EXHIBIT A

Lycopene, Tomatoes, Tomato-Based Food Products and the Prevention of Cancer

Based on my review of the reliable and credible scientific literature regarding the effects of tomato and tomato-based food product consumption and of dietary supplementation with lycopene on various cancers, I conclude that there is significant scientific agreement in support of the following health claims:

- Lycopene may reduce the risk of cancer.
- Lycopene may reduce the risk of prostate cancer.
- Lycopene may reduce the risk of lung cancer.
- Lycopene may reduce the risk of gastric cancer.
- Lycopene may reduce the risk of colorectal cancer.
- Lycopene may reduce the risk of breast cancer.
- Lycopene may reduce the risk of cervical cancer.
- Lycopene may reduce the risk of endometrial cancer.
- Lycopene may reduce the risk of ovarian cancer.
- Lycopene may reduce the risk of pancreatic cancer.
- Tomatoes may reduce the risk of cancer.
- Tomatoes may reduce the risk of prostate cancer.
- Tomatoes may reduce the risk of lung cancer.
- Tomatoes may reduce the risk of gastriccancer.
- Tomatoes may reduce the risk of colorectal cancer.
- Tomatoes may reduce the risk of breast cancer.
- Tomatoes may reduce the risk of cervical cancer.
- Tomatoes may reduce the risk of endometrial cancer.
- Tomatoes may reduce the risk of ovarian cancer.
- Tomatoes may reduce the risk of pancreatic cancer.
- Lycopene-containing tomato-based foods may reduce the risk of cancer.
- Lycopene-containing tomato-based foods may reduce the risk of prostate cancer.
- Lycopene-containing tomato-based foods may reduce the risk of lung cancer.
- Lycopene-containing tomato-based foods may reduce the risk of gastric cancer.
- Lycopene-containing tomato-based foods may reduce the risk of colorectal cancer.

- Lycopene-containing tomato-based foods may reduce the risk of breast cancer.
- Lycopene-containing tomato-based foods may reduce the risk of cervical cancer.
- Lycopene-containing tomato-based foods may reduce the risk of endometrial cancer.
- Lycopene-containing tomato-based foods may reduce the risk of ovarian cancer.
- Lycopene-containing tomato-based foods may reduce the risk of pancreatic cancer.

I. Lycopene

A. Chemistry

Lycopene ($C_{40}H_{56}$) is a natural fat-soluble pigment found in plants where it serves as an accessory light-gathering pigment and free radical quencher. This carotenoid is an open chain polyisoprenoid with 11 conjugated double bonds. Lycopene occurs in food sources predominantly as all-*trans*-lycopene. Various *cis*-isomers also are found in human blood and tissues, suggesting post-ingestive isomerization. Because lycopene is acyclic it does not serve as a substrate for β-carotene 15,15'-dioxygenase and therefore cannot be converted to vitamin A.[1-4]

B. Food Sources

The major food sources of lycopene are raw red or pink grapefruit (1419 mcg of lycopene per 100 g edible fruit), raw watermelon (4532 mcg of lycopene per 100 g edible fruit), raw tomatoes (year-round average: 2573 mcg of lycopene per 100 g edible fruit) and processed food products containing tomatoes (tomato juice, 9037 mcg of lycopene per 100 g juice; canned whole tomatoes, 4035 mcg of lycopene per 100 g edible portion; tomato sauce, 15152 mcg of lycopene per 100 g sauce; tomato puree, 21754 to 28764 mcg of lycopene per 100 g puree; tomato paste, 29330 mcg of lycopene per 100 g paste; tomato soup, 14596 mcg of lycopene per 100 g soup; catsup, 17007 mcg of lycopene per 100 g of catsup).[5] Little lycopene is lost during heat processing; for example, the six-fold concentration of tomatoes during the conversion of whole tomatoes into tomato paste is accompanied by a six-fold concentration of lycopene.[6] Similarly, between 90% and 95% of the total lycopene in tomatoes is in the form of *trans*-lycopene, with the remainder as various *cis*-isomers; the ratio of *trans*- to *cis*-isomers is not affected by the conversion of raw tomatoes into tomato paste.[2,7-10]

Lycopene in foods and food products is extraordinarily stable.[11] Estimates of losses in total lycopene content during the heat processing of tomatoes into tomato juice, paste, soup or sauce have ranged from nil to less than 15%;[9,12-14] Further cooking on a stove for 1 hour did not affect the product's total lycopene content,[12,14] although the ratio of *trans*-lycopene to *cis*-lycopene was decreased slightly.[12] Storage of processed tomato juice at 25° C or 37° C for 12 months had no effect on total lycopene content, while storage at 4° C for 12 months reduced total lycopene content by 3%.[12]

C. Bioavailability

Lycopene naturally occurs in plants and is closely associated with the organic matrix of plant cells.[15,16] It appears that lycopene must be released from this matrix in order for absorption to occur.[16,17] This release is effected by gastric acidity[18,19] and by thermal processing of foods containing lycopene prior to their ingestion.[8,11,20] Several investigators have reported that the bioavailability of lycopene (assessed from analysis of

acute and subacute changes in post-ingestive circulating total lycopene concentrations) is increased following the conversion of raw tomatoes into juice, paste or puree.[8,20-23] Others have reported that the bioavailability of lycopene in the tomato oleoresin extracts supplied as dietary supplements is greater than is the bioavailability of the lycopene in raw tomatoes but is not different from the bioavailability of lycopene in tomato juice.[24]

Following release from its native organic matrix, or after ingestion as an extract, free lycopene is absorbable only after its incorporation into micelles.[2] *Cis*-isomers maybe more readily absorbed than *trans*-isomers (as has been found in ferrets[19]) as a consequence of the greater solubility in mixed micelles of *cis*-isomers.[2] Any conditions or factors (such as hypochlorhydria, achlorhydria, biliary insufficiency, liver failure, the consumption of a fat-free diet, etc.) that interfere with or reduce postprandial micellar formation will decrease the absorbability of ingested lycopene.[16,25] Conversely, conditions that promote the solubility of lycopene in mixed micelles, such as the presence of monounsaturated fatty acids, will increase the absorbability of ingested lycopene (although low-fat diets appear to have no effect[26,27]).[21,28] Micellar dispersal at the brush border releases lycopene to enter enterocytes via passive diffusion; within enterocytes, lycopene is incorporated into chylomicrons for secretion into the mesenteric lymph system 2 to 6 hours after the consumption of lycopene-containing foods.[2,8] Acting on chylomicrons in the circulation, lipoprotein lipase releases lycopene for uptake by peripheral tissues and organs, including the liver, which repackages lycopene into lipoproteins that are secreted into the circulation 12 to 48 hours later.[8]

In the only study reporting quantitative data on lycopene absorption obtained through the application of compartmental modeling techniques to serum appearance and disappearance data, healthy men were reported to absorb an average of 4.7 mg of total lycopene from daily intakes ranging from 10 to 120 mg.[29] The amount of lycopene absorbed was independent of intake, suggesting the possibility of the potential for saturation of lycopene absorptive mechanisms. Mean efficiencies of absorption of oral lycopene ranged from 34% (10 mg of lycopene consumed) to 5% to 7% (60 mg to 120 mg of lycopene consumed). These estimates of lycopene absorption are greater than that obtained through the use of an *in vitro* model, which produced an estimate that about 3% of the total lycopene in a stir-fried meal of fresh vegetables was incorporated into micelles (and therefore absorbable),[30] an in vivo model of human micellar formation in situ, which produced an estimate of the efficiency of lycopene absorption of about 2%[31] and an *in vivo* model of lycopene absorption through association with triglycerides, which resulted in an estimate of the efficiency of lycopene absorption of about 2.5%.[32]

The bioavailabilities of synthetic lycopene preparations have been compared to the bioavailabilities of the lycopene in raw tomatoes and processed tomato products. The bioavailabilities of the synthetic lycopene in microencapsulated beadlets (Lycopene 5% TG, D.S.M. N.V., Heerlen, The Netherlands; LycoVit 10%, BASF, Ludwigshafen, Germany; containing isomeric distributions of lycopene similar to that found in raw tomatoes[23,33]), the extracted "natural source" lycopene in a bead formulation (Lyc-O-

Mato™ 6%, LycoRed Natural Products Industries Ltd., Beer-Sheva, Israel) and lycopene in cooked tomato soup have been found to be nearly identical.[23,34] Consistent with the differences in the bioavailabilities of lycopene in raw and processed tomato-based foods,[8,20-23] the bioavailability of synthetic lycopene has been reported to be significantly greater than the bioavailability of lycopene in unprocessed (raw) tomato juice.[23]

II. The Relationships among the Consumption of Tomatoes and Tomato-Based Foods Containing Lycopene, Dietary Supplementation with Lycopene and Typical Circulating Lycopene Concentrations in Humans

The measured serum or plasma total lycopene concentrations of over 95% of the subjects in a vast array of studies have ranged between 0.1 x 10^{-6} *M* and 2 x 10^{-6} *M*.[7,10,12,22,29,33-148] These reports are consistent with population survey data that have produced the estimates of serum total lycopene concentrations in the U.S. summarized in Table 1.

Table 1. Serum total lycopene concentrations measured in the National Health and Nutrition Examination Survey III (NHANES III) between 1988 and 1994.[149]

	Serum Total Lycopene Concentration					
	Mean		1st Percentile		99th Percentile	
Sex and Age	mcg/dL	x 10^{-6} *M*	mcg/dL	x 10^{-6} *M*	mcg/dL	x 10^{-6} *M*
Males and females:						
4 – 8 years	23.3	0.43	7.1	0.13	46.7	0.87
Males:						
9 – 13 years	25.0	0.47	8.2	0.15	50.7	0.94
14 – 18 years	25.3	0.47	10.2	0.19	48.9	0.91
19 – 30 years	26.8	0.50	9.2	0.17	51.4	0.96
31 – 50 years	26.0	0.48	6.9	0.13	54.6	1.05
51 – 70 years	22.0	0.41	4.2	0.08	51.0	0.95
over 70 years	15.5	0.29	2.7	0.05	39.5	0.74
Females:						
9 – 13 years	24.4	0.45	9.7	0.18	50.7	0.94
14 – 18 years	23.4	0.44	8.7	0.16	46.0	0.86
19 – 30 years	24.8	0.46	7.9	0.15	53.2	0.99
31 – 50 years	22.9	0.43	6.5	0.12	47.8	0.89
51 – 70 years	20.9	0.39	4.3	0.08	50.1	0.93
over 70 years	17.0	0.32	2.9	0.05	45.9	0.85
All	23.4	0.44	5.6	0.10	50.8	0.95

Data from several studies confirm that circulating total lycopene concentrations decline among older adults.[43,121,145] In one study, the mean serum total lycopene concentration of a cohort of men with a mean age of 73 years was only 57% of the mean serum total lycopene concentration of a cohort of men with a mean age of 24 years.[121]

Table 2. Daily lycopene intakes estimated from data obtained in the National Health and Nutrition Examination Survey III (NHANES III) between 1988 and 1994.[154]

	Daily Lycopene Intake (mcg per day)					
			Percentiles			
Sex and Age	Mean	Median	10th	25th	75th	99th
Males and females:						
2 – 6 months	164	0	0	0	0	2707
7 – 12 months	1873	0	0	0	780	21577
1 – 3 years	5278	1361	0	0	6366	43262
4 – 8 years	6951	2902	0	23	9125	52255
Males:						
9 – 13 years	10111	4301	0	242	12771	89687
14 – 18 years	11547	5211	0	133	15355	123299
19 – 30 years	12656	5079	0	511	16000	110395
31 – 50 years	9882	2902	0	0	11832	76642
51 – 70 years	6635	1625	0	0	6853	60917
over 70 years	6666	1376	0	0	5627	83429
Females:						
9 – 13 years	8262	2902	0	0	11482	50216
14 – 18 years	7980	2902	0	0	10179	72465
19 – 30 years	7438	2420	0	0	9709	62806
31 – 50 years	5972	1836	0	0	7053	57600
51 – 70 years	5388	1361	0	0	4877	47917
over 70 years	4332	842	0	0	3409	52255
Pregnant	8713	3802	0	696	13467	71038
Lactating	9513	3969	0	1625	12058	48076
All:						
not including pregnant or lactating females	7753	2141	0	0	9152	65522
including pregnant or lactating females	7774	2167	0	0	9226	65517

Data from the National Health and Nutrition Examination Survey III (NHANES III) indicate that cigarette smokers have significantly lower serum total lycopene concentrations than do nonsmokers.[150] This conclusion is consistent with data obtained from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.[38]

Less data are available concerning lycopene intake. Several surveys (1986 Continuing Survey of Food Intake by Individuals;[151] 1992 National Health Interview Survey;[152] Nutritional Factors in Eye Disease Study[146]) have suggested that mean daily lycopene intake in the U.S. is between 1.6 and 2.6 mg.[149] However, data obtained from the 83,234 participants in the Nurses' Health Study indicates that those women consumed more lycopene on a routine basis (median intake: 6077 mcg).[153] Data obtained from the participants in the NHANES III study (Table 2) contradict these reports, with mean daily lycopene intakes for adults ranging from 4332 mcg to 12656, and median daily lycopene intakes for adults ranging from 842 mcg to 5211 mcg, depending on sex and age.[154] Interestingly, both mean and median daily lycopene intakes were greater among pregnant and lactating adult women than among nonpregnant and nonlactating premenopausal adult women. However, with the exception of men aged 19 to 30 years, over 25% of the participants in the NHANES III study reported no consumption of lycopene-containing foods (and between 10% and 25% of men aged 19 to 30 years reported no consumption of lycopene-containing foods).

Daily lycopene intakes estimated from USDA nutrient composition[5] and food consumption data[155] suggest that lycopene intakes may well average 3- to 10-fold higher than is indicated by other estimates. According to USDA data, per capita consumption of fresh tomatoes averaged 23.3 g daily in 2002 (providing about 0.6 mg of lycopene daily) and is forecast to average 23.7 g daily in 2003 (providing about 0.6 mg of lycopene daily). The consumption of all other tomato-containing foods averaged 87.8 g daily in 2002 (equivalent to 0.7 tomatoes daily[5]) providing between 9 and 27 mg of lycopene daily, depending upon the specific foods and food products consumed) and is forecast to average 89.4 mg daily in 2003 (providing between 9 and 27 mg of lycopene daily, depending upon the specific foods and food products consumed). These data indicate that total daily lycopene consumption averaged between 9 and 28 mg daily in the U.S. in 2002 and 2003. According to these same USDA data, the consumption of tomatoes, tomato-containing foods and food products and lycopene have not changed since 1990.

Data from the 38,445 women participating in the Women's Health Study indicate that lycopene intake is determined primarily by the consumption of tomatoes and tomato-based food products.[156] Among 946 women participating in the Women's Health Initiative, serum total lycopene concentration was independently significantly correlated with the consumption of fresh tomatoes, cooked tomatoes, tomato juice, tomato sauce and tomato salsa.[43] The results of several human studies have demonstrated that serum or plasma total lycopene concentration is significantly correlated with lycopene intake in healthy men and women[43,65,68,141,144,146] and is unvarying within individuals over a number of years (probably reflecting the relative stability of adult dietary

habits).[60,66,77,92,98,111] Therefore, it has been asserted that the measurement of circulating total lycopene concentration in single blood samples provides predictors of long-term lycopene intakes that are sufficiently valid for epidemiologic studies.[111]

In contrast, intentional reduction in lycopene intake produces a significant decrease in circulating lycopene concentrations.[124,125,157] Furthermore, increasing lycopene intake has produced significant increases in serum or plasma total lycopene concentrations in healthy men and women.[12,22,24,34,77-79,85,89,124-126,138] Similarly, increased consumption of tomatoes and tomato-containing foods and food products significantly increased serum or plasma total lycopene concentrations in healthy men and women[23,24,36,43,47,51,69,70,78,79,85,89,91,109,110,122-125,130,134,158] as well as in women with breast cancer,[66,92] men and women with colorectal adenomas,[98] men with prostate cancer,[105] men and women with diabetes,[136] male and female renal transplant recipients,[100] male and female cancer survivors[63] and lactating women.[38]

III. Cancer

A. Cancer Mortality

Cancer is the second leading cause of death in the U.S.[159] The American Cancer Society forecast 556,500 deaths from cancer in 2003.[159] Overall, the 5-year relative survival rate is 62%.[159] The rate of survival is drastically reduced by the presence of malignancy. Between 60% and 65% of the estimated 285,900 men dying from cancer in 2003 will die from lung, bronchial, prostate or colorectal cancers. About 75% of the estimated 270,600 women dying from cancer in 2003 will die from cancers of the lungs, bronchi, breast, colon or rectum. In addition to the termination of these cases by death, about 675,300 men and 658,800 women are predicted to become newly-diagnosed with cancer during 2003, resulting in a net increase of about 10% in the number of individuals in the U.S. with cancer. Total cancer-related health care costs during 2002 were approximately 171.6 billion dollars (approximately 61 billion dollars for direct medical expenditures).[159]

B. Cell Culture Studies Provide Scientific Support for the Conclusion that Risk of Developing Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods Containing Lycopene

Mouse C3H/10T1/2 embryonic fibroblasts are well-studied and are known to undergo neoplastic transformation in response to many chemical and physical carcinogens in a dose-dependent manner.[160,161] Following pretreatment of cultures of C3H/10T1/2 cells with the cell transformation inducing agent, methylcholanthrene, the addition of lycopene (3×10^{-6} *M*) to the culture medium significantly inhibited the generation of foci of transformed cells, producing about 50% inhibition.[161] This inhibition occurred only upon exposure to lycopene during the postinitiation period; lycopene (10×10^{-6} *M*) exposure concurrent with exposure to methylcholanthrene did not affect transformation. The neoplastic transformation-inhibiting activity of lycopene was strongly correlated with

lycopene-induced upregulation of expression of connexin 43[162] and stimulation of intercellular gap junctional communication.[163] In various cancers, including human prostate cancer, the expression of connexin 43 is inversely proportional to the degree of disease progression and the induction of increased connexin 43 expression in epithelial cells from prostate tumors has been accompanied by deceleration of proliferation and the induction of cellular differentiation (i.e., reversal of disease progression).[164] Lycopene (3×10^{-6} *M*) also has significantly stimulated expression of connexin 43 and intercellular gap junctional communication while significantly inhibiting proliferation in cultures of human KB-1 oral tumor cells.[165] Similarly, lycopene (0.1×10^{-6} *M*) significantly stimulated gap junctional communication in cultures of human fetal skin fibroblasts, although in that cell culture system lycopene did not affect connexin expression.[166]

Gap junction channels consist of apposed cylindrical aggregates of six subunits each in adjacent cell membranes and are found throughout the body.[167,168] Extracellular loops that extend from the transmembrane-spanning domains of each of the six protein subunits across intercellular space interact with similar loops extending from an adjacent cell and establish the junction. At each gap junction, each cell contributes a hemiconnexon consisting of six identical protein units (connexins) assembled radially to encircle and enclose a water-filled pore that allows direct cytoplasmic-to-cytoplasmic communication of ions and low molecular weight water-soluble compounds (such as cyclic AMP) via passive diffusion down concentration gradients between the two cells without loss to the extracellular space. A variety of connexins exist within the human body; connexin 43 is the most widely distributed.

An important function of gap junctions is to serve as conduits for antiproliferative signals generated by proliferation-inhibited normal cells and that act to suppress the proliferation of carcinogen-initiated cells thereby preventing their transformation into tumor cells.[169,170] Cells deficient in the ability to receive or respond to such signals originating from proliferation-inhibited normal cells as a result of reduced or absent expression of connexin genes (as occurs in most human tumor cell lines) are at a relative proliferative advantage. Conversely, agents that increase gap junctional communication between cells deficient in this function and proliferation-inhibited normal cells should produce inhibition of the proliferation of previously-deficient cells. However, increased gap junctional communication between cells deficient in this function and proliferation-inhibited normal cells requires that the functionally deficient cells not have progressed from the initiation or promotion stages of carcinogenesis to the gap junctional communication-resistant stage of cell transformation into tumor cells.[169,171] This apparent requirement is consistent with reports that many tumor promoting substances inhibit gap junctional communication and that potency as tumor promoter is correlated with potency as inhibitor of connexin expression and gap junctional communication.[168] In addition, reduced expression of connexin genes may be a required precursor lesion preceding cell transformation and stimulation of connexin gene expression with resultant increase in gap junctional communication may be a key cancer-preventing property of connexin-inducing agents.[167,168]

C. Human Studies Provide Scientific Support for the Conclusion that Risk of Developing Cancer is Reduced by the Consumption of Lycopene, or Tomatoes or Tomato-Based Foods Containing Lycopene

Oxidative damage to DNA can produce genetic changes associated with the initiation and progression of cancer.[172,173] Oxidative damage to DNA has been proposed as a biologically significant contributor to the development of colon, breast, rectum and prostate cancers.[174,175] Several products of DNA base oxidation, including 8-hydroxyguanine, 2-hydroxyadenine, 5-hydroxycytosine, 5-hydroxyuracil and formyluracil, are known to be mutagenic in concentrations that mimic their frequency in endogenous DNA.[176-179] It has been reasoned that, based on the available experimental evidence, the extent of oxidative DNA damage in human cells is a biomarker with some ability to predict risk for the development of cancer and reduction in the extent of oxidative DNA damage in human cells is consistent with reduced risk for the development of cancer.[180]

Lycopene has been demonstrated to be the most potent free radical antioxidant among the carotenoids.[51,181,182] The potential for the consumption of foods providing significant amounts of dietary lycopene to exert chemoprotection against oxidative damage to DNA was examined in healthy nonsmoking men.[183] Compared to the end of a 2-week period of intentional lycopene depletion, after 2 weeks of dietary supplementation with tomato juice containing 40 mg of lycopene daily, the number of endogenous DNA strand breaks was significantly reduced in circulating lymphocytes. Although endogenous DNA strand breaks was significantly reduced, this short-term consumption of additional lycopene-containing tomato-based food product was insufficient to produce a statistically significant decrease in the physiologic effector of DNA strand breaks, oxidative base damage. In contrast, the ingestion of a single serving of fresh tomatoes (8 g per kg body weight) by healthy men and women significantly reduced the endogenous production of oxidized DNA base adducts in circulating lymphocytes and leukocytes.[7]

Consistent with the conclusion that increased lycopene intake reduces endogenous damage to DNA, 2 weeks of dietary supplementation with tomato puree containing 7 mg of lycopene daily significantly reduced the number of exogenously-induced DNA strand breaks in circulating lymphocytes harvested from healthy women.[85] This chemopreventive effect was accompanied by significant increases in plasma total lycopene concentration and lymphocyte lycopene content. Both plasma total lycopene concentration and lymphocyte lycopene content were significantly inversely correlated with the extent of exogenously-induced oxidative damage to DNA. In another experiment in which total supplemental lycopene exposure was similar, lymphocytes harvested from healthy men and women whose diets were supplemented with semi-purified lycopene (15 mg daily) for 1 week exhibited significantly increased resistance to exogenously-induced oxidative damage to DNA.[184] The magnitude of effect was reflective of the extent to which dietary supplementation with lycopene produced increase in plasma total lycopene concentration. Similarly, lymphocytes harvested from healthy women supplemented with tomato puree containing 16.5 mg of lycopene exhibited significantly greater resistance to exogenously-induced DNA oxidation than

was exhibited by lymphocytes harvested from healthy women whose diets were not supplemented,[158] and the consumption of a single serving of fresh tomatoes (8 g of tomatoes per kg body weight) significantly reduced the frequency of oxidative DNA base damage in circulating white blood cells.[185]

In an *in vitro* test system, both hydrophilic and lipophilic extracts of fresh tomatoes, tomato paste and tomato puree significantly inhibited oxidative reactions catalyzed by xanthine oxidase and neutrophil-derived myeloperoxidase, major *in vivo* physiologic producers of superoxide, hydrogen peroxide and hypochloric acid.[186] In addition, the lipophilic extracts significantly inhibited copper-catalyzed oxidation of linoleic acid (lipid peroxidation). In confluent cultures of mouse C3H/10T1/2 embryonic fibroblasts, lycopene (1×10^{-6} *M*) significantly inhibited lipid peroxidation.[163]

The published scientific evidence strongly supports the conclusion that the risk of developing any cancer is reduced by dietary supplementation with lycopene and by the consumption of tomatoes and tomato-based foods containing lycopene.

D. Human Studies Provide Significant Scientific Support for the Conclusion that Risk for Dying from Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods Containing Lycopene

The findings of three studies support the conclusion that tomato and tomato-based food product consumption or dietary supplementation with lycopene reduce the risk of dying of cancer.[57,58,187] The results of a 5-year prospective study of 1,271 men and women aged 66 years or older indicated that the age-adjusted risk of dying from any cancer was significantly reduced by 50% (95% CI: 0.3, 0.8) in individuals who consumed an average of more than 1 serving of tomatoes weekly, compared to the risk of dying from any cancer of individuals who consumed an average of less than 1 serving of tomatoes weekly.[187] In another 8-year prospective study of 929 men and 1,424 women, the geometric mean serum total lycopene concentration of the subjects who died from cancer (0.28×10^{-6} *M*) was significantly lower than the geometric mean serum total lycopene concentration of the subjects who did not die during the study (0.37×10^{-6} *M*).[58]

In a 9-year prospective study of 949 men and 1,495 women, 48 men and 28 women died from cancers.[57] Among these 2,444 subjects, the geometric mean serum total lycopene concentrations of the subjects who died from cancer (men: 0.16×10^{-6} *M*; women: 0.22×10^{-6} *M*) were significantly lower than the geometric mean serum total lycopene concentrations of the subjects who did not die during the study (men: 0.21×10^{-6} *M*; women: 0.31×10^{-6} *M*). The application of Cox's proportional hazard model to the data from the entire cohort revealed that the multivariate-adjusted risk of death from any cancer was significantly reduced among those subjects with serum total lycopene concentrations in the highest tertile of serum total lycopene concentrations, compared to the risk among those subjects with serum total lycopene concentrations in the lowest tertile of serum total lycopene concentrations (hazard ratio: 0.37; 95% CI: 0.19, 0.72). This relationship was strengthened when only deaths occurring after the first three years

of the study were included (hazard ratio: 0.36; 95% CI: 0.21, 0.61), when the analysis was restricted to only non-smoking subjects and only deaths occurring after the first three years of the study were included (hazard ratio: 0.33; 95% CI: 0.12, 0.90) and when the analysis was restricted to only subjects with serum total cholesterol concentrations greater than 250 mg/dL and only deaths occurring after the first three years of the study were included (hazard ratio: 0.33; 95% CI: 0.12, 0.90).

The published scientific evidence strongly supports the conclusion that the risk for dying from any cancer is reduced by dietary supplementation with lycopene and by the consumption of tomatoes and tomato-based foods containing lycopene.

