Eur J Nutr (2005) 44 : 105–113
DOI 10.1007/s00394-004-0500-4

ORIGINAL CONTRIBUTION

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The relation between nutritional factors and insulin-like growth factor-I in premenopausal women of different ethnicity

Summary *Background* Alterations in the insulin-like growth factor-I (IGF-I) system have been proposed as a metabolic link between nutritional factors and cancer risk. *Aim of the study* This study explored dietary determinants of circulating IGF-I and IGFbinding protein-3 (IGFBP-3) levels among premenopausal women from different ethnic groups. *Methods* In a cross-sectional design, 258 women with a mean age of 43 ± 2.7 years donated blood approximately 5 days after ovulation and completed a validated Food Frequency Questionnaire. The majority of the 97 Caucasian, 96 Asian, and 65 Mixed/Other subjects were born in the US. Serum concentrations of IGF-I and IGFBP-3 were measured by double-antibody ELISA. After creating quartiles for 13 food and 13 nutrient density variables, least-square means of IGF-I, IGFBP-3, and the IGF-I/IGFBP-3 ratio were calculated by quartile, while adjusting for age, ethnicity, body mass index, and year of laboratory analysis. *Results* Whereas body mass index and dietary intakes varied significantly by ethnicity, IGF-I, IGFBP-3, and their ratio were similar by group. As the only food, fish showed a suggestive inverse association with IGF-I and the IGF-I/IGFBP-3 ratio. Dietary fiber and vitamin A were positively related to IGF-I ($p = 0.004$ and 0.03), zinc with IGFB-3 ($p = 0.0008$), and iron with the IGF-I/IGFBP-3 ratio ($p = 0.048$), but the differences between the bottom and top quartile were less than 10 %. Total energy, protein, carbohydrates, and total fat intake were not related to any serum measurements. *Conclusions* This study detected no ethnic differences in serum IGF-I, but it showed weak associations with dietary variables that require further investigation.

Key words insulin-like growth factor-I – ethnicity – nutrition – risk factors – women

Received: 21 August 2003
Accepted: 27 February 2004
Published online: 22 April 2004

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Background

Insulin-like growth factor I (IGF-I) and its binding protein IGFBP-3 are increasingly implicated in the development of cancer [1], particularly cancers of the prostate [2], colorectum [3], and breast [4–8]. It is still relatively unclear, however, what specific genetic or lifestyle factors may alter IGF-I or IGFBP-3 levels. A recent study from Hawaii and Los Angeles [9] found lower IGF-I concentrations among Latino Americans, who experience lower breast cancer incidence rates than African Americans, Japanese Americans, and Non-Latino Whites. Although nutritional factors – particularly energy balance and protein intake – appear to play a role in regulating IGF-I levels [1, 10], only a few studies have examined the relationship with the intake of specific nutrients or major food groups. Some of these cross-sectional investigations showed positive associations between total caloric intake and IGF-I [11–13], but others did not [14–16]. Likewise, animal protein intake was positively associated with IGF-I, IGFBP-3 and the IGF-I/IGFBP-3 ratio only in some studies [11, 14, 17]; carbohydrate intake was independently and inversely associated with IGF-I and negatively associated with IGFBP-3 in two studies [12, 16]; and total fat intake was positively asso-

ciated with IGF-I concentrations [12] and negatively associated with IGFBP-3 [13, 18]. Saturated fat intake was positively associated with IGF-I in one study [12], negatively in another [19], and negatively with IGFBP-3 in the Nurses' Health Study (NHS) [13]. With regard to major food groups, milk and fish consumption has been found to be directly related to IGF-I [11, 13] and a study comparing meat-eaters, vegetarians and vegans described lower IGF-I concentrations among the vegans [14]. In the present paper, we describe associations between serum IGF-I levels and dietary intakes in a population of premenopausal women with different ethnic backgrounds. Our main hypothesis was that consumption of animal protein would be directly related to IGF-I levels.

Subjects and methods

Study population

This analysis used baseline information for women who participated in a nutritional intervention study [20] and in an isoflavone clinical trial [21] in Hawaii. Subjects for both studies were recruited at mammography clinics in Honolulu. Eligible women had to be between 34 and 46 years of age, have a normal mammogram at baseline, be free of serious medical conditions, have no previous history of cancer, have regular menstrual periods and an intact uterus and ovaries, not be on oral contraceptives or any hormone preparations at baseline and within the past three months, and have no intention of becoming pregnant within the next year. Due to the design of the nutritional interventions, women who reported 6 or more servings of soy food per week in their regular diet were also excluded.

