Dietary Insulin Index and Insulin Load in Relation to Endometrial Cancer Risk in the Nurses' Health Study

Jennifer Prescott1,3, Ying Bao1, Akila N. Viswanathan2, Edward L. Giovannucci1,4, Susan E. Hankinson1,5, and Immaculata De Vivo1,3

Abstract

**Background:** Although unopposed estrogen exposure is considered the main driver of endometrial carcinogenesis, factors associated with states of insulin resistance and hyperinsulinemia are independently associated with endometrial cancer risk. We used dietary insulin load and insulin index scores to represent the estimated insulin demand of overall diets and assessed their association with endometrial cancer risk in the prospective Nurses’ Health Study.

**Methods:** We estimated incidence rate ratios (RR) and 95% confidence intervals (CI) for risk of invasive endometrial cancer using Cox proportional hazards models. Between the baseline dietary questionnaire (1980) and 2010, we identified a total of 798 incident-invasive epithelial endometrial adenocarcinomas over 1,417,167 person-years of follow-up.

**Results:** Dietary insulin scores were not associated with overall risk of endometrial cancer. Comparing women in the highest with the lowest quintile, the multivariable-adjusted RRs of endometrial cancer were 1.07 (95% CI, 0.84–1.35) for cumulative average dietary insulin load and 1.03 (95% CI, 0.82–1.31) for cumulative average dietary insulin index. Findings did not vary substantially by alcohol consumption, total dietary fiber intake, or body mass index and/or physical activity ($P_{\text{heterogeneity}} > 0.10$).

**Conclusions:** Intake of a diet predicted to stimulate a high postprandial insulin response was not associated with endometrial cancer risk in this large prospective study. Considering the complex interplay of diet, lifestyle, and genetic factors contributing to the hyperinsulinemic state, dietary measures alone may not sufficiently capture absolute long-term insulin exposure.

**Impact:** This study is the first to investigate dietary insulin scores in relation to endometrial cancer risk. Cancer Epidemiol Biomarkers Prev; 23(8); 1512–20. ©2014 AACR.
Dietary Insulin Scores and Endometrial Cancer Risk

less refined foods (22). Type, amount, and digestibility of dietary carbohydrate intake have direct physiologic effects on circulating insulin levels (22–24), which are highly correlated with postprandial blood glycermia ($r = 0.70; P < 0.001$; ref. 22). Given the putative link between insulin signaling and endometrial tumor growth, frequent consumption of foods associated with elevated insulin or blood glucose response has been hypothesized to increase endometrial cancer risk.

Epidemiologic studies have investigated dietary carbohydrate quality (glycemic index, GI) and/or a measure of both carbohydrate quality and quantity (glycemic load, GL) as surrogates of insulin and blood glucose levels with respect to endometrial cancer risk. Except for the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (25), prior studies observed nonsignificant elevations in endometrial cancer risk among women in the highest category of GL compared with the lowest. This translated into a modest, but significant approximately 20% elevation in risk associated with a high GL diet in a recent meta-analysis (26). However, although postprandial blood glycermia from carbohydrate consumption is highly correlated with circulating insulin levels, protein and fat can induce insulin secretion without raising blood glucose (22). Thus, quantifying the postprandial insulin response for various food items, including those with low or no carbohydrate content, may address the insulin hypothesis more directly. In this analysis, we used novel dietary insulin index (II) and insulin load (IL) scores developed for the Nurses’ Health Study (NHS) cohort to investigate prospectively whether diets high in insulinogetic foods are associated with endometrial cancer risk.

Materials and Methods

Study population

The NHS is an ongoing prospective cohort following 121,700 female registered nurses ages 30 to 55 years from 11 U.S. states at enrollment in 1976. At baseline and biennially thereafter, participants completed self-administered questionnaires providing detailed information on anthropometric, lifestyle, menstrual, and reproductive factors. Participants also report their medical history from which newly diagnosed cancers and other diseases are identified. Follow-up of the cohort is high, with >90% of total possible person-years. Vital status was ascertained through next-of-kin, the U.S. Postal Service, and the National Death Index. These methods have identified an estimated 98% of deaths in the cohort (27). Completion of the self-administered questionnaire was considered to imply informed consent. The NHS protocol was approved by the Human Research Committee of Brigham and Women’s Hospital (Boston, MA).

