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RESEARCH ARTICLE

Serum micronutrient and antioxidant levels at baseline and the natural history of men with localised prostate cancer on active surveillance

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Abstract The aim of this study was to determine whether serum concentrations of micronutrients, antioxidants and vitamins predict rate of disease progression in untreated, localised prostate cancer. Patients with localised prostatic adenocarcinoma on a prospective study of active surveillance underwent monitoring with serial PSA levels and repeat prostate biopsies. Disease progression was defined as either adverse histology on repeat biopsy (primary Gleason grade ≥4 or >50% positive cores of total) or radical treatment for PSA velocity >1 ng ml^{-1} $year^{-1}$. Time to disease progression was analysed with respect to baseline levels of alpha-tocopherol, gamma-tocopherol, alpha-carotene and beta-carotene, lycopene, retinol and selenium. One hundred four patients were evaluable, with a median follow-up of 2.5 years. Thirty-eight patients experienced disease progression, 13 biochemical and 25 histologic progression. Median time to disease progression was 2.62 years. No significant association was seen between time to disease progression and baseline serum levels of alpha-tocopherol (p=0.86), gamma-tocopherol (p=0.84), alpha-carotenoid (p=0.66), beta-carotene (p=0.65), lycopene (p=0.0.15), retinol (p=0.76) or selenium (p=0.76). No significant association was seen between serum levels of the micronutrients, antioxidants or vitamins and either adverse histology on repeat biopsy or PSA velocity. Our data do not support the hypothesis that high serum concentrations of micronutrients, antioxidants and vitamins prevent disease progression in men with localised prostate cancer.

Keywords Prostate · Active surveillance · Antioxidants · Micronutrients · Vitamins

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Introduction

Micronutrients, antioxidants and vitamins have been shown to block initiation and suppress promotion and progression of cancer [1–3]. Studies have shown a reduced risk of prostate cancer with high intake and high serum levels of these micronutrients/antioxidants [3–9]. Intervention with tocopherol and selenium has been shown to reduce the incidence of prostate cancer in prospective randomised controlled trials [7, 9, 10]. Lycopene supplementation has been shown to reduce PSA and disease progression in localised prostate cancer patients when given preoperatively and to improve response to hormonal treatment [11–13]. Current prostate research suggests that the role of antioxidants and micronutrients may be greater in determining progression or stimulation of established tumours rather than in the development of new tumours [5, 11, 12, 14–17]

Prostate cancer is the commonest cancer in UK men, with over 27,000 cases diagnosed annually. There is extraordinarily wide inter-patient variation in the natural history of the disease, but accurate prediction of individual prostate cancer behaviour at the time of diagnosis is not currently possible. However, accurate prediction of individual prostate cancer behaviour at the time of diagnosis is not currently possible, and so immediate radical treatment for all cases is a standard approach. Curative intervention should ideally be targeted to the minority of men with significant cancers so that the remainder, with biologically irrelevant 'disease', are spared the risks of incontinence and impotence that are associated with treatment [18–20].

Active surveillance of early prostate cancer is an approach to managing localised prostate cancer in which the choice between curative treatment and observation is based on evidence of disease progression during a period of close monitoring [20–22]. The rate of rise of PSA shows significant inter-patient variation and is the major determinant of time to clinical progression [22–24]. Curative treatment is targeted to those men on active surveillance who have either a rapid PSA doubling time or adverse features on repeat biopsy [25, 26]. There is an unmet need for biomarkers of prostate cancer behaviour that could identify, at the time of diagnosis, those patients who could safely avoid radical treatment [20]. Active surveillance provides a uniquely valuable opportunity to study biomarkers of early prostate cancer behaviour [27]. If all prostate cancer patients receive immediate radical treatment, only 5–15% develop recurrence, which typically is detected years later; thousands of patients would need to be followed for many years for proper evaluation of candidate biomarkers. Furthermore, among the 85–95% that remain disease-free, it is impossible to distinguish the biologically irrelevant cancers from those that were significant but successfully treated. In contrast, outcome in terms of PSA kinetics and repeat biopsies is available for all men on active surveillance within a matter of months, so that candidate biomarkers can be evaluated rapidly, and in relatively few patients.