Data collection

The participants completed a validated Food Frequency Questionnaire (FFQ) [22], which asked about diet during the past year, along with demographic information, reproductive, personal and family medical history. The subjects marked all applicable ethnic categories for themselves and their parents. We assigned summary categories according to the following rules: A woman was classified as Caucasian if both parents had some Caucasian ancestry and shared no other ethnic background. Subjects who reported not more than three ethnic backgrounds were classified as Chinese, Japanese, or Filipino, if both parents were of the same ethnicity or if the mother was of the respective ethnic background and the parents shared no other ethnic background. Because of the small sample sizes in some groups, the 61 Japanese, 21 Chinese, and 14 Filipino women were combined into one Asian category. In agreement with rules applied in the State of Hawaii [23], women with any Hawaiian background were classified as Native Hawaiian. Because of their mixed ancestries, the Native Hawaiian women (N = 31) were combined into a category for other ethnicities and women with mixed ethnic backgrounds that did not fit one of the above groups (N = 34). Women with missing information in the FFQ were recontacted in order to obtain complete dietary information. None of the women in the analysis had any missing dietary values.

After scanning the FFQs, food and nutrient intakes were estimated from the Cancer Research Center's food composition database, which contains information for more than 2,200 foods items. For each food, the concentration (per 100 grams) of up to 130 nutrients and other dietary components is available. Data come primarily from the US Department of Agriculture [24], but also from various international and commercial publications. A recipe file is used to determine the ingredients in food mixtures from the questionnaires and reflects the practices of the multiethnic participants. In addition, the database estimates the daily intake in grams for 30 food groups based on the Food Guide Pyramid, a consumer guide to healthy eating that was developed by the US Department of Agriculture in 1992 [25]. Using the recipe file, the individual ingredients of mixed dishes are identified and assigned to the respective food groups.

Serum analysis

Participants donated blood samples at baseline after an overnight fast, 5 days after ovulation or approximately on day 19 of a 28-day cycle. The samples were put immediately on ice, centrifuged, and serum was drawn off and aliquoted and stored at –80 °C. The IGF-I and IGFBP-3 assays were performed in the laboratory of the Hormones and Cancer Group, at the International Agency for Research on Cancer (Lyon, France). Serum concentration of IGF-I and IGFBP-3 were measured by double-antibody ELISA (Diagnostic Systems Laboratories, Webster, Texas) as previously validated [26]. Although half of the samples were analyzed in 2001 and the other half in 2002, mean intra-batch coefficients of variation (CV) for IGF-I and IGFBP-3 were 5.1 % and 8.6 %, respectively. Due to the different lot numbers of the assay kits, the overall inter-batch CVs were 10.2 % (5.1 % and 2.7 % by year) for IGF-I and 18.5 % (4.9 % and 8.3 % by year) for IGFBP-3. The details of the method have been described previously [27].

Statistical analyses

After excluding three women whose serum measurements were outliers, 258 women were available for

analysis. Body mass index (BMI) was calculated based on measured body weight and height at the time of entry into the study. As an index of physical activity, we calculated the sum of scores for three physical activity variables (hours of strenuous, vigorous, and moderate activity) in the FFQ. The molar ratio IGF-I/IGFBP-3 was computed after converting the IGF-I and IGFBP-3 values from ng to nmol using the respective factors of 0.13 and 0.035. To test for ethnic differences in age, reproductive variables, BMI, serum measurements, and dietary characteristics, we applied analysis of variance using the GLM procedure in SAS [28] for numeric variables. For non-normally distributed variables, such as BMI and several dietary factors, the tests were performed on the natural logarithm of the original variables. For categorical variables, χ^2-tests were applied to determine significant differences among groups.

On the basis of published evidence, we focused on foods and nutrients that are related to protein intake and can distinguish between animal and plant-based food sources. Therefore, we separated the major food sources of protein into meat, red meat, poultry, fish, legumes, and eggs. In addition, we analyzed the relation of serum measurements with some minerals and vitamins that were found to be associated with IGF-I or IGFBP-3 in the past [11, 13, 15]. Because previous studies described associations between age, BMI, smoking status, history of diabetes, physical activity, and reproductive behavior with IGF-I [17, 29–32], we explored these possible relationships with simple linear regression models. For comparability, all nutrient and food intakes were expressed per 1000 kcal. This nutrient density approach of adjusting for total energy intake minimizes errors due to under- and over-reporting of total energy intake and helps to rank women into quartiles of dietary intake that are independent of individual energy intake [33]. All models were adjusted for the potential confounding effects of age, BMI, and ethnicity (3 categories). Because the mean IGF-I and IGFBP-3 levels differed between the first and second year, year of laboratory analysis was also included as a covariate. After creating quartiles for 13 food and 13 nutrient density variables, we computed median values for each dietary variable and quartile, and estimated least-square means for the three outcome variables, IGF-I, IGFBP-3, and the IGF-I/IGFBP-3 ratio. Then we employed the PROC GLM procedure with the option of LSMEANS in order to adjust for confounding variables [28]. Finally, we performed trend tests to investigate a possible dose-response relation between the different nutritional variables and the serum measurements. We regressed the mean level of the outcome variable onto the median of the quartiles for each dietary variable.

