

# Lycopene supplementation elevates circulating insulin-like growth factor-binding protein-1 and -2 concentrations in persons at greater risk of colorectal cancer<sup>1-3</sup>

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## ABSTRACT

**Background:** Higher circulating insulin-like growth factor I (IGF-I) concentrations have been related to a greater risk of cancer. Lycopene intake is inversely associated with cancer risk, and experimental studies have shown that it may affect the IGF system, possibly through an effect on IGF-binding proteins (IGFBPs).

**Objective:** The objective of our study was to investigate the effect of an 8-wk supplementation with tomato-derived lycopene (30 mg/d) on serum concentrations of total IGF-I, IGF-II, IGFBP-1, IGFBP-2, and IGFBP-3.

**Design:** We conducted a randomized, placebo-controlled, double-blinded crossover study in 40 men and 31 postmenopausal women with a family history of colorectal cancer, a personal history of colorectal adenoma, or both.

**Results:** Lycopene supplementation significantly ( $P = 0.01$ ) increased serum IGFBP-1 concentrations in women (median relative difference between serum IGFBP-1 concentrations after lycopene supplementation and after placebo, 21.7%). Serum IGFBP-2 concentrations were higher in both men and women after lycopene supplementation than after placebo, but to a lesser extent (mean relative difference 8.2%; 95% CI: 0.7%, 15.6% in men and 7.8%; 95% CI: -5.0%, 20.6% in women). Total IGF-I, IGF-II, and IGFBP-3 concentrations were not significantly altered by lycopene supplementation.

**Conclusions:** This is the first study known to show that lycopene supplementation may increase circulating IGFBP-1 and IGFBP-2 concentrations. Because of high interindividual variations in IGFBP-1 and IGFBP-2 effects, these results should be confirmed in larger randomized intervention studies. *Am J Clin Nutr* 2007; 86:1456–62.

**KEY WORDS** Lycopene, intervention, colorectal cancer, IGF-I, IGFBPs

## INTRODUCTION

A Western lifestyle is positively associated with cancer risk, partially through effects on insulin and the insulin-like growth factors (IGFs) (1). Both insulin and IGF-I can stimulate tumor growth by inducing proliferation and inhibiting apoptosis. IGF-binding proteins (IGFBPs) are considered to both inhibit and stimulate the interaction of IGF-I with the IGF-I receptor (2). Prospective epidemiologic studies indicate that relatively high

circulating total IGF-I concentrations are associated with greater risks of prostate, premenopausal breast, and colorectal cancer, whereas both positive and negative associations have been reported for IGFBP-3 (3). In addition, a few reports suggest that higher IGF-II (4) and lower IGFBP-1 (5, 6) and IGFBP-2 (5) concentrations are associated with a greater risk of colorectal cancer. Circulating concentrations of IGFs and various IGFBPs are known to be influenced by dietary habits and other lifestyle factors (7).

Lycopene, the major carotenoid in tomatoes and tomato products, may inhibit cancer cell proliferation by interfering with the IGF system. In vitro studies in mammary and prostate cancer cells found that lycopene reduced IGF-I receptor signaling by increasing the concentrations of (membrane-associated) IGFBPs (8–10). In ferrets, both low- and high-dose lycopene supplementation for 9 wk (equivalent to 15 and 60 mg/d, respectively, in humans) significantly increased plasma IGFBP-3 concentrations and significantly decreased lung cancer development, whereas plasma IGF-I concentrations did not change significantly (11). Several studies in mice and rats also showed a reduction in cancer risk after lycopene supplementation but did not investigate effects on the IGF system (12, 13).

Habitual dietary intake of lycopene in humans (mean intake range: 0.6–10.9 mg/d) did not appear to significantly affect colo-

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rectal cancer risk in a recent pooled analysis of 11 cohort studies (14), whereas results for prostate (15) and premenopausal breast (16) cancer have remained inconsistent. In 3 of 6 cross-sectional studies (17–22), higher intakes of cooked or processed tomatoes or lycopene were associated with either lower IGF-I concentrations (18), higher IGFBP-3 concentrations (19), or a lower molar ratio of IGF-I to IGFBP-3 (20). In the other 3 studies, no such associations were found (17, 21, 22). However, habitual dietary lycopene intake is generally low and weakly correlated with blood lycopene concentrations (23). To accurately investigate whether lycopene can affect the IGF system in humans, supplementation studies are needed.