Biomarkers of prostate cancer behaviour could be important not just to avoid overtreatment of indolent disease but also to provide mechanistic insights into the extraordinary inter-patient variation seen in prostate cancer behaviour and thus inform the search for novel therapeutic targets. Serum micronutrient/antioxidant levels are attractive candidate markers of prostate cancer behaviour not just because of the evidence from epidemiological, in vitro and in vivo studies referred to above but also because if validated in patients by prospective randomised studies, they would provide an obvious opportunity for a low-toxicity intervention with the aim of preventing prostate cancer progression.

We have therefore studied the clinical outcomes in men with localised prostate cancer on active surveillance with respect to baseline serum levels of micronutrients/antioxidants.

Patients and methods

A prospective study of active surveillance of localised prostate cancer opened at the Royal Marsden Hospital in 2002. Eligibility criteria comprised histologically proven adenocarcinoma prostate, stage T1/2a N0/Nx with PSA levels <15 ng/ml, composite Gleason score ≤7 with primary grade ≤3 and percentage of positive biopsy cores ≤50% of total cores. All patients had monitoring of serum PSA every 3 months. PSA velocity was calculated using all the PSA values available from entry to the study until treatment or last follow-up, with a minimum of three consecutive PSA values a month apart. As part of the prospective protocol, all patients had repeat trans-rectal, ultrasound-guided, eight-core prostate biopsy at 18–24 months after entry to study. All pathology was verified centrally to avoid inter-observer variability. Radical treatment was recommended in the case of PSA progression defined as a PSA velocity >1 ng ml^{-1} $year^{-1}$ or adverse histology on repeat biopsy defined as primary Gleason grade ≥4 or composite Gleason score more than 7% or >50% of the total cores positive for involvement. The study was approved by the Local Research Ethics Committee, and all patients gave written informed consent.

The active surveillance study protocol included banking of baseline serum samples for analysis of candidate prognostic biomarkers with respect to subsequent clinical outcomes. As part of an exploratory analysis, in a cohort of 104 consecutive patients, these baseline serum samples were analysed for levels of alpha-tocopherol, gamma-tocopherol, alpha-carotene and beta-carotene, lycopene, retinol and selenium using high-performance liquid chromatography/tandem mass spectrometry.

Statistical analysis

The main endpoint was time to disease progression, with disease progression defined as either histologic progression on repeat biopsy or radical treatment for PSA progression. Secondary endpoints were time to histologic disease progression and PSA velocity. Serum micronutrient/antioxidant levels were considered both as continuous variables and after dichotomising about the median. Univariate analysis of the relationship between time to progression or treatment and serum micronutrient/antioxidant levels was conducted by Cox regression method. The correlation of PSA velocity and the blood concentration of each micronutrient/antioxidant level was analysed using the Spearman

rank correlation coefficient. Chi-squared test was utilised to analyse the difference between groups of patients who had adverse histology on repeat biopsy and the serum micronutrient/antioxidant levels dichotomised across the median, and a p value <0.05 was considered significant. Multivariate logistic regression with a backward stepwise selection process was utilised. Analysis was undertaken by SPSS 14 (SPSS Inc., IL).

Results

Blood samples from a cohort of 104 consecutive patients on the prospective active surveillance protocol were analysed. The patient characteristics are shown in Table 1. Median follow-up from the time of diagnosis was 2.5 years (95% CI 1–4 years). The median PSA velocity was 0.72 ng ml^{-1} $year^{-1}$ (95% CI −1.47 to 3.33). Thirteen patients had treatment initiation on account of PSA progression. Twenty-five patients of the 91 patients who had a repeat biopsy had adverse histology on repeat biopsy. The median time to progression was 2.62 years (95% CI 2.2–3.03 years). None of the patients on active surveillance has developed distant metastasis or death from prostate cancer. The distribution of serum micronutrients/antioxidants levels in the study population are shown in Table 2. There was no correlation between baseline blood levels of alpha-tocopherol, gamma-tocopherol, alpha-carotene and beta-carotene, lycopene, retinol and selenium and clinical characteristics such as age, PSA, Gleason, PSA density or free/total PSA ratio (data not shown).

