The Association between Diet and Serum Concentrations of IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 in the European Prospective Investigation into Cancer and Nutrition


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Abstract

Circulating concentrations of insulin-like growth factor I (IGF-I) and IGF binding proteins (IGFBP) have been associated with the risk of several types of cancer. Dietary correlates of IGF-I and IGFBPs are not yet well established. The objective of this study was to assess the association between dietary intake and serum concentrations of IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 in a cross-sectional analysis of 4,731 men and women taking part in the European Prospective Investigation into Cancer and Nutrition. Diet was assessed using country-specific validated dietary questionnaires. Serum concentrations of IGF-I, IGFBP-1, IGFBP-2 and IGFBP-3 were measured, and the associations between diet and IGF-I and IGFBPs were assessed using multiple linear regression adjusting for sex, age, body mass index, smoking status, and alcohol and energy intake. Each 1 SD increment increase in total and dairy protein and calcium intake was associated with an increase in IGF-I concentration of 2.5%, 2.4%, and 3.3%, respectively (P for trend < 0.001 for all) and a decrease in IGFBP-2 of 3.5%, 3.5%, and 5.4% (P for trend < 0.001 for all), respectively. There were no significant associations between the intake of protein or calcium from nondairy sources and IGF-I. The results from this large cross-sectional analysis show that either the intake of dairy protein or calcium is an important dietary determinant of IGF-I and IGFBP-2 concentrations; however, we suggest that it is more likely to be protein from dairy products.
Introduction

Insulin-like growth factor I (IGF-I) is a polypeptide hormone that has been implicated in the pathophysiology of many chronic diseases due to its roles in the differentiation and proliferation of cells and its anti-apoptotic properties (1, 2). In the circulation, IGF-I is mostly bound to six IGF binding proteins (IGFBP-1 to IGFBP-6), which serve to regulate the bioavailability of IGF-I (3). There is evidence from several large prospective studies that circulating concentrations of IGF-I and IGFBPs are associated with the risk of prostate (4), breast, colon, and rectum cancers (5, 6). These cancers account for a substantial proportion of cancer incidence worldwide (7); therefore, understanding the determinants of IGF concentrations may make an important contribution to alleviating the burden of cancer (8).

A number of factors are associated with IGF concentrations and results from several observational studies have shown that IGF concentrations differ by age, genotype, height, weight, and body mass index (BMI; refs. 9, 10). Apart from body weight, the majority of determinants of IGF concentrations identified thus far are nonmodifiable. There has been considerable effort to identify whether more modifiable factors such as diet are associated with IGF concentrations, but evidence from cross-sectional analyses is not consistent (11-15). Results from several studies suggest that the source of protein is an important determinant of serum IGF-I, with three studies demonstrating a positive association between the intake of animal protein and serum IGF-I concentrations (11, 12, 16). There is also evidence to suggest that intake of calcium is positively related to concentrations of IGF-I (15, 17, 18).

The majority of studies evaluating the association between diet and IGF levels have focused on IGF-I and the main binding protein IGFBP-3. There are few studies that have reported on the relation between diet and concentrations of IGFBP-1 and IGFBP-2, binding proteins that acutely regulate IGF-I bioavailability and may also be influenced by diet (19). The association between intake of some foods and nutrients and IGF-I and IGFBP-3 has been described previously among the controls in the case-control study of breast cancer nested within the European Prospective Investigation into Cancer and Nutrition (EPIC; ref. 20) and in several other EPIC cohorts (16, 21-23). Here, we extend the findings of Norat et al. (20) in a larger population of the cohort and include measurements of IGFBP-1 and IGFBP-2.

The objective of this study was to investigate the association between intake of the major macronutrients with a focus on the sources of protein, as well as the intake of calcium, and serum concentrations of IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 in controls from a series of nested-case control studies of men and women taking part in EPIC.

Materials and Methods

Study Cohort. EPIC is a multicenter prospective study designed to assess the associations between diet, lifestyle, and environmental factors and cancer. More details of the recruitment and study design have been published previously (24). The study population used in this analysis included 1,142 men and 3,589 men and women recruited from nine European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, and the United Kingdom. The cohorts in Sweden were not included in the present analysis. Participants were controls in the nested case-control analyses of various biomarkers and cancer risk and more detailed descriptions of the nested case-control studies for breast, colorectal, endometrial, ovarian, and prostate cancers have been published elsewhere (25-29). Briefly, controls were selected from the entire cohort of men and women without cancer (except nonmelanoma skin cancer) at the time of diagnosis of the index case. The matching criteria varied between studies; however, sex, age (± 6 months), study center, time of day of blood collection, and time between last consumption of food or drink and blood collection (<3, 3-6, >6 h) were used as matching criteria for all studies.