IV. Prostate Cancer

Prostate cancer is the leading cause of newly-diagnosed cancer in males in the US.[159] About 220,900 new cases of prostate cancer were forecast for the US for the year 2003, while nearly 30,000 men in the US were expected to die from this disease that year.[159] When all stages of prostate cancer are combined, the 5-year relative survival rate is 97%, 10-year relative survival is 79% and 15-year relative survival is 57%.[159]

A. Pathogenesis of Prostate Cancer

Prostate cancer results from the proliferation of epithelial cells located predominantly in the peripheral zone of the prostate gland.[188,189] Carcinogenesis in the prostate occurs in a multistage process involving a series of genetic alterations with progression through a variety of pathways from precancerous lesions, including proliferative inflammatory atrophy and low-grade prostatic intraepithelial neoplasia, to a high-grade focus of accelerated proliferation without invasion of the basement membrane ("high-grade prostatic intraepithelial neoplasia"; HGPIN) through the development of a small latent androgen-dependent carcinoma to higher-grade androgen-independent metastatic disease.[188-194] HGPIN is recognized as a reversible precursor to prostate cancer.[188-194]

Reactive oxygen species (such as the hydroxyl radical OH˙) may be implicated in the pathogenesis of prostate cancer. A common early event in both HGPIN and prostate cancer is inactivation of the GSTP1 gene coding for the glutathione *S*-transferase P1 detoxification enzyme that catalyzes the conjugation of reactive oxygen species to glutathione within the prostate; elevated reactive oxygen activity results.[193] Evidence from two human studies suggests that oxidative changes in prostate tissue DNA (mutagenic lesions of adenine and guanine residues typical of those induced by hydroxyl radicals) are significantly increased in cancerous prostate tissue.[195,196] In addition, the extent of carcinogenic change was significantly correlated with the extent of hydroxyl radical-induced DNA damage.[195]

The insulin-like growth factors (IGF-I and IGF-II) are circulating mitogens that interact with target cells via the cell membrane-bound IGF-receptor to influence the regulation of

cell proliferation, differentiation, apoptosis and neoplastic transformation.[197,198] In particular, IGF-I is a potent mitogen that stimulates DNA synthesis and the progression of the cell cycle from the G_1 phase to the S phase while also stimulating the expression of proapoptotic Bcl proteins and suppressing the expression of antiapoptotic Bax proteins.[199] Epithelial cells harvested from noncancerous human prostate glands have demonstrated an abundance of IGF-I receptors[200] and the *in vivo* proliferation of normal murine prostate epithelial cells appears to be IGF-I-dependent.[201]

There is evidence that the risk of neoplastic transformation within a cell population increases as the proliferation rate of cells within the population increases,[202,203] suggesting that IGF-I availability to IGF-I-dependent tissues (such as the prostatic epithelium) contributes to risk of developing tissue-specific cancer.[201] Furthermore, increased IGF-I availability may accelerate the proliferation and clonal expansion of epithelial undergoing the process of neoplastic transformation.[201] The dependence of human prostate cancer on IGF-I is suggested by the results of transplantation studies in which the proliferation of human androgen-independent PC-3 prostate cancer cells was curtailed following transplantation into IGF-I deficient mice but not after transplantation into normal mice.[201] Human prostate epithelial cells in primary culture proliferate in response to the addition of IGF-I to the culture medium; maximal response was observed with medium IGF-I concentration of 10 ng/ml and half-maximal response was observed at 1 ng/ml.[200] There is evidence that prostate-specific antigen acts to increase circulating and perhaps local concentrations of free IGF-I by cleaving IGF-binding protein-3 (IGF-BP-3) and thereby reducing its affinity for IGF-I; the addition of prostate-specific antigen to culture medium containing both IGF-I and IGF-BP-3 restored the rate of proliferation of human prostate epithelial cells to that of cells in medium containing only IGF-I.[198]

The findings of three retrospective case-control epidemiologic human studies support the hypothesis that increased systemic circulating concentrations of IGF-I increase the risk of developing prostate cancer.[204-206] In an examination of 152 men with prostate cancer and 152 randomly-selected cancer-free men nested within the prospective Physicians' Health Study, men with plasma IGF-I concentrations greater than 293 ng/ml were at significantly greater risk of developing prostate cancer than were men with plasma IGF-I concentrations less than 185 ng/ml (multivariate-adjusted Relative Risk Ratio (RR): 4.32; 95% confidence interval (CI): 1.76, 10.6; adjusted for height, weight, body mass index, the presence or absence of androgen receptor CAG polymorphisms, and plasma concentrations of IGF-I, IGF-binding protein-3 and prostate-specific antigen).[204] Other investigators found that when 52 men with prostate cancer were age-matched to 52 cancer-free men, the risk of developing prostate cancer was significantly correlated with serum IGF-I concentration; every increase in serum IGF-I concentration of 60 ng/ml was accompanied by a doubling of the multivariate-adjusted odds ratio (OR) for the development of prostate cancer (adjusted for age, height, body mass index, years of schooling and serum concentrations of testosterone, estradiol, dihydrotestosterone, dehydroepiandrosterone sulfate and sex hormone-binding protein).[205] In another case-control study of 224 men with prostate cancer and 224 age-matched men without cancer,

the mean serum IGF-I concentration of men with prostate cancer was significantly greater than that of men without prostate cancer.[206] Among the 90 men younger than 70 years of age with prostate cancer and the 84 men younger than 70 years of age without prostate cancer, the risk of developing prostate cancer was significantly correlated with serum IGF-I concentration; every increase in serum IGF-I concentration of 100 ng/ml was accompanied by a tripling of the multivariate-adjusted odds ratio (OR) for the development of prostate cancer (adjusted for age, height and body mass index). This relationship was not statistically significant among the men 70 years of age or older.

B. Cell Culture Studies Provide Scientific Support for the Conclusion that Risk of Developing Prostate Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods Containing Lycopene

Lycopene in physiological concentrations has been found to inhibit significantly the rates of proliferation of various human prostate carcinoma cell lines in culture. In concentrations as low as 10^{-8} *M*, lycopene has been observed to inhibit significantly the proliferation of human LNCaP prostate carcinoma cells in culture.[207] In concentrations as low as 10^{-6} *M*, lycopene has been observed to reduce significantly the viability of cultures of PC-3, DU-145 and LNCaP human prostate carcinoma cells.[208] In the presence of 50 x 10^{-6} *M* alpha-tocopherol, 10^{-6} *M* lycopene significantly inhibited (by 50% to 90%) the proliferation of PC-3 and DU-145 human prostate carcinoma cells in culture.[209]

C. Human Clinical Trials Provide Scientific Support for the Conclusion that Risk of Developing Prostate Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods Containing Lycopene

The hypothesis that the risk for developing prostate cancer is reduced by consumption of either supplemental lycopene or of tomatoes and tomato-based foods containing lycopene is supported by the results of a randomized placebo-controlled clinical trial[62,210] and an uncontrolled clinical trial,[44,115,211] the findings of five prospective observational studies[212-216] and ten retrospective case-control studies,[64,67,90,107,114,215-211] a case series[222] and a case report.[223]

In a randomized placebo-controlled clinical trial, men with newly diagnosed localized prostate cancer received daily dietary supplementation (one capsule twice daily) with a commercially available tomato oleoresin extract (Lyc-O-Mato® capsules, LycoRed Natural Products Industries, Beer-Sheva, Israel) containing, per capsule, 14.5 to 15.5 mg of lycopene, 1.45 to 1.55 mg of phytoene, 1.25 to 1.5 mg of phytofluene, 0.25 to 0.5 mg of β–carotene, 17.25 to 19.25 mg of total mixed carotenoids, 3.75 to 6.25 mg of total tocopherols, 35 to 40 mg of total phospholipids, 1.25 to 1.75 mg of total phytosterols and 182.5 to 190 mg of tomato oil (average total daily supplemental lycopene intake: 30 mg).[62,210] Daily supplementation was begun 3 weeks before the study subjects underwent radical prostatectomy with removal of the entire prostate gland, the seminal vesicles and the surrounding soft tissues. Examination of tissue and blood samples

obtained during radical prostatectomy revealed that dietary supplementation with tomato oleoresin extract was associated with significantly less cancerous invasion of surgical margins and extra-prostatic tissues (cancer was confined to the prostate in 73% of the supplemented patients and in only 18% of the unsupplemented men) and significantly less diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia, the precursor of prostate cancer[188-194] (cancer was limited to focal involvement in 33% of the supplemented patients but was multifocal and diffuse in all of the unsupplemented men). However, average Gleason tumor score, tumor volume, plasma concentrations of prostate-specific antigen (PSA), IGF-1, IGFBP-3 and total lycopene, malignant prostate tissue content of connexin 43, bcl-2 and bax proteins and total lycopene, benign prostate tissue content of connexin 43, bcl-2 and bax proteins and total lycopene, and peripheral blood lymphocyte 5-OHmdU concentrations were not affected by 3 weeks of daily dietary supplementation with tomato oleoresin extract. The results of this small preliminary study suggest that even short-term dietary supplementation with an amount of tomato oleoresin extract providing the lycopene equivalent of only 4 to 6 fresh tomatoes or 200g of tomato sauce[5] may effectively interrupt the progression of the precursor lesion, HGPIN, to prostate cancer, even in the absence of statistically significant changes in putative biomarkers of risk for prostate cancer.

In an uncontrolled study, 32 patients (60 to 74 years old) with localized prostate adenocarcinoma (clinical stage T1 or T2) consumed tomato sauce-based pasta dishes containing 200 g of Hunt's Spaghetti Sauce (Hunt-Wesson, Inc., Irvine, CA) daily for 3 weeks prior to radical prostatectomy.[44,115,211] These foods added an additional 30 mg of lycopene daily to a prescribed diet providing 40% of energy as fat and 15% of energy as protein. Daily consumption of tomato-based foods averaged 81.6% of the intended amount. During the 3 weeks of dietary supplementation, these men experienced significant increases in mean serum total lycopene concentration (96% increase; 95% confidence interval (CI): 42%, 151%; $p = 0.0029$), mean serum all-*trans*-lycopene concentration (119% increase; 95% CI: 56%, 183%; $p = 0.0019$), mean prostate tissue total lycopene content (196% increase; 95% CI: 68%, 323%; $p = 0.0071$), mean prostate tissue all-*trans*-lycopene content (310% increase; 95% CI: 92%, 527%; $p = 0.0105$), mean ratio of all-*trans*-lycopene to total *cis*-isomers in prostate tissue (85% increase; 95% CI: 22%, 148%; $p = 0.0134$) and mean proportion of total lycopene as all-*trans*-lycopene in prostate tissue (69% increase; 95% CI: 17%, 121%; $p = 0.0154$). However, the mean ratio of all-*trans*-lycopene to total *cis*-isomers in serum and the mean proportion of total lycopene as all-*trans*-lycopene in serum were not affected by dietary supplementation with tomato sauce. Serum total lycopene concentration and prostate total lycopene content were significantly correlated ($r = -0.51$; $p = 0.005$). In contrast, dietary supplementation with tomato sauce significantly reduced mean serum PSA concentration by 17.5% ($p = 0.002$) and mean circulating leukocyte 8OHdG concentration by 21.3% ($p = 0.005$). Prostate tissues obtained at surgery exhibited significantly lower mean 8OHdG content than did an historical control group (28.3% decrease; $p = 0.03$). Similarly, mean cancer cell 8OHdG staining of Gleason Score-matched resected prostate sections was significantly reduced in mean nuclear density (by an average of 40.5%; $p = 0.005$) and in mean area (by an average of 36.4%; $p = 0.018$) compared to tissues obtained via biopsy prior to the study. In contrast, the apoptotic

indices of both hyperplastic and neoplastic prostate epithelial cells were significantly increased. These data indicate that the daily consumption of foods containing at least 30 mg of lycopene significantly increased the lycopene contents of blood and prostate tissue, which was accompanied by significant reductions in DNA damage in leukocytes and prostate tissue and significant increases in anticarcinogenic apoptosis among both hyperplastic and neoplastic prostate epithelial cells.[44,115,211]

The findings of five prospective observational studies[212-216] have confirmed the beneficial relationship between lycopene consumption (whether as a dietary supplement or consumed as tomatoes or tomato-based foods) and reduced risk for developing prostate cancer. In the 6-year Health Professionals Follow-Up Study, a prospective study of 47,894 men who initially were prostate cancer-free, the daily consumption of more than 6.5 mg of lycopene significantly reduced the risk for developing prostate cancer, compared to the risk among men who consumed less than 2.3 mg of lycopene daily (RR: 0.79; 95% CI: 0.64, 0.99; adjusted for age and daily dietary total energy intake).[212] Similarly, the consumption of tomatoes more than once a week significantly reduced the risk for developing prostate cancer, compared to the risk among men who consumed tomatoes an average of one or fewer times a week (RR: 0.74; 95% CI: 0.58, 0.93; adjusted for age and daily dietary total energy intake). The consumption of tomato sauce once weekly significantly reduced the risk for developing prostate cancer, compared to the risk among men who consumed tomato sauce an average of less than once weekly (RR: 0.77; 95% CI: 0.62, 0.95; adjusted for age and daily dietary total energy intake). In contrast, tomato juice consumption appeared in this study to have no effect on the risk for developing prostate cancer.

In a further 6-year extension of the Health Professionals Follow-Up Study, it was determined that the multivariate-adjusted risk for prostate cancer was significantly decreased in men with routine daily lycopene intakes greater than 18.8 mg at the end of the study compared to the risk in men with routine daily lycopene intakes less than 3.4 mg at the end of the study (RR: 0.84; 95% CI: 0.74, 0.96; adjusted for age, study time period, ancestry, body mass index at age 21 years and dietary daily intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat and α–linolenic acid).[213] Similarly, the multivariate-adjusted risk for prostate cancer was significantly decreased in men with average estimated cumulative 12-year daily lycopene intakes greater than 18.8 mg compared to the risk in men with average estimated cumulative daily 12-year lycopene intakes less than 3.4 mg (RR: 0.84; 95% CI: 0.73, 0.96; adjusted for age, study time period, ancestry, body mass index at age 21 years and dietary daily intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat and α–linolenic acid). However, estimated lycopene intake at the beginning of the study was not associated with risk for prostate cancer. Risk for prostate cancer also was significantly decreased in men consuming two or more servings of tomato sauce (a strong determinant of plasma lycopene concentration[68]) weekly compared to the risk in men consuming less than one serving of tomato sauce monthly, at the beginning of the study (RR: 0.75; 95% CI: 0.64, 0.88; adjusted for age, study time period, ancestry, body mass index at age 21 years and dietary daily intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat and α–linolenic acid), during the 12 years of the

study (RR: 0.77; 95% CI: 0.66, 0.90; adjusted for age, study time period, ancestry, body mass index at age 21 years and dietary daily intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat and α–linolenic acid) and at the end of the study (RR: 0.84; 95% CI: 0.72, 0.99; adjusted for age, study time period, ancestry, body mass index at age 21 years and dietary daily intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat and α–linolenic acid). The prostate cancer-preventing properties of two or more weekly servings of tomato sauce were evident in men of Southern European ancestry (RR: 0.66; 95% CI: 0.47, 0.93; adjusted for age, study time period, ancestry, body mass index at age 21 years and dietary daily intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat and α–linolenic acid) and men of other Caucasian ancestry (RR: 0.79; 95% CI: 0.65, 0.98; adjusted for age, study time period, ancestry, body mass index at age 21 years and dietary daily intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat and α–linolenic acid). The prostate cancer-preventing properties of two or more weekly servings of tomato sauce remained statistically significant when additionally adjusted for olive oil preference (RR: 0.77; 95% CI: 0.66, 0.91) or fruit and vegetable intake (RR: 0.78; 95% CI: 0.66, 0.91).

These investigators detected no evidence that "detection bias," changes in the relative frequency of diagnosis of prostate cancer during the study that might result from advances in diagnostic and screening practices and technologies that may have occurred during the 12 years of the study, influenced the evidence that the consumption of the highest quintile of lycopene intake, and in particular, of two or more servings of tomato sauce weekly, significantly reduced the risk of developing prostate cancer.

In another prospective study, dietary and lifestyle characteristics were evaluated in relation to subsequent prostatic cancer risk in approximately 14,000 Seventh-day Adventist men who were observed for 6 years (some 78,000 man-years of observation).[214] Among these men, the consumption of one or more tomatoes weekly significantly decreased their age-adjusted risk for prostate cancer, compared to the risk among men who consumed tomatoes less than once a week (RR: 0.62; 95% CI: 0.40, 0.96). This reduction in relative risk was not affected by age, education, or intakes during the sixth year of the study of meat, poultry, fish, beans, legumes, peas, citrus fruit, dry fruit or nuts.

In a 5- to 8-year prospective observational study of 1,575 cancer-free men aged 40 to 86 years at the beginning of the study, the risk for developing prostate cancer was significantly reduced among the men with the highest tertile of daily dietary lycopene intake, compared to the risk among men with the lowest tertile of daily dietary lycopene intake (RR: 0.5; 95% CI: 0.3, 0.9; adjusted for age and dietary daily total energy intake).[215] The reduction in risk for the development of advanced prostate cancer reportedly was even greater (data not given).

In an ecologic epidemiologic study of diet and prostate cancer worldwide it was found that, in 28 those countries where tomatoes were consumed regularly, mortality from prostate cancer was significantly inversely correlated with tomato intake.[216]

The findings of four retrospective case-control studies[217-220] also support the conclusion that the risk for developing prostate cancer is reduced by consumption of either supplemental lycopene or of tomatoes and tomato-based products containing lycopene. In a study of 223 men with prostate cancer and 446 matched cancer-free men, the consumption of tomatoes or tomato-based products 14 or more times a month significantly reduced the risk for developing prostate cancer, compared to the risk among men consuming tomatoes or tomato-based products less than 3 times monthly (odds ratio (OR): 0.71; significantly different from OR = 1.0, $p < 0.05$).[217] Similarly, in a study of 320 men with prostate cancer and 246 cancer-free men, the consumption of cooked tomatoes at least 4 times weekly significantly reduced the risk for the development of prostate cancer, compared to the risk among men who consumed cooked tomatoes twice weekly (OR: 0.85; 95% CI: 0.75, 0.97; adjusted for age, height, education and daily dietary total energy intake).[218]

In a study of 617 men with prostate cancer and 636 men without prostate cancer, daily consumption of more than 110 g of tomatoes significantly reduced the risk for developing prostate cancer, compared to the risk for men consuming less than 9 g of tomatoes daily (OR: 0.64; 95% CI: 0.45, 0.91; adjusted for vasectomy status, age, cigarette smoking status, marital status, study area, body mass index, education, current or recent use of multivitamin dietary supplements, and dietary intakes of total energy, grains, fruit, vegetables, all plants, all carotenoids, folate and folic acid, dietary fiber, conjugated linoleic acid, vitamin E, vitamin C, retinol, total fat and linoleic acid).[219] Among these men, lycopene intake was not associated with the multivariate –adjusted risk for developing prostate cancer, even though 25% of these men consumed over 12.7 mg of lycopene daily. However, in a study of 77 men with prostate cancer and 183 cancer-free men, the median daily lycopene intake of the men with prostate cancer (0.817 mg) was significantly less than the median daily lycopene intake of the men without prostate cancer (1.120 mg).[220]

The findings of six retrospective case-control studies[64,67,90,107,114,221] support the conclusion that the risk for developing prostate cancer is reduced among those men with the greatest serum or plasma total lycopene concentrations (reflecting the greatest routine lycopene intakes). This conclusion is consistent with and provides additional support for the conclusion that the risk for developing prostate cancer is reduced by consumption of either supplemental lycopene or of tomatoes and tomato-based products containing lycopene.

A prospective case-control study, nested within the randomized placebo-controlled Physicians' Health Study of aspirin and β-carotene, compared 578 men who developed prostate cancer during 13 years of the study to 1294 age- and smoking status-matched men who did not develop prostate cancer during 13 years of the study.[114] Pre-study median plasma total lycopene concentration was significantly lower in the men who later developed prostate cancer (0.69×10^{-6} *M*) than it was in the men who remained prostate cancer-free (0.72×10^{-6} *M*). Although the risk for developing any type of prostate cancer

was not affected by pre-study plasma total lycopene concentrations (OR: 0.75; 95% CI: 0.54, 1.06; adjusted for exercise frequency, body mass index, alcohol consumption, use of multivitamin dietary supplements and plasma total cholesterol concentration), the risk for developing aggressive prostate cancer was significantly decreased in men with pre-study plasma total lycopene concentrations greater than 1.1×10^{-6} *M*, compared to the risk for developing aggressive prostate cancer in men with pre-study plasma total lycopene concentrations less than 0.5×10^{-6} *M* (OR: 0.56; 95% CI: 0.34, 0.91; adjusted for exercise frequency, body mass index, alcohol consumption, use of multivitamin dietary supplements and plasma total cholesterol concentration). In the men whose diets were supplemented with placebo but not with aspirin or β-carotene, the risk for developing aggressive prostate cancer was significantly decreased in men with pre-study plasma total lycopene concentrations greater than 1.1×10^{-6} *M*, compared to the risk for developing aggressive prostate cancer in men with pre-study plasma total lycopene concentrations less than 0.5×10^{-6} *M* (OR: 0.40; 95% CI: 0.19, 0.84; adjusted for exercise frequency, body mass index, alcohol consumption, use of multivitamin dietary supplements and plasma total cholesterol concentration). Similarly, in the men whose diets were supplemented with β-carotene but not with aspirin or placebo, the risk for developing aggressive prostate cancer was significantly decreased in men with pre-study plasma total lycopene concentrations greater than 1.1×10^{-6} *M*, compared to the risk for developing aggressive prostate cancer in men with pre-study plasma total lycopene concentrations less than 0.5×10^{-6} *M* (OR: 0.48; 95% CI: 0.24, 0.94; adjusted for exercise frequency, body mass index, alcohol consumption, use of multivitamin dietary supplements and plasma total cholesterol concentration). These reductions in the risks for developing aggressive prostate cancer were not affected by age, smoking status, body mass index, exercise level, alcohol consumption, multivitamin dietary supplementation, or plasma total cholesterol concentration and suggest that lycopene may differentially impair the development of more aggressive, invasive and diffuse forms of prostate cancer.

In a case-control study of 65 men with prostate cancer and 132 matched cancer-free men, mean plasma total lycopene concentration was significantly lower among the men with prostate cancer (0.22×10^{-6} *M*) than among the men without cancer (0.31×10^{-6} *M*).[64] Among all 197 men, the risk for developing prostate cancer among those men with plasma total lycopene concentrations greater than 0.40×10^{-6} *M* was significantly lower than the risk among those men with plasma total lycopene concentrations lower than 0.18×10^{-6} *M* (OR: 0.17; 95% CI: 0.04, 0.78; adjusted for age, race, years of education, daily total caloric intake, number of pack-years of cigarette smoking, alcohol consumption and family history of prostate cancer). This significant risk reduction was readily apparent among men younger than 60 years (multivariate-adjusted OR: 0.05; 95% CI: 0.01, 0.51) but was not apparent among men 60 years of age or older (multivariate-adjusted OR: 0.10; 95% CI: 0.01, 3.31). However, estimated lycopene intake was not associated with multivariate-adjusted risk for developing prostate cancer in this study, with only 25% of these men consuming more than 3.5 mg of lycopene daily.

In a retrospective case-control study of 12 men with prostate cancer and 12 cancer-free men, mean serum total lycopene concentration was significantly lower among the men with prostate cancer (0.24×10^{-6} *M*) than among the cancer-free men (0.43×10^{-6} *M*).[90] .In addition, mean prostate tissue total lycopene content also was significantly lower among the men with prostate cancer. Similarly, in a study of 24 men with prostate cancer and 18 men without prostate cancer but undergoing surgical transurethral resection or radical cystoprostatectomy, mean serum total lycopene concentration was significantly lower among the men with prostate cancer than among cancer-free men (data not shown).[221] In addition, mean total lycopene contents of benign prostate tissue were significantly lower among the men with prostate cancer.

In a study of 209 men with prostate cancer and 228 cancer-free men, serum total lycopene concentrations greater than 0.46×10^{-6} *M* were associated with significantly reduced risk for the development of aggressive prostate cancer, compared to the risk of men with serum total lycopene concentrations less than 0.20×10^{-6} *M* (OR: 0.37; 95% CI: 0.15, 0.94; adjusted for age, race, study center and month of blood sampling).[107] In contrast, serum total lycopene concentration was not associated with multivariate-adjusted risk for developing nonaggressive prostate cancer and the median serum total lycopene concentrations were not different among the men with or without prostate cancer (African Americans without cancer: 0.29×10^{-6} *M*; African Americans with prostate cancer: 0.27×10^{-6} *M*; Caucasian Americans without cancer: 0.35×10^{-6} *M*; Caucasian Americans with prostate cancer: 0.31×10^{-6} *M*).

In another case-control study of 15 men with prostate cancer and 30 cancer-free men, the median plasma total lycopene concentration of men with prostate cancer (0.12×10^{-6} *M*) was significantly lower than that of men without cancer (0.34×10^{-6} *M*).[67]

The findings of an analysis of a series of 112 men without cancer suggest that daily consumption of one serving of cooked tomatoes significantly decreased serum IGF-I concentration by 31.5%.[222]

A case report supports the conclusion that the risk of developing prostate cancer is reduced by consumption of supplemental lycopene. In this case, a man with androgen-independent pharmacologically-refractive terminal prostate cancer experienced remission within one month of beginning daily dietary supplementation with a combination of 30 mg of lycopene and 900 mg of saw palmetto extract.[223] At the time of submission of this report, the individual had been in continuing remission (with continued daily dietary supplementation) for 18 months.

Several retrospective epidemiologic case-control observational studies have failed to observe the beneficial protective effect of the consumption of lycopene, tomatoes and tomato-based foods on the risk for developing prostate cancer.[224-232] In these studies, lycopene intake or the consumption of tomatoes or tomato-based foods was minimal or absent in a large percentage of the study subjects and failure to observe the beneficial

protective effect of the consumption of dietary ingredients that were not consumed on the risk for developing prostate cancer was predictable.

In one such study of 328 men diagnosed with prostate cancer before the age of 75 years and 328 age-matched cancer-free men, no statistically significant relationships were observed between the daily consumption of lycopene, raw tomatoes or cooked tomatoes and risks for developing prostate cancer (adjusted for social class).[224] However, fewer than 25% of these men consumed at least 0.7 mg of lycopene (amount of lycopene in one-half teaspoon of catsup[5]) daily, fewer than 20% consumed at least 1 serving of raw tomatoes daily and fewer than 20% consumed at least 2 servings of cooked tomato products weekly.

In a study of men 40 to 64 years of age, 628 newly diagnosed with aggressive prostate cancer and 602 who were free of cancer, no statistically significant relationships were observed between the daily consumption of lycopene, raw tomatoes or cooked tomatoes and risks for developing prostate cancer.[225] However, only half of these men routinely consumed over 2 mg of lycopene (less than the amount of lycopene in a level tablespoon of catsup[5]) daily, only 25% consumed at least 10 mg of lycopene daily and fewer than 30% consumed more than an average of one-half of a serving of cooked or raw tomato products daily.

In a retrospective case-control study of 449 African-American men and 483 Caucasian men with prostate cancer and 543 African-American men and 658 Caucasian cancer-free men, the rates of daily consumption of raw tomatoes, cooked tomatoes or tomato sauces, tomato juice, watermelon or these foods combined were not associated with the risks (adjusted for age, study site, daily caloric intake, and race) for developing either early or advanced prostate cancer among African-American men, Caucasian men or both groups of men combined.[226] However, only 25% of these men consumed at least one serving of any of these foods daily.

In a case-control study nested within a 6-year prospective observational study of 58,279 initially cancer-freemen aged 55 to 69 years at the beginning of the study, daily lycopene intake was not associated with the risk for developing any degree of prostate cancer (adjusted for age, family history of prostate cancer, socioeconomic status and alcohol consumption) among 642 men who developed prostate cancer and 1525 men who did not.[227] However, among both groups of men, mean daily lycopene intake was estimated to be 1 mg (less than the amount of lycopene in a level teaspoon of catsup[5]) and fewer than 3% of the men who developed prostate cancer consumed more than 3.4 mg of lycopene daily and fewer than 3% of the men who did not develop prostate cancer routinely consumed more than 2.6 mg of lycopene daily.

In a case-control study of 317 men with prostate cancer and 480 matched cancer-free men, daily lycopene intake, raw tomato consumption and consumption of cooked foods containing tomatoes were not associated with the risks for developing prostate cancer (adjusted for age, height, use of nonsteroidal anti-inflammatory medications and

socioeconomic status).[228] However, only 25% of these men consumed more than 35 g (equivalent to one-quarter serving[5]) of raw tomatoes daily, more than 64 g (including water) of cooked foods containing tomatoes or more than 2 mg of lycopene from all sources daily.

In a study of 610 men with prostate cancer and 456 cancer-free men, daily mean tomato and tomato juice intakes did not differ between those with prostate cancer and those without.[229] Tomato and tomato juice consumption were without effect on the risk for prostate cancer (adjusted for age, family history of prostate cancer, socioeconomic status, fruit consumption and vegetable consumption). Among these men, less than 3% consumed more than 60 g of tomatoes and tomato juice combined daily.

In a study of 1619 men with prostate cancer and 1618 cancer-free men, the daily intakes of either all tomato products or of cooked tomato products only were not associated with the risks for developing any prostate cancer or advanced prostate cancer (adjusted for age, education, ethnicity, geographic area of residence and daily total caloric intake).[230] However, only 20% of these men consumed over 108 g of total tomato products (equivalent to three-quarters of one serving[5]) daily. The results were similar when the men were subgrouped by ethnicity (African-Americans, Caucasian-Americans, Chinese-Americans, Japanese-Americans).

