Endogenous carotenoid concentrations in cancerous and non-cancerous tissues of gastric cancer patients in Korea*

SAR Paiva1,2 MD, PhD, K-J Yeum1 PhD, KS Lee3 MD, PhD, IS Park3 MD, PhD, YC Lee-Kim4 PhD and RM Russell1 MD

1Jean Mayer United States Department of Agriculture, Human Nutrition Research Center on Ageing at Tufts University, Boston, MA, USA
2Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP), São Paulo, Brazil
3School of Medicine, Yonsei University, Seoul, Korea
4Department of Food and Nutrition, Yonsei University, Seoul, Korea

Carotenoid concentrations were measured in serum and in both non-cancerous and cancerous gastric mucosal tissues of Korean patients with gastric cancer (n = 18). Carotenoids in serum and gastric tissue were extracted with chloroform/methanol (2:1), and measured using reverse-phase high-performance liquid chromatography with a C30 column. Cryptoxanthin and β-carotene were the major carotenoids in the Korean blood and they had a median ratio of non-cancerous tissue/serum levels which was less than 1.0. No significant differences of cryptoxanthin and β-carotene levels were found between non-cancerous and cancerous tissues. After incubation of β-carotene with gastric tissue, significantly higher levels of β-carotene breakdown products were produced in the homogenates of cancerous tissue when compared with non-cancerous tissue. Lutein, zeaxanthin and α-carotene were the minor carotenoid constituents in the blood and their median ratio of non-cancerous tissue/serum levels was greater than 1.0. Cancerous tissue had significantly lower levels of lutein, zeaxanthin and α-carotene than did non-cancerous tissue. It appears that the increased breakdown of β-carotene and cryptoxanthin in cancerous tissue can be compensated for by an increased uptake of circulating carotenoids by cancerous tissue, whereas lutein, zeaxanthin and α-carotene levels in cancerous tissue are not able to be maintained.

Key words: β-carotene, cryptoxanthin, lycopene, carotenoids, gastric cancer, mucosa, serum, Korea.

Introduction
Gastric cancer is a common cancer of the digestive tract. Despite a declining incidence, gastric cancer remains a major cause of cancer death worldwide. The United States has one of the lowest stomach cancer mortality rates (mortality rates per 100 000) in the world for both males and females (6.6 for males and 3.0 for females).1 The highest rates around the world were noted in Asian countries. In Korea, the mortality rate for gastric cancer is 54.6 for males and 23.7 for females.3

A large body of literature which includes in vitro studies, animal studies and human observational studies has suggested that β-carotene has promise as a potential cancer preventive agent. This has led to the design of intervention trials in humans to determine whether a high dose supplement of β-carotene prevents cancer. In one of these trials, the Linxian trial, subjects taking a combination of nutrients (β-carotene, vitamin E and selenium) showed a reduction in cancer mortality and in stomach cancer mortality.3 However, in two other trials, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC study) in Finland4 and the Beta Carotene and Retinol Efficacy Trial (CARET) in the USA,5 showed that the combination of β-carotene with other supplements had no benefit and may have had an adverse effect on the incidence of lung cancer and on the risk of death from lung cancer. In a subgroup of the ATBC study, subjects with a gastric precancer lesion, supplementation with α-toco-

*Presented at Experimental Biology 1998, April 1998, San Francisco, California, USA.

Correspondence address: RM Russell, Jean Mayer United States Department of Agriculture, Human Nutrition Research Center on Ageing at Tufts University, Boston, MA 02111, USA. Tel: 1 617 556 3335; Fax: 1 617 556 3344. Email: Russell@hnrc.tufts.edu. Accepted 9 December 1998.
Carotenoids in gastric mucosa tissues

Preparations of the homogenates of stomach mucosal (cancerous and non-cancerous) tissues for HPLC analyses were as follows. The gastric mucosa was scraped with a scalpel and the wet weight of the scraping was recorded. The gastric mucosa was homogenized for 30 s on ice in a Brinkmann (Westbury, NY, USA) Polytron homogenizer with 5 mL of chloroform: methanol (2:1, v/v) and an internal standard (echinenone). Following this, 500 µL of saline was added. The tube was vortexed and centrifuged at 800 × g at 4°C for 10 min. The chloroform layer was transferred to a 13 × 100 mm test tube, and the remaining sample in the aqueous layer was extracted with hexane (3 mL). The tube was vortexed and centrifuged at 800 × g at 4°C for 10 min. The hexane layer was then removed and combined with the chloroform extract. The combined extracts were evaporated to dryness under nitrogen in a water bath at 40°C. The residue was redissolved in 100 µL of ethanol. The tube was vortexed and sonicated for 30 s. A 50 µL aliquot was injected onto the HPLC.