Case ascertainment

On each questionnaire, women reported whether they had been diagnosed with endometrial cancer during the previous 2 years. We then sought permission to obtain the relevant medical records and pathology reports. Study physicians blinded to questionnaire data reviewed the documents to verify and establish the date of diagnosis. As <10% of NHS endometrial cancer cases were diagnosed with serous, clear cell, or other rare histologic types, we restricted our analysis to cases with invasive endometrial adenocarcinoma (stages IA–IV) diagnosed between return of the 1980 dietary questionnaire and June 1, 2010. Over 1,417,167 person-years of follow-up, we identified 798 incident invasive epithelial endometrial adenocarcinomas.

Dietary assessment

Dietary information was first assessed in 1980 when a 61 semiquantitative food frequency questionnaire (FFQ) was sent to participants. Expanded questionnaires inquiring about annual average intake of over 130 individual foods and 22 beverages were sent in 1984, 1986, and every 4 years thereafter. FFQs asked, on average, how often during the previous year participants consumed each food or beverage using standard portion sizes. Nine responses were possible, ranging from never or less than once per month to 6 or more times per day. Nutrient intakes were calculated by multiplying the portion size of a single serving of each food by its reported frequency of intake, then multiplying the amount consumed by the nutrient content of the food, and summing the nutrient contributions of all food items using the U.S. Department of Agriculture food composition data (28). Reproducibility of the FFQ has been reported elsewhere (29–31).

II values for individual food items were obtained from published estimates (31 foods; refs. 22, 32) or provided by Dr. Jennie Brand-Miller of the University of Sydney, Australia (73 foods). U.S. food samples were shipped to the laboratory in Sydney for testing as previously described (22). The food II value was calculated by dividing the area under the insulin response curve for 1,000 kilojoules of the reference food (glucose). The II value for each test food represents the mean response of 11 to 13 subjects. On the basis of these data, we built an II database for a large number of foods queried on our FFQs. II values for individual foods ranged from 2.0 (butter) to 120.0 (jelly beans). For foods not directly tested, II values were either assigned values from similar foods (meats, fish, poultry, fats, and oils) or calculated using an adjustment based on percentage of carbohydrates/1,000 kilojoule (cereal grains, baked goods, sweets and snack foods, beverages, fruits, and dairy foods), an inverse water ratio (nonstarchy vegetables), or inverse dietary fiber content ratio (starchy vegetables).

We calculated the average dietary II for each participant by multiplying the II value of each food and beverage by its energy content, and summing values for all items reported [$\sum f o o d I I \times k i l o c a l o r i e s / p e r s e r v i n g \times s e r v i n g s / d a y$]). Each unit of dietary II represents the equivalent insulin response generated by 1 kilocalorie of glucose. The dietary II for the overall diet, which is the weighted mean...
of II values for each of the component foods, was calculated by dividing dietary IL by total energy intake \(\text{[IL/} \Sigma \text{ (kilocalories per serving} \times \text{servings per day)]}\). For secondary analyses, we calculated average dietary IL and II scores excluding the estimated insulin response to alcoholic beverages (beer, wine, and liquor).

Bao et al. assessed validity of dietary IL in predicting the actual insulin response (33). Healthy participants \((n = 10\) or 11 for each meal) consumed 13 different isoenergetic \((2,000 \text{ kilojoules})\) mixed meals of varying macronutrient content. Despite limited statistical power, dietary IL strongly correlated with the observed postprandial insulin response \((r = 0.78, P = 0.002)\), suggesting that dietary IL may be a valid measure of actual insulin response to composite meals.

**Assessment of non-dietary factors**

On the questionnaire administered in 1976, women reported current weight, height, smoking history, age at menarche, OC use, pregnancy history, menopausal status, age at menopause, use of postmenopausal HT, and personal history of other diseases. OC use and parity were asked on each questionnaire until 1984, whereas most other covariate data (except height and age at menarche) were updated on each biennial questionnaire. Type of postmenopausal hormone used \(\text{(i.e., estrogen alone or estrogen with progesterone)}\) was first asked in 1978 and on all subsequent questionnaires. Weight at age 18 was reported on the 1980 questionnaire. First-degree family history of endometrial cancer was collected in 1996 and 2008. Family history of colorectal cancer was first collected in 1982, updated in 1988 and biennially thereafter. Starting in 1980, participants were asked hours per week of overall moderate and vigorous physical activity. Hours spent on specific leisure-time activities were first reported in 1986 and updated every 2 to 4 years. From the frequency, duration, and intensity of reported activities, we calculated total metabolic equivalent (MET) hours of activity per week (34, 35). Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters \((\text{kg/m}^2)\). Pack-years of smoking were calculated by multiplying the duration and dose of smoking; 1 pack-year is equivalent to having smoked 20 cigarettes per day for 1 year.

