium intake and risk of colon cancer in women and men (letter). *J Natl Cancer Inst* 2003;95:169.
395. Almendingen K, Trygg K, Larsen S, Hofstad B, Vatn MH. Dietary factors and colorectal polyps: A case-control study. *Eur J Cancer Prev* 1995;4:239-246.
396. Nakaji S, Shimoyama T, Wada S, Sugawara K, Tokunaga S, MacAuley D, Baxter D. No preventive effect of dietary fiber against colon cancer in the Japanese population: A cross-sectional analysis. *Nutr Cancer* 2003;45:156-159.
397. Arbman G, Axelson O, Ericsson-Begodzki AB, Fredriksson M, Nilsson E, Sjodahl R. Cereal fiber, calcium, and colorectal cancer. *Cancer* 1992;69:2042-2048.
398. Marcus PM, Newcomb PA. The association of calcium and vitamin D, and colon and rectal cancer in Wisconsin women. *Int J Epidemiol* 1998;27:788-793.
399. Yang G. [Relationship between colorectal cancer and ten inorganic elements.] *Zhonghua Yu Fang Yi Xue Za Zhi* 1993;27:282-285.
400. Yang G, Gao Y-T, Ji B-T. [A case-control study on colorectal cancer and dietary fiber and calcium of various sources.] *Zhonghua Yu Fang Yi Xue Za Zhi* 1994;28:195-198.
401. Slattery ML, Edwards SL, Boucher KM, Anderson K, Caan BJ. Lifestyle and colon cancer: an assessment of factors associated with risk. *Am J Epidemiol* 1999;150:869-877.
402. Kearney J, Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Wing A, Kampman E, Willett WC. Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. *Am J Epidemiol* 1996;143:907-917.
403. Kampman E, Giovannucci E, van 't Veer P, Rimm E, Stampfer MJ, Colditz GA, Kok FJ, Willett WC. Calcium, vitamin D, dairy foods, and the occurrence of colorectal adenomas among men and women in two prospective studies. *Am J Epidemiol* 1994;139:16-29.
404. De Stefani E, Mendilaharsu M, Deneo-Pellegrini H, Ronco A. Influence of dietary levels of fat, cholesterol, and calcium on colorectal cancer. *Nutr Cancer* 1997;29:83-89.
405. Ferraroni M, La Vecchia C, D'Avanzo B, Negri E, Franceschi S, Decarli A. Selected micronutrient intake and the risk of colorectal cancer. *Br J Cancer* 1994;70:1150-1155.
406. Peters RK, Pike MC, Garabrant D, Mack TM. Diet and colon cancer in Los Angeles County, California. *Cancer Causes Control* 1992;3:457-473.
407. Satia-Abouta J, Galanko JA, Martin CF, Potter JD, Ammerman A, Sandler RS. Associations of micronutrients with colon cancer risk in African Americans and whites: Results from the North Carolina Colon Cancer Study. *Cancer Epidemiol Biomarkers Prev* 2003;12:747-754.
408. Kune S, Kune GA, Watson LF. Case-control study of dietary etiological factors: The Melbourne Colorectal Cancer Study. *Nutr Cancer* 1987;9:21-42.
409. Slattery ML, Potter JD, Sorenson AW. Age and risk factors for colon cancer (United States and Australia): Are there implications for understanding

differences in case-control and cohort studies? *Cancer Causes Control* 1994;5:557-563.

410. Yang C-Y, Chiu H-F, Chiu J-F, Tsai S-S, Cheng M-F. Calcium and magnesium in drinking water and risk of death from colon cancer. *Jpn J Cancer Res* 1997;88:928-933.
411. Yang C-Y, Chiu H-F. Calcium and magnesium in drinking water and risk of death from rectal cancer. *Int J Cancer* 1998;77:528-532.
412. Yang C-Y, Hung C-F. Colon cancer mortality and total hardness levels in Taiwan's drinking water. *Arch Environ Contam Toxicol* 1998;35:148-151.
413. Yang C-Y, Tsai S-S, Lai T-C, Hung C-F, Chiu H-F. Rectal cancer mortality and total hardness levels in Taiwan's drinking water. *Environ Res* 1999;80:311-316.
