Relation of insulin-like growth factor (IGF) I and IGF-binding protein 3 concentrations with intakes of fruit, vegetables, and antioxidants[1–3]

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ABSTRACT

Background: Fruit, vegetable, and antioxidant intakes may reduce the risk of several insulin-like growth factor (IGF)–related chronic diseases, such as certain types of cancers and cardiovascular diseases.

Objective: This study investigated whether intakes of fruit, vegetables, and antioxidants (β-carotene, lycopene, and vitamin C) are associated with plasma IGF-I and IGF-binding protein 3 (IGFBP-3) concentrations.

Design: Plasma IGF-I and IGFBP-3 concentrations were measured in 1542 healthy women by enzyme-linked immunosorbent assay. A self-administered semiquantitative food-frequency questionnaire was used to estimate mean daily dietary intakes of fruit, vegetables, and antioxidants over the year preceding blood sampling. Multivariate analyses were performed by using generalized linear models to evaluate the association of quintiles of daily intakes with concentrations of growth factors.

Results: A higher intake of citrus fruit was associated with higher concentrations of IGF-I (215 ng/mL for quintile 5 compared with 205 ng/mL for quintile 1; P for trend = 0.04) and with lower concentrations of IGFBP-3 (4803 ng/mL for quintile 5 compared with 4960 ng/mL for quintile 1; P for trend = 0.04). Higher dietary vitamin C intake was associated with higher concentrations of IGF-I (214 ng/mL for quintile 5 compared with 204 ng/mL for quintile 1; P for trend = 0.02) and lower concentrations of IGFBP-3 (4813 ng/mL for quintile 5 compared with 4953 ng/mL for quintile 1; P for trend = 0.03). Total intake of fruit and vegetables and intakes of other botanical fruit and vegetable subgroups, β-carotene, and lycopene were not related to either IGF-I or IGFBP-3 concentrations.

Conclusion: Women with higher intakes of citrus fruit or dietary vitamin C tend to have higher plasma concentrations of IGF-I and lower plasma concentrations of IGFBP-3.

KEY WORDS Diet, fruit, vegetables, antioxidants, nutrients, insulin-like growth factor, insulin-like growth factor binding protein

INTRODUCTION

There is growing evidence that intakes of all or some fruit and vegetables and their constituents have potentially important effects on the risk of some chronic diseases such as certain types of cancers and cardiovascular diseases. Protective effects of fruit and vegetable intakes against ischemic heart diseases (IHD) and stroke have been reported in several prospective studies (1–5), but not all (6, 7). In particular, a greater beneficial effect on IHD or stroke was suggested for certain botanical or phytochemical subgroups of fruit and vegetables and their related antioxidants, such as cruciferous vegetables (1), green leafy vegetables (1, 2), citrus fruit (1, 6), vitamin C–rich fruit and vegetables (2), vitamin C (3, 8), and carotenoids (3, 9). Likewise, total fruit and vegetable intake has been proposed to play a role in the prevention of some types of cancers including stomach, breast, bladder, and colorectal cancer, although these associations appeared to be weak [reviewed by McCullough and Giovannucci (10) and Key et al (11)]. According to the authors, certain botanical subgroups, such as tomato and cruciferous vegetable intakes, may be associated with a reduction in the risk of some specific sites of cancer including prostate and bladder cancer. In addition, intakes of antioxidants such as lycopene may protect against prostate cancer (12).

Similarly, members of the insulin-like growth factor (IGF) family have been suggested to play a role in the occurrence of some of the same chronic diseases. For instance, prospective epidemiologic studies showed that higher IGF-I concentrations, lower IGF-binding protein 3 (IGFBP-3) concentrations, or both were associated with a reduced risk of ischemic heart disease (13), heart failure (14), and of ischemic heart disease mortality (15). In contrast, prospective epidemiologic studies reported an association of higher IGF-I concentrations, lower IGFBP-3 concentrations, or both with an increased risk of premenopausal breast (16–18), prostate (19, 20), and colorectal (21) cancers, although other prospective studies did not observe such associations (22–24) [reviewed by Renehan et al (25)]. Thus, an interindividual fluctuation in IGF concentrations may modulate the risk of some chronic diseases, and this fluctuation could be due

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to genetic, environmental, or lifestyle factors including nutrition (26).

It is well known that severe energy and protein deprivation is related to lower IGF-I concentrations (27). However, the possibility that fruit, vegetable, and antioxidant intakes may be linked to circulating IGF-I and IGFBP-3 concentrations has not been fully addressed. Moreover, lower IGF-I concentrations and higher concentrations of both IGFBP-1 and IGFBP-2 were observed in vegans than in meat eaters and vegetarians (28, 29). However, so far, studies merely examined the association of total fruit, total vegetables, legumes, tomatoes, and their related antioxidant intakes with IGF-I and IGFBP-3 concentrations and found inconsistent results (30–35). To our knowledge, few studies (30, 32, 34, 35) have classified fruit and vegetable intakes by using botanical or phytochemical subgroups, and none have evaluated the association between each such subgroup and concentrations of growth factors.

The aim of the present analysis was to examine, among 1542 healthy women in Quebec City, whether circulating concentrations of IGF-I and IGFBP-3 were associated with intakes of total fruit and vegetables, intakes of specific subgroups of fruit and vegetables based on their botanical and phytochemical classifications, or with intakes of related antioxidants, namely vitamin C, lycopene, and β-carotene.

SUBJECTS AND METHODS

Study population

Details of the study design and methods were published elsewhere (36). Briefly, the study participants were women who had screening mammograms at 2 private radiological clinics in Quebec City between February 2001 and March 2002. Women were considered premenopausal if they had $\geq$1 natural menstrual cycle within the past 12 mo or were younger than 48 y (if a nonsmoker) or 46 y (if a smoker) after hysterectomy without bilateral oophorectomy or use of hormonal derivatives. The women were considered postmenopausal if they reported complete cessation of menstruations for $\geq$12 mo, radiation-induced menopause or bilateral oophorectomy, or were aged $\geq$56 y (if a nonsmoker) or 54 y (if a smoker) after hysterectomy without bilateral oophorectomy, or use of hormonal derivatives (37). Eligible women had not used hormonal derivatives within 3 mo of the mammography, were never diagnosed with cancer, had never taken tamoxifen or raloxifene, were not pregnant, and had none of the following conditions: thyroid, adrenal, or hepatic disease or diabetes. Finally, women with a cognitive deficiency from any cause that did not allow informed consent were excluded. There was no restriction with respect to the age of the women. The present study was reviewed and approved by the Research Ethics Committee of the Centre hospitalier affilié universitaire de Québec (Quebec, Canada). All study participants provided written informed consent.

A total of 1574 women were recruited. Of these, 11 women did not provide the food-frequency questionnaire, 3 were excluded because they reported an extremely low ($<$600 kcal) or high ($>$5000 kcal) daily caloric intake, and 18 women provided no information on their physical activity, hormone use, or alcohol intake. Hence, the total number of subjects included in the present analysis was 1542 women.

Data collection

At the radiology clinic, the anthropometric measures, such as weight, height, and waist and hip circumferences, and blood specimens (20 mL) of the participants were collected by a trained research nurse. A telephone interview was carried out with each woman to document known or suspected breast cancer risk factors, including reproductive and menstrual history, family history of breast cancer, personal history of breast biopsies, past use of contraceptives and hormone replacement therapy, smoking status, education, and physical activity. The level of physical activity, expressed as metabolic equivalent (MET)–hour per week (38), was assessed by using the Nurses' Health Study II Activity and Inactivity Questionnaire (39).