The men and women included in this analysis were recruited from the population residing in defined geographic areas in each of the nine countries. Participants were from the general population in most centers, with some exceptions; women members of a health insurance scheme for state school employees in France, women attending breast cancer screening in Florence (Italy) and Utrecht (the Netherlands), blood donors in Ragusa (Italy) and in the Spanish centers, blood donors and staff at the National Health Service in Turin (Italy), and participants in the Oxford (United Kingdom) “health conscious” subcohort were recruited throughout the entire United Kingdom to enroll a large number of vegetarians and vegans. Eligible participants were invited to take part in the study, and those who accepted provided written informed consent and filled out questionnaires pertaining to their diet, lifestyle (including information on their lifetime history of consumption of tobacco and alcoholic beverages), and medical history. Study participants were also invited to their local center where a blood sample and anthropometric measurements were collected. Height and weight were measured according to standard techniques, except for participants recruited in the Oxford and the French centers where height and weight were self-reported but measured in a subgroup of participants. Quetelet’s BMI [weight (kg)/height (m)^2] was calculated. The ethnicity of almost all participants was white European. Approval for this study was obtained from the ethical review boards of the IARC and from all local institutions where participants had been recruited.

Diet and Lifestyle Questionnaires. Dietary intake during the year before recruitment was measured by country-specific validated dietary questionnaires that were designed to capture local dietary patterns. More details and information on the validation of the food questionnaires has been published elsewhere (24, 30). Estimated intakes were calculated by multiplying the nutrient content of each food of a specific portion size or quantity (g) by the frequency of consumption as stated on the food questionnaire using country-specific national food tables. In this analysis, animal protein refers to protein from meat and meat products, dairy products, fish and shellfish, and eggs and egg products. Protein
from meat and meat products includes protein from red meat, poultry, and processed meats; protein from dairy products includes protein from milk, milk beverages, yogurt, and cheese; and protein from fish and shellfish includes protein from fish, crustaceans, mollusks, and fish products. Plant protein was calculated as total protein minus animal protein. The 149 participants from Greece were not included in the analyses of protein from various food sources because there was limited information for these particular food items in the central database. Intake of supplemental calcium was not included in this analysis.

**Laboratory Analysis.** Blood samples were drawn from participants into tubes containing no anticoagulant. Participants were not required to fast but the time since last consumption of food or beverages was recorded. All samples except for those from the Oxford center were stored at 5°C to 10°C and protected from light from the time of collection through their transfer to local laboratories in each of the recruitment centers, where they were further processed and separated into aliquots. For study subjects recruited through the Oxford center, blood samples were collected by a network of general practitioners in the United Kingdom and transported to a central laboratory in Norfolk by mail; they were protected from light but were exposed to ambient temperature. For participants in all centers except Denmark, 0.5-mL serum aliquots were placed in plastic straws, which were heat sealed and stored in liquid nitrogen (−196°C). In Denmark, 1-mL aliquots of serum were placed into Nunc tubes and stored in the vapor phase of liquid nitrogen containers (−150°C).

All hormone assays were done at the Laboratory of Hormones and Cancer at the IARC. Serum concentrations of IGF-I and IGFBP-3 were measured by ELISA, IGFBP-I was measured by immunoradiometric assay, and IGFBP-2 was measured byRIA, all from Diagnostic System Laboratories. The IGF-I assays included an acid-ethanol precipitation step to separate IGF-I from the IGFBP binding proteins. The serum samples had not undergone any freeze-thaw cycles. The mean intrabatch coefficients of variation for IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 ranged from 2.5% to 6.2%, 4.6% to 5.1%, 4.7% to 5.2%, and 3.7% to 7.2%, respectively, and the interbatch coefficients of variation were 12.2% to 16.2%, 19.5% to 23.7%, and 3.7% to 7.2%, respectively, and the interbatch coefficients of variation were 12.2% to 16.2%, 19.5% to 23.7%, and 3.7% to 7.2%, respectively.