In a re-analysis of previously-published data from a retrospective case-control study of 452 prostate cancer cases and 899 cancer-free individuals that was conducted between 1970 and 1983 among the multiethnic population of Hawaii, investigators reported failure to discover a statistically significant relationship between the consumption of tomatoes and the risk for developing prostate cancer.[231] The percentage of these men who consumed at least 1 mg of lycopene or 1 tomato daily could not be determined from the data provided. In another case-control study in which daily lycopene intakes cannot be determined, daily lycopene intakes of 215 men with prostate cancer and 593 matched cancer-free men were not associated with risk for developing prostate cancer (adjusted for age, education, family history of prostate cancer and total daily energy intake).[232]

In four retrospective case-control studies, the risk for developing prostate cancer was not observed to be associated with serum or plasma total lycopene concentrations.[54,75,233,234] In one such study, nested within a 13-year prospective epidemiologic observational study, no statistically significant relationship was observed between serum total lycopene concentration and the risk for developing prostate cancer (OR comparing the highest quartile of serum total lycopene concentration with the lowest quartile of serum total lycopene concentration (0.50) was not different from 1.0; 95% CI: 0.20, 1.29).[233] However, the 75th percentile of serum total lycopene concentration was only 45 mcg/dL, a concentration only 65% of the mean serum total lycopene concentration achieved with daily dietary supplementation with 30 mg of lycopene in a prospective intervention study (and therefore only 65% of the serum total lycopene concentration achieved by about half of the men that received daily dietary supplementation with 30 mg of lycopene in a prospective intervention study).[211]

In a retrospective case-control study of 182 men with prostate cancer and 364 matched cancer-free men (the "CLUE I" study), median serum total lycopene concentrations were not different between men with (0.64×10^{-6} *M*) and without prostate cancer (0.66×10^{-6} *M*) and no statistically significant relationship was observed between serum total lycopene concentration and the risk for developing prostate cancer.[54] In a similar study of 142 men with prostate cancer and 284 matched cancer-free men (the "CLUE II" study), median serum total lycopene concentrations were not different between men with (0.72×10^{-6} *M*) and without prostate cancer (0.78×10^{-6} *M*) and no statistically significant relationship was observed between serum total lycopene concentration and the risk for developing prostate cancer.[54]

In a retrospective case-control study of 142 men with prostate cancer and 142 matched cancer-free men, median serum total lycopene concentrations were not different between men with and without prostate cancer (0.25×10^{-6} *M* in both groups) and no statistically significant relationship was observed between serum total lycopene concentration and the risk for developing prostate cancer.[75] In another retrospective case-control study of 103 men with prostate cancer and 103 cancer-free men, serum total lycopene concentration was not observed to be associated with the risk for developing prostate cancer.[234]

D. The Available Evidence Provides Significant Scientific Support for the Conclusion that Risk for Developing Prostate Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The results of the only relevant randomized placebo-controlled clinical trial,[210] the only relevant uncontrolled clinical trial[44,115,211] and all of the published prospective observational studies[212-216] consistently demonstrate a beneficial protective effect of the consumption of lycopene, tomatoes and tomato-based foods on the risk for developing prostate cancer. This compelling evidence of risk reduction is strengthened by the findings of ten retrospective case-control studies[64,67,90,107,114,217-221] and by a case series[222] and case report.[223] Other reviewers have concluded that "Several case-control and prospective cohort studies focusing on dietary assessment suggest that the consumption of tomato and tomato products may be associated with a lower risk of prostate cancer."[235] In addition, "Food processing or cooking of tomatoes does not seem to reduce the benefits and may in fact provide greater advantage by improving the bioavailability of beneficial components."[235]

Although there have been reports of retrospective case-control studies that have failed to observe this protective effect,[54,75,224-234] these reports likely reflect failure of study subjects to consume lycopene, tomatoes or tomato-based foods, as well as confounding by related factors and heterogeneity of effect (this can occur when a subpopulation of nonresponders dilutes the overall effect of a chemopreventive agent or food and obscures the association in responders), resulting in underestimation of the effects of the nutrient or food of interest on chemoprevention.[236] Furthermore, no report has claimed that an

increase in the risk for developing prostate cancer was associated with the consumption of lycopene, tomatoes or tomato-based foods.

The published scientific evidence strongly supports the conclusion that the risk of developing prostate cancer is reduced by dietary supplementation with lycopene and by the consumption of tomatoes and tomato-based products containing lycopene.

V. Lung Cancer

Lung cancer is the second leading cause of newly-diagnosed cancer in males and females in the US.[159] About 171,900 new cases of lung cancer were forecast for the US for the year 2003, while nearly 89,000 men and 69,000 women in the US were expected to die from this disease that year (accounting for about 28% of all cancer-related deaths).[159] The 1-year relative survival rate for individuals diagnosed with lung cancer is 42% and the 5-year relative survival rate for all lung cancers combined is 15%, although the 5-year relative survival rate is 49% when the disease is localized when detected.[159]

A. Pathogenesis of Lung Cancer

Carcinogenesis in the lung occurs in a multistage process involving a series of genetic alterations with progression through a variety of pathways from initial reversible lesions to the development of metastatic disease.[237] The initial triggers of carcinogenic change may be varied as may be the factors that provide the impetus for continued disease progression. For example, reactive oxygen species (such as the hydroxyl radical $OH^{\cdot}$) may be implicated in the pathogenesis of lung cancer.[237] Exposure of the lung to ozone produces oxidative damage similar to that of the lesions observed in precancerous change in the lungs.[237,238] Experimental ozone exposure of the human lung to ozone *in vivo* produces oxidative damage and an increase in the frequency of single-stand DNA damage in lung epithelial cells.[239,240]

The insulin-like growth factors (IGF-I and IGF-II) are circulating mitogens that interact with target cells via the cell membrane-bound IGF-receptor to influence the regulation of cell proliferation, differentiation, apoptosis and neoplastic transformation.[195,196] In particular, IGF-I is a potent mitogen that stimulates DNA synthesis and the progression of the cell cycle from the G_1 phase to the S phase while also stimulating the expression of proapoptotic Bcl proteins and suppressing the expression of antiapoptotic Bax proteins.[197] There is evidence that the risk of neoplastic transformation within a cell population increases as the proliferation rate of cells within the population increases,[200,201] suggesting that IGF-I availability to IGF-I-responsive tissues contributes to risk of developing tissue-specific cancer.[199] Furthermore, increased IGF-I availability may accelerate the proliferation and clonal expansion of epithelial undergoing the process of neoplastic transformation.[199] The results of a retrospective case-control study support the hypothesis that IGF-I is associated with lung cancer.[241] In that study, individuals

with the highest quartile of plasma IGF-I concentrations were at significantly increased risk of developing lung cancer, compared to the risk among subjects with the lowest quartile of plasma IGF-I concentrations (OR: 2.75; 95% CI: 1.37, 5.53; adjusted for plasma IGF-BP-3 concentration).

B. Cell Culture Studies Provide Scientific Support for the Conclusion that Risk of Developing Lung Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The addition of physiological concentrations of lycopene (1 to 2 x 10^{-6} *M*) to cultures of NCI-H226 human lung cancer cells significantly inhibited both basal and IGF-I-stimulated rates of DNA synthesis and cell proliferation.[242]

C. Animal Studies Provide Scientific Support for the Conclusion that Risk of Developing Lung Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The hypothesis that the risk for developing lung cancer is reduced by consumption of supplemental lycopene or of tomatoes and tomato-based foods containing lycopene is supported by the results of studies in experimental animals. Ferrets exposed to cigarette smoke for 9 weeks developed accelerated epithelial cell proliferation and squamous metaplasia of the lungs which were significantly inhibited by concurrent dietary supplementation with lycopene in amounts equivalent to human intakes of 15mg or 60 mg daily.[243] In addition, both levels of dietary supplementation with lycopene prevented cigarette smoke-induced deactivation of the apoptosis-promoting Bcl-2 proteins. In mice, dietary supplementation with lycopene during the postinitiation stage of lung carcinogenesis significantly reduced the extent of lung neoplasia induced by combined pretreatment with diethylnitrosamine plus *N*-methyl-*N*-nitrosourea plus 1,2-dimethyl hydrazine HCl.[244]

D. Human Clinical Trials Provide Scientific Support for the Conclusion that Risk of Developing Lung Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The hypothesis that the risk for developing lung cancer is reduced by consumption of supplemental lycopene or of tomatoes and tomato-based foods containing lycopene is supported by the results of the findings of two prospective observational studies,[68,245,246] a retrospective cohort study[247] and five retrospective case-control studies.[248-252]

The findings of two prospective observational studies[245,246] have confirmed the beneficial relationship between lycopene consumption (whether as a dietary supplement or consumed as tomatoes or tomato-based foods) and reduced risk for developing lung cancer. When data from the 10-year prospective Health Professionals Follow-Up Study of 46,924 men and the 12-year prospective Nurses' Health Study of 77,283 women were combined, the men and women with a median daily lycopene intake of 14.7 mg experienced a significantly reduced risk for the development of lung cancer, compared to the risk experienced by men and women with a median daily lycopene intake of 4.4 mg

(RR: 0.80; 95% CI: 0.64, 0.99; adjusted for age, smoking status, age when cigarette smoking began, daily dietary total caloric intake and whether the subject joined a study during years 1-4, 5-8 or 9-12).[68,246] Interestingly, the chemopreventive effect of lycopene was not evident among the men and women who either never smoked cigarettes or who had quit smoking prior to or during the study, while men and women who were continuing to smoke at the end of the study with a median daily lycopene intake of 14.7 mg experienced a significantly reduced risk for the development of lung cancer, compared to the risk experienced by men and women who were continuing to smoke at the end of the study with a median daily lycopene intake of 4.4 mg (RR: 0.63; 95% CI: 0.45, 0.88; adjusted for age, age when cigarette smoking began, severity of cigarette smoking at the end of the study, daily dietary total caloric intake and whether the subject joined a study during years 1-4, 5-8 or 9-12).

In a re-analysis of the data obtained during the prospective Alpha-Tocopherol, Beta-Carotene Cohort Study of 27,084 male smokers who completed a 276-food item dietary questionnaire when they each joined the cohort, it was reported that daily intake of lycopene in excess of 1.17 mg significantly reduced the risk for the development of lung cancer, compared to the risk among men who consumed less than 0.23 mg of lycopene daily (RR: 0.72; 95% CI: 0.61, 0.84; adjusted for age, years of cigarette smoking, number of cigarettes smoked daily, whether supplemented with alpha-tocopherol or β-carotene, whether dietary supplements containing β-carotene or vitamin A were consumed, and dietary daily intakes of total energy, total fat and cholesterol).[245]

On the island of Oahu, Hawai'i, among a cohort of 463 men and 212 women with lung cancer, the daily consumption of more than 50 g of tomatoes or tomato-based foods by men with lung cancer significantly reduced the risk of death from lung cancer, compared to the risk among men with lung cancer who consumed less than 6.5 g of tomatoes or tomato-based foods daily (RR: 0.77; significantly different from RR = 1.0, $p < 0.05$; adjusted for age at diagnosis, stage of lung cancer, histologic appearance of lung cancer and body mass index).[247] Among the cohort of women with lung cancer, the daily consumption of more than 42 g of tomatoes or tomato-based foods significantly reduced the risk of death from lung cancer, compared to the risk among women with lung cancer who consumed less than 6.5 g of tomatoes or tomato-based foods daily (RR: 0.50; significantly different from RR = 1.0, $p < 0.05$; adjusted for age at diagnosis, stage of lung cancer, histologic appearance of lung cancer and body mass index). However, attempts to determine whether this beneficial effect of tomato consumption was specific to specific types of lung cancer (i.e., adenocarcinoma, small cell cancer or squamous cell cancer) were unsuccessful.

The findings of five retrospective case-control studies[248-252] also support the conclusion that the risk for developing lung cancer is reduced by consumption of tomatoes and tomato-based foods and of lycopene. In a study of 230 men and 102 women with lung cancer and 597 men and 268 women who were cancer-free, those subjects with the highest quartile of consumption of tomatoes or tomato-based foods experienced significantly lower risk for developing lung cancer than did those subjects with the lowest quartile of consumption of tomatoes or tomato-based foods (men: OR: 0.43;

significantly different from RR = 1.0, $p < 0.05$; women: OR: 0.27; significantly different from RR = 1.0, $p < 0.05$; adjusted for age, ethnicity, smoking status, number of pack-years of cigarette smoking and dietary daily cholesterol intake).[248] However, among this subject population, despite the chemopreventive effect of tomato consumption, estimated lycopene intake was not associated with reduced risk for developing lung cancer.[253]

In another retrospective case-control study of 402 men and 104 women with lung cancer and 741 men and 304 women who were cancer-free, tomato consumption again was protective against the development of lung cancer.[249] Men and women who consumed one or more servings of tomatoes daily experienced significantly lower risk for developing adenocarcinoma of the lung than did men and women who consumed only one serving per week (OR: 0.5; 95% CI: 0.4, 0.6; adjusted for age, sex and study center). However, tomato consumption did not appear to affect the risk for developing either small cell carcinoma or squamous cell carcinoma of the lung.

Among another sample of women, 103 with lung cancer and 206 without, although mean tomato intake was not different between those with and those without cancer, the risk of developing lung cancer was significantly altered by tomato intake.[250] Women with the highest tertile of daily tomato intake experienced a significantly lower risk of developing any lung cancer than did women with the lowest tertile of daily tomato intake (OR: 0.45; 95% CI: 0.22, 0.91; adjusted for smoking status of number of pack-years of cigarette smoking). Although the risk for adenocarcinoma of the lung among all 306 women was not affected by tomato intake, among the 230 women who had never smoked cigarettes, those with the highest tertile of daily tomato intake experienced a significantly lower risk of developing any lung cancer than did women with the lowest tertile of daily tomato intake (unadjusted OR: 0.38; 95% CI: 0.17, 0.83).

Similarly, among 183 men with lung cancer and 183 cancer-free men, men with the highest quartile of daily tomato intake experienced a significantly lower risk of developing any lung cancer than did men with the lowest quartile of daily tomato intake (OR: 0.42; 95% CI: 0.25, 0.99; adjusted for lifetime exposure to tobacco, age at time of diagnosis of lung cancer, height, number of meals usually eaten at home daily, income, education and occupation).[251] In addition, the mean daily tomato intake of the men without lung cancer was significantly greater than that of the men with lung cancer.

The influence of plasma lycopene concentration on the risk of developing lung cancer was examined in 93 subjects with non-small cell lung cancer and 102 cancer-free men and women.[252] Among these individuals, mean plasma total lycopene concentration was significantly greater among the men and women without lung cancer. In addition, subjects with the highest tertile of plasma total lycopene concentrations had significantly reduced risk for developing any non-small cell form of lung cancer than had subjects with the lowest tertile of plasma total lycopene concentrations (OR: 0.37; significantly different from OR = 1.0, $p < 0.05$; adjusted for age, sex and race). Among African-Americans with the highest tertile of plasma total lycopene concentrations, the risk for developing any non-small cell form of lung cancer was even lower (OR: 0.12;

significantly different from OR = 1.0, $p < 0.05$; adjusted for age and sex). In addition, among all subjects, those with the highest tertile of plasma total lycopene concentrations had significantly reduced risk for developing squamous cell lung cancer, compared to the risk of subjects with the lowest tertile of plasma total lycopene concentrations (OR: 0.25; significantly different from OR = 1.0, $p < 0.05$; adjusted for age, sex and race).

The results of several prospective observational studies have failed to demonstrate the beneficial protective effect of the consumption of lycopene, tomatoes and tomato-based foods on the risk of developing lung cancer.[254-258] In most of these studies, lycopene intake or the consumption of tomatoes or tomato-based foods was minimal or absent in a large percentage of the study subjects and failure to observe the beneficial protective effect of the consumption of dietary ingredients that were not consumed on the risk for developing lung cancer was predictable.[254-257]

For example, in the 6-year prospective Netherlands Cohort Study on Diet and Cancer, daily lycopene intake appeared to have no effect on the multivariate-risk of developing any lung cancer, small cell carcinoma of the lung, squamous cell carcinoma of the lung or adenocarcinoma of the lung in 58,279 men.[254] However, fewer than 5% of these men consumed more than 4 mg of lycopene (equivalent to 1.5 level tablespoons of catsup[5]) daily. Similarly, in a prospective observational study of 4,545 men, daily lycopene intake appeared to have no effect on the age- and smoking status-adjusted risk of developing any lung cancer; less than 30% of these men consumed more than 1 mg of lycopene daily.[255] In another, 11.5-year prospective study of 13,785 men and 2,928 women, of whom only 5% consumed at one-half of a serving of tomatoes daily, tomato consumption was not related to risk for developing lung cancer.[256] In a much larger prospective 16-year study of 121,700 women in the U.S. (the Nurses' Health Study), neither tomato consumption nor lycopene intake were significantly related to the incidence of lung cancer; however, the lycopene consumption by these subjects cannot be determined.[257] However, the results of a large 6-year prospective study of 34,198 California Seventh-Day Adventists, one-third of whom consumed at least one serving of tomatoes daily, failed to demonstrate a significantly protective effect of tomato consumption on risk of developing lung cancer.[258]

The investigators of a number of retrospective case-control studies have failed to observe significant risk-reducing relationships between tomato consumption and lung cancer or between lycopene intake and lung cancer.[45,59,253,259-271] However, in most of these studies, the consumption of tomatoes or lycopene was minimal or absent in a large percentage of the study subjects and failure to observe the beneficial protective effect of the consumption of dietary ingredients that were not consumed on the risk for developing lung cancer was predictable.[45,59,253,259-268]

In one retrospective case-control study of 230 men and 102 women with lung cancer and 597 men and 268 women who were cancer-free, lycopene intake did not affect the multivariate-risk of developing lung cancer by either the men or the women.[253] However, 75% of the men consumed less than 4.2 mg of lycopene daily and 75% of the

women consumed less than 3.6 mg of lycopene (equivalent to 1.5 level tablespoons of catsup[5]) daily. Similarly, although lycopene intake did not affect the risk of developing lung cancer among 103 women with lung cancer and 206 women without lung cancer, fewer than 25% of these women consumed more than 2 mg of lycopene daily.[259] In another sample of 541 men with lung cancer and 540 matched cancer-free men, although lycopene intake did not affect the risk of developing lung cancer, fewer than 25% of these men consumed more than 2 mg of lycopene daily.[260] In another retrospective case-control study (nested within a much larger prospective study) in which the mean lycopene intake of men with lung cancer was no different from the mean intake of men without lung cancer, less than 3% of the 4,538 subjects consumed more than 2.5 mg of lycopene (the amount of lycopene in one level tablespoon of catsup[5]) daily.[261]

In a retrospective case-control study of 75 men with lung cancer and 97 cancer-free men, tomato consumption did not affect the multivariate-risk of developing lung cancer; 67% of these men consumed less than 29 g (one-quarter serving) of tomatoes daily.[262] In another study of 425 men with lung cancer and 1007 cancer-free men, tomato consumption did not affect the multivariate-risk of developing lung cancer; 75% of these men consumed tomatoes less than 0.8 times per month.[263] Among 541 men with lung cancer and 540 matched men without lung cancer, only one-third of whom consumed more than 1.5 servings of tomatoes weekly, such meager tomato consumption had no apparent effect on the prevalence of lung cancer.[260] In a case-control study nested within a larger prospective observational study, although the tomato consumption of 138 women with lung cancer and 2,814 randomly selected women without lung cancer had no apparent effect on the prevalence of lung cancer, only one-third of these women consumed at least three servings of tomatoes per week.[264] In four additional retrospective case-control studies that failed to observe a protective effect of tomato or lycopene intake on risk of developing lung cancer, the percentages of study subjects with minimal tomato consumption or lycopene intake could not be determined.[265-268]

In contrast, tomato consumption or lycopene intake has been substantial in three retrospective case-control studies that have failed to observe a protective effect of tomato or lycopene intake on risk of developing lung cancer.[269-271] For example, in a randomly selected subcohort of a much larger study, the daily lycopene intake of 155 women with lung cancer and 5,361 women without lung cancer had no effect on the risk of developing lung cancer, even though more than 25% of these women had daily intakes of lycopene greater than 14 mg.[268] Similarly, the daily lycopene intake of 763 men with lung cancer and 564 men without lung cancer had no effect on the risk of developing lung cancer, even though more than 25% of these men had daily intakes of lycopene greater than 9 mg.[270] In another study limited to men, the daily tomato consumption of 281 men with lung cancer and 1,207 men without lung cancer had no effect on the risk of developing lung cancer, even though 39% of these men consumed at least 0.5 servings of tomatoes daily.[271]

In two retrospective case-control studies, the mean serum total lycopene concentration was not different between subjects with lung cancer and those without lung cancer[59] and serum total lycopene concentration had no effect on the risk of developing lung cancer[45] or on the risk of dying from lung cancer.[59]

E. The Available Evidence Provides Significant Scientific Support for the Conclusion that Risk for Developing Lung Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The results of two prospective observational studies[245,246] and of a retrospective cohort study[247] demonstrate a beneficial protective effect of the consumption of lycopene and tomatoes and tomato-based foods on the risk for developing lung cancer. This evidence of risk reduction is strengthened by the findings of five retrospective case-control studies[248-252] and by a case report.[233]

Although there have been reports of retrospective case-control studies that have failed to observe this protective effect,[45,59,253,258-271] most of those studies[45,59,253,258-268] have examined subjects with very little routine consumption of tomatoes or lycopene; their failure to observe the beneficial protective effect of the consumption of dietary ingredients that were not consumed on the risk for developing lung cancer was predictable and not relevant to the evaluation of the scientific evidence supporting the conclusion that the consumption of lycopene and tomatoes and tomato-based foods confers a beneficial protective effect on the risk for developing lung cancer. Furthermore, no report has claimed that an increase in the risk for developing lung cancer was associated with the consumption of lycopene, tomatoes or tomato-based foods.

The published scientific evidence strongly supports the conclusion that the risk of developing lung cancer is reduced by dietary supplementation with lycopene and by the consumption of tomatoes and tomato-based products containing lycopene.

VI. 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.[159] 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 forecast for the US in 2003.[159] Colorectal cancer occurs with nearly equal frequency in men and women.[159] Five-year survival following diagnosis is between 10% and 90%, depending on the stage of disease at first diagnosis.[159]

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.[272-274] Colonocytes turnover

rapidly, with an average lifespan of only 2 to 3 days.[275,276] 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.[273,274] During migration along the crypt axis toward the luminal surface the 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.[277] Following 36 to 48 hours of mature differentiated function, senescent absorptive cells extrude into the lumen and die in a regulated manner by apoptosis.[272]

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.[278] 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.[279,280] The most important characteristic of this self-destruction is that apoptotic cells themselves actively provide the molecules necessary for the apoptotic mechanism to proceed.[281]

The first step in apoptotic change is the opening of the permeability transition pores in the inner mitochondrial membrane.[282] The onset of the mitochondrial permeability transition (MPT; depolarization of the mitochondrial membrane) is the key event in apoptotic cell death.[283,284] 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.[283,285] 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.[52,54] 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.[283,285]

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).[286,287] 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.[172,288]

Mutations in the adenomatous polyposis coli (APC) gene (such as occur in individuals with familial adenomatous polyposis) increase the risk for colon cancer.[289-293] Mutations in this gene may be the initiating events in the development of most or all colorectal neoplasia.[294-296] 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.[295,296] 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.[297-302] 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).[303] Aberrant crypt foci (ACF) are preneoplastic lesions predictive of increased risk for colon cancer.[304-316]

The normal reparative hyperproliferative response increases colorectal tissue sensitivity to chemically-induced carcinogenesis. For example, injecting 1,2-dimethylhydrazine dihydrochloride (DMH) into rats and mice produces (compared to vehicle) significant increases in the rate of colorectal crypt cell proliferation,[317-323] colonocyte content of damaged DNA,[320] the formation of aberrant crypt foci,[317,320,321,323] the formation of adenomatous polyps,[317,322,324,325] the growth of adenomatous polyps[326] and the progression of adenomas to carcinomas.[317,324] DMH-induced rat colon carcinogenesis closely resembles human colon neoplasia in all of these characteristics.[327,328]

In rats, hepatic conversion of ingested azoxymethane (AOM) to activated methyl-azoxymethane also produces significant increases in the rate of colorectal crypt cell proliferation,[329-331] the formation of aberrant crypt foci,[330-334] the formation of adenomatous polyps,[336-339] the growth of adenomatous polyps,[339] and the progression of adenomas to carcinomas.[339]

The ingestion of *N*-methyl-*N*-nitrosourea (MNU) results in the induction of invasive carcinomas of the colon and rectum in laboratory rodents.[340-342]

Although the adenoma-to-carcinoma sequence results primarily from a series of mutations affecting cell growth, differentiation and programmed cell death,[343-347] 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[348,349] and produces predisposition to colorectal adenoma and carcinoma.[350,351] For example, hereditary nonpolyposis colorectal cancer is characterized by defective DNA mismatch repair enzymes.[349,350,352-356]

C. 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 injection with 1,2-dimethylhydrazine dihydrochloride (DMH),[317-323] and ingestion of *N*-methyl-*N*-nitrosourea (MNU),[340,341] *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine[357] or azoxymethane (AOM).[329-331] In such animals, increased cellular proliferation in the colonic crypts is associated with colonic hyperplasia and a statistically significantly increased incidence of tumorigenesis along the length of the large intestine.[317-323,340,341] 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.[317-321,323]

D. 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[358,359] and is procarcinogenic.[358-361] On the other hand, a decrease in the rate of colorectal epithelial cell proliferation significantly decreases the risk for colorectal cancer in humans.[362] Compared with cancer-free individuals and those at low risk for colon cancer, patients with current or previous colon cancer[358-360,363-368] and patients at high risk for colon cancer (patients with sporadic adenoma,[361,366-377] familial adenomatous polyposis,[359,378,379] ulcerative colitis,[366,379-382] or a family history of colon cancer[358,367,373,384] or following intestinal bypass surgery[385] and most elderly individuals[386,387]), 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.[388,373,376,381,388,389] 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.[304,307-313,368,387-394] In patients with previous colon cancer or sporadic adenomas, these changes also predict adenoma recurrence.[365,371] 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.[395-399]

E. Cell Culture Studies Provide Scientific Support for the Conclusion that Risk of Developing Colorectal Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

Two lines of human colon carcinoma cells have been developed that either spontaneously lack DNA mismatch repair enzymes (HCT116 cells) or have received the addition of normal human chromosome 3, restoring mismatch repair capability (HCT116/ch3

cells).[400] In the absence of lycopene, the rate of spontaneous mutagenesis in HCT116 cells is more than 20-fold greater than the rate in HCT116/ch3 cells. In the presence of a physiologically-relevant concentration of lycopene (5×10^{-6} *M*), the rate of spontaneous mutation was significantly reduced in HCT116 cells and was no longer greater than the rate in HCT116/ch3 cells. These results indicate that in human colon carcinoma cells unable to repair DNA mismatch mutations, lycopene prevented the initiation of such defects.

F. Animal Studies Provide Scientific Support for the Conclusion that Risk of Developing Colorectal Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The colonic mucosal epithelium responds to subcutaneous injections of DMH with a hyperproliferative response reflected in the rate of incorporation of 5-bromo-2'-deoxyuridine (BrdU) into newly synthesized DNA.[401] Supplementation of the diets of DMH-injected mice with lycopene significantly reduced the rate of DMH-stimulated synthesis of new DNA.

