ABSTRACT Mounting evidence over the past decade suggests that the consumption of fresh and processed tomato products is associated with reduced risk of prostate cancer. The emerging hypothesis is that lycopene, the primary red carotenoid in tomatoes, may be the principle phytochemical responsible for this reduction in risk. A number of potential mechanisms by which lycopene may act have emerged, including serving as an important in vivo antioxidant, enhancing cell-to-cell communication via increasing gap junctions between cells, and modulating cell-cycle progression. Although the effect of lycopene is biologically relevant, the tomato is also an excellent source of nutrients, including folate, vitamin C, and various other carotenoids and phytochemicals, such as polyphenols, which also may be associated with lower cancer risk. Tomatoes also contain significant quantities of potassium, as well as some vitamin A and vitamin E. Our laboratory has been interested in identifying specific components or combination of components in tomatoes that are responsible for reducing prostate cancer risk. We carried out cell culture trials to evaluate the effects of tomato carotenoids and tomato polyphenols on growth of prostate cancer cells. We also evaluated the ability of freeze-dried whole-tomato powder or lycopene alone to reduce growth of prostate tumors in rats. This paper reviews the epidemiological evidence, evaluating the relationship between prostate cancer risk and tomato consumption, and presents experimental data from this and other laboratories that support the hypothesis that whole tomato and its phytochemical components reduce the risk of prostate cancer. J. Nutr. 134: 3486S–3492S, 2004.

KEY WORDS: tomato • lycopene • prostate cancer • phytochemicals
USDA's Economic Research Service has estimated that 35% of tomatoes are used for sauces, 18% for pastes, 17% for canned tomatoes, 15% for catsup, and 15% for juices (10). Interestingly, teenage boys (12–19 y old) have the highest per capita consumption of catsup, whereas both fresh tomato and tomato juice consumption rise with increased age for both men and women (10). Because of their frequent consumption, tomatoes and tomato products serve as a convenient way to supply nutrients and various phytochemicals to humans (7).

Nutrient and phytochemical composition of tomatoes

Tomato products are excellent sources of potassium; folate; and vitamins A, C, and E (Table 1) (11). Tomato products contain similar amounts of potassium and folate but are superior sources of α-tocopherol and vitamin C (11). When compared with the other regularly consumed vegetables, only carrots are a better dietary source of vitamin A than tomato-based foods. Fiber is another dietary component that has been associated with decreased cancer risk, and appreciable amounts are found in tomato products. The tomato product with the most fiber is tomato paste (USDA NDBN 11546), with 11.8 g fiber per cup (12).

Tomatoes also contain a variety of phytochemicals, including carotenoids and polyphenols. In tomatos and tomato products, lycopene is the carotenoid with the highest concentration, but tomatoes also contain other carotenoids, including phytoene, phytofluene, and the provitamin A carotenoid β-carotene (Table 2) (11,13). Other sources of lycopene include fresh watermelon (45.3 μg/g) and pink grapefruit (14.2 μg/g), but 85% of lycopene exposure comes from tomato sources, such as canned tomato sauces (287.6 μg/g) (12,14). Tomatoes are also a concentrated source of flavonols, with up to 98% of the total flavonols contained in the tomato skin as conjugated forms of quercetin and kaempferol (15). The flavanone naringenin is present in small quantities in tomatoes in its conjugated form (16). Many of these nutrients and phytochemicals have antioxidant properties and in combination with lycopene may contribute to the numerous health benefits of tomatoes.

Epidemiological evidence

Many, but not all, epidemiological studies support the hypothesis that higher intakes of tomatoes, tomato products, and lycopene are significantly associated with a reduced risk of prostate cancer (4,5,17,18). Of particular relevance is the