**Statistical Analysis.** Serum concentrations of IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 were log transformed to

| Table 1. Characteristics of men and women with IGF measurements in the EPIC study |
|-----------------------------------|----------------|----------------|
|                                   | Men (n = 1,142) | Women (n = 3,589) |
| Age at recruitment (y)*           | 59.9 ± 6.5     | 55.7 ± 8.4     |
| Height (cm)                       | 173.0 ± 6.9    | 160.6 ± 6.8    |
| Weight (kg)                       | 81.0 ± 11.8    | 67.2 ± 11.7    |
| BMI (kg/m²)                       | 27.0 ± 3.5     | 26.1 ± 4.6     |
| Alcohol intake (g/d)              | 23.7 ± 26.8    | 7.8 ± 11.3     |
| Smoking status†                   |                |                |
| Never                             | 321 (28.1)     | 2100 (58.5)    |
| Former                            | 493 (43.2)     | 851 (23.7)     |
| Current                           | 317 (27.8)     | 614 (17.1)     |
| Unknown                           | 11 (1.0)       | 24 (0.7)       |
| Dietary intake‡                   |                |                |
| Energy (kJ)³                       | 9,876 ± 2,827  | 8,215 ± 2,410  |
| Protein intake                    | 16.4 ± 2.9     | 17.2 ± 3.0     |
| Plant protein                     | 6.0 ± 1.4      | 6.3 ± 1.3      |
| Animal protein                    | 10.5 ± 3.3     | 10.9 ± 3.3     |
| Meat protein                      | 5.5 ± 2.3      | 4.9 ± 2.6      |
| Dairy protein                     | 3.2 ± 1.8      | 4.3 ± 2.1      |
| Fish and shellfish protein        | 1.3 ± 1.1      | 1.3 ± 1.2      |
| Egg and egg products protein      | 0.4 ± 0.4      | 0.5 ± 0.4      |
| Total fat                         | 33.8 ± 5.9     | 35.1 ± 6.0     |
| Saturated fat                     | 12.6 ± 3.2     | 13.1 ± 3.1     |
| Monounsaturated fat               | 12.6 ± 3.2     | 13.5 ± 4.0     |
| Polyunsaturated fat               | 5.8 ± 2.0      | 5.9 ± 2.2      |
| Carbohydrate                      | 40.3 ± 7.0     | 42.5 ± 6.5     |
| Starch                            | 20.9 ± 6.4     | 21.4 ± 6.1     |
| Sugars                            | 17.4 ± 6.3     | 20.3 ± 6.3     |
| Fiber (g)                         | 24.2 ± 8.5     | 22.7 ± 7.7     |
| Calcium (mg)                      | 984 ± 417      | 1,006 ± 425    |

| Serum IGF concentrations (nmol/L)³*|                |                |
| IGF-I                             | 24.0 (23.5-24.6)| 28.0 (27.6-28.3)| 26.9 (26.5-27.2)|
| IGFBP-1                           | 0.30 (0.27-0.32)| 0.31 (0.48-0.34)| 0.42 (0.40-0.44)|
| IGFBP-2                           | 10.6 (10.0-11.2)| 11.9 (11.4-12.4)| 11.4 (11.0-11.8)|
| IGFBP-3                           | 135 (133-137)   | 129 (127-130)   | 130 (129-132)   |

*Values are mean ± SD.
†Values are n; percentage in parentheses.
‡Not all participants have a value for each dietary measurement: energy, n = 4,723; protein, n = 4,574; fat, n = 4,723; carbohydrate, n = 4,574; fiber, n = 4,723.
§All dietary variables are reported as a percent of total energy unless stated otherwise.
⁴Not all participants have a value for each IGF measurement: IGF-I, n = 4,201; IGFBP-1, n = 1,598; IGFBP-2, n = 1,575, and IGFBP-3, n = 4,117.
⁵Values are geometric means (95% confidence intervals).

approximate normal distributions. Analyses of the associations of dietary intake and covariates with serum IGF concentrations were conducted using multiple linear regression. To control for any effect of the different blood collection procedures ("blood protocol") between centers and countries and the batch of the IGF assay on concentrations of IGF, regression models were fitted that adjusted for the combination of these variables. These models were used to calculate concentrations of IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 adjusted for blood protocol and batch and these "corrected" values were used to investigate the association between IGF concentrations and diet.

For the associations between diet and IGF concentrations, adjustments were made for sex, age at blood collection (<50, 50-54, 55-59, 60-64, or >65 years), sex-specific fifths of BMI (cut points for men: 24.2, 25.9, 27.6, and 29.6 kg/m² and women: 22.3, 24.4, 26.5, and 29.4 kg/m²), smoking status (never, former, current, unknown), alcohol (men: <8, 8-15, 16-39, and >40 g/d and women: <1, 1-7, 8-15, and >16 g/d), and energy intake (MJ/d; continuous). Due to the strong influence of fasting on concentrations of IGFBP-1 (19), for all associations between dietary intake and IGFBP-1 a further adjustment for time since last meal.

