Symposium: Relative Bioactivity of Functional Foods and Related Dietary Supplements

The Tomato As a Functional Food[1,2]

Kirstie Canene-Adams, Jessica K. Campbell, Susan Zaripheh, Elizabeth H. Jeffery, and John W. Erdman, Jr.[3]

Department of Food Science and Human Nutrition and the Division of Nutritional Sciences, University of Illinois at Urbana-Champaign, Urbana, IL 61801

ABSTRACT Tomatoes are the fourth most commonly consumed fresh vegetable and the most frequently consumed canned vegetable in the American diet. There is emerging epidemiology data supporting the connection between increased tomato consumption and reduced risk for both cardiovascular disease and prostate cancer. Here we will summarize the nutrient and the phytochemical content of tomatoes and tomato products, and how these bioactive components might act together to modulate disease development. Recent animal studies have investigated tomatoes, lycopene, and prostate cancer using the *N*-methyl-*N*-nitrosourea and Dunning rat models. These animal studies also suggest that diets containing tomatoes may decrease the risk or the progression of prostate cancer. Due to the frequency and the extent of tomato consumption, the supporting epidemiological and animal data, which connect increased intakes with decreased cancer and cardiovascular disease risk, tomato's role in the American diet is of undeniable importance as part of a healthy diet. J. Nutr. 135: 1226–1230, 2005.

KEY WORDS: • *tomato* • *lycopene* • *prostate cancer* • *cardiovascular disease*

Annually, the average American consumes 17.9 pounds of fresh tomatoes (*Lycopersicon esculentum*) and 68.7 pounds of processed tomato products, as shown in **Table 1** (1,2). Onions, head lettuce, and potatoes are the only fresh vegetables consumed more frequently than tomatoes in America, whereas tomatoes are by far the most frequently consumed canned vegetable (1,2). The Economic Research Service of the USDA estimates that 35% of raw tomatoes are processed into sauces, 18% into tomato paste, 17% for canned tomatoes, 15% into juices, and 15% into catsup (2). Interestingly, teenage boys (ages 12–19 y) have the highest per capita consumption of catsup, with fresh tomato and tomato juice consumption rising with increased age in both men and women (2). Many tomato products are good sources of potassium, folate, and the vitamins A, C, and E, as demonstrated in **Table 2** (3). Tomato products contain similar amounts of potassium and folate compared with other popular vegetables, but tomato products are a superior source of alpha-tocopherol and vitamin C (3). In comparison with the other regularly consumed vegetables, only carrots are a better dietary source of vitamin A than tomato-based foods.

In addition to their micronutrient benefits, tomatoes also contain valuable phytochemicals, including carotenoids and polyphenols. For instance, carotenoids, such as the red pigmented lycopene, β-carotene, a pro-vitamin A compound; phytoene, and phytofluene are all found in abundance in raw tomatoes and tomato products (**Table 3**) (3,4). Flavonol content of tomatoes is also high, with up to 98% of the total flavonols contained in the skin as the conjugated forms of quercetin and kaempferol (5). Of lycopene consumption, 85% comes from tomato sources, such as canned tomato sauces (~288 μg/g) and other food sources of lycopene include fresh watermelon (~45 μg/g) and pink grapefruit (~14 μg/g) (6,7).

These tomato phytochemicals are thought to contribute to the reduced risk of human ailments such as cardiovascular disease (CVD)[4] and prostate cancer. With prostate cancer, it appears that appropriate food choices can slow the onset of the disease and can play a role in prevention (8,9). In 2005, the estimated new cases of prostate cancer in the United States will reach over 232,000 men; accounting for 33% of new cancer cases; therefore making prostate cancer the most frequent newly diagnosed cancer (10). The estimated deaths

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[3] To whom correspondence should be addressed.
E-mail: jwerdman@uiuc.edu.

[4] Abbreviations used: CCA-IMT, common carotid artery; CVD, cardiovascular disease; NMU, *N*-methyl-*N*-nitrosourea; PSA, prostate specific antigen.

