Role of Antioxidants in the Prevention of Cancer

Lunawati L. Bennett 1*, Stephen Rojas 2, Teresa Seefeldt 3

1 Union University, Jackson, Tennessee, Jackson, Tennessee, USA
2 Palm Beach Atlantic University, West Palm Beach, Florida, USA
3 South Dakota State University, Brookings, South Dakota, USA

1 Introduction

Cancer is currently the second leading cause of death in the United States behind cardiovascular diseases. It is estimated that more than 1.6 million new cases of cancer were diagnosed in 2012.1 According to the World Health Organization, cancer is a leading cause of death worldwide accounting for 7.6 million deaths (around 13% of all deaths) in 2008.2 Deaths from cancer worldwide are projected to continue rising, with an estimated 13.1 million deaths in 2030.3 The lifetime probability of being diagnosed with an invasive cancer is more than 40%.3 Cancer is characterized by the proliferation of abnormal cells that fail to respond correctly to normal regulatory mechanisms. Carcinogenesis, a term used to describe cancer development, is a multiple-step process consisting of initiation, promotion, and progression of uncontrolled cells. At the initiation step, damage to deoxyribonucleic acid (DNA) occurs. Cells begin to proliferate and expand into abnormal cells during the promotion step. Finally during the progression step, further changes occur to these abnormal cells, leading to formation of malignant cells.4

Proposed ways to reduce cancer progression include the avoidance of biological, chemical, or physical agents that can promote cancer and the consumption of a healthy diet of vegetables and fruits while maintaining optimum body weight.5 Chemoprevention is defined as prevention, slowing down, or reversal of cancer progression using naturally occurring or synthetic agents.

Natural dietary agents have drawn a great deal of attention because of their potential to suppress cancers and to reduce risk of cancer development using decreasing oxidative stress.5 Oxidative stress plays a significant role in the pathogenesis of numerous disorders and pathophysiological processes including cardiovascular diseases, diabetes, and cancer.6 Oxidative stress is the result of an imbalance between the production and the removal of reactive oxygen species (ROS) or reactive nitrogen species (RNS).7 ROS or RNS can be generated from exogenous and endogenous sources. The body's antioxidant defense mechanisms include glutathione, superoxide dismutase, and catalase, protect against oxidative stress.8 Excess production of ROS has been associated with carcinogenesis with damage to nucleic acids, proteins, or lipids. During carcinogenesis, breaks in DNA strands and formation of abnormal DNA linkages have been observed.9–11

Because of the impact of cancer on the society, efforts to prevent or to treat cancer are an ongoing research interest; studies that are attempting to find the link between oxidative stress and the process of carcinogenesis have found potential chemo preventive compounds and compounds with antioxidant activities.9 This review is focused on the roles of selenium, vitamin E, carotenoids, flavonoids, and resveratrol as potential antioxidants for cancer prevention and treatment.

* Corresponding author. Lunawati L. Bennett, Union University, 1050 Union University Drive, Jackson, TN 38305, USA.
E-mail: L.L. Bennett <llbennett@uu.edu>
2. Selenium

Selenium is a trace element found in selenoenzymes including glutathione peroxidase (GPx) an antioxidant enzyme for detoxification of hydrogen peroxide, and thioredoxin reductase (TrxR), an enzyme involved in the reduction of protein disulfides. Both organic and inorganic selenium supplements have been studied for their effects on physiologic functions and human health, but the optimal form to be used in dietary supplementation has not been determined.

Preclinical studies using cell culture indicated that selenium can decrease cell proliferation, promote cell cycle arrest, and induce apoptosis in cancer cells. Experiments in animal models and cell culture showed that selenium can either inhibit the carcinogenesis process acted as a cancer preventive agent or have failed to show an anticancer effect. Observational studies of selenium and cancer risk have shown mixed results.