**Statistical analysis**

We used the 1980 dietary questionnaire as baseline. We sequentially excluded women who did not respond to the 1980 FFQ, left an extensive number of items blank \((n = 29,232)\), had been diagnosed with cancer before 1980 (other than nonmelanoma skin cancer; \(N = 3,678\)), were born before 1920 or had an unknown date of birth \((N = 58)\), or had undergone hysterectomy with or without oophorectomy or experienced menopause due to pelvic irradiation as of the 1980 questionnaire \((N = 20,625)\). Because obesity is an important risk factor for endometrial cancer, we also excluded women missing BMI \((N = 138)\); these women could reenter the analysis in subsequent cycles once information on BMI was available) for a total analytic population of 67,969 women at baseline. Person-time of follow-up for each eligible participant started with the return date of the baseline questionnaire and ended with date of endometrial cancer diagnosis, diagnosis of another cancer (except nonmelanoma skin cancer), hysterectomy, pelvic irradiation, death from any cause, or end of follow-up (June 1, 2010), whichever occurred first.

Cox proportional hazards regression models estimated incidence rate ratios (RR) and 95% confidence intervals (CI) with age in months and 2-year questionnaire cycle as the time scale. Average dietary IL, dietary II, dietary GI, dietary GL, and total dietary fiber intake were energy-adjusted by the residual method (36). This addresses the question of whether the composition of the diet, independent of total energy intake, is most relevant to endometrial cancer risk. Participants were classified according to dietary insulin score tertiles or quintiles based on the distribution observed within the cohort. Women in the lowest quantile of each score served as the reference group in analyses.

To assess the importance of timing, we analyzed dietary insulin scores in three ways: (i) using 1980 baseline values to reflect past exposure, (ii) simple update, to assess most recent dietary exposure, and (iii) cumulatively updating the average dietary insulin scores with each successive questionnaire data to reflect long-term exposure. To illustrate the cumulative average method, we used the average of dietary IL from 1980 and 1984 to predict endometrial cancer risk from 1984 to 1986. Similarly, we averaged IL scores from 1980, 1984, and 1986 to predict risk from 1986 to 1988. Factors included in the final multivariable analyses are listed in table footnotes. We additionally assessed dietary GI (quintiles), dietary GL (quintiles), total dietary fiber intake (quintiles), BMI at age 18 (continuous), physical activity \(\leq 3, 3 \text{ to} < 9, 9 \text{ to} < 18, 18 \leq 27, 27 + \text{ METs/week}, \text{unknown})\), alcohol consumption (none, \(\leq 5, 5-14.9, 15+ \text{ grams/day})\), coffee consumption (continuous), caffeine intake (quintiles), and personal history of diabetes (no, yes) as potential confounders. Because results remained similar, these factors were not included in final models.

We performed a number of sensitivity analyses. We used the 1984 dietary questionnaire as baseline because the FFQ included more food items than the 1980 FFQ. To minimize the possibility that prediagnostic disease influenced dietary assessment, we examined associations after incorporating a 4-year time lag between exposure assessment and endometrial cancer diagnosis (e.g., 1980 exposure to predict disease risk from 1984 to 1986). We repeated analyses in which the dietary insulin scores were not energy-adjusted by the residual method and with dietary insulin scores that excluded the alcohol component. We additionally conducted an analysis restricted to women who did not report a personal history of diabetes to reduce dietary changes occurring as a result of a diabetes diagnosis.
We used the Wald test to assess linear trends of dietary insulin score variables assigned the median value for each intake category. Likelihood ratio tests assessed heterogeneity by BMI (<30 vs. ≥30 kg/m²) and total physical activity (high vs. low, using the median as the cutpoint) strata. We additionally assessed heterogeneity by alcohol intake (drinkers vs. nondrinkers) and total dietary fiber intake (above vs. below the median). We tested the proportional hazards assumption by comparing the log likelihood of models with and without interaction terms between age and the dietary insulin score trend variables. The proportional hazards assumption was not violated (P ≥ 0.14). P values were based on two-sided tests and considered statistically significant at P < 0.05. All analyses were conducted using SAS version 9.3 (SAS Institute Inc.).