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Raw tomatoes</th>
<th>Catsup</th>
<th>Tomato juice</th>
<th>Tomato sauce</th>
<th>Tomato soup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium, mg</td>
<td>237</td>
<td>382</td>
<td>229</td>
<td>331</td>
<td>181</td>
</tr>
<tr>
<td>α-Tocopherol, mg</td>
<td>0.54</td>
<td>1.46</td>
<td>0.32</td>
<td>2.08</td>
<td>0.50</td>
</tr>
<tr>
<td>Vitamin A, IU</td>
<td>839</td>
<td>933</td>
<td>450</td>
<td>348</td>
<td>193</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>12.7</td>
<td>15.1</td>
<td>18.3</td>
<td>7.0</td>
<td>27.3</td>
</tr>
<tr>
<td>Total folate, μg</td>
<td>15</td>
<td>15</td>
<td>20</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

1 USDA Nutrient Data Bank Numbers (NDB No.): raw tomatoes, 11529; catsup, 11935; tomato juice, 11540; tomato sauce, 11549; tomato soup, 06359 (11).

TABLE 2

<table>
<thead>
<tr>
<th>Carotenoid content of tomatoes and related tomato products1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tomato products</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Raw tomatoes</td>
</tr>
<tr>
<td>Catsup</td>
</tr>
<tr>
<td>Tomato juice</td>
</tr>
<tr>
<td>Tomato sauce</td>
</tr>
<tr>
<td>Tomato soup</td>
</tr>
<tr>
<td>Phytoene</td>
</tr>
</tbody>
</table>

1 USDA Nutrient Data Bank Numbers (NDB No.): raw tomatoes, 11529; catsup, 11935; tomato juice, 11540; tomato sauce, 11549; tomato soup, 06359 (11).

2 Adapted from Tonucci, L. et al. (13).

Health Professionals Follow-up Study (HPFS), a prospective epidemiological study of ~47,000 men (19). These study participants were followed from 1986 through 1992 and answered FFQs and lifestyle questionnaires periodically. In this cohort, 773 prostate cancer cases were diagnosed by 1992. Statistical analysis indicated that consumption of 2–4 servings per wk of raw tomatoes was associated with a significant 26% reduced risk of prostate cancer when compared with no servings per wk. In addition, tomato products, including pizza and tomato sauce, were also significantly associated with a reduced risk of prostate cancer by 15% and 34%, respectively, when consumed 2–4 times per wk compared with no intake. When all dietary sources of tomatoes were combined, consumption of >10 servings per wk was associated with a significant 35% reduced prostate cancer risk when compared with fewer than 1.5 servings per wk. Men with the highest quintile of lycopene intake had a 21% reduction of prostate cancer risk compared with those in the lowest quintile of lycopene intake (>6.5 vs. <2.3 mg/d, respectively).

Recently, a longer follow-up period from the HPFS cohort was evaluated to confirm the association between frequent intake of tomato products and decreased prostate cancer risk (20). In this same population, 2481 of the 47,365 men had been diagnosed with prostate cancer by 1998, and, again, tomato sauce consumption was associated with a 23% reduction in prostate cancer risk when two or more servings were compared with <1 serving per wk. Higher lycopene intake was also significantly associated with a 16% reduced risk for prostate cancer incidence when high vs. low quintile of lycopene intake were compared (median quintile intakes of 3.4 and 18.8 mg/d, respectively). A nested case-control study within this cohort found a significant inverse association between plasma lycopene concentrations and prostate cancer risk that appeared to be strongest in older men (>65 y) and individuals without a prior family history of prostate cancer incidence (21). These findings support the hypothesis that tomato and lycopene intake may demonstrate stronger protection in cases.
of sporadic prostate cancer rather than in cases with a strong genetic component. Overall, the numerous and consistent findings from the HPFS cohort suggest that frequent intake of tomatoes, tomato products, or lycopene may decrease prostate cancer incidence.

Another prospective analysis was conducted to determine whether plasma concentrations of different antioxidants, such as carotenoids, α-tocopherol, or γ-tocopherol, were related to risk of prostate cancer. In this nested case-control study, plasma samples obtained at enrollment were used from participants in the Physicians’ Health Study, a randomized placebo-controlled trial of β-carotene and aspirin (22). Within the 13 y of follow-up, 578 men developed prostate cancer and were compared with 1294 control subjects matched for age and smoking status. In this study the highest and lowest quintiles of plasma lycopene were defined as >1.08 μmol/L (>580 μg/L) and <0.488 μmol/L (<262 μg/L), respectively. Among all antioxidants analyzed, only plasma lycopene concentration was significantly lower in prostate cancer cases than in matched controls. In addition, the odds ratios for prostate cancer declined slightly with increasing quintile of plasma lycopene concentrations, and a significant inverse relationship was found between aggressive prostate cancer cases and increasing quintile of plasma lycopene.