414. Slattery ML, Sorenson AW, Ford MH. Dietary calcium intake as a mitigating factor in colon cancer. *Am J Epidemiol* 1988;128:504-514.
415. Martinez ME, Marshall JR, Sampliner R, Wilkinson J, Alberts DS. Calcium, vitamin D, and risk of adenoma recurrence (United States). *Cancer Causes Control* 2002;13:213-220.
416. Slattery ML, Caan BJ, Potter JD, Berry TD, Coates A, Duncan D, Edwards SL. Dietary energy sources and colon cancer risk. *Am J Epidemiol* 1997;145:199-210.
417. Martinez ME, McPherson RS, Levin B, Glober GA. A case-control study of dietary intake and other lifestyle risk factors for hyperplastic polyps. *Gastroenterology* 1997;113:423-429.
418. Whelan RL, Horvath KD, Gleason NR, Forde KA, Treat MD, Teitelbaum SL, Bertram A, Neugut AI. Vitamin and calcium supplement use is associated with decreased adenoma recurrence in patients with a previous history of neoplasia. *Dis Colon Rectum* 1999;42:212-217.
419. Levi F, Pasche C, Lucchini F, La Vecchia C. Selected micronutrients and colorectal cancer: A case-control study from the canton of Vaud, Switzerland. *Eur J Cancer* 2000;36:2115-2119.
420. Whittemore AS, Wu-Williams AH, Lee M, Shu Z, Gallagher RP, Deng-ao J, Lun Z, Xianghui W, Kun C, Jung D, Teh C-Z, Chengde L, Yao XJ, Paffenbarger RS, Henderson BE. Diet, physical activity, and colorectal cancer among Chinese in North America and China. *JNCI* 1990;82:915-926.
421. Kampman E, Slattery ML, Caan B, Potter JD. Calcium, vitamin D, sunshine exposure, dairy products and colon cancer risk (United States). *Cancer Causes Control* 2000;11:459-466.
422. La Vecchia C, Braga C, Negri E, Franceschi S, Russo A, Conti E, Falcini F, Giacosa A, Montella M, Decarli A. Intake of selected micronutrients and risk of colorectal cancer. *Int J Cancer* 1997;73:525-530.
423. Govosdis B, Triantafillidis JK, Chrisochou H, Kalogerakos S, Perdicouris P. Effect of calcium intake on the incidence of sporadic colorectal polyps (letter). *Am J Gastroenterol* 1994;89:952-953.
424. White E, Shannon JS, Patterson RE. Relationship between vitamin and calcium supplement use and colon cancer. *Cancer Epidemiol Biomarkers Prev* 1997;6:769-774.

425. Wong H-L, Seow A, Arakawa K, Lee H-P, Yu MC, Ingles SA. Vitamin D receptor start codon polymorphism and colorectal cancer risk: Effect modification by dietary calcium and fat in Singapore Chinese. *Carcinogenesis* 2003;24:1091-1095.
426. Boyapati SM, Bostick RM, McGlynn KA, Fina MF, Roufail WM, Geisinger KR, Wargovich M, Coker A, Hebert JR. Calcium, vitamin D, and risk for colorectal adenoma: Dependency on vitamin D receptor BsmI polymorphism and nonsteroidal anti-inflammatory drug use? *Cancer Epidemiol Biomarkers Prev* 2003;12:631-637.
427. Ma J, Giovannucci E, Pollak M, Chan JM, Gaziano JM, Willett W, Stampfer MJ. Milk intake, circulating levels of insulin-like growth factor-I, and risk of colorectal cancer in men. *J Natl Cancer Inst* 2001;93:1330-1336.
428. Martinez ME, Giovannucci EL, Colditz GA, Stampfer MJ, Hunter DJ, Speizer FE, Wing A, Willett WC. Calcium, vitamin D, and the occurrence of colorectal cancer among women. *J Natl Cancer Inst* 1996;88:1375-1382.