TABLE 1

Fresh and canned vegetable utilization per capita of the United States, 2001[1]

Vegetable	Fresh consumption	Canned consumption
	pound/y	
Carrots	10.6	—
Tomatoes	17.9	68.7
Onions	18.1	—
Head lettuce	24.2	—
Potatoes	46.7	—
Snap beans	—	3.7
Pickles	—	3.8
Corn	—	9.2

[1] Ref. (1).

from prostate cancer will be 30,350, which comprises 10% of all male cancer deaths, making prostate cancer the second leading cause of cancer death in men (10). Proper nutrition has also shown to be effective in the prevention and the treatment of CVD, and the American Heart Association has set up guidelines for reducing the risk of developing CVD (11). Over 70 million Americans have some form of CVD, and this disease will account for 38% of all deaths, making CVD the number one killer of Americans at one death every 34 seconds (12). Due to the overwhelming number of Americans suffering from these 2 diseases, a successful nutrition intervention could have a profound impact on health care cost and improvement in quality of life. A great deal of research is needed to determine the mechanisms by which diet may delay or prevent the onset of CVD and prostate cancer.

Tomatoes, lycopene, and prostate cancer risk

Epidemiological evidence. Several epidemiological studies have reported an inverse relation between consumption of tomatoes and/or its major carotenoid lycopene, and reduced prostate cancer risk. Using plasma samples from men enrolled in the Physicians' Health Study, a randomized and placebo-controlled trial of aspirin and β-carotene, lycopene was found to be the only antioxidant at significantly lower levels in prostate cancer cases than in the matched controls ($P = 0.04$) (13). This inverse association was particularly evident for aggressive types of prostate cancer and for men not taking a β-carotene supplement. A case-control study was performed to examine plasma carotenoids and the risk for prostate cancer, using a standard epidemiological questionnaire and serum carotenoid analysis via HPLC in 65 prostate cancer patients and 132 cancer-free controls (14). An 83% reduction in prostate cancer risk was observed in the group with the highest plasma lycopene concentration (0.40 μm/L) in comparison with the lowest lycopene group (0.18 μm/L) (14). In the Health Professionals Follow-Up Study, similar results were found, where an intake of $\geq$2 servings a week of tomato products resulted in a lower risk of prostate cancer (15). This particular study examined 51,529 male heath professionals between 40 and 75 y of age and evaluated lycopene and tomato product intakes and established that a greater risk reduction for prostate cancer occurred with tomato sauce [relative risk (RR) = 0.77 for 2+ servings/wk vs. <1 serving/mo; 95% CI: 0.66–0.90; $P_{trend} < 0.001$] than with lycopene intake alone (RR = 0.84 for high vs. low quintiles; 95% CI: 0.73–0.96; $P_{trend} = 0.003$) (15). A nested case-control study from the Health Professionals Follow-Up Study cohort further examined the association between plasma carotenoids and prostate cancer risk (16). By matching 450 cases with 450 controls, it was determined that there was a significant inverse relation between a higher concentration of serum lycopene and a lower risk of prostate cancer. This finding was restricted to older men and those without a family history of prostate cancer. The authors speculated that these findings indicate that tomatoes have the ability to protect against sporadic prostate cancer better than familial prostate cancer.

A recent meta-analysis searched both MEDLINE and EMBASE for relevant tomato and prostate cancer papers and 11 case-control studies and 10 cohort studies were chosen for analysis (17). At the time of this meta-analysis, the case-control study described above (16) was not yet published and therefore was not included. This meta-analysis found that, compared with infrequent consumers of raw tomatoes, the RR for prostate cancer in the highest quartile of intake was 0.89 (95% CI: 0.80–1.00), and for those consuming cooked tomato products, the RR was 0.81 (95% CI: 0.71–0.92) (17). The authors noted that the effect seen was modest even with high levels of tomato intake. Overall, epidemiological evidence supports further investigation of the relation between tomato product consumption and reduced risk for developing prostate cancer. Animal studies would allow scientists to elucidate the possible mechanisms of action, as well as the dose and the form of tomatoes that might provide optimum cancer risk reduction, before more expensive and time-consuming clinical trials.