Randomized clinical trials of selenium and cancer prevention have also been conducted. Overall, results have been mixed. There has been significant variability in the size of the trials, the dosage of selenium, and the form of selenium supplementation in these studies, which complicates data comparison between trials. To illustrate this, we summarized two randomized clinical trials of selenium and its effect on prostate cancer. The Nutritional Prevention of Cancer (NPC) study was a double-blind, randomized clinical trial that enrolled 1312 patients and examined the effect of selenized yeast (200 µg selenium/day) in the prevention of recurrent nonmelanoma skin cancer; a secondary analysis was conducted to examine risk of other types of cancer. Analysis of data from the 974 men enrolled in the study revealed a 63% lower incidence of prostate cancer in those receiving the supplemental selenium compared to the placebo group (p = 0.002). The SELECT trial (Selenium and Vitamin E Cancer Prevention Trial) was a phase III, randomized, placebo-controlled trial in 35,533 men that sought to examine the effects of selenium (L-selenomethionine; 200 µg/day), vitamin E (α-tocopherol; 400 IU/day) or both on the risk of prostate cancer development. The trial was supposed to have at least a 7-year follow up period; however, the trial was stopped early following an interim review. Selenium supplementation, alone or in combination with vitamin E, failed to reduce the occurrence of prostate cancer in the 5-year period.

Toxicity is known to occur with chronic or acute ingestion of high amounts of selenium. Common symptoms of selenosis include brittle hair and nails change and potential loss of hair and nails. However, toxicity has also been reported from the range of doses used for supplemental selenium as well. Findings from the SELECT and NPC trials showed an increased risk of elevated blood sugar and development of type 2 diabetes in patients supplemented with selenium. A statistically significant increased risk of nonmelanoma skin cancer was observed in patients receiving the selenium supplementation in the NPC trial.

Based on current data, use of selenium for cancer prevention should not be recommended. Although certain populations may benefit from taking selenium for cancer prevention, further research is needed to identify exactly what patient populations will benefit from vitamin E supplementation and the optimal dose that will be beneficial.

3. Vitamin E

Vitamin E is a fat-soluble vitamin with antioxidant activity that plays an important role in protecting the cell membrane from oxidation. Vitamin E consists of tocotrienols and tocopherols. In the investigation of the clinical antioxidant effects of vitamin E, α-tocopherol (either RRR-α-tocopherol or all-rac-α-tocopherol) is used most often because of its high biological activity.

Similar to selenium, vitamin E’s effects on cancer cells have also been investigated in preclinical models, observational studies, and randomized clinical trials. Results from these studies have been inconclusive with many demonstrating no difference in cancer incidence and some showing an increased cancer risk. Table 1 summarizes the major clinical trials of vitamin E alone or in combination with other antioxidants. In addition to the lack of benefit observed in these clinical trials, adverse effects from vitamin E supplementation have been observed. The HOPE-TOO trial revealed an increased risk of heart failure and hospitalizations from heart failure in the vitamin E group. The ATBC and PHS II studies showed an increased risk of hemorrhagic stroke.

Based on current data, the use of vitamin E for cancer prevention should not be recommended. Although certain populations may benefit from taking vitamin E for cancer prevention, further research is needed to identify exactly what patient populations will benefit from vitamin E supplementation and the optimal dose that will be beneficial.

4. Carotenoids

Carotenoids are a group of pigments found in a wide range of vegetables and fruits that have antioxidant activities. More than 600 carotenoids have been identified, with only a few having significant biological importance, in particular beta-carotene and lycopene. Beta-carotene is mainly found in yellow-orange fruits and vegetables, such as carrots, sweet potatoes, and pumpkin, while lycopene is found in tomato or tomato-based products.

Beta-carotene has been the most studied carotenoid with respect to disease prevention. Although beta-carotene has shown to be beneficial in preclinical and epidemiological studies, results from large clinical trials have been disappointing. In the ATBC trial, beta-carotene supplementation is associated with an 18% increase in lung cancer incidence. Increases in stomach cancer and prostate cancer have also been observed. Mortality from prostate cancer is increased in the beta-carotene group. No benefit or harm is found with cancers at other sites.