429. Kampman E, Goldbohm RA, van den Brandt PA, van 't Veer P. Fermented dairy products, calcium, and colorectal cancer in The Netherlands Cohort Study. *Cancer Res* 1994;54:3186-3190.
430. Gaard M, Tretli S, Loken EB. Dietary factors and risk of colon cancer: A prospective study of 50,535 young Norwegian men and women. *Eur J Cancer Prev* 1996;5:445-454.
431. Slob ICM, Lambregts JLMC, Schuit AJ, Kok FJ. Calcium intake and 28-year gastro-intestinal cancer mortality in Dutch civil servants. *Int J Cancer* 1993;54:20-25.
432. Hyman J, Baron JA, Dain BJ, Sandler RS, Haile RW, Mandel JS, Mott LA, Greenberg ER. Dietary and supplemental calcium and the recurrence of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* 1998;7:291-295.
433. Stemmermann GN, Nomura A, Chyou P-H. The influence of dairy and nondairy calcium on subsite large-bowel cancer risk. *Dis Colon Rectum* 1990;33:190-194.
434. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 1990;323:1664-1672.
435. Jarvinen R, Knekt P, Hakulinen T, Aromaa A. Prospective study on milk products, calcium and cancers of the colon and rectum. *Eur J Clin Nutr* 2001;55:1000-1007.
436. Malila N, Virtanen M, Pietinen P, Virtamo J, Albanes D, Hartman AM, Heinonen OP. A comparison of prospective and retrospective assessments of diet in a study of colorectal cancer. *Nutr Cancer* 1998;32:146-153.
437. Heilbrun LK, Hankin JH, Nomura AM, Stemmermann GN. Colon cancer and dietary fat, phosphorus, and calcium in Hawaiian-Japanese men. *Am J Clin Nutr* 1986;43:306-309.
438. Morimoto LM, Newcomb PA, Ulrich CM, Bostick RM, Lais CJ, Potter JD. Risk factors for hyperplastic and adenomatous polyps: Evidence for malignant potential? *Cancer Epidemiol Biomarkers Prev* 2002;11:1012-1018.

439. Negri E, La Vecchia C, D'Avanzo B, Franceschi S. Calcium, dairy products, and colorectal cancer. *Nutr Cancer* 1990;13:255-262.
440. Pritchard RS, Baron JA, Gerhardsson de Verdier M. Dietary calcium, vitamin D, and the risk of colorectal cancer in Stockholm, Sweden. *Cancer Epidemiol Biomarkers Prev* 1996;5:897-900.
441. Levine AJ, Harper JM, Ervin CM, Chen YH, Harmon E, Xue S, Lee ER, Frankel HD, Haile RW. Serum 25-hydroxyvitamin D, dietary calcium intake, and distal colorectal adenoma risk. *Nutr Cancer* 2001;39:35-41.
442. Meyer F, White E. Alcohol and nutrients in relation to colon cancer in middle-aged adults. *Am J Epidemiol* 1993;138:225-236.
443. Martinez ME, McPherson RS, Annegers JF, Levin B. Association of diet and colorectal adenomatous polyps: Dietary fiber, calcium, and total fat. *Epidemiology* 1996;7:264-268.
444. Tseng M, Murray SC, Kupper LL, Sandler RS. Micronutrients and the risk of colorectal adenomas. *Am J Epidemiol* 1996;144:1005-1014.
445. Lee HP, Gourley L, Duffy SW, Esteve J, Lee J, Day NE. Colorectal cancer and diet in an Asian population: A case-control study among Singapore Chinese. *Int J Cancer* 1989;43:1007-1016.
446. Tuyns AJ, Haelterman M, Kaaks R. Colorectal cancer and the intake of nutrients: Oligosaccharides are a risk factor, fats are not: A case-control study in Belgium. *Nutr Cancer* 1987;10:181-196.
447. Freudenheim JL, Graham S, Marshall JR, Haughey BP, Wilkinson G. A case-control study of diet and rectal cancer in western New York. *Am J Epidemiol* 1990;131:612-624.