Experimental evidence. There are several established animal models that can be used to study prostate cancer initiation, promotion, and progression, some of which are appropriate for dietary intervention studies. One such model, is the

TABLE 2

Nutrient composition of tomatoes and related tomato products[1]

Nutrient	Tomato products (*per 100 g*)[2]				
	Raw tomatoes	Catsup	Tomato juice	Tomato sauce	Tomato soup
Potassium, *mg*	237	382	229	331	181
α-tocopherol, *mg*	0.54	1.46	0.32	2.08	0.50
Vitamin A, *IU*	833	933	450	348	193
Vitamin C, *mg*	12.7	15.1	18.3	7.0	27.3
Total folate, μ*g*	15	15	20	9	7

[1] Ref. (3).
[2] USDA Nutrient Data Bank numbers: raw tomatoes, 11529; catsup, 11935; tomato juice, 11540; tomato sauce, 11549; tomato soup, 06359.

TABLE 3

Carotenoid content of tomatoes and related tomato products[1]

Carotenoid[a]	Tomato products[2]				
	Raw tomatoes	Catsup	Tomato juice	Tomato sauce	Tomato soup
			mcg/100 g		
β-carotene[2]	449	560	270	290	75
α-carotene[2]	101	0	0	0	0
Lycopene[2]	2573	17007	9037	15152	5084
Lutein + zeaxanthin[2]	123	0	60	0	1
Phytoene[3]	1860	3390	1900	2950	1720
Phytofluene[3]	820	1540	830	1270	720

[1] Ref. (3,4).
[2] USDA Nutrient Data Bank numbers: raw tomatoes, 11529; catsup, 11935; tomato juice, 11540; tomato sauce, 11549; tomato soup, 06359.
[3] Adapted from Ref. 4.

N-methyl-*N*-nitrosourea (NMU) and testosterone-induced prostate cancer model, developed by Bosland (18,19). This model was used by our laboratory to examine the effects of tomato or lycopene consumption on prostate cancer development. In this study, rats were fed an AIN-93G based diet containing 10% tomato powder or 0.025% lycopene. Feeding tomato powder resulted in significantly longer survival due to fewer prostate cancer deaths than rats given the control diet (hazard ratio = 0.74; 95% CI: 0.59–0.93; $P = 0.009$) (20). The lycopene-containing diet (hazard ratio = 0.91; 95% CI: 0.61–1.35; $P = 0.630$) resulted in a nonsignificant reduction in survival from prostate cancer, suggesting that there may be phytochemicals, in addition to lycopene, contained in tomatoes, which may aid in cancer prevention.

The Dunning R-3327H transplantable tumor model examines the later stages of cancer in prostate cells placed subcutaneously in Copenhagen male rats (21,22). Our laboratory examined effects of diets containing tomato powder, lycopene, broccoli powder, and a combination of tomato plus broccoli powder, to determine which dietary additions were most effective in decreasing prostate tumor growth. Results from the pilot study suggest that diets containing broccoli, tomato, lycopene, and a combination of tomato and broccoli powders can all reduce the Dunning R-3327H prostate tumor growth rate (23). Further animal trials will be performed in the coming year to more clearly examine these dietary interventions, as well as to evaluate possible additive effects between broccoli and tomato powder. Possible mechanisms of action will also be tested to determine how these dietary interventions might reduce tumor growth.

A recently published study examined the effects of lycopene and/or vitamin E, 2 components of tomatoes, on prostate tumor growth using the Dunning MatLyLu rat model (24). In this model, rapidly growing tumor cells are injected directly into the ventral prostate of rats. Whereas no dietary interventions decreased tumor size, lycopene, vitamin E, and their combination all increased the fractional area of tumor tissue, which was necrotic, compared with the untreated and vehicle-treated animals. Microarray analysis of tumor tissues showed a reduction in androgen signaling via vitamin E, whereas lycopene acted by downregulating 5-alpha reductase 1, insulin-like growth factor-1, and IL-6 expression.