Diet was assessed with a validated self-administrated 161-item semiquantitative food-frequency questionnaire (FFQ; 97GP copyrighted at Harvard University, Boston, MA) (40), which included 28 vegetable and 16 fruit items. For each food item, a standard portion size was specified and the participants were asked how often, on average (ranging from "never" to "6 or more" times/d), they had consumed this item during the year preceding blood collection. The participants also provided, through the FFQ, the duration, brand, type, and weekly dose of multivitamins and the daily dose of vitamin C and β-carotene supplements. Some brands of multivitamins available in Canada had no specific code in the Harvard database and were assigned a generic code. Food and supplement intakes were translated in dietary, supplemental, and total nutrient intakes at the Channing Laboratory of Harvard University (Boston, MA) by using the nutrient content of foods derived from the US Department of Agriculture source supplemented with data from the manufacturers. Total intake of a specific nutrient includes intakes from foods, multivitamins, and individual supplements.

Blood samples collected at study entry were kept on ice until centrifugation at 1500 $\times$ *g* for 20 min at 4 °C. Blood constituents were divided into aliquots and stored at $-$80 °C until analysis. The time between blood donation and plasma storage was $<$3 h for 99.4% of the participants. Aliquots of frozen plasma were sent on dry ice in batches of 39 samples for laboratory analyses without any information on the women. Four blinded split samples were randomly included in each batch to assess the variability in intraassay and interassay laboratory measurements. An enzyme-linked immunosorbent assay with reagent from Diagnostic Systems Laboratory (Webster, TX) was used to measure IGF-I and IGFBP-3. For the present study, the intrabatch CVs were 10.5% and 13.2% and the interbatch CVs were 7.9% and 10.5% for IGF-I and IGFBP-3, respectively.

Statistical analysis

For each study participant, the mean daily number of servings of individual fruit and vegetables were summed to estimate total daily fruit and vegetable intakes. Using the criteria established by Smith et al (41) and the report on Food, Nutrition and the Prevention of Cancer published by World Cancer Research Fund (42), we classified fruit and vegetables into specific subgroups based on botanical and phytochemical classifications (detailed classifications are presented in **Table 1**). Similar to the estimation of total daily fruit and vegetable intakes, a daily intake of any subgroup of fruit and vegetables was computed by adding the daily intake of each fruit and vegetable that were included in the

TABLE 1
Botanical and phytochemical classifications of collected fruit and vegetable items

	Food
Botanical classification	
Cruciferous vegetables	Broccoli, cabbage, cauliflower, kale, and Brussels sprouts
Yellow vegetables	Carrots, yellow squash, and yams
Green leafy vegetables	Spinach and lettuce
Legumes	Beans, peas, soy and soy products
Tomatoes	Tomatoes and tomato products
Onion	Onion
Citrus fruit	Orange, orange juice, grapefruit, and grapefruit juice
Rose	Apple, peach, plum, strawberries, and pear
Phytochemical classification	
Fruit and vegetables rich in vitamin C (cutoff ≥50 mg/100 g food)	Broccoli, cabbage, cauliflower, Brussels sprouts, green peppers, orange, orange juice, grapefruit, grapefruit juice, peach, strawberries, and other fruit juice
Fruit and vegetables rich in β-carotene (cutoff ≥1900 μg/100 g food)	Carrots, yellow squash, yams, spinach, kale, lettuce, mixed vegetables, peach, apricot, plum, and avocado[1]
Fruit and vegetables rich in lycopene (cutoff ≥750 μg/100 g food)	Tomatoes and tomato products
Other classification	
Other vegetables	Corn, celery, eggplant, avocado, peppers, and mixed vegetables[1]
Other fruit	Grape, blueberries, banana, cantaloupe, and other fruit juice

[1] Mixed vegetables are peas, beans, carrots, and corn in equal quantities.

specific subgroup. Nutrient intakes from food or supplements were studied separately and in combination.

All fruit, vegetable, and nutrient intakes were categorized in quintiles. Adjusted least-squares mean concentrations of growth factors for each quintile of intake were estimated by using generalized linear models. Statistical differences between any of the adjusted means were evaluated with P for heterogeneity, whereas the linear trend across quintiles was tested by using a linear contrast with the median of daily intakes within each of the quintiles as the value. Linear regression models ($\beta \pm$ SE) were used to assess the association between continuous levels of food or nutrient daily intakes and continuous concentrations of growth factors.

Covariates considered a priori as factors known or suspected to be associated with IGF concentrations, the diet, or both were included in 2 multivariate models. In model 1, the associations of food and nutrient intakes with concentrations of growth factors were adjusted for menopausal status (pre- or postmenopausal); age at mammography (y); body mass index (kg/m^2); physical activity (MET-h/wk); energy intake (kcal/d); duration of past use of hormone replacement therapy and oral contraceptive (y); lactation (mo); number of full-term pregnancies; age at first full-term birth (y); age at menarche (y); number of breast biopsy samples; family history of breast cancer (yes or no); education (primary or less, secondary, or college or university diploma),which was treated as a continuous variable; alcohol intake (drinks/wk); smoking status (never, former, or current smoker); and either IGF-I or IGFBP-3 (ng/mL) when applicable. Model 2 was further adjusted for other dietary factors, including intakes of animal protein (mg/d), animal fat (mg/d), and red meat (servings/d). However, results of this analysis remain similar when minimum adjustment is made (for example, including only age at mammography, body mass index, physical activity, energy intake, alcohol intake, and IGF-I or IGFBP-3, when applicable, in model 1). Statistical significance was based on two-sided $P < 0.05$. All statistical analyses were carried out with the use of SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

The present study included 1542 women, of which 771 were premenopausal and 771 were postmenopausal. The characteristics of the study population are described in **Table 2**. Briefly, the mean (±SD) age of the participants was 54.1 ± 9.4 y. The mean total intakes of fruit and vegetables were 2.7 ± 1.6 and 4.3 ± 2.3 servings/d, respectively. The average concentrations of IGF-I and IGFBP-3 were 208.5 ± 67.4 and 4888.1 ± 989.0 ng/mL, respectively.

The associations of total and botanical subgroups of fruit and vegetable intakes with IGF-I and IGFBP-3 concentrations are shown in **Table 3**. A positive association between cruciferous vegetable intakes and IGF-I concentrations was observed before adjustment for other dietary factors [model 1: P for trend = 0.05; $\beta \pm$ SE (P) = 7.7 ± 3.2 (0.02)], but not after full adjustment for all covariates [model 2: P for trend = 0.19; $\beta \pm$ SE (P) = 5.5 ± 3.3 (0.09)]. Higher intake of citrus fruit was significantly associated with higher IGF-I concentrations [215 ng/mL for quintile 5 compared with 205 ng/mL for quintile 1; P for trend = 0.04; $\beta \pm$ SE (P) = 3.6 ± 1.6 (0.03)] and with lower IGFBP-3 concentrations [4803 ng/mL for quintile 5 compared with 4960 ng/mL for quintile 1; P for trend = 0.04; $\beta \pm$ SE (P) = −57.5 ± 25.4 (0.02)] even after adjustment for all covariates (model 2). Concentrations of growth factors were not significantly associated with other measures of fruit and vegetable intakes (total fruit, total vegetables, total fruit and vegetables, or with intakes of other botanical subgroups of fruit and vegetables).

Among the 3 antioxidants examined, a significant dose-response association was observed between dietary vitamin C intake and concentrations of IGF-I and IGFBP-3 (**Table 4**). After adjustment for all covariates (model 2), increases of 100 mg/d of dietary vitamin C intake were associated with a 5.2 ± 1.9 ng/mL increase in IGF-I concentrations (P = 0.009) and a 77.2 ± 30.9 ng/mL decrease in IGFBP-3 concentrations (P = 0.01). In contrast, total or supplement vitamin C intakes were not significantly related to concentrations of IGF-I or IGFBP-3. No significant associations between intakes of β-carotene or lycopene from food, supplements, or both and IGF-I or IGFBP-3 concentrations were observed.