The above studies are representative examples of a series of analyses with data relevant to the relationship of tomato and lycopene with prostate cancer that were pooled and examined in a recent meta-analysis (23). A total of 11 case-control and 10 cohort or nested case-control studies were included, and the authors concluded that tomato products may play a role in the prevention of prostate cancer. However, this effect is modest and is strongest in men with high tomato consumption (i.e., when highest and lowest quintiles of tomato product intake were compared). Overall, the accumulating data from human epidemiological studies supports the hypothesis that tomatoes and tomato products are related to a reduced risk of prostate cancer. These studies suggest that specific components of these foods, including lycopene and other phytochemicals and nutrients, may mediate health benefits, and thus the studies provide justification for experimental studies designed to further investigate this relationship.

**Experimental models and in vitro studies**

**Cell culture studies with tomato polyphenols.** Tomatoes contain a variety of polyphenols, such as quercetin, kaempferol, and naringenin, which are hypothesized to have both antioxidant and anticarcinogenic effects (24). A wide variety of polyphenols common in fruits and vegetables have demonstrated antiproliferative and antiapoptotic effects in prostate cancer cell lines (8,25–28). Recently, our laboratory has investigated the antiproliferative effects of tomato polyphenols in a human prostate cancer cell line, LNCaP, and in a mouse hepatocyte cell line, Hepa1c1c7 (29). Preliminary data show that after treatment for 48–72 h, tomato aglycone polyphenols, including quercetin, kaempferol, and naringenin, inhibited cancer cell proliferation in both LNCaP and Hepa1c1c7 cells, in a dose-dependent manner (10–50 μmol/L), without having cytotoxic effects. In contrast, the glucose polyphenols, rutin, quercetin, and naringin, did not decrease cell growth at 50 or 100 μmol/L, suggesting that LNCaP and Hepa1c1c7 cells may not respond to glycosylated forms of the polyphenols. Whereas quercetin, kaempferol, and naringenin inhibited cell proliferation in LNCaP and Hepa1c1c7 cancer cell lines in a dose-dependent manner, combination treatments (25, 40, and 50 μmol/L total) of quercetin, kaempferol, and naringenin produce additive and perhaps synergistic inhibition of growth in both cell lines. Overall, preliminary results from this work indicate that individual tomato polyphenols, specifically quercetin, kaempferol, and naringenin, decrease cancer cell growth in vitro and that combinations of these polyphenols, which are present in whole foods, may have additive effects in decreasing cancer proliferation.

**N-methyl-N-nitrosourea (NMU)–androgen-induced prostate cancer model.** Our laboratory recently published an in vivo study comparing the effects of AIN-93G diets containing 10% tomato powder, 0.025% lycopene (from beadlets), and 20% dietary energy restriction on the development of prostate cancer in the NMU–androgen-induced prostate cancer model (30). Compared with the control group, rats fed tomato powder experienced a significant 26% decrease in prostate cancer-specific mortality, whereas the 9% decrease of mortality by lycopene consumption did not reach significance. Dietary energy restriction independently decreased prostate cancer-specific mortality by 32% compared with the rats fed unrestricted amounts of food.

Recently, we carried out additional analysis of the data from this study of NMU–androgen-induced prostate cancer. Interestingly, if the analysis was separated into 2 periods, before and after 45 wk post-NMU administration, dietary energy restriction significantly decreased the hazard risk for prostate cancer by 48% during the first 45 wk but had no effect after 45 wk (Table 3). In contrast, tomato powder and lycopene had little effect during the first 45 wk but significantly decreased the hazard risk for prostate cancer death by 56% and 44%, respectively, after 45 wk (Table 3). There was no statistically significant interaction detected between the type of diet (tomato powder, lycopene, or control) and dietary energy restriction on risk of prostate cancer. Because the delay in prostate cancer by tomato and lycopene consumption and dietary energy restriction occurred at different times, it is possible that these two dietary interventions work by different mechanisms.