Table 2. Macronutrient intake and serum IGFs among men and women in the EPIC study

<table>
<thead>
<tr>
<th>Macronutrient (% total energy)</th>
<th>SD increment</th>
<th>Men Women</th>
<th>IGF-1</th>
<th>IGF-I (Mean (95% CI) change in serum IGFBP-1</th>
<th>IGF-I</th>
<th>IGFBP-2</th>
<th>IGFBP-2</th>
<th>IGFBP-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein intake</td>
<td>2.9</td>
<td>3.0</td>
<td>2.45 (1.42 to 3.48) 1</td>
<td>1.08 (−2.87 to 5.20) -3.52 (−6.24 to −0.73) 1</td>
<td>0.32 (−0.32 to 0.96)</td>
<td></td>
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</tr>
<tr>
<td>Plant protein intake</td>
<td>1.4</td>
<td>1.3</td>
<td>−0.16 (−1.16 to 0.85)</td>
<td>4.09 (−0.38 to 8.76)</td>
<td>3.04 (−0.12 to 6.30)</td>
<td>0.14 (−0.50 to 0.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal protein intake</td>
<td>3.3</td>
<td>3.3</td>
<td>2.33 (1.31 to 3.37) 1</td>
<td>0.04 (−3.89 to 4.14)</td>
<td>−3.73 (−6.45 to −0.93) 1</td>
<td>0.24 (−0.40 to 0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat and meat products</td>
<td>2.5</td>
<td>2.6</td>
<td>0.89 (−0.11 to 1.90)</td>
<td>0.93 (−3.21 to 5.26)</td>
<td>−1.86 (−4.77 to 1.13) 1</td>
<td>0.13 (−0.51 to 0.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dairy protein intake</td>
<td>1.8</td>
<td>2.1</td>
<td>2.37 (1.35 to 3.39) 1</td>
<td>−0.45 (−4.43 to 3.69)</td>
<td>−3.45 (−6.20 to −0.61) 1</td>
<td>0.42 (−0.21 to 0.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish and shellfish</td>
<td>1.1</td>
<td>1.2</td>
<td>0.40 (−0.59 to 1.39)</td>
<td>−0.93 (−4.78 to 3.08)</td>
<td>−2.46 (−5.19 to 0.34) 1</td>
<td>0.00 (−0.63 to 0.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eggs and egg products</td>
<td>0.4</td>
<td>0.4</td>
<td>0.14 (−0.84 to 1.14)</td>
<td>0.08 (−3.86 to 4.18)</td>
<td>0.53 (−2.31 to 3.45)</td>
<td>−0.42 (−1.05 to 0.21)</td>
<td></td>
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</tr>
</tbody>
</table>

NOTE: IGF concentrations were corrected for the combination of batch and blood protocol, and adjusted for sex, age, sex-specific fifths of BMI, smoking status, and alcohol and energy intake. Concentrations of IGFBP-1 were further adjusted for time since last meal.

Abbreviation: 95% CI, 95% confidence interval.

1 P < 0.001.
1 P < 0.05.
1 P < 0.01.

Results

Concentrations of IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 were available for 4,201, 1,598, 1,575, and 4,117 participants, respectively. Values for at least one IGF measurement were available for 4,731 participants. Results in Table 1 show the lifestyle characteristics, dietary intake, and mean concentrations of serum IGF-I and IGFBPs for men and women separately. Men were, on average, 60 years old and women were 56 years old and men had a higher BMI than women. Compared with men, a higher proportion of women had never smoked (59% versus 28%) and a lower proportion of women were current smokers (17% versus 28%). Women had higher concentrations of IGF-I, IGFBP-1, and IGFBP-2 compared with men, whereas IGFBP-3 was lower.

The percent change in the concentrations of IGF-I and IGFBPs for a sex-specific 1 SD increment increase in the specific dietary nutrients are shown in Table 2. After adjusting for sex, age, BMI, smoking, and alcohol and...
total energy intake, the intake of protein was positively associated with IGF-I concentrations ($P < 0.001$) and inversely associated with IGFBP-2 concentrations ($P < 0.001$). There were also similar associations for the intake of animal protein and IGF-I and IGFBP-2 ($P < 0.001$ for both) but not for the intake of protein from plant sources. When animal protein was broken down further, the results showed no significant associations between the intakes of protein from meat and meat products, fish and shellfish and egg and egg products, and IGF-I or IGFBP-2 concentrations. The intake of dairy protein was, however, highly significantly positively associated with concentrations of IGF-I and inversely associated with concentrations of IGFBP-2. Each 1 SD increase in the intake of dairy protein was associated with an increase in IGF-I of 2.4% ($P < 0.001$) and a decrease in IGFBP-2 of 3.5% ($P < 0.001$). There was also a highly significant positive relation between calcium intake and concentrations of serum IGF-I and IGFBP-3 and an inverse relation with IGFBP-2. Each 1 SD increment increase in calcium corresponded to an increase in IGF-I of 3.3% ($P < 0.001$) and IGFBP-3 of 0.8% ($P < 0.05$) and a decrease in IGFBP-2 of 5.4% ($P < 0.01$).

Several other dietary variables were also significantly associated to IGF-I and the IGFBPs (Table 2). The intake of monounsaturated fat was positively related to IGFBP-2 ($P < 0.05$); however, there were no other statistically significant associations between the intake of total, saturated, and polyunsaturated fat and concentrations of IGF-I or IGFBPs. The intake of starch was positively associated with concentrations of IGFBP-2; a SD increment increase in starch corresponded to an increase in IGFBP-2 of 3.8% ($P < 0.05$). Each SD increase in the percent of energy from sugar was associated with a decrease in IGFBP-1 concentrations of 5.0% ($P < 0.05$). There was a positive association between the intake of fiber and IGF-I concentrations; each 1 SD increase in intake was associated with an increase in IGF-I of 1.9% ($P < 0.01$).

Figure 1 and 2 show the association between the fifths of total and dairy protein intake (% of total energy) and serum IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 concentrations. There was a significant positive trend in IGF-I concentrations across the fifths of total and dairy protein intake; the differences in IGF-I between the lowest and highest fifths were both 2.0 nmol/L. The overall test for trend for the inverse association between the intake of total and dairy protein and IGFBP-2 was significant and a lower IGFBP-2 concentration was clearly evident for participants in the 4th and 5th fifth of protein intake.

There was no significant association between calcium from nondairy sources and concentrations of IGF-I ($P = 0.128$) and neither was there evidence of significant heterogeneity of the trends for serum concentrations of IGF-I with protein, dairy protein, or calcium between men and women. The association between dietary intake and the ratio of IGF-I/IGFBP-3 was assessed but because there was little association between any of the dietary variables and IGFBP-3 concentrations, associations between dietary factors and this ratio were similar to those for IGF-I (results not shown).
Discussion

To date, this is the largest study to assess the associations between diet, IGF-I, and several of the IGFBPs. In this cross-sectional analysis of the EPIC study, we found that several components of diet were significantly related to serum concentrations of IGF-I and IGFBPs. Notably, higher intakes of total and dairy protein and calcium were highly significantly associated with elevated concentrations of IGF-I and lower concentrations of IGFBP-2.

The association between the intake of dairy protein and IGF-I concentrations has not been assessed previously; however, a positive association between the consumption of dairy products or milk and IGF-I concentrations has been reported in several cross-sectional analyses (11, 12, 17, 18, 31, 32), including a subgroup of women from the current study population (20). Moreover, IGF-I concentrations have been found to be significantly lower in vegans compared with lacto-ovo vegetarians and omnivores participating in the EPIC-Oxford cohort (16, 21). Results from other analyses have also shown a positive association between calcium intake and concentrations of IGF-I (14, 17, 32). In the Nurses’ Health Study, Holmes et al. (11) found a positive relation between IGF-I concentrations and calcium from foods but there was little association if calcium from supplements was included. Results from other analyses have also shown a positive association between calcium intake and concentrations of IGF-I (14, 17, 32). In the Nurses’ Health Study, Holmes et al. (11) found a positive relation between IGF-I concentrations and calcium from foods but there was little association if calcium from supplements was included. The most compelling evidence to support a role for dairy intake and elevated IGF-I concentrations lies with findings from intervention studies that show an increase in IGF-I in response to a higher intake of milk and dairy products in both younger (33-35) and older (36-38) participants.

There are several mechanisms through which the intake of protein from dairy products or calcium may increase serum concentrations of IGF-I. The presence of specific essential amino acids in dairy protein at particular concentrations may influence IGF-I concentrations either by up-regulating IGF-I gene expression (39) or reducing the clearance of IGF-I from the circulation (40). Alternatively, it could be some other component in cow’s milk such as IGF-I or growth hormone that is driving the positive association between IGF-I and protein from dairy products. Evidence from earlier animal models indicated that IGF-I present in cow’s milk were not well absorbed; however, more recent findings have shown small but biologically significant increases in circulating concentrations of labeled IGF-I when animals were fed 125I-labeled IGF-I (41). There is also evidence to support a role for calcium in elevating IGF-I concentrations with results from an in vitro study showing that increased exposure to calcium stimulated the production of IGF-I (42).

Even given that dairy foods rich in protein also tend to be high in calcium and there is a strong correlation between these two variables, it is difficult to disentangle the positive association between dairy protein and IGF-I from calcium and IGF-I. For this reason, we could not adjust the association between dairy protein and IGF-I concentrations for the intake of calcium and vice versa. The most likely explanation for these associations is that
it is some component in dairy products that is responsible for increasing serum concentrations of IGF-I because we showed no evidence for an association between the intake of protein or calcium from nondairy sources and IGF-I. Because there is only limited evidence to support an increase in IGF-I concentrations with calcium supplementation alone (35, 43, 44), we suggest that our finding of a positive association between calcium and IGF-I is unlikely to be due to calcium intake per se and could instead be due to another factor in dairy products, namely protein. Notwithstanding the positive association between dairy protein or calcium intake and IGF-I concentrations, and plausible biological mechanisms, the effect of reducing the consumption of milk or dairy, or calcium intake on concentrations of serum IGF-I and IGFBP-3 remains untested.

We also report an inverse association between the intake of total and dairy protein and serum concentrations of IGFBP-2. Results from Allen et al. (16) are also consistent with an inverse association between animal protein intake and IGFBP-2. One of the proposed roles of the IGFBPs is to bind to and modulate the activity of IGF-I (10, 45). The physiological role of IGFBP-2 is not yet well understood. IGFBP-2 has a much higher binding affinity for IGF-II compared with IGF-I; however, results from in vitro studies have suggested that IGFBP-2 may be involved in inhibiting the growth-stimulating properties of IGF-I (3). The most abundant IGF binding protein in serum is IGFBP-3, which binds ~90% of all circulating IGF-I (3). We found very little evidence for an association between any of the dietary variables and IGFBP-3 concentrations.

Our results showed an inverse relation between the intake of sugar and concentrations of IGFBP-1, which is consistent with results from one other study also reporting this association (46). Despite being present in smaller concentrations than the other binding proteins, some evidence indicates that IGFBP-1 has an influence on the concentrations of biologically active IGF-I and is inversely related to concentrations of free IGF-I (1, 10). The major determinant of circulating concentrations of IGFBP-1 is insulin, as the hepatic synthesis of IGFBP-1 is inversely related to concentrations of free IGF-I (1, 10). Dietary fiber and IGF-I concentrations is being driven by circulating concentrations of insulin.

We found no evidence for an association between total, saturated, and polyunsaturated fat intake and concentrations of serum IGF-I and IGFBP-3; however, we report a positive association between monounsaturated fat intake and IGFBP-2. The majority of other studies have reported a null association between the intake of total fat, the subtypes of fat, and IGF concentrations (11-13, 15, 17, 48). Similarly, our finding of a positive association between dietary fiber intake and IGF-I concentrations differs from those that suggest little or no association between dietary fiber and IGF-I (11, 15, 22). Additionally, results from an intervention study showed no effect of a low-fat, high-fiber diet on IGF-I concentrations of healthy weight stable women (49). Because there were a large number of comparisons made in this study, it is possible that the associations we found between monounsaturated fat and serum IGFBP-2 and dietary fiber and IGF-I concentrations were due to chance.

There are several limitations to our study. The assessment of macronutrient intake using dietary questionnaires will have resulted in a degree of misclassification of dietary intake (50). Moreover, different dietary questionnaires and food composition tables specific to the dietary pattern of each country were used in this analysis. It is likely, however, that any misclassification according to dietary intake was nondifferential, which would have attenuated the true association between diet and serum IGF concentrations. Given the cross-sectional design of our study, it is not possible to conclude whether the associations we observe between specific dietary components and IGF is causal.

In summary, the results from this large cross-sectional analysis of dietary factors and the concentrations of IGF-I and IGFBPs have shown a number of potentially important associations. One of the key findings was that higher intakes of dairy protein and calcium were positively associated with IGF-I concentrations and inversely related to IGFBP-2. These associations may be important to help understand the etiology of cancers associated with diet as a potential means of modifying the risk of certain cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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