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Vegetables, Fruits, Associated Micronutrients, and Risk of Prostate Cancer

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INTRODUCTION

Greater fruit and vegetable intake is recommended to prevent cancer generally, but it is unknown if it protects against prostate cancer specifically. A comprehensive review on nutrition, food, and prostate cancer was published in 1997 by the World Cancer Research Fund and the American Institute for Cancer Research titled *Food, Nutrition, and the Prevention of Cancer: a Global Perspective* (1) (hereafter referred to as the 1997 Global Review). This report will summarize briefly the conclusions from that review on fruits and vegetables and their major nutrients and phytochemicals, discuss major studies published since 1997, and a few earlier studies not mentioned in the 1997 Global Review, and suggest directions for future research.

CAROTENOIDS

Carotenoids may be beneficial for several different cancer sites, including the prostate gland. One proposed anticancer mechanism is based on vitamin A, which we receive from animal sources in the form of retinol and from fruits and vegetables in the form of carotenoids, some of which have provitamin A properties. Epithelial tissues rely on retinoids for normal cellular differentiation. In addition, many carotenoids have antioxidant capabilities that could protect against free-radical damage to DNA (2).

While some evidence from experimental studies supports a role for vitamin A (3–6) and carotenoids (7–9) to protect against development of prostate cancer, results from epidemiologic studies have been ambiguous. The conclusion of the 1997 Global Review was that no judgement was possible given the inconsistent nature of study results. Since the publication of that report, two clinical trials (10–12), a dietary cohort study (13), 12 case-control studies (14–25), and three prospective serum studies (26–29) have examined the relation between carotenoids and prostate cancer.

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Abbreviations: CI, confidence interval; RR, relative risk.

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Of the 12 recent case-control studies, only three reported statistically significant relative risks for specific carotenoids (21, 22, 25), and one of these was a positive association (21). Oishi et al. (25) observed a relative risk of 2.13 (95 percent confidence interval (CI): 1.20, 3.77) for low versus high intakes of β-carotene. Jain et al. (21) reported an elevated risk of prostate cancer associated with greater cryptoxanthin intake (relative risk (RR) = 1.44, $p = 0.03$), while Cohen et al. (22) found a borderline statistically significant 32 percent decreased multivariate relative risk for higher intakes of lutein plus zeaxanthin ($p = 0.09$). A cohort study among 1,900 Western Electric workers in Chicago observed no association for dietary intake of β-carotene and prostate cancer risk (13).

The Physicians' Health Study investigated β-carotene supplementation (50 mg on alternate days) with cancer and cardiovascular disease among 22,000 US physicians in a randomized clinical trial and found no association with prostate cancer (11). However, low versus high baseline serum measures of β-carotene was associated with a 45 percent increase in prostate cancer risk ($p = 0.06$). Among men with low baseline plasma β-carotene levels, β-carotene supplementation was inversely associated with prostate cancer incidence over 12 years of randomized treatment (RR = 0.68, $p = 0.04$) (10). Baseline plasma α-carotene, β-cryptoxanthin, and lutein levels were not associated with prostate cancer risk during 13 years of follow-up, while baseline plasma lycopene was associated with a 44 percent reduction in risk (RR = 0.56 comparing highest with lowest quintiles, $p = 0.05$) (27). Interestingly, this reduction in risk was only evident among men on placebo. Men receiving β-carotene supplementation had a lower risk of prostate cancer compared with men on placebo only if they had low plasma lycopene or plasma β-carotene levels, suggesting a ceiling on the achievable benefits of high dietary lycopene intake or β-carotene supplementation (10, 27).

In the Alpha-Tocopherol Beta-Carotene Cancer Prevention Trial, 29,133 Finnish male smokers were randomized to either 50 IU of α-tocopherol, 20 mg of β-carotene, both, or placebo. After a median follow-up of 6.1 years, the investigators reported that men receiving β-carotene supplementation experienced a statistically significant elevation in stages II–IV prostate cancer incidence (RR = 1.35, 95 percent CI: 1.01, 1.80) (12).

Eichholzer et al. (28) reported no association between serum carotene and risk of fatal prostate cancer in a Swiss population with 17 years of follow-up. Nomura et al. (26) examined serum levels of total carotene, as well as lutein,

lycopene, α- and β-carotene, zeaxanthin, and β-cryptoxanthin among Japanese-Americans in Hawaii and observed no association with prostate cancer risk.