**The Dunning MatLyLu prostate cancer model.** Using the Dunning MatLyLu subline, a less differentiated and aggressive transplantable rat prostate cancer cell line, the effects of lycopene and vitamin E, 2 components of tomatoes, were tested on the growth of prostate tumors by Silber et al. (31). The authors observed no significant effect of lycopene (220 μg/g), vitamin E (540 μg/g), or dietary supplementation of both on overall tumor growth. However, in vivo analysis of tumors by MRI suggested changes in tumor composition with rats fed lycopene, vitamin E, and their combination, demonstrating tumor necrotic areas of 36, 36, and 29%, respectively. The changes in tumor composition of the rats fed lycopene did not reach significance. Dietary energy restriction decreased prostate cancer-specific mortality by 44%, but the combination of dietary energy restriction and lycopene supplementation decreased prostate cancer-specific mortality by 50%.

**TABLE 3**

 proportional hazard analysis of risk for prostate cancer before and after 45 wk after NMU administration

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>P-value</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Before 45 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restricted vs. unrestricted</td>
<td>0.52</td>
<td>0.017</td>
<td>0.31 0.89</td>
</tr>
<tr>
<td>Tomato vs. control</td>
<td>0.99</td>
<td>0.29</td>
<td>0.51 1.90</td>
</tr>
<tr>
<td>Lycopene vs. control</td>
<td>1.37</td>
<td>0.98</td>
<td>0.77 2.45</td>
</tr>
<tr>
<td>After 45 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restricted vs. unrestricted</td>
<td>1.00</td>
<td>0.99</td>
<td>0.62 1.61</td>
</tr>
<tr>
<td>Tomato vs. control</td>
<td>0.44</td>
<td>0.006</td>
<td>0.24 0.79</td>
</tr>
<tr>
<td>Lycopene vs. control</td>
<td>0.56</td>
<td>0.048</td>
<td>0.31 0.99</td>
</tr>
</tbody>
</table>

1 Unpublished secondary analysis from Boileau et al. (30).
and vitamin E were significantly different from the untreated and vehicle-treated animals, which had tumor necrotic areas of 20% and 23%, respectively. The relevance of these findings remains to be determined. More rapidly growing tumors in rodents often show significant central necrosis because of the metabolic demands of the tumor cells exceeding the ability of the vasculature to provide oxygen and nutrients and to remove metabolic waste products. The authors completed microarray analysis on the tumor tissue and found that vitamin E reduced androgen signaling, whereas lycopene downregulated 5 α-reductase 1, insulin growth factor-1 (IGF-1), and IL-6 expression. On the basis of their findings, the authors propose that the dietary agents act via an inhibition of androgen metabolism; however, this hypothesis may not be relevant to prostate cancer models that are relatively androgen insensitive.

**Rat study using the Dunning R-3327H transplanted tumor model.** Our laboratory has continued interest in whether whole foods, combination of foods, or a single bioactive component more effectively reduces prostate cancer growth in vivo. We recently used the Dunning R-3327H transplanted rat model, with groups fed diets containing 0.025% lycopene (from beadlets), 10% tomato, and 10% broccoli powders, individually or a combination of 10% tomato and 10% broccoli powders, to determine whether the dietary interventions were able to decrease prostate tumor growth. Preliminary results from the pilot study indicated that diets containing broccoli, tomato, lycopene, and a combination of tomato plus broccoli reduced Dunning R-3327H prostate tumor growth rate compared with the control diet (32). Further trials are underway as follow-up and to evaluate possible additive effects of broccoli and tomato powders.