Carotenoids were assayed with a C30 carotenoid column. The Waters 994 programmable photodiode array detector was set at 450 nm. The HPLC mobile phase was methanol: methyl-tert-butyl ether: water (83:15:2, by volume, with 1.5% ammonium acetate in the water; solvent A) and methanol: methyl-tert-butyl ether: water (8:90:2, by volume, with 1% ammonium acetate in the water; solvent B). The gradient procedure, at a flow rate of 1 mL/min (16°C), was as follows: (i) 90% solvent A and 10% solvent B for 5 min; (ii) a 12 min linear gradient to 55% solvent A; (iii) a 12 min linear gradient to 95% solvent B; (iv) a 5 min hold at 95% solvent B; and (v) a 2 min gradient back to 90% solvent A and 10% solvent B. Lutein, zeaxanthin, cryptoxanthin, α-carotene, 13-cis β-carotene, all-trans β-carotene, 9-cis β-carotene/ζ-carotene, and trans and cis lycopene were adequately separated with this method.

Carotenoids were quantified by determining peak areas in the HPLC chromatograms calibrated against known amounts of standards. Concentrations were corrected for extraction and handling losses by monitoring the recovery of the internal standard. The lower limit of detection was 0.2 pmol for carotenoids. The total carotenoid level represents the sum of each of the individual carotenoid levels (lutein, zeaxanthin, cryptoxanthin, α-carotene, 13-cis β-carotene, all-trans β-carotene, 9-cis β-carotene/ζ-carotene, and trans and cis lycopene) measured in the sample. All sample processing was done under red light.

Incubation. Preparations of the homogenates of stomach mucosal (cancerous and non-cancerous) tissues for incubation were essentially the same as described above. Incubation of β-carotene with gastric mucosal homogenates was done in duplicate. β-Carotene was purified using a 5% water-weakened alumina column. The purity was checked by HPLC, as described below. Tissue homogenates (100 µL, 0.5–1 mg protein) were incubated (standard incubation conditions) under red light in glass vials at 37°C in a shaking water bath for 30 min with the following additions: 20 mmol Heps buffer (pH 7.35), 150 mmol KC1, 1.8 µmol β-carotene (dissolved in 10 µL of propylene glycol), NAD+ (2 mmol), and dihydrothreitol (2 mmol), in a final volume of 1 mL. Two control vials were run lacking either β-carotene or tissue homogenates. The vials were uncovered and the incubation...
mixture was exposed to room air as the gas phase. The protein concentrations of samples were determined by using the BCA (bicinchoninic acid) Protein Assay (Pierce Co., Rockford, IL, USA). The incubation mixture was extracted using the same method described above to analyse serum and tissue by HPLC. The carotenoid and retinoid analyses were assayed with a C18 column. The Waters 994 programmable photodiode array detector was set at 340 nm for retinoids, 450 nm for carotenoids.

The HPLC mobile phase was acetonitrile : tetrahydrofuran : water (50:20:30, v/v/v, 1% ammonium acetate in water, solvent A) and acetonitrile : tetrahydrofuran : water (50: 44: 6, v/v/v, 1% ammonium acetate in water, solvent B). The gradient procedure at a flow rate of 1 mL/min was as follows: 100% solvent A was used for 3 min followed by a 10 min linear gradient to 100% solvent B, a 13 min hold at 100% solvent B, then a 2 min gradient back to 100% solvent A. β-Apo-carotenoids, retinal and retinoic acid were quantified by determining peak areas in HPLC chromatograms calibrated against known amounts of standards. Levels were corrected for extraction and handling losses by monitoring the recovery of internal standards (γ-carotene and retinyl acetate). The lower limits of detections were 0.2 pmol for β-apo-8', -10', and -12'-carotenals, 0.5 pmol for β-apo-14'-carotenal, 0.8 pmol for β-apo-13'-carotenone and retinal and 2.6 pmol for retinoic acid.