On univariate analysis, no significant association was seen between time to disease progression and serum levels of either alpha-tocopherol (p=0.86), gamma-tocopherol (p=0.84), alpha-carotenoid (p=0.66), beta-carotene (p=0.65), lycopene (p=0.0.15), retinol (p=0.76) or selenium (p=0.76), as shown in Table 2. Multivariate regression analysis with a backward stepwise selection process did not produce any significant combination of variables to predict for disease progression. The analysis was repeated after accounting for confounding factors like age, initial PSA, etc. and also comparing the lowest and highest quartiles of individual serum values of the micronutrients and vitamins to predict for disease progression, which again did not yield any statistically significant results (data not shown).

No significant association was seen between adverse histology on repeat biopsy and serum levels of either alpha-tocopherol (p=0.38), gamma-tocopherol (p=0.98), alpha-carotenoid (p=0.40), beta-carotene (p=0.33), lycopene (p=0.19), retinol (p=0.55) or selenium (p=0.70), as shown in Table 3. There was no significant correlation between PSA velocity and serum levels of either alpha-tocopherol (p=0.22), gamma-tocopherol (p=0.81), alpha-carotenoid (p=0.99), beta-carotene (p=0.97), lycopene (p=0.97), retinol (p=0.99) or selenium (p=0.60), as shown in Table 2.

Table 1 Patient characteristics

	Number	Range
Total patients	104	
Age (years)	65.5	48–77
Median initial PSA (ng/ml)	6.65	0.22–14.7
Composite Gleason score at initial biopsy		
≤6	94	
7	10	
Median PSA velocity (ng $ml^{-1}year^{-1}$)	0.72	−2.7 to 8.3
Treatment due to PSA progression prior to biopsy	13	
Histologic progression on repeat biopsy	25	
Median time to progression	2.62 years	3 months–4.2 years

Discussion

From our prospective study of active surveillance, analysis of early clinical outcomes in a cohort of 104 consecutive patients with localised prostate cancer did not yield a significant correlation between the serum micronutrient/antioxidant levels and rate of disease progression. The hypothesis that blood levels of alpha-tocopherol, gamma-tocopherol, alpha-carotene and beta-carotene, lycopene, retinol and selenium are associated with the rate of disease progression in prostate cancer may require further investigation because if true, it could have important implications for the tertiary prevention of prostate cancer.

There is a considerable body of evidence from previous studies that prostate cancer patients have lower circulating concentrations of micronutrients and antioxidants such as lycopene, beta-carotene, alpha-tocopherol and retinol [6, 28]. Lycopene supplementation has lead to reduced PSA levels, has delayed or prevented progression of high-grade prostatic intraepithelial neoplasia to cancer and has improved the responses to hormonal treatment [13, 29, 30]. Kucuk et al. [11] have shown that lycopene supplementation before radical prostatectomy resulted in a reduction in PSA, reduction in tumour size, lesser involvement of surgical margins and extra-prostatic tissues with cancer and less diffuse high-grade prostatic intraepithelial neoplasia. Chang et al. [4] have suggested that higher circulating levels of alpha-carotene and trans-beta-carotene may contribute to lower prostate cancer risk. Weinstein et al. [9] reported from the results of the ATBC study that

Table 2 Univariate analysis of baseline biochemical parameters to predict for time to progression or treatment by Cox regression and analysis of the correlation of blood micronutrient / antioxidant levels with PSA kinetics