Lycopene has recently been reviewed extensively for its potential anticarcinogenic properties in several organs, including the prostate gland (30). Lycopene, which is not converted to vitamin A, is the most potent quencher of single oxygen among the carotenoids (31), is a powerful trapper of nitrogen oxide species (32), and suggestive in vitro data support a role for lycopene in suppressing the growth of prostate cancer (30). Dietary lycopene intake has been studied in two cohort (33, 34) and six case-control (18, 20–24) studies (including studies mentioned in the 1997 Global Review). Of these, only the Health Professionals Follow-up Study observed a statistically significant inverse association between risk of prostate cancer and lycopene intake (33). Two (27, 35) out of three (26, 27, 35) serum studies on plasma lycopene and prostate cancer risk have observed inverse associations, although only the Physicians' Health Study was statistically significant (27). Tomato products, which are by far the major source of lycopene in our diets, have also been studied specifically with regard to prostate cancer (see the section on Vegetables below).

In conclusion, most epidemiologic studies suggest no association for total carotenoids, but further research is warranted on the potential beneficial effects of β-carotene, lutein, zeaxanthin, lycopene, and on potential interactions among these nutrients.

VITAMIN E

Vitamin E has been hypothesized to protect against chronic disease via its strong antioxidant properties and positive effects on immune function (36, 37). The experimental evidence that vitamin E can suppress cancer growth has been reviewed in detail elsewhere (38). Israel et al. (39) recently demonstrated that vitamin E succinate can induce apoptosis in LnCaP cells, but not in normal prostate cells. Vitamin E refers to several compounds—α-, β-, γ-, and δ-tocopherol, and the tocotrienols. Human diets predominantly contain α-tocopherol, which is the most potent tocopherol biologically (40). However, some recent evidence suggests a role for γ-tocopherol in protecting against prostate cancer (41, 42). γ-Tocopherol is also a potent trapper of nitrogen oxide species (32).

The 1997 Global Review summarized three epidemiologic studies (35, 43, 44) on vitamin E and prostate cancer risk and concluded that no judgement was possible given the limited evidence. One of these studies found no association for vitamin E intake (43); the other two studies observed suggestive but not statistically significant inverse associations for serum vitamin E and prostate cancer risk (35, 44), although in one study this was only among men younger than age 70 years (35).

Since that report, two cohort (45, 46) and four case-control (16, 18, 21, 24) studies observed no association for dietary or supplemental vitamin E intake (18, 46) and prostate cancer risk. In contrast, three case-control studies from distinct countries (Serbia, Greece, and Uruguay) observed inverse associations between dietary vitamin E and prostate cancer risk (19, 20, 47), with statistically significant reductions of 40 percent or greater.

The most provocative evidence for a protective effect of vitamin E on prostate cancer risk comes from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Trial (12). The investigators observed an approximate statistically significant 40 percent reduction in prostate cancer incidence and mortality among men receiving 50 mg (equivalent to 50 IU) supplements of α-tocopherol daily. In the Health Physicians' Follow-up Study, null associations were observed for total, advanced, and fatal prostate cancer and self-reported vitamin E supplement intake (46), but there was a borderline statistically significant relative risk of 0.5 for metastatic and fatal prostate cancer among smokers.

Studies on circulating vitamin E and total prostate cancer not mentioned in the 1997 Global Review have generally not shown a clear association (26–28, 45), while two studies that stratified on smoking observed statistically significant inverse associations for plasma vitamin E levels and risk of advanced (27) and fatal (28) prostate cancer only among smokers. In addition, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Trial was conducted exclusively among smokers, and the apparent benefit of vitamin E was considerably stronger in longer-term and heavier smokers (12). Smoking may be more of a risk factor for fatal (48–51) rather than total (52–58) prostate cancer, suggesting that it promotes the development of more aggressive or metastatic tumors. The hypothesis that vitamin E specifically counteracts the adverse promoting effect of smoking, but is less beneficial among nonsmokers, warrants further research.

VITAMIN C

Vitamin C, or ascorbic acid, may reduce damage to cells by neutralizing toxic oxygen radicals, thereby protecting the body against aging and chronic diseases such as cancer (59). In contrast, recent experimental studies suggest that vitamin C may inhibit the growth of androgen-independent prostate cancer cells in vitro by creating reactive oxygen species that kill the tumor cells (60, 61). Vitamin C and vitamin K3 combinations are toxic to DU145 prostate cancer cells in vitro (62), suggesting therapeutic implications (60, 61).