Similarly, dietary supplementation with lycopene significantly inhibited AOM-induced aberrant crypt foci formation in the colons of rats.[139] Interestingly, the oral consumption of tomato paste also significantly inhibited AOM-induced hyperproliferation and suppression of apoptosis, resulting in significantly decreased development of aberrant crypt foci, in the colons of rats.[402]

Intrarectal administration of MNU results in the induction of precarcinogenic colonic aberrant crypt foci and invasive carcinomas of the colon and rectum in laboratory rodents.[340-342,403,404] Dietary supplementation with lycopene, tomato juice or lycopene-enriched tomato juice following MNU administration all significantly inhibited subsequent development of MNU-induced precarcinogenic colonic aberrant crypt foci and invasive carcinomas of the colon.[403,404]

G. Human Clinical Trials Provide Scientific Support for the Conclusion that Risk of Developing Colorectal Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The hypothesis that the risk for developing colorectal cancer is reduced by consumption of either supplemental lycopene or of tomatoes and tomato-based foods containing lycopene is supported by the results of the findings of seven retrospective case-control studies.[67,73,82,405-409] In a study that compared 56 men and 55 women with colon cancer to 56 matched men and 55 matched women without colon cancer, the consumption of more than 15 kg of tomatoes annually (about 40 g daily) significantly reduced the risk of developing colon cancer, compared to the risk associated with the consumption of less than 15 kg annually (OR calculated using estimates of tomato consumption in 1966: 0.26; 95% CI: 0.12, 0.56; OR calculated using estimates of tomato consumption in 1985: 0.40; 95% CI: 0.17, 0.94).[405] Similarly, although tomato consumption had no apparent effect on the risk for developing rectal cancer by 109 women with rectal cancer and 109

matched cancer-free women, the consumption of more than 20 kg of tomatoes annually (about 55 g daily) by 116 men with rectal cancer and 116 matched men without rectal cancer significantly reduced their risk of developing rectal cancer, compared to the risk associated with the consumption of less than 20 kg annually (OR calculated using estimates of tomato consumption in 1985: 0.40; 95% CI: 0.17, 0.94).[405]

In a retrospective case-control study, 955 men and women with colon cancer and 620 men and women with rectal cancer were compared to 2,879 cancer-free men and women.[406] Tomato consumption reduced the risk of developing cancer at both sites. The consumption of tomatoes at least once daily reduced the risk of developing colon cancer by 61%, compared to the risk associated with consuming tomatoes less than three times per week (OR: 0.39; 95% CI: 0.31, 0.49; adjusted for age, sex, education, dietary daily total caloric intake, alcohol consumption, smoking status and study center). Similarly, the consumption of tomatoes at least once daily reduced the risk of developing rectal cancer by 58%, compared to the risk associated with consuming tomatoes less than three times per week (OR: 0.42; 95% CI: 0.32, 0.55; adjusted for age, sex, education, dietary daily total caloric intake, alcohol consumption, smoking status and study center).

In a retrospective case-control study, 1225 men and women with colon cancer and 728 men and women with rectal cancer were compared to 4,154 cancer-free men and women.[407] Tomato consumption reduced the risk of developing cancer at both sites. The consumption of at least 3.5 servings of tomatoes per week reduced the risk of developing any colorectal cancer by 24%, compared to the risk associated with consuming less than 3.5 servings of tomatoes per week (OR: 0.76; 95% CI: 0.6, 0.9; adjusted for age, sex, body mass index, dietary daily total caloric intake and physical exercise). The consumption of at least 3.5 servings of tomatoes per week reduced the risk of developing colon cancer by 21%, compared to the risk associated with consuming less than 3.5 servings of tomatoes per week (OR: 0.79; 95% CI: 0.6, 0.9; adjusted for age, sex, body mass index, dietary daily total caloric intake and physical exercise). Similarly, the consumption of at least 3.5 servings of tomatoes per week reduced the risk of developing rectal cancer by 29%, compared to the risk associated with consuming less than 3.5 servings of tomatoes per week (OR: 0.71; 95% CI: 0.5, 0.9; adjusted for age, sex, body mass index, dietary daily total caloric intake and physical exercise).

In a retrospective case-control study of 154 subjects with gastric cancer, 252 subjects with colorectal cancer and 812 subjects without any cancer, compared to the risk of developing gastrointestinal cancer among those subjects who never consumed tomatoes or tomato-based foods, the daily consumption of tomatoes or tomato-based foods significantly reduced the risk of developing gastrointestinal cancer anywhere along the gastrointestinal tract (OR: 0.82; significantly different from OR = 1.0; $p < 0.05$).[408]

In a small retrospective case-control study of 11 subjects with colorectal cancer and 30 cancer-free individuals, mean plasma total lycopene concentration was significantly lower in the subjects with colorectal cancer (0.02×10^{-6} *M*) than in the subjects who were without cancer (0.34×10^{-6} *M*).[67]

In a small study, the lycopene content of mucosal tissues harvested from 10 patients with adenomatous polyps was significantly lower (by about 90%) than that of colonic mucosal tissue donated by patients without adenomatous polyps.[73] Nonadematous human colonic epithelium receives lycopene from the systemic circulation.[409] If present in sufficient concentration, lycopene enters actively proliferating deep crypt cells. If lycopene is not present in the circulation in sufficient concentration, actively proliferating deep crypt cells will be lycopene-deficient and at increased risk for carcinogenesis. In another small study, the lycopene content of mucosal tissues harvested from 7 patients with adenomatous polyps and 7 patients with colon cancer was significantly lower than that of both colonic and rectal mucosal tissue donated by patients without adenomatous polyps.[82]

InConsistent with these reports describing the chemopreventive effects of lycopene intake and tomato consumption on risk reduction for colorectal cancer, the investigators of a prospective observational study[410] and seven retrospective case-control studies have failed to observe the beneficial protective effect of the consumption of lycopene, tomatoes and tomato-based foods on the risk of developing colorectal cancer.[234,411-417] In several of these studies, the consumption of tomatoes or lycopene was minimal or absent in a large percentage of the study subjects and failure to observe the beneficial protective effect of the consumption of dietary ingredients that were not consumed on the risk for developing colorectal cancer was predictable.[410-412]

For example, in a subset of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study of male cigarette smokers, lycopene intakes of less than 1.5 mg daily did not reduce the risk of developing colorectal cancer (90% of the men in this study had daily lycopene intakes of less than 1.5 mg, slightly more than the amount of lycopene in a level teaspoon of catsup[5]).[410] In a simplistic retrospective case-control study of 453 subjects with colon cancer, 365 subjects with rectal cancer and 2,851 cancer-free subjects, when compared to no consumption of tomatoes or tomato-based foods, any such consumption failed to significantly affect the risk of developing either colon or rectal cancer.[411] In a study that compared 27 men and 15 women with colon cancer and 25 men and 26 women with rectal cancer to 111 men and 75 women without cancer, tomato consumption (only once or more weekly) had no effect on the risk of developing either colon or rectal cancer.[412]

In a study of 488 subjects with colorectal adenomas and 488 matched subjects without adenomas, 90% consumed less than 7.2 mg of lycopene daily, with no effect of lycopene intake on the risk for developing colorectal adenomas.[413] In a study comparing 437 men and 291 women with rectal cancer and 688 men and 537 women with colon cancer to 2,073 cancer-free men and 2,081 cancer-free women, lycopene intake had no effect on the risks for developing any colorectal cancer, colon cancer or rectal cancer; however, 80% of these subjects consumed less than 11.7 mg of lycopene daily.[414] In a study comparing 1,993 subjects with colon cancer to 2,410 cancer-free men and women, mean lycopene intakes did not differ between subjects with and without colon cancer and

lycopene intake had no effect on the risks for developing either proximal or distal colon cancer; however, 83% of these subjects consumed less than 13 mg of lycopene daily and 97% consumed less than 20 mg of lycopene daily.[415] In a study comparing 295 women with colorectal cancer to 5,334 cancer-free women, lycopene intake had no effect on the risk for developing colorectal cancer; however; 80% of these women consumed less than 17 mg of lycopene daily.[416] In a retrospective case-control study, estimated lycopene intakes did not affect the multivariate-adjusted risk of developing colorectal cancer among 142 men and 81 women with colorectal cancer and 211 men and 280 women without cancer.[417] However, lycopene intakes were not given.

In a retrospective case-control observational study, serum total lycopene concentration was not associated with the risk for developing rectal cancer.[234] However, lycopene intakes were not given.

H. The Available Evidence Provides Significant Scientific Support for the Conclusion that Risk for Developing Colorectal Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The results of seven retrospective case-control studies[67,73,82,405-409] demonstrate a beneficial effect of the consumption of lycopene and tomatoes and tomato-based foods on the risk for developing colorectal cancer. The results of a prospective observational study[410] and of retrospective case-control studies[234,411-417] have confirmed that the consumption of lycopene, tomatoes or tomato-based foods is required in order for this benefit to be realized.

The published scientific evidence strongly supports the conclusion that the risk of developing colorectal cancer is reduced by dietary supplementation with lycopene and by the consumption of tomatoes and tomato-based foods containing lycopene.

VII. Gastric Cancer

Although gastric cancer is the second most common cancer in the world, its prevalence in the US has been declining.[159] The American Cancer Society forecast about 22,400 new diagnoses of gastric cancer, and about 12,100 deaths related to gastric cancer, for the US in 2003.[159] Gastric cancer occurs with nearly equal frequency in men and women.[160] Overall 5-year relative survival is 20% or less, but increases to about 60% in the small percentages of cases where the tumor is localized to the stomach.[159]

A. Pathogenesis of Gastric Cancer

Gastric cancer may be differentiated into the intestinal type, with well-differentiated tissue, and the diffuse type consisting largely of undifferentiated cells.[418] The pathogenesis of gastric cancer depends on its initiating mutations; diffuse-type gastric cancer follows mutations in the E-cadherin gene while intestinal-type gastric cancer appears to follow a multistage model, progressing from the interactions of normal

mucosa with *Helicobacter pylori* organisms that produce chronic superficial gastritis to chronic atrophic gastritis, intestinal metaplasia, dysplasia and carcinoma.[419,420] Intragastric formation of carcinogenic *N*-nitroso compounds is carcinogenic in animals.[421] In humans it may be potentiated by the gastric alkalinization that accompanies atrophy and facilitates gastric microbial conversion of ingested nitrates to nitrites and then to *N*-nitrosamines.[419] *N*-nitrosamines may initiate or accelerate the carcinogenic sequence in humans.[419,421,422]

B. Animal Studies Provide Scientific Support for the Conclusion that Risk of Developing Gastric Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

Rats fed tomato paste containing lycopene (236 ppm) exhibited significant inhibition of the hepatic damage (centrolobular necrosis, exangia and appearance of pyknotic nuclei) typical after treatment with the combination of aminopyrin and sodium nitrite, precursors of intragastric *N*-nitrosamine formation.[423] Similarly, oral gavage with lycopene (2.5 mg per kg body weight) significantly inhibited the development of gastric carcinogenesis typically induced by intragastric intubation with the combination of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine and saturated sodium chloride.[424,425]

C. Human Clinical Trials Provide Scientific Support for the Conclusion that Risk of Developing Gastric Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The hypothesis that the risk for developing gastric cancer is reduced by consumption of supplemental lycopene or tomatoes and tomato-based foods containing lycopene is supported by the results of seven retrospective case-control studies.[405,406,426-430] In a study that compared 520 men and 221 women with gastric cancer to 520 matched men and 221 matched women without gastric cancer, the consumption of the highest tertile of tomato intake significantly reduced the risk of developing gastric cancer, compared to the risk associated with the consumption of the lowest tertile of tomato intake (OR: 0.77; significantly different from OR = 1.0; $p < 0.05$).[426] In another study that compared 220 men and women with gastric cancer to 440 men and women without cancer, the consumption of four or more servings of tomatoes per month significantly reduced the risk of developing gastric cancer, compared to the risk of men and women consuming less than 4 servings per month (sex-adjusted OR: 0.51; significantly different from OR = 1.0; $p < 0.05$).[427]

In another study that compared 723 men and women with gastric cancer to 2,024 men and women without cancer, the consumption of seven or more servings of tomatoes per week significantly reduced the risk of developing gastric cancer, compared to the risk of men and women consuming less than 2 servings per week (OR: 0.43; 95% CI: 0.34, 0.59; adjusted for age, sex, education, study center, alcohol consumption, smoking status and dietary daily total caloric intake).[405] In another study that compared 65 African-American men and women with gastric cancer to 82 African-American men and women without cancer, tomato consumption greater than the sample median (not given)

significantly reduced the risk of developing gastric cancer, compared to the risk of men and women consuming less than the sample median of tomatoes (OR: 0.56; 95% CI: 0.34, 0.90; adjusted for age, sex, education, income, alcohol consumption and tobacco use).[428]

In a retrospective case-control study of 154 subjects with gastric cancer, 252 subjects with colorectal cancer and 812 subjects without any cancer, compared to the risk of developing gastrointestinal cancer among those subjects who never consumed tomatoes or tomato-based foods, the daily consumption of tomatoes or tomato-based foods significantly reduced the risk of developing gastrointestinal cancer anywhere along the gastrointestinal tract (OR: 0.82; significantly different from OR = 1.0; $p < 0.05$).[406]

A study compared the lifetime dietary habits of 218 men and 120 women with gastric cancer to those habits of 444 men and 235 women without cancer.[429] The consumption of more than three servings of tomatoes per month during adolescence significantly reduced the risk of developing gastric cancer in adulthood, compared to the risk after tomatoes and tomato-based foods were completely avoided during adolescence (OR: 0.36; 95% CI: 0.23, 0.58; adjusted for age, sex and socioeconomic status). However, the risk of developing gastric cancer during adulthood was not affected by tomato consumption during adulthood.

In another study that matched 85 men and 35 women with gastric cancer to 255 men and 105 women without cancer, the consumption of more than 3.5 mg of lycopene daily significantly reduced the risk of developing gastric cancer, compared to the risk of men and women consuming less than 2 mg of lycopene daily (OR: 0.37; -95% CI: 0.19, 0.73; adjusted for age, sex, area of residence, education, family history of gastric cancer, body mass index and dietary daily intakes of total calories, vitamin C and fructose).[430]

The results of a prospective observational study do not supports the conclusion that the consumption of lycopene and tomatoes and tomato-based foods reduces the risk for developing gastric cancer.[431] In this study (the 6-year Netherlands Cohort Study of 120,852 men and women), although dietary lycopene intake had no effect on the risk of developing gastric cancer, fewer than 3% of these subjects consumed at least 3 mg of lycopene (slightly more than the amount of lycopene in a level tablespoon of catsup[5]) daily. The absence or virtual absence of lycopene from the diets of almost all study subjects rendered the failure of these investigators to observe the beneficial effect of the consumption of lycopene and tomatoes and tomato-based foods on the risk for developing gastric cancer both predictable and irrelevant.

The results of several retrospective case-control studies do not support the conclusion that the consumption of lycopene and tomatoes and tomato-based foods reduces the risk for developing gastric cancer.[104,105,412.427,432-437] In these studies, the absence or virtual absence of lycopene from the diets of almost all study subjects rendered the failure of these investigators to observe the beneficial effect of the consumption of lycopene and tomatoes and tomato-based foods on the risk for developing gastric cancer both

predictable and irrelevant. For example, in a retrospective case-control study of 282 men and women with gastric carcinoma and 3,123 cancer-free men and women, dietary lycopene intake was reported to have to influence on the risk of developing disease.[432] However, less than 3% of this population consumed more than 3 mg of lycopene (slightly more than the amount of lycopene in a level tablespoon of catsup[5]) daily.

80 Caucasian men and women with gastric cancer and 91 Caucasian men and women without gastric cancer, the consumption of tomatoes in amounts greater than the sample median did not reduce the risk of gastric cancer experienced by men and women consuming less than the median amount of tomatoes.[427] In a study that compared 59 men and 34 women with gastric cancer to 111 men and 75 women without cancer, tomato consumption (once or more weekly) had no effect on the risk of developing gastric cancer.[412] In another retrospective case-control study of 235 men and 119 women with gastric cancer and 235 men and 119 women without gastric cancer, lycopene intake had no effect on the risk of developing gastric cancer.[433] However, fewer than 25% of these subjects consumed at least 2 mg of lycopene (less than the amount of lycopene in a level tablespoon of catsup[5]) daily. The results of three retrospective case-control studies are consistent with the conclusion that avoidance or minimization of tomato consumption or lycopene intake does not reduce the risk of developing gastric cancer; however, actual intakes were not given.[434-436]

The results of one retrospective case-control study suggest that the risk of dying from gastric cancer is independent of regional mean plasma total lycopene concentration.[103,104]

D. The Available Evidence Provides Significant Scientific Support for the Conclusion that Risk for Developing Gastric Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The results of seven retrospective case-control studies[405,406,426-430] demonstrate a beneficial effect of the consumption of lycopene and tomatoes and tomato-based foods on the risk for developing gastric cancer. Although the results of a prospective observational study[431] and retrospective case-control studies[103,104,412.427,432-436] have not confirmed this conclusion, the absence or virtual absence of lycopene from the diets of almost all subjects in these studies rendered the failure of these investigators to observe the beneficial effect of the consumption of lycopene and tomatoes and tomato-based foods on the risk for developing gastric cancer both predictable and irrelevant to an evaluation of the scientific support for the conclusion that the consumption of lycopene and tomatoes and tomato-based foods reduces the risk for developing gastric cancer.

The published scientific evidence supports the conclusion that the risk of developing gastric cancer is reduced by dietary supplementation with lycopene and by the consumption of tomatoes and tomato-based foods containing lycopene.

VIII. Breast Cancer

The American Cancer Society forecast 211,300 new cases of invasive breast cancer for the US in 2003.[159] Over 99% of these cases occurred in women and about 20% will lead to premature death; over 40,000 breast cancer-related deaths were predicted for the US in 2003.[159] 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;[437] however, 5% to 10% of cases of DCIS are characterized by microinvasion of the ductal basement membrane.[438] Breast cancer ranks second (to lung cancer) among cancer deaths in women and is the most frequently diagnosed non-skin cancer in women.[159] The 5-year relative survival rate for localized breast cancer is 97%, for regionally invasive breast cancer, 78%, and for metastatic breast cancer, 23%.[159,438] 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.[159,439-441] Risk may be decreased by physical activity and maintenance of appropriate body weight.[159]

A. Pathogenesis of Breast Cancer

The pathogenesis of breast cancer is multifactorial and only incompletely understood.[442] However, similarities suggest that breast cancer follows a multistage pathogenesis not unlike that of other epithelial cancers such as lung, prostate and colorectal cancer.[442]

Insulin-like growth factor-I (IGF-I) is a potent circulating mitogen that interacts with target cells via the cell membrane-bound IGF-receptor to stimulate DNA synthesis and the progression of the cell cycle from the G_1 phase to the S phase while inhibiting apoptosis.[197-199] Breast tumor tissue overexpresses IGF-I receptors[443] and therefore is hypersensitive to this mitogen.

There is evidence that the risk of neoplastic transformation within a cell population increases as the proliferation rate of cells within the population increases,[202,203] suggesting that IGF-I availability to IGF-I-responsive tissues (such as in the breast) contributes to risk of developing tissue-specific cancer.[201] Furthermore, increased IGF-I availability may accelerate the proliferation and clonal expansion of epithelial undergoing the process of neoplastic transformation.[201] Elevated plasma IGF-I concentration was found to increase the risk of developing breast cancer among premenopausal women under the age of 50 years participating in the Nurses' Health Study.[444]

B. Cell Culture Studies Provide Scientific Support for the Conclusion that Risk of Developing Breast Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The addition of physiological concentrations of lycopene (0.75 to 3.0 x 10^{-6} *M*) to cultures of MCF7, MDA-MB-231 and T-47D human mammary cancer cells significantly inhibited both basal and IGF-I-stimulated rates of DNA synthesis and cell proliferation and suppressed IGF-I-stimulated cell cycle progression.[242,445-448] In these systems, lycopene was without effect on the rates of cellular apoptosis.

C. Animal Studies Provide Scientific Support for the Conclusion that Risk of Developing Breast Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

Dietary supplementation with lycopene significantly decreased the incidence of spontaneous mammary gland tumors in SHN virgin mice.[449] Similarly, lycopene-enriched tomato oleoresin significantly inhibited 7,12-dimethyl-benz[a]anthracene-induced mammary tumors in rats,[450] although this dietary supplement had no effect on the induction of mammary tumorigenesis in rats treated with *N*-methylnitrosourea.[451]

D. Human Clinical Trials Provide Scientific Support for the Conclusion that Risk of Developing Breast Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The hypothesis that the risk for developing breast cancer is reduced by consumption of supplemental lycopene or tomatoes and tomato-based foods containing lycopene is supported by the results of six retrospective case-control studies.[56,67,94,452-454] For example, in a study that compared 289 women with breast cancer to 442 matched women without breast cancer, lycopene intakes greater than 5 mg daily was associated with significantly reduced risk of developing breast cancer, compared to the risk associated with lycopene intakes of less than 2 mg daily (OR: 0.43; 95% CI: 0.28, 0.66; adjusted for age, education, parity, menopausal status, body mass index, alcohol consumption and dietary daily total caloric intake).[452] The chemopreventive effect of lycopene was not apparent among premenopausal subjects in this study but among postmenopausal women, lycopene intakes greater than 5 mg daily was associated with significantly reduced risk of developing breast cancer, compared to the risk associated with lycopene intakes of less than 2 mg daily (OR: 0.42; 95% CI: 0.26, 0.66; adjusted for age, education, parity, body mass index, alcohol consumption and dietary daily total caloric intake). Lycopene intakes greater than 5 mg daily were associated with significantly reduced risk of developing breast cancer, compared to the risk associated with lycopene intakes of less than 2 mg daily, among women with body mass index of 25 or more (OR: 0.37; 95% CI: 0.21, 0.66; adjusted for age, education, parity, menopausal status, alcohol consumption and dietary daily total caloric intake) as well as among women with body mass index less than 25 (OR: 0.51; 95% CI: 0.33, 0.80; adjusted for age, education, parity, menopausal status, alcohol consumption and dietary daily total caloric intake). Lycopene intakes greater than 5 mg daily were associated with significantly reduced risk of developing breast cancer, compared to the risk associated with lycopene intakes of less than 2 mg daily, among women who consumed alcohol (OR: 0.45; 95% CI: 0.27, 0.75; adjusted for age, education, parity, body mass index, menopausal status and dietary daily total caloric intake) as well as among women who abstained from alcohol consumption

(OR: 0.57; 95% CI: 0.34, 0.97; adjusted for age, education, parity, body mass index, menopausal status and dietary daily total caloric intake).

Among another sample of 400 women with breast cancer and 405 cancer-free women, women who consumed more than 4.3 mg of lycopene daily experienced significantly reduced risk of developing breast cancer, compared with the risk among women who consumed less than 2.3 mg of lycopene daily (OR: 0.30; 95% CI: 0.19, 0.47; adjusted for age, area of residence, urban or rural status, family history of breast cancer in a first-degree relative, body mass index, age at menarche, parity, menopausal status and dietary daily total caloric intake), suggesting that simply doubling the daily consumption of lycopene may well significantly reduce an individual woman's risk of developing breast cancer.[453] The chemopreventive effect of lycopene remained statistically significant even after further adjustment of the data for dietary daily intakes of all vegetables, dietary fiber, β-carotene, alpha-carotene, lutein, zeaxanthin, β-cryptoxanthin, vitamin C, vitamin E, folate, phytosterols, and glutathione (OR: 0.35; 95% CI: 0.21, 0.59). In addition, women who consumed more than three servings of foods enriched with tomato sauce weekly significantly reduced their risk of developing breast cancer, compared to women who consumed fewer than 1.5 servings of foods enriched with tomato sauce weekly (OR: 0.30; 95% CI: 0.17, 0.52; adjusted for age, residence, urban/rural status, family history of breast cancer in a first-degree relative, body mass index, age at menarche, parity, menopausal status and dietary daily total energy intake), indicating that simply doubling the consumption of such foods may well significantly reduce an individual woman's risk of developing breast cancer. Furthermore, women who consumed more than 5.5 servings of all tomato-containing foods weekly significantly reduced their risk of developing breast cancer, compared to women who consumed fewer than 2 servings of all tomato-containing foods weekly (OR: 0.30; 95% CI: 0.17, 0.52; adjusted for age, residence, urban/rural status, family history of breast cancer in a first-degree relative, body mass index, age at menarche, parity, menopausal status and dietary daily total energy intake).

Consistent with the findings of these consumption studies,[452,453] a retrospective case-control study of 295 women with breast and 295 matched women without breast cancer observed that the median serum total lycopene concentration of the women with breast cancer was significantly lower than was the median serum total lycopene concentration of the women without breast cancer.[94] However, in this study, serum total lycopene concentration did not appear to influence the risk of developing breast cancer (adjusted for menopausal status, family history of breast cancer, maternal age at first child's birth, age at menarche, alcohol consumption, smoking status, body mass index, duration of periods of lactation, education, serum total cholesterol concentration, length of time between most recent meal and blood sampling and use of hormonal replacement therapy). In contrast, another study of 206 women with breast cancer and 211 women without breast cancer concluded that the mean serum total lycopene concentration of women with breast cancer was significantly lower than the mean serum total lycopene concentration of women without breast cancer.[56] This conclusion was unchanged after separating the women into subgroups according to menopausal status. A similar smaller study of 15 women with breast cancer and 30 women without breast cancer also concluded that the mean plasma total lycopene concentration of women with breast cancer was significantly

lower than the mean plasma total lycopene concentration of women without breast cancer.[67]

In a retrospective case-control study of breast adipose tissues donated by 46 women with breast cancer and 63 women without breast cancer, women with breast adipose tissue lycopene contents above the combined median were at significantly reduced risk of developing breast cancer, compared to the risk among women with breast adipose tissue lycopene contents below the combined median (OR: 0.32; 95% CI: 0.11, 0.94; adjusted for age, smoking status and menopausal status).[454]

Contrary to these reports describing the chemopreventive effects of lycopene intake and tomato consumption on risk reduction for breast cancer, the results of one prospective observational study[153] and an analysis of pooled prospective (largely unpublished) epidemiologic data[455] do not support the conclusion that the consumption of lycopene and tomatoes reduces the risk of developing breast cancer.[455]

In the prospective study, at the end of 14 years of observation of 83,234 nurses (the Nurses' Health Study), it was reported that lycopene intake was not associated with the risk of developing breast cancer (adjusted for age, length of time observed in the study, parity, age at first child's birth, age at menarche, history of breast cancer in mother or a sister, history of benign breast disease in subject, alcohol consumption, body mass index at age 18 years, weight change from age 18 years until the end of the study, height and dietary daily total caloric intake).[153] However, the highest quintile of daily lycopene intake among these women averaged only 12.7 mg of lycopene intake daily. A pooled analysis of the raw data collected during eight prospective epidemiologic studies reported that the consumption of tomatoes was not related to the risk of developing breast cancer.[455] However, the basis of effect was the consumption of increments of 100 g of tomatoes daily; very few of the over 350,000 subjects in these studies consumed even one increment of tomatoes daily.

Several retrospective case-control studies have failed to observe the beneficial effect of tomato consumption or lycopene intake on the multivariate-adjusted risk of developing breast cancer.[55,97,101,112,117-119,234,456-461] However, in these studies, lycopene intake or consumption of tomatoes or tomato-based foods was minimal in a large percentage of study participants or was not reported and therefore their relevance cannot be ascertained.

Two retrospective case-control studies reported that no effect of tomato consumption on the prevalence of breast cancer was observed; however, tomato consumption was not reported.[456,457] Similarly, it was reported that lycopene intake had no effect on the prevalence of breast cancer, although lycopene intakes were not reported.[458] In another retrospective case-control study of 297 women with breast cancer and 311 women without breast cancer, lycopene intake was reported to have no influence on the risk of developing breast cancer, although 75% of these women consumed less than 7 mg of lycopene daily.[459] In a similar study that compared 2,569 women with breast cancer to 2,588 women without breast cancer, lycopene intake was reported to have no influence

on the risk of developing breast cancer, although 80% of these women consumed less than 8.5 mg of lycopene daily.[460] In another retrospective case-control study of 1,452 women with breast cancer and 5,239 women without breast cancer, lycopene intake was reported to have had no effect on the risk of developing breast cancer (adjusted for age, screening center, allocation, smoking status, body mass index, hours of vigorous physical activity daily, education, family history of breast cancer, subject history of benign breast disease, age at menarche, parity, menopausal status, oral contraceptive use, use of estrogen replacement therapy, practice of breast self-examination, multivitamin supplement use, alcohol consumption and dietary daily intakes of total calories, dietary fiber, folate and calcium).[461] However, 70% of these subjects consumed less than 13 mg of lycopene daily.