The Beta-Carotene and Retinol Efficacy Trial (CARET) was a large trial that enrolled participants with at high risk for developing lung cancer either because of smoking or previous asbestos exposure. The intervention used in this study was 30 mg/day of beta-carotene and 25,000 IU of retinol, and the study’s primary endpoint was lung cancer incidence. The trial was halted early after an interim analysis has revealed a 28% increased risk of lung cancer in the intervention group as compared to placebo. Mortality is also higher in the intervention group. Because two agents were used in this trial, the effects of the individual supplements cannot be separated; however the results show a similar trend to that has been observed from beta-carotene alone in the ATBC trial.

Other studies have shown no effect on cancer incidence including no effect on total cancer in the Physicians’ Health Study and the Women Antioxidant Cardiovascular Study but no effect on recurrent nonmelanoma skin cancer in the Skin Cancer Prevention Study. Because of the lack of benefit and potential for harm observed in the clinical trials with beta-carotene, this agent should not be recommended for cancer prevention.

5. Flavonoids

Flavonoids are polyphenolic compounds found in herbs, apples, tea, grapes, honey, red wine, fruits and vegetables that have been shown to have anti-inflammatory, anti-diabetic, antifungal, antiallergic,
Table 1  Several major clinical trials of vitamin E (α-tocopherol) or vitamin E in combination with other antioxidants

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Duration (yrs)</th>
<th>N</th>
<th>Age (yrs)</th>
<th>Sex/other sample characteristics (if relevant)</th>
<th>Dose of vitamin E</th>
<th>Dose of other compounds</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATBC55,56,60</td>
<td>DB, R, PC</td>
<td>6.1</td>
<td>29,133</td>
<td>50–69</td>
<td>Male smokers</td>
<td>50 mg all- rac-α- tocopherol/d</td>
<td>20 mg/d β-carotene</td>
<td>Decreased incidence of prostate cancer by 34% (p &lt; 0.01) Decreased mortality from prostate cancer Increased incidence of stomach cancer by 25% Decreased incidence of colorectal cancer by 15% No effect on incidence of lung cancer</td>
</tr>
<tr>
<td>SELECT52</td>
<td>DB, R, PC</td>
<td>5</td>
<td>35,533</td>
<td>≥50 (African American), ≥55 (all other men)</td>
<td>Males without prostate cancer at baseline</td>
<td>400 IU all-rac-α-tocopherol/d</td>
<td>200 µg/d L-selenomethionine</td>
<td>No statistically significant differences in prostate cancer rates between study groups although there was a trend towards increased incidence with vitamin E (vitamin E HR, 1.13; 99% CI, 0.95-1.35); unblinded follow-up revealed a statistically significant increase in prostate cancer for vitamin E (HR, 1.17; 99% CI, 1.004-1.36; p = 0.008)</td>
</tr>
<tr>
<td>HOPE and HOPE-TOO57</td>
<td>DB, R, PC</td>
<td>7</td>
<td>9541 in HOPE; 3,994 continue in HOPE-TOO</td>
<td>≥55</td>
<td>History of vascular disease or diabetes mellitus</td>
<td>400 IU RRR-α-tocopherol/day</td>
<td>No effect on incidence of cancer between treatment and placebo groups (RR, 0.94; 95% CI, 0.84-1.06; p = 0.30)</td>
<td></td>
</tr>
<tr>
<td>PHS II58</td>
<td>DB, R, PC</td>
<td>10</td>
<td>14,641</td>
<td>&gt;50</td>
<td>Males</td>
<td>400 IU all-rac-α-tocopherol every other day</td>
<td>500 mg/d vitamin C</td>
<td>No effect on the incidence of prostate cancer (HR, 0.97; 95% CI, 0.85-1.09; p = 0.58) or total cancer (HR, 1.04; 95% CI, 0.95-1.13; p = 0.41) between treatment and placebo groups</td>
</tr>
<tr>
<td>WACS59</td>
<td>DB, R, PC</td>
<td>9.4</td>
<td>7627</td>
<td>≥40</td>
<td>Females</td>
<td>600 IU RRR-α-tocopherol every other day</td>
<td>50 mg every other day β-carotene, 500 mg/day vitamin C</td>
<td>No effect on cancer incidence (vitamin E group RR, 0.93; 95% CI, 0.79 to 1.09) or death (vitamin E group RR, 0.87; 95% CI, 0.65-1.17)</td>
</tr>
</tbody>
</table>