Therefore, we conducted a randomized, placebo-controlled trial to investigate the effect of a 2-mo supplementation with tomato-derived lycopene (30 mg/d) on serum concentrations of IGF-I and -II and IGFBP-1, -2, and -3 in men and women at greater risk of colorectal cancer. This population and other populations at greater risk of cancer could potentially benefit the most from this intervention.

## SUBJECTS AND METHODS

### Study population

We selected men aged 40–75 y and postmenopausal women aged 50–75 y who have had colorectal adenoma or who had  $\geq 1$  first-degree family member with a history of colorectal cancer. Asymptomatic persons scheduled to undergo a colonoscopy for screening purposes were selected from medical registries and pathology databases and were sent a letter inviting them to participate in the study. Exclusion criteria were a history of cancer, familial adenomatous polyposis syndrome, familial Li-Fraumeni syndrome, chronic inflammatory bowel disease, diabetes mellitus, acromegaly, significant liver or renal disease, (partial) bowel resection, nonremitive celiac disease, diverticulitis, other severe comorbidity, laxative abuse, or the use of food supplements containing lycopene. Participants were recruited between July 2003 and September 2005, and they were randomly assigned to the lycopene trial described here or to a trial of isoflavones that was described previously (24). In total, 146 men and 182 women were invited to participate in the present trial. Of 126 eligible men, 60 were willing to participate (48% response), of whom 42 were included in this trial. Of 156 eligible women, 41 were willing to participate (26% response), of whom 34 were included in the present trial. Most of those who were unwilling to participate indicated that they had no time to participate or had no interest in the study. The study was conducted in 4 hospitals in the Netherlands: the Antoni van Leeuwenhoek Hospital (Amsterdam), the Gelderse Vallei Hospital (Ede), the Slotervaart Hospital (Amsterdam), and the Sint Antonius Hospital (Nieuwegein).

We obtained written informed consent from all participants. The study protocol was approved by the medical ethics committees of all participating centers.

### Design

We conducted a randomized, placebo-controlled, double-blinded crossover study. The total duration of the study was  $\approx 6$  mo; it consisted of two 8-wk intervention periods, separated by an 8-wk wash-out period. Subjects were allocated to receive lycopene capsules in the first and placebo capsules in the second

intervention period or vice versa, according to a randomization scheme with permuted blocks. The lycopene capsules (Lyc-O-Mato; LycoRed Natural Product Industries, Beer-Sheva, Israel) contained an extract (oleoresin) derived from tomatoes that represented  $\approx 15$  mg total lycopene/capsule. Subjects were asked to take 2 capsules/d—1 capsule with breakfast and 1 with dinner (total dose: 30 mg lycopene/d). Subjects were asked to maintain their habitual diet and lifestyle.

### Data collection

At the start of the study, subjects filled in a general questionnaire about their smoking behavior, family history of cancer, and hormonal factors. They visited their respective hospitals at the beginning and end of both intervention periods. At each of the 4 visits, body weight and circumferences of waist and hip were measured. Dietary intake on the day before each visit was assessed during an in-person interview by using a 24-h recall method. Most of the men (41 of the 42) and 5 of the 34 women had to undergo bowel preparation for colonoscopy (for screening purposes) on the day before the second visit. In these cases, the 24-h recall related to the second day before the visit. The methods of interviewing and coding of foods and portion sizes were standardized, and these procedures were performed by trained nutritionists and graduate students in nutrition. Energy and nutrient intakes were calculated by using the VBS food calculating system (BAS nutrition software, version 4.0.57; B-Ware Nutrition Software, Wageningen, Netherlands) based on the Dutch Food Composition Table (25).

Habitual physical activity over the 2 mo preceding each visit was assessed by using the validated self-administered short questionnaire to assess health-enhancing physical activity (26). During both intervention periods, subjects kept a daily notebook in which they recorded information about their health, medicine use, smoking, and frequency of consumption of products rich in lycopene (ie, tomato products and specific fruit). Compliance was measured by a counting of returned capsules, self-reported supplement intake from daily notebooks, and measurement of serum lycopene concentrations at the beginning and end of both intervention periods.

