

## Review

# Impact of diet on prostate cancer: a review

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Epidemiological studies suggest that environmental factors may mediate the transformation of latent prostate cancer into clinically apparent tumors and that diet appears to influence this progression. Close correlations between average per capita fat intake and prostate cancer mortality internationally generated interest in underlying mechanisms for this link, such as through serum levels of androgens, free radicals, proinflammatory fatty acid metabolites, or insulin-like growth factor. Much interest currently lies in the potential of HMG-CoA reductase inhibitors (statins) to play a chemopreventative role in prostate cancer. Lycopene, a potent antioxidant found in tomatoes, may exert a protective effect in the prostate. Selenium and vitamin E have also been shown to decrease the risk of prostate cancer in some men. Calcium may support vitamin D-related antiproliferative effects in prostate cancer. Certain soy proteins, common in the Asian diet, have been shown to inhibit prostate cancer cell growth. Finally, green tea may also have a chemopreventive effect by inducing apoptosis. Despite confounding factors present in clinical studies assessing the effect of diet on cancer risk, the data remain compelling that a variety of nutrients may prevent the development and progression of prostate cancer.

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## Introduction

Prostate cancer remains the most common noncutaneous malignancy in American men with an estimated lifetime risk of disease of 16.6% for Caucasians and 18.1% for African-Americans and a lifetime risk of death of 3.5 and 4.3%, respectively.<sup>1</sup> The discrepancy between the clinical incidence and mortality rate reveals that not all prostate cancers behave similarly. Most remain latent and never manifest clinically. Indeed, foci of prostate cancer may be found in 30% of men over age 50 y, a percentage that continues to increase with age. Nonetheless, prostate cancer remains the second leading cause of male cancer

death with approximately 30 000 deaths per year in the US.<sup>2</sup>

The pathologic incidence of small, latent prostatic carcinomas is similar across many populations.<sup>3</sup> However, marked variations exist in the clinical incidence of prostate cancer, ranging from 1 in 100 000 in China to 45–65 in 100 000 in US white subjects to 102 in 100 000 in African-Americans.<sup>4</sup> These rates change when men relocate to different geographic areas. That the incidence of prostate cancer in Chinese and Japanese men increases substantially after migration to the US<sup>5,6</sup> suggests a strong environmental influence. From these observations stems the hypothesis that environmental factors may act as late stage promoters involved in the transformation of prostate cancer from a latent form to a more aggressive form. Investigators have examined whether dietary factors contribute to cancer progression. We review the literature on dietary components that have attracted the most interest.

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## Dietary fat

The observation of a close correlation between the average per capita fat intake and prostate cancer mortality in 31 countries including the US, France, Germany, Israel, Japan, New Zealand, Singapore, and the United Kingdom<sup>7,8</sup> sparked an interest in a potential link between dietary fat and prostate cancer risk. Conflicting preclinical evidence exists relating to a possible association. Studies in animal models have shown increased tumor growth with high fat intake and inhibition of growth with low fat intake.<sup>9–11</sup> Investigators have also demonstrated that reduced dietary fat intake in LAPC-4 xenografted severe combined immunodeficient mice delays the progression of prostate cancer to androgen-insensitivity and significantly prolongs survival.<sup>11</sup> Other preclinical studies have found no relationship between the growth of transplanted prostate carcinoma and variations in dietary fat.<sup>12–14</sup> In addition, Mukherjee *et al*<sup>15</sup> found that limiting energy intake via caloric restriction in rats with transplanted prostate cancer resulted in a reduction of tumor growth that was independent of dietary fat concentration. These experiments suggest that a decrease in energy intake and dietary fat impact prostate cancer growth.<sup>16</sup>

Most clinical evidence detailing the effect of dietary fat intake on prostate cancer risk derives from observational rather than interventional studies. The three serum-based studies that sought to link total fat and prostate cancer risk showed no association.<sup>17–19</sup> Likewise, the Netherlands Cohort Study, a large prospective cohort study, found no association between prostate cancer and total fat intake.<sup>20</sup> In contrast, three other prospective cohort studies found a moderate positive association (RR 1.1–1.3) between fat consumption and prostate cancer risk.<sup>21–23</sup> In accordance with this result, the majority of the published case-control studies demonstrated a positive correlation between fatty food consumption and prostate cancer risk. However, many of these investigations differed with respect to the selection of controls and the method of dietary assessment.<sup>24</sup>