It is notable that studies with 3 rat models of prostate cancer provided encouraging results. Clearly, more animal model research needs to be performed. At this time, the animal work, in combination with the epidemiology, supports the need for clinical trials in human subjects, focused upon diets containing tomatoes, tomato-based foods, and tomato phytochemicals.

Tomatoes, lycopene, and CVD risk

Several epidemiological studies have linked elevated plasma lycopene concentration with a lower risk for developing CVD (25). For example, the Kuopio Ischemic Heart Disease Risk Factor Study examined the relation between serum antioxidants and intima-mediated thickness of the common carotid artery (CCA-IMT), a marker related to the risk of having an acute coronary event. They reported that lower levels of plasma lycopene were seen in men who had a coronary event compared with men who did not (26,27). In addition, a higher concentration of serum lycopene was inversely correlated with a decrease in the mean and maximal CCA-IMT (P for linear trend < 0.001) with low lycopene, resulting in an 18% increase in CCA-IMT (27). The Eupopean Multicenter Case-Control Study on Antioxidants, Myocardial Infarction and Breast Cancer Study, better known as the EURAMIC Study, is another case-control study that examined the correlation between adipose lycopene concentration and CVD risk. In that study, adipose samples were analyzed for carotenoid content, because this tissue is considered a long-term storage depot for carotenoids. A higher lycopene concentration was found to be independently protective against CVD. Specifically, the odds ratio for lycopene's protective effect was 0.52 when contrasting the 10th and 90th percentiles of adipose lycopene concentrations (28).

Since 1984, CVD has caused more deaths in females than males, claiming one death per minute, accounting for half a million women a year (12). The Women's Health Study is a continuing randomized, double-blind, placebo controlled 2 $\times$ 2 factorial study examining the effect of vitamin E and aspirin on the prevention of CVD and cancer in women (29,30). The participants filled out FFQs and women in the first quintile of tomato consumption ($<$1.5 servings a week) were compared with those eating 1.5 to $<$4, 4 to $<$7, 7 to $<$10, or $\geq$10 servings a week. The RRs of CVD with tomato intake were 1.02, 1.04, 0.68, and 0.71, respectively (P for trend = 0.029). It was also reported that a decreased risk for developing CVD was more strongly associated with higher tomato intake than with lycopene intake (29). Blood samples were analyzed for lycopene concentration, and the women in the upper 3 quartiles of plasma lycopene were found to have a

significant, multivariate, 50% risk reduction for developing CVD compared with those in the lowest quartile (95% CI: 0.33–0.82, $P = 0.005$) (30). This epidemiological work suggests that examination of the effects of tomato and tomato phytochemical consumption on CVD development in animal models may provide some interesting data to help establish the role of tomatoes in a cardioprotective diet.

Tomato bioactive components and modes of action

Tomatoes contain many bioactive components, including those that act as antioxidants, such as the vitamins C and E, and many carotenoids. As the main carotenoid in tomatoes, lycopene is often assumed to be responsible for the positive health effects seen with increased tomato intake. Particularly, lycopene is the most efficient carotenoid at scavenging singlet oxygen and reactive oxygen species (31,32). The antioxidant effect of lycopene is potentially beneficial in disease prevention for both CVD and prostate cancer. In regard to CVD, lycopene and tomatoes could possibly reduce the disease development by reducing inflammation, inhibiting cholesterol synthesis, or improving immune function (25).