### Laboratory analyses

Fasting serum and EDTA-plasma samples were frozen and stored at  $-30$  and  $-80$  °C, respectively, until further analysis. Serum total IGF-I, IGF-II, IGFBP-1, IGFBP-2, and IGFBP-3 concentrations were measured at the end of both intervention periods. Serum total IGF-I was measured by using an immunometric technique on the Immulite 1000 analyzer (Diagnostics Products Corporation, Los Angeles, CA). The sensitivity established in our laboratory was  $12.0$   $\mu\text{g/L}$ ; intraassay CVs were  $<4.0\%$  at 45, 150, and 370  $\mu\text{g}$  mean serum IGF-I/L; and interassay CVs were 7.0%, 6.5% and 7.0% at 45, 150, and 370  $\mu\text{g}$  mean serum IGF-I/L, respectively. Serum IGF-II concentrations were measured in C18 extracts (Sep-Pak cartridges; Waters Corp, Milford, MA) of serum by using a radioimmunoassay, as described previously (27, 28). The sensitivity established in our laboratory was  $0.09$   $\mu\text{g/L}$ ; the intraassay and interassay CVs were 6.7% and 8.8%, respectively, at 505  $\mu\text{g}$  mean serum IGF-II/L. Serum IGFBP-1, IGFBP-2, and IGFBP-3 concentrations were measured by using specific radioimmunoassays. Relevant technical details were described previously (27, 29, 30). Assays



for total IGF-I, IGF-II, IGFBP-1, IGFBP-2, and IGFBP-3 were performed at the Department of Endocrine and Metabolic Diseases, University Medical Center Utrecht.

Plasma concentrations of lycopene were measured at all 4 time points by using HPLC according to the method described by Gueguen et al (31). Samples were kept in the dark and stored at  $-80^{\circ}\text{C}$  until HPLC analysis was conducted. HPLC separation was achieved on a glass column (10 cm  $\times$  3-mm internal diameter; Varian Chrompack, Palo Alto, CA) packed with Nucleosil C18 material (Machery-Nagel, Duren, Germany) with the use of a mobile phase consisting of methanol:acetonitrile:tetrahydrofuran (75:20:5; vol/vol/vol) delivered at a flow rate of 0.4 mL/min; detection was conducted at 472 nm. The sensitivity in our laboratory was established as 0.01  $\mu\text{mol/L}$ .

Because the IGF system may be influenced by changes in estradiol, sex hormone binding globulin (SHBG), and insulin concentrations, we also measured estradiol and SHBG concentrations in women and insulin concentrations in both men and women. The immunoassays were based on the electrochemiluminescence principle and were used on the E170 immunoanalyzer (Elecsys module; Roche Diagnostics, Mannheim, Germany). Lycopene, estradiol, and SHBG assays were performed at the Department of Clinical Chemistry, The Netherlands Cancer Institute.

### Statistical analyses

The main variable of interest in our statistical analysis was the relative crossover difference (*see* equations below), expressed as a percentage relative to the concentration after placebo. The crossover differences in IGF-I, IGF-II, IGFBP-2, IGFBP-3, SHBG, and insulin (in women) were normally distributed. The mean crossover difference for each of these variables was calculated for both intervention groups and then pooled to adjust for period effects. We tested whether the pooled crossover difference significantly deviated from the null value by using a *t* test in men and women separately (2-sided  $\alpha = 0.05$ ,  $df = 39$ , and  $df = 30$ , respectively) with the use of pooled SEM crossover differences (32) as calculated by the following equations:

$$\begin{aligned} \text{Relative crossover difference } [\Delta(\text{IP}) \text{ or } \Delta(\text{PI})] \\ = [\text{concentration after intervention } (C_I) \\ - \text{concentration after placebo } (C_P)]/C_P \quad (1) \end{aligned}$$

$$\begin{aligned} \text{Pooled crossover difference} \\ = 1/2(\text{mean}_{\Delta(\text{IP})} + \text{mean}_{\Delta(\text{PI})}) \quad (2) \end{aligned}$$

$$\begin{aligned} \text{Pooled variance } (s^2) \\ = [(n_{\text{IP}} - 1)SD_{\Delta\text{IP}}^2 + (n_{\text{PI}} - 1)SD_{\Delta\text{PI}}^2]/(n_{\text{IP}} + n_{\text{PI}} - 2) \quad (3) \end{aligned}$$

$$\begin{aligned} \text{Standard error of the pooled crossover difference} \\ = 1/2\sqrt{[(s^2/n_{\text{IP}}) + (s^2/n_{\text{PI}})]} \quad (4) \end{aligned}$$

where IP is isoflavones-placebo, PI is placebo-isoflavones,  $s^2$  is pooled variance,  $n$  is the number of subjects in the specific group, and  $SD^2$  is the SD of the specific group. Because of the skewed distribution of IGFBP-1, estradiol, and insulin (in men), the median crossover differences were compared with the null value by using a univariate sign test.