**Statistical analysis**

When there was a normal distribution, comparisons between the two tissues were made by paired \( t \)-tests. When data showed a non-normal distribution, comparisons between the two tissues were made by the Wilcoxon rank sum test. Values are presented as mean (± SD) or medians (including the lower quartile and upper quartile). To represent the statistical values, two kinds of graphics are used: in the normal distribution, a scatter plot with SD bars; in a non-normal distribution, a box plot graph with 10th, 25th, 50th, 75th and 90th percentiles indicated. Data analyses were carried out with SigmaStat version 2.0 for Windows 95, NT & 3.1 (Jandel Scientific Software, San Rafael, CA, USA).

**Results**

HPLC chromatograms of carotenoids extracted from serum and from a gastric mucosal tissue from the same patient are shown in Fig. 1. A similar pattern was observed in both samples.

The proportion of the individual carotenoids in serum and gastric mucosa tissue (non-cancerous and cancerous) in the Korean gastric cancer patients are shown in Table 1. Cryptoxanthin and all-trans-carotene are the major carotenoids in serum. They represent 55.8% and 22.0% of the total cryptoxanthin and all-trans-carotene carotenoids, respectively, in serum (Table 1). Also, in the gastric mucosa tissues (non-cancerous and cancerous), cryptoxanthin and all-trans-carotene are the predominant carotenoids (Table 1). The median serum lycopene concentration (0.01 µmol/L) was one of the lowest values among the carotenoids analysed, and this substance was not detected in the majority of either non-cancerous or cancerous tissues.

When comparison between non-cancerous and cancerous gastric mucosa was made, we observed that cancerous tissues had significant lower values than non-cancerous gastric mucosa tissues for lutein, zeaxanthin and α-carotene (Fig. 2).

**Table 1.** Serum, non-cancerous and cancerous gastric mucosa tissue carotenoid composition in Korean patients with gastric cancer

<table>
<thead>
<tr>
<th></th>
<th>Serum 9</th>
<th>Non-cancerous 9</th>
<th>Cancerous 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeaxanthin</td>
<td>3.24 (2.02–4.83)</td>
<td>6.17 (3.54–8.13)</td>
<td>4.68 (3.12–7.28)</td>
</tr>
<tr>
<td>Cryptoxanthin</td>
<td>55.79 (47.29–64.80)</td>
<td>34.70 (29.83–41.34)</td>
<td>37.16 (31.54–48.07)</td>
</tr>
<tr>
<td>α-Carotene</td>
<td>2.86 (2.08–3.37)</td>
<td>11.25 (5.60–21.31)</td>
<td>6.17 (3.99–8.25)</td>
</tr>
<tr>
<td>Lycopene</td>
<td>0.57 (0.31–1.99)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Data are expressed as percentage (median) of total carotenoids; \( n = 18; \) numbers in parentheses represent lower quartile and upper quartile.
However, no significant differences in cryptoxanthin and all-trans-carotene levels were found between non-cancerous and cancerous tissues (Fig. 3).

A chromatogram of the β-carotene cleavage products after incubation of β-carotene with mucosal homogenates is shown in Fig. 4. The incubation of β-carotene with gastric mucosal homogenates showed a significantly greater production of retinoic acid and β-apo-carotenoids in the cancerous tissue compared with the non-cancerous tissue (Table 2). Incubation of other pro-vitamin A carotenoids (α-carotene and β-cryptoxanthin) with non-cancerous gastric mucosal tissue showed a similar pattern in breakdown products when compared with the incubation with β-carotene (Fig. 4).

When the ratios between non-cancerous gastric tissue carotenoid levels versus serum carotenoid levels were calculated, we observed that cryptoxanthin and all-trans-carotene had median ratios that were less than one (Table 3). However, lutein, zeaxanthin and α-carotene had ratios of non-cancerous tissue levels versus serum levels that were greater than one (Table 3).