When fruit and vegetables are categorized into subgroups based on the phytochemical classification, a higher intake of fruit and vegetables rich in vitamin C was significantly associated

TABLE 2
Characteristics of the study population[1]

Variables	All women (n = 1542)
	%
Menopausal status (premenopausal)	50.0
Hormonal contraceptive use ever (yes)	72.8
Hormone replacement therapy use ever (yes)	22.5
Lactation history (yes)[2]	45.7
History of breast biopsy (yes)	15.3
Family history of breast cancer (yes)[3]	33.4
Education (highest degree completed)	
Primary or less	16.3
Secondary	32.6
College	19.6
University	31.5
Smoking status	
Never	52.1
Former	33.8
Current	14.1
Alcohol intake (drinks/wk)	
0	12.3
>0 to ≤1	36.1
>1 to ≤6	36.9
>6	14.7
IGF-I (ng/mL)	208.5 ± 67.4[4]
IGFBP-3 (ng/mL)	4888.1 ± 989.0
Age at mammography (y)	54.1 ± 9.4
BMI (kg/m^2)	26.1 ± 4.7
Physical activity (MET-hour/wk)	26.3 ± 22.8
Full-term pregnancies (no.)	1.9 ± 1.6
Age at first full-term birth (y)[2]	25.7 ± 4.2
Age at menarche (y)	12.7 ± 1.6
Food and nutrient intakes	
Fruit and vegetables (servings/d)	6.9 ± 3.2
Vegetables (servings/d)	4.3 ± 2.3
Fruit (servings/d)	2.7 ± 1.6

[1] IGF-I, insulin-like growth factor I; IGFBP-3, IGF-binding protein 3; MET, metabolic equivalents.
[2] In parous women (n = 1161).
[3] Mother, sister, and daughter.
[4] $\bar{x}$ ± SD (all such values).

with higher IGF-I concentrations [216 ng/mL for quintile 5 compared with 207 ng/mL for quintile 1; P for trend = 0.01; β ± SE (P) = 2.9 ± 1.2 (0.02)] and with lower IGFBP-3 concentrations [4801 ng/mL for quintile 5 compared with 4911 ng/mL for quintile 1; P for trend = 0.05; β ± SE (P) = −46.9 ± 19.2 (0.02)] after full adjustment for all covariates. No significant association was observed between growth factor concentrations and intakes of fruit and vegetables rich in β-carotene or lycopene (data not shown).

Because menopausal status, alcohol intake, and smoking status could affect diet intake, the antioxidant capacity of the diet, or concentrations of growth factors, analyses were performed after stratification for these factors. Associations of food and nutrient intakes with concentrations of growth factors were comparable between pre- and postmenopausal women, smokers and ex- or nonsmokers, and moderate alcohol consumers (<3 servings/wk) and high alcohol consumers (≥3 drinks/wk). Thus, these factors had little or no significant modifying effect in our study (data not shown).

DISCUSSION

The present cross-sectional study suggests that higher intakes of citrus fruit and dietary vitamin C are associated with higher IGF-I and lower IGFBP-3 concentrations. These findings support the notion that a diet rich in vitamin C (ascorbic acid), especially from citrus fruit, may affect circulating IGF-I and IGFBP-3 concentrations.

In the present study, intakes of total vegetables and total fruit did not relate significantly to IGF-I and IGFBP-3 concentrations. These findings are consistent with previous studies on these associations (30–33). With regard to botanical subgroups and their related antioxidants, one study found a negative association between intake of cooked tomatoes and IGF-I concentrations (34) and another found a positive association between lycopene intake and IGFBP-3 concentrations (31). However, some investigators have observed no association of legume (32, 35), tomato (30, 35), or total β-carotene (31) intakes with IGF-I and IGFBP-3 concentrations and no association of lycopene intake with IGF-I (31, 35) or IGFBP-3 concentrations (35) and no association of lycopene intake with either IGF-I (31, 35) or IGFBP-3 (35) concentrations, which is consistent with our observations.

In our study, we observed a positive dose-response association of dietary vitamin C intake with IGF-I concentrations, and an inverse dose-response association of dietary vitamin C intake with concentrations of IGFBP-3. These results are only partly consistent with those observed in the study conducted by Holmes et al (31). These investigators found a positive association of dietary vitamin C intake not only with IGF-I but also with IGFBP-3 concentrations; the latter reached statistical significance. However, no significant association was observed between total or supplemental intakes of vitamin C and IGF concentrations in the present study as well as in others (31, 32).

To our knowledge, the present study is the first to report that higher citrus fruit intakes are associated with higher concentrations of IGF-I and lower concentrations of IGFBP-3. In addition, we observed a positive association, although not statistically significant, between cruciferous vegetable intakes and IGF-I concentrations. Because the phytochemical subgroup of fruit and vegetables rich in vitamin C is mainly composed of citrus fruit and cruciferous vegetables, these findings further support the idea that intake of vitamin C from food may affect IGF concentrations. The biological mechanisms through which vitamin C from food may increase IGF-I and reduce IGFBP-3 concentrations are not known. Nevertheless, in animal models, Palka et al (43) found that serum IGF-I concentrations of guinea pig under ascorbate-free (vitamin C–free) diet for 24–28 d (acutely scorbutic) was decreased to 25% of normal concentrations. The extent of growth factor concentration changes in the serum of vitamin C–deficient guinea pigs was correlated with the extent of weight loss. Hence, these authors suggested that dietary vitamin C could play a role in regulation of growth through the IGF system.

Our observation of an association between vitamin C–rich fruit and vegetables and IGF concentrations may explain, at least in part, 2 independent sets of epidemiologic studies of IHD and

TABLE 3
Associations of plasma insulin-like growth factor I (IGF-I) and IGF-binding protein 3 (IGFBP-3) concentrations with quintiles (Q) of fruit and vegetable intakes[1]