**Human clinical trials.** Twenty-five carotenoids and 9 metabolites have been identified and characterized in human serum; breast milk; and several organs, including the breast, lung, liver, cervix, colon, skin, and prostate (33). Human studies have shown that changes in tomato product intake can significantly alter lycopene concentration in the blood and its isomer profile. Because plasma lycopene has a 10- to 14-day half-life (34), many human studies designed to examine changes in plasma lycopene begin with a washout period with a diet containing low amounts of carotenoids. For example, after a 1-wk washout period, dietary intervention for 15 d significantly increased total lycopene concentrations in 60 subjects consuming condensed tomato soup, ready-to-serve tomato soup, or vegetable juice by 123% (0.784 μmol/L), 57% (0.545 μmol/L), and 112% (0.569 μmol/L), respectively (35). During the washout period, all-trans-lycopene concentrations decreased from 44.4% of total plasma lycopene isomers to 39.6%, whereas total cis isomers of lycopene significantly increased from 55.6% to 60.4%. This shift in lycopene isomer profile was reversed by dietary intervention with tomato products.

A similar study was designed to examine alterations in plasma and buccal mucosal cell lycopene concentrations in 36 subjects consuming spaghetti sauce, tomato soup, or vegetable juice after a 2-wk washout period (36). Total plasma lycopene concentrations significantly decreased to ~0.54 μmol/L after the washout period and increased significantly with the 4-wk dietary intervention of sauce, soup, and juice to 2.08, 0.91, and 0.99 μmol/L, respectively. A similar shift in plasma lycopene isomer profile was seen in this study; during the washout period, the ratio of all-trans- to cis-lycopene isomers decreased but was reversed with 2 wk of dietary intervention with tomato products. The decrease in the proportion of all-trans-lycopene during study washout periods may be due to several mechanisms, such as preferential tissue uptake, more rapid body clearance, and conversion to cis-lycopene isomers. The increase in plasma cis isomers may be due to mobilization of tissue lycopene stores, where lycopene is primarily found as cis isomers (35,36). Although researchers did not find significant changes of buccal mucosal cell lycopene concentrations during the washout, these concentrations increased by 165, 42, and 48% after the 4-wk intervention of sauce, soup, and juice, respectively (36). The overall conclusion from this work is that blood lycopene more closely reflects recent dietary intake, whereas tissue concentrations reflect long-term lycopene intake and gradually fluctuate with time (36).

Although tomato and tomato products contain primarily the all-trans-isomer of lycopene, various studies have found that both serum and tissues of humans and animals accumulate cis-lycopene isomers preferentially (6,37,38). In a study by Stahl and Sies (37), serum from healthy human subjects contained 55% cis-lycopene isomers after consumption of tomato juice, which only contained 20% cis-lycopene isomers. In the ferret, an animal that absorbs carotenoids similarly to humans, our laboratory found significantly greater absorption of cis-lycopene isomers (~50%) in mucosa, lymph, blood, and tissues compared with stomach or intestinal contents after a lycopene dose containing only 9% cis isomers (38). Results from in vitro experiments suggest that cis isomers of lycopene are more readily taken up by lipid micelles than all-trans-lycopene and thus may be more easily absorbed by enterocytes (38). The specific biological role of cis-lycopene isomers in human health remains undefined.

Lycopene is the most abundant carotenoid present in the prostate (6), but a variety of other tomato carotenoids accumulate as well, including phytoene; phytofluene; and cis, β-, and γ-carotene (33). Lycopene metabolites, such as 2,6-cyclopycopene-1,5-diols A and B, have also been found in human serum, milk, lung, breast, liver, colon, skin, and prostate (33), yet the specific biological significance of these metabolites is unclear. Clinton et al. (6) analyzed carotenoid and vitamin A concentrations in paired benign and malignant prostate tissues from 25 men (53–74 y old) undergoing prostatectomy for localized prostate cancer. Total carotenoid concentrations ranged from 0.75 to 5.0 nmol/g; of all carotenoids measured, lycopene had the highest mean concentration (0.80 nmol/g ± 0.08 nmol/g). Further analysis demonstrated that although tomato and tomato products consist primarily of all-trans-lycopene (79–91%), cis-lycopene accounts for 79–88% of total lycopene in malignant and benign prostate tissues. However, the specific role of cis-lycopene isomers in relation to prostate carcinogenesis is not understood.