448. Graham S, Marshall J, Haughey B, Mittelman A, Swanson M, Zielezny M, Byers T, Wilkinson G, West D. Dietary epidemiology of cancer of the colon in western New York. *Am J Epidemiol* 1988;128:490-503.
449. Macquart-Moulin G, Riboli E, Cornee J, Charnay B, Berthezene P, Day N. Case-control study on colorectal cancer and diet in Marseilles. *Int J Cancer* 1986;38:183-191.
450. Benito E, Cabeza E, Moreno V, Obrador A, Bosch FX. Diet and colorectal adenomas: A case-control study in Majorca. *Int J Cancer* 1993;55:213-219.
451. Peters U, McGlynn KA, Chatterjee N, Gunter E, Garcia-Closas M, Rothman N, Sinha R. Vitamin D, calcium, and vitamin D receptor polymorphism in colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* 2001;10:1267-1274.
452. Macquart-Moulin G, Riboli E, Cornee J, Kaaks R, Berthezene P. Colorectal polyps and diet: A case-control study in Marseilles. *Int J Cancer* 1987;40:179-188.
453. Neugut AI, Horvath K, Whelan RL, Terry MB, Garbowski GC, Bertram A, Forde KA, Treat MR, Waye J. The effect of calcium and vitamin supplements on the incidence and recurrence of colorectal adenomatous polyps. *Cancer* 1996;78:723-728.
454. Ghadirian P, Lacroix A, Maisonneuve P, Perret C, Potvin C, Gravel D, Bernard D, Boyle P. Nutritional factors and colon carcinoma: A case-control study involving French Canadians in Montreal, Quebec, Canada. *Cancer* 1997;80:858-864.

455. Kampman E, van 't Veer P, Hiddink GJ, van Aken-Schneijder P, Kok FJ, Hermus RJ. Fermented dairy products, dietary calcium and colon cancer: A case-control study in The Netherlands. *Int J Cancer* 1994;59:170-176.
456. Benito E, Stiggelbout A, Bosch FX, Obrador A, Kaldor J, Mulet M, Munoz N. Nutritional factors in colorectal cancer risk: A case-control study in Majorca. *Int J Cancer* 1991;49:161-167.
457. Zaridze D, Filipchenko V, Kustov V, Serdyuk V, Duffy S. Diet and colorectal cancer: Results of two case-control studies in Russia. *Eur J Cancer* 1993;29A:112-115.
458. Breuer-Katschinski B, Nemes K, Marr A, Rump B, Leiendecker B, Breuer N, Goebell H. Colorectal adenomas and diet: a case-control study. Colorectal Adenoma Study Group. *Dig Dis Sci* 2001;46:86-95
459. Boutron M-C, Faivre J, Marteau P, Couillault C, Senesse P, Quipourt V. Calcium, phosphorus, vitamin D, dairy products and colorectal carcinogenesis: A French case--control study. *Br J Cancer* 1996;74:145-151.
460. Peleg II, Lubin MF, Cotsonis GA, Clark WS, Wilcox CM. Long-term use of nonsteroidal antiinflammatory drugs and other chemopreventors and risk of subsequent colorectal neoplasia. *Dig Dis Sci* 1996;41:1319-1326.
461. Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: A randomised intervention trial. European Cancer Prevention Organisation Study Group. *Lancet* 2000;356:1300-1306.
462. Slattery ML, Potter JD. Physical activity and colon cancer: Confounding or interaction? *Med Sci Sports Exerc* 2002;34:913-919.
463. Wu AH, Paganini-Hill A, Ross RK, Henderson BE. Alcohol, physical activity and other risk factors for colorectal cancer: A prospective study. *Br J Cancer* 1987;55:687-694.
464. Bergsma-Kadijk JA, van 't Veer P, Kampman E, Burema J. Calcium does not protect against colorectal neoplasia. *Epidemiology* 1996;7:590-597.
465. Wargovich MJ, Lynch PM, Levin B. Modulating effects of calcium in animal models of colon carcinogenesis and short-term studies in subjects at increased risk for colon cancer. *Am J Clin Nutr* 1991;54(1 Suppl.):202S-205S.