Investigators have also searched for a potential association between specific kinds of fat and prostate cancer. Results have been mixed.<sup>24</sup> Essential fatty acids found in fish inhibit the growth of prostate cancer cells *in vitro* and *in vivo*.<sup>25</sup> Of the three epidemiological studies to date in humans, two reported a reduced risk of prostate cancer in men with the highest intake of fatty fish,<sup>25,26</sup> while the other found no association.<sup>27</sup> The two fatty acids whose potential association with prostate cancer risk is most frequently investigated are alpha-linolenic acid and linoleic acid. Alpha-linolenic acid was positively associated with prostate cancer risk in two serum-based studies,<sup>28,19</sup> while two prospective cohort studies using food-frequency questionnaire data yielded mixed results.<sup>23,20</sup> For linoleic acid, the predominate omega-6 fatty acid in the Western diet, three of four studies showed no effect.<sup>29</sup>

Two interventional pilot studies coupling a low-fat diet with supplementation with specific fatty acids deserve mention. In 2001, Demark-Wahnefried *et al*<sup>30</sup> published a small trial of 25 patients awaiting prostatectomy for prostate cancer placed on a diet (mean of 34 days), which was low in fat (20% of kilocalories or fewer) and supplemented with 30 mg/day of flaxseed, a compound

rich in alpha-linolenic acid and lignans with phytoestrogenic properties. Compared with a control population of historical cases matched for age, race, PSA at diagnosis, and biopsy Gleason sum, no significant differences were found between surgical Gleason sum, tumor volume, seminal vesicle or bladder neck involvement, perineural or extracapsular invasion, or margin positivity. The proliferation index, however, was significantly lower for the group on the diet (5.0 *vs* 7.4, ( $P = 0.049$ )). Also in 2001, Aronson *et al*<sup>31</sup> published a preliminary trial in nine men with prostate cancer who consumed a low-fat diet supplemented with omega-3 fatty acids contained in fish oil for 3 months. Following the intervention, the omega-3/omega-6 fatty acid ratio in plasma and gluteal adipose tissue increased significantly ( $P = 0.002$ ,  $P = 0.002$ ) and COX-2 expression in prostatic tissue obtained by biopsy decreased in four of the seven patients in which tissue was studied. Interestingly, Ngo *et al*<sup>32</sup> demonstrated that dietary fat reduction combined with a regular exercise intervention in men decreased serum IGF-1 and increased serum IGFBP-1 levels resulting in decreased growth of LNCaP human prostate cancer cells cultured in media containing patient serum. Further large-scale prospective trials incorporating surrogate biomarkers are required to understand the role of altering the quantity and quality of dietary fat for primary and secondary prostate cancer prevention.

Researchers have proposed several mechanisms to explain a possible association between dietary fat and prostate cancer development and progression. First, the observation that men who consume less fat have lower levels of testosterone has led some investigators to hypothesize that fat may affect risk through an alteration of androgen levels.<sup>33</sup> Second, others have focused on the free radicals produced by dietary fat as the relevant factor.<sup>34</sup> Proinflammatory fatty acid metabolites such as specific leukotrienes and prostaglandins may also be carcinogenic and promote tumor growth.<sup>35</sup> In addition, dietary fat reduction may impact serum insulin-like growth factor levels in the serum.<sup>36</sup> Certainly, a more thorough understanding of the possible association between dietary fat and prostate cancer risk requires further inquiry.

## Serum cholesterol and statin therapy

Much interest currently lies in the potential of HMG-CoA reductase inhibitors (statins) to play a chemopreventive role against various human cancers. *In vitro* studies have demonstrated that lovastatin and simvastatin suppress the growth of normal and tumor cell lines of mouse, hamster, and human origins by causing the cells to pause in the G<sub>1</sub> phase of the mitotic cycle<sup>37</sup> and by increasing apoptosis.<sup>38</sup> Five randomized, controlled trials provide a limited body of information about cancer incidence in patients using statins. One trial using pravastatin saw significantly fewer colon cancer cases and significantly more breast cancer cases in the treatment group.<sup>39</sup> Another study of lovastatin found significantly fewer melanoma cases in the treatment group.<sup>40</sup> No other significant differences were noted in any of these trials.