Again, however, while the experimental evidence is intriguing, the conclusion of the 1997 Global Review was that high dietary vitamin C intake had no relation to prostate cancer risk. Of relevant studies not included in the previous report, two of two cohort (13, 63), one of one prospective serum (28), and 11 of 12 case-control (14, 16–19, 21, 22, 24, 25, 64, 65) studies reported no association for vitamin C and prostate cancer risk. To our knowledge, only one study recently reported a statistically significant decreased risk of prostate cancer associated with high vitamin C intake (RR = 0.40, $p = 0.008$) (20). Thus, we conclude that vitamin C is unlikely to affect prostate cancer risk.

FRUITS

The conclusion of the 1997 Global Review for fruits and prostate cancer risk was that results were "markedly inconsistent" and no judgement was possible. Studies published more recently have shed little additional light on this topic. Two large cohort studies conducted in Hawaii (66) and Finland (34) observed no association for total fruits. In contrast, The Netherlands Cohort Study reported statistically significant positive linear trends for greater total ($p = 0.02$) and citrus ($p = 0.01$) fruit intake and prostate cancer risk (67), and a case-control study conducted among 156 cases in Uruguay observed a 70 percent elevation in prostate cancer risk with greater fruit intake ($p = 0.04$) (68). Of eight additional case-control studies, one observed a borderline statistically significant 45 percent increase for citrus fruits (18), one reported a statistically significant 50 percent increase for total, citrus, and non-citrus fruits (21), two observed borderline inverse associations (20, 69) (though one reported this among white but not black men), and four reported null associations for various measures of fruit intake (14, 22, 47, 70).

Thus, we conclude that fruit intake is not substantially related to risk of prostate cancer, and if anything, may be associated with a slightly elevated risk.

VEGETABLES

A wide variety of vegetables have been examined in association with prostate cancer risk in diverse ethnic populations, and the 1997 Global Review concluded that diets high in vegetable intake could possibly decrease risk of prostate cancer; in the least, there is little evidence of any detrimental effect. Specific and total vegetables have been statistically significantly inversely associated with prostate cancer risk in one cohort (67) and seven case-control (18, 20–22, 47, 69, 71) studies not mentioned in the previous report. In contrast, two cohort (34, 66) and six case-control (23, 68, 70, 72–74) studies observed no association between various vegetable categories and prostate cancer risk.

Individual studies have categorized vegetables in various ways, making general conclusions about specific vegetables challenging. While results are mixed, it appears that beans, legumes, pulses and nuts (18, 21, 22, 67, 75), carrots (22, 76), green leafy (21, 71, 76), and possibly cruciferous (22, 76) vegetables may offer some protection against prostate cancer.

Tomatoes or tomato products have been associated with 15–50 percent reductions in prostate cancer risk in two cohort (33, 75) and three case-control (21, 47, 69) studies, while null associations were reported in two cohort (48, 67) and two case-control (22, 23) studies. The current literature regarding tomatoes and cancer risk was recently reviewed in detail (30).

We conclude that there is reasonable though mixed evidence for an inverse association between prostate cancer risk and vegetables, including tomatoes, legumes, and beans.

CONCLUSIONS

Fruits are unlikely to substantially influence prostate cancer risk, while vegetables and their associated nutrients and phytochemicals may have anti-prostate cancer properties. Each of these, however, requires further study, and several biologic and methodological issues should be considered.

Firstly, there may be biologic interaction among nutrients and phytochemicals. Some tocopherols and carotenoids may protect against similar reactive chemical species; thus, the relative roles of each may differ in populations depending on their average levels. Secondly, some factors may be important in the context of other exposures, such as vitamin E among smokers. Thirdly, varying diagnostic and screening technologies may cause substantial biologic heterogeneity in prostate cancer across studies; the impact of a factor may be different for early-stage prostate-specific antigen-detected tumors versus aggressive fatal cancers.

Vegetables are a complex entity, and variations in follow-up time, study design (retrospective versus prospective), and the comprehensiveness of questionnaires may influence results. Randomized intervention trials may be appropriate to examine the most promising nutrients and phytochemicals, but even these studies may yield conflicting results due to varying doses, follow-up times, or issues of biologic complexity, such as presence or absence of modifying cofactors. In conclusion, we recommend additional studies on specific vegetables, micronutrients, and prostate cancer, with careful consideration of the above issues.