Results

A total of 258 women, comprising 97 Caucasian, 61 Japanese, 21 Chinese, 14 Filipino, 31 Hawaiian, and 34 Other/Mixed ancestries, were included in the analysis. Their ages ranged from 34 to 46 years with a mean of 43 years (Table 1). More than 85 % of women in each ethnic group, except Filipino, were born in the United States. Among Caucasian and Hawaiian women, 90 % and 87 % of parents were both born in the United States, whereas the respective numbers for Japanese, Chinese, and Filipino women were 79 %, 57 %, and 14 %. Two-thirds of the women had never smoked. Asian women had a significantly lower BMI than the two other groups. There were no significant differences in IGF-I, IGFBP-3, and the IGF-I/IGFBP-3 ratio by ethnicity although the respective means and 95 % confidence limits (95 % CL) of IGF-I were lower among Caucasians (275 ng/ml; 95 % CL: 260–289 ng/ml) than among Asians (280 ng/ml; 95 % CL: 268–292 ng/ml) and Others (286 ng/ml; 95 % CL: 269–303 ng/ml). Likewise, the IGF-I/IGFBP-3 ratio was lower among Caucasians (0.29; 95 % CL: 0.28–0.31) than among Asians (0.30; 95 % CL: 0.28–0.32) and Others (0.31; 95 % CL: 0.29–0.33). In contrast, IGFBP-3 was lower among Others (3547 ng/ml; 95 % CL: 3360–3734 ng/ml) than among Caucasians (3577 ng/ml; 95 % CL: 3421–3733 ng/ml) and Asians (3579 ng/ml; 95 % CL: 3453–3706 ng/ml). Neither IGF-I nor IGFBP-3 was significantly related to age, BMI, total energy intake, physical activity, and reproductive factors.

We observed several significant differences in nutrient and food intake variables among the three ethnic categories. Women of Asian ancestry had a 23 % lower dairy intake, a 52 % lower alcohol intake, a 14 % higher fish intake, and a 40 % higher grain intake per 1,000 kcal than Caucasian women. Meat intake was actually 18 % higher (red meat even 32 % higher) among Asians than Caucasians. In terms of nutrients, Asian women consumed relatively more carbohydrates, vitamin C, but less saturated fat, dietary fiber, calcium, iron, vitamin A and B12 than the other two groups.

Women within the highest fish intake quartile had 5.5 % lower IGF-I levels ($p = 0.07$) and a 6.2 % lower IGF-I/IGFBP-3 ratio ($p = 0.07$) than women in the lowest quartile (Table 2). We observed no significant associations between meat, dairy products and any of the three outcome variables. Milk by itself was also not associated with IGF-I. Although the following associations did not reach statistical significance, there were weak trends of higher IGF-I levels with higher intake of grains and fruits, as well as higher IGFBP-3 levels with high grain intake.

We detected no statistically significant associations between total energy, protein, carbohydrates, and total fat intake and any of the outcomes (Table 3). However, women in the top quartiles of dietary fiber, vitamin A,