Preclinical data indicate that statins may play a role in prostate cancer biology. Treatment of cells from trans-

genic mice with adenocarcinoma of the prostate (TRAMP cells) with lovastatin caused inactivation of the small GTPase RhoA, actin stress fiber disassembly, cell rounding, growth arrest in the G<sub>1</sub> phase of the cell cycle, cell detachment and apoptosis.<sup>41</sup> Lovastatin also caused growth arrest in PC-3-M cells, a p53-null human prostate carcinoma cell line, by inducing critical downstream regulatory events leading to transcriptional activation of p21.<sup>42</sup> Finally, lovastatin has proven to be a powerful inducer of apoptosis in the LNCaP cell line.<sup>43</sup>

Despite the promising preclinical evidence, no large clinical trial has demonstrated a significant association between statin use and a reduced risk of prostate cancer. In 2002, Coogan *et al*<sup>44</sup> compared 1009 men with prostate cancer with 1387 controls admitted to the hospital for conditions unrelated to statin use. The odds ratio for prostate cancer overall was 1.2 (95% CI = 0.8–1.7), and thus did not support a protective effect of statin use against prostate cancer. Friis *et al*<sup>45</sup> conducted a population-based cohort study using a study population of 334 754 individuals for the period of 1989–2002. In this population, 34 of the 6935 men who were prescribed statins developed prostate cancer, compared to 1373 of the 161 198 nonusers. The calculated age-standardized rate ratio of 1.01 (0.70–1.41) demonstrates that no significant difference existed between the groups. In 2004, Graaf *et al*<sup>46</sup> published a large case–control study conducted to compare the risk of incident cancer between users of statins and users of other cardiovascular medication. The trial matched a total of 3129 cancer cases with 16 976 control subjects. The use of statin drugs was associated with a 20% reduction in the risk for cancer (OR = 0.80) and a 36% reduction in cancer risk (OR = 0.60) when taken for longer than 4 y. Statin use was also associated with a 63% reduction in prostate cancer, although this difference lacked statistical significance.

While strong epidemiological evidence linking statin use with a reduced risk of prostate cancer is lacking, Moyad<sup>47</sup> argues that a statin should be utilized in the next major chemoprevention trial. He bases his argument largely on the fact that cardiovascular disease is the primary or at least secondary cause of death in the majority of patients diagnosed with prostate cancer.<sup>48</sup> Moyad reasons that the beneficial effect that statins would have on reducing the primary cause of death in patients with prostate cancer, coupled with the possible decrease in prostate cancer related morbidity and mortality, justifies the use of statins in the clinical trial setting.

## Lycopene

Lycopene is a red–orange carotenoid found primarily in tomatoes and tomato-derived products such as tomato sauce, tomato paste and ketchup. Research has shown lycopene to be a potent antioxidant and accordingly it has been evaluated for anticancer effects. Lycopene is currently thought either to protect prostatic cells from reactive oxygen species or to block IGF-mediated cellular proliferation.<sup>49</sup>

Obermuller-Jevic *et al*<sup>50</sup> demonstrated that lycopene inhibits the growth of benign and malignant prostatic epithelial cells *in vitro*. To characterize further the effect

of tomatoes and lycopene on prostate cancer, Boileau *et al*<sup>51</sup> used an *in vivo* rat model and found a protective effect for both calorie restriction and tomato powder, but not for pure lycopene, suggesting that tomato products contain additional compounds that modify prostate carcinogenesis.<sup>1</sup>

The epidemiological evidence that lycopene consumption is associated with a lower risk of prostate cancer is mixed. Lycopene consumption showed an inverse association with prostate cancer risk in two serum-based studies.<sup>52,53</sup> However, data from prospective cohort studies using food-frequency questionnaires proved equivocal.<sup>54–56</sup> Giovannucci *et al*<sup>55</sup> evaluated 51 529 men in the Health Professionals Follow-Up Study and found a moderate benefit for lycopene (RR for high *vs* low quintiles = 0.84; 95% CI, 0.66–0.90) and a somewhat stronger benefit for tomato sauce, the food source with the best lycopene bioavailability (RR for 2+ servings/week *vs* <1 serving/month = 0.77; 95% CI, 0.66–0.90). The investigators postulated that several factors may contribute to the inconsistency of the literature on lycopene and prostate cancer risk. First, they explain that dietary questionnaires may not capture all the sources of lycopene and do not account for its bioavailability. Second, the time period covered by the questionnaire may not adequately encompass the long period of carcinogenesis of prostate cancer. Finally, tomato products may represent part of a healthy eating pattern that may independently reduce the risk of prostate cancer.