466. Sandler RS. Epidemiology and risk factors for colorectal cancer. *Gastroenterol Clin North Am* 1996;25:717-735.
467. Garland CF, Garland FC, Gorham ED. Calcium and vitamin D. Their potential roles in colon and breast cancer prevention. *Ann N Y Acad Sci* 1999;889:107-119.
468. Martinez ME, Willett WC. Calcium, vitamin D, and colorectal cancer: A review of the epidemiologic evidence. *Cancer Epidemiol Biomarkers Prev* 1998;7:163-168.
469. Pignone M, Levin B. Recent developments in colorectal cancer screening and prevention. *Am Fam Physician* 2002;66:297-302.
470. Gatof D, Ahnen D. Primary prevention of colorectal cancer: Diet and drugs. *Gastroenterol Clin North Am* 2002;31:587-623.

471. Anonymous. The role of calcium in peri- and postmenopausal women: Consensus opinion of The North American Menopause Society. *Menopause* 2001;8:84-95.
472. Nakhlis F, Morrow M. Ductal carcinoma in situ. *Surg Clin North Am* 2003;83:821-839.
473. Adamovich TL, Simmons RM. Ductal carcinoma in situ with microinvasion. *Am J Surg* 2003;186:112-116.
474. Graham S, Hellmann R, Marshall J, Freudenheim J, Vena J, Swanson M, Zielezny M, Nemoto T, Stubbe N, Raimondo T. Nutritional epidemiology of postmenopausal breast cancer in western New York. *Am J Epidemiol* 1991;134:552-566.
475. Willett W. The search for the causes of breast and colon cancer. *Nature* 1989;338:389-394.
476. Singletary SE. Rating the risk factors for breast cancer. *Ann Surg* 2003;237:474-482.
477. Welsh J, Wietzke JA, Zinser GM, Smyczek S, Romu S, Tribble E, Welsh JC, Byrne B, Narvaez CJ. Impact of the Vitamin D_3 receptor on growth-regulatory pathways in mammary gland and breast cancer. *J Steroid Biochem Mol Biol* 2002;83:85-92.
478. Manni A. Polyamine involvement in breast cancer phenotype. *In Vivo* 2002;16:493-500.
479. Manni A, Grove R, Kunselman S, Demers L. Involvement of the polyamine pathway in breast cancer progression. *Cancer Lett* 1995;92:49-57.
480. Glikman P, Manni A, Demers L, Bartholomew M. Polyamine involvement in the growth of hormone-responsive and –resistant human breast cancer cells in culture. *Cancer Res* 1989;49:1371-1376.
481. Manni A. The role of polyamines in the hormonal control of breast cancer cell proliferation. *Cancer Treat Res* 1994;71:209-225.
482. Shah N, Thomas TJ, Lewis JS, Klinge CM, Shirahata A, Gelinas C, Thomas T. Regulation of estrogenic and nuclear factor κB functions by polyamines and their role in polyamine analog-induced apoptosis of breast cancer cells. *Oncogene* 2001;20:1715-1729.
483. Thomas T, Gallo MA, Klinge CM, Thomas TJ. Polyamine-mediated conformational perturbations in DNA alter the binding of estrogen receptor to poly(dG-m^5dC)·poly(dG-m^5dC) and a plasmid containing the estrogen response element. *J Steroid Biochem* 1995;54:89-99.
484. Persson L, Rosengren E. Increased formation of N_1-acetylspermidine in human breast cancer. *Cancer Lett* 1989;45:83-86.
485. Canizares F, Salinas J, de las Heras M, Diaz J, Tovar I, Martinez P, Penafiel R. Prognostic value of ornithine decarboxylase and polyamines in human breast cancer: Correlation with clinicopathologic parameters. *Clin Cancer Res* 1999;5:2035-2041.
486. Manni A, Astrow SH, Gammon S, Thompson J, Mauger D, Washington S. Immunohistochemical detection of ornithine decarboxylase in primary and metastatic human breast cancer specimens. *Breast Cancer Res Treat* 2001;67:147-156.