ATBC – Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI – confidence interval; DB – double blind; HOPE-TOO – Heart Outcomes Prevention Evaluation-The Ongoing Outcomes; HR – hazard ratio; PC – placebo-controlled; PHS – Physicians’ Health Study; RR – relative risk; SELECT – Selenium Vit.E Cancer Prevention Trial; WACS – Women’s Antioxidant Cardiovascular Study.
antiviral, antioxidant, and anticancer properties.73–80 Flavonoids are categorized into the following classes: flavones, flavonols, flava-
nones, flavonols, anthocyanidins, isoflavones, and chalcones.

Dietary flavonoids that possess anticancer properties are also known to have antioxidant activities because of their ability to scaveng e free radicals,74–76,81,82 and to prevent initiation, promo-
tion, and progression of cancer development through interact selec tively with protein kinase signaling cascades involved in cell defense.74,80,81 Flavonoids can also suppress the proinflammatory transcription of nuclear factor kappa-light-chain-enhancer of activ ated B cells (NF-κB) pathways.75 Uregulated NF-κB increases oxidative stress and genotoxic stress occur in the respiratory tract of smokers.83 Nicotine induces angiogenesis by up-regulation of matrix metalloproteinase (MMPs), vascular endothelial growth factor (VEGF) and cyclo-oxygenase (COX), thus causing tumor invasion and metastasis in different cancers.84,85

The flavones group, which consists of wogonin, wogonoside, baicalin, baicalein, and apigenin (4',5,7-trihydroxyflavone) possess anticarcinogenic and anticancer effects by inhibiting the p14ARF-Mdm2-p53 pathway and by lowering tyrosine kinase activities in breast cancer. A synthetic small molecule anti-vascular drug, dimethylxanthenone-4-acetic acid (DMXAA), is now undergoing phase 3 clinical trials. This compound induced anticancer activity against non-small cell lung and ovarian cancers.73

The isoflavones group, which consists of genistein, daidzein, genistin, and formononetin, display estrogenic and anticancer properties, has been shown to be of benefit in leukemia, breast, and prostate cancer. Several synthetic isoflavones have also caused inhibition of the aromatase enzyme, which could be useful for the treatment of hormone-dependent breast cancer.

The flavanols group consisting of quercetin, myricetin, and kaempferol also has cancer-preventive and antioxidant activities by inhibiting enzymes responsible for causing carcinogens and by modifying signal transduction pathways.81,82

Numerous pathways that alter gene transcription and smoking-
induced tumorigenesis have been proposed.86 Chemopreventive using natural dietary compounds found in fruits and vegetable for the prevention and reduction of cigarette smoking-induced human cancer has been summarized.87

A double-blind, placebo-controlled clinical trial was conducted in 60 men with prostate intraepithelial neoplasia to determine the safety and efficacy of GTCs for the prevention of prostate cancer. Half of the group received placebo while the other half received three 200 mg GTCs capsules (600 mg/day). The primary endpoint of this study was the prevalence of prostate cancer. The GTCs group has shown a significantly lower incidence of prostate cancer than the placebo group with no adverse effects being observed. This study showed that GTCs are safe and effective for treating prema-
lignant lesions prior to the development of prostate cancer.88