The proposed mechanisms of action of lycopene in prostate cancer prevention includes inhibition of proliferation, antiandrogen and antigrowth factor effects (33,34). Foods rich in lycopene have been found to decrease endogenous levels of DNA strand breaks in human lymphocytes (35). In an attempt to understand mechanisms that might explain the inverse relation between dietary intakes of lycopene/tomato and prostate cancer risk, 15 men were given either placebo or Lyc-O-Mato, containing 15 mg of lycopene, 2.5 mg phytoene and phytofluene, and other minor carotenoids, twice a day for 3 wk before radical prostatectomy (36). Researchers ascertained that the lycopene supplemented group had less cancer at the surgical margins and in extraprostatic tissues, smaller tumors, and an 18% reduction in prostate specific antigen (PSA) levels, whereas the control group's PSA levels increased by 14%. Lycopene treatment was also found to increase expression of connexin 43 in cancerous prostate tissue. Connexin 43 is a recognized tumor suppressor gene, which can increase gap junction communication and therefore suppress overgrowth of cells (36).

In a second small clinical trial, 32 prostate cancer patients consumed tomato-sauce–based pasta dishes daily, containing 30 mg lycopene, for 3 wk before their scheduled radical prostatectomy (37). Although there was no control group, the tomato-product consumption resulted in a decrease in serum PSA levels from 10.9 to 8.7 μg/L ($P = < 0.001$). Leukocyte oxidative DNA damage was statistically lower after regular tomato consumption than before the dietary intervention. In addition, prostate tissue also showed a reduced amount of oxidative DNA damage in men who were treated compared with those who were randomly selected.

CONCLUSIONS

Emerging epidemiological evidence regarding lycopene, tomatoes, and CVD has shown promising protective effects with more frequent consumption. Epidemiology, in vitro studies, animal studies, and small clinical human trials all provide support for significant effects of tomato consumption on prostate cancer development, although many questions still remain. For example, the mechanistic action of tomato components, including lycopene and other carotenoids, and their interactions with each other warrants further investigation. Scientists should be mindful that tomato products contain a variety of compounds in addition to lycopene, such as vitamins C and E, soluble fiber, other carotenoids, and polyphenols. Moreover, health effects derived from tomato components could also be due in part to the effects of the metabolic products of these bioactive compounds. Research is required to determine how tomato phytochemicals interact with other food components, such as sulforophane in broccoli, isoflavones in soy, and various herbal products. Only then can we truly understand the disease prevention capabilities of tomatoes and how to properly process and consume tomato products for maximal health benefits. Due to the large volume of tomatoes that Americans consume, tomatoes are a convenient matrix by which nutrients and bioactive components can be delivered for human consumption (38). Overall, no matter if you are trying to reduce the risk of CVD or prostate cancer, a diet that regularly contains tomatoes appears to be a healthy choice and beneficial for us all.