Results

Characteristics of women according to selected quintiles of dietary IL and II at the midpoint of follow-up (1994) are shown in Table 1. Women in higher categories of the dietary insulin scores were slightly older, had a higher intake of carbohydrates and total dietary fiber, but consumed less protein, total fat, alcohol, and caffeine, and were less likely to have ever smoked or taken OCs. Among women that had used OCs, duration of use was shorter among those in the highest categories of the dietary insulin scores. Parity, menopausal status, BMI, total physical activity, and family history of endometrial or colorectal cancer did not differ by categories of the dietary insulin scores. Cumulative average dietary insulin scores were highly correlated with each other (r = 0.96) and with cumulative average dietary GI (r = 0.75 with dietary IL; r = 0.73 with dietary II), but only modestly correlated with cumulative average GI (r = 0.37 and 0.39, respectively).

Past, recent, and long-term measures of dietary insulin scores were not associated with endometrial cancer risk in age- or multivariable-adjusted analyses. Women in the highest quintile of cumulative average dietary IL had an RR of 1.07 (95% CI, 0.84–1.35; P_trend = 0.51; Table 2) compared with women in the lowest quintile after adjusting for established and suspected endometrial cancer risk factors. The comparable RR for cumulative average dietary II was 1.03 (95% CI, 0.81–1.31; P_trend = 0.59). We observed similar associations using the 1984 FFQ as baseline. Results remained essentially unchanged after incorporating a 4-year time lag between exposure assessment and diagnosis. Dietary insulin scores were not associated with endometrial cancer risk after additionally adjusting for dietary GI, dietary GL, total dietary fiber intake, BMI at age 18, total physical activity, personal history of diabetes, hypertension, caffeine intake, alcohol consumption, or coffee consumption. Similar results were obtained when the dietary insulin scores were not energy-adjusted by the residual method, when the alcohol component was removed from the scores, or when analyses were restricted to women without a personal history of diabetes (data not shown). Estimates did not differ by alcohol drinking status (P_heterogeneity ≥ 0.71).

Because higher dietary fiber content lowers insulin response to foods (37), we stratified our analysis by total dietary fiber intake (above vs. below median intake). Cumulative average dietary insulin scores were not associated with endometrial cancer risk among women with higher total dietary fiber intake (P_trend ≥ 0.10). Among women who consumed less total dietary fiber, those in the highest tertiles of cumulative average dietary insulin scores had significant 35% to 40% increased risks of endometrial cancer (P_trend = 0.03) compared with women in the lowest tertiles. However, heterogeneity by total dietary fiber intake was not significant (P_heterogeneity ≥ 0.77).

Food intake among insulin-resistant individuals stimulates greater insulin production to overcome the decreased responsiveness of target tissues (38). Obese or less active individuals are more likely to exhibit insulin resistance (39) and, therefore, may experience the greatest detriment from a high insulinogenic diet. We examined whether the association with cumulative average dietary insulin scores differed by BMI and total physical activity. We did not observe a positive association between cumulative average dietary insulin scores and endometrial cancer risk among obese women or among women who reported total physical activity less than the median of the study population. Likewise, no association was observed in the group of women expected to have the highest proportion of insulin-resistant individuals (obese and low physical activity; Table 3). We observed a marginal increased risk associated with the highest compared with lowest tertile of cumulative average dietary II among nonobese women with high levels of physical activity (RR, 1.37; 95% CI, 0.99–1.90; P_trend = 0.06; P_heterogeneity = 0.26). However, the same trend was not observed using the 1984 FFQ as baseline or in the 4-year lagged analysis, suggesting the observation is due to chance. Finally, because postmenopausal HT use may alter insulin responsiveness (12, 40), we conducted an analysis restricted to women who never used postmenopausal hormones. Cumulative average dietary insulin scores were not associated with endometrial cancer risk among these women (data not shown).