More recently, van Breeman et al. (39) investigated lycopene isomer profiles in human serum and prostate tissues after dietary supplementation with tomato products. In this small clinical study, a pasta dish based on tomato sauce (30 mg/d of lycopene) was provided daily to 32 men with clinical stage prostate cancer (T1 or T2) for 3 wk before prostatectomy. Prostate tissue samples were obtained from 11 men by needle biopsy before dietary intervention and by prostatectomy after supplementation, and total lycopene and lycopene isomers were quantified. Results from this study show a 3.0-fold increase of total lycopene (from 0.20 to 0.58 mg/mg) in the prostate after tomato product supplementation. In addition, all-trans-lycopene accounted for ~12.4% of total lycopene in the prostate before supplementation and increased to 22.7% after dietary intervention. In another study, prostate tissue and leukocyte oxidative DNA damage and serum prostate-specific antigen (PSA) levels were all significantly lower in men receiving a dietary intervention than in randomly selected patients (40). Furthermore, leukocyte oxidative damage and...
Another small clinical trial was conducted to evaluate the effects of lycopene supplementation in prostate cancer patients. In this study, 26 men diagnosed with prostate cancer (T1 or T2) were randomly assigned to no supplementation or tomato oleoresin supplementation containing 15 mg lycopene and smaller quantities of other tomato carotenoids, including phytoene, phytofluene, ξ-carotene, and y-carotene. Supplementation was provided twice daily for 3 wk before radical prostatectomy. Data from this study suggest that supplementation positively modulated the volume and grade of prostate intraepithelial neoplasia compared with the control. PSA levels also decreased by 18% in the supplementation group, whereas PSA levels increased in the control group. In addition, tomato oleoresin supplementation altered biomarkers of cell growth and differentiation, including increased expression of connexin 43.

These laboratory and clinical trials have provided intriguing results: the accumulation of various lycopene isomers and metabolites in the human serum and prostate, and the potential for dietary supplementation of tomato products and extracts to modulate plasma lycopene concentrations and various biomarkers of prostate carcinogenesis. Although these results are encouraging, the number of tissues and subjects used for some studies were small and future studies with larger group sizes are needed.

### Potential mechanism of action of tomatoes and tomato phytochemicals

Several plausible mechanisms of action were proposed for the anticarcinogenic effects of tomatoes and tomato phytochemicals. Both carotenoids and polyphenols present in tomatoes have distinct antioxidant properties, thereby quenching free radicals (24,42). When compared with other commonly consumed carotenoids, lycopene is the most potent antioxidant in quenching singlet oxygen in vitro (43–45). Healthy subjects supplemented for 15 d with tomato products exhibited a significant increase in ex vivo lipoprotein oxidation lag period (35), and several studies showed that tomato and tomato juice consumption lead to decreased lymphocyte DNA damage (46–48). These studies suggest that tomato consumption may provide protection from in vivo oxidative damage, thereby potentially preventing mutations associated with cancer initiation and progression.

Tomato phytochemicals have also been shown to alter xenobiotic metabolism. Brienholz et al. (49) found that lycopene significantly induced phase I enzymes, such as cytochrome P450-dependent enzymes, in a dose-dependent manner and increased hepatic quinone reductase (QR), a phase II enzyme, by 2-fold. Other studies demonstrated that lycopene induced phase II detoxification enzymes in a variety of animal models (50–52). This class of enzymes is important for the removal of foreign substances and carcinogens from the body. As reviewed by Birt et al. (24), tomato flavonoids, such as kaempferol, quercetin, and naringenin, have demonstrated high potencies and selectivities for the inhibition of cytochrome P450–1A isoforms, and other studies showed that quercetin induces QR.

Tomato phytochemicals have also been hypothesized to modulate hormone and growth factor signaling in prostate cells. Alterations in IGF-1 activity, which stimulates proliferation and apoptotic resistance in cells, were examined in a case-control study of 112 men (53). Cooked tomato consumption was associated with a 31.5% decrease in serum IGF-1 levels. Lycopene supplementation was found to significantly decrease tumor IGF-1 expression in rats (31). A significant trend toward lower serum IGF-1 and higher insulin growth factor binding protein-3 (IGFBP-3) was found with higher weekly consumption of catsup and tomato juice in 344 disease-free men (54), and a similar decrease in the ratio of IGF-1 to IGFBP3 was found in ferrets fed lycopene (55). A lower ratio of IGF-1 to IGFBP-3 is considered beneficial, because IGFBP-3 binds IGF-1, thereby preventing IGF-1 from stimulating cell proliferation. Both lycopene and tomato polyphenols, including quercetin, kaempferol, and rutin, were shown to interfere with IGF-1 signaling in vitro, thus preventing the growth factor from stimulating cell proliferation (8,56).