LITERATURE CITED

1. Agriculture Statistics (2003) Chapter IV: Statistics of Vegetables and Melons. USDA National Agricultural Statistic Services, 2003. United States Government Printing Office, Washington, DC.
2. Lucier, G., Lin, B., Allshouse, J. & Kantor, L. (2002) Factors Affecting Tomato Consumption in the United States. Vegetables and Specialities/VGS-282/November 2000. Economic Research Service, USDA. http://www.ers.usda.gov/briefing/consumption/gallery/tomatoconsumption.pdf [accessed June 15, 2004].
3. USDA Nutrient Data Bank [Online]. http://www.nal.usda.gov/ [accessed June 2004].
4. Tonucci, L., Holden, J., Beecher, G., Khackik, F., Davis, C. & Mulokozi, G. (1995) Carotenoid content of thermally processed tomato-based food products. J. Agric. Food Chem. 43: 579–586.
5. Stewart, A., Bozonnet, S., Mullen, W., Jenkins, G., Lean, M. & Crozier, A. (2000) Occurrence of flavonols in tomatoes and tomato-based products. J. Agric. Food Chem. 48: 2663–2669.
6. USDA National Nutrient Database for Standard Reference, Release 16–1. (2004) Lycopene Content of Selected Foods, Per Common Measure, Sorted by Nutrient Content. http://www.nal.usda.gov/fnic/foodcomp [accessed July 2004].
7. Levy, J. & Sharoni, Y. (2004) The functions of tomato lycopene and its role in human health. Herbal Gram. 62: 49–56.
8. Wilkinson, S. & Chodak, G. W. (2003) Critical review of complementary therapies for prostate cancer. J. Clin. Oncol. 21: 2199–2110.
9. Cohen, L. A. (2002) Nutrition and prostate cancer: a review. Ann. N.Y. Acad. Sci. 963: 148–155.
10. Cancer Facts and Figures (2005) The American Cancer Society. http://www.cancer.org/docroot/stt/stt_o.dsp [accessed March 2005].
11. Krauss, R. M., Eckel, R. H., Howard, B., Lawrence, J. Appel, L. J., Daniels, S. R., Deckelbaum, R. J., Erdman, J. W. Jr., Kris-Etherton, P., et al. (2000) AHA dietary guidelines: revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation 102: 2284–2299.
12. Heart Disease and Stroke Statistics (2005) Update. American Heart Association. http://www.americanheart.org/downloadable/heart/1105390918119HOSStats2005update.pdf [accessed March 2005].
13. Gann, P., Ma, J., Giovannucci, E., Willett, W., Sacks, F., Hennekens, C. & Stampfer, M. (1999) Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. Cancer Res. 59: 1225–1230.
14. Lu, Q., Hung, J., Heber, D., Go, V., Reuter, V., Crordon-Cardo, C., Scher, H., Marshall, J. & Zhang, Z. (2001) Inverse associations between plasma lycopene and other carotenoids and prostate cancer. Cancer Epidemiol. Biomarkers Prev. 10: 749–756.
15. Giovannucci, E., Rimm, E., Liu, Y., Stampfer, M. & Willett, W. (2002) A prospective study of tomato products, lycopene, and prostate cancer risk. J. Natl. Cancer Inst. 94: 391–398.
16. Wu, K., Erdman, J. W., Jr., Schwartz, S. J., Platz, E. A., Leitzmann, M., Clinton, S. K., DeGroff, V., Willett, W. C. & Giovannucci, E. (2004) Plasma and dietary carotenoids, and the risk of prostate cancer: a nested case-control study. Cancer Epidemiol. Biomarkers Prev. 13: 260–269.
17. Etminan, M., Takkouche, B. & Caamano-Asorna, F. (2004) The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. Cancer Epidemiol. Biomarkers Prev. 13: 340–345.
18. Bosland, M. C. (1992) Animal models for the study of prostate carcinogenesis. J. Cell Biochem. Suppl. 16H: 89–98.
19. Bosland, M. C., Prinsen, M. K. & Kroes, R. (1983) Adenocarcinomas of the prostate induced by *N*-nitroso-*N*-methylurea in rats pretreated with cyproterone acetate and testosterone. Cancer Lett. 18: 69–78.
20. Boileau, T. W., Liao, Z., Kim, S., Lemeshow, S., Erdman, J. W. Jr. & Clinton, S. K. (2003) Prostate carcinogenesis in *N*-methyl-*N*-nitrosourea

(NMU)-testosterone-treated rats fed tomato powder, lycopene, or energy-restricted diets. J. Natl. Cancer Inst. 95: 1578–1586.

21. Tennant, T. R., Kim, H., Sokoloff, M. & Rinker-Schaeffer, C. W. (2000) The Dunning Model. Prostate 43: 295–302.

22. Isaacs, J. T., Isaacs, W. B., Feitz, W.F.J. & Scheres, J. (1986) Establishment and characterization of seven Dunning rat prostatic cancer cell lines and their use in developing methods for predicting metastatic abilities of prostatic cancers. Prostate 9: 261–281.

23. Canene-Adams K., Clinton, S. K., King, J. L., Lindshield, B. L., Wharton C., Jeffery, E. & Erdman, J. W. Jr. (2004) The growth of the Dunning R-3327-H transplantable prostate adenocarcinoma in rats fed diets containing tomato, broccoli, lycopene, or receiving finasteride treatment. FASEB J. 18: A886 (591.4).