	Mean	Median	Range	Cox regression analysis for time to progression or treatment[a]			Correlation with initial PSA[b]		Correlation with PSA velocity[b]	
				p value	Hazard ratio	95.0% CI for HR	Spearman's rho	*p* value (two-tailed)	Spearman's rho	p value (two-tailed)
Alpha-carotene (μmol/L)	0.056	0.05	0.005–0.29	0.665	6.12	0.002–22,472.755	−0.059	0.567	0.001	0.997
Alpha-tocopherol (μmol/L)	9.61	8.85	4.8–37.1	0.857	1.01	0.895–1.142	0.036	0.729	−0.129	0.219
Beta-carotene (μmol/L)	0.22	0.17	0.031–1.17	0.646	1.48	0.279–7.858	−0.015	0.882	0.003	0.974
Gamma-tocopherol	0.49	0.43	0.11–1.33	0.839	0.87	0.236–3.232	−0.013	0.904	−0.025	0.809
Lycopene (μmol/L)	0.12	0.105	0.01–0.51	0.149	10.44	0.431–253.094	−0.072	0.487	−0.004	0.973
Retinol (μmol/L)	0.46	0.43	0.19–1.6	0.762	1.42	0.147–13.757	−0.073	0.484	−0.001	0.993
Selenium (μmol/L)	1.193	1.14	0.71–3.23	0.758	0.99	0.985 –1.011	−0.154	0.118	0.049	0.600

[a] Significance of continuous variables to predict for time to progression assessed by Cox's proportional hazards method and $p < 0.05$ considered significant

[b] Correlation of variables assessed by Spearman rank correlation method with p value <0.05 considered significant

patients with a high-circulating alpha- and gamma-tocopherol levels had a lower risk of prostate cancer and that alpha-tocopherol supplementation reduced the incidence of prostate cancer by 32%. Prospective placebo-controlled clinical trial by Clark et al. in 974 patients have shown that supplementation with selenium resulted in a 63% reduction in the incidence of prostate cancer and a significant reduction in mortality from cancer [7, 10].

However, there is also evidence to the contrary like the SELECT study which showed no benefit from selenium and vitamin E in preventing prostate cancer in healthy men [17]. Similarly, the VITAL study did not show a significant correlation between the incidence of prostate cancer and the intake of vitamin E or selenium, though risk of clinically relevant advanced disease was reduced with greater long-term vitamin E supplementation [31]. In the large prospective Physician's Health Study of Vitamin E and C supplementation, no appreciable reduction in prostate cancer or other malignancies were noted [32]. Plasma selenium concentration did not correlate with the risk of prostate cancer in a matched controlled European study [33].

Our study has several limitations. Though the blood levels of micronutrients/antioxidants may mirror intracellular levels of these chemicals, whether they are sufficient surrogate measurements to predict significant effect of biochemical parameters on disease progression is controversial. A snapshot of blood levels may also not be representative of or be predictive of the behaviour of prostate cancer considering the long natural history, with the wide fluctuations in the blood levels of these chemicals expected during this period. The lack of significant correlations between histologic progression and blood levels of micronutrients may also be due to tumour heterogeneity especially in biopsy specimens. The criteria for assessing progression in patients on active surveillance are not yet well defined, limitations of which include the use of PSA velocity as a 'surrogate' of long-term outcomes and the possibility of sampling error on repeat biopsy [25, 26]. Another drawback of our study is the short follow-up

Table 3 Univariate analysis of dichotomised blood micronutrient and antioxidant levels to predict for adverse histology on repeat biopsy on repeat biopsy using the chi-squared test

		Adverse histology on repeat biopsy				
		No	Yes	Total	Chi-squared[a]	*p* value
Alpha-carotene	≤Median	29	14	43	0.686	0.407
	>Median	31	10	41		
Alpha-tocopherol	≤Median	33	10	43	0.754	0.385
	>Median	28	13	41		
Beta-carotene	≤Median	32	10	42	0.933	0.334
	>Median	28	14	42		
Gamma-tocopherol	≤Median	32	12	44	0.001	0.981
	>Median	29	11	40		
Lycopene	≤Median	32	9	41	1.720	0.190
	>Median	28	15	43		
Retinol	≤Median	30	13	43	0.360	0.548
	>Median	31	10	41		
Selenium	=Median	34	14	48		
	>Median	32	11	43	0.146	0.702