The results of several retrospective case-control studies have not demonstrated that the risk of developing breast cancer was influenced by serum or plasma total lycopene concentration.[55,97,101,112,117-119,234] However, the results of one such study suggest that serum total lycopene concentrations in excess of 0.5×10^{-6} *M* (commonly attained with dietary supplementation with lycopene or with increased consumption of tomato-based foods) may reduce the risk of developing breast cancer.[119]

In a retrospective study of breast adipose tissues donated by 46 women with benign breast disease and 44 women with breast cancer, breast adipose tissue lycopene content was not significantly different in cancerous or benign diseased tissues.[112]

E. The Available Evidence Provides Significant Scientific Support for the Conclusion that Risk for Developing Breast Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The results of six retrospective case-control studies[56,67,94,452-454] demonstrate a beneficial effect of the consumption of lycopene and tomatoes and tomato-based foods on the risk for developing breast cancer. Although the results of a prospective observational study[153] and retrospective case-control studies[55,97,101,112,117-119,234,456-461] have not confirmed this conclusion, the absence or virtual absence of lycopene from the diets of almost all subjects in these studies rendered the failure of these investigators to observe the beneficial effect of the consumption of lycopene and tomatoes and tomato-based foods on the risk for developing gastric cancer both predictable and irrelevant to an evaluation of the scientific support for the conclusion that the consumption of lycopene and tomatoes and tomato-based foods reduces the risk for developing breast cancer.

The published scientific evidence supports the conclusion that the risk of developing breast cancer is reduced by dietary supplementation with lycopene and by the consumption of tomatoes and tomato-based foods containing lycopene.

IX. Cervical Cancer

The American Cancer Society forecast 12,200 new cases of cervical cancer and 4,100 deaths from cervical cancer in the US during 2003. Survival for women with preinvasive lesions (CIN) is nearly 100%.[159] The 5-year relative survival for women with invasive cervical cancer detected early is 92%.[159]

A. Pathogenesis of Cervical Cancer

Cervical cancer begins as preneoplastic lesions (cervical dysplasia; cervical intraepithelial neoplasia; CIN). In early disease development (CIN grade I), intracellular lesions often undergo spontaneous remission.[462] CIN grade I may progress to CIN grade II and then to CIN grade III (carcinoma *in situ*), a recognized immediate precursor of invasive cervical cancer.[462] Multiple genetic events and human papillomavirus-induced disruptions in cell cycle regulation appear to be involved in the progression of cervical dysplasia to invasive cervical cancer.[462-465]

B. Human Clinical Trials Provide Scientific Support for the Conclusion that Risk of Developing Cervical Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The hypothesis that the risk for developing cervical cancer is reduced by consumption of either supplemental lycopene or of tomatoes and tomato-based foods containing lycopene is supported by the results of five retrospective case-control studies.[72,81,83,106,466] In a study that compared 257 women with cervical dysplasia, a well-recognized precursor to cervical cancer, to 705 women without cervical dysplasia, the consumption of tomatoes more than twice a week significantly reduced the risk of developing cervical dysplasia, compared to the risk associated with never consuming tomatoes (unadjusted OR: 0.63; 95% CI: 0.42, 0.94)[466] Similarly, in another study that compared 102 women with premalignant cervical intraepithelial neoplasia (CIN) to 102 matched women without CIN, the highest quartile of dietary lycopene intakes significantly reduced the risk of developing CIN, compared to the risk in women consuming the lowest quartile of dietary lycopene intakes (OR: 0.19; 95% CI: 0.04, 0.77; adjusted for dietary daily total caloric intake, smoking status at the time of the study, monthly personal income bracket, number of sexual partners, dietary daily vitamin C intake, frequency of Pap smear testing, use of spermicidal contraceptive agents, history of genital warts and body mass index).[106] In the same groups of women, the highest quartile of serum total lycopene concentrations also was associated with significantly reduced risk of developing CIN, compared to the risk associated with the lowest quartile of serum total lycopene concentrations (OR: 0.26; 95% CI: 0.08, 0.91; adjusted for smoking status at the time of the study, monthly personal income bracket, number of sexual partners, dietary daily vitamin C intake, frequency of Pap smear testing, use of spermicidal contraceptive agents, history of genital warts and body mass index).

In a study of 27 women with cervical cancer, 33 women with CIN and 27 women without cervical lesions, the mean plasma total lycopene concentration was significantly lower in the women with cervical cancer than in the women with either CIN or no lesions.[83] However, there was no difference in the mean plasma total lycopene concentrations of women with CIN and women without cervical lesions. In another study of 15 women with cervical cancer, 56 women with grade I CIN, 40 women with grade II CIN, 29 women with grade III CIN and 95 women without cervical lesions, plasma total lycopene concentrations were significantly inversely correlated with the severity of cervical disease.[81] In a study of 156 women with cervical dysplasia and 156 matched dysplasia-free women, the mean serum total lycopene concentration of women with cervical dysplasia was significantly lower than the serum total lycopene concentration of women without cervical dysplasia.[72] However, among these women, the multivariate-adjusted risk of developing cervical dysplasia was not associated with serum total lycopene concentration.

In contrast, the reported findings of eight retrospective case-control epidemiologic studies have not demonstrated significant relationships between tomatoes or lycopene and cervical disease.[50,61,87,88,95,96,120,467] For example, among a subset of 201 women participating in the prospective Young Women's Health Study, lycopene intake was not associated with the prevalence of human papillomavirus infection (a predominant cause of invasive cervical cancer[462-465]).[96] Similarly, when 32 women with CIN were compared to 113 women free of cervical disease, estimated lycopene intake was not significantly associated with multivariate-adjusted disease risk, although the unadjusted risk was significantly lower for women who consumed more than 1 mg of lycopene (less than the amount of lycopene in a level teaspoon of catsup[5]) daily.[61] In a case-control study of 513 women with cervical cancer and 490 women without cervical disease, the mean daily consumption of tomatoes was not different between the two groups of women.[467]

Seven retrospective studies have not observed any relationship between circulating concentrations of lycopene and cervical disease.[50,61,87,88,95,96,120] For example, among a subset of 201 women participating in the prospective Young Women's Health Study, neither plasma *trans*-lycopene or *cis*-lycopene concentrations were associated with the prevalence of human papillomavirus infection.[96] Among 32 women with CIN and 113 women free of cervical disease, serum total lycopene concentration did not affect either unadjusted or multivariate-adjusted risk of developing CIN, even though the median serum total lycopene concentration among women with CIN was only 65% that of women without CIN.[61] Similarly, among 81 women with CIN and 160 without, serum total lycopene concentration did not affect the multivariate-adjusted risk of developing CIN.[95] In four other studies, the mean serum total lycopene concentrations of women with or without cervical cancer were not different[87,88,120] and did not affect the prevalence of cervical cancer.[50,87,120]

C. The Available Evidence Provides Significant Scientific Support for the Conclusion that Risk for Developing Cervical Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Food Products

The results of five retrospective case-control studies[72,81,83,106,466] demonstrate a beneficial effect of the consumption of lycopene and tomatoes and tomato-based food products on the risk for developing cervical cancer. In contrast, the findings of eight retrospective case-control epidemiologic studies have not demonstrated significant relationships between tomatoes or lycopene and cervical disease;[50,61,87,88,95,96,120,467] these reports likely reflect confounding by related factors, very low lycopene intakes by study participants or heterogeneity of effect (this can occur when a subpopulation of nonresponders dilutes the overall effect of a chemopreventive agent or food and obscures the association in responders), resulting in underestimation of the effects of the nutrient or food of interest on chemoprevention.[236]

The published scientific evidence supports the conclusion that the risk of developing cervical cancer is reduced by dietary supplementation with lycopene and by the consumption of tomatoes and tomato-based foods containing lycopene.

X. Endometrial Cancer

The American Cancer Society forecast 40,100 new cases of endometrial cancer and 6,800 deaths associated with endometrial cancer in the US during 2003.[160] The survivability of endometrial cancer is inversely proportional to its severity when first diagnosed, with the 5-year relative survival rate ranging from 96% for localized cancer to 26% for metastatic disease.[160]

A. Pathogenesis of Endometrial Cancer

Endometrial cancer results from the progression of hyperestrogenic endometrial hyperproliferation, perhaps secondary to defective DNA mismatch repair systems.[468] The loss of expression of one of the DNA mismatch repair enzymes, usually hMLH1 or hMSH2, can result in microsatellite instability and produce predisposition to endometrial cancer.[469]

B. Cell Culture Studies Provide Scientific Support for the Conclusion that Risk of Developing Endometrial Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The addition of physiological concentrations of lycopene (1 to 2 x 10^{-6} *M*) to cultures of Ishikawa and ECC-1 human endometrial cancer cells significantly inhibited both basal and IGF-I-stimulated rates of DNA synthesis and cell proliferation.[242,446]

C. Human Clinical Trials Provide Scientific Support for the Conclusion that Risk of Developing Endometrial Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The hypothesis that the risk for developing endometrial cancer is reduced by consumption of either supplemental lycopene or of tomatoes and tomato-based foods containing lycopene is supported by the results of two retrospective studies of cohorts of women with and without endometrial cancer.[470,471] Among 221 women with endometrial cancer and 3,697 women with healthy endometrial tissues, the daily consumption of at least 14 mg of lycopene significantly reduced the risk of developing endometrial cancer, compared to the risk in women consuming less than 4.5 mg of lycopene daily (RR: 0.63; 95% CI: 0.43, 0.94; adjusted for age, body mass index, smoking status, oral contraceptive use, hormone replacement therapy use, education, parity, age at menarche and dietary daily total caloric intake). The findings of a retrospective case-control study of 232 women with endometrial cancer and 639 women without endometrial cancer suggest that the routine daily intake of more than 7.3 mg of lycopene significantly reduced the risk of developing endometrial cancer, compared to the risk in women with routine daily lycopene intakes less than 3.5 mg (trend for increasing lycopene intake to reduce risk of endometrial cancer: significantly different from no trend, $p = 0.01$; OR, daily intake of lycopene greater than 7.3 mg vs. daily intake of lycopene less than 4.5 mg: 0.6; 95% CI: 0.4, 1.0; adjusted for age, education, body mass index, diabetes, hypertension, number of pack-years of cigarette smoking, age at menarche, parity, oral contraceptive use, menopausal status, postmenopausal estrogenuse and dietary daily total caloric intake).[471]

The published scientific evidence supports the conclusion that the risk of developing endometrial cancer is reduced by dietary supplementation with lycopene and by the consumption of tomatoes and tomato-based foods containing lycopene.

XI. Ovarian Cancer

The American Cancer Society forecast 25,400 new cases of ovarian cancer and 14,300 deaths associated with ovarian cancer in the US during 2003.[159] The survivability of ovarian cancer is inversely proportional to its severity when first diagnosed, with the 5-year relative survival rate ranging from 95% for localized cancer to 31% for metastatic disease.[159]

A. Pathogenesis of Ovarian Cancer

Ovarian cancer usually begins in a single layer of the epithelial that line the surface of the ovary that may have lost the regulation of its normal post-ovulatatory proliferative phase.[472] Loss of cell cycle regulation in the ovarian epithelium results from multiple genetic alterations in proto-oncogenes as well as mutation of the p53 tumor suppressor gene.[472]

B. Human Clinical Trials Provide Scientific Support for the Conclusion that Risk of Developing Ovarian Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The hypothesis that the risk for developing ovarian cancer is reduced by consumption of either supplemental lycopene or of tomatoes and tomato-based foods containing lycopene is supported by the results of a retrospective case-control study.[473] Among 549 women with ovarian cancer and 516 women with healthy ovaries, the daily consumption of at least 15 mg of lycopene significantly reduced the risk of developing ovarian cancer, compared to the risk in women consuming less than 5 mg of lycopene daily (OR: 0.53; 95% CI: 0.35, 0.82; adjusted for age, body mass index, oral contraceptive use, family history of breast, ovarian or prostate cancer in a first-degree relative, tubal ligation, education, parity, marital status and dietary daily total caloric intake). Although this relationship was not statistically significant among only the postmenopausal members of this study, it was even stronger among the study's premenopausal participants (OR: 0.37; 95% CI: 0.20, 0.66; adjusted for age, body mass index, oral contraceptive use, family history of breast, ovarian or prostate cancer in a first-degree relative, tubal ligation, education, parity, marital status and dietary daily total caloric intake). In addition, the consumption of tomato sauce more than once a week significantly reduced the risk of developing ovarian cancer, compared to the risk in women consuming tomato sauce less than once a month (OR: 0.60; 95% CI: 0.37, 0.99; adjusted for age, body mass index, oral contraceptive use, family history of breast, ovarian or prostate cancer in a first-degree relative, tubal ligation, education, parity, marital status and dietary daily total caloric intake). Interestingly, the risk of developing ovarian cancer did not appear to be affected by the rate of consumption of either raw tomatoes or tomato juice, suggesting that heating or cooking the organic matrix of plant sources of lycopene substantially increases the bioavailability and chemopreventive effectiveness of naturally-occurring lycopene in the ovary. Circulating lycopene concentrations were not reported in this study; in a much smaller case-control study, serum total lycopene concentrations were reportedly not predictive of risk for ovarian cancer in 35 women with ovarian cancer and 67 women without ovarian cancer.[52]

Although not abundant, the published scientific evidence supports the conclusion that the risk of developing ovarian cancer is reduced by dietary supplementation with lycopene and by the consumption of tomatoes and tomato-based foods containing lycopene.

XII. Pancreatic Cancer

It was expected that 30,700 new cases of pancreatic cancer would be diagnosed in the US in 2003 and that 30,000 deaths related to pancreatic cancer would occur.[159] For all stages of pancreatic cancer combined, the 1-year relative survival rate is 21% and the 5-year relative survival rate is 4%.[159] When the initial diagnosis is localized disease, the 5-year relative survival rate rises to 17%.[159] Mutations in cellular proto-oncogenes and tumor suppressor genes are implicated in the pathogenesis of pancreatic cancer.[474]

A. Human Clinical Trials Provide Scientific Support for the Conclusion that Risk of Developing Pancreatic Cancer is Reduced by the Consumption of Lycopene, Tomatoes or Tomato-Based Foods

The hypothesis that the risk for developing pancreatic cancer is reduced by consumption of either supplemental lycopene or of tomatoes and tomato-based products containing lycopene is supported by the results of three retrospective studies.[116,233,475,476] Among 164 men and women with pancreatic cancer and 480 men and women without evidence of pancreatic disease, the daily consumption of the highest quintile of raw tomatoes significantly reduced the risk of developing pancreatic cancer, compared to the risk in subjects consuming the lowest quintile of raw tomatoes (OR: 0.23; significantly different from OR = 1.0, $p < 0.05$; adjusted for age, sex, smoking status and dietary daily total caloric intake).[475] In another study of 52 men and 52 women with pancreatic cancer and 142 cancer-free men and 111 cancer-free women, mean tomato consumption by subjects with pancreatic cancer was significantly less than that by cancer-free subjects.[476]

Consistent with the chemopreventive effectiveness of tomato consumption, mean serum total lycopene concentration was significantly higher among 18 men and 26 women without cancer than among 9 men and 13 women with pancreatic cancer.[116,233] In addition, subjects with the serum total lycopene concentrations greater than 1.01×10^{-6} *M* experienced significantly less risk of developing pancreatic cancer than did subjects with serum total lycopene concentrations less than 0.66×10^{-6} *M* (unadjusted OR: 0.19; significantly different from OR = 1.0, $p < 0.05$). Furthermore, subjects with the serum total lycopene concentrations greater than 0.66×10^{-6} *M* experienced significantly less risk of developing pancreatic cancer than did subjects with serum total lycopene concentrations less than 0.66×10^{-6} *M* (unadjusted OR: 0.16; 95% CI: 0.04, 0.57).

In contrast to these reports, the results of a 6-year prospective study of 34,556 Seventh-Day Adventists suggested that tomato consumption had no effect on the age and sex-adjusted incidence of pancreatic cancer.[477]

Although the results of the only published prospective study of the relationship between tomato intake and pancreatic cancer did not observe a relationship,[477] all of the published retrospective epidemiologic data consistently indicate the presence of a chemoprotective relationship.[116,233,475,476]

The published scientific evidence supports the conclusion that the risk of developing pancreatic cancer is reduced by dietary supplementation with lycopene and by the consumption of tomatoes and tomato-based foods containing lycopene.

XIII. Amounts of Supplemental Dietary Lycopene and Tomatoes and Tomato-Based Foods that Are Effective in Reducing the Risks of Developing Cancers of the Prostate, Lung, Stomach, Colon, Rectum, Breast, Cervix, Endometrium, Ovaries and Pancreas

The reliable and credible scientific literature indicates that daily dietary supplementation with lycopene or the daily consumption of tomatoes and tomato-based foods to ensure a daily intake of at least 15 mg of lycopene will be effective in reducing the risks of prostate, lung, gastric, colorectal, breast, cervical, endometrial, ovarian and pancreatic cancer.

XIV. Safety of Dietary Supplementation with Lycopene in Amounts that Are Effective in Reducing the Risks of Developing Cancers of the Prostate, Lung, Stomach, Colon, Rectum, Breast, Cervix, Endometrium, Ovaries and Pancreas

There have been no reports of adverse reactions to supplemental lycopene reported in the literature.

No signs of toxicity have been observed in rats fed supplemental lycopene in amounts up to 500 mg of lycopene per kg of body weight daily for 14 weeks or up to 1000 mg of lycopene per kg of body weight daily for 4 weeks.[478] No teratogenic effects occurred in rats in a 2-generation study of animals fed 1000 ppm of lycopene or 1000 mg of lycopene per kg of body weight.[478] The oral LD50 in the mouse is at least 3,000 mg per kg body weight; the oral LD50 in the rat is at least 4,000 mg per kg body weight.[479] Supplemental lycopene is not hepatotoxic, genotoxic or mutagenic.[478,479]

The concurrent ingestion of 60 mg of β-carotene and 60 mg of lycopene had no effect on the bioavailability of β-carotene but significantly increased the apparent absorption of lycopene.[127] Dietary supplementation with 15 mg of synthetic lycopene (LycoVit 10%, BASF, Ludwigshafen, Germany) had no effect on serum concentrations of α-carotene, β-carotene, β-cryptoxanthin, lutein or zeaxanthin.[34]

Synthetic lycopene (LycoVit 10%, BASF, Ludwigshafen, Germany) has been found to be stable at room temperature (less than 5% loss in 12 months) and at 60° C (less than 5% loss in 40 days).[33] Such excellent stability may result from the significantly greater resistance of synthetic lycopene to oxidative degradation.[33]

Adults treated with either cholestyramine or probucol have exhibited significant 30% decreases in serum total lycopene concentrations, suggesting that individuals receiving those medications require restorative dietary supplementation with lycopene.[480]

The concurrent consumption of plant stanol esters has significantly decreased plasma total lycopene concentrations[132] or has had no effect on plasma total lycopene concentrations.[148] The consumption of food products containing olestra significantly reduced serum total lycopene concentrations.[128]

XV. Safety of the Consumption of Tomatoes and Tomato-Based Foods in Amounts that Are Effective in Reducing the Risks of Developing Cancers of the Prostate, Lung, Stomach, Colon, Rectum, Breast, Cervix, Endometrium, Ovaries and Pancreas

There have been no cases of tomato overdose reported in the literature.

Conclusions

- The prevention of cancer is a national priority.
- Every means of preventing cancer deserves widespread dissemination.
- Lycopene absorbed from tomatoes, tomato-based foods and dietary supplements containing lycopene can significantly increase circulating total lycopene concentrations.
- Individuals with the greatest circulating concentrations of total lycopene are at the lowest risk of developing certain kinds of cancer.
- Individuals with the greatest circulating concentrations of total lycopene are at the lowest risk of developing prostate cancer.
- Individuals with the greatest circulating concentrations of total lycopene are at the lowest risk of developing lung cancer.
- Individuals with the greatest circulating concentrations of total lycopene are at the lowest risk of developing gastric cancer.
- Individuals with the greatest circulating concentrations of total lycopene are at the lowest risk of developing colorectal cancer.
- Individuals with the greatest circulating concentrations of total lycopene are at the lowest risk of developing breast cancer.
- Individuals with the greatest circulating concentrations of total lycopene are at the lowest risk of developing cervical cancer.
- Individuals with the greatest circulating concentrations of total lycopene are at the lowest risk of developing endometrial cancer.
- Individuals with the greatest circulating concentrations of total lycopene are at the lowest risk of developing ovarian cancer.
- Individuals with the greatest circulating concentrations of total lycopene are at the lowest risk of developing pancreatic cancer.
- Individuals with the greatest daily intakes of lycopene are at the lowest risk of developing prostate cancer.

- Individuals with the greatest daily intakes of lycopene are at the lowest risk of developing lung cancer.
- Individuals with the greatest daily intakes of lycopene are at the lowest risk of developing gastric cancer.
- Individuals with the greatest daily intakes of lycopene are at the lowest risk of developing colorectal cancer.
- Individuals with the greatest daily intakes of lycopene are at the lowest risk of developing breast cancer.
- Individuals with the greatest daily intakes of lycopene are at the lowest risk of developing cervical cancer.
- Individuals with the greatest daily intakes of lycopene are at the lowest risk of developing endometrial cancer.
- Individuals with the greatest daily intakes of lycopene are at the lowest risk of developing ovarian cancer.
- Individuals with the greatest daily intakes of lycopene are at the lowest risk of developing pancreatic cancer.
- Individuals consuming the greatest amounts of tomatoes and tomato-based foods on a daily basis are at the lowest risk of developing prostate cancer.
- Individuals consuming the greatest amounts of tomatoes and tomato-based foods on a daily basis are at the lowest risk of developing lung cancer.
- Individuals consuming the greatest amounts of tomatoes and tomato-based foods on a daily basis are at the lowest risk of developing gastric cancer.
- Individuals consuming the greatest amounts of tomatoes and tomato-based foods on a daily basis are at the lowest risk of developing colorectal cancer.
- Individuals consuming the greatest amounts of tomatoes and tomato-based foods on a daily basis are at the lowest risk of developing breast cancer.
- Individuals consuming the greatest amounts of tomatoes and tomato-based foods on a daily basis are at the lowest risk of developing cervical cancer.
- Individuals consuming the greatest amounts of tomatoes and tomato-based foods on a daily basis are at the lowest risk of developing endometrial cancer.

- Individuals consuming the greatest amounts of tomatoes and tomato-based foods on a daily basis are at the lowest risk of developing ovarian cancer.
- Individuals consuming the greatest amounts of tomatoes and tomato-based foods on a daily basis are at the lowest risk of developing pancreatic cancer.
- Supplemental lycopene is safe.
- Tomatoes are safe.
- Tomato-based foods containing lycopene are safe.
- Routine ingestion of sufficient amounts of tomatoes, tomato-based foods and supplemental lycopene to reduce the risks of developing cancer is safe.

Summary Conclusions

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

- Lycopene may reduce the risk of cancer.
- Lycopene may reduce the risk of prostate cancer.
- Lycopene may reduce the risk of lung cancer.
- Lycopene may reduce the risk of gastric cancer.
- Lycopene may reduce the risk of colorectal cancer.
- Lycopene may reduce the risk of breast cancer.
- Lycopene may reduce the risk of cervical cancer.
- Lycopene may reduce the risk of endometrial cancer.
- Lycopene may reduce the risk of ovarian cancer.
- Lycopene may reduce the risk of pancreatic cancer.
- Tomatoes may reduce the risk of cancer.
- Tomatoes may reduce the risk of prostate cancer.
- Tomatoes may reduce the risk of lung cancer.
- Tomatoes may reduce the risk of gastric cancer.
- Tomatoes may reduce the risk of colorectal cancer.
- Tomatoes may reduce the risk of breast cancer.
- Tomatoes may reduce the risk of cervical cancer.
- Tomatoes may reduce the risk of endometrial cancer.
- Tomatoes may reduce the risk of ovarian cancer.
- Tomatoes may reduce the risk of pancreatic cancer.
- Lycopene-containing tomato-based foods may reduce the risk of cancer.
- Lycopene-containing tomato-based foods may reduce the risk of prostate cancer.
- Lycopene-containing tomato-based foods may reduce the risk of lung cancer.
- Lycopene-containing tomato-based foods may reduce the risk of gastric cancer.
- Lycopene-containing tomato-based foods may reduce the risk of colorectal cancer.
- Lycopene-containing tomato-based foods may reduce the risk of breast cancer.

- Lycopene-containing tomato-based foods may reduce the risk of cervical cancer.
- Lycopene-containing tomato-based foods may reduce the risk of endometrial cancer.
- Lycopene-containing tomato-based foods may reduce the risk of ovarian cancer.
- Lycopene-containing tomato-based foods may reduce the risk of pancreatic cancer.

[original signed and dated]

Michael J. Glade, Ph.D., F.A.C.N., C.N.S.

References Cited

1. Khachik F, Carvalho L, Bernstein PS, Muir GJ, Zhao DY, Katz NB. Chemistry, distribution, and metabolism of tomato carotenoids and their impact on human health. *Exp Biol Med* 2002;227:845-851.
2. Boileau TW-M, Boileau AC, John W. Erdman JW Jr. Bioavailability of *all-trans* and *cis*-isomers of lycopene. *Exptl Biol Med* 2002;227:914-919.
3. Olson JA. The conversion of radioactive β-carotene into vitamin A by rat small intestine *in vivo*. *J Biol Chem* 1961;236:349-356.
4. Olson JA. Provitamin A function of carotenoids: The conversion of β-carotene into vitamin A. *J Nutr* 1989;119:105-108.
5. United States Department of Agriculture. *USDA Tables of the Nutrient Composition of Foods, Release 16*. United States Department of Agriculture, Washington, DC, 2003.
6. Tonucci LH, Holden JM, Beecher GR, Khachik F, Davis CS, Mulokozi G. Carotenoid content of thermally processed tomato-based food products. *J Agric Food Chem* 1995;43:579-586.
7. Clinton SK, Emenhiser C, Schwartz SJ, Bostwick DG, Williams AW, Moore BJ, Erdman JW Jr. *cis-trans* lycopene isomers, carotenoids and retinol in the human prostate. *Cancer Epidemiol Biomarkers Prev* 1996;5:823-833.
8. Gartner C, Stahl W, Sies H. Lycopene is more bioavailable from tomato paste than from fresh tomatoes. *Am J Clin Nutr* 1997;66:116-122.
9. Nguyen ML, Schwartz SJ. Lycopene stability during food processing. *Proc Soc Exp Biol Med* 1998;218:101-105.
10. Schierle J, Bretzel W, Buhler I, Faccin N, Hess D, Steiner K, Schuep W. Content and isomeric ratios of lycopene in food and human blood plasma. *Food Chem* 1997;59:459-465.
11. Shi J, Le Maguer M. Lycopene in tomatoes: Chemical and physical properties affected by food processing. *Crit Rev Biotechnol* 2000;20:293-334.
12. Agarwal A, Shen H, Agarwal S, Rao AV. Lycopene content of tomato products: Its stability, bioavailability and *in vivo* antioxidant properties. *J Med Food* 2001;4:9-15.
13. Khachik F, Goli MB, Beecher GR, Holden J, Lusby WR, Tenorio MD, Barrera MR. The effect of food preparation on qualitative and quantitative distribution of major carotenoid constituents of tomatoes and several green vegetables. *J Agric Food Chem* 1992;40:390-398.
14. United States Department of Agriculture. *USDA Table of Nutrient Retention Factor, Release 5*. United States Department of Agriculture, Washington, DC, 2003.
15. Clinton SK. Lycopene: Chemistry, biology, and implications for human health and disease. *Nutr Rev* 1998;56:35-51.
16. Williams AW, Boileau TWM, Erdman JW Jr. Factors influencing the uptake and absorption of carotenoids. *Proc Exp Biol Med* 1998;218:106-108.
17. van het Hof KH, de Boer BC, Tijburg LB, Lucius BR, Zijp I, West CE, Hautvast JG, Weststrate JA. Carotenoid bioavailability in humans from tomatoes processed in different ways determined from the carotenoid response in the

triglyceride-rich lipoprotein fraction of plasma after a single consumption and in plasma after four days of consumption. *J Nutr* 2000;130:1189-1196.
18. Re R, Fraser PD, Long M, Brameley PM, Rice-Evans C. Isomerization of lycopene in the gastric milieu. *Biochem Biophys Res Commun* 2001;281:576-581.
19. Boileau AC, Merchen NR, Wasson K, Atkinson CA, Erdman JW Jr. Cis-lycopene is more bioavailable than trans lycopene *in vitro* and also *in vivo* in the lymph cannulated ferret. *J Nutr* 1999;129:1176-1181.
20. Porrini M, Riso P, Testolin G. Absorption of lycopene from single or daily portions of raw and processed tomato. *Br J Nutr* 1998;80:353-361.
21. Stahl W, Sies H. Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessed tomato juice in humans. *J Nutr* 1992;122:2161-2166.
22. Holloway DE, Yang M, Paganga G, Rice-Evans CA, Bramley PM. Isomerization of dietary lycopene during assimilation and transport in plasma. *Free Radic Res* 2000;32:93-102.
23. Cohn W, Schalch W, Thurmann P, Aebischer C, Schierle J, Elliott J. Lycopene concentrations in plasma after consumption of tablets containing lycopene in beadlets or lycopene from natural sources (abstract). *Proceedings, International Symposium on the Role of Tomato Products and Carotenoids in Disease Prevention*, New York City, April 10, 2001, poster 12, unpaged.
24. Bohm V, Bitsch R. Intestinal absorption of lycopene from different matrices and interactions to other carotenoids, the lipid status, and the antioxidant capacity of human plasma. *Eur J Nutr* 1999;38:118-125.
25. Norrish AE, Jackson RT, Sharpe SJ, Skeaff CM. Men who consume vegetable oils rich in monounsaturated fat: their dietary patterns and risk of prostate cancer (New Zealand). *Cancer Causes Control* 2000;11:609-615.
26. Djuric Z, Uhley VE, Naegeli L, Lababidi S, Macha S, Heilbrun LK. Plasma carotenoids, tocopherols, and antioxidant capacity in a 12-week intervention study to reduce fat and/or energy intakes. *Nutrition* 2003;19:244-249.
27. Velthuis-te Wierik EJM, van den Berg H, Weststrate JA, van het Hof KH, de Graaf C. Consumption of reduced-fat products: effects on parameters of anti-oxidative capacity. *Eur J Clin Nutr* 1996;50:214-219.
28. Clark RM, Yao L, She L, Furr HC. A comparison of lycopene and astaxanthin absorption from corn oil and olive oil emulsions. *Lipids* 2000;35:803-806.
29. Diwadkar-Navsariwala V, Novotny JA, Gustin DM, Sosman JA, Rodvold KA, Crowell JA, Stacewicz-Sapuntzakis M, Bowen PE. A physiological pharmacokinetic model describing the disposition of lycopene in healthy men. *J Lipid Res* 2003, published in electronic form July 16, 2002, as manuscript M300130-JLR200.
30. Garrett DA, Failla ML, Sarama RJ. Estimation of carotenoid bioavailability from fresh stir-fried vegetables using an in vitro digestion/Caco-2 cell culture model. *J Nutr Biochem* 2000;11:574-580.
31. Tyssandier V, Reboul E, Dumas JF, Bouteloup-Demange C, Armand M, Marcand J, Sallas M, Borel P. Processing of vegetable-borne carotenoids in the human stomach and duodenum. *Am J Physiol Gastrointest Liver Physiol* 2003;284:G913-G923.