An epidemiologic prospective observational study known as the European Prospective Investigation into Cancer and Nutrition (EPIC) recruited 521,448 participants to explore the association between vegetable and fruit consumption and the risk of bladder cancer.89 The participants who were between the ages of 25–70 years were recruited from 10 European countries in 23 centers between 1992–2000. Cox proportional hazard models were used to calculate rate ratios, stratified by age at recruitment, sex, and study center, and adjusted for energy intake, smoking status and duration, and life-time intensity of smoking. After a follow-up of almost 9 years, data collected from 478,533 participants revealed that 1015 of the participants were newly diagnosed with bladder cancer. The researchers concluded that the combined consumption of 100 g/day of fruits and vegetables had no effect on bladder cancer risk therefore, high fruit and vegetable consumption are not associated with decrease in bladder cancer risk.74,89

A series of case-control studies involving 10,000 cases of various cancers and more than 16,000 patients admitted to hospitals were conducted in the 1990s to find the association between flavonoids and risk of various neoplasms. Data regarding the dietary content of the different flavonoids and personal and sociodemographic character-
istics were acquired through a standard questionnaire administered by centrally trained interviewers during hospital stay. The results of the study have shown odds ratios between 0.32–0.81 showing inverse relationships between flavonoid intake and cancer.75

Another study has also shown evidence for the protective role of flavonoids in oral, laryngeal, esophageal, colorectal, breast, and renal cancers.75

Among the flavonoids, EGCG, which is one of the most impor-
tant components of the GTCs, provides the most promising data as chemopreventive agent. Presently, there are more than ten clinical trials recruiting participants to investigate the effects of this flavonoid as a cancer preventive agent. Green tea catechins (GTCs), in particular (-)-epigallocatechin gallate (EGCG), have been shown to have antioxidant and anti-cancer properties. This compound inhibits cancer proliferation by decreasing nucleoside diphosphate kinase-B activity, suppressing androgen receptor expression and signaling transduction, inhibiting telomerase activity, and reducing the accumulation of genes that cause cancer.73–75,80

Although small clinical trials of GTCs showed promising data for cancer prevention, further research through larger clinical trials is needed to determine the optimal dosage and formulation of GTCs that elicit antioxidant and anticarcinogenic effects. Furthermore, although theoretical idea of taking natural dietary compounds as chemoprevention in decreasing smoking-induced tumorigenesis represent inexpensive and approachable way, clinical trials is needed to determine the population, how advanced the smokers are, and the amount of natural dietary consumption needed before benefits are seen.

6. Resveratrol

Resveratrol is a plant-derived polyphenol, phytoalexin that is found in red wine, grapes, peanuts, and mulberries.90 The amount of resveratrol in natural foods ranges from 16 ng/g (bilberries) to 14.3 mg/L (red wines). The trans-resveratrol form is biologically more active than its cis isofomer.91 Resveratrol has been known to prevent or slow the progression of a wide variety of diseases, including cardiovascular diseases,92 ischemic injuries,93,94 and Alzheimer disease95 as well as to enhance stress resistance96 and cancer prevention.97 It also acts as an antioxidant and an anti-
inflammatory drug in animal studies by causing inhibition of cyclo-oxygenase-1 and by blocking adhesion of blood cells to vessel walls.98,99 In preclinical studies, resveratrol has been shown to inhibit ROS and lipid peroxidation100 and decrease phosphorylation of NF-κB that regulates genes involved in inflammation, tumor genesis, and metastasis in prostate cancer cell lines.100,101 Resveratrol has been shown to reduce the number and size of esophageal, intestinal, and colon tumors,102,103 and to prevent the development of mammary carcinogenesis in mice and in cell lines.104–106 It is also effective against a number of other cancer types, such as liver, pancreatic, gastrointestinal, lung, and soft-tissue tumors.93,105–113