		Crude model		Model 1[2]		Model 2[3]	
Dietary variables	Median	IGF-I	IGFBP-3	IGF-I	IGFBP-3	IGF-I	IGFBP-3
		ng/mL		*ng/mL*		*ng/mL*	
Cruciferous vegetables (servings/d)							
Q1 (n = 345)	0.12	206 ± 4[4]	4778 ± 53	211 ± 3	4810 ± 43	212 ± 3	4810 ± 43
Q2 (n = 311)	0.28	207 ± 4	4864 ± 56	206 ± 3	4898 ± 44	206 ± 3	4899 ± 44
Q3 (n = 261)	0.34	205 ± 4	4952 ± 61	201 ± 3	4998 ± 48	201 ± 3	4999 ± 48
Q4 (n = 310)	0.56	213 ± 4	4964 ± 56	209 ± 3	4923 ± 44	208 ± 3	4923 ± 44
Q5 (n = 315)	1.02	212 ± 4	4871 ± 56	215 ± 3	4804 ± 44	213 ± 3	4802 ± 45
P for trend[5]		0.15	0.40	0.05	0.31	0.19	0.30
P for heterogeneity[6]		0.49	0.11	0.02	0.01	0.03	0.01
β ± SE (P)[7]		6.7 ± 4.1 (0.10)	59.3 ± 60.7 (0.33)	7.7 ± 3.2 (0.02)	−68.9 ± 49.9 (0.17)	5.5 ± 3.3 (0.09)	−75.5 ± 51.4 (0.14)
Green leafy vegetables (servings/d)							
Q1 (n = 297)	0.14	205 ± 4	4867 ± 57	207 ± 3	4903 ± 46	209 ± 3	4904 ± 47
Q2 (n = 326)	0.32	213 ± 4	4944 ± 55	210 ± 3	4911 ± 43	210 ± 3	4912 ± 43
Q3 (n = 333)	0.57	206 ± 4	4891 ± 54	204 ± 3	4921 ± 43	204 ± 3	4922 ± 43
Q4 (n = 280)	0.90	213 ± 4	4836 ± 59	213 ± 3	4800 ± 47	213 ± 3	4801 ± 47
Q5 (n = 306)	1.31	206 ± 4	4859 ± 57	208 ± 3	4858 ± 45	207 ± 3	4855 ± 46
P for trend[5]		0.93	0.45	0.62	0.17	0.99	0.16
P for heterogeneity[6]		0.37	0.71	0.26	0.31	0.28	0.31
β ± SE (P)[7]		−0.1 ± 3.0 (0.97)	−19.9 ± 43.5 (0.65)	0.2 ± 2.3 (0.9)	−32.4 ± 35.9 (0.37)	−0.8 ± 2.3 (0.74)	−34.9 ± 36.3 (0.34)
Yellow vegetables (servings/d)							
Q1 (n = 315)	0.16	208 ± 4	4815 ± 56	207 ± 3	4849 ± 45	208 ± 3	4850 ± 46
Q2 (n = 288)	0.44	206 ± 4	4851 ± 58	206 ± 3	4887 ± 46	206 ± 3	4888 ± 46
Q3 (n = 375)	0.73	216 ± 4	4900 ± 51	213 ± 3	4848 ± 40	213 ± 3	4850 ± 40
Q4 (n = 274)	1.04	211 ± 4	4954 ± 60	210 ± 3	4922 ± 47	210 ± 3	4921 ± 47
Q5 (n = 290)	1.80	199 ± 4	4889 ± 58	205 ± 3	4913 ± 48	205 ± 3	4910 ± 48
P for trend[5]		0.09	0.29	0.77	0.33	0.66	0.37
P for heterogeneity[6]		0.02	0.51	0.30	0.69	0.37	0.72
β ± SE (P)[7]		−4.9 ± 2.6 (0.06)	37.9 ± 38.3 (0.32)	−0.86 ± 2.1 (0.69)	31.1 ± 33.0 (0.35)	−1.1 ± 2.1 (0.59)	28.6 ± 33.2 (0.39)
Tomatoes (servings/d)							
Q1 (n = 344)	0.18	201 ± 4	4801 ± 53	206 ± 3	4864 ± 43	206 ± 3	4865 ± 43
Q2 (n = 277)	0.32	208 ± 4	4870 ± 59	205 ± 3	4916 ± 47	205 ± 3	4920 ± 47
Q3 (n = 357)	0.59	211 ± 3	4963 ± 52	212 ± 3	4899 ± 42	212 ± 3	4899 ± 41
Q4 (n = 258)	0.73	214 ± 4	4898 ± 62	209 ± 3	4872 ± 49	209 ± 3	4871 ± 49
Q5 (n = 306)	1.14	210 ± 4	4871 ± 57	210 ± 3	4857 ± 46	209 ± 3	4852 ± 46
P for trend[5]		0.09	0.44	0.21	0.63	0.26	0.55
P for heterogeneity[6]		0.15	0.30	0.34	0.87	0.36	0.83
β ± SE (P)[7]		5.9 ± 4.0 (0.14)	30.2 ± 58.7 (0.61)	3.1 ± 3.2 (0.33)	−26.8 ± 49.1 (0.59)	2.8 ± 3.2 (0.38)	−32.4 ± 49.5 (0.51)
Legumes (servings/d)							
Q1 (n = 323)	0.06	207 ± 4	4812 ± 55	207 ± 3	4856 ± 45	208 ± 3	4860 ± 45
Q2 (n = 346)	0.16	212 ± 4	4921 ± 53	212 ± 3	4869 ± 42	212 ± 3	4871 ± 42
Q3 (n = 299)	0.24	205 ± 4	4827 ± 57	207 ± 3	4857 ± 45	207 ± 3	4858 ± 45
Q4 (n = 263)	0.32	209 ± 4	4917 ± 61	205 ± 3	4953 ± 48	204 ± 3	4950 ± 48
Q5 (n = 311)	0.71	210 ± 4	4930 ± 56	211 ± 3	4883 ± 45	210 ± 3	4878 ± 46
P for trend[5]		0.69	0.21	0.54	0.62	0.84	0.73
P for heterogeneity[6]		0.71	0.39	0.35	0.58	0.32	0.62
β ± SE (P)[7]		2.2 ± 5.1 (0.66)	44.9 ± 75.4 (0.55)	5.0 ± 3.9 (0.20)	−22.6 ± 61.3 (0.71)	3.8 ± 4.0 (0.35)	−38.3 ± 62.9 (0.54)
Onion (servings/d)							
Q1 (n = 315)	0.04	210 ± 4	4844 ± 56	210 ± 3	4861 ± 44	211 ± 3	4862 ± 44
Q2 (n = 367)	0.22	206 ± 4	4856 ± 52	206 ± 3	4886 ± 41	206 ± 3	4886 ± 41
Q3 (n = 182)	0.45	216 ± 5	4847 ± 73	216 ± 4	4783 ± 58	215 ± 3	4785 ± 58
Q4 (n = 344)	0.82	206 ± 4	4928 ± 53	204 ± 3	4950 ± 42	204 ± 3	4951 ± 42
Q5 (n = 334)	1.23	208 ± 4	4913 ± 54	210 ± 3	4877 ± 43	211 ± 3	4874 ± 44
P for trend[5]		0.57	0.21	0.80	0.42	0.75	0.46
P for heterogeneity[6]		0.45	0.73	0.08	0.21	0.07	0.22
β ± SE (P)[7]		−0.5 ± 3.3 (0.87)	57.9 ± 48.6 (0.23)	0.6 ± 2.6 (0.81)	15.6 ± 40.0 (0.69)	0.5 ± 2.6 (0.83)	12.3 ± 40.1 (0.76)
Other vegetables (servings/d)							
Q1 (n = 312)	0.18	208 ± 4	4802 ± 56	211 ± 3	4810 ± 45	213 ± 3	4811 ± 46
Q2 (n = 287)	0.36	215 ± 4	4867 ± 58	212 ± 3	4842 ± 46	213 ± 3	4842 ± 46
Q3 (n = 341)	0.61	206 ± 4	4939 ± 54	204 ± 3	4969 ± 42	204 ± 3	4972 ± 42
Q4 (n = 293)	0.96	204 ± 4	4869 ± 58	206 ± 3	4891 ± 45	206 ± 3	4889 ± 45
Q5 (n = 309)	1.53	210 ± 4	4921 ± 56	210 ± 3	4883 ± 46	208 ± 3	4880 ± 47
P for trend[5]		0.58	0.24	0.44	0.33	0.19	0.37
P for heterogeneity[6]		0.36	0.44	0.18	0.11	0.12	0.10
β ± SE (P)[7]		−1.3 ± 2.9 (0.66)	30.9 ± 42.5 (0.47)	−0.4 ± 2.4 (0.87)	3.4 ± 36.6 (0.93)	−1.7 ± 2.4 (0.47)	−0.29 ± 37.3 (0.99)

(*Continued*)

TABLE 3 (*Continued*)