All statistical analyses were conducted on the basis of the intention-to-treat principle, including all participants who were randomly assigned and who donated a blood sample on all 4 study visits, irrespective of compliance with the intervention protocol. As a secondary approach, per-protocol analyses were conducted, excluding all participants who were noncompliant—ie, who took  $<80\%$  of capsules (according to the count of returned capsules), who had a  $<20\%$  increase in serum lycopene concentration after lycopene intervention, or both.

Descriptive characteristics were computed for men and women separately for the 2 randomized groups. We calculated whether dietary and lifestyle factors known to influence the IGF system—ie, dietary intake of macronutrients, body weight, waist and hip circumferences, total physical activity score, dietary intake of products relatively rich in lycopene (tomato products and specific fruit)—were significantly different in the lycopene period than in the placebo period. Statistical analyses were performed by using SPSS software (version 12.0; SPSS Inc, Chicago, IL).

### RESULTS

After randomization, 5 persons dropped out of the trial (dropout rate: 7%). Only one participant dropped out of the study during the lycopene intervention period, and the reason was nausea. This left 21 men and 14 women in the lycopene-placebo (L-P) group and 19 men and 17 women in the placebo-lycopene (P-L) group who completed the study protocol.

Men in the P-L group were older, somewhat heavier, and less likely to be current smokers and had a lower baseline energy intake than those in the L-P group (**Table 1**). Women in the L-P group did not differ significantly from women in the P-L group with respect to these general characteristics. The number of participants (men and women separately) with a family history of colorectal cancer, a personal history of colorectal adenoma, or both was equally distributed between the 2 groups. Hormonal factors in women (ie, age at menopause, parity, and past hormone use) did not differ significantly between the 2 groups (data not shown).

Lycopene supplementation did not significantly affect serum total IGF-I and IGF-II concentrations in men or in women (**Table 2**). We observed a large interindividual variation in IGFBP-1 and IGFBP-2 responses to lycopene supplementation in both men and women (data not shown). Serum IGFBP-1 concentrations were not affected in men; however, IGFBP-1 was significantly higher in women after lycopene supplementation than after placebo (median relative difference between lycopene and placebo: 21.7%;  $P = 0.01$ ). Serum IGFBP-2 was significantly higher in men after lycopene supplementation than after placebo (mean: 8.2%; 95% CI: 0.7%, 15.6%), and it was similarly but not significantly higher in women (mean: 7.8%; 95% CI:  $-5.0\%$ , 20.6%). Serum IGFBP-3 concentrations were not significantly affected by lycopene supplementation. However, we observed a positive association between relative changes in lycopene concentrations and relative changes in serum IGFBP-3 ( $r = 0.46$ ,  $P < 0.01$ ) and IGF-I ( $r = 0.37$ ,  $P = 0.08$ ) in women. Estradiol concentrations in women did not differ significantly after lycopene supplementation (median: 2.0%;  $P = 0.47$ ), whereas SHBG concentrations were significantly higher (mean: 7.8%; 95% CI: 1.7%, 14.0%).



**TABLE 1**

Characteristics at the first visit for the lycopene-placebo (L-P) and placebo-lycopene (P-L) supplementation groups of men and women