Discussion

Serum levels of carotenoids generally reflect dietary intakes. Also, physiological, lifestyle and dietary factors

Table 2. The cleavage metabolites of β-carotene after 30 min incubation of β-carotene with gastric mucosa homogenates of gastric cancer patients

<table>
<thead>
<tr>
<th>Products</th>
<th>Non-cancerous</th>
<th>Cancerous</th>
<th>P (test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinoic Acid</td>
<td>11.3 ± 6.8</td>
<td>14.7 ± 6.1</td>
<td>0.020 (t)</td>
</tr>
<tr>
<td>Retinal</td>
<td>36.0 ± 16.7</td>
<td>48.2 ± 23.9</td>
<td>0.067 (t)</td>
</tr>
<tr>
<td>β-Apo-13-carotenone</td>
<td>94.0 ± 41.7</td>
<td>111.9 ± 48.7</td>
<td>0.104 (t)</td>
</tr>
<tr>
<td>β-Apo-carotenals 14⁻</td>
<td>21.5 ± 11.5</td>
<td>39.2 ± 27.8</td>
<td>0.014 (t)</td>
</tr>
<tr>
<td>12⁻</td>
<td>20.0 ± 6.2</td>
<td>30.6 ± 17.0</td>
<td>0.047 (t)</td>
</tr>
<tr>
<td>10⁻</td>
<td>19.9 ± 8.2</td>
<td>26.5 ± 10.3</td>
<td>0.033 (t)</td>
</tr>
<tr>
<td>8⁻</td>
<td>2.0 (1.7–2.4)</td>
<td>3.1 (1.8–3.5)</td>
<td>0.042 (W)</td>
</tr>
</tbody>
</table>

Data are expressed as pmol/30min/mg protein; n = 11; (mean ± SD); median (lower quartile – upper quartile); t, paired t-test; W, Wilcoxon rank sum test.

Figure 3. (a) Median and box plot of cryptoxanthin concentrations in serum, non-cancerous and cancerous. Comparisons between non-cancerous and cancerous by Wilcoxon rank sum test (P = 0.832). (b) Median and box plot of all-trans-carotene concentrations in serum, non-cancerous and cancerous. Comparisons between non-cancerous and cancerous by Wilcoxon rank sum test (P = 0.702).
have been identified which influence carotenoid concentrations in serum.\textsuperscript{18–20} It is well known that individual fruits and vegetables provide specific carotenoids. Yellow or orange vegetables such as carrots and squash, have high levels of $\alpha$-carotene and $\beta$-carotene; green leafy vegetables such as spinach and broccoli contain lutein, zeaxanthin and $\beta$-carotene;\textsuperscript{21} oranges are a major contributor of cryptoxanthin\textsuperscript{22} and tomatoes contain high amounts of lycopene.\textsuperscript{23}

Foods habits and the cultural and social environments of Asian people are different from those of Western people.\textsuperscript{24} Therefore, it is not surprising that cryptoxanthin and all-trans $\beta$-carotene were the major carotenoids in Korean blood, while lycopene was a minor carotenoid. The Korean National Nutritional Survey revealed that Korean people have a high consumption of tangerines and yellow and green leafy vegetables, but an extremely low consumption of tomato and tomato products.\textsuperscript{25} This pattern is reflected in the blood of healthy Chinese and Korean adults.\textsuperscript{26} In this latter study, serum lycopene concentrations in Koreans were more than 10 times lower than those found in Caucasian Americans.\textsuperscript{26}

When serum assessment is done at the time invasive cancer is found, there is the possibility that any nutritional deficiency may be a consequence rather than an underlying cause of the neoplastic process. However, in our study the values of the serum carotenoids were comparable with the median values of healthy people\textsuperscript{20} and the values in the elderly participants of the Framingham Heart Study.\textsuperscript{27} However, cryptoxanthin and lycopene were exceptions, having a higher value than the 95th percentile and a lower value than the 5th percentile, respectively, of the Framingham Heart study group.\textsuperscript{27} These data suggest that our patients with gastric cancer had an adequate recent intake of carotenoids. Further, our Asian patients had no extremely high serum $\beta$-carotene values, which would have suggested the use of supplements of $\beta$-carotene on a regular basis, as all of them had values lower than the 95th percentile of those found in

Table 3. Median ratio between carotenoid concentrations in tissue (non-cancerous and cancerous) and serum in Korean patients with gastric cancer