487. Leveque J, Bansard JY, Watier E, Catros-Quemener V, Havouis R, Moulinoux JP, Grall JY, Seiler N. Polyamines in human breast cancer and its relations to classical prognostic features: Clinical implications. *Anticancer Res* 1999;19:2275-2279.
488. Leveque J, Foucher F, Bansard JY, Havouis R, Grall JY, Moulinoux JP. Polyamine profiles in tumor, normal tissue of the homologous breast, blood, and urine of breast cancer sufferers. *Breast Cancer Res Treat* 2000;60:99-105.
489. Leveque J, Foucher F, Havouis R, Desury D, Grall JY, Moulinoux JP. Benefits of complete polyamine deprivation in hormone responsive and hormone resistant MCF-7 human breast adenocarcinoma *in vivo*. *Anticancer Res* 2000;20:97-101.
490. Manni A, Wechter R, Gilmour S, Verderame MF, Mauger D, Demers LM. Ornithine decarboxylase over-expression stimulates mitogen-activated protein kinase and anchorage-independent growth of humam breast epithelial cells. *Int J Cancer* 1997;70:175-182.
491. Miller FR, Soule HD, Tait L, Pauley RJ, Wolman SR, Dawson PI, Heppner GH. Xenograft model of progressive human proliferative breast disease. *J Natl Cancer Inst* 1993;85:1725-1731.
492. Glikman P, Vegh I, Pollina A, Mosto A, Levy C. Ornithine decarboxylase activity, prolactin blood levels, and estradiol and progesterone in human breast cancer. *Cancer* 1987;60:2237-2243.
493. Manni A, Mauger D, Gimotty P, Badger B. Prognostic influence on survival of increased ornithine decarboxylase activity in human breast cancer. *Clin Cancer Res* 1996;2:1901-1905.
494. Manni A, Washington S, Griffith JW, Verderame MF, Mauger D, Demers LM, Saman RS, Welch DR. Influence of polyamines on *in vitro* and *in vivo* features of aggressive and metastatic behavior by human breast cancer cells. *Clin Exptl Metastasis* 2002;19:95-105.
495. Manni A, Badger B, Martel J, Demers L. Role of polyamines in the growth of hormone-responsive and –resistant human breast cancer cells in nude mice. *Cancer Lett* 1992;66:1-9.
496. Manni A, Wright C. Polyamines as mediators of estrogen action on the growth of experimental breast cancer in rats. *J Natl Cancer Inst* 1984;73:511-514.
497. Glikman PI, Manni A, Bartholomew M, Demers L. Polyamine involvement in basal and estradiol stimulated insulin-like growth factor I secretion and action in breast cancer cells in culture. *J Steroid Biochem Mol Biol* 1990;37:1-10.
498. Manni A, Badger B, Lynch J, Demers L. Selectivity of polyamine involvement in hormone action on normal and neoplastic target tissues of the rat. *Breast Cancer Res Treat* 1990;17:187-196.
499. Thompson HJ, Meeker LD, Herbst EJ, Ronan AM, Minocha R. Effect of concentration of D,1-2-difluoromethylornithine on murine mammary carcinogenesis. *Cancer Res* 1985;45:1170-1173.

500. Green JE, Shibata MA, Shibata E, Moon RC, Anver MR, Kelloff G, Lubert R. 2-difluoromethylornithine and dehydroepiandrosterone inhibit mammary tumor progression but not mammary or prostate tumor initiation in C3(1)/SV40 T/t-antigen transgenic mice. *Cancer Res* 2001;61:7449-7455.
501. Xue L, Lipkin M, Newmark H, Wang J. Influence of dietary calcium and vitamin D on diet-induced epithelial cell hyperproliferation in mice. *J Natl Cancer Inst* 1999;91:176-181.
502. Shin MH, Holmes MD, Hankinson SE, Wu K, Colditz GA, Willett WC. Intake of dairy products, calcium, and vitamin D and risk of breast cancer. *J Natl Cancer Inst* 2002;94:1301-1311.
503. Knekt P, Jarvinen R, Seppanen R, Pukkala E, Aromaa A. Intake of dairy products and the risk of breast cancer. *Br J Cancer* 1996;73:687-691.