32. O'Neill ME, Thurnham DI. Intestinal absorption of beta-carotene, lycopene and lutein in men and women following a standard meal: Response curves in the triacylglycerol-rich lipoprotein fraction. *Br J Nutr* 1998;79:149-159.
33. Musaeus N, Nowakowsky B, Kramer K. A new stabilized form of lycopene (abstract). *Contributions to the 13th International Carotenoid Society Symposium*, Honolulu, January 6 – 11, 2002, unpaged.
34. Hoppe PP, Kramer K, van den Berg H, Steenge G, van Vliet T. Synthetic and tomato-based lycopene have identical bioavailability in humans (abstract). *Contributions to the 13th International Carotenoid Society Symposium*, Honolulu, January 6 – 11, 2002, unpaged.
35. Record IR, Dreosti IE, McInerney JK. Changes in plasma antioxidant status following consumption of diets high or low in fruit and vegetables or following dietary supplementation with an antioxidant mixture. *Br J Nutr* 2001;85:459-464.
36. Ahuja KD, Ashton EL, Ball MJ. Effects of a high monounsaturated fat, tomato-rich diet on serum levels of lycopene. *Eur J Clin Nutr* 2003;57:832-841.
37. Albanes D, Virtamo J, Taylor PR, Rautalahti M, Pietinen P, Heinonen OP. Effects of supplemental beta-carotene, cigarette smoking, and alcohol consumption on serum carotenoids in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Clin Nutr* 1997;66:366-372.
38. Allen CM, Smith AM, Clinton SK, Schwartz SJ. Tomato consumption increases lycopene isomer concentrations in breast milk and plasma of lactating women. *J Am Diet Assoc* 2002;102:1257-1262.
39. Breslow RA, Alberg AJ, Helzlsouer KJ, Bush TL, Norkus EP, Morris JS, Spate VE, Comstock GW. Serological precursors of cancer: malignant melanoma, basal and squamous cell skin cancer, and prediagnostic levels of retinol, beta-carotene, lycopene, alpha-tocopherol, and selenium. *Cancer Epidemiol Biomarkers Prev* 1995;4:837-842.
40. Brown ED, Micozzi MS, Craft NE, Bieri JG, Beecher G, Edwards BK, Rose A, Taylor PR, Smith JC Jr. Plasma carotenoids in normal men after a single ingestion of vegetables or purified beta-carotene. *Am J Clin Nutr* 1989;49:1258-1265.
41. Buiatti E, Munoz N, Kato I, Vivas J, Muggli R, Plummer M, Benz M, Franceschi S, Oliver W. Determinants of plasma anti-oxidant vitamin levels in a population at high risk for stomach cancer. *Int J Cancer* 1996;65:317-322.
42. Caperle M, Maiani G, Azzini E, Conti EM, Raguzzini A, Ramazzotti V, Crespi M. Dietary profiles and anti-oxidants in a rural population of central Italy with a low frequency of cancer. *Eur J Cancer Prev* 1996;5:197-206.
43. Casso D, White E, Patterson RE, Agurs-Collins T, Kooperberg C, Haines PS. Correlates of serum lycopene in older women. *Nutr Cancer* 2000;36:163-169.
44. Chen L, Stacewicz-Sapuntzakis M, Duncan C, Sharifi R, Ghosh L, van Breemen R, Ashton D, Bowen PE. Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. *J Natl Cancer Inst* 2001;93:1872-1879.
45. Comstock GW, Alberg AJ, Huang HY, Wu K, Burke AE, Hoffman SC, Norkus EP, Gross M, Cutler RG, Morris JS, Spate VL, Helzlsouer KJ. The risk of developing lung cancer associated with antioxidants in the blood: Ascorbic acid,

carotenoids, alpha-tocopherol, selenium, and total peroxyl radical absorbing capacity. *Cancer Epidemiol Biomarkers Prev* 1997;6:907-916.
46. Dietrich M, Block G, Norkus EP, Hudes M, Traber MG, Cross CE, Packer L. Smoking and exposure to environmental tobacco smoke decrease some plasma antioxidants and increase gamma-tocopherol *in vivo* after adjustment for dietary antioxidant intakes. *Am J Clin Nutr* 2003;77:160-166.
47. Edwards AJ, Vinyard BT, Wiley ER, Brown ED, Collins JK, Perkins-Veazie P, Baker RA, Clevidence BA. Consumption of watermelon juice increases plasma concentrations of lycopene and beta-carotene in humans. *J Nutr* 2003;133:1043-1050.
48. Giuliano AR, Papenfuss M, Nour M, Canfield LM, Schneider A, Hatch K. Antioxidant nutrients: associations with persistent human papillomavirus infection. *Cancer Epidemiol Biomarkers Prev* 1997;6:917-923.
49. Gomez-Aracena J, Bogers R, Van't Veer P, Gomez-Gracia E, Garcia-Rodriguez A, Wedel H, Fernandez-Crehuet Navajas J. Vegetable consumption and carotenoids in plasma and adipose tissue in Malaga, Spain. *Int J Vitam Nutr Res* 2003;73:24-31.
50. Goodman MT, Kiviat N, McDuffie K, Hankin JH, Hernandez B, Wilkens LR, Franke A, Kuypers J, Kolonel LN, Nakamura J, Ing G, Branch B, Bertram CC, Kamemoto L, Sharma S, Killeen J. The association of plasma micronutrients with the risk of cervical dysplasia in Hawaii. *Cancer Epidemiol Biomarkers Prev* 1998;7:537-544.
51. Hadley CW, Clinton SK, Schwartz SJ. The consumption of processed tomato products enhances plasma lycopene concentrations in association with a reduced lipoprotein sensitivity to oxidative damage. *J Nutr* 2003;133:727-732.
52. Helzlsouer KJ, Alberg AJ, Norkus EP, Morris JS, Hoffman SC, Comstock GW. Prospective study of serum micronutrients and ovarian cancer. *J Natl Cancer Inst* 1996;88:32-37.
53. Helzlsouer KJ, Comstock GW, Morris JS. Selenium, lycopene, alpha-tocopherol, beta-carotene, retinol, and subsequent bladder cancer. *Cancer Res* 1989;49:6144-6148.
54. Huang HY, Alberg AJ, Norkus EP, Hoffman SC, Comstock GW, Helzlsouer KJ. Prospective study of antioxidant micronutrients in the blood and the risk of developing prostate cancer. *Am J Epidemiol* 2003;157:335-344.
55. Hulten K, Van Kappel AL, Winkvist A, Kaaks R, Hallmans G, Lenner P, Riboli E. Carotenoids, alpha-tocopherols, and retinol in plasma and breast cancer risk in northern Sweden. *Cancer Causes Control* 2001;12:529-357.
56. Ito Y, Gajalakshmi KC, Sasaki R, Suzuki K, Shanta V. A study on serum carotenoid levels in breast cancer patients of Indian women in Chennai (Madras), India. *J Epidemiol* 1999;9:306-314.
57. Ito Y, Suzuki K, Suzuki S, Sasaki R, Otani M, Aoki K. Serum antioxidants and subsequent mortality rates of all causes or cancer among rural Japanese inhabitants. *Int J Vitam Nutr Res* 2002;72:237-250.
58. Ito Y, Suzuki S, Yagyu K, Sasaki R, Suzuki K, Aoki K. Relationship between serum carotenoid levels and cancer death rates in the residents, living in a rural area of Hokkaido, Japan. *J Epidemiol* 1997;7:1-8.

59. Ito Y, Wakai K, Suzuki K, Tamakoshi A, Seki N, Ando M, Nishino Y, Kondo T, Watanabe Y, Ozasa K, Ohno Y; JACC Study Group. Serum carotenoids and mortality from lung cancer: A case-control study nested in the Japan Collaborative Cohort (JACC) study. *Cancer Sci* 2003;94:57-63.
60. John JH, Ziebland S, Yudkin P, Roe LS, Neil HA; Oxford Fruit and Vegetable Study Group. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: A randomised controlled trial. *Lancet* 2002;359:1969-1974.
61. Kanetsky PA, Gammon MD, Mandelblatt J, Zhang ZF, Ramsey E, Dnistrian A, Norkus EP, Wright TC Jr. Dietary intake and blood levels of lycopene: Association with cervical dysplasia among non-Hispanic, black women. *Nutr Cancer* 1998;31:31-40.
62. Kucuk O, Sarkar FH, Sakr W, Djuric Z, Pollak MN, Khachik F, Li YW, Banerjee M, Grignon D, Bertram JS, Crissman JD, Pontes EJ, Wood DP Jr. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. *Cancer Epidemiol Biomarkers Prev* 2001;10:861-868.
63. Le Marchand L, Hankin JH, Carter FS, Essling C, Luffey D, Franke AA, Wilkens LR, Cooney RV, Kolonel LN. A pilot study on the use of plasma carotenoids and ascorbic acid as markers of compliance to a high fruit and vegetable dietary intervention. *Cancer Epidemiol Biomarkers Prev* 1994;3:245-251.
64. Lu QY, Hung JC, Heber D, Go VL, Reuter VE, Cordon-Cardo C, Scher HI, Marshall JR, Zhang ZF. Inverse associations between plasma lycopene and other carotenoids and prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2001;10:749-756.
65. Mayne ST, Cartmel B, Silva F, Kim CS, Fallon BG, Briskin K, Zheng T, Baum M, Shor-Posner G, Goodwin WJ Jr. Plasma lycopene concentrations in humans are determined by lycopene intake, plasma cholesterol concentrations and selected demographic factors. *J Nutr* 1999;129:849-854.
66. McEligot AJ, Rock CL, Flatt SW, Newman V, Faerber S, Pierce JP. Plasma carotenoids are biomarkers of long-term high vegetable intake in women with breast cancer. *J Nutr* 1999;129:2258-2263.
67. McMillan DC, Talwar D, Sattar N, Underwood M, O'Reilly DS, McArdle C. The relationship between reduced vitamin antioxidant concentrations and the systemic inflammatory response in patients with common solid tumours. *Clin Nutr* 2002;21:161-164.
68. Michaud DS, Giovannucci EL, Ascherio A, Rimm EB, Forman MR, Sampson L, Willett WC. Associations of plasma carotenoid concentrations and dietary intake of specific carotenoids in samples of two prospective cohort studies using a new carotenoid database. *Cancer Epidemiol Biomarkers Prev* 1998;7:283-290.
69. Micozzi MS, Brown ED, Edwards BK, Bieri JG, Taylor PR, Khachik F, Beecher GR, Smith JC Jr. Plasma carotenoid response to chronic intake of selected foods and beta-carotene supplements in men. *Am J Clin Nutr* 1992;55:1120-1125.
70. Muller H, Bub A, Watzl B, Rechkemmer G. Plasma concentrations of carotenoids in healthy volunteers after intervention with carotenoid-rich foods. *Eur J Nutr* 1999;38:35-44.

71. Nagao T, Ikeda N, Warnakulasuriya S, Fukano H, Yuasa H, Yano M, Miyazaki H, Ito Y. Serum antioxidant micronutrients and the risk of oral leukoplakia among Japanese. *Oral Oncol* 2000;36:466-470.
72. Nagata C, Shimizu H, Yoshikawa H, Noda K, Nozawa S, Yajima A, Sekiya S, Sugimori H, Hirai Y, Kanazawa K, Sugase M, Kawana T. Serum carotenoids and vitamins and risk of cervical dysplasia from a case-control study in Japan. *Br J Cancer* 1999;81:1234-1237.
73. Nair S, Norkus EP, Hertan H, Pitchumoni CS. Serum and colon mucosa micronutrient antioxidants: Differences between adenomatous polyp patients and controls. *Am J Gastroenterol* 2001;96:3400-3405.
74. Nierenberg DW, Dain BJ, Mott LA, Baron JA, Greenberg ER. Effects of 4 y of oral supplementation with beta-carotene on serum concentrations of retinol, tocopherol, and five carotenoids. *Am J Clin Nutr* 1997;66:315-319.
75. Nomura AM, Stemmermann GN, Lee J, Craft NE. Serum micronutrients and prostate cancer in Japanese Americans in Hawaii. *Cancer Epidemiol Biomarkers Prev* 1997;6:487-491.
76. Nomura AM, Ziegler RG, Stemmermann GN, Chyou PH, Craft NE. Serum micronutrients and upper aerodigestive tract cancer. *Cancer Epidemiol Biomarkers Prev* 1997;6:407-412.
77. Olmedilla B, Granado F, Southon S, Wright AJ, Blanco I, Gil-Martinez E, van den Berg H, Thurnham D, Corridan B, Chopra M, Hininger I. A European multicentre, placebo-controlled supplementation study with alpha-tocopherol, carotene-rich palm oil, lutein or lycopene: Analysis of serum responses. *Clin Sci* 2002;102:447-456.
78. Paetau I, Khachik F, Brown ED, Beecher GR, Kramer TR, Chittams J, Clevidence BA. Chronic ingestion of lycopene-rich tomato juice or lycopene supplements significantly increases plasma concentrations of lycopene and related tomato carotenoids in humans. *Am J Clin Nutr* 1998;68:1187-1195.
79. Paetau I, Rao D, Wiley ER, Brown ED, Clevidence BA. Carotenoids in human buccal mucosa cells after 4 wk of supplementation with tomato juice or lycopene supplements. *Am J Clin Nutr* 1999;70:490-494.
80. Palan PR, Chang CJ, Mikhail MS, Ho GY, Basu J, Romney SL. Plasma concentrations of micronutrients during a nine-month clinical trial of beta-carotene in women with precursor cervical cancer lesions. *Nutr Cancer* 1998;30:46-52.
81. Palan PR, Mikhail MS, Goldberg GL, Basu J, Runowicz CD, Romney SL. Plasma levels of beta-carotene, lycopene, canthaxanthin, retinol, and alpha- and tau-tocopherol in cervical intraepithelial neoplasia and cancer. *Clin Cancer Res* 1996;2:181-185.
82. Pappalardo G, Maiani G, Mobarhan S, Guadalaxara A, Azzini E, Raguzzini A, Salucci M, Serafini M, Trifero M, Illomei G, Ferro-Luzzi A. Plasma (carotenoids, retinol, alpha-tocopherol) and tissue (carotenoids) levels after supplementation with beta-carotene in subjects with precancerous and cancerous lesions of sigmoid colon. *Eur J Clin Nutr* 1997;51:661-666.
83. Peng Y-M, Peng Y-S, Childers JM, Hatch KD, Roe DJ, Lin Y, Lin P. Concentrations of carotenoids, tocopherols, and retinol in paired plasma and

cervical tissue of patients with cervical cancer, precancer, and noncancerous diseases. *Cancer Epidemiol Biomarkers Prev* 1998;7:347-350.
84. Peng Y-M, Peng Y-S, Lin Y, Moon T, Baier M. Micronutrient concentrations in paired skin and plasma of patients with actinic keratoses: Effect of prolonged retinol supplementation. *Cancer Epidemiol Biomarkers Prev* 1993;2:145-150.
85. Porrini M, Riso P. Lymphocyte lycopene concentration and DNA protection from oxidative damage is increased in women after a short period of tomato consumption. *J Nutr* 2000;130:189-192.
86. Potischman N, Byers T, Houghton L, Root M, Nemoto T, Campbell TC. Effects of breast cancer treatments on plasma nutrient levels: Implications for epidemiological studies. *Cancer Epidemiol Biomarkers Prev* 1992;1:555-559.
87. Potischman N, Herrero R, Brinton LA, Reeves WC, Stacewicz-Sapuntzakis M, Jones CJ, Brenes MM, Tenorio F, de Britton RC, Gaitan E. A case-control study of nutrient status and invasive cervical cancer. II. Serologic indicators. *Am J Epidemiol* 1991;134:1347-1355.
88. Potischman N, Hoover RN, Brinton LA, Swanson CA, Herrero R, Tenorio F, de Britton RC, Gaitan E, Reeves WC. The relations between cervical cancer and serological markers of nutritional status. *Nutr Cancer* 1994;21:193-201.
89. Rao AV, Agarwal S. Bioavailability and in vivo antioxidant properties of lycopene from tomato products and their possible role in the prevention of cancer. *Nutr Cancer* 1998;31:199-203.
90. Rao AV, Fleshner N, Agarwal S. Serum and tissue lycopene and biomarkers of oxidation in prostate cancer patients: A case-control study. *Nutr Cancer* 1999;33:159-164.
91. Richelle M, Bortlik K, Liardet S, Hager C, Lambelet P, Baur M, Applegate LA, Offord EA. A food-based formulation provides lycopene with the same bioavailability to humans as that from tomato paste. *J Nutr* 2002;132:404-408.
92. Rock CL, Flatt SW, Wright FA, Faerber S, Newman V, Kealey S, Pierce JP. Responsiveness of carotenoids to a high vegetable diet intervention designed to prevent breast cancer recurrence. *Cancer Epidemiol Biomarkers Prev* 1997;6:617-623.
93. Sasaki S, Tsubono Y, Okubo S, Hayashi M, Kakizoe T, Tsugane S. Effects of three-month oral supplementation of beta-carotene and vitamin C on serum concentrations of carotenoids and vitamins in middle-aged subjects: A pilot study for a randomized controlled trial to prevent gastric cancer in high-risk Japanese population. *Jpn J Cancer Res* 2000;91:464-470.
94. Sato R, Helzlsouer KJ, Alberg AJ, Hoffman SC, Norkus EP, Comstock GW. Prospective study of carotenoids, tocopherols, and retinoid concentrations and the risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2002;11:451-457.
95. Schiff MA, Patterson RE, Baumgartner RN, Masuk M, van Asselt-King L, Wheeler CM, Becker TM. Serum carotenoids and risk of cervical intraepithelial neoplasia in Southwestern American Indian women. *Cancer Epidemiol Biomarkers Prev* 2001;10:1219-1222.
96. Sedjo RL, Roe DJ, Abrahamsen M, Harris RB, Craft N, Baldwin S, Giuliano AR. Vitamin A, carotenoids, and risk of persistent oncogenic human papillomavirus infection. *Cancer Epidemiol Biomarkers Prev* 2002;11:876-884.

97. Simon MS, Djuric Z, Dunn B, Stephens D, Lababidi S, Heilbrun LK. An evaluation of plasma antioxidant levels and the risk of breast cancer: A pilot case control study. *Breast J* 2000;6:388-395.
98. Smith-Warner SA, Elmer PJ, Tharp TM, Fosdick L, Randall B, Gross M, Wood J, Potter JD. Increasing vegetable and fruit intake: Randomized intervention and monitoring in an at-risk population. *Cancer Epidemiol Biomarkers Prev* 2000;9:307-317.
99. Stryker WS, Stampfer MJ, Stein EA, Kaplan L, Louis TA, Sober A, Willett WC. Diet, plasma levels of beta-carotene and alpha-tocopherol, and risk of malignant melanoma. *Am J Epidemiol* 1990;131:597-611.
100. Sutherland WH, Walker RJ, De Jong SA, Upritchard JE. Supplementation with tomato juice increases plasma lycopene but does not alter susceptibility to oxidation of low-density lipoproteins from renal transplant recipients. *Clin Nephrol* 1999;52:30-36.
101. Toniolo P, Van Kappel AL, Akhmedkhanov A, Ferrari P, Kato I, Shore RE, Riboli E. Serum carotenoids and breast cancer. *Am J Epidemiol* 2001;153:1142-1147.
102. Trichopoulou A, Benetou V, Lagiou P, Gnardellis Ch, Stacewicz-Sapunzakis M, Papas A. Plasma carotenoid levels in relation to the Mediterranean diet in Greece. *Int J Vitam Nutr Res* 2003;73:221-225.
103. Tsubono Y, Tsugane S, Gey KF. Plasma antioxidant vitamins and carotenoids in five Japanese populations with varied mortality from gastric cancer. *Nutr Cancer* 1999;34:56-61.
104. Tsugane S, Tsuda M, Gey F, Watanabe S. Cross-sectional study with multiple measurements of biological markers for assessing stomach cancer risks at the population level. *Environ Health Perspect* 1992;98:207-210.
105. van Breemen RB, Xu X, Viana MA, Chen L, Stacewicz-Sapuntzakis M, Duncan C, Bowen PE, Sharifi R. Liquid chromatography-mass spectrometry of *cis*- and all-*trans*-lycopene in human serum and prostate tissue after dietary supplementation with tomato sauce. *J Agric Food Chem* 2002;50:2214-2219.
106. VanEenwyk J, Davis FG, Bowen PE. Dietary and serum carotenoids and cervical intraepithelial neoplasia. *Int J Cancer* 1991;48:34-38.
107. Vogt TM, Mayne ST, Graubard BI, Swanson CA, Sowell AL, Schoenberg JB, Swanson GM, Greenberg RS, Hoover RN, Hayes RB, Ziegler RG. Serum lycopene, other serum carotenoids, and risk of prostate cancer in US Blacks and Whites. *Am J Epidemiol* 2002;155:1023-1032.
108. Wahlqvist ML, Wattanapenpaiboon N, Macrae FA, Lambert JR, MacLennan R, Hsu-Hage BH. Changes in serum carotenoids in subjects with colorectal adenomas after 24 mo of beta-carotene supplementation. Australian Polyp Prevention Project Investigators. *Am J Clin Nutr* 1994;60:936-943.
109. Watzl B, Bub A, Blockhaus M, Herbert BM, Luhrmann PM, Neuhauser-Berthold M, Rechkemmer G. Prolonged tomato juice consumption has no effect on cell-mediated immunity of well-nourished elderly men and women. *J Nutr* 2000;130:1719-1723.

110. Watzl B, Bub A, Brandstetter BR, Rechkemmer G. Modulation of human T-lymphocyte functions by the consumption of carotenoid-rich vegetables. *Br J Nutr* 1999;82:383-389.
111. Wu K, Schwartz SJ, Platz EA, Clinton SK, Erdman JW Jr, Ferruzzi MG, Willett WC, Giovannucci EL. Variations in plasma lycopene and specific isomers over time in a cohort of U.S. men. *J Nutr* 2003;133:1930-1936.
112. Yeum K-J, Ahn SH, Rupp de Paiva SA, Lee-Kim YC, Krinsky NI, Russell RM. Correlation between carotenoid concentrations in serum and normal breast adipose tissue of women with benign breast tumor or breast cancer. *J Nutr* 1998;128:1920-1926.
113. Yu M-W, Chiu Y-H, Chiang Y-C, Chen C-H, Lee T-H, Santella RM, Chern H-D, Liaw Y-F, Chen C-J. Plasma carotenoids, glutathione *S*-transferase M1 and T1 genetic polymorphisms, and risk of hepatocellular carcinoma: independent and interactive effects. *Am J Epidemiol* 1999;149:621-629.
114. Gann PH, Ma J, Giovannucci E, Willett W, Sacks FM, Hennekens CH, Stampfer MJ. Lower prostate cancer risk in men with elevated plasma lycopene levels: Results of a prospective analysis. *Cancer Res* 1999;59:1225-1230.
115. Bowen P, Chen L, Stacewicz-Sapuntzakis M, Duncan C, Sharifi R, Ghosh L, Kim HS, Christov-Tzelkov K, van Breemen R. Tomato sauce supplementation and prostate cancer: Lycopene accumulation and modulation of biomarkers of carcinogenesis. *Exp Biol Med* 2002;227:886-893.
116. Burney PGJ, Comstock GW, Morris JS. Serologic precursors of cancer: Serum micronutrients and the subsequent risk of pancreatic cancer. *Am J Clin Nutr* 1989;49:895-900.
117. Dorgan JF, Sowell A, Swanson CA, Potischman N, Miller R, Schussler N, Stephenson HE Jr. Relationships of serum carotenoids, retinol, α-tocopherol, and selenium with breast cancer risk: Results from a prospective study in Columbia, Missouri (United States). *Cancer Causes Control* 1998;9:89-97.
118. London SJ, Stein EA, Henderson IC, Stampfer MJ, Wood WC, Remine S, Dmochowski JR, Robert NJ, Willett WC. Carotenoids, retinol, and vitamin E and risk of proliferative benign breast disease and breast cancer. *Cancer Causes Control* 1992;3:503-512.
119. Potischman N, McCulloch CE, Byers T, Nemoto T, Stubbe N, Milch R, Parker R, Rasmussen KM, Root M, Graham S, Campbell TC. Breast cancer and dietary and plasma concentrations of carotenoids and vitamin A. *Am J Clin Nutr* 1990;52:909-915.
120. Batieha AM, Armenian HK, Norkus EP, Morris JS, Spate VE, Comstock GW. Serum micronutrients and the subsequent risk of cervical cancer in a population-based nested case-control study. *Cancer Epidemiol Biomarkers Prev* 1993;2:335-339.
121. Sugerman SB, Mobarhan S, Bowen PE, Stacewicz-Sapuntzakis M, Langenberg P, Henderson C, Kiani R, Friedman H, Lucchesi D. Serum time curve characteristics of a fixed dose of β-carotene in young and old men. *J Am Coll Nutr* 1991;10:297-307.