<table>
<thead>
<tr>
<th>Carotenoid</th>
<th>Ratio non-cancerous (tissue/serum)</th>
<th>Ratio cancerous (tissue/serum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutein</td>
<td>2.17 (1.03–2.56)</td>
<td>1.31 (0.94–1.88)</td>
</tr>
<tr>
<td>Zeaxanthin</td>
<td>2.28 (1.38–3.11)</td>
<td>1.65 (1.33–2.45)</td>
</tr>
<tr>
<td>Cryptoxanthin</td>
<td>0.72 (0.61–1.57)</td>
<td>0.84 (0.71–1.130)</td>
</tr>
<tr>
<td>$\alpha$-Carotene</td>
<td>4.20 (2.06–7.62)</td>
<td>2.41 (1.13–4.55)</td>
</tr>
<tr>
<td>All-trans-carotene</td>
<td>0.90 (0.60–1.33)</td>
<td>1.16 (0.63–2.01)</td>
</tr>
<tr>
<td>Lycopene</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

$\alpha = 18$; median (lower quartile – upper quartile).

Figure 4. HPLC chromatograms of the cleavage metabolites of $\beta$-carotene, $\alpha$-carotene and cryptoxanthin after incubation with stomach mucosa tissue homogenates for 30 min. The numbered peaks are: 1, retinoic acid; 2, $\beta$-apo-13'-carotenone; 3, retinal; 4, retinyl acetate; 5, $\beta$-apo-14'-carotenal; 6, $\beta$-apo-12'-carotenal; 7, $\beta$-apo-10'-carotenal; 8, $\beta$-apo-8'-carotenal; 9, $\gamma$-carotene; 10, $\beta$-carotene; 11, $\alpha$-carotene; 12, cryptoxanthin.
Carotenoids in gastric mucosa tissues

the United States National Health and Nutrition Examination Survey – NHANES-III. None of our Asian patients had higher values than those found in any of the supplemented groups in the various β-carotene intervention trials: Linxian, ATBC study, CARET trial and Physicians Health Study.

Generally, serum concentrations of carotenoids are considered to be an index of tissue status. However, one previous study showed that median values of specific carotenoids vary dramatically between different tissues. Examples of this situation include the macular pigment of the human eye, that selectively accumulates lutein and zeaxanthin, and lycopene, which accounts for 30% of total carotenoids in the prostate. The mechanisms that account for tissue specificity in carotenoid patterns have not been established. Sanderson et al. found that plasma and gastric mucosal concentrations correlated well, and that the concentrations in plasma and gastric tissue were of a similar order of magnitude.

It is expected that cancerous tissue would have higher rates of breakdown of carotenoids due to a higher rate of metabolism, more enzymatic activity, and more free radical formation. Pappalardo et al. showed that patients with colonic cancer exhibited a significant reduction of carotenoids in many tissues as compared with those of healthy subjects or subjects with polyps. When comparison between non-cancerous and cancerous tissues was made, we observed that cancerous gastric mucosal tissue had lower carotenoid values than did non-cancerous gastric tissue for lutein, zeaxanthin and α-carotene. However, cryptoxanthin and all-trans β-carotene showed no significant differences in their levels in non-cancerous and cancerous tissues.

The lower concentrations in the cancerous gastric tissue suggest that an increased breakdown of lutein, zeaxanthin and α-carotene is occurring in this tissue. Moreover, the incubation of β-carotene with gastric mucosa tissue homogenates showed a significant increase in the production of retinoic acid and β-apo-carotenoids in the cancerous tissue compared with the non-cancerous tissue (Table 2). These data suggest that an increased breakdown of β-carotene is also taking place in the cancerous tissue. Furthermore, the findings of the similar breakdown pattern of other pro-vitamin A carotenoids as compared with β-carotene, such as α-carotene and cryptoxanthin when incubated with non-cancerous gastric mucosa tissue (Figs 3,4), suggests the possibility of increased degradation of these carotenoids in the cancerous tissues.