Dietary variables	Median	Crude model		Model 1[2]		Model 2[3]	
		IGF-I	IGFBP-3	IGF-I	IGFBP-3	IGF-I	IGFBP-3
		ng/mL		*ng/mL*		*ng/mL*	
Total vegetables (servings/d)							
Q1 (n = 308)	1.79	209 ± 4[4]	4821 ± 56	209 ± 3	4844 ± 47	210 ± 3	4846 ± 47
Q2 (n = 312)	2.93	204 ± 4	4809 ± 56	205 ± 3	4876 ± 44	205 ± 3	4881 ± 45
Q3 (n = 303)	3.93	217 ± 4	4969 ± 56	213 ± 3	4896 ± 44	213 ± 3	4897 ± 44
Q4 (n = 310)	5.07	204 ± 4	4899 ± 56	204 ± 3	4937 ± 45	203 ± 3	4936 ± 45
Q5 (n = 309)	7.07	208 ± 4	4907 ± 56	212 ± 3	4853 ± 47	211 ± 3	4846 ± 48
P for trend[5]		0.90	0.19	0.62	0.77	0.98	0.89
P for heterogeneity[6]		0.11	0.24	0.09	0.59	0.09	0.57
β ± SE (P)[7]		−0.04 ± 0.8 (0.95)	11.0 ± 11.1 (0.32)	0.5 ± 0.6 (0.42)	−2.9 ± 10.0 (0.77)	0.2 ± 0.7 (0.79)	−4.7 ± 10.3 (0.65)
Citrus fruit (servings/d)							
Q1 (n = 307)	0.10	208 ± 4	4946 ± 56	205 ± 3	4956 ± 45	205 ± 3	4960 ± 45
Q2 (n = 326)	0.47	211 ± 4	4875 ± 55	208 ± 3	4879 ± 43	208 ± 3	4882 ± 43
Q3 (n = 302)	1.00	208 ± 4	4837 ± 57	209 ± 3	4855 ± 45	209 ± 3	4856 ± 45
Q4 (n = 302)	1.28	205 ± 4	4862 ± 57	205 ± 3	4902 ± 45	205 ± 3	4904 ± 45
Q5 (n = 305)	2.08	211 ± 4	4886 ± 57	215 ± 3	4813 ± 46	215 ± 3	4803 ± 46
P for trend[5]		0.90	0.53	0.05	0.06	0.04	0.04
P for heterogeneity[6]		0.83	0.73	0.13	0.24	0.09	0.18
β ± SE (P)[7]		0.01 ± 2.0 (0.99)	−15.4 ± 29.9 (0.61)	3.6 ± 1.6 (0.03)	−50.9 ± 25.1 (0.04)	3.6 ± 1.6 (0.03)	−57.5 ± 25.4 (0.02)
Rose (servings/d)							
Q1 (n = 332)	0.16	207 ± 4	4770 ± 54	208 ± 3	4828 ± 45	210 ± 3	4833 ± 46
Q2 (n = 277)	0.42	214 ± 4	4882 ± 59	209 ± 3	4873 ± 47	209 ± 3	4878 ± 47
Q3 (n = 323)	0.69	212 ± 4	4957 ± 55	209 ± 3	4930 ± 43	208 ± 3	4930 ± 43
Q4 (n = 298)	1.12	207 ± 4	4957 ± 57	207 ± 3	4940 ± 45	206 ± 3	4942 ± 45
Q5 (n = 312)	1.85	204 ± 4	4848 ± 56	210 ± 3	4837 ± 46	209 ± 3	4826 ± 47
P for trend[5]		0.14	0.48	0.85	0.95	0.82	0.86
P for heterogeneity[6]		0.35	0.08	0.94	0.24	0.93	0.21
β ± SE (P)[7]		−3.0 ± 2.3 (0.18)	25.5 ± 33.1 (0.44)	−0.1 ± 1.8 (0.97)	7.7 ± 28.7 (0.79)	−0.1 ± 1.9 (0.74)	−0.1 ± 29.6 (0.99)
Other fruit (servings/d)							
Q1 (n = 308)	0.16	210 ± 4	4904 ± 56	208 ± 3	4911 ± 46	208 ± 3	4914 ± 46
Q2 (n = 301)	0.34	216 ± 4	4933 ± 57	211 ± 3	4896 ± 45	211 ± 3	4901 ± 45
Q3 (n = 342)	0.61	203 ± 4	4824 ± 54	205 ± 3	4873 ± 42	205 ± 3	4876 ± 42
Q4 (n = 271)	1.00	210 ± 4	4859 ± 60	210 ± 3	4848 ± 47	210 ± 3	4847 ± 47
Q5 (n = 320)	1.47	205 ± 4	4891 ± 55	209 ± 3	4876 ± 46	209 ± 3	4865 ± 46
P for trend[5]		0.14	0.67	0.71	0.49	0.89	0.36
P for heterogeneity[6]		0.09	0.68	0.56	0.91	0.57	0.87
β ± SE P[7]		−6.0 ± 2.9 (0.04)	−18.1 ± 43.0 (0.67)	−0.5 ± 2.4 (0.82)	−11.8 ± 37.1 (0.75)	−1.0 ± 2.4 (0.67)	−21.2 ± 38.1 (0.58)
Total fruit (servings/d)							
Q1 (n = 310)	0.95	209 ± 4	4879 ± 56	204 ± 3	4925 ± 47	205 ± 3	4937 ± 48
Q2 (n = 312)	1.75	213 ± 4	4934 ± 57	207 ± 3	4934 ± 45	208 ± 3	4940 ± 45
Q3 (n = 305)	2.38	212 ± 4	4854 ± 56	213 ± 3	4830 ± 44	212 ± 3	4834 ± 44
Q4 (n = 307)	3.20	200 ± 4	4837 ± 56	205 ± 3	4881 ± 45	205 ± 3	4878 ± 45
Q5 (n = 308)	4.65	207 ± 4	4902 ± 56	213 ± 3	4836 ± 48	213 ± 3	4817 ± 50
P for trend[5]		0.23	0.90	0.15	0.18	0.20	0.08
P for heterogeneity[6]		0.11	0.76	0.14	0.38	0.17	0.26
β ± SE (P)[7]		−1.6 ± 1.1 (0.15)	−0.9 ± 16.1 (0.95)	1.2 ± 0.9 (0.22)	−18.1 ± 15.0 (0.23)	1.0 ± 1.0 (0.30)	−25.8 ± 15.8 (0.10)
Total fruit and vegetables (servings/d)							
Q1 (n = 309)	3.43	205 ± 4	4742 ± 56	206 ± 3	4823 ± 48	208 ± 3	4830 ± 49
Q2 (n = 310)	5.11	217 ± 4	4989 ± 56	210 ± 3	4926 ± 45	210 ± 3	4930 ± 45
Q3 (n = 307)	6.46	206 ± 4	4832 ± 56	209 ± 3	4857 ± 44	209 ± 3	4860 ± 44
Q4 (n = 309)	8.15	210 ± 4	4957 ± 56	208 ± 3	4939 ± 44	207 ± 3	4937 ± 45
Q5 (n = 307)	11.23	204 ± 4	4884 ± 56	210 ± 3	4859 ± 49	209 ± 3	4848 ± 51
P for trend[5]		0.35	0.22	0.67	0.74	0.95	0.95
P for heterogeneity[6]		0.15	0.02	0.88	0.30	0.94	0.29
β ± SE (P)[7]		−0.4 ± 0.5 (0.46)	5.3 ± 7.8 (0.50)	0.6 ± 0.5 (0.21)	−6.5 ± 7.7 (0.40)	0.4 ± 0.5 (0.46)	−9.7 ± 8.1 (0.23)

[1] Means (±SEs) of IGF-I or IGFBP-3 were estimated from generalized linear models.

[2] Adjusted for menopausal status, age at mammography, BMI, physical activity, energy intake, duration of past use of hormone replacement therapy and oral contraceptives, duration of lactation, number of full-term pregnancies, age at first full-term birth, age at menarche, number of breast biopsy samples, family history of breast cancer, education, alcohol intake, smoking status, and either IGF-I or IGFBP-3 when applicable.

[3] Adjusted for all variables included in model 1 plus intakes of animal protein, animal fat, and red meat.

[4] $\bar{x}$ ± SE (all such values).

[5] F test of the linear contrast with the median of daily intakes within each of the quintiles as the value.