[a] Differences between groups assessed by chi-squared test with $p < 0.05$ significant

time compared to the long natural history of prostate cancer. It remains possible that blood levels of micronutrient and antioxidant levels in our cohort may be associated with important long-term outcomes such as time to metastasis, but to investigate this possibility will require many years of follow-up. Though our study may be underpowered due to low patient numbers, we could not detect any trend towards significance for any of the parameters analysed to predict for disease progression.

Supplementing early-stage prostate cancer patients with micronutrients/antioxidants, even in a study of short duration, has been shown to alter surrogate markers of proliferation such as serum PSA [13, 34]. Patients on active surveillance for localised prostate cancer may be ideal candidates for such supplementation, and it may be more effective in a population with low blood levels of these micronutrients/antioxidants. Prospective randomised controlled interventional studies are required to investigate and to assess the true preventive and therapeutic effects of these compounds and whether supplementation of these micronutrients/antioxidants, to produce adequate tissue concentration needed to induce suppression of tumour progression, would alter the biology of prostate cancer.

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References

1. Elstner E, Campbell MJ, Munker R, Shintaku P, Binderup L, Heber D, et al. Novel 20-epi-vitamin D3 analog combined with 9-*cis*-retinoic acid markedly inhibits colony growth of prostate cancer cells. Prostate. 1999;40:141–9.
2. Quader ST, Bello-DeOcampo D, Williams DE, Kleinman HK, Webber MM. Evaluation of the chemopreventive potential of retinoids using a novel in vitro human prostate carcinogenesis model. Mutat Res. 2001;496:153–61.
3. Blumenfeld AJ, Fleshner N, Casselman B, Trachtenberg J. Nutritional aspects of prostate cancer: a review. Can J Urol. 2000;7:927–35. discussion 936.
4. Chang S, Erdman Jr JW, Clinton SK, Vadiveloo M, Strom SS, Yamamura Y, et al. Relationship between plasma carotenoids and prostate cancer. Nutr Cancer. 2005;53:127–34.
5. Brett T. Prostate cancer. What part does diet play? Aust Fam Physician. 2000;29:1122–4.
6. Almushatat AS, Talwar D, McArdle PA, Williamson C, Sattar N, O'Reilly DS, et al. Vitamin antioxidants, lipid peroxidation and the systemic inflammatory response in patients with prostate cancer. Int J Cancer. 2006;118:1051–3.
7. Duffield-Lillico AJ, Dalkin BL, Reid ME, Turnbull BW, Slate EH, Jacobs ET, et al. Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. BJU Int. 2003;91:608–12.
8. Kumar NB, Besterman-Dahan K. Nutrients in the chemoprevention of prostate cancer: current and future prospects. Cancer Control. 1999;6:580–6.
9. Weinstein SJ, Wright ME, Pietinen P, King I, Tan C, Taylor PR, et al. Serum alpha-tocopherol and gamma-tocopherol in relation to prostate cancer risk in a prospective study. J Natl Cancer Inst. 2005;97:396–9.
10. Clark LC, Dalkin B, Krongrad A, Combs Jr GF, Turnbull BW, Slate EH, et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. Br J Urol. 1998;81:730–4.
11. Kucuk O, Sarkar FH, Sakr W, Djuric Z, Pollak MN, Khachik F, et al. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. Cancer Epidemiol Biomarkers Prev. 2001;10:861–8.
12. Kucuk O, Sarkar FH, Djuric Z, Sakr W, Pollak MN, Khachik F, et al. Effects of lycopene supplementation in patients with localized prostate cancer. Exp Biol Med (Maywood). 2002;227:881–5.
13. Ansari MS, Gupta NP. A comparison of lycopene and orchidectomy vs orchidectomy alone in the management of advanced prostate cancer. BJU Int. 2003;92:375–8. discussion 378.
14. Bowen PE. Selection of surrogate endpoint biomarkers to evaluate the efficacy of lycopene/tomatoes for the prevention/progression of prostate cancer. J Nutr. 2005;135:2068S–70S.
15. Huss WJ, Lai L, Barrios RJ, Hirschi KK, Greenberg NM. Retinoic acid slows progression and promotes apoptosis of spontaneous prostate cancer. Prostate. 2004;61:142–52.
16. Peehl DM, Feldman D. The role of vitamin D and retinoids in controlling prostate cancer progression. Endocr Relat Cancer. 2003;10:131–40.
17. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). Jama. 2009;301:39–51.
18. Klotz L. Active surveillance with selective delayed intervention for favorable risk prostate cancer. Urol Oncol. 2006;24:46–50.
19. Parker C. Active surveillance: towards a new paradigm in the management of early prostate cancer. Lancet Oncol. 2004;5:101–6.
20. Parker C. Active surveillance of early prostate cancer: rationale, initial results and future developments. Prostate Cancer Prostatic Dis. 2004;7:184–7.
21. van den Bergh RC, Vasarainen H, van der Poel HG, Vis-Maters JJ, Rietbergen JB, Pickles T, et al. Short-term outcomes of the prospective multicentre 'Prostate Cancer Research International: Active Surveillance' study. BJU Int 2009 Oct 8.
22. Klotz LH. Active surveillance for good risk prostate cancer: rationale, method, and results. Can J Urol. 2005;12 Suppl 2:21–4.
23. Klotz L. Active surveillance with selective delayed intervention is the way to manage 'good-risk' prostate cancer. Nat Clin Pract Urol. 2005;2:136–42. quiz 131 p following 149.
24. D'Amico AV, Renshaw AA, Sussman B, Chen MH. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. Jama. 2005;294:440–7.
25. Venkitaraman R, Norman A, Woode-Amissah R, Dearnaley D, Horwich A, Huddart R, et al. Prostate-specific antigen velocity in untreated, localized prostate cancer. BJU Int. 2008;101:161–4.
26. Venkitaraman R, Norman A, Woode-Amissah R, Fisher C, Dearnaley D, Horwich A, et al. Predictors of histological disease progression in untreated, localized prostate cancer. J Urol. 2007;178:833–7.
27. Jhavar S, Bartlett J, Kovacs G, Corbishley C, Dearnaley D, Eeles R, et al. Biopsy tissue microarray study of Ki-67 expression in untreated, localized prostate cancer managed by active surveillance. Prostate Cancer Prostatic Dis. 2009;12:143–7.