Table 1 Characteristics of the study population

Category	Characteristic	Caucasians	Asians	Others	All	Std	*P*-value*
Descriptive variables	Number	97	96	65	258	–	–
	Age (years)	42.8	43.3	42.3	42.9	2.7	0.06
	Born in the United States (%)	90.7	86.5	92.3	90.6	–	0.44
	Never-smoker (%)	60.4	71.6	59.4	64.3	–	0.17
	BMI (m/kg^2)	26.1	24.3	25.9	25.4	5.5	0.05
Serum measurements	IGF-I (ng/ml)	275	280	286	280	67	0.60
	IGFBP-3 (ng/ml)	3577	3579	3547	3570	714	0.96
	IGF-I/IGFBP-3 ratio	0.29	0.30	0.31	0.30	0.08	0.36
Food intake (g/1000 kcal)	Meat	45.6	54.0	61.6	52.7	26.0	0.0005
	Red meat	18.3	24.1	26.5	22.5	13.5	0.0004
	Poultry	15.9	17.5	20.8	17.7	14.5	0.04
	Eggs	8.0	7.4	8.9	8.0	9.2	0.83
	Fish	9.9	11.3	12.4	11.0	8.9	0.04
	Dairy products	183.0	140.7	171.9	164.5	107.7	0.006
	Milk	104.1	82.9	100.0	95.2	91.9	0.13
	Legumes	14.8	16.2	18.3	16.2	12.9	0.22
	Grains	137.0	192.6	148.7	160.6	74.6	< 0.0001
	Vegetables	116.6	108.1	118.9	114.0	56.1	0.50
	Fruits	99.6	84.7	91.9	92.1	72.7	0.22
	Fat and oils	7.4	8.1	7.6	7.7	3.2	0.11
	Alcoholic beverages	45.0	21.6	24.7	31.2	59.5	0.0002
Macronutrients	Energy intake (kcal)	1940	1768	1776	1835	739	0.11
	Protein (g/1000 kcal)	37.8	37.4	40.6	38.3	6.6	0.005
	Carbohydrates (g/1000 kcal)	129.9	133.7	125.8	130.3	19.9	0.05
	Dietary fiber (g/1000 kcal)	11.1	9.4	10.3	10.3	3.6	0.002
	Fat (g/1000 kcal)	36.8	34.9	37.7	36.3	6.6	0.02
	Saturated fat (g/1000 kcal)	12.8	11.3	12.6	12.2	2.8	0.0007
	% energy from protein	14.8	14.8	16.0	15.1	2.6	0.006
	% energy from carbohydrates	50.7	52.7	49.4	51.1	7.6	0.02
	% energy from fat	32.4	31.0	33.3	32.1	5.9	0.04
Micronutrients	Vitamin A (IU/1000 kcal)	5787	4847	5725	5422	3293	0.19
	Vitamin B12 (µg/1000 kcal)	2.5	2.1	2.6	2.4	1.1	0.004
	Vitamin C (mg/1000 kcal)	76.3	79.1	74.9	77.0	44.3	0.92
	Calcium (mg/1000 kcal)	514	410	476	466	151.3	< 0.0001
	Zinc (mg/1000 kcal)	6.4	5.8	6.4	6.2	2.0	0.41
	Iron (mg/1000 kcal)	8.1	7.0	7.7	7.6	2.9	0.01
	Cholesterol (mg/1000 kcal)	108.3	108.8	121.0	111.7	44.1	0.25

* Analysis of variance was used for numeric variables and χ^2-tests for categorical variables

and iron had higher IGF-I levels than women in the bottom quartiles with respective differences of 5.7% ($p = 0.004$), 4.9% ($p = 0.03$), and 8.3% ($p = 0.10$). For IGFBP-3, women in the top quartiles of saturated fat and zinc intake had 2.4% ($p = 0.09$) and 4.7% (p = 0.0008) higher levels than women in the bottom quartiles. The IGF-I/IGFBP-3 ratio was 4.1% ($p = 0.09$) greater in the highest as compared to the lowest quartile of vitamin A. The respective values for calcium and iron were 2% ($p = 0.06$) and 6.8% ($p = 0.048$).

Additional analyses for associations between dietary and serum measurements without adjustment for ethnicity showed similar results except that the positive association of IGF-I with vitamin A intake became insignificant ($p = 0.12$), the positive association of IGF-I/IGFBP-3 ratio with iron became nonsignificant ($p = 0.16$), and the suggestive positive association of IGF-I/IGFBP-3 ratio with vitamin A reached statistical significance ($p = 0.03$).

Discussion

In this population of multiethnic women in Hawaii, we detected no ethnic differences in IGF-I and IGFBP-3 levels. Although we observed some differences in dietary intakes among ethnic groups, these were relatively small. The fact that the women with Asian ancestry consumed only slightly less fat and more meat, in particular red meat, than Caucasians indicates the Westernized eat-