504. Negri E, La Vecchia C, Franceschi S, D'Avanzo B, Talamini R, Parpinel M, Ferraroni M, Filiberti R, Montella M, Falcini F, Conti E, DeCarli A. Intake of selected micronutrients and the risk of breast cancer. *Int J Cancer* 1996;65:140-144.
505. Zaridze D, Lifanova Y, Maximovitch D, Day NE, Duffy SW. Diet, alcohol consumption and reproductive factors in a case-control study of breast cancer in Moscow. *Int J Cancer* 1991;48:493-501.
506. Boyapati SM, Shu XO, Jin F, Dai Q, Ruan Z, Gao YT, Zheng W. Dietary calcium intake and breast cancer risk among Chinese women in Shanghai. *Nutr Cancer* 2003;46:38-43.
507. Van't veer P, van Leer EM, Rietdijk A, Kok FJ, Schouten EG, Hermus RJ, Sturmans F. Combination of dietary factors in relation to breast cancer occurrence. *Int J Cancer* 1991;47:649-653.
508. Katsouyanni K, Willett W, Trichopoulos D, Boyle P, Trichopoulou A, Vasilaros S, Papadiamantis J, MacMahon B. Risk of breast cancer among Greek women in relation to nutrient intake. *Cancer* 1988;61:181-185.
509. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. *CA Cancer J Clin* 2001;51:15-36.
510. Willis MS, Wians FH. The role of nutrition in preventing prostate cancer: A review of the proposed mechanism of action of various dietary substances. *Clin Chim Acta* 2003;330:57-83.
511. Vlajinac HD, Marinkovic JM, Ilic MD, Kocev NI. Diet and prostate cancer: A case-control study. *Eur J Cancer* 1997;33:101-107.
512. Berndt SI, Carter HB, Landis PK, Tucker KL, Hsieh LJ, Metter EJ, Platz EA. Calcium intake and prostate cancer risk in a long-term aging study: The Baltimore Longitudinal Study of Aging. *Urology* 2002;60:1118-1123.
513. Chan JM, Pietinen P, Virtanen M, Malila N, Tangrea J, Albanes D, Virtamo J. Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus (Finland). *Cancer Causes Control* 2000;11:859-867.
514. Schuurman AG, van den Brandt PA, Dorant E, Goldbohm RA. Animal products, calcium, and protein and prostate cancer risk in the Netherlands Cohort Study. *Br J Cancer* 1999;80:1107-1113.

515. Kristal AR, Cohen JH, Qu P, Stanford JL. Associations of energy, fat, calcium, and vitamin D with prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* 2002;11:719-725.
516. Tavani A, Gallus S, Franceschi S, La Vecchia C. Calcium, dairy products, and the risk of prostate cancer. *Prostate* 2001;48:118-121.
517. Hayes RB, Ziegler RG, Gridley G, Swanson C, Greenberg RS, Swanson GM, Schoenberg JB, Silverman DT, Brown LM, Pottern LM, Liff J, Schwartz AG, Fraumeni JF Jr, Hoover RN. Dietary factors and risk for prostate cancer among blacks and whites in the United States. *Cancer Epidemiol Biomarkers Prev* 1999;8:25-34.
518. Kristal AR, Stanford JL, Cohen JH, Wicklund K, Patterson RE. Vitamin and mineral supplement use is associated with reduced risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 1999;8:887-892.
519. Ohno Y, Yoshida O, Oishi K, Okada K, Yamabe H, Schroeder FH. Dietary beta-carotene and cancer of the prostate: A case-control study in Kyoto, Japan. *Cancer Res* 1988;48:1331-1336.
520. Tzonou A, Signorello LB, Lagiou P, Wuu J, Trichopoulos D, Trichopoulou A. Diet and cancer of the prostate: A case-control study in Greece. *Int J Cancer* 1999;80:704-708.
521. Zhang Y, Kiel DP, Ellison RC, Schatzkin A, Dorgan JF, Kreger BE, Cupples LA, Felson DT. Bone mass and the risk of prostate cancer: The Framingham Study. *Am J Med* 2002;113:734-739.