	Men		Women	
	L-P group (n = 21)	P-L group (n = 19)	L-P group (n = 14)	P-L group (n = 17)
Age (y)	54.9 ± 11.5 <sup>1</sup>	61.3 ± 7.2	62.1 ± 6.1	60.0 ± 5.8
Weight (kg)	83 ± 13	86 ± 9	75 ± 10	75 ± 8
Height (cm)	178.6 ± 8.1	178.3 ± 6.5	166.6 ± 5.9	166.7 ± 4.4
BMI (kg/m <sup>2</sup> )	25.9 ± 2.7	27.1 ± 2.9	27.1 ± 4.8	27.2 ± 2.9
Waist circumference (cm)	95.6 ± 7.5	101.5 ± 9.2	90.4 ± 12.4	90.6 ± 9.5
Hip circumference (cm)	103.7 ± 6.1	105.8 ± 5.2	108.8 ± 10.4	109.4 ± 6.1
Waist-to-hip ratio	0.92 ± 0.05	0.96 ± 0.05	0.83 ± 0.07	0.83 ± 0.06
Smoking status [n (%)]				
Current	6 (29)	2 (11)	3 (21)	2 (12)
Never	6 (29)	5 (26)	4 (29)	8 (47)
Past	9 (43)	12 (63)	7 (50)	7 (41)
History of cancer or adenoma [n (%)]				
Family history of colorectal cancer	7 (33)	2 (11)	0 (0)	2 (12)
Personal history of adenoma	6 (29)	10 (53)	9 (64)	9 (53)
Both	8 (38)	7 (37)	5 (36)	6 (35)
Energy (kJ/d)	10 241 ± 2949	7693 ± 2061	8331 ± 2264	7281 ± 2284
Protein (% of energy)	17 ± 5	18 ± 6	16 ± 4	16 ± 4
Fat (% of energy)	35 ± 8	34 ± 9	39 ± 11	36 ± 8
Carbohydrates (% of energy)	45 ± 10	40 ± 8	42 ± 10	45 ± 9
Alcohol (% of energy)	5 ± 7	9 ± 9	4 ± 5	4 ± 6

<sup>1</sup>  $\bar{x} \pm SD$  (all such values).

Insulin concentrations did not differ significantly between the lycopene and the placebo intervention periods (Table 2). However, insulin concentrations in men were significantly lower after the first intervention period (when the colonoscopy was performed) than after the second intervention period (median: 30.0 and 45.4 pmol/L, respectively;  $P \leq 0.001$ ), a difference that is

also expressed in the longer fasting duration after the first intervention period (mean: 18 and 12 h, respectively;  $P \leq 0.001$ ). In women, no significant differences in insulin concentrations were observed (mean: 53.5 and 55.3 pmol/L, respectively;  $P = 0.63$ ). Because insulin concentrations are known to be inversely related to IGFBP-1 and, to a lesser extent, IGFBP-2 concentrations, we

**TABLE 2**Circulating insulin-like growth factor (IGF) system component concentrations after lycopene and placebo treatment and the within-person crossover difference between the lycopene and the placebo treatment<sup>1</sup>

	Concentration		Within-person difference between treatments	
	After lycopene	After placebo	Absolute mean	Relative mean (95% CI) %
<b>Men (n = 40)</b>				
Total IGF-I ( $\mu\text{g/L}$ )	138.8 ± 40.8 <sup>2</sup>	144.7 ± 46.0	-5.9	-2.2 (-7.6, 3.2)
Total IGF-II ( $\mu\text{g/L}$ )	533.3 ± 106.7	552.7 ± 130.9	-19.4	-1.2 (-6.4, 4.0)
IGFBP-1 ( $\mu\text{g/L}$ ) <sup>3</sup>	37 (15, 49)	32 (19, 43)	-2	-9.5 (-40.0, 19.5)
IGFBP-2 ( $\mu\text{g/L}$ )	287.7 ± 150.8	276.4 ± 139.3	11.3	8.2 (0.7, 15.6)
IGFBP-3 (mg/L)	1.97 ± 0.28	2.01 ± 0.33	-0.03	-0.9 (-4.1, 2.2)
Insulin (pmol/L) <sup>3</sup>	32 (24, 63)	37 (30, 56)	-6.5	-9.5 (-37.0, 58.7)
<b>Women (n = 31)</b>				
Total IGF-I ( $\mu\text{g/L}$ )	118.2 ± 32.8	127.8 ± 52.7	-9.6	-3.2 (-9.5, 3.0)
Total IGF-II ( $\mu\text{g/L}$ )	549.1 ± 112.8	522.4 ± 81.3	26.7	5.4 (-0.9, 11.7)
IGFBP-1 ( $\mu\text{g/L}$ ) <sup>3</sup>	33 (22, 55)	28 (16, 48)	5.0	21.7 (-1.0, 47.2)
IGFBP-2 ( $\mu\text{g/L}$ )	257.4 ± 119.9	254.7 ± 126.0	2.7	7.8 (-5.0, 20.6)
IGFBP-3 (mg/L)	2.25 ± 0.27	2.23 ± 0.34	0.01	1.7 (-2.4, 5.8)
Insulin (pmol/L)	53 ± 26	57 ± 34	-4.0	0.1 (-11.0, 11.2)