Overall, stronger data exist supporting the protective effect of lycopene in tomato sauce compared to that in supplements. In 2003, Kim *et al*<sup>57</sup> published a small interventional trial following up on a 2001 study, which found that tomato sauce consumption prior to prostatectomy decreased serum PSA and decreased oxidative DNA damage. The 2003 study compared prostatic tissue in 32 patients given tomato sauce pasta entrees (30 mg lycopene/day) for 3 weeks prior to prostatectomy with that from 34 patients who did not consume the sauce. In tumor areas with the most apoptotic cells, tomato sauce consumption increased apoptotic cells in carcinomas 3.3-fold ( $P = 0.0003$ ).<sup>58</sup> These data provided the first *in vivo* evidence that tomato sauce consumption may suppress the progression of prostate cancer by increasing apoptotic cell death. However, larger trials are needed to confirm the findings of this study.

## Selenium

Selenium is a trace element found in bread, cereals, fish and chicken. *In vitro* studies and animal models have demonstrated a chemoprotective role for selenium against a variety of malignancies. Using a stable monomethylated selenium metabolite developed for *in vitro* studies, Dong *et al*<sup>59</sup> demonstrated dose and time-dependent growth inhibition and induction of apoptosis in the PC3 human prostate cancer cell line. This and other evidence from the studies examining the antineoplastic effect of selenium suggest that it works early in the carcinogenic pathway by blocking cell proliferation, promoting apoptosis and inducing antioxidant enzymes.<sup>1</sup>

Interest in the effect of selenium on prostate cancer began with the Nutritional Prevention of Cancer Trial, a randomized study of oral selenium in 1312 patients with nonmelanoma skin cancer whose primary endpoint was the recurrent incidence of skin cancer. While the study demonstrated no significant effect on skin cancer recurrence, daily supplementation with 200 ng of selenium significantly reduced prostate cancer incidence (RR 0.37,  $P=0.002$ ) after a mean follow-up of 7.4 years.<sup>60</sup> However, this reduced risk was restricted to patients in the lowest two tertiles. In five of six subsequent biomarker-based studies, selenium was associated with either a significantly lower risk of prostate cancer,<sup>61,62</sup> or a nonsignificant trend toward a lower risk of prostate cancer.<sup>63–65</sup> The significant inverse associations between selenium and prostate cancer in these studies only existed when comparing men with the highest level of toenail selenium to men with the lowest.

The promising evidence supporting the benefit of selenium in reducing the risk of prostate cancer provided the basis for the ongoing Selenium and vitamin E Cancer Prevention Trial (SELECT) trial, a National Cancer Institute sponsored phase III, randomized, double-blind, placebo-controlled, population-based clinical trial designed to test the efficacy of selenium and vitamin E in the prevention of prostate cancer. The results of the SELECT trial are expected in 2013.

## Vitamin E

Vitamin E, a potent antioxidant, has been shown to inhibit the growth of established prostate LNCaP tumors in nude mice.<sup>66</sup> It has been postulated to either cause G<sub>1</sub> cell cycle arrest or to prevent oxidation and peroxidation of membrane phospholipids. Vitamin E is present in the diet in two forms, gamma-tocopherol and alpha-tocopherol, the most active form.<sup>67</sup>

The alpha-tocopherol, beta-carotene (ATBC) cancer prevention trial constitutes the most significant study of vitamin E and prostate cancer completed to date. This randomized, double-blind, placebo-controlled study in 29 133 male smokers found a 32% reduction in prostate cancer incidence and a 41% lower mortality in those receiving 50 mg of alpha-tocopherol daily for 5–8 y.<sup>68</sup> Analysis in the 6-year post-trial follow-up assessment found that the relative risk (RR) in the alpha-tocopherol group increased from 0.64 (95% CI, 0.44–0.94) during the trial to 0.73 (95% CI, 0.51–1.04) by 1996 and finally to 0.94 (95% CI, 0.72–1.24) by 1999.<sup>69</sup> As the RR returned toward 1.0, the post-intervention study concluded that the beneficial effects of alpha-tocopherol supplementation disappeared after the intervention, suggesting that benefit from vitamin E requires long-term supplement use. Other studies corroborate the benefit of vitamin E in prostate cancer risk. Three serum-based case-control studies<sup>65,70,71</sup> support its protective effect on prostate cancer.