Resveratrol can also act as a phytoestrogen by activating estrogen receptors that regulate the transcription of estrogen-
responsive target genes on breast cancer cells, causing apoptosis and depletion of glutathione114 by inhibiting aromatase115 as well as by causing angiogenesis105 and other mechanisms in myeloma cells.116 It also can block androgen receptors involved in the development and progression of prostate cancer.117,118

Paradoxically, resveratrol can act as a pro-oxidant affecting DNA or protein.119 It has been known that dietary polyphenols are
Antioxidants in cancer prevention

metabolized by peroxidase to form pro-oxidant phenoxyl radicals which are reactive to co-oxidize glutathione (GSH) or NADH by causing ROS formation leading to oxidative DNA damage or apoptosis. Therefore, resveratrol can alter cellular redox by exhibiting antioxidant effects in normal cells and pro-oxidant effects in cancer cells.

Resveratrol provides diverse health benefits in a dose-response manner. At higher concentrations (10–40 mM), it has cancer prevention properties, while at lower concentrations (5–20 μM), it has cardioprotective properties. After oral administration, more than 70% of resveratrol is absorbed, with ratio of serum resveratrol/metabolite at the highest concentration after 30 minutes of consumption. Resveratrol undergoes extensive glucuronide and sulphate conjugation in the intestine and liver, producing five major metabolites, of which the 3- and 4-O-sulfate metabolites are known to have anticancer activities.

A clinical trial was conducted in twenty colorectal cancer patients. The patients were given either one or two 500-mg resveratrol caplets daily for 8 consecutive days prior to surgical resection. During surgery, samples of tumor and normal colon tissue were obtained for analysis. Besides resveratrol, six metabolites were identified in the tissue, with resveratrol-3-O-sulfate glucuronide having had the maximal concentration in 14 out of the 20 patients. It was shown that consumption of resveratrol can reduce tumor proliferation by 5%. The results of this trial suggest that daily oral doses of 500 or 1,000 mg produce resveratrol levels in the gastrointestinal tract that are sufficient to elicit antarcinogenic effects, showing resveratrol as a potential cancer chemopreventive agent.

A randomized, double-blind study was conducted in 40 healthy volunteers (10 per group) who were given resveratrol for 29 days at a daily dose of 500, 1,000, 2,500, or 5,000 mg. Resveratrol was safe as indicated by clinical, biochemical, or hematological profiles during the intervention and 2-week follow-up phase.Repeated administration of resveratrol-generated metabolites (in particular, the 3-O-sulfate, 4’-O-glucuronide, and 3-O-glucuronide) which were much higher than the parent drug in the plasma. The researchers predicted that decreases in circulating insulin-like growth factor-1 and insulin-like growth factor binding protein-3 may have contributed to the chemo-preventive activity of resveratrol. At the dose higher than 1,000 mg, 28 volunteers reported to have mild and four reported moderate gastrointestinal symptoms; therefore, recommended daily doses of resveratrol should not exceed 1,000 mg.

Now more than a dozen yet-to-be-completed studies involving resveratrol are aimed to investigate the role of resveratrol in the management of type 2 diabetes, obesity, Alzheimer disease, and cancer. Several currently published clinical trials have mostly been conducted in healthy males and females, ranging from 3–31 participants using different forms of resveratrol (given as wine, grape juice, capsules, or intravenously). Doses ranging from 246 mcg to 2.5 g have been used to determine the pharmacokinetic and metabolite profile of resveratrol.

Although preclinical studies and clinical trials of resveratrol with small numbers of participants or healthy volunteers have shown promising data, further research through larger clinical trials is needed to determine the optimal dosage and formulation of resveratrol that elicit antioxidant and anticarcinogenic effects.

7. Summary

Several clinical trials using antioxidants and natural compounds have been conducted to observe if these compounds have anticancer or chemo-preventive properties. Although in the past few years the knowledge base using in vitro studies or preclinical trials with selenium, vitamin E, or carotene have shown that these compounds exhibit pharmacologic and biologic effects as anti-cancer agents, when it comes to larger clinical trials, the above compounds have failed to show promising results.