28. Gann PH, Ma J, Giovannucci E, Willett W, Sacks FM, Hennekens CH, et al. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. Cancer Res. 1999;59:1225–30.
29. Mohanty NK, Saxena S, Singh UP, Goyal NK, Arora RP. Lycopene as a chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia. Urol Oncol. 2005;23:383–5.
30. Stacewicz-Sapuntzakis M, Bowen PE. Role of lycopene and tomato products in prostate health. Biochim Biophys Acta. 2005;1740:202–5.
31. Peters U, Littman AJ, Kristal AR, Patterson RE, Potter JD, White E. Vitamin E and selenium supplementation and risk of prostate cancer in the Vitamins and Lifestyle (VITAL) Study cohort. Cancer Causes Control. 2008;19:75–87.
32. Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2009;301:52–62.
33. Allen NE, Appleby PN, Roddam AW, Tjonneland A, Johnsen NF, Overvad K, et al. Plasma selenium concentration and prostate cancer risk: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr. 2008;88:1567–75.
34. Schroder FH, Roobol MJ, Boeve ER, de Mutsert R, Zuijdgeest-van Leeuwen SD, Kersten I, et al. Randomized, double-blind, placebo-controlled crossover study in men with prostate cancer and rising PSA: effectiveness of a dietary supplement. Eur Urol. 2005;48:922–30. discussion 930–921.