522. Chan JM, Stampfer MJ, Ma J, Gann PH, Gaziano JM, Giovannucci EL. Dairy products, calcium and prostate cancer risk in the Physicians' Health Study. *Am J Clin Nutr* 2001;74:549-554.
523. Giovannucci E, Rimm EB, Wolk A, Ascherio A, Stampfer MJ, Colditz GA, Willett WC. Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Res* 1998;58:442-447.
524. Chan JM, Giovannucci E, Anderson S-O, Yuen J, Adami H-O, Wolk A. Dairy products, calcium, phosphorus, vitamin D, and risk of prostate cancer. *Cancer Causes Control* 1998;9:559-566.
525. Chan JM, Giovannucci EL. Dairy products, calcium, and vitamin D and risk of prostate cancer. *Epidemiol Rev* 2001;23:87-92.
526. Heaney RP, Dowell SD, Bierman J, Hale CA, Bendich A. Absorbability and cost effectiveness in calcium supplementation. *J Am Coll Nutr* 2001;20:239-246.
527. Martini L, Wood RJ. Relative bioavailability of calcium-rich dietary sources in the elderly. *Am J Clin Nutr* 2002;76:1345-1350.
528. Recker RR. Calcium absorption and achlorhydria. *N Engl J Med* 1985;313:70-73.
529. Institute of Medicine. Summary. In: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* National Academy Press, Washington, DC, 1997, summary.
530. Institute of Medicine. Uses of dietary reference intakes. In: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* National Academy Press, Washington, DC, 1997, chapter IX.

531. Food and Drug Admin istration. Food labeling; health claims; calcium and osteoporosis. Proposed Rule. *Fed Reg* 1991;56:60689-.
532. Food and Drug Administration. Food labeling; health claims; calcium and osteoporosis. Final Rule. *Fed Reg* 1993;58:2665-2677.
533. Malberti F, Surian M, Poggio F, Minoia C, Salvadeo A. Efficacy and safety of long-term treatment with calcium carbonate as a phosphate binder. *Am J Kidney Dis* 1988;12:487-491.
534. Moriniere P, Hocine C, Boudailliez B, Belbrik S, Renaud H, Westeel PF, Solal MC, Fournier A. Long-term efficacy and safety of oral calcium as compared to $Al(OH)_3$ as phosphate binders. *Kidney Int* 1989;36(Suppl. 27):S133-S135.
535. Tsukamoto Y, Moriya R, Nagaba Y, Morishita T, Izumida I, Okubo M. Effect of administering calcium carbonate to treat secondary hyperparathyroidism in nondialyzed patients with chronic renal failure. *Am J Kidney Dis* 1995;25:879-886.
536. Nolan CR, Qunibi WY. Calcium salts in the treatment of hyperphosphatemia in hemodialysis patients. *Curr Opin Nephrol Hypertens* 2003;12:373-379.
537. Clark AGB, Oner A, Ward G, Turner C, Rigden SPA, Haycock GB, Chantler C. Safety and efficacy of calcium carbonate in children with chronic renal failure. *Nephrol Dial Transplant* 1989;4:539-544.
538. Orwoll ES. The milk-alkali syndrome: Current concepts. *Ann Intern Med* 1982;97:242-248.
539. Adams ND, Gray RW, Lemann J Jr. The effects of oral $CaCO_3$ loading and dietary calcium deprivation on plasma 1,25-dihydroxyvitamin D concentrations in healthy adults. *J Clin Endocrinol Metab* 1979;48:1008-1016.
540. Heaney RP, Recker RR. Calcium supplements: Anion effects. *Bone Miner* 1987;2:433-439.
541. Lagman R, Walsh D. Dangerous nutrition? Calcium, vitamin D, and shark cartilage nutritional supplements and cancer-related hypercalcemia. *Support Care Cancer* 2003;11:232-235.
542. Burtis WJ, Gay L, Insogna KL, Ellison A, Broadus AE. Dietary hypercalciuria in patients with calcium oxalate kidney stones. *Am J Clin Nutr* 1994;60:424-429.