[6] F test evaluating the differences between any of the adjusted means.

[7] Estimated from linear regression models. These values represent absolute mean (±SE) decrease or increase in IGF-I or IGFBP-3 concentrations for increments of one serving per day of fruit, vegetables, or both.

TABLE 4
Associations of plasma insulin-like growth factor I (IGF-I) and IGF-binding protein 3 (IGFBP-3) concentrations with quintiles (Q) of antioxidant intakes[1]

		Crude model		Model 1[2]		Model 2[3]	
Dietary variables	Median	IGF-I	IGFBP-3	IGF-I	IGFBP-3	IGF-I	IGFBP-3
		ng/mL		*ng/mL*		*ng/mL*	
β-Carotene from food (μg/d)							
Q1 (n = 307)	1945.14	208 ± 4[4]	4798 ± 56	207 ± 3	4846 ± 47	207 ± 3	4847 ± 47
Q2 (n = 308)	3602.15	214 ± 4	4854 ± 56	210 ± 3	4852 ± 45	211 ± 3	4854 ± 45
Q3 (n = 308)	5103.44	211 ± 4	4944 ± 56	209 ± 3	4916 ± 44	209 ± 3	4919 ± 44
Q4 (n = 312)	6808.77	209 ± 4	4908 ± 56	209 ± 3	4898 ± 44	209 ± 3	4897 ± 44
Q5 (n = 307)	10 607.39	201 ± 4	4901 ± 56	208 ± 3	4893 ± 47	207 ± 3	4889 ± 48
P for trend[5]		0.06	0.22	0.90	0.46	0.81	0.52
P for heterogeneity[6]		0.18	0.40	0.93	0.79	0.91	0.79
β ± SE (P)[7]		−0.8 ± 0.5 (0.1)	8.8 ± 7.1 (0.22)	0.2 ± 0.4 (0.55)	2.7 ± 6.4 (0.67)	0.1 ± 0.4 (0.80)	2.0 ± 6.5 (0.76)
β-Carotene from supplement (μg/d)							
Q1 (n = 73)	85.50	211 ± 8	4938 ± 109	206 ± 6	4917 ± 86	205 ± 6	4913 ± 86
Q2 (n = 92)	150.00	204 ± 7	4876 ± 97	209 ± 5	4872 ± 78	210 ± 5	4877 ± 78
Q3 (n = 40)	300.00	206 ± 11	4990 ± 147	206 ± 8	4908 ± 116	205 ± 8	4902 ± 117
Q4 (n = 57)	1200.00	207 ± 9	4679 ± 123	207 ± 7	4729 ± 98	208 ± 7	4731 ± 99
Q5 (n = 58)	1500.00	203 ± 9	4921 ± 122	201 ± 7	4960 ± 97	201 ± 7	4960 ± 97
P for trend[5]		0.72	0.35	0.53	0.73	0.56	0.75
P for heterogeneity[6]		0.96	0.46	0.92	0.51	0.87	0.54
β ± SE (P)[7]		−3.3 ± 1.9 (0.07)	−22.9 ± 25.9 (0.38)	−2.3 ± 1.4 (0.09)	7.4 ± 20.7 (0.72)	−2.2 ± 1.4 (0.13)	7.5 ± 20.8 (0.69)
Total β-carotene (μg/d)							
Q1 (n = 307)	2012.72	209 ± 4	4795 ± 56	208 ± 3	4834 ± 47	208 ± 3	4836 ± 47
Q2 (n = 307)	3710.39	214 ± 4	4895 ± 56	209 ± 3	4884 ± 45	209 ± 3	4885 ± 45
Q3 (n = 309)	5226.19	212 ± 4	4929 ± 56	211 ± 3	4890 ± 44	211 ± 3	4892 ± 44
Q4 (n = 311)	7031.62	206 ± 4	4879 ± 56	207 ± 3	4897 ± 44	207 ± 3	4896 ± 44
Q5 (n = 308)	10 773.53	201 ± 4	4908 ± 56	208 ± 3	4900 ± 47	207 ± 3	4896 ± 47
P for trend[5]		0.02	0.29	0.81	0.41	0.57	0.46
P for heterogeneity[6]		0.10	0.49	0.92	0.87	0.87	0.89
β ± SE (P)[7]		−0.9 ± 0.5 (0.04)	6.7 ± 6.9 (0.33)	0.01 ± 0.4 (0.97)	3.2 ± 6.1 (0.60)	−0.1 ± 0.4 (0.78)	2.6 ± 6.2 (0.68)
Lycopene (μg/d)							
Q1 (n = 307)	2698.48	200 ± 4	4828 ± 56	207 ± 3	4868 ± 46	207 ± 3	4870 ± 46
Q2 (n = 307)	4500.80	203 ± 4	4839 ± 56	206 ± 3	4876 ± 45	207 ± 3	4878 ± 45
Q3 (n = 311)	5862.32	213 ± 4	4924 ± 56	210 ± 3	4888 ± 44	211 ± 3	4890 ± 44
Q4 (n = 307)	7942.49	214 ± 4	4966 ± 56	209 ± 3	4925 ± 45	209 ± 3	4921 ± 45
Q5 (n = 310)	13 267.75	213 ± 4	4847 ± 56	210 ± 3	4850 ± 45	210 ± 3	4846 ± 46
P for trend[5]		0.01	0.74	0.40	0.81	0.50	0.73
P for heterogeneity[6]		0.02	0.33	0.83	0.81	0.86	0.82
β ± SE (P)[7]		0.7 ± 0.3 (0.04)	1.7 ± 5.1 (0.74)	0.1 ± 0.3 (0.65)	−0.4 ± 4.3 (0.92)	0.1 ± 0.3 (0.70)	−0.9 ± 4.3 (0.83)
Vitamin C from food (mg/d)							
Q1 (n = 308)	76.02	209 ± 4	4895 ± 56	204 ± 3	4943 ± 48	204 ± 3	4953 ± 48
Q2 (n = 309)	121.88	203 ± 4	4854 ± 56	204 ± 3	4911 ± 44	205 ± 3	4915 ± 45
Q3 (n = 309)	158.74	210 ± 4	4910 ± 56	209 ± 3	4901 ± 44	208 ± 3	4903 ± 44
Q4 (n = 308)	197.90	211 ± 4	4842 ± 56	212 ± 3	4823 ± 45	212 ± 3	4821 ± 45
Q5 (n = 308)	270.33	210 ± 4	4904 ± 56	214 ± 3	4827 ± 48	214 ± 3	4813 ± 49
P for trend[5]		0.47	0.92	0.01	0.06	0.02	0.03
P for heterogeneity[6]		0.59	0.88	0.11	0.36	0.17	0.23
β ± SE (P)[7]		1.4 ± 2.1 (0.51)	0.8 ± 31.4 (0.98)	5.4 ± 1.9 (0.005)	−64.1 ± 29.9 (0.03)	5.2 ± 1.9 (0.009)	−77.2 ± 30.9 (0.01)
Vitamin C from supplement (mg/d)[8]							
Q1 (n = 95)	8.40	219 ± 7	5011 ± 102	213 ± 5	4938 ± 79	213 ± 5	4937 ± 79
Q2 (n = 109)	60.00	209 ± 7	4924 ± 95	207 ± 5	4941 ± 73	207 ± 5	4942 ± 74
Q3 (n = 180)	234.20	211 ± 5	4855 ± 74	214 ± 4	4857 ± 57	214 ± 4	4859 ± 57
Q4 (n = 34)	500.01	199 ± 12	4844 ± 170	201 ± 9	4992 ± 134	200 ± 9	4987 ± 134
Q5 (n = 95)	1000.00	207 ± 7	5022 ± 102	207 ± 5	5020 ± 79	207 ± 5	5019 ± 79
P for trend[5]		0.29	0.72	0.42	0.29	0.35	0.29
P for heterogeneity[6]		0.64	0.60	0.51	0.53	0.48	0.56
β ± SE (P)[7]		−0.6 ± 0.9 (0.49)	9.5 ± 12.9 (0.46)	−0.6 ± 0.7 (0.36)	14.2 ± 9.9 (0.16)	−0.7 ± 0.7 (0.31)	14.0 ± 10.0 (0.16)
Total vitamin C (mg/d)							
Q1 (n = 306)	83.76	210 ± 4	4910 ± 57	205 ± 3	4937 ± 47	205 ± 3	4944 ± 48
Q2 (n = 311)	139.18	204 ± 4	4842 ± 56	206 ± 3	4888 ± 44	206 ± 3	4889 ± 44
Q3 (n = 310)	187.38	212 ± 4	4850 ± 56	212 ± 3	4833 ± 44	211 ± 3	4835 ± 44
Q4 (n = 306)	253.74	210 ± 4	4891 ± 57	212 ± 3	4854 ± 45	212 ± 3	4850 ± 45
Q5 (n = 309)	664.89	207 ± 4	4914 ± 56	208 ± 3	4893 ± 45	208 ± 3	4888 ± 45
P for trend[5]		0.79	0.56	0.64	0.92	0.72	0.79
P for heterogeneity[6]		0.63	0.84	0.37	0.57	0.49	0.52
β ± SE (P)[7]		0.05 ± 0.7 (0.93)	12.7 ± 9.6 (0.19)	0.08 ± 0.5 (0.87)	6.4 ± 7.7 (0.41)	0.02 ± 0.5 (0.96)	5.5 ± 7.8 (0.48)