Table 2 Relation between serum measurements and food intakes*

Foods	Quartile	Median intake (g/1000 kcal)	IGF-1 (ng/ml)	IGFBP-3 (ng/ml)	IGF-1/ IGFBP-3 ratio
Grains	1	90.9	276	3504	0.30
	2	127.0	281	3544	0.30
	3	165.0	277	3617	0.29
	4	238.9	285	3615	0.30
	P (trend)	–	*0.19*	*0.13*	*0.78*
Meat	1	24.5	297	3509	0.32
	2	44.3	273	3621	0.29
	3	59.3	274	3560	0.30
	4	81.4	275	3590	0.29
	P (trend)	–	*0.26*	*0.48*	*0.39*
Red meat	1	6.7	278	3546	0.30
	2	16.4	274	3411	0.30
	3	26.5	282	3640	0.30
	4	37.9	284	3685	0.30
	P (trend)	–	*0.22*	*0.30*	*0.82*
Poultry	1	5.1	285	3628	0.30
	2	11.0	282	3589	0.30
	3	17.5	272	3514	0.30
	4	33.0	280	3550	0.30
	P (trend)	–	*0.67*	*0.35*	*0.20*
Fish	1	3.0	284	3530	0.31
	2	7.0	287	3626	0.30
	3	10.8	279	3514	0.30
	4	20.6	268	3610	0.29
	P (trend)	–	*0.07*	*0.61*	*0.07*
Eggs	1	2.5	286	3584	0.31
	2	4.4	289	3756	0.30
	3	7.2	261	3301	0.30
	4	12.9	282	3641	0.30
	P (trend)	–	*0.75*	*0.93*	*0.62*
Dairy products	1	64.5	277	3555	0.30
	2	119.4	274	3619	0.29
	3	171.5	286	3502	0.31
	4	274.6	282	3606	0.30
	P (trend)	–	*0.43*	*0.81*	*0.94*
Milk	1	18.9	279	3584	0.30
	2	48.3	279	3516	0.31
	3	92.5	282	3629	0.30
	4	185.5	278	3552	0.30
	P (trend)	–	*0.83*	*0.96*	*0.52*
Legumes	1	4.3	279	3497	0.30
	2	10.0	277	3515	0.30
	3	17.1	278	3649	0.29
	4	29.3	285	3620	0.30
	P (trend)	–	*0.22*	*0.21*	*0.72*
Vegetables	1	60.4	275	3601	0.29
	2	86.7	282	3523	0.31
	3	115.3	272	3568	0.29
	4	181.4	289	3589	0.31
	P (trend)	–	*0.32*	*0.83*	*0.50*
Fruits	1	20.3	272	3603	0.29
	2	56.2	270	3494	0.29
	3	96.2	288	3582	0.31
	4	180.8	289	3603	0.30
	P (trend)	–	*0.17*	*0.69*	*0.44*
Fat and oils	1	4.6	282	3512	0.30
	2	6.4	272	3565	0.29
	3	8.0	275	3478	0.30
	4	11.3	290	3727	0.30
	P (trend)	–	*0.46*	*0.23*	*0.64*
Alcoholic beverages	1	0.02	291	3673	0.30
	2	0.06	270	3509	0.30
	3	15.8	283	3473	0.31
	4	72.1	274	3629	0.29
	P (trend)	–	*0.65*	*0.73*	*0.33*

* Least-square means adjusted for age, ethnicity, BMI, and year of laboratory analysis

ing patterns of this population. Red meat consumption may partially explain the very high risk of colorectal cancer among Japanese-Americans [34]. Alcohol intake was low in all groups and even the intake among Caucasian women was within the range of national recommendations [35]. Of all foods, fish showed the strongest relation with IGF-I and the IGF-I/IGFBP-3 ratio. In terms of nutrients, dietary fiber, vitamin A, zinc, and iron each were positively associated with one of the outcomes, but the differences between bottom and top quartile were less than 10 %.

Our finding of no difference in IGF-I levels across ethnic groups is in agreement with results from the multiethnic cohort study in Hawaii and Los Angeles [9], which showed that IGF-I levels were lower among Latino Americans, the most recent immigrants, compared to African Americans, Japanese Americans, and Non-Latino Whites, who all had similar levels. Due to the relatively small number of recent immigrants in our study, a separate analysis for such a subgroup was not feasible. Our study also did not include Latino women as a separate subgroup because of the very small proportion of Latinos in Hawaii. As shown by the information on parents' birthplace, the majority of Asian women in Hawaii are second or third generation migrants, whereas Latino Americans in California are primarily first generation immigrants. The small number of foreign-born participants may explain the lack of ethnic differences in IGF-I. A study from the United Kingdom [36] also described lower IGF-I levels in Pakistani migrants than in Europeans. These migrants may be less acculturated and may still have similar disease risks as the population in their country of origin.

Mean IGF-I levels in our study are higher than in studies with older populations [11, 13]. In contrast to other reports [11, 13], total energy intake was not associated with serum measurements in our study, possibly due to the fact that all study subjects were well nourished. Hence, an effect of protein intake may not be no-

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Table 3 Relation between serum measurements and nutrient intakes*