In our study, we observed that cryptoxanthin and all-trans β-carotene were the major carotenoids in blood and in gastric mucosa (non-cancerous) tissue (Table 1), probably due to the high ingestion by Koreans of foods rich in these carotenoids. The less than one value for the ratio of non-cancerous tissue to serum values of β-carotene and cryptoxanthin suggest that a gradient exists between these two compartments, with the predominance of the serum compartment. However, lutein, zeaxanthin and α-carotene (minor carotenoids in the blood, Table 1) have a ratio of non-cancerous tissue/serum that is greater than one (Table 3). This suggests storage or accumulation of these nutrients in the gastric mucosa. The increased concentration in the gastric mucosa tissues could be due to a higher rate of uptake or a decreased rate of a breakdown.Clinton et al. suggests that there may be a selective tissue-specific mechanism for the cellular uptake of individual carotenoids. Thus, selective uptake of carotenoids could be contributing to the specific patterns observed in our study.

Our findings with regard to cryptoxanthin and β-carotene are: (i) they are the major carotenoids in Korean blood; (ii) no significant difference of these carotenoid levels exists between non-cancerous and cancerous tissues; (iii) after incubation of β-carotene with gastric tissue, significantly higher levels of β-carotene breakdown products are produced in the homogenates of cancerous tissue when compared with the non-cancerous tissue; and (iv) median ratios of non-cancerous tissue/serum values were less than one. These data suggest that an increased breakdown of cryptoxanthin and β-carotene in cancerous tissue can be compensated for by increased cancerous tissue uptake of circulating carotenoids or because the high amount of these carotenoids in tissue and the greater variability of values makes the statistical test less powerful, and thus less able, to detect a difference.

Our findings with regard to lutein, zeaxanthin and α-carotene are: (i) they are the minor carotenoids in Korean blood; (ii) cancerous tissue had lower levels of these carotenoids than did non-cancerous tissue; and (iii) the median ratio of non-cancerous tissue/serum was greater than one. These data suggest an increased breakdown of lutein, zeaxanthin and α-carotene in cancerous tissue, which cannot be adequately compensated for by cancerous tissue uptake of circulating carotenoids.

In summary, our data support the hypothesis that there is a greater breakdown of carotenoids in cancerous tissue, leading to a depletion of the carotenoids in such tissue. However, we could not find any significant difference in some tissue carotenoid concentrations between non-cancerous and cancerous tissues of gastric cancer patients. The blood concentrations of carotenoids could be the major determining factor affecting the tissue concentrations. We hypothesize that the increased breakdown of carotenoids in cancerous tissue can be adequately compensated for by increasing circulating carotenoids by dietary means. However, the benefits of increasing the concentrations of carotenoids in the gastric cancerous tissues remains to be investigated.

Acknowledgements. Supported in part by Federal funds from the United States Department of Agriculture, Agriculture Research Service under contract number 53-3K06-5-10. SARP was supported by a grant from the ‘Fundação de Amparo à Pesquisa do Estado de São Paulo’ (FAPESP), São Paulo, Brazil.

The contents of this publication do not necessarily reflect the views or policies of the United States Department of Agriculture nor does mention of trade names, commercial products, or organizations imply endorsement by the United States Government.

References

4. Anonymous. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-
6. Varis K, Taylor PR, Sipponen P et al. Gastric cancer and premalig- 
nant lesions in atrophic gastritis: A controlled trial on the effect of supple- 
10. Strickland S, Smith KK, Marotti KR. Hormonal induction of differ- 
etiation in teratocarcinoma stem cells: generation of parietal endo- 
19. Omenn GS, Goodman GE, Thornquist MD et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta- 
20. Hennekens CH, Buring JE, Manson JE et al. Lack of effect of long- 
21. Kaplan LA, Lau JM, Stein EA. Carotenoid composition, concentra- 
23. Clinton SK, Emenhiser C, Schwartz SJ et al. cis-trans lycopene iso- 
mers, carotenoids, and retinol in the human prostate. Cancer Epide- 
26. Hudson MA, McReynolds LM. Urokinase and the urokinase recep- 
tor: association with 
31. Kaplan LA, Lau JM, Stein EA. Carotenoid composition, concentra- 
33. Clinton SK, Emenhiser C, Schwartz SJ et al. cis-trans lycopene iso- 
mers, carotenoids, and retinol in the human prostate. Cancer Epide- 
36. Hudson MA, McReynolds LM. Urokinase and the urokinase recep- 
tor: association with 
38. Pappalardo G, Maiani G, Morbahban S et al. Plasma (carotenoids, retinol, alpha-tocopherol) and tissue (carotenoids) levels after sup- 
plementation with beta-carotene in subjects with precancerous and 