122. Broekmans WM, Klopping-Ketelaars IA, Schuurman CR, Verhagen H, van den Berg H, Kok FJ, van Poppel G. Fruits and vegetables increase plasma carotenoids and vitamins and decrease homocysteine in humans. *J Nutr* 2000;130:1578-1583.
123. Broekmans WM, Klopping-Ketelaars IA, Weststrate JA, Tijburg LB, van Poppel G, Vink AA, Berendschot TT, Bots ML, Castenmiller WA, Kardinaal AF. Decreased carotenoid concentrations due to dietary sucrose polyesters do not affect possible markers of disease risk in humans. *J Nutr* 2003;133:720-726.
124. Bowen PE, Mobarhan S, Smith JC. Carotenoid absorption in humans. *Methods Enzymol* 1993;214:3-17.
125. Chopra M, O'Neill ME, Keogh N, Wortley G, Southon S, Thurnham DI. Influence of increased fruit and vegetable intake on plasma and lipoprotein carotenoids and LDL oxidation in smokers and nonsmokers. *Clin Chem* 2000;46:1818-1829.
126. Corridan BM, O'Donoghue M, Hughes DA, Morrissey PA. Low-dose supplementation with lycopene or beta-carotene does not enhance cell-mediated immunity in healthy free-living elderly humans. *Eur J Clin Nutr* 2001;55:627-635.
127. Johnson EJ, Qin J, Krinsky NI, Russell RM. Ingestion by men of a combined dose of beta-carotene and lycopene does not affect the absorption of beta-carotene but improves that of lycopene. *J Nutr* 1997;127:1833-1837.
128. Koonsvitsky BP, Berry DA, Jones MB, Lin PY, Cooper DA, Jones DY, Jackson JE. Olestra affects serum concentrations of alpha-tocopherol and carotenoids but not vitamin D or vitamin K status in free-living subjects. *J Nutr* 1997;127(8 Suppl.):1636S-1645S.
129. Martini MC, Campbell DR, Gross MD, Grandits GA, Potter JD, Slavin JL. Plasma carotenoids as biomarkers of vegetable intake: The University of Minnesota Cancer Prevention Research Unit Feeding Studies. *Cancer Epidemiol Biomarkers Prev* 1995;4:491-496.
130. Maruyama C, Imamura K, Oshima S, Suzukawa M, Egami S, Tonomoto M, Baba N, Harada M, Ayaori M, Inakuma T, Ishikawa T. Effects of tomato juice consumption on plasma and lipoprotein carotenoid concentrations and the susceptibility of low density lipoprotein to oxidative modification. *J Nutr Sci Vitaminol* 2001;47:213-221.
131. McEligot AJ, Rock CL, Shanks TG, Flatt SW, Newman V, Faerber S, Pierce JP. Comparison of serum carotenoid responses between women consuming vegetable juice and women consuming raw or cooked vegetables. *Cancer Epidemiol Biomarkers Prev* 1999;8:227-231.
132. Raeini-Sarjaz M, Ntanios FY, Vanstone CA, Jones PJ. No changes in serum fat-soluble vitamin and carotenoid concentrations with the intake of plant sterol/stanol esters in the context of a controlled diet. *Metabolism* 2002;51:652-656.
133. Scott KJ, Thurnham DI, Hart DJ, Bingham SA, Day K. The correlation between the intake of lutein, lycopene and beta-carotene from vegetables and fruits, and blood plasma concentrations in a group of women aged 50-65 years in the UK. *Br J Nutr* 1996;75:409-418.

134. Stahl W, Heinrich U, Wiseman S, Eichler O, Sies H, Tronnier H. Dietary tomato paste protects against ultraviolet light-induced erythema in humans. *J Nutr* 2001;131:1449-1451.
135. Thurmann PA, Steffen J, Zwernemann C, Aebischer CP, Cohn W, Wendt G, Schalch W. Plasma concentration response to drinks containing beta-carotene as carrot juice or formulated as a water dispersible powder. *Eur J Nutr* 2002;41:228-235.
136. Upritchard JE, Sutherland WH, Mann JI. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. *Diabetes Care* 2000;23:733-738.
137. van der Gaag MS, van den Berg R, van den Berg H, Schaafsma G, Hendriks HF. Moderate consumption of beer, red wine and spirits has counteracting effects on plasma antioxidants in middle-aged men. *Eur J Clin Nutr* 2000;54:586-591.
138. Wright AJ, Hughes DA, Bailey AL, Southon S. Beta-carotene and lycopene, but not lutein, supplementation changes the plasma fatty acid profile of healthy male non-smokers. *J Lab Clin Med* 1999;134:592-598.
139. Yeum K-J, Booth SL, Sadowski JA, Liu C, Tang G, Krinsky NI, Russell RM. Human plasma carotenoid response to the ingestion of controlled diets high in fruits and vegetables. *Am J Clin Nutr* 1996;64:594-602.
140. Coates RJ, Eley JW, Block G, Gunter EW, Sowell AL, Grossman C, Greenberg RS. An evaluation of a food frequency questionnaire for assessing dietary intake of specific carotenoids and vitamin E among low-income black women. *Am J Epidemiol* 1991;134:658-671.
141. Forman MR, Lanza E, Yong L-C, Holden JM, Graubard BI, Beecher GR, Melitz M, Brown ED, Smith JC. The correlation between two dietary assessments of carotenoid intake and plasma carotenoid concentrations: Application of a carotenoid food-composition database. *Am J Clin Nutr* 1993;58:519-524.
142. Campbell DR, Gross MD, Martini MC, Grandits GA, Slavin JL, Potter JD. Plasma carotenoids as biomarkers of vegetable and fruit intake. *Cancer Epidemiol Biomarkers Prev* 1994;3:493-500.
143. Peng Y-M, Peng Y-S, Lin Y, Moon T, Roe DJ, Ritenbaugh C. Concentrations and plasma-tissue diet relationships of carotenoids, retinoids, and tocopherols in humans. *Nutr Cancer* 1995;23:233-246.
144. Ritenbaugh C, Peng Y-M, Aickin M, Graver E, Branch M, Alberts DS. New carotenoid values for foods improve relationship of food frequency questionnaire intake estimates to plasma values. *Cancer Epidemiol Biomarkers Prev* 1996;5:907-912.
145. Brady WE, Mares-Perlman JA, Bowen P, Stacewicz-Sapuntzakis M. Human serum carotenoid concentrations are related to physiologic and lifestyle factors. *J Nutr* 1996;126:129-137.
146. Vandenlangenberg GM, Brady WE, Nebeling LC, Block G, Forman M, Bowen PE, Stacewicz-Sapuntzakis M, Mares-Perlman JA. Influence of using different sources of carotenoid data in epidemiologic studies. *J Am Diet Assoc* 1996;96:1271-1275.

147. Freeman VL, Meydani M, Yong S, Pyle J, Wan Y, Arvizu-Durazo R, Liao Y. Prostatic levels of tocopherols, carotenoids, and retinol in relation to plasma levels and self-reported usual dietary intake. *Am J Epidemiol* 2000;151:109-118.
148. Plat J, Mensink RP. Effects of diets enriched with two different plant stanol ester mixtures on plasma ubiquinol-10 and fat-soluble antioxidant concentrations. *Metabolism* 2001;50:520-529.
149. Food and Nutrition Board, Institute of Medicine, Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of DRIs, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids.* National Academy Press, Washington, DC, 2000, pp. 456-457.
150. Wei W, Kim Y, Boudreau N. Association of smoking with serum and dietary levels of antioxidants in adults: NHANES III, 1988-1994. *Am J Public Health* 2001;91:258-264.
151. Chug-Ahuja JK, Holden JM, Forman MR, Mangels AR, Beecher GR, Lanza E. The development and application of a carotenoid database for fruits, vegetables, and selected multicomponent foods. *J Am Diet Assoc* 1993;93:318-323.
152. Nebeling LC, Forman MR, Graubard BI, Snyder RA. Changes in carotenoid intake in the United States: The 1987 and 1992 National Health Interview Surveys. *J Am Diet Assoc* 1997;97:991-996.
153. Zhang S, Hunter DJ, Forman MR, Rosner BA, Speizer FE, Colditz GA, Manson JE, Hankinson SE, Willett WC. Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. *J Natl Cancer Inst* 1999;91:547-556.
154. Food and Nutrition Board, Institute of Medicine, Panel on Micronutrients, Subcommittees on Upper Reference Levels of Nutrients and of Interpretation and Use of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vandium and Zinc.* National Academy Press, Washington, DC, 2002, pp. 604-605.
155. Economic Research Service, United States Department of Agriculture. *Vegetables and Melons Outlook.* United States Department of Agriculture, Washington, DC, Publication VGC-297, June 20, 2003.
156. Sesso HD, Liu S, Gaziano JM, Buring JE. Dietary lycopene, tomato-based food products and cardiovascular disease in women. *J Nutr* 2003;133:2336-2341.
157. Rock CL, Swendseid ME, Jacob RA, McKee RW. Plasma carotenoid levels in human subjects fed a low carotenoid diet. *J Nutr* 1992;122:96-100.
158. Riso P, Pinder A, Santangelo A, Porrini M. Does tomato consumption effectively increase the resistance of lymphocyte DNA to oxidative damage? *Am J Clin Nutr* 1999;69:712-718.
159. American Cancer Society. *Cancer Facts and Figures 2003.* (51 pages) http://www.cancer.org.
160. Reznikoff CA, Bertram JS, Brankow DW, Heidelberger C. Quantitative and qualitative studies of chemical transformation of cloned C3H mouse embryo cells

sensitive to postconfluence inhibition of cell division. *Cancer Res* 1973;33:3239-3249.
161. Bertram JS, Pung A, Churley M, Kappock TJ 4D, Wilkins LR, Cooney RV. Diverse carotenoids protect against chemically induced neoplastic transformation. *Carcinogenesis* 1991;12:671-678.
162. Zhang L-X, Cooney RV, Bertram JS. Carotenoids up-regulate connexin 43 gene expression independent of their pro-vitamin A or antioxidant properties. *Cancer Res* 1992;52:5707-5712.
163. Zhang L-X, Cooney RV, Bertram JS. Carotenoids enhance gap junctional communication and inhibit lipid peroxidation in C3H/10T1/2 cells: Relationship to their cancer chemopreventive action. *Carcinogenesis* 1991;12:2109-2114.
164. Mehta P, Perez-Stable C, Nadji M, Mian M, Asotra K, Roos BA. Suppression of human prostate cancer cell growth by forced expression of connexin genes. *Develop Gene* 1999;24:91-110.
165. Livny O, Kaplan I, Reifen R, Polak-Charcon S, Madar Z, Schwartz B. Lycopene inhibits proliferation and enhances gap-junction communication of KB-1 human oral tumor cells. *J Nutr* 2002;132:3754-3759.
166. Stahl W, von Laar J, Martin HD, Emmerich T, Sies H. Stimulation of gap junctional communication: Comparison of acyclo-retinoic acid and lycopene. *Arch Biochem Biophys* 2000;373:271-274.
167. Bertram JS. Carotenoids and gene regulation. *Nutr Rev* 1999;57:182-191.
168. Hotz-Wagenblatt A, Shalloway D. Gap junctional communication and neoplastic transformation. *Cit Rev Oncogenesis* 1993;4:541-558.
169. Mehta PP, Bertram JS, Loewenstein WR. Growth inhibition of transformed cells correlates with their junctional communication with normal cells. *Cell* 1986;44:187-196.
170. Loewenstein WR. Junctional intercellular communication and the control of growth. *Biochim Biophys Acta* 1979;560:1-65.
171. Ames BN, Shigenaga MK, Gold LS. DNA lesions, inducible DNA repair, and cell division: Three key factors in mutagenesis and carcinogenesis. *Environ Health Perspect* 1993;101(Suppl.):35-44.
172. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990;61:759-767.
173. Wattenberg LW. Inhibition of carcinogenesis by minor dietary constituents. *Cancer Res* 1992;52(Suppl.):2085s-2091s.
174. Totter JR. Spontaneous cancer and its possible relationship to oxygen metabolism. *Proc Natl Acad Sci USA* 1980;77:1763-1767.
175. Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants and the degenerative diseases of aging. *Proc Natl Acad Sci USA* 1993;90:7915-7922.
176. Kasai H. Analysis of a form of oxidative DNA damage, 8-hydroxy-2'-deoxyguanosine, as a marker of cellular oxidative stress during carcinogenesis. *Mutat Res* 1997;387:146-163.
177. Wang D, Kreutzer DA, Essigmann JM. Mutagenicity and repair of oxidative DNA damage: Insights from studies using defined lesions. *Mutat Res* 1998;400:99-115.

178. Arashidani K, Iwamoto-Tanaka N, Muraoka M, Kasai H. Genotoxicity of ribo- and deoxyribonucleosides of 8-hydroxyguanine, 5-hydroxycytosine, and 2-hydroxyadenine. Induction of SCE in human lymphocytes and mutagenicity in *Salmonella typhimurium* TA100. *Mutat Res* 1998;403:223-227.
179. Fujikawa K, Kamiya H, Kasai H. The mutations induced by oxidatively damaged nucleotides, 5-formyl-dUTP and 5-hydroxy-dCTP, in *Escherichia coli*. *Nucleic Acids Res* 1998;26:4582-4587.
180. Halliwell B. Why and how should we measure oxidative DNA damage in nutritional studies? How far have we come? *Am J Clin Nutr* 2000;72:1082-1087.
181. Di Mascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. *Arch Biochem Biophys* 1989;274:532-538.
182. Sies H, Stahl W. Lycopene: Antioxidant and biological effects and its bioavailability in the human. *Proc Soc Exp Biol Med* 1998;218:121-124.
183. Pool-Zobel BL, Bub A, Muller H, Wollowski I, Rechkemmer G. Consumption of vegetables reduces genetic damage in humans: First results of a human intervention trial with carotenoid-rich foods. *Carcinogenesis* 1997;18:1847-1850.
184. Torbergsen AC, Collins AR. Recovery of human lymphocytes from oxidative DNA damage; the apparent enhancement of DNA repair by carotenoids is probably simply an antioxidant effect. *Eur J Nutr* 2000;39:80-85.
185. Rehman A, Bourne LC, Halliwell B, Rice-Evans CA. Tomato consumption modulates oxidative DNA damage in humans. *Biochem Biophys Res Commun* 1999;262:828-831.
186. Lavelli V, Peri C, Rissolo A. Antioxidant activity of tomato products as studied by model reactions using xanthine oxidase, myeloperoxidase, and copper-induced lipid peroxidation. *J Agric Food Chem* 2000;48:1442-1448.
187. Colditz GA, Branch LG, Lipnick RJ, Willett WC, Rosner B, Posner BM, Hennekens CH. Increased green and yellow vegetable intake and lowered cancer deaths in an elderly population. *Am J Clin Nutr* 1985;41:32-36.
188. Sakr WA. Prostatic intraepithelial neoplasia: A marker for high-risk groups and a potential target for chemoprevention. *Eur Urol* 1999;35:474-478.
189. Bostwick DG, Brawer MK. Prostate intra-epithelial neoplasia and early invasion in prostate cancer. *Cancer* 1987;59:788-794.
190. Bostwick DG, Pacelli A, Lopez Beltran A. Ultrastructure of prostatic intraepithelial neoplasia. *Prostate* 1997;33:32-37.
191. McNeal JE, Villers A, Redwine EA, Freiha FS, Stamey TA. Microcarcinoma in the prostate: Its association with duct-acinar dysplasia. *Hum Pathol* 1991;22:644-652.
192. Willis MS, Wians FH Jr. 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.
193. Pathak SK, Sharma RA, Mellon JK. Chemoprevention of prostate cancer by diet-derived antioxidant agents and hormonal manipulation (Review). *Int J Oncol* 2003;22:5-13.
194. Nelson PS, Montgomery B. Unconventional therapy for prostate cancer: Good, bad or questionable? *Nat Rev Cancer* 2003;3:845-858.

195. Malins DC, Polissar NL, Gunselman SJ. Models of DNA structure achieve almost perfect discrimination between normal prostate, benign prostatic hyperplasia (BPH), and adenocarcinoma and have a high potential for predicting BPH and prostate cancer. *Proc Natl Acad Sci USA* 1997;94:259-264.
196. Malins DC, Johnson PM, Wheeler TM, Barker EA, Polissar NL, Vinson MA. Age-related radical-induced DNA damage is linked to prostate cancer. *Cancer Res* 2001;61:6025-6028.
197. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: Biological actions. *Endocr Rev* 1995;16:3-34.
198. Cohen P, Peehl DM, Rosenfeld RG. The IGF axis in the prostate. *Hormone Metab Res* 1994;26:81-84.
199. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst* 2000;92:1472-1489.
200. Cohen P, Peehl DM, Lamson G, Rosenfeld RG. Insulin-like growth factors (IGFs), IGF receptors, and IGF-binding proteins in primary cultures of prostate epithelial cells. *J Clin Endocrinol Metab* 1991;73:401-407.
201. Pollak M, Beamer W, Zhang JC. Insulin-like growth factors and prostate cancer. *Cancer Met Rev* 1998-1999;17:383-390.
202. Cohen SM, Ellwein LB. Cell proliferation in carcinogenesis. *Science* 1990;249:1007-1011.
203. Butterworth BE, Goldsworthy TL. The role of cell proliferation in multistage carcinogenesis. *Proc Soc Exptl Biol Med* 1991;198:683-687.
204. Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, Hennekens CH, Pollak M. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* 1998;279:563-566.
205. Mantzoros CS, Tzonou A, Signorello LB, Stampfer M, Trichopoulos D, Adami HO. Insulin-like growth factor-1 in relation to prostate cancer and benign prostatic hyperplasia. *Br J Cancer* 1997;76:1115-1118.
206. Wolk A, Mantzoros CS, Andersson SO, Bergstrom R, Signorello LB, Lagiou P, Adami HO, Trichopoulos D. Insulin-like growth factor-1 and prostate cancer risk: A population-based, case-control study. *J Natl Cancer Inst* 1998;90:911-915.
207. Kim L, Rao AV, Rao LG. Effect of lycopene on prostate LNCaP cancer cells in culture. *J Med Food* 2002;5:181-187.
208. Kotake-Nara E, Kushiro M, Zhang H, Sugawara T, Miyashita K, Nagao A. Carotenoids affect proliferation of human prostate cancer cells. *J Nutr* 2001;131:3303-3306.
209. Pastori M, Pfander H, Boscoboinik D, Azzi A. Lycopene in association with alpha-tocopherol inhibits at physiological concentrations proliferation of prostate carcinoma cells. *Biochem Biophys Res Commun* 1998;250:582-585.
210. Kucuk O, Sarkar FH, Djuric Z, Sakr W, Pollak MN, Khachik F, Banerjee M, Bertram JS, Wood DP Jr. Effects of lycopene supplementation in patients with localized prostate cancer. *Exp Biol Med* 2002;227:881-885.
211. Van Breemen RB, Xu X, Viana MA, Chen L, Stacewicz-Sapuntzakis M, Duncan C, Bowen PE, Sharifi R. Liquid chromatography-mass spectrometry of *cis*- and

all-*trans*-lycopene in human serum and prostate tissue after dietary supplementation with tomato sauce. *J Agric Food Chem* 2002;50:2214-2219.
212. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. *J Natl Cancer Inst* 1995;87:1767-1776.
213. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. *J Natl Cancer Inst* 2002;94:391-398.
214. Mills PK, Beeson WL, Phillips RL, Fraser GE. Positive associations between dietary intake of lycopene and prostate cancer. Cohort study of diet, lifestyle, and prostate cancer in Adventist men. *Cancer* 1989;64:598-604.
215. Cerhan J, Chiu B, Putnam S, Parker A, Robbins M, Lynch C, Cantor K, Torner J, Wallace R. A cohort study of diet and prostate cancer risk (abstract). *Cancer Epidemiol Biomarkers Prev* 1998;7:175.
216. Grant WB. An ecologic study of dietary links to prostate cancer. *Altern Med Rev* 1999;4:162-169.
217. Miller EC, Giovannucci E, Erdman JW Jr, Bahnson R, Schwartz SJ, Clinton SK. Tomato products, lycopene, and prostate cancer risk. *Urol Clin North Am* 2002;29:83-93.
218. 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.
219. Jain MG, Hislop GT, Howe GR, Ghadirian P. Plant foods, antioxidants, and prostate cancer risk: Findings from case-control studies in Canada. *Nutr Cancer* 1999;34:173-184.
220. van Gils CH, Bostick RM, Stern MC, Taylor JA. Differences in base excision repair capacity may modulate the effect of dietary antioxidant intake on prostate cancer risk: an example of polymorphisms in the XRCC1 gene. *Cancer Epidemiol Biomarkers Prev* 2002;11:1279-1284.
221. Fleshner N, Agarwal S, Rao V. Serum and tissue lycopene and biomarkers of oxidation in prostate cancer patients: A case control study (abstract). *Prostate Cancer Prostatic Dis* 2000;3(Suppl. 1):S13.
222. Mucci LA, Tamimi R, Lagiou P, Trichopoulou A, Benetou V, Spanos E, Trichopoulos D. Are dietary influences on the risk of prostate cancer mediated through the insulin-like growth factor system? *BJU Int* 2001;87:814-820.
223. Matlaga BR, Hall MC, Stindt D, Torti FM. Response of hormone refractory prostate cancer to lycopene. *J Urol* 2001;166:613.
224. Key TJ, Silcocks PB, Davey GK, Appleby PN, Bishop DT. A case-control study of diet and prostate cancer. *Br J Cancer* 1997;76:678-687.
225. Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. *J Natl Cancer Inst* 2000;92:61-68.
226. 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 risks for prostate cancer among blacks and whites in the United States. *Cancer Epidemiol Biomarkers Prev* 1999;8:25-34.

227. Schuurman AG, Goldbohm RA, Brants HA, van den Brandt PA. A prospective cohort study on intake of retinol, vitamins C and E, and carotenoids and prostate cancer risk (Netherlands). *Cancer Causes Control* 2002;13:573-582.
228. Norrish AE, Jackson RT, Sharpe SJ, Skeaff CM. Prostate cancer and dietary carotenoids. *Am J Epidemiol* 2000;151:119-123.
229. Schuurman AG, Goldbohm RA, Dorant E, van den Brandt PA. Vegetable and fruit consumption and prostate cancer risk: A cohort study in the Netherlands. *Cancer Epidemiol Biomarkers Prev* 1998;7:673-680.
230. Kolonel LN, Hankin JH, Whittemore AS, Wu AH, Gallagher RP, Wilkens LR, John EM, Howe GR, Dreon DM, West DW, Paffenbarger RS Jr. Vegetables, fruits, legumes and prostate cancer: A multi-ethnic case-control study. *Cancer Epidemiol Biomarkers Prev* 2000;9:795-804.
231. Le Marchand L, Hankin JH, Kolonel LN, Wilkens LR. Vegetable and fruit consumption in relation to prostate cancer risk in Hawaii: a reevaluation of the effect of dietary beta-carotene. *Am J Epidemiol* 1991;133:215-219.
232. Meyer F, Bairati I, Fradet Y, Moore L. Dietary energy and nutrients in relation to preclinical prostate cancer. *Nutr Cancer* 1997;29:120-126.
233. Hsing AW, Comstock GW, Abbey H, Polk BF. Serologic precursors of cancer. Retinol, carotenoids, and tocopherol and risk of prostate cancer. *J Natl Cancer Inst* 1990;82:941-946.
234. Comstock GW, Helzlsouer KJ, Bush TL. Prediagnostic serum levels of carotenoids and vitamin E as related to subsequent cancer in Washington County, Maryland. *Am J Clin Nutr* 1991;53(Suppl.):260S-264S.
235. Pohar KS, Gong MC, Bahnson R, Miller EC, Clinton SK. Tomatoes, lycopene and prostate cancer: A clinician's guide for counseling those at risk for prostate cancer. *World J Urol* 2003;21:9-14.
236. Arab L, Steck-Scott S, Bowen P. Participation of lycopene and beta-carotene in carcinogenesis: defenders, aggressors, or passive bystanders? *Epidemiol Rev* 2001;23:211-230.
237. Arab L, Steck-Scott S, Fleishauer AT. Lycopene and the lung. *Exp Biol Med* 2002;227:894-899.
238. Samet JM, Hatch GE, Horstman D, Steck-Scott S, Arab L, Bromberg PA, Levine M, McDonnell W, Devlin RB. Effect of antioxidant supplementation on ozone-induced lung injury in human subjects. *Am J Respir Crit Care Med* 2001;164:819-825.
239. Steck SE, Madden M, Samet J, Arab L. The prevention of ozone-induced DNA damage in human lung epithelial cells by dietary antioxidants (abstract). *FASEB J* 2000;14:4.
240. Steck SE, Samet J, Craft N, Kohlmeier L. Correlation between lung macrophage and plasma carotenoid levels in humans (abstract). *FASEB J* 1999;13:14.
241. Giovanucci E. Insulin-like growth factor-1 and binding protein-3 and risk of cancer. *Horm Res* 1999;51(Suppl. 3):34-41.
242. Levy J, Bosin E, Feldman B, Giat Y, Miinster A, Danilenko M, Sharoni Y. Lycopene is a more potent inhibitor of human cancer cell proliferation than either alpha-carotene or beta-carotene. *Nutr Cancer* 1995;24:257-266.

243. Liu C, Lian F, Smith DE, Russell RM, Wang XD. Lycopene supplementation inhibits lung squamous metaplasia and induces apoptosis via up-regulating insulin-like growth factor-binding protein 3 in cigarette smoke-exposed ferrets. *Cancer Res* 2003;63:3138-3144.
244. Kim DJ, Takasuka N, Kim JM, Sekine K, Ota T, Asamoto M, Murakoshi M, Nishino H, Nir Z, Tsuda H. Chemoprevention by lycopene of mouse lung neoplasia after combined initiation treatment with DEN, MNU and DMH. *Cancer Lett* 1997;120:15-22.
245. Holick CN, Michaud DS, Stolzenberg-Solomon R, Mayne ST, Pietinen P, Taylor PR, Virtamo J, Albanes D. Dietary carotenoids, serum beta-carotene, and retinol and risk of lung cancer in the alpha-tocopherol, beta-carotene cohort study. *Am J Epidemiol* 2002;156:536-547.
246. Michaud DS, Feskanich D, Rimm EB, Colditz GA, Speizer FE, Willett WC, Giovannucci E. Intake of specific carotenoids and risk of lung cancer in 2 prospective US cohorts. *Am J Clin Nutr* 2000;72:990-997.
247. Goodman MT, Kolonel LN, Wilkins LR, Yoshizawa CN, Le Marchand L, Hankin JH. Dietary factors in lung cancer prognosis. *Eur J Cancer* 1992;28:495-501.
248. Le Marchand, L, Yoshizawa CN, Kolonel LN, Hankin JH, Goodman MT. Vegetable consumption and lung cancer risk: A population-based case-control study in Hawaii. *J Natl Cancer Inst* 1989;81:1158-1164.
249. Brennan P, Fortes C, Butler J, Agudo A, Benhamou S, Darby S, Gerken M, Jockel K-H, Kreuzer M, Mallone S, Nyberg F, Pohlabein H, Ferro G, Boffetta P. A multi-center case-control study of diet and lung cancer among non-smokers. *Cancer Causes Control* 2000;11:49-58.
250. Agudo A, Esteve MG, Pallares C, Martinez-Ballarin I, Fabregat X, Malats N, Machengs I, Badia A, Gonzalez CA. Vegetable and fruit intake and the risk of lung cancer in women in Barcelona. *Spain Eur J Cancer* 1997;33:1256-1261.
251. Forman MR, Yao SX, Graubard BI, Qiao YL, McAdams M, Mao BL, Taylor PR. The effect of dietary intake of fruits and vegetables on the odds ratio of lung cancer among Yunnan tin miners. *Int J Epidemiol* 1992;21:437-441.
252. Li Y, Elie M, Blaner WS, Brandt-Rauf P, Ford J. Lycopene, smoking and lung cancer (abstract). *Proc Am Assoc Cancer Res* 1997;38:A758.
253. Le Marchand, L, Hankin JH, Kolonel LN, Beecher GR, Wilkens LR, Zhao LP. Intake of specific carotenoids and lung cancer risk. *Cancer Epidemiol Biomarkers Prev* 1993;2:183-187.
254. Voorrips LE, Goldbohm RA, Brants HA, van Poppel GA, Sturmans F, Hermus RJ, van den Brandt PA. A prospective cohort study on antioxidant and folate intake and male lung cancer risk. *Cancer Epidemiol Biomarkers Prev* 2000;9:357-365.
255. Knect P, Jarvinen R, Teppo L, Aromaa A, Seppanen R. Role of various carotenoids in lung cancer prevention. *J Natl Cancer Inst* 1999;91:182-184.
256. Kvale, G, Bjelke E, Gart JJ. Dietary habits and lung cancer risk. *Int J Cancer* 1983;31:397-405.
257. Speizer FE, Colditz GA, Hunter DJ, Rosner B, Hennekens C. Prospective study of smoking, antioxidant intake, and lung cancer in middle-aged women (USA). *Cancer Causes Control* 1999;10:475-482.