REFERENCES

1. World Cancer Research Fund and American Institute for Cancer Research. Food, nutrition and the prevention of cancer: a global perspective. Washington, DC: American Institute for Cancer Research, 1997.
2. Brody T. Vitamin A. In: Nutritional biochemistry. Boston, MA: Academic Press, 1999:554- -65.
3. Dahiya R, Park HD, Cusick J, et al. Inhibition of tumorigenic potential and prostate-specific antigen expression in LnCaP human prostate cancer cell line by 13-cis-retinoic acid. Int J Cancer 1994;59:126–32.
4. Dahiya R, Boyle B, Park HD, et al. 13-cis-Retinoic acid-mediated growth inhibition of DU-145 human prostate cancer cells. Biochem Mol Biol Int 1994;32:1–12.
5. Dahiya R, Zhang DY, Ho RJ, et al. Regression of LNCaP human prostate tumor xenografts in athymic nude mice by 13-cis-retinoic acid and androgen ablation. Biochem Mol Biol Int 1995;35:487–98.
6. Pasquali D, Thaller C, Eichele G. Abnormal level of retinoic acid in prostate cancer tissues. J Clin Endocrinol Metab 1996;81:2186–91.
7. Levy J, Bosin E, Feldman B, et al. Lycopene is a more potent inhibitor of human cancer cell proliferation than either α-carotene or β-carotene. Nutr Cancer 1995;24:257–66.
8. Pastori M, Pfander H, Boscoboinik D, et al. Lycopene in association with alpha-tocopherol inhibits at physiological concentrations proliferation of prostate carcinoma cells. Biochem Biophys Res Commun 1998;250:582–5.
9. Clinton SK, Emenhiser C, Schwartz SJ, et al. cis-Translycopene isomers, carotenoids, and retinol in the human prostate. Cancer Epidemiol Biomarkers Prev 1996;5:823–33.
10. Cook NR, Stampfer MJ, Ma J, et al. Beta-carotene supplementation for patients with low baseline levels and decreased risks of total and prostate carcinoma. Cancer 1999;86:1783–92.
11. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N