<sup>1</sup> IGFBP-1, IGF-binding protein.<sup>2</sup> Pooled  $\bar{x} \pm SD$  (all such values).<sup>3</sup> Data for IGFBP-1 and insulin in men and for IGFBP-1 in women were not normally distributed; values are medians; interquartile ranges in parentheses.  $P = 0.20$ ,  $P = 0.27$ , and  $P = 0.01$ , respectively (sign test).

determined whether relative changes in insulin and the IGFbps were correlated. We observed strong inverse correlations between relative insulin changes and relative changes in IGFBP-1 ( $r = -0.51, P \leq 0.001$ ) and IGFBP-2 ( $r = -0.62, P \leq 0.001$ ) in men but no significant correlations in women ( $r = -0.35, P = 0.054$ , and  $r = 0.001, P = 0.995$ , respectively).

According to both returned-capsule counts and recordings in the daily notebooks, 94% of the participants were compliant ( $\geq 80\%$  of capsules taken). Serum lycopene concentrations were significantly ( $P < 0.001$ ) higher after lycopene intervention than at all other time points. A mean 259% increase from  $0.17 \pm 0.13 \mu\text{mol/L}$  at baseline to  $0.61 \pm 0.22 \mu\text{mol/L}$  after lycopene intervention was observed. Exclusion of subjects who were noncompliant ( $n = 5$ ) according to serum lycopene concentrations, returned-pill counts, or both did not materially change the results (data not shown). Body weight, waist and hip circumferences, total physical activity score, dietary macronutrient intake, and the number of days on which products rich in lycopene were consumed did not materially differ between the lycopene and the placebo intervention periods (data not shown).

## DISCUSSION

In this randomized, placebo-controlled, double-blinded crossover study, lycopene supplementation at 30 mg/d for 2 mo did not significantly alter serum total IGF-I, IGF-II, and IGFBP-3 concentrations in men and women at greater risk of colorectal cancer. However, serum IGFBP-1 in women and serum IGFBP-2 in men were significantly higher after supplementation, which may result in less IGF-I bioavailability.

This is the first randomized trial investigating the effects of lycopene supplementation on the circulating IGF system and on IGFBP-1 and -2 in a population at greater risk of colorectal cancer. This population and other populations at greater risk of cancer could potentially benefit the most from this intervention. We used a crossover design, which has the important advantage that the results were not affected by the high interindividual variation in circulating IGF component concentrations. Moreover, small baseline differences in age, weight, energy intake, and smoking status between the men in the L-P and P-L groups are not likely to have affected our results. The dropout rate was very low (7%) and unrelated to supplement intake. Compliance, based on capsule counts and daily notebooks, was very high, and this was also reflected in strongly increased serum lycopene concentrations in 96% of the participants. Serum lycopene concentrations after lycopene intervention and after baseline were within the range of those previously observed in other studies using 15–60 mg tomato oleoresin supplements/d (33–35). Blinding was confirmed by the fact that only 20% of the participants correctly guessed the period in which they received the lycopene supplementation. Dietary and lifestyle factors that are thought to influence circulating concentrations of IGFs and IGFbps did not differ significantly between the lycopene and the placebo intervention periods.

For practical reasons (ie, bowel preparation for colonoscopy), the duration of fasting before blood withdrawal was significantly longer in the male participants at the end of the first intervention period than at the end of the second period. As a consequence, at the end of the first intervention period, we found significantly lower serum concentrations of insulin. However, the period of fasting and, hence, the serum insulin concentrations were similar