[1] Means (±SEs) of IGF-I or IGFBP-3 were estimated from generalized linear models.

[2] Adjusted for menopausal status, age at mammography, BMI, physical activity, energy intake, duration of past use of hormone replacement therapy and oral contraceptives, duration of lactation, number of full-term pregnancies, age at first full-term birth, age at menarche, number of breast biopsy samples, family history of breast cancer, education, alcohol intake, smoking status, and either IGF-I or IGFBP-3 when applicable.

[3] Adjusted for all variables included in model 1 plus intakes of animal protein, animal fat, and red meat.

[4] $\bar{x}$ ± SE (all such values).

[5] F test of the linear contrast with the median of daily intakes within each of the quintiles as the value.

[6] F test evaluating the differences between any of the adjusted means.

[7] Estimated from linear regression models. These values represent absolute mean (±SE) decrease or increase in IGF-I or IGFBP-3 concentrations for increments of 1000 μg/d of β-carotene or lycopene intakes and for increments of 100 mg/d of vitamin C intakes.

[8] In supplement users.

stroke. On the one hand, there is some evidence that the risk of IHD or stroke may be lower among those with a diet rich in fruit, vegetables, and antioxidants, more specifically with higher intake of vitamin C–rich fruit and vegetables (1, 2, 6) and of dietary vitamin C (3, 8, 44), although in other studies these associations were not observed (9, 45). On the other hand, a reduced risk of IHD or stroke has been suggested to be related to higher circulating IGF-I concentrations, lower circulating IGFBP-3 concentrations, or both (13–15). Hence, our findings raise the possibility that vitamin C–rich fruit and vegetables, such as citrus fruit and dietary vitamin C intakes, may affect IHD and stroke, at least in part, by modulating the biological activities of the IGF system.

The association between fruit and vegetable intakes and cancer risk has been extensively investigated in the past decades [reviewed by McCullough and Giovannucci (10) and Key et al (11)]. The protective effect of fruit and vegetable intakes against some site-specific types of cancer seems largely attributed to certain phytochemical or botanical subgroups, such as tomatoes for prostate cancer and cruciferous vegetables for bladder cancer. As for cardiovascular disease and stroke, IGF has been proposed to play a role in the etiology of some cancers but the effect of these growth factors on cancer risk appears to be opposite that on IHD risk (26). Several epidemiologic studies reported that higher concentrations of IGF-I, lower concentrations of IGFBP-3, or both were related to higher risk of breast cancer in premenopausal women (16–18) and of prostate (19, 20) and colorectal (21) cancers. In the present study, higher intakes of citrus fruit, vitamin C–rich fruit and vegetables, and dietary vitamin C related to higher IGF-I and lower IGFBP-3 concentrations, which may paradoxically suggest an increase in the risk of IGF-related malignant tumor development. These results have to be interpreted with caution. Vitamin C (ascorbic acid) may have effects that counterbalance its possible impact on growth factor concentrations. It is well-known that the proliferative and antiapoptotic activities of IGF-I is mainly mediated by its receptor (IGF-IR). However, some in vitro studies showed that ascorbyl stearate (a liphophilic derivative of ascorbic acid) inhibited the proliferation of human glioblastoma multiforme (T98G) and pancreatic carcinoma cells possibly by down-regulating the expression of IGF-IR (46, 47). From another point of view, vitamin C is known to prevent human cancer cell line progression by neutralizing reactive oxygen species before they damage DNA and initiate tumor growth. However, in addition to its antioxidant role, vitamin C has been proposed as a prooxidant that could react with lipid hydroperoxide to induce a mutagenic lesion in human DNA (48). As a result, the biological double-edged properties of vitamin C (some linked to an increase and others linked to a reduction in cancer risk) may explain the lack of consistent results between studies that examined the association of intakes of vitamin C, citrus fruit, and fruit and vegetables rich in vitamin C with certain types of cancers.

Our study had several strengths, including a relatively large sample size, a rigorous process of blood sample collection and analysis, and detailed information on potential confounding factors. However, there are some limitations of the present study. First, the FFQ used for the assessment of fruit, vegetable, and antioxidant intakes was not specifically designed for this purpose. Nevertheless, it covers intake of 28 items of vegetables and 16 items of fruit that include most of the fruit and vegetables found in the Canadian market. In addition, the FFQ has been shown to be valid and reliable (40). Second, a conversion process of food to dietary nutrient intake was based on the US Department of Agriculture nutrient file rather than that of Canada. Any misclassification of nutrient intake, however, is likely to be nondifferential and, therefore, such misclassification will tend to underestimate the observed associations rather than create spurious ones. Third, intake of nutrients from multivitamins is especially susceptible to misclassification, because a generic code was used for supplements available in Canada but not in the United States. In addition, intake of vitamin C from supplements accounts for a major proportion of the variance in total vitamin C intake (90%). Thus, this random misclassification may explain why no significant relation was observed between total or supplemental vitamin C intakes and IGF concentrations. Fourth, recall bias may influence dietary estimation. However, recall bias is likely to be the same irrespective of IGF concentrations because the women studied were not aware of the specific study objectives at the time of data collection. Hence, this misclassification would also tend to be random and is unlikely to explain observed associations. Finally, the possibility that some of the significant findings could be due to chance cannot be totally excluded because an exploratory approach was used and multiple testing was assessed.

In conclusion, we found that women with higher intakes of citrus fruit and dietary vitamin C had higher circulating concentrations of IGF-I and lower concentrations of IGFBP-3. These results raise the possibility that higher intake of this fruit subgroup and its vitamin C constituent may be associated with a decreased risk of some cardiovascular diseases, at least in part, because of their influence on concentrations of growth factors.

JB, SB, and MP were involved in the study design. JB, CD, and SB supervised the data collection work. MP performed the growth factors analyses. CDT, CD, and SB performed the statistical analyses. CDT wrote the first draft of the manuscript. All authors contributed to subsequent drafts of the manuscript and approved the final version.