Engl J Med 1996;334:1145–9.
12. Heinonen OP, Albanes D, Virtamo J, et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. J Natl Cancer Inst 1998;90:440–6.
13. Daviglus M, Dyer A, Persky V, et al. Dietary beta-carotene, vitamin C, and risk of prostate cancer: results from the Western Electric Study. Epidemiology 1996;7:472–7.
14. Lee MM, Wang RT, Hsing AW, et al. Case-control study of diet and prostate cancer in China. Cancer Causes Control 1998;9:545–52.
15. Talamini R, Franceschi S, La Vecchia C, et al. Diet and prostatic cancer: a case-control study in Northern Italy. Nutr Cancer 1992;18:277–86.
16. Andersson SO, Wolk A, Bergström R, et al. Energy, nutrient intake and prostate cancer risk: a population-based case-control study in Sweden. Int J Cancer 1996;68:716–22.
17. Ghadirian P, Lacroix A, Maisonneuve P, et al. Nutritional factors and prostate cancer: a case-control study of French Canadians in Montreal, Canada. Cancer Causes Control 1996;7:428–36.
18. Key TJA, Silcocks PB, Davey GK, et al. A case-control study of diet and prostate cancer. Br J Cancer 1997;76:678–87.
19. Vlajinac HD, Marinkovic JM, Ilic MD, et al. Diet and prostate cancer: a case-control study. Eur J Cancer 1997;33:101–7.
20. Deneo-Pellegrini H, De Stefani E, Ronco A, et al. Foods, nutrients and prostate cancer: a case-control study in Uruguay. Br J Cancer 1999;80:591–7.
21. Jain MG, Hislop GT, Howe GR, et al. Plant foods, antioxidants, and prostate cancer risk: findings from case-control studies in Canada. Nutr Cancer 1999;34:173–84.
22. Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intake and prostate cancer risk. J Natl Cancer Inst 2000;92:61–8.
23. Norrish AE, Jackson RT, Sharpe SJ, et al. Prostate cancer and dietary carotenoids. Am J Epidemiol 2000;151:119–23.
24. Meyer F, Bairati I, Fradet Y, et al. Dietary energy and nutrients in relation to preclinical prostate cancer. Nutr Cancer 1997;29:120–6.
25. Oishi K, Okada K, Yoshida O, et al. A case-control study of prostatic cancer with reference to dietary habits. Prostate 1988;12:179–90.
26. Nomura AMY, Stemmermann GN, Lee J, et al. Serum micronutrients and prostate cancer in Japanese Americans in Hawaii. Cancer Epidemiol Biomarkers Prev 1997;6:487–91.
27. Gann PH, Ma J, Giovannucci E, et al. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. Cancer Res 1999;59:1225–30.
28. Eichholzer M, Stahelin HB, Gey KF, et al. Prediction of male cancer mortality by plasma levels of interacting vitamins: 17-year follow-up of the prospective Basel study. Int J Cancer 1996;66:145–50.
29. Eichholzer M, Stahelin H, Ludin E, et al. Smoking, plasma vitamins C, E, retinol, and carotene, and fatal prostate cancer: seventeen-year follow-up of the prospective Basel study. Prostate 1999;38:189–98.
30. Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. J Natl Cancer Inst 1999;91:317–31.
31. Clinton S. The dietary antioxidant network and prostate cancer. Cancer 1999;86:1629–31.
32. Christen S, Woodall AA, Shigenaga MK, et al. Gamma-tocopherol traps mutagenic electrophiles such as NO(X) and complements alpha-tocopherol: physiologic implications. Proc Natl Acad Sci U S A 1997;94:3217–22.
33. Giovannucci E, Ascherio A, Rimm EB, et al. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst 1995;87:1767–76.
34. Chan JM, Pietinen P, Virtanen M, et al. Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorous (Finland). Cancer Causes Control 2000;11:859–67.
35. Hsing AW, Comstock GW, Abbey H, et al. Serologic precursors of cancer: retinol, carotenoids, and tocopherol and risk of prostate cancer. J Natl Cancer Inst 1990;82:941–6.
36. Packer L. Protective role of vitamin E in biological systems. Am J Clin Nutr 1991;53(suppl):1050S–5S.
37. Grimble RF. Effect of antioxidative vitamins on immune function with clinical applications. Int J Vitam Nutr Res 1997;67:312–20.
38. Shklar G, Oh SK. Experimental basis for cancer prevention by vitamin E. Cancer Invest 2000;18:214–22.
39. Israel K, Yu W, Sanders BG, et al. Vitamin E succinate induces apoptosis in human prostate cancer cells: role for Fas in vitamin E succinate-triggered apoptosis. Nutr Cancer 2000;36:90–100.
40. Brody T. Vitamin E. In: Nutritional biochemistry. Boston, MA: Academic Press, 1999:628–37.
41. Kapoor N, Degroff VL, Cornwell DG, et al. Anti-proliferative and pro-apoptotic effects of gamma-tocopherol quinone in human prostate cancer cell lines in vitro. American Association for Cancer Research 91st annual meeting—proceedings. Vol 41. Linthicum, MD: Cadmus Journal Services, 2000:339.
42. Huang HY, Alberg AJ, Hoffman SC, et al. Association of blood concentrations of antioxidant micronutrients and the risk of prostate cancer. American Association for Cancer Research 91st annual meeting—proceedings. Vol 41. Linthicum, MD: Cadmus Journal Services, 2000:809.
43. Rohan TE, Howe GR, Burch JD, et al. Dietary factors and risk of prostate cancer: a case-control study in Ontario, Canada. Cancer Causes Control 1995;6:145–54.
44. Hayes RB, Bogdanovicz JFAT, Schroeder FH, et al. Serum retinol and prostate cancer. Cancer 1988;62:2021–6.
45. Hartman T, Albanes D, Pietinen P, et al. The association between baseline vitamin E, selenium, and prostate cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Cancer Epidemiol Biomarkers Prev 1998;7:335–40.
46. Chan JM, Stampfer MJ, Ma J, et al. Supplemental vitamin E intake and prostate cancer risk in a large cohort of men in the United States. Cancer Epidemiol Biomarkers Prev 1999;8:893–9.
47. Tzonou A, Signorello LB, Lagiou P, et al. Diet and cancer of the prostate: a case-control study in Greece. Int J Cancer 1999;80:704–8.
48. Hsing AW, McLaughlin JK, Schuman LM, et al. Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. Cancer Res 1990;50:6836–40.
49. Hsing AW, McLaughlin JK, Hrubec Z, et al. Tobacco use and prostate cancer: 26-year follow-up of US veterans. Am J Epidemiol 1991;133:437–41.
50. Coughlin SS, Neaton JD, Sengupta A. Cigarette smoking as a predictor of death from prostate cancer in 348,874 men screened for the Multiple Risk Factor Intervention Trial. Am J Epidemiol 1996;143:1002–6.
51. Giovannucci E, Rimm EB, Ascherio A, et al. Smoking and risk of total and fatal prostate cancer in United States health professionals. Cancer Epidemiol Biomarkers Prev 1999;8:277–82.
52. Nomura AM, Kolonel LN. Prostate cancer: a current perspective. Epidemiol Rev 1991;13:200–27.
53. Pienta KJ, Esper PS. Risk factors for prostate cancer. Ann Intern Med 1993;118:793–803.
54. Engeland A, Andersen A, Haldorsen T, et al. Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women. Cancer Causes Control 1996;7:497–506.
55. Slattery ML, West DW. Smoking, alcohol, coffee, tea, caffeine, and theobromine: risk of prostate cancer in Utah (United States). Cancer Causes Control 1993;4:559–63.
56. Talamini R, Franceschi S, La Vecchia C, et al. Smoking habits and prostate cancer: a case-control study in northern Italy. Prev Med 1993;22:400–8.
57. Siemiatycki J, Krewski D, Franco E, et al. Associations between cigarette smoking and each of 21 types of cancer: a