in women in both intervention periods. Circulating total IGF-I, IGF-II, and IGFBP-3 concentrations were previously found not to be influenced by fasting for up to 72 h (36, 37). In contrast, fasting for shorter times readily leads to an increase in IGFBP-1 in the circulation, which is induced by a depressed insulin secretion (36, 37). The magnitude of the fasting-induced rise in the concentration of IGFBP-1 in the serum is related to insulin sensitivity (38) and may therefore vary among the subjects investigated. Therefore, it is difficult to draw definite conclusions with respect to the relative contribution of lycopene supplementation to the observed alterations in circulating IGFBP-1 concentrations in the male subjects. Of the female participants, only 5 underwent bowel preparation for colonoscopy. Exclusion of these women did not significantly change the IGFBP-1 results for the total group (24.4%;  $P = 0.01$ ), but it did strengthen the IGFBP-2 results (13.0%; 95% CI: 0.0%, 26.0%). Thus, the increase in IGFBP-1 in women is likely to be the result of a direct lycopene effect and is unlikely to be mediated by a decrease in insulin concentrations, which have previously been inversely associated with lycopene concentrations (39, 40). Although the effect of short-term fasting on IGFBP-2 is still controversial, we also observed a high interindividual variation in IGFBP-2 effects that were due to lycopene supplementation in both men and women. Therefore, some caution must be taken in the interpretation of these results.

Lycopene may inhibit cancer growth by various mechanisms, and increasing experimental evidence suggests that lycopene may affect the IGF system (8–11, 41, 42). However, evidence with respect to lycopene and the circulating IGF system in humans is sparse. To our knowledge, only 4 small human intervention studies investigating the effect of lycopene supplementation on circulating IGF components have been conducted thus far (43–46). Kucuk et al (43) observed in a parallel study of 26 prostate cancer patients that plasma IGF-I and IGFBP-3 decreased from baseline in the intervention group receiving Lyc-O-Mato lycopene capsules (30 mg lycopene/d) for 3 wk. However, plasma lycopene concentrations did not change during the study period, and similar decreases in IGF-I and IGFBP-3 were observed in the control group who received no supplementation. Riso et al (44) conducted a crossover study in 20 healthy young persons (8 M, 12 F) in which they compared the consumption of one Lyc-O-Mato drink/d (5.7 mg lycopene/d) for 26 d with that of a placebo drink without lycopene. In that study, changes in lycopene concentrations were inversely correlated with those in serum IGF-I in the total group, whereas IGFBP-3 concentrations were not affected by lycopene supplementation. Serum IGF-I was reduced in subjects with a relatively high lycopene response of an increase of  $>0.25 \mu\text{mol/L}$ , or  $\geq 100\%$  of the basal concentrations. Graydon et al (45) observed a positive association between changes in lycopene concentrations and IGFBP-3 concentrations in a parallel study in 10 healthy men receiving lycopene supplementation for 4 wk (15 mg/d). No overall differences in serum IGF-I and IGFBP-3 were found between those 10 men and 10 men in the placebo group. In a recent, larger parallel study of 56 colon cancer patients by Walfisch et al (46), a significant 25% reduction in serum IGF-I was observed in the intervention group receiving Lyc-O-Mato lycopene capsules (30 mg lycopene/d) for various durations (mean: 10 d; range: 2–49 d), whereas serum IGF-I in the placebo group did not change significantly. No changes in serum IGFBP-3 and IGF-II were observed.



In the present study, which was of stronger design and had a larger sample size than did the studies discussed above, we did not observe any effects of lycopene on serum IGF-I and IGFBP-3 in the total group or in the high-lycopene responders as defined by Riso et al (44). Although we did observe a positive association between relative changes in serum lycopene concentrations and relative changes in circulating IGF-I and IGFBP-3 concentrations in the female participants, we could not confirm such an association in the male participants, and interpretation of the results is difficult. However, these results suggest that lycopene may increase IGFBP-1 and -2 concentrations.

In conclusion, lycopene supplementation did not influence serum total IGF-I and IGFBP-3 concentrations in our randomized, placebo-controlled, double-blinded crossover trial in a population at greater risk of colorectal cancer. However, lycopene supplementation may decrease IGF-I bioavailability by increasing IGFBP-1 and -2 concentrations. Thus, it may provide a means of ultimately reducing colorectal cancer risk and potentially the risks of other major cancers such as prostate and premenopausal breast cancer. However, interindividual variation in IGFBP-1 and -2 effects was high, possibly complicated by differences in fasting duration and, consequently, insulin concentrations. Therefore, results must be confirmed in larger randomized intervention studies with control for the duration of fasting.

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