Natural compounds such as flavonoids, in particular ECGC and resveratrol were shown to have a promising future as antioxidants and anti-carcinogenesis agents. These compounds can be consumed through fruits and vegetables. However, the idea that fruit and vegetable consumption alone is associated with a decreased risk of cancer is still not yet conclusive. It must be highlighted that further research is needed because in vitro experiments cannot be directly extrapolated to the large-scale and long-term intervention, controlled clinical trials that are necessary to prove health benefits. In addition, antioxidants may interfere with the cancer treatment in patients through chemotherapy or radiation.

References

thione with topical and oral vitamin E on pigmentation and skin cancer
induced by ultraviolet irradiation in SKH:2 hairless mice. J Am Acad Dermatol
27. Waters DJ, Shen S, Cooley DM, Bostwick DG, Qian J, Combs Jr GF, Glickman LT,
et al. Effects of dietary selenium supplementation on DNA damage and apoptosis
28. Venkateswaran V, Flesher NE, Sugar LM, Klotz LH. Antioxidants block prostate
Björnstedt M et al. Selenium prevents tumor progression in a rat model for
30. Dansky ND, Randolph C, Bosland MC. Differential effects of selenium on
benign and malignant prostate epithelial cells: stimulation of LNCAp cell
growth by noncytotoxic, low selenium concentrations. Nutr Cancer 2009;61:
251–64.
31. Ozten N, Horton L, Lasano S, Bosland MC. Selenomethionine and alpha-
tocopherol do not inhibit prostate carcinogenesis in the testosterone plus
32. Klein EA, Thompson IM, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ,
et al. Decreased incidence of prostate cancer with selenium (SELECT). J Natl
33. Clark LC, Combs GF, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS,
et al. Gamma-tocopherol induces apoptosis in androgen-
cycle arrest and apoptosis in human prostate carcinoma cell lines. J Natl
34. Jiang Q, Wong J, Ames BN. Gamma-tocopherol induces apoptosis in androgen-
cycle arrest and apoptosis in human prostate carcinoma cell lines. J Natl
36. Paiva SA, Russell RM. Beta-carotene and other carotenoids as antioxidants.
37. Johnson EJ. The role of carotenoids in human health. Nutr Clin Care
38. Ziegler RG. A review of epidemiologic evidence that carotenoids reduce the
39. Sampaio ARD, Chagas CEA, Ong TP. Vitamin A and beta-carotene inhibitory
effect during 1,2-dimethylhydrazine induced hepatocarcinogenesis potenti-
40. Palozza P, Serini S, Maggiano N, Angelini M, Boninsegna A, DiNicuolo F,
carcinoma cell lines by beta-carotene through down-regulation of cyclin A and
41. Greenberg ER, Baron JA, Stuelke TA, Stevens MM, Mandel JS, Spencer SK,
Elia PM, et al. A clinical trial of beta carotene to prevent basal-cell and
squamous-cell cancers of the skin. The Skin Cancer Prevention Study Group.
Cancer 2001;91:782–95.
42. Alabaster O, Tang Z, Frost A, Shivapurkar N. Effect of beta-carotene and wheat
fibra on colonic aberrant crypt and tumor formation in rats exposed to
43. Ziegler RG. A review of epidemiologic evidence that carotenoids reduce the
44. Orsini N, Gnech D, Bousquet J, Gagnon A, Deschênes E, Mandel JS, et al. The
45. Greenberg ER, Baron JA, Stuelke TA, Stevens MM, Mandel JS, Spencer SK,
Elia PM, et al. A clinical trial of beta carotene to prevent basal-cell and
squamous-cell cancers of the skin. The Skin Cancer Prevention Study Group.
Cancer 2001;91:782–95.
fibra on colonic aberrant crypt and tumor formation in rats exposed to
47. Ziegler RG. A review of epidemiologic evidence that carotenoids reduce the