258. Fraser GE, Beeson L, Phillips RL. Diet and lung cancer in California Seventh-Day Adventists. *Am J Epidemiol* 1991;133:683-693.
259. Garcia-Closas R, Agudo A, Gonzalez CA, Riboli E. Intake of specific carotenoids and flavonoids and the risk of lung cancer in women in Barcelona, Spain. *Nutr Cancer* 1998;32:154-158.
260. de Stefani E, Boffetta P, Deneo-Pellegrini H, Mendilaharsu M, Carzoglio JC, Ronco A, Olivera L. Dietary antioxidants and lung cancer risk: A case-control study in Uruguay. *Nutr Cancer* 1999;34:100-110.
261. Knekt P, Jarvinen R, Seppanen R, Rissanen A, Aromaa A, Heinonen OP, Albanes D, Heinonen M, Pukkala E, Teppo L. Dietary antioxidants and the risk of lung cancer. *Am J Epidemiol* 1991;134:471-479.
262. Harris RW, Key TJ, Silcocks PB, Bull D, Wald NJ. A case-control study of dietary carotene in men with lung cancer and in men with other epithelial cancers. *Nutr Cancer* 1991;15:63-68.
263. Swanson CA, Mao BL, Li JY, Lubin JH, Yao SX, Wang JZ, Cai SK, Hou Y, Luo QS, Blot WJ. Dietary determinants of lung cancer risk: Results from a case-control study in Yunnan Province. *China Int J Cancer* 1992;50:876-880.
264. Steinmetz KA, Potter JD, Folsom AR. Vegetables, fruit, and lung cancer in the Iowa Women's Health Study. *Cancer Res* 1993;53:536-543.
265. Axelsson G, Liljeqvist T, Andersson L, Bergman B, Rylander R. Dietary factors and lung cancer among men in west Sweden. *Int J Epidemiol* 1996;25:32-39.
266. Mayne ST, Janerich DT, Greenwald P, Chorost S, Tucci C, Zaman MB, Melamed MR, Kiely M, McKneally MF. Dietary β–carotene and lung cancer risk in U.S. nonsmokers. *J Natl Cancer Inst* 1994;86:33-38.
267. Candelora EC, Stockwell HG, Armstrong AW, Pinkham PA. Dietary intake and risk of lung cancer in women who never smoked. *Nutr Cancer* 1992;17:263-270.
268. Bond GG, Thompson FE, Cook RR. Dietary vitamin A and lung cancer: Results of a case-control study among chemical workers. *Nutr Cancer* 1987;9:109-121.
269. Rohan TE, Jain M, Howe GR, Miller AB. A cohort study of dietary carotenoids and lung cancer risk in women (Canada). *Cancer Causes Control* 2002;13:231-237.
270. Ziegler RG, Colavito EA, Hartge P, McAdams MJ, Schoenberg JB, Mason TJ, Fraumeni JF Jr. Importance of α–carotene, β-carotene and other phytochemicals in the etiology of lung cancer. *J Natl Cancer Inst* 1996;81:612-614.
271. Sankaranarayanan R, Varghese C, Duffy SE, Padmakumary G, Day NE, Nair MK. A case-control study of diet and lung cancer in Kerala, south India. *Int J Cancer* 1994;58:644-649.
272. 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.
273. Gordon JI, Schmidt GH, Roth KA. Studies of intestinal stem cells using normal, chimeric and transgenic mice. *FASEB J* 1992;6:3039-3050.
274. 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.

275. 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.
276. 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.
277. 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.
278. 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.
279. Arends MJ, Wyllie AH. Apoptosis: Mechanisms and roles in pathology. *Int Rev Exp Pathol* 1991;32:223-254.
280. Patel T, Gores GJ, Kaufmann SH. The role of proteases during apoptosis. *FASEB J* 1996;10:587-597.
281. Arends MJ, Morris RG, Wyllie AH. Apoptosis: The role of the endonuclease. *Am J Pathol* 1990;136:593-608.
282. Raff M. Cell suicide for beginners. *Nature* 1998;396:119-122.
283. Richter C. Pro-oxidants and mitochondrial Ca^{2+}: Their relationship to apoptosis and oncogenesis. *FEBS Lett* 1993;325:104-107.
284. 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.
285. Zamzami N, Kroemer G. The mitochondrion in apoptosis: How Pandora's box opens. *Nat Rev Mol Cell Biol* 2001;2:67-71.
286. Krishnan K, Brenner DE. Chemoprevention of colorectal cancer. *Gastroenterol Clin North Am* 1996;25:821-858.
287. Sporn MB. Approaches to prevention of epithelial cancer during the preneoplastic period. *Cancer Res* 1976;36:2699-2702.
288. Gwyn K, Sinicrope FA. Chemoprevention of colorectal cancer. *Am J Gastroenterol* 2002;97:13-21.
289. 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.
290. 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.
291. 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.

292. 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.
293. 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.
294. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell* 1996;87:159-170.
295. Potter JD. Colorectal cancer: Molecules and populations. *J Natl Cancer Inst* 1999;91:916-932.
296. Houlston RS. What we could do now: Molecular pathology of colorectal cancer. *J Clin Pathol Mol Pathol* 2001;54:206-214.
297. 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.
298. 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.
299. 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.
300. 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.
301. Wargovich MJ, Eng VWS, Newmark HL, Bruce WR. Calcium ameliorates the toxic effect of deoxycholic acid on colonic epithelium. *Carcinogenesis* 1983;4:1205-1207.
302. 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.
303. McLellan EA, Bird RP. Aberrant crypts: Potential preneoplastic lesions in the murine colon. *Cancer Res* 1988;48:6187-6192.
304. 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.
305. Correa P. Epidemiology of polyps and cancer. *Major Prob Pathol* 1978;10:126-152.
306. Hill MJ. Etiology of the adenoma-carcinoma sequence. *Major Prob Pathol* 1978;10:153-162.
307. 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.
308. 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.

309. 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.
310. 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.
311. 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.
312. 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.
313. 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.
314. Bird RP. Role of aberrant crypt foci in understanding the pathogenesis of colon cancer. *Cancer Lett* 1995;93:55-71.
315. Pretlow TP, O'Riordan MA, Pretlow TG, Stellato TA. Aberrant crypts in human colon mucosa: Putative preneoplastic lesions. *J Cell Biochem* 1992;(Suppl. 16G):55-62.
316. 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.
317. 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.
318. 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.
319. 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.
320. 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.
321. 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.
322. 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.
323. Barthold SW, Beck D. Modification of early dimethylhydrazine carcinogenesis by colonic mucosa hyperplasia. *Cancer Res* 1980;40:4451-4455.
324. Pence BC, Buddingh F. Inhibition of dietary fat-promoted colon carcinogenesis in rats by supplemental calcium or vitamin D3. *Carcinogenesis* 1988;9:187-190.

325. Moorghen M, Ince P, Finney KJ, Sunter JP, Appleton D, Watson AJ. A protective effect of sulindac against chemically-induced primary colonic tumors in mice. *J Pathol* 1988;156:341.
326. 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.
327. Ahnen J. Are animal models of colon cancer relevant to human diseases? *Dig Dis Sci* 1985;30:103S-106S.
328. Chang WWL. Histogenesis of colon cancer in experimental animals. *Scand J Gastroenterol* 1984;19(Suppl. 104):27-43.
329. 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.
330. 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.
331. 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.
332. 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.
333. 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.
334. 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.
335. Appleton GV, Davies PW, Bristol JB, Williamson RC. Inhibition of intestinal carcinogenesis by dietary supplementation with calcium. *Br J Surg.* 1987;74:523-525.
336. 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.
337. 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.
338. 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.
339. 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.

340. 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.
341. 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.
342. 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.
343. 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.
344. Boland CR. The biology of colorectal cancer: Implications for pretreatment and follow-up management. *Cancer* 1993;71:4180-4186.
345. Fearon ER. Molecular genetic studies of the adenoma-carcinoma sequence. *Adv Intern Med* 1994;39:123-147.
346. Rustgi AK. Molecular genetics and colorectal cancer. *Gastroenterology* 1993;104:1223-1225.
347. 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.
348. Eshleman JR, Markowitz SD. Microsatellite instability in inherited and sporadic neoplasms. *Curr Opin Oncol* 1995;7:83-89.
349. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. *Science* 1993;260:816-819.
350. 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.
351. Liu B, Nicolaides NC, Markowitz S, Willson JK, Parsons RE, Jen J, Papadopolous N, Peltomaki P, de la Chapelle A, Hamilton SR. Mismatch repair gene defects in sporadic colorectal cancers with microsatellite instability. *Nature Genet* 1995;9:48-55.
352. 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.
353. Marra G, Boland CR. Hereditary nonpolyposis colorectal cancer: The syndrome, the genes, and historical perspectives. *J Natl Cancer Inst* 1995;87:1114-1125.
354. 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.
355. Bronner CE, Baker SM, Morrison PT, Warren G, Smith LG, Lescoe MK, Kane M, Earabino C, Lipford J, Lindblom A. Mutation in the DNA mismatch repair

gene homologue hMLH1 is associated with hereditary non-polyposis colon cancer. *Nature* 1994;368:258-261.
356. Fishel R, Lescoe MK, Rao MR, Copeland NG, Jenkins NA, Garber J, Kane M, Kolodner R. Human mutator gene homologue (hMSH-2) and its association with hereditary non-polyposis colon cancer. *Cell* 1993;75:1027-1038.
357. 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.
358. 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.
359. Ames BN, Gold LS, Willett WC. The causes and prevention of cancer. *PNAS USA* 1995;92:5258-5265.
360. Lipkin M, Blattner WE, Fraumeni JF Jr, Lynch HT, Deschner E, Winawer S. Tritiated thymidine ($ø_p$, $ø_h$) labeling distribution as a marker for hereditary predisposition to colon cancer. *Cancer Res* 1983;43:1899-1904.
361. 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.
362. 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.
363. 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.
364. Palmieri GMA. Dietary calcium and colonic cancer (letter). *N Engl J Med* 1986;314:1388.
365. 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.
366. Bleiberg H, Buyse M, Galand P. Cell kinetic indicators of premalignant stages of colorectal cancer. *Cancer* 1985;56:124-129.
367. 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.
368. 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.
369. 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.

370. 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.
371. 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.
372. 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.
373. 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.
374. 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.
375. 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.
376. 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.
377. 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.
378. 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.
379. 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.
380. Riddell RH. Dysplasia and cancer in ulcerative colitis: A soluble problem? *Scand J Gastroenterol* 1984;19 (Suppl. 104):137-149.
381. 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.
382. 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.
383. Deschner EE, Winawer SJ, Katz S, Katzka I, Kahn E. Proliferation defects in ulcerative colitis patients. *Cancer Invest* 1983;1:41-47.

384. 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.
385. 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.
386. 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.
387. 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.
388. 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.
389. 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.
390. 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.
391. 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.
392. 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.
393. 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.
394. 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.
395. Wargovich MJ. Phytic acid, a major calcium chelator from fiber-rich cereals stimulates colonic cellular proliferation (abstract). *Gastroenterology* 1986;90:1684.
396. 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.

397. 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.
398. 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.
399. Lamprecht SA, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin D and folate: Molecular mechanisms. *Nat Rev Cancer* 2003;3:601-614.
400. Mure K, Rossman TG. Reduction of spontaneous mutagenesis in mismatch repair-deficient and proficient cells by dietary antioxidants. *Mutat Res* 2001;480-481:85-95.
401. Kim JM, Araki S, Kim DJ, Park CB, Takasuka N, Baba-Toriyama H, Ota T, Nir Z, Khachik F, Shimidzu N, Tanaka Y, Osawa T, Uraji T, Murakoshi M, Nishino H, Tsuda H. Chemopreventive effects of carotenoids and curcumins on mouse colon carcinogenesis after 1,2-dimethylhydrazine initiation. *Carcinogenesis* 1998;19:81-85.
402. Sengupta A, Ghosh S, Das S. Tomato and garlic can modulate azoxymethane-induced colon carcinogenesis in rats. *Eur J Cancer Prev* 2003;12:195-200.
403. Narisawa T, Fukaura Y, Hasebe M, Nomura S, Oshima S, Sakamoto H, Inakuma T, Ishiguro Y, Takayasu J, Nishino H. Prevention of N-methylnitrosourea-induced colon carcinogenesis in F344 rats by lycopene and tomato juice rich in lycopene. *Jpn J Cancer Res* 1998;89:1003-1008.
404. Narisawa T, Fukaura Y, Hasebe M, Ito M, Aizawa R, Murakoshi M, Uemura S, Khachik F, Nishino H. Inhibitory effects of natural carotenoids, alpha-carotene, beta-carotene, lycopene and lutein, on colonic aberrant crypt foci formation in rats. *Cancer Lett* 1996;107:137-142.
405. Hu J, Liu Y, Yu Y, Zhao T, Liu S, Wang Q. Diet and cancer of the colon and rectum: A case-control study in China. *Int J Epidemiol* 1991;20:362-367.
406. Francheschi S, Bidoli E, La Vecchia C, Talamini R, D'Avanzo B, Negri E. Tomatoes and risk of digestive-tract cancers. *Int J Cancer* 1994;59:181-184.
407. Francheschi S, Favero A, La Vecchia C, Negri E, Conti E, Montella M, Giacosa A, Nanni O, Decarli A. Food groups and risk of colorectal cancer in Italy. *Int J Cancer* 1997;72:56-61.
408. Modan B, Cuckle H, Lubin F. A note on the role of dietary retinol and carotene in human gastro-intestinal cancer. *Int J Cancer.* 1981;28:421-424.
409. Nair PP, Lohani A, Norkus EP, Feagins H, Bhagavan HN. Uptake and distribution of carotenoids, retinol, and tocopherols in human colonic epithelial cells in vivo. *Cancer Epidemiol Biomarkers Prev* 1996;5:913-916.
410. Malila N, Virtamo J, Virtanen M, Pietinen P, Albanes D, Teppo L. Dietary and serum α-tocopherol, β-carotene and retinol, and risk for colorectal cancer in male smokers. *Eur J Clin Nutr* 2002;56:615-621.
411. Tuyns AJ, Kaaks R, Haelterman. Colorectal cancer and the consumption of foods: A case control study in Belgium. *Nutr Cancer* 1988;11:189-204.
412. Tajima K, Tominaga S. Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Jpn J Cancer Res* 1985;76:705-716.

413. Enger SM, Longnecker MP, Chen MJ, Harper JM, Lee ER, Frankl HD, Haile RW. Dietary intake of specific carotenoids and vitamins A, C, and E, and prevalence of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* 1996;5:147-153.
414. 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.
415. Slattery ML, Benson J, Curtin K, Ma KN, Schaeffer D, Potter JD. Carotenoids and colon cancer. *Am J Clin Nutr* 2000;71:575-582.
416. Terry P, Jain M, Miller AB, Howe GR, Rohan TE. Dietary carotenoid intake and colorectal cancer risk. *Nutr Cancer* 2002;42:167-172.
417. 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.
418. Lauren P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal type carcinoma. *Acta Path Microbiol Scand* 1965;64:31-49.
419. Correa P. A human model of gastric carcinogenesis. *Cancer Res* 1988;48:3554-3560.
420. Yuasa Y. Control of gut differentiation and intestinal-type gastric carcinogenesis. *Nat Rev Cancer* 2003;3:592-600.
421. Mirvish SS. The etiology of gastric cancer: intragastric nitrosamide formation and other theories. *J Natl Cancer Inst* 1983;71:629-647.
422. Forman D. Dietary exposure to *N*-nitroso compounds and the risk of human cancer. *Cancer Surv* 1987;6:719-739.
423. Atanasova-Goranova VK, Dimova PI, Pevicharova GT. Effect of food products on endogenous generation of *N*-nitrosamines in rats. *Br J Nutr* 1997;78:335-345.
424. Velmurugan B, Bhuvaneswari V, Burra UK, Nagini S. Prevention of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine and saturated sodium chloride-induced gastric carcinogenesis in Wistar rats by lycopene. *Eur J Cancer Prev* 2002;11:19-26.
425. Velmurugan B, Bhuvaneswari V, Nagini S. Antiperoxidative effects of lycopene during *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine-induced gastric carcinogenesis. *Fitoterapia* 2002;73:604-611.
426. Boeing H, Jedrychowski W, Wahrendorf J, Popiela T, Tobiasz-Adamczyk B, Kulig A. Dietary risk factors in intestinal and diffuse types of stomach cancer: A multicenter case-control study in Poland. *Cancer Causes Control* 1991;2:227-233.
427. Haenszel W, Kurihara M, Segi M, Lee RK. Stomach cancer among Japanese in Hawaii. *J Natl Cancer Inst* 1972;49:969-988.
428. Correa P, Fontham E, Pickle LW, Chen V, Lin YP, Haenszel W. Dietary determinants of gastric cancer in south Louisiana inhabitants. *J Natl Cancer Inst* 1985;75:645-654.
429. Hansson LE, Nyren O, Bergstrom R, Wolk A, Lindgren A, Baron J, Adami HO. Diet and risk of gastric cancer. A population-based case-control study in Sweden. *Int J Cancer* 1993;55:181-189.

430. De Stefani E, Boffetta P, Brennan P, Deneo-Pellegrini H, Carzoglio JC, Ronco A, Mendilaharsu M. Dietary carotenoids and risk of gastric cancer: A case-control study in Uruguay. *Eur J Cancer Prev* 2000;9:329-334.
431. Botterweck AA, van den Brandt PA, Goldbohm RA. Vitamins, carotenoids, dietary fiber, and the risk of gastric carcinoma: Results from a prospective study after 6.3 years of follow-up. *Cancer* 2000;88:737-748.
432. Garcia-Closas R, Gonzalez CA, Agudo A, Riboli E. Intake of specific carotenoids and flavonoids and the risk of gastric cancer in Spain. *Cancer Causes Control* 1999;10:71-75.
433. Gonzalez CA, Sanz JM, Marcos G, Pita S, Brullet E, Saigi E, Badia A, Riboli E. Dietary factors and stomach cancer in Spain: A multi-centre case-control study. *Int J Cancer* 1991;49:513-519.
434. La Vecchia C, Negri E, Decarli A, D'Avanzo B, Franceschi S. A case-control study of diet and gastric cancer in northern Italy. *Int J Cancer* 1987;40:484-489.
435. Ramon JM, Serra L, Cerdo C, Oromi J. Dietary factors and gastric cancer risk. A case-control study in Spain. *Cancer* 1993;71:1731-1735.
436. Tuyns AJ, Kaaks R, Haelterman M, Riboli E. Diet and gastric cancer. A case-control study in Belgium. *Int J Cancer* 1992;51:1-6.
437. Nakhlis F, Morrow M. Ductal carcinoma in situ. *Surg Clin North Am* 2003;83:821-839.
438. Adamovich TL, Simmons RM. Ductal carcinoma in situ with microinvasion. *Am J Surg* 2003;186:112-116.
439. 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.
440. Willett W. The search for the causes of breast and colon cancer. *Nature* 1989;338:389-394.
441. Singletary SE. Rating the risk factors for breast cancer. *Ann Surg* 2003;237:474-482.
442. 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.
443. Papa V, Gliozzo B, Clark GM, McGuire WL, Moore D, Fujita-Yamaguchi Y, Vigneri R, Goldfine ID, Pezzino V. Insulin-like growth factor-I receptors are overexpressed and predict a low risk in human breast cancer. *Cancer Res* 1993;53:3736-3740.
444. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M. Circulating concentrations of insulin-like growth factor I and risk of breast cancer. *Lancet* 1998;351:1393-1396.
445. Karas M, Amir H, Fishman D, Danilenko M, Segal S, Nahum A, Koifmann A, Giat Y, Levy J, Sharoni Y. Lycopene interferes with cell cycle progression and insulin-like growth factor I signaling in mammary cancer cells. *Nutr Cancer* 2000;36:101-111.

446. Nahum A, Hirsch K, Danilenko M, Watts CK, Prall OW, Levy J, Sharoni Y. Lycopene inhibition of cell cycle progression in breast and endometrial cancer cells is associated with reduction in cyclin D levels and retention of p27(Kip1) in the cyclin E-cdk2 complexes. *Oncogene* 2001;20:3428-3436.
447. Ben-Dor A, Nahum A, Danilenko M, Giat Y, Stahl W, Martin HD, Emmerich T, Noy N, Levy J, Sharoni Y. Effects of acyclo-retinoic acid and lycopene on activation of the retinoic acid receptor and proliferation of mammary cancer cells. *Arch Biochem Biophys* 2001;391:295-302.
448. Prakash P, Russell RM, Krinsky NI. In vitro inhibition of proliferation of estrogen-dependent and estrogen-independent human breast cancer cells treated with carotenoids or retinoids. *J Nutr* 2001;131:1574-1580.
449. Nagasawa H, Mitamura T, Sakamoto S, Yamamoto K. Effects of lycopene on spontaneous mammary tumour development in SHN virgin mice. *Anticancer Res* 1995;15:1173-1178.
450. Sharoni Y, Giron E, Rise M, Levy J. Effects of lycopene-enriched tomato oleoresin on 7,12-dimethyl-benz[a]anthracene-induced rat mammary tumors. *Cancer Detect Prev* 1997;21:118-123.
451. Cohen LA, Zhao Z, Pittman B, Khachik F. Effect of dietary lycopene on N-methylnitrosourea-induced mammary tumorigenesis. *Nutr Cancer* 1999;34:153-159.
452. Levi F, Pasche C, Lucchini F, La Vecchia C. Dietary intake of selected micronutrients and breast-cancer risk. *Int J Cancer* 2001;91:260-263.
453. Ronco A, de Stefani E, Boffetta P, Deneo-Pellegrini H, Mendilaharsu M, Leborgne F. Vegetables, fruits, and related nutrients and risk of breast cancer: A case-control study in Uruguay. *Nutr Cancer* 1999;35:111-119.
454. Zhang S, Tang G, Russell RM, Mayzel KA, Stampfer MJ, Willett WC, Hunter DJ. Measurement of retinoids and carotenoids in breast adipose tissue and a comparison of concentrations in breast cancer cases and control subjects. *Am J Clin Nutr* 1997;66:626-632.
455. Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter DJ. Intake of fruits and vegetables and risk of breast cancer: A pooled analysis of cohort studies. *JAMA* 2001;285:769-776.
456. Levi F, La Vecchia C, Gulie C, Negri E. Dietary factors and breast cancer risk in Vaud, Switzerland. *Nutr Cancer* 1993;19:327-335.
457. Ewertz M, Gill C. Dietary factors and breast-cancer risk in Denmark. *Int J Cancer* 1990;46:779-784.
458. Jarvinen R, Knekt P, Seppanen R, Teppo L. Diet and breast cancer risk in a cohort of Finnish women. *Cancer Lett* 1997;11:251-253.
459. Freudenheim JL, Marshall JR, Vena JE, Laughlin R, Brasure JR, Swanson MK, Nemoto T, Graham S. Premenopausal breast cancer risk and intake of vegetables, fruits, and related nutrients. *J Natl Cancer Inst* 1996;88:340-348.
460. La Vecchia C, Ferraroni M, Negri E, Franceschi S. Role of various carotenoids in the risk of breast cancer. *Int J Cancer* 1998;75:482-483.

461. Terry P, Jain M, Miller AB, Howe GR, Rohan TE. Dietary carotenoids and risk of breast cancer. *Am J Clin Nutr* 2002;76:883-888.
462. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition and the Prevention of Cancer: A Global Perspective.* American Institute for Cancer Research, Washington, DC, 1997, p. 303.
463. Cuzick J, Terry G, Ho L, Hollingworth T, Anderson M. Human papillomavirus type 16 DNA in cervical cancers as a predictor of high-grade cervical cancer. *Lancet* 1992;339:959-960.
464. Bosch FX, Munoz N, de Sanjose S, Guerrerro E, Ghaffari AM, Kaldor J, Castellsague X, Shah KV, Gaffari AM. Importance of human papillomavirus endemicity in the incidence of cervical cancer: An extension of the hypothesis on sexual behaviour. *Cancer Epidemiol Biomarkers Prev* 1994;3:375-379.
465. Pillai MR, Halabi S, McKalip A, Jayaprakash PG, Rajalekshmi TN, Nair MK, Herman B. The presence of human papillomavirus-16/-18 ET AL6, p53, and Bcl-2 protein in cervicovaginal smears from patients with invasive cervical cancer. *Cancer Epidemiol Biomarkers Prev* 1996;5:329-335.
466. de Vet HC, Knipschild PG, Grol MEC, Schouten HJA, Sturmans F. The role of beta-carotene and other dietary factors in the etiology of cervical dysplasia: results of a case-control study. *Int J Epidemiol* 1991;20:603-610.
467. Marshall JR, Graham S, Byers T, Swanson M, Brasure J. Diet and smoking in the epidemiology of cancer of the cervix. *J Natl Cancer Inst* 1983;70:847-851.
468. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition and the Prevention of Cancer: A Global Perspective.* American Institute for Cancer Research, Washington, DC, 1997, p. 296.
469. Duggan BD, Felix JC, Muderspach LI, Tourgeman D, Zheng J, Shibata D. Microsatellite instability in sporadic endometrial carcinoma. *J Natl Cancer Inst* 1994;86:1216-1221.
470. Jain MG, Rohan TE, Howe GR, Miller AB. A cohort study of nutritional factors and endometrial cancer. *Eur J Epidemiol* 2000;16:899-905.
471. McCann SE, Freudenheim JL, Marshall JR, Brasure JR, Swanson MK, Graham S. Diet in the epidemiology of endometrial cancer in western New York (United States). *Cancer Causes Control* 2001;11:965-974.
472. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition and the Prevention of Cancer: A Global Perspective.* American Institute for Cancer Research, Washington, DC, 1997, p. 290.
473. Cramer DW, Kuper H, Harlow BL, Titus-Ernstoff L. Carotenoids, antioxidants and ovarian cancer risk in pre- and postmenopausal women. *Int J Cancer* 2001;94:128-134.
474. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition and the Prevention of Cancer: A Global Perspective.* American Institute for Cancer Research, Washington, DC, 1997, p. 178.
475. Bueno de Mesquita HB, Maisonneuve P, Runia S, Moerman CJ. Intake of foods and nutrients and cancer of the exocrine pancreas: A population-based case-control study in the Netherlands. *Int J Cancer* 1991;48:540-549.

476. Baghurst PA, McMichael AJ, Slavotinek AH, Baghurst KI, Boyle P, Walker AM. A case-control study of diet and cancer of the pancreas. *Am J Epidemiol* 1991;134:167-179.
477. Mills PK, Beeson WL, Abbey DE, Fraser GE, Phillips RL. Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer* 1988;61:2578-2585.
478. McClain MR, Bausch J. Summary of safety studies conducted with synthetic lycopene. *Regul Toxicol Pharmacol* 2003;37:274-285.
479. Product Data. Lycopene 5% TG. Product Data Sheet 1080, July 13, 2001. D.S.M. N.V., Heerlen, The Netherlands.
480. Elinder LS, Hadell K, Johansson J, Molgaard J, Holme I, Olsson AG, Walldius G. Probucol treatment decreases serum concentrations of diet-derived antioxidants. *Arterioscler Thromb Vascr Biol* 1995;15:1057-1063.