Nutrient	Quartiles	Median intake	IGF-1 (ng/ml)	IGFBP-3 (ng/ml)	IGF-1/ IGFBP-3 ratio
Total energy (kcal/day)	1	1109	280	3554	0.30
	2	1463	275	3468	0.30
	3	1907	283	3670	0.30
	4	2646	280	3590	0.30
	P (trend)	–	*0.72*	*0.56*	*0.51*
Protein (g/1000 kcal)	1	31.3	284	3493	0.31
	2	36.2	282	3640	0.30
	3	39.9	268	3563	0.29
	4	45.2	284	3585	0.31
	P (trend)	–	*0.79*	*0.55*	*0.77*
Carbohydrates (g/1000 kcal)	1	109.2	279	3645	0.30
	2	123.3	278	3557	0.30
	3	135.5	272	3473	0.30
	4	153.0	289	3608	0.30
	P (trend)	–	*0.52*	*0.72*	*0.11*
Dietary fiber (g/1000 kcal)	1	6.6	273	3566	0.30
	2	8.6	276	3627	0.29
	3	10.7	282	3505	0.31
	4	14.3	288	3583	0.31
	P (trend)	–	*0.004*	*0.89*	*0.28*
Total fat (g/1000 kcal)	1	28.8	289	3596	0.30
	2	34.1	259	3430	0.29
	3	38.8	291	3612	0.31
	4	43.5	279	3645	0.30
	P (trend)	–	*0.99*	*0.58*	*0.97*
Saturated fat (g/1000 kcal)	1	9.0	287	3539	0.31
	2	11.3	273	3534	0.30
	3	13.1	282	3593	0.30
	4	15.4	278	3615	0.30
	P (trend)	–	*0.57*	*0.09*	*0.24*
Cholesterol (mg/1000 kcal)	1	72.6	290	3591	0.31
	2	97.3	275	3564	0.29
	3	117.1	268	3493	0.29
	4	145.7	285	3635	0.30
	P (trend)	–	*0.75*	*0.81*	*0.70*
Vitamin A (IU/1000 kcal)	1	2858	276	3628	0.29
	2	3972	275	3511	0.30
	3	5174	279	3523	0.30
	4	8334	289	3621	0.30
	P (trend)	–	*0.03*	*0.78*	*0.09*
Vitamin B12 (µg/1000 kcal)	1	1.5	275	3485	0.30
	2	1.9	275	3539	0.30
	3	2.3	289	3667	0.30
	4	3.3	280	3589	0.30
	P (trend)	–	*0.56*	*0.43*	*0.91*
Vitamin C (mg/1000 kcal)	1	32.9	272	3666	0.29
	2	58.0	289	3613	0.31
	3	77.2	269	3463	0.30
	4	126.1	289	3539	0.31
	P (trend)	–	*0.53*	*0.37*	*0.21*
Calcium (mg/1000 kcal)	1	315.1	273	3511	0.30
	2	407.9	273	3563	0.30
	3	482.9	289	3661	0.30
	4	638.5	283	3545	0.30
	P (trend)	–	*0.35*	*0.75*	*0.06*
Zinc (mg/1000 kcal)	1	4.7	279	3499	0.30
	2	5.5	272	3545	0.29
	3	6.1	283	3576	0.30
	4	7.6	284	3662	0.30
	P (trend)	–	*0.39*	*0.0008*	*0.88*
Iron (mg/1000 kcal)	1	5.6	268	3469	0.29
	2	6.5	282	3626	0.30
	3	7.4	278	3611	0.30
	4	9.7	291	3573	0.31
	P (trend)	–	*0.10*	*0.62*	*0.048*

* Least-square means adjusted for age, ethnicity, BMI, and year of laboratory analysis

ticeable. In malnourished populations, associations of protein and energy intake with IGF-I have been observed and are considered evidence for the nutritional influence on IGF-I levels [10]. Although we did not detect a relation of overall protein intake with the outcome variables, a suggestive inverse relation of fish intake with IGF-I and the IGF-I/IGFBP-3 ratio was observed. This finding is in disagreement with those from the Health Professionals Follow-Up Study, which indicated a positive association [11]. Lower levels of IGF-I and the IGF-I/IGFBP-3 ratio among women with higher fish consumption contrast with the hypothesis that animal protein increases IGF-I, but are consistent with a protective effect of fish against colorectal, breast, and ovarian cancer as indicated by some studies [37].

In accordance with a past study [13], vitamin A intake was positively associated with IGF-I. It is difficult to interpret this finding since high vitamin A intake has been linked to a lower risk for several cancers [37]. Our findings about minerals agree with a previous report of a positive association between mineral intake and IGF-I levels [11]. However, the positive associations between iron and IGF-I and the IGF-I/IGFBP-3 ratio have not been described before. Furthermore, iron intake may be an indicator for animal food consumption and may have served as a surrogate for animal protein intake, in particular, as an indicator for red meat intake. This may point toward an underlying effect of red meat intake on IGF-I. Associations of red meat [37] and of IGF-I [38] with colorectal cancer are well supported by published evidence. A study among meat-eaters, vegetarians, and vegans suggested lower IGF-I levels in vegans than in the other two groups [14]. Our finding of a positive association of IGFBP-3 with zinc intake disagrees with the two reports describing positive relations of zinc with IGF-I [13, 15]. The weak association of calcium with the IGF-I/IGFBP-3 ratio is compatible with the positive association of IGF-I with calcium intake in the NHS [13] and the association of the IGF-I/IGFBP-3 ratio with calcium intake [39].

Strengths of this study were the careful collection of blood samples timed to the menstrual cycle and the exclusion of women taking hormones. Oral contraceptives and menopausal status are known to influence IGF-I levels [29]. Moreover, we included women of different ethnic groups, thereby adding more variation in dietary intake. Interestingly, dietary habits (Table 1) of people in Hawaii tend to be a combination of foods and customs from different cultures, an observation also noted in a large multiethnic cohort [40]. It can be argued that adjustment for ethnicity when examining associations between dietary habits and serum measurements eliminates the effect of diet. However, in our population it is unlikely that ethnicity alone explains the underlying variation in dietary habits given the relatively small size of differences between categories.