REFERENCES

1. Joshipura KJ, Ascherio A, Manson JE, et al. Fruit and vegetable intake in relation to risk of ischemic stroke. JAMA 1999;282:1233–9.
2. Joshipura KJ, Hu FB, Manson JE, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. Ann Intern Med 2001;134: 1106–14.
3. Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. Am J Epidemiol 1994;139:1180–9.
4. Liu S. Intake of vegetables rich in carotenoids and riske of coronary heart disease in men: the Physisians' Health Study. Int J Epidemiol 2001;30: 130–5.
5. Bazzano LA, He J, Ogden LG, et al. Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Am J Clin Nutr 2002;76:93–9.
6. Dauchet L, Ferrieres J, Arveiler D, et al. Frequency of fruit and vegetable consumption and coronary heart disease in France and Northern Ireland: the PRIME study. Br J Nutr 2004;92:963–72.
7. Steffen LM, Jacobs DR Jr, Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 2003;78:383–90.
8. Hirvonen T, Virtamo J, Korhonen P, Albanes D, Pietinen P. Intake of flavonoids, carotenoids, vitamins C and E, and risk of stroke in male smokers. Stroke 2000;31:2301–6.
9. Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA,

Willett WC. Vitamin E consumption and the risk of coronary heart disease in men. N Engl J Med 1993;328:1450–6.
10. McCullough ML, Giovannucci EL. Diet and cancer prevention. Oncogene 2004;23:6349–64.
11. Key TJ, Schatzkin A, Willett WC, Allen NE, Spencer EA, Travis RC. Diet, nutrition and the prevention of cancer. Public Health Nutr 2004; 7:187–200.
12. Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. J Natl Cancer Inst 1999;91: 317–31.
13. Juul A, Scheike T, Davidsen M, Gyllenborg J, Jorgensen T. Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease: a population-based case-control study. Circulation 2002; 106:939–44.
14. Vasan RS, Sullivan LM, D'Agostino RB, et al. Serum insulin-like growth factor I and risk for heart failure in elderly individuals without a previous myocardial infarction: the Framingham Heart Study. Ann Intern Med 2003;139:642–8.
15. Laughlin GA, Barrett-Connor E, Criqui MH, Kritz-Silverstein D. The prospective association of serum insulin-like growth factor I (IGF-I) and IGF-binding protein-1 levels with all cause and cardiovascular disease mortality in older adults: the Rancho Bernardo Study. J Clin Endocrinol Metab 2004;89:114–20.
16. Muti P, Quattrin T, Grant BJ, et al. Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 2002;11:1361–8.
17. Hankinson SE, Willett WC, Colditz GA, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998;351:1393–6.
18. Toniolo P, Bruning PF, Akhmedkhanov A, et al. Serum insulin-like growth factor-I and breast cancer. Int J Cancer 2000;88:828–32.
19. Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 1998;279: 563–6.
20. Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB. Serum levels of insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein-3, and prostate-specific antigen as predictors of clinical prostate cancer. J Clin Endocrinol Metab 2000;85:4258–65.
21. Ma J, Pollak MN, Giovannucci E, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. J Natl Cancer Inst 1999;91:620–5.
22. Kaaks R, Toniolo P, Akhmedkhanov A, et al. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. J Natl Cancer Inst 2000;92:1592–600.
23. Krajcik RA, Borofsky ND, Massardo S, Orentreich N. Insulin-like growth factor I (IGF-I), IGF-binding proteins, and breast cancer. Cancer Epidemiol Biomarkers Prev 2002;11:1566–73.
24. Woodson K, Tangrea JA, Pollak M, et al. Serum insulin-like growth factor I: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. Cancer Res 2003;63:3991–4.
25. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004;363: 1346–53.
26. Juul A. Serum levels of insulin-like growth factor I and its binding proteins in health and disease. Growth Horm IGF Res 2003;13:113–70.
27. Thissen JP, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. Endocr Rev 1994;15:80–101.
28. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. Cancer Epidemiol Biomarkers Prev 2002;11:1441–8.
29. Allen NE, Appleby PN, Davey GK, Key TJ. Hormones and diet: low insulin-like growth factor-I but normal bioavailable androgens in vegan men. Br J Cancer 2000;83:95–7.
30. Gunnell D, Oliver SE, Peters TJ, et al. Are diet-prostate cancer associations mediated by the IGF axis? A cross-sectional analysis of diet, IGF-I and IGFBP-3 in healthy middle-aged men. Br J Cancer 2003;88:1682–6.
31. Holmes MD, Pollak MN, Willett WC, Hankinson SE. Dietary correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. Cancer Epidemiol Biomarkers Prev 2002;11:852–61.
32. Maskarinec G, Takata Y, Kaaks R. The relation between nutritional factors and insulin-like growth factor-I in premenopausal women of different ethnicity. Eur J Nutr 2005;44:105–13.
33. Kaklamani VG, Linos A, Kaklamani E, Markaki I, Koumantaki Y, Mantzoros CS. Dietary fat and carbohydrates are independently associated with circulating insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 concentrations in healthy adults. J Clin Oncol 1999;17:3291–8.
34. Mucci LA, Tamimi R, Lagiou P, et al. Are dietary influences on the risk of prostate cancer mediated through the insulin-like growth factor system? BJU Int 2001;87:814–20.
35. Vrieling A, Voskuil DW, Bueno de Mesquita HB, et al. Dietary determinants of circulating insulin-like growth factor (IGF)-I and IGF binding proteins 1, −2 and −3 in women in the Netherlands. Cancer Causes Control 2004;15:787–96.
36. Diorio C, Pollak M, Byrne C, et al. Insulin-like growth factor-I, IGF-binding protein-3, and mammographic breast density. Cancer Epidemiol Biomarkers Prev 2005;14:1065–73.
37. London SJ, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Speizer FE. Prospective study of relative weight, height, and risk of breast cancer. JAMA 1989;262:2853–8.
38. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71–80.
39. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol 1994;23:991–9.
40. Caan BJ, Slattery ML, Potter J, Quesenberry CP Jr, Coates AO, Schaffer DM. Comparison of the Block and the Willett self-administered semiquantitative food frequency questionnaires with an interviewer-administered dietary history. Am J Epidemiol 1998;148:1137–47.
41. Smith SA, Campbell DR, Elmer PJ, Martini MC, Slavin JL, Potter JD. The University of Minnesota Cancer Prevention Research Unit vegetable and fruit classification scheme (United States). Cancer Causes Control 1995;6:292–302.
42. Research World Cancer Research Fund. Food, nutrition, and the prevention of cancer: a global perspective. Washington, DC: American Institute for Cancer Research, 1997.
43. Palka J, Bird TA, Oyamada I, Peterkofsky B. Similar hormonal changes in sera from scorbutic and fasted (vitamin C-supplemented) guinea pigs, including decreased IGF-I and appearance of an IGF-I reversible mitogenic inhibitor. Growth Factors 1989;1:147–56.
44. Gale CR, Martyn CN, Winter PD, Cooper C. Vitamin C and risk of death from stroke and coronary heart disease in cohort of elderly people. BMJ 1995;310:1563–6.
45. Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, Bostick RM. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. N Engl J Med 1996;334:1156–62.
46. Naidu KA, Tang JL, Prockop LD, Nicosia SV, Coppola D. Antiproliferative and apoptotic effect of ascorbyl stearate in human glioblastoma multiforme cells: modulation of insulin-like growth factor-I receptor (IGF-IR) expression. J Neurooncol 2001;54:15–22.
47. Naidu KA, Karl RC, Coppola D. Antiproliferative and proapoptotic effect of ascorbyl stearate in human pancreatic cancer cells: association with decreased expression of insulin-like growth factor 1 receptor. Dig Dis Sci 2003;48:230–7.
48. Naidu KA. Vitamin C in human health and disease is still a mystery? An overview. Nutr J 2003;2:1–10.