Lycopene induced cell-cycle arrest in a number of cancer cell lines by blocking the transition from G1 to S phase of the cell cycle. In normal prostate epithelial cells, lycopene treatment led to a dose-dependent decrease in cyclin D1, which is a protein that regulates the G1-to-S phase transition in cells (57). In MCF-7 and T-47D breast cancer cells and ECC-1 endometrial cancer cells, lycopene was also found to decrease cyclin D1 levels and to retain p27 levels in cyclin E-cdk2 complexes (58). p27 is a cyclin-dependent kinase inhibitor that prevents the transition from G1 to S phase, thus causing cell-cycle arrest. Similar effects of lycopene on p27 levels in prostate cancer cells have not been thoroughly examined and still need to be determined.

Although cell-culture models allow researchers to examine molecular and cellular events potentially modulated by phytochemicals, investigators should take caution when evaluating the effects of carotenoids in vitro. As seen in studies by our laboratory and others, carotenoids are often oxidized and degraded during experimental in vitro conditions (59–61). Therefore, biological effects of carotenoids may not be due only to the parent compound of interest but also to degradation products of carotenoids produced during incubation.

Lycopene and lycopene metabolites were also proposed to increase gap junction communication between cells by increasing the levels of connexin 43 (62–66). Formation of gap junctions allows for cell-to-cell communication, which is important in the regulation of uncontrolled, rapid cell growth. Interestingly, in PC-3MM2 (metastatic prostate cancer cells) and normal oral mucosal cells, lycopene failed to inhibit growth or increase connexin 43 levels, whereas in PC-3 prostate, MCF-7 breast, and KB-1 oral cancer cells, the inhibition of growth by lycopene was mirrored by increased connexin 43 levels (67,68), thus suggesting that upregulation of connexin 43 may be important to the anticancer action of lycopene.

Overall, several potential mechanisms of action have been identified for tomato phytochemicals, including antioxidant potential, altering xenobiotic metabolism, modulation of the IGF-1 axis, inhibiting cell-cycle progression, and increasing the formation of gap junctions. Although varied, the mechanisms may be complementary and overlapping, and a combination of these mechanisms may be responsible for the anticancer effects of tomato phytochemicals seen in epidemiological and animal studies.

### Conclusions

A majority of prospective and case-control epidemiological studies support the hypothesis that diets rich in tomatoes and tomato products are associated with a reduced risk of prostate cancer (5,23). In vitro studies and animal trials using tomato and tomato phytochemicals have provided further data supporting these epidemiological associations. Several small clinical trials have also suggested that supplementation with to-
matoes or tomato extract may positively influence biomarkers related to prostate carcinogenesis consistent with a reduction in risk. The various components of tomatoes, including carotenoids and polyphenols, that may mediate anticarcinogenic effects remain speculative. Considerable attention has focused on lycopene as the primary compound that may contribute to decreased prostate cancer risk, yet this hypothesis requires further investigation as studies of pure lycopene as a chemopreventive agent are only beginning to be reported (30–32). Other components may influence prostate carcinogenesis, such as other tomato carotenoids and polyphenols, perhaps in combination with lycopene, and warrant further investigation in animal and human studies. Although several plausible anticarcinogenic mechanisms of tomato components have been proposed, it is essential to emphasize the necessity of research in humans to support these hypotheses. Because of the abundance of supporting data from epidemiological, in vitro, animal, and small clinical studies, it is time to begin to evaluate the relation of tomatoes to prostate cancer risk in larger intervention studies, which would provide a more definitive test of the hypothesis that increased intake of tomatoes and tomato products decreases the risk of prostate cancer.

LITERATURE CITED