24. Siler, U., Barella, L., Spitzer, V., Schnorr, J., Lein, M., Goralczyk, R. & Wertz, K. (2004) Lycopene and vitamin E interfere with autocrine/paracrine loops in the Dunning prostate cancer model. FASEB J. 18: 1019–1021.

25. Petr, L. & Erdman, J. W. (2005) Lycopene and risk of cardiovascular disease. In: Carotenoids and Retinoids: Biological Actions and Human Health. (Packer, L., Obermueller-Jevic, U., Kramer, K. & Sies, H., eds.), pp. 204–217. AOCS Press, Champaign, IL.

26. Rissanen, T., Voutilainen, S., Nyyssonen, K. & Salonon, J. (2002) Lycopene, atherosclerosis, and coronary heart disease. Exp. Biol. Med. 227: 900–907.

27. Rissanen, T., Voutilainen, S., Nyyssonen, K., Salonon, J., Kaplan, G. & Salonen, J. (2003) Serum lycopene concentration and carotid atherosclerosis: the Kuopio Ischaemic Heart Disease Risk Factor Study. Am. J. Clin. Nutr. 77: 133–138.

28. Kohlmeier, L., Kark, J. D., Gomez-Gracia, E., Martin, B. C., Steck, S. E., Kardinaal, A. F., Ringstad, J., Thamm, M., Masaev, V., et al. (1997) Lycopene and myocardial infarction risk in the EURAMIC Study. Am. J. Epidemiol. 146: 618–626.

29. Sesso, H. D., Liu, S., Gaziano, J. M. & Buring, J. E. (2003) Dietary lycopene, tomato-based food products and cardiovascular disease in women. J. Nutr. 133: 2336–2341.

30. Sesso, H. D., Buring, J. E., Norkus, E. P. & Gaziano, J. M. (2004) Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in women. Am. J. Clin. Nutr. 79: 47–53.

31. Di Mascio, P., Kaiser, S. & Sies, H. (1989) Lycopene as the most efficient biological carotenoid singlet oxygen quencher. Arch. Biochem. Biophys. 274: 532–538.

32. Conn, P. F., Schalch, W. & Truscott, T. G. (1991) The singlet oxygen and carotenoid interaction. J. Photochem. Photobiol. B 11: 41–47.

33. Nelsom, W. G., De Marzo, A. M. & Isaacs, W. B. (2003) Mechanisms of disease: prostate cancer. N. Engl. J. Med. 349: 366–381.

34. Wang, S., DeGroff, V. L. & Clinton, S. K. (2003) Tomato and soy polyphenols reduce insulin-like growth factor-1-stimulated rat prostate cancer cell proliferation and apoptotic resistance in vitro via inhibition of intracellular signaling pathways involving tyrosine kinase. J. Nutr. 133: 2367–2376.

35. Pool-Zobel, B. L., Bub, A., Muller, H., Wollowski, I. & Rechkemmer, G. (1997) Consumption of vegetables reduces genetic damage in humans: first results of a human intervention trial with carotenoid-rich foods. Carcinogenesis 18: 1847–1850.

36. Kucuk, O., Sarkar, F. H., Sakr, W., Djuric, Z., Pollak, M. N., Khachik, F., Li, Y. W., Banerjee, M., Grignon, D., et al. (2001) Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. Cancer Epidemiol. Biomarkers Prev. 10: 861–868.

37. Chen, L., Stacewicz-Sapuntzakis, M., Duncan, C., Sharifi, R., Ghosh, L., van Breemen, R., Ashton, D. &, Bowen, P. E. (2001) Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. J. Natl. Cancer Inst. 93: 1872–1879.

38. Beecher, G. R. (1998) Nutrient content of tomatoes and tomato products. Proc. Soc. Exp. Biol. Med. 218: 98–100.