multi-site case-control study. Int J Epidemiol 1995;24: 504–14.
58. Adami HO, Bergström R, Engholm G, et al. A prospective study of smoking and risk of prostate cancer. Int J Cancer 1996;67:764–8.
59. Brody T. Ascorbic acid (vitamin C). In: Nutritional biochemistry. Boston, MA: Academic Press, 1999:617–27.
60. Menon M, Maramag C, Malhotra RK, et al. Effect of vitamin C on androgen independent prostate cancer cells (PC-3 and Mat-Ly-Lu) in vitro: involvement of reactive oxygen species-effect on cell number, viability, and DNA synthesis. Cancer Biochem Biophys 1998;16:17–30.
61. Maramag C, Menon M, Balaji KC, et al. Effect of vitamin C on prostate cancer cells in vitro: effect on cell number, viability, and DNA synthesis. Prostate 1997;32:188–95.
62. Jamison M, Gilloteaux J, Venugopal M, et al. Flow cytometric and ultrastructural aspects of the synergistic antitumor activity of vitamin C-vitamin K3 combinations against human prostatic carcinoma cells. Tissue Cell 1996;28:687–701.
63. Kolonel LN, Hankin JH, Lee J, et al. Nutrient intakes in relation to cancer incidence in Hawaii. Br J Cancer 1981;44: 332–9.
64. Ohno Y, Yoshida O, Oishi K, et al. Dietary beta-carotene and cancer of the prostate: a case-control study in Kyoto, Japan. Cancer Res 1988;48:1331–6.
65. Fincham SM, Hill GB, Hanson J, et al. Epidemiology of prostatic cancer: a case-control study. Prostate 1990;17:189–206.
66. Le Marchand L, Kolonel LN, Wilkens LR, et al. Animal fat consumption and prostate cancer: a prospective study in Hawaii. Epidemiology 1994;5:276–82.
67. Shuurman AG, Goldbohm RA, Dorant E, et al. Vegetable and fruit consumption and prostate cancer risk: a cohort study in The Netherlands. Cancer Epidemiol Biomarkers Prev 1998; 7:673–80.
68. De Stefani E, Fierro L, Barrios E, et al. Tobacco, alcohol, diet and risk of prostate cancer. Tumori 1995;81:315–20.
69. Hayes RB, Ziegler RG, Gridley G, et al. Dietary factors and risk for prostate cancer among blacks and whites in the United States. Cancer Epidemiol Biomarkers Prev 1999;8: 25–34.
70. Whittemore AS, Kolonel LN, Wu AH, et al. Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada. J Natl Cancer Inst 1995;87:652–61.
71. Ross RK, Shimizu H, Paganini-Hill A, et al. Case-control studies of prostate cancer in blacks and whites in Southern California. J Natl Cancer Inst 1987;78:869–74.
72. Ewings P, Bowie C. Case-control study of cancer of the prostate in Somerset and East Devon. Br J Cancer 1996;74: 661–6.
73. Talamini R, La Vecchia C, Decarli A, et al. Nutrition, social factors, and prostatic cancer in a Northern Italian population. Br J Cancer 1986;53:817–21.
74. Graham S, Haughey B, Marshall J, et al. Diet in the epidemiology of carcinoma of the prostate gland. J Natl Cancer Inst 1983;70:687–92.
75. Mills PK, Beeson WL, Phillips RL, et al. Cohort study of diet, lifestyle, and prostate cancer in Adventist men. Cancer 1989;64:598–604.
76. Walker ARP, Walker BF, Tsotetsi NG, et al. Case-control study of prostate cancer in black patients in Soweto, South Africa. Br J Cancer 1992;65:438–41.