However, another serum-based study showed no association between vitamin E level and prostate cancer risk,<sup>52</sup> and six of seven prospective cohort studies based on questionnaire data failed to show a significant association. One of these studies was the Cancer Prevention Study II Nutrition Cohort, a study of 74 704 men that found no protective role for vitamin E

supplements in prostate cancer (RR 1.0). The only prostate cancer benefit of vitamin E suggested by the CPS II Nutrition Cohort was a non-significant protective trend among the men who smoked.<sup>67</sup> This and other evidence has shed doubt on the belief that vitamin E is at least somewhat protective against prostate cancer. In addition, a recent meta-analysis warned against supplementation of vitamin E in doses greater than 400 IU/day based on increases in all-cause mortality.<sup>72</sup> Another study on vitamin E supplementation (400 IU/day) in patients over 55 with vascular disease or diabetes found no significant difference in cancer incidence or cardiovascular events, but an increased risk of heart failure.<sup>73</sup> More information about the role of vitamin E in prostate cancer will be elucidated by the SELECT trial.

## Calcium

Current guidelines recommend an intake of 1200 mg/day of calcium in men over 50 y. However, calcium from dietary or supplemental sources has been linked to a higher risk of prostate cancer in several epidemiological studies. The hypothesized reason for this association is based on the relationship between calcium and vitamin D. High intake of calcium reduces 1.25(OH)<sub>2</sub> vitamin D production. Preclinical studies show an antiproliferative, antimetastatic and differentiating effect of 1.25(OH)<sub>2</sub> vitamin D in prostate cancer.

Epidemiological observations sparked the initial interest on the effect of vitamin D and calcium on prostate cancer risk. First, men living in northern latitudes with less exposure to sunlight (which converts inactive to active vitamin D in the skin) have a higher mortality rate from prostate cancer. Second, prostate cancer occurs more frequently in older men in whom vitamin D deficiency is more common. Third, African-Americans, whose skin melanin blocks UV radiation thereby inhibiting the activation of vitamin D, have the highest worldwide incidence and mortality rates from prostate cancer. Clearly, however, many covariates influence these observations.

To date, four prospective studies using survey data relating calcium and prostate cancer risk have been published. While two showed no association (mean intake in highest quintile 1330 and 1840 mg/day), two cohort studies showed that very high calcium intake (mean intake >2000 mg/day from both food and supplements) significantly increased prostate cancer risk.<sup>74,75</sup> One of these studies came from questionnaire data obtained from the 86 404 member CPS-II Nutritional Cohort. Investigators found that very high calcium intake from a combination of diet and supplements (RR 1.2) and from dietary calcium alone (RR 1.6) were independently associated with increased prostate cancer risk for those consuming >2000 *vs* <700 mg/day. Neither dairy products nor moderate levels of dietary calcium were associated with increased risk.<sup>75</sup> Investigators utilizing the Physicians Health Study population found an even stronger association, with an increased risk of total (RR 1.71), advanced (RR 2.97), and metastatic prostate cancer (RR 4.57) in those consuming >2000 mg/day.<sup>74</sup> However, only 1% of men consume >2000 mg/day of calcium, and neither study showed an increased

risk of prostate cancer in men consuming a more moderate amount of calcium.

While Rodriguez *et al*<sup>75</sup> found no association between dairy food intake and prostate cancer risk, five of nine prospective studies have demonstrated an association between dairy products (the main source of dietary calcium and vitamin D) and prostate cancer. The extent to which the consumption of calcium, compared with fat, in milk and other dairy products contributes to prostate cancer risk remains unclear.