Discussion

We used novel dietary insulin scores to assess the impact of diets high in insulinogenic foods on endometrial cancer risk. We did not find evidence for increased endometrial cancer risk associated with dietary IL or II in this large cohort of U.S. women. Further, the scores were not associated with elevated risk among heavy and/or less active individuals, subgroups of women who collectively experience greater postprandial insulin response due to a higher proportion of insulin-resistant individuals (39).

Prior studies assessed endometrial cancer risk using dietary GI and GI scores to reflect the postprandial glucose response of carbohydrate-containing foods and to act as surrogates of insulin response to different diets. With the exception of PLCO, which observed significant
### Table 1. Age-standardized characteristics of NHS participants at the midpoint of follow-up (1994)

<table>
<thead>
<tr>
<th>Quintile 1</th>
<th>Quintile 3</th>
<th>Quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>(217–621; n = 9,558)</td>
<td>(668–706; n = 9,556)</td>
<td>(755–1,279; n = 9,795)</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>59.3 (6.9)</td>
<td>59.5 (7.2)</td>
</tr>
<tr>
<td><strong>Age at menarche (y)</strong></td>
<td>12.6 (1.4)</td>
<td>12.5 (1.4)</td>
</tr>
<tr>
<td><strong>Parous, %</strong></td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td><strong>Postmenopausal, %</strong></td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td><strong>Age at menopause (y)</strong></td>
<td>49.9 (3.7)</td>
<td>50.1 (3.3)</td>
</tr>
<tr>
<td><strong>Ever use of postmenopausal hormones, %</strong></td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>Never smoker, %</strong></td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td><strong>Past smoker, %</strong></td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td><strong>Current smoker, %</strong></td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td><strong>BMI at age 18 (kg/m²)</strong></td>
<td>21.1 (3.4)</td>
<td>21.2 (3.4)</td>
</tr>
<tr>
<td><strong>Current BMI (kg/m²)</strong></td>
<td>26.1 (5.2)</td>
<td>26.6 (5.3)</td>
</tr>
<tr>
<td><strong>Total physical activity (METs/week)</strong></td>
<td>19.7 (25.7)</td>
<td>19.3 (25.0)</td>
</tr>
</tbody>
</table>

**Dietary IL**

<table>
<thead>
<tr>
<th>Quintile 1</th>
<th>Quintile 3</th>
<th>Quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>(13.9–38.8; n = 9,448)</td>
<td>(41.7–44.1; n = 9,568)</td>
<td>(47.0–80.9; n = 9,729)</td>
</tr>
<tr>
<td><strong>GL</strong></td>
<td>85.8 (17.5)</td>
<td>109 (14)</td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td>175 (30)</td>
<td>210 (24)</td>
</tr>
<tr>
<td><strong>Total fat (grams/day)</strong></td>
<td>59.7 (12.4)</td>
<td>52.3 (9.6)</td>
</tr>
<tr>
<td><strong>Total dietary fiber (grams/day)</strong></td>
<td>17.7 (6.8)</td>
<td>18.8 (5.5)</td>
</tr>
<tr>
<td><strong>Alcohol intake (grams/day)</strong></td>
<td>13.0 (15.4)</td>
<td>3.7 (6.0)</td>
</tr>
<tr>
<td><strong>Caffeine intake (mg/day)</strong></td>
<td>309 (231)</td>
<td>266 (218)</td>
</tr>
<tr>
<td><strong>Caloric intake (kcal/day)</strong></td>
<td>1,711 (550)</td>
<td>1,777 (524)</td>
</tr>
<tr>
<td><strong>Personal history of diabetes, %</strong></td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td><strong>Personal history of hypertension, %</strong></td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td><strong>Family history of endometrial cancer, %</strong></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Family history of colon cancer, %</strong></td>
<td>13</td>
<td>15</td>
</tr>
</tbody>
</table>

**Dietary II**

<table>
<thead>
<tr>
<th>Quintile 1</th>
<th>Quintile 3</th>
<th>Quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
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<td>(41.7–44.1; n = 9,568)</td>
<td>(47.0–80.9; n = 9,729)</td>
</tr>
<tr>
<td><strong>Dietary IL</strong></td>
<td>570 (48)</td>
<td>687 (11)</td>
</tr>
<tr>
<td><strong>Carbohydrates (grams/day)</strