Long-term low-protein, low-calorie diet and endurance exercise modulate metabolic factors associated with cancer risk

Luigi Fontana, Samuel Klein, and John O Holloszy

ABSTRACT

Background: Western diets, obesity, and sedentary lifestyles are associated with increased cancer risk. The mechanisms responsible for this increased risk, however, are not clear.

Objective: We hypothesized that long-term low protein, low calorie intake and endurance exercise are associated with low concentrations of plasma growth factors and hormones that are linked to an increased risk of cancer.

Design: Plasma growth factors and hormones were evaluated in 21 sedentary subjects, who had been eating a low-protein, low-calorie diet for 4.4 ± 2.8 y (x ± SD age: 53.0 ± 11 y); 21 endurance runners matched by body mass index (BMI; in kg/m^2); and 21 age- and sex-matched sedentary subjects eating Western diets.

Results: BMI was lower in the low-protein, low-calorie diet (21.3 ± 3.1) and runner (21.6 ± 1.6) groups than in the Western diet (26.5 ± 2.7; P < 0.005) group. Plasma concentrations of insulin, free sex hormones, leptin, and C-reactive protein were lower and sex hormone–binding globulin was higher in the low-protein, low-calorie diet and runner groups than in the sedentary Western diet group (all P < 0.05). Plasma insulin-like growth factor I (IGF-I) and the concentration ratio of IGF-I to IGF binding protein 3 were lower in the low-protein, low-calorie diet group (139 ± 37 ng/mL and 0.033 ± 0.01, respectively) than in the runner (177 ± 37 ng/mL and 0.044 ± 0.01, respectively) and sedentary Western (201 ± 42 ng/mL and 0.046 ± 0.01, respectively) diet groups (P < 0.005).

Conclusions: Exercise training, decreased adiposity, and long-term consumption of a low-protein, low-calorie diet are associated with low plasma growth factors and hormones that are linked to an increased risk of cancer. Low protein intake may have additional protective effects because it is associated with a decrease in circulating IGF-I independent of body fat mass.


KEY WORDS Protein restriction, calorie restriction, cancer prevention, growth factors, bioavailable sex hormones, inflammation, insulin-like growth factor I, IGF-I

INTRODUCTION

Data from epidemiologic studies suggest that the modern lifestyle of industrialized countries, which includes high calorie and protein consumption, low physical activity, and greater adiposity, increases the risk of developing cancer (1, 2). It has been hypothesized that the mechanisms responsible for this relation involve an increase in circulating concentrations of growth factors, anabolic hormones, and inflammatory cytokines and a decrease in circulating concentrations of sex hormone–binding globulin (SHBG) (3). Greater adiposity due to excessive energy intake and minimal physical activity promotes hormonal, metabolic, and inflammatory alterations that modulate carcinogenesis (1, 3). These factors include chronic hyperinsulinemia, elevated plasma insulin-like growth factor I (IGF-I) concentrations, higher bioavailability of steroid sex hormones, and systemic inflammation (1, 3, 4). However, the effect of long-term lifestyle modifications on the factors linked to an increased risk of cancer has not been sufficiently investigated.

It is difficult to evaluate the effect of major long-term lifestyle modifications on cancer risk by using the gold standard of randomized controlled trials (5), because of poor long-term adherence to changes in dietary intake and physical activity (6). However, studying specific populations who have successfully made long-term lifestyle modifications could provide important insights into the potential efficacy of diet and endurance exercise on tumororigenesis. We identified 2 groups of middle-aged men and women who had made long-term changes in either dietary intake or physical activity: one group had decreased their calorie and protein intakes by eating uncooked and unprocessed plant-based foods, and the other group had increased their physical activity by participating in regular endurance exercise.

The purpose of the present study was to evaluate the relations between calorie and protein intakes, physical activity, and adiposity on the plasma growth factors and hormones linked to an increased risk of cancer. Circulating concentrations of insulin, IGF-I, steroid sex hormones, SHBG, and C-reactive protein (CRP) were measured in men and women consuming a low-protein, low-calorie diet; in endurance runners matched by body mass index (BMI; in kg/m^2); and in nonobese sedentary subjects consuming typical Western diets. We hypothesized that lower...
protein and calorie intakes, greater physical activity, and lower adiposity would be associated with beneficial effects on the plasma growth factors and hormones linked to an increased risk of cancer.

**SUBJECTS AND METHODS**

**Subjects**

Three groups of subjects (21 subjects per group consisting of 13 men and 8 women) participated in this study. Group 1 subjects were recruited by contacting the St Louis Vegetarian Society and an online raw food magazine (Raw Food News; Internet: www.rawfoodsnsmagazine.com). These subjects had been consuming a low-protein, low-calorie diet composed of raw plant-derived foods for ≥2 y (x ± SD: 4.4 ± 2.8 y; range: 2–10 y). Group 2 subjects were recruited by contacting local running clubs. These subjects participated in regular endurance running exercise and had been running an average of 48 miles/wk (range: 20–90 mi/wk) for an average of 21 y (range: 5–35 y). Endurance runners were matched with the low-protein, low-calorie diet group by age, sex, and BMI. Group 3 subjects were recruited through local advertising. These subjects were healthy, nonobese (BMI < 30) subjects eating typical Western diets. They were matched with the low-protein, low-calorie diet group by age, sex, and height. These subjects served as a nonobese sedentary control group.

The characteristics of the study subjects are shown in Table 1. All subjects underwent a comprehensive medical evaluation, including a medical history, physical examination, routine blood tests, and urinalysis. None of the subjects had evidence of chronic disease, including cardiovascular, lung, gastrointestinal, or autoimmune diseases; type 2 diabetes; or cancer, and none smoked tobacco. In addition, no subject was taking hormone replacement therapy or other medications that could have affected the outcome variables. All subjects had been weight stable (ie, <2 kg weight change) for ≥6 mo before the study. The low-protein, low-calorie diet and Western diet subjects were sedentary (regular endurance exercise <1 h/wk). Five women in group 1, 4 in group 2, and 7 in group 3 were postmenopausal. The study was approved by the Human Studies Committee and the General Clinical Research Center Scientific Advisory Committee of Washington University School of Medicine, and all subjects gave informed consent before their participation.

**Study protocol**

**Dietary assessment**

Subjects were instructed by a research dietitian to record all food and beverages consumed, including preparation methods and portion sizes, for 7 consecutive days. Measuring spoon and cup sets and food diaries with a ruler imprinted on the back cover were provided to the participants to assist with portion size determinations. Food records were analyzed by using the NDS-R program (version 4.03_31), which is the Nutrition Data System for research from the Nutrition Coordinating Center at the University of Minnesota (7).

**Assessment of risk factors for cancer**

Subjects were admitted to the outpatient facilities of Washington University School of Medicine General Clinical Research Center in the morning after they had fasted for 12 h overnight. Height was measured without shoes to the nearest 0.1 cm. Body weight was obtained on a balance scale. Total-body fat mass and lean body mass were determined by using dual-energy X-ray absorptiometry (QDR 1000/w; Hologic, Waltham, MA). A venous blood sample was obtained to measure plasma total testosterone and estradiol, SHBG, IGF-I, IGF binding protein 3 (IGFBP-3), dehydroepiandrosterone sulfate (DHEAS), insulin, C-peptide, leptin, and CRP concentrations.

### Table 1

<table>
<thead>
<tr>
<th>Total fiber (g/d)</th>
<th>Low-protein, low-calorie diet group (n = 18)</th>
<th>Endurance runners (n = 20)</th>
<th>Western diet group (n = 18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.2 ± 0.365</td>
<td>5.9 ± 2.5</td>
<td>6.9 ± 3.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>0.8 ± 0.965</td>
<td>3.7 ± 2.5</td>
<td>4.5 ± 1.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Carbohydrate (% of energy)</td>
<td>47.8 ± 6.55</td>
<td>54.2 ± 9.5</td>
<td>48.8 ± 6.0</td>
<td>0.01</td>
</tr>
</tbody>
</table>

1 All values are x ± SD. SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.
2 Nonsignificant interaction between sex and group in 2-factor ANOVA; therefore, the sexes were analyzed together.
3 Significantly different from endurance runners, P < 0.05 (post hoc Tukey’s test).
4 Significantly different from endurance runners, P < 0.05 (post hoc Games-Howell’s test).
5 Significantly different from Western diet group, P < 0.01 (post hoc Games-Howell’s test).
6 Significantly different from Western diet group, P < 0.006 (post hoc Tukey’s test).
7 Significant interaction between sex and group (P < 0.05) in 2-factor ANOVA; therefore, the sexes were analyzed separately.
This index is highly correlated \((r = 0.73, P = 0.0001)\) with the rate of whole-body glucose disposal assessed during a euglycemic-hyperinsulinemic clamp procedure.

**Statistical methods**

Data are expressed as means ± SDs. Comparisons of variables between groups were made by using analysis of variance (ANOVA). Data for men and women were pooled, unless a significant interaction between group and sex was present. If the interaction term from the ANOVA was significant, post hoc comparisons were performed with Tukey’s test for normally distributed variables and with the Games-Howell test for distributions for which equal variances could not be assumed. Pearson correlation was used to assess associations between continuous variables. Statistical significance was set at \(P < 0.05\) for all tests. All data were analyzed by using SPSS for WINDOWS software, version 13.0 (SPSS Inc, Chicago, IL).

### RESULTS

#### Nutrient intake

Subjects consuming a low-protein, low-calorie diet ate a wide variety of raw vegetables, fruit, nuts, seeds, sprouted grains and cereals, and olive oil and strictly avoided processed and refined foods (eg, partially hydrogenated oils, refined flours, sweets, free sugars, and soft-drinks) and foods of animal origin. Daily energy intake in the low-protein, low-calorie diet group was significantly lower than in the endurance runners and tended to be lower than in the Western diet group (Table 1). Daily protein intake was significantly lower in the low-protein, low-calorie diet group than in both the endurance runners and the Western diet group (Table 1). Intakes of total fat, monounsaturated fatty acids, and polyunsaturated fatty acids, expressed as a percent of energy intake, were significantly higher in the low-protein, low-calorie diet group than in either the endurance runners or the Western diet groups, whereas relative saturated fatty acid intake was significantly lower in the low-protein, low-calorie diet group than in the Western diet group (Table 1). The endurance runners and the Western diet subjects ate typical Western diets, which contained foods of both plant and animal origin. Daily total trans fatty acids and total dietary fiber intake did not differ significantly between the endurance runners and the Western diet group. Total fiber intake was markedly higher, and trans fatty acid intake was much lower, in the low-calorie, low-protein group than in the other 2 groups (Table 1). Daily protein intake, expressed as g protein/kg body wt, tended to be higher in the endurance runners than in the Western diet group \((P = 0.084; \text{Table 1})\). No subject consuming a low-protein, low-calorie diet was taking supplements, whereas many of the control subjects were taking supplements, ranging from one multivitamin per day to combinations of vitamins, antioxidants, selenium, and folate.

#### Body composition

BMI, percentage of body weight as fat, and percentage of trunk weight as truncal fat were significantly lower in the low-protein, low-calorie diet and endurance runner groups than in the Western diet group (Table 2). Percentage of body weight from fat and percentage of trunk weight from truncal fat tended to be lower in...
the endurance runners than in the low-protein, low-calorie diet group ($P = 0.071$), but the differences were significant only in men for percentage body fat (Table 3). Lean body mass was significantly lower in the low-protein, low-calorie diet group than in the endurance runners (Table 3).

**Growth factors, anabolic hormones, and inflammatory markers**

Both IGF-I and IGF-I:IGFBP-3 were much lower in the low-protein, low-calorie diet group than in the Western diet group (Table 4). Plasma IGF-I concentrations and IGF-I:IGFBP-3 were also significantly lower in the low-protein, low-calorie diet group than in the BMI-matched endurance runners group (Table 4). Neither IGF-I nor IGF-I:IGFBP-3 differed significantly between the endurance runners and the Western diet groups. The plasma IGF-I concentration correlated linearly with dietary total protein intake ($r = 0.498$, $P = 0.036$) and energy intake ($r = 0.513$, $P = 0.029$) in the Western diet group and inversely with energy intake ($r = 0.478$, $P = 0.033$) in the endurance runners group (Figure 1). Circulating IGFBP-3 concentrations did not differ significantly between groups (Table 4).

Fasting plasma insulin and C-peptide concentrations were lower in the low-protein, low-calorie diet and endurance runners groups than in the Western diet group. In the low-protein, low-calorie diet group, insulin sensitivity, assessed by the Matsuda ISI, was much higher than in the Western diet group but was significantly lower than in the endurance runners group (Table 4). Plasma concentrations of CRP and leptin were much lower in the low-protein, low-calorie diet and endurance runners groups than in the Western diet group (Table 4).

**Sex steroids**

Plasma concentrations of total testosterone, 17β-estradiol, and DHEAS did not differ significantly between the groups in either men or women (Table 5). In both men and women, plasma SHBG concentrations were much higher in the low-protein, low-calorie diet and endurance runners groups than in the Western diet group, but the difference was statistically significant only

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### Table 3

Body composition of the study subjects

<table>
<thead>
<tr>
<th></th>
<th>Low-protein, low-calorie diet group</th>
<th>Endurance runners</th>
<th>Western diet group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body fat (%)</td>
<td>Low-protein, low-calorie diet group</td>
<td>Endurance runners</td>
<td>Western diet group</td>
</tr>
<tr>
<td>Men</td>
<td>13.7 ± 2.8/a</td>
<td>9.2 ± 4.2/b</td>
<td>21.0 ± 7.1</td>
</tr>
<tr>
<td>Women</td>
<td>26.9 ± 8.3/b</td>
<td>20.9 ± 6.5/b</td>
<td>42.3 ± 5.3</td>
</tr>
<tr>
<td>Trunk fat (%)</td>
<td>Low-protein, low-calorie diet group</td>
<td>Endurance runners</td>
<td>Western diet group</td>
</tr>
<tr>
<td>Men</td>
<td>10.3 ± 3.4/c</td>
<td>6.2 ± 4.9/c</td>
<td>21.5 ± 9.7</td>
</tr>
<tr>
<td>Women</td>
<td>20.8 ± 9.8/c</td>
<td>13.8 ± 6.1/c</td>
<td>39.9 ± 6.1</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>Low-protein, low-calorie diet group</td>
<td>Endurance runners</td>
<td>Western diet group</td>
</tr>
<tr>
<td>Men</td>
<td>53.2 ± 5.6</td>
<td>59.2 ± 5.6</td>
<td>58.1 ± 9.2</td>
</tr>
<tr>
<td>Women</td>
<td>40.1 ± 5.3</td>
<td>38.9 ± 4.7</td>
<td>41.8 ± 4.5</td>
</tr>
</tbody>
</table>

1 All values are ± SD.
2 Significant interaction between sex and group ($P < 0.05$) in 2-factor ANOVA; therefore, the sexes were analyzed separately.
3.4 Significantly different from Western diet group (post hoc Games-Howell’s test): $^3P ≤ 0.009$, $^4P = 0.0001$.

### Table 4

Plasma concentrations of cancer risk factors among the groups of study subjects

<table>
<thead>
<tr>
<th></th>
<th>Low-protein, low-calorie diet group</th>
<th>Endurance runners</th>
<th>Western diet group</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (ng/mL)/a</td>
<td>139 ± 37/b</td>
<td>177 ± 37</td>
<td>201 ± 42</td>
</tr>
<tr>
<td>IGFBP-3 (ng/mL)/b</td>
<td>4210 ± 548</td>
<td>4013 ± 548</td>
<td>4332 ± 542</td>
</tr>
<tr>
<td>IGF-I:IGFBP-3/a</td>
<td>0.033 ± 0.015/a</td>
<td>0.044 ± 0.01</td>
<td>0.046 ± 0.01</td>
</tr>
<tr>
<td>Fasting insulin (μU/mL)/b</td>
<td>2.8 ± 2/b</td>
<td>2.1 ± 2/b</td>
<td>5.9 ± 4</td>
</tr>
<tr>
<td>Fasting C-peptide (ng/mL)/b</td>
<td>1.0 ± 0.3/b</td>
<td>1.2 ± 0.3/b</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>Matsuda ISI/b</td>
<td>13.6 ± 5.9/b</td>
<td>19.7 ± 7.5/b</td>
<td>7.3 ± 4.6</td>
</tr>
<tr>
<td>Leptin (mg/mL)/b</td>
<td>2.0 ± 0.7/b</td>
<td>1.8 ± 0.5/b</td>
<td>5.3 ± 3.3</td>
</tr>
<tr>
<td>hsCRP (mg/L)/b</td>
<td>6.3 ± 4.7/b</td>
<td>5.2 ± 2.7/b</td>
<td>27.2 ± 14</td>
</tr>
</tbody>
</table>

1 All values are ± SD. IGF-I, insulin-like growth factor I; IGFBP-3, IGF binding protein 3; ISI, insulin sensitivity index (9); hsCRP, high-sensitivity C-reactive protein.
2 Non-significant interaction between sex and group in 2-factor ANOVA; therefore, the sexes were analyzed together.
3 Significantly different from endurance runners, $P ≥ 0.008$ (post hoc Tukey’s test).
4 Significantly different from Western diet group (post hoc Tukey’s test): $^4P = 0.0001$.
5 Significantly different from Western diet group (post hoc Games-Howell’s test): $^5P ≤ 0.027$, $^6P ≤ 0.008$, $^7P = 0.05$.
8 Significant interaction between sex and group ($P < 0.05$) in 2-factor ANOVA; therefore, the sexes were analyzed separately.
between the low-protein, low-calorie diet group and the Western diet group (Table 5). Plasma SHBG concentrations were inversely correlated with plasma C-peptide concentrations and plasma IGF-I concentrations (Figure 2).

In men, the FAI was significantly lower in the low-protein, low-calorie diet group than in the Western diet group (Table 5). In both men and women, estradiol:SHBG was significantly lower in the low-protein, low-calorie diet group than in the Western diet group (Table 5).

DISCUSSION

The data from the present study show that consuming a low-protein, low-calorie diet or participating in regular endurance exercise training is associated with a decrease in plasma factors that are linked with some types of cancer. Plasma concentrations of insulin, free sex hormones, and inflammatory markers were lower in subjects consuming a low-protein, low-calorie diet and in subjects who were endurance runners than in nonobese, sedentary subjects who were consuming typical Western diets. Moreover, subjects eating a low-protein, low-calorie diet had much lower plasma IGF-I concentrations and IGF-I:IGFBP-3 than did BMI-matched endurance runners, which suggests that dietary factors may provide additional protective effects, independent of body fat mass. These results help to identify potential mechanisms by which long-term lifestyle modifications in diet or physical activity can selectively reduce circulating factors that are associated with increased cancer risk.

### TABLE 5

<table>
<thead>
<tr>
<th></th>
<th>Low-protein, low-calorie diet group (n = 21)</th>
<th>Endurance runners (n = 21)</th>
<th>Western diet group (n = 21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total testosterone (nmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>18.6 ± 4.3</td>
<td>18.2 ± 3.5</td>
<td>16.8 ± 6.7</td>
<td>NS</td>
</tr>
<tr>
<td>Women</td>
<td>2.3 ± 0.9</td>
<td>2.7 ± 0.8</td>
<td>1.8 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>I(^{17})Estradiol (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>15.8 ± 4</td>
<td>16.3 ± 4</td>
<td>17.9 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Women</td>
<td>21.4 ± 16</td>
<td>24.8 ± 13</td>
<td>30.9 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>257 ± 79(^{f})</td>
<td>205 ± 67</td>
<td>164 ± 93</td>
<td>0.021</td>
</tr>
<tr>
<td>Women</td>
<td>440 ± 125(^{f})</td>
<td>323 ± 160</td>
<td>176 ± 82</td>
<td>0.001</td>
</tr>
<tr>
<td>Free androgen index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>7.8 ± 2.8(^{f})</td>
<td>9.8 ± 3.8</td>
<td>12.6 ± 6.0</td>
<td>0.031</td>
</tr>
<tr>
<td>Women</td>
<td>0.6 ± 0.3</td>
<td>1.1 ± 0.7</td>
<td>1.5 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol:SHBG(^{f})</td>
<td>22.5 ± 11(^{f})</td>
<td>37.6 ± 34</td>
<td>61.3 ± 36</td>
<td>0.0001</td>
</tr>
<tr>
<td>DHEA-S (ng/mL)</td>
<td>1091 ± 1295</td>
<td>637 ± 356</td>
<td>683 ± 379</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^{1}\) All values are \(\bar{x} \pm SD\). SHBG, sex hormone–binding globulin; DHEA-S, dehydroepiandrosterone sulfate.

\(^{2}\) Significant interaction between sex and group \((P < 0.05)\) in 2-factor ANOVA; therefore, the sexes were analyzed separately.

\(^{3}\) Significantly different from Western diet group, \(P \leq 0.05\) (post hoc Tukey’s test).

\(^{4}\) Nonsignificant interaction between sex and group in 2-factor ANOVA; therefore, the sexes were analyzed together.

\(^{5}\) Significantly different from Western diet group, \(P = 0.0001\) (post hoc Games-Howell’s test).

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**FIGURE 1.** Relation between plasma insulin-like growth factor I (IGF-I) concentrations and total dietary protein intake and energy intake in the low-protein, low-calorie diet group (○), endurance runners (●), and sedentary Western diet group (▲). Pearson correlation was used to assess associations between continuous variables. A significant interaction was found between group and protein intake and between group and energy intake \((P < 0.05)\). The plasma IGF-I concentration correlated linearly with dietary total protein intake \((r = 0.498, P = 0.036)\) and energy intake \((r = 0.513, P = 0.029)\) in the Western diet group and inversely with energy intake \((r = 0.478, P = 0.033)\) in the endurance runners group.

**FIGURE 2.**
Nutrient intake is a major regulator of circulating IGF-I, which promotes tumor development by stimulating cell proliferation and inhibiting cell death (10–12). Data from epidemiologic studies have shown an association between higher plasma IGF-I concentrations and a greater risk of breast (premenopausal), prostate, and colon cancers (13–16). In rodents, calorie restriction lowers plasma IGF-I concentrations and protects against carcinogenesis, which is reversed by infusing IGF-I (17). Data from several short-term studies conducted in healthy human subjects showed that short-term protein and energy restriction reduces plasma IGF-I concentrations (18, 19).

The results from our study suggest that the effect of protein and energy intakes on IGF-I is not transient and that long-term protein and calorie restriction can cause a chronic decrease in plasma IGF-I concentrations, independent of body fat mass. We found that protein and energy intake were both directly correlated with plasma IGF-I concentrations in sedentary volunteers eating Western diets. Moreover, plasma IGF-I concentrations were lower in our low-protein, low-calorie diet group (≈9% of calories from protein) than in our lean distance runners and our sedentary control group (≈16% of calories from protein). The mechanism or mechanisms responsible for the relation between the intake of protein rich in essential amino acids, the intake of calories, and IGF-I that has been shown in other cross-sectional studies (20, 21) is not known, but both decreased IGF-I production and increased clearance may be involved. Decreased dietary protein intake correlates with reduced steady-state concentrations of hepatic IGF-I mRNA (22) and increased clearance of serum IGF-I (23).

Data from epidemiologic studies indicate that obesity is a risk factor for several types of cancer, including colon, breast, endometrial, kidney, and pancreas cancer (1). Increased adipose tissue may be involved in the pathogenesis of specific cancers, because of adipokine production, insulin resistance, hyperinsulinemia, and chronic inflammation (1, 3, 4, 24–27). In addition, higher circulating concentrations of endogenous sex hormones (including estradiol, testosterone, and DHEA) and low plasma SHBG concentrations are associated with an increased risk of breast and endometrial cancers (28–30), possibly because free estrogens and androgens are strong mitogens for mammary cells and stimulate the development and growth of breast tumors (31). We found that our subjects consuming a low-protein, low-calorie diet or performing regular endurance exercise had lower body fat mass and alterations in metabolic factors associated with decreased body fat, including lower plasma concentrations of insulin, leptin, and CRP and greater insulin sensitivity than did nonobese sedentary men and women consuming a Western diet. In addition, our lean subjects had higher plasma SHBG concentrations, which decrease the proportion of free sex hormones (32), than did the sedentary men and women consuming a Western diet. Therefore, the mechanism responsible for the beneficial relation between a low-protein, low-calorie diet or exercise training and these metabolic factors associated with cancer may be related to the effect of reduced calorie intake or increases in energy expenditure on body fat mass.

Our study has several limitations. First, because of the cross-sectional design, we were able to show only associations between diet, physical activity, and circulating factors associated with cancer and could not determine true causal relations. A long-term randomized controlled trial would be needed to determine cause-and-effect relations. However, this type of trial would be difficult to perform, because of the difficulty in achieving dietary compliance with moderate low-calorie intake and very low protein intake for such a long time. Second, our study evaluated plasma factors associated with increased cancer risk but did not evaluate the prevalence of cancer itself. It is not known whether these surrogate markers will reflect the incidence of cancer in our study subjects. Finally, the small sample size and the cross-sectional nature of this study do not allow us to exclude that other unknown factors could play a role in the reported differences. However, the significant differences observed in this cross-sectional study are a first-step in elucidating the effects of long-term low-protein, low-calories diets; adiposity; and endurance exercise on plasma growth factors and hormones linked to cancer risk in humans.
Finally, a low-protein diet may have detrimental effects on bone mass and strength in older persons with already low serum IGF-I concentrations (33).

In conclusion, our data show that the consumption of a low-protein, low-calorie diet; exercise training; and increased adiposity are associated with low plasma insulin, C-peptide, FAI, leptin, and C-reactive protein and high SHBG concentrations, which are circulating factors linked with some types of cancer. Furthermore, our data suggest that a lower protein and calorie intake may have additional protective effects against some types of cancer, because it is associated with a decrease in circulating IGF-1 independent of body fat mass.

LF participated in the concept, design, and implementation of the study; undertook the plausibility testing; and drafted the report. SK participated in the design of the study and the drafting of the report. JOH participated in the concept, design, and implementation of the study and the drafting of the report. All the authors declared that they participated in the study as mentioned above and that they reviewed and approved the manuscript in its final version. None of the authors had any conflicts of interest.

REFERENCES