## Soy protein

Phytoestrogens, found in large quantities in soy products, are plant compounds that have estrogen-like activity. Scientists have postulated that the soy-rich diet of Asian men may partially explain why their risk of clinical prostate cancer remains much lower than that of men of other ethnicities. Indeed, isoflavones, plant pigments found in vegetables of which the soya bean is a major source, have been shown to inhibit prostate cancer cell culture growth. Genistein, the most abundant isoflavone component in soy, is being studied in ongoing clinical trials based on previous data that indicates a possible chemopreventive role in cancer progression in carcinogen-triggered rat models of prostate cancer<sup>76,77</sup> and a reduced incidence of advanced prostate cancer in TRAMP mice.<sup>78</sup> Additionally, animal studies have suggested that isoflavones in soy may suppress the development of invasive prostate cancers.<sup>79</sup> To explain this effect, scientists have proposed that the antineoplastic effect of phytoestrogens may be due to their inherent estrogenic properties, or due to the inhibition of 5- $\alpha$ -reductase.

To date, the clinical evidence examining the effect of phytoestrogens on prostate cancer risk remains limited. One study indicated a beneficial role of soy in reducing the level of androgenic steroids. The only large-scale epidemiological study of the effects of soy-derived products on prostate cancer development was a cross-national study conducted in 59 countries. In this study, Hebert *et al*<sup>80</sup> found soy products significantly protective ( $P < 0.001$ ).

## Green tea

Initial interest in a potential preventative effect of green tea on prostate cancer stemmed from the epidemiological observation of the low incidence of prostate cancer among Japanese and Chinese populations<sup>81</sup> with a high dietary intake of green tea.<sup>1</sup> Several epidemiological studies have demonstrated that those who regularly consume tea have a lower incidence of prostate cancer,<sup>82–84</sup> while others have shown no association.<sup>85–87</sup> The cancer chemopreventive effects of green tea have been attributed to its major polyphenolic constituent, (–)-epigallocatechin-3-gallate (EGCG).<sup>88</sup> Cell-culture experiments on prostate cancer cells by Adhami *et al*<sup>89</sup> demonstrated that EGCG induces apoptosis, cell-growth inhibition, and cyclin kinase inhibitor WAF-1/p21-mediated cell-cycle dysregulation. In addition, treatment of LNCaP cells with EGCG results in the induction of genes with growth-inhibitory effects and repression of

genes in the G-protein signaling network. Finally, in animal studies using TRAMP mice, oral infusion of a polyphenolic fraction isolated from green tea at a dose equivalent to six cups of green tea/day in humans significantly inhibits prostate cancer development and metastasis. More recently, the same research group published their finding that EGCG inhibits COX-2 without affecting COX-1 expression at both the mRNA and protein levels, in androgen-sensitive LNCaP and androgen-insensitive PC-3 human prostate carcinoma cells.<sup>90</sup> Based on the considerable promise of COX-2 inhibition in the prevention or treatment of certain human cancers, this finding raises the possibility that EGCG may play a supplementary role in the future chemoprevention or therapy of prostate and other types of cancer.

## Conclusion

The evidence linking prostate cancer risk to the aforementioned dietary factors remains compelling but inconsistent. Comparison of these studies is hampered by differences in sample size, duration of follow-up, and extensiveness of dietary evaluation. However, despite the plethora of confounding factors present in clinical studies assessing the effect of diet on cancer risk, the sum total of data remains compelling in regards to the potential for a variety of nutrients to potentially prevent the development and progression of prostate cancer. Data from migration studies provide evidence that environmental factors are responsible for the transformation of latent prostate cancer to a clinically apparent form and that diet appears to influence this progression.

Insufficient clinical evidence exists to warrant recommending wholesale dietary changes to patients to reduce their risk of prostate cancer. However, until more interventional studies are carried out, physicians should recognize the importance of dietary modification in a patient's overall health profile. Although prostate cancer is the most common non-skin cancer in American men and the second leading cause of cancer death, cardiovascular disease was the leading cause of patient mortality in each of the previously mentioned clinical trials. Dietary changes that reduce the risk of cardiovascular disease, such as reducing dietary fat should be recommended to all patients. Some mechanisms potentially involved in increasing a man's risk for heart disease may also increase his risk of prostate cancer.<sup>91,92</sup> The most practical approach for physicians is to recommend changes that may favorably benefit the risk of both cardiovascular and prostate cancer. Fortunately, many of the lifestyle changes proven to reduce cardiovascular risk seem helpful in reducing prostate cancer risk as well. This fact should be reinforced with patients who inquire about ways to lessen their risk of prostate cancer.<sup>93</sup>

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