A limitation of our study may have been the somewhat selected population since the nutritional intervention studies required low soy intake at baseline. It is possible that women at increased risk of breast cancer due to a family history, reproductive behavior, or high educational achievement preferentially volunteered for our studies. Because nutritional supplement intake was not collected in detail and not included in the analysis, we have almost certainly underestimated the intake of vitamins and minerals. It is difficult to estimate the error introduced by the fact that the women whose laboratory analysis was performed during the second year had relatively higher BMIs and IGF-I levels than women in the first year. As in all dietary analysis, differential underreporting of energy and nutrient intake by ethnicity or body weight may have led to biased results. Because of the exploratory approach and the multiple testing, some of the significant findings are probably due to chance. Finally, unmeasured confounders may also have affected the associations between nutritional variables and IGF-I.

We observed no ethnic differences in IGF-I and IGFBP-3 and relatively weak associations between IGF levels and dietary intakes. As illustrated by the positive association between vitamin A intake and IGF-I, difficulties in interpreting an association between diet and IGF levels in the context of diet and cancer risk need to be addressed. Associations between diet and IGF levels warrant further investigation. Moreover, instead of examining the effect of many single food items on IGF-I levels, it may be advisable to explore the influence of dietary patterns on these outcomes.

Acknowledgments The project was funded in part by a grant from the National Cancer Institute (R01CA80843), by a contract from the Pharmavite Corporation in San Fernando, California, by a Developmental Funds award from the Cancer Center Support grant to the Cancer Research Center of Hawaii (P30CA071789), and by a grant from the American Institute of Cancer Research (02A021). We are very grateful to the participating women and to the study staff for their effort to complete these projects.

References

1. Kaaks R, Lukanova A (2001) Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc 60:91–106
2. Stattin P, Bylund A, Rinaldi S, Biessy C, Dechaud H, Stenman UH, et al. (2000) Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. J Natl Cancer Inst 92: 1910–1917
3. Palmqvist R, Hallmans G, Rinaldi S, Biessy C, Stenling R, Riboli E, et al. (2002) Plasma insulin-like growth factor 1, insulin-like growth factor binding protein 3, and risk of colorectal cancer: a prospective study in northern Sweden. Gut 50:642–646
4. LeRoith D, Roberts CT Jr (2003) The insulin-like growth factor system and cancer. Cancer Lett 195:127–137
5. Pollak M (2000) Insulin-like growth factor physiology and cancer risk. Eur J Cancer 36:1224–1228
6. Yu H, Rohan T (2000) Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst 92:1472–1489
7. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, et al. (1998) Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 351:1393–1396
8. Toniolo P, Bruning PF, Akhmedkhanov A, Bonfrer JM, Koenig KL, Lukanova A, et al. (2000) Serum insulin-like growth factor-I and breast cancer. Int J Cancer 88:828–832
9. DeLellis K, Ingles S, Kolonel L, McKean-Cowdin R, Henderson B, Stanczyk F, et al. (2003) IGF1 genotype, mean plasma level and breast cancer risk in the Hawaii/Los Angeles multiethnic cohort. Br J Cancer 88:277–282
10. Thissen JP, Ketelslegers JM, Underwood LE (1994) Nutritional regulation of the insulin-like growth factors. Endocr Rev 15:80–101
11. Giovannucci E, Pollak M, Liu Y, Platz EA, Majeed N, Rimm EB, et al. (2003) Nutritional Predictors of Insulin-like Growth Factor I and Their Relationships to Cancer in Men. Cancer Epidemiol Biomarkers Prev 12:84–89
12. Heald AH, Cade JE, Cruickshank JK, Anderson S, White A, Gibson JM (2003) The influence of dietary intake on the insulin-like growth factor (IGF) system across three ethnic groups: a population-based study. Public Health Nutr 6:175–180
13. Holmes MD, Pollak MN, Willett WC, Hankinson SE (2002) Dietary correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. Cancer Epidemiol Biomarkers Prev 11:852–861
14. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ (2002) 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 11:1441–1448
15. Devine A, Rosen C, Mohan S, Baylink D, Prince RL (1998) Effects of zinc and other nutritional factors on insulin-like growth factor I and insulin-like growth factor binding proteins in postmenopausal women. Am J Clin Nutr 68:200–206
16. Kaklamani VG, Linos A, Kaklamani E, Markaki I, Koumantaki Y, Mantzoros CS (1999) 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 17:3291–3298
17. Chang S, Wu X, Yu H, Spitz MR (2002) Plasma concentrations of insulin-like growth factors among healthy adult men and postmenopausal women: associations with body composition, lifestyle, and reproductive factors. Cancer Epidemiol Biomarkers Prev 11: 758–766
18. Nagata C, Shimizu H, Takami R, Hayashi M, Takeda N, Yasuda K (2003) Dietary soy and fats in relation to serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels in premenopausal Japanese women. Nutr Cancer 45:185–189
19. Baibas N, Bamia C, Vassilopoulou E, Sdrolias J, Trichopoulou A, Trichopoulos D (2003) Dietary and lifestyle factors in relation to plasma insulin-like growth factor I in a general population sample. Eur J Cancer Prev 12:229–234
20. Maskarinec G, Robbins C, Riola B, Kane-Sample L, Franke A, Murphy S (2003) Three measures show high compliance in soy intervention among premenopausal women. J Am Diet Assoc 103:861–866
21. Maskarinec G, Williams AE, Stanczyk FZ, Stanczyk FZ, Franke AA (2002) A randomized isoflavone intervention among premenopausal women. Cancer Epidemiol Biomarkers Prev 11:195–201
22. Stram DO, Hankin JH, Wilkens LR, Henderson B, Kolonel LN (2000) Calibration of the dietary questionnaire for a multiethnic cohort in Hawaii and Los Angeles. Am J Epidemiol 151:358–370
23. Hawaii Department of Business and Economic Development (2002) 2001 State of Hawaii data book: a statistical abstract. http://www.hawaii.gov/dbedt/db01/index.html. Accessed on 9-19-2002
24. United States Department of Agriculture (2002) USDA Nutrient Database for Standard Reference Release 15. http://www.nal.usda.gov/fnic/foodcomp/Data/SR15/sr15. html. Riverdale, United States Department of Agriculture. Accessed on 9-20-0002
25. United States Department of Agriculture (1992) The Food Guide Pyramid. Home and Garden Bulletin No. 252. Washington, D.C., US Government Printing Office
26. Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Dechaud H, et al. (2000) Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. J Natl Cancer Inst 92: 1592–1600
27. Maskarinec G, Williams AE, Kaaks R (2003) A cross-sectional investigation of breast density and insulin-like growth factor I. Int J Cancer 107: 991–996
28. SAS OnlineDoc, Version 8 (2002) SAS Institute Inc., Cary, NC
29. Jernstrom H, Deal C, Wilkin F, Chu W, Tao Y, Majeed N, et al. (2001) Genetic and nongenetic factors associated with variation of plasma levels of insulin-like growth factor-I and insulin-like growth factor-binding protein-3 in healthy premenopausal women. Cancer Epidemiol Biomarkers Prev 10:377–384
30. Lukanova A, Sodergard R, Stattin P, Palmqvist R, Lundin E, Rinaldi S, et al. (2002) Non-linear relationship of insulin-like growth factor (IGF)-I and IGF-I/IGF-binding protein-3 ratio with indices of adiposity and plasma insulin concentrations. Cancer Causes Control 13:509–516
31. Lukanova A, Toniolo P, Akhmedkhanov A, Hunt K, Rinaldi S, Zeleniuch-Jacquotte A, et al. (2001) A cross-sectional study of IGF-I determinants in women. Eur J Cancer Prev 10:443–452
32. Voskuil DW, Buenode Mesquita HB, Kaaks R, Van Noord PA, Rinaldi S, Riboli E, et al. (2001) Determinants of circulating insulin-like growth factor (IGF)-I and IGF binding proteins 1–3 in premenopausal women: physical activity and anthropometry (Netherlands). Cancer Causes Control 12:951–958
33. Willett W (1998) Nutritional epidemiology. Oxford University Press, New York
34. Le Marchand L, Hankin JH, Wilkens LR, Pierce LM, Franke A, Kolonel LN, et al. (2001) Combined effects of well-done red meat, smoking, and rapid N-acetyltransferase 2 and CYP1A2 phenotypes in increasing colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 10:1259–1266

35. US Department of Agriculture, US Department of Health and Human Services (1995) Nutrition and your health: Dietary Guidelines for Americans. Consumer Information Center, Pueblo, CO
36. Cruickshank JK, Heald AH, Anderson S, Cade JE, Sampayo J, Riste LK, et al. (2001) Epidemiology of the insulin-like growth factor system in three ethnic groups. Am J Epidemiol 154:504–513
37. World Cancer Research Fund (1997) Food, nutrition and the prevention of cancer: a global perspective. American Institute for Cancer Research, Washington, D.C.
38. Giovannucci E (2001) Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 131: 3109S–3120S
39. Gunnell D, Oliver SE, Peters TJ, Donovan JL, Persad R, Maynard M, et al. (2003) 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 88:1682–1686
40. Kolonel LN, Henderson BE, Hankin JH, Nomura AMY, Wilkens LR, Pike MC, et al. (2000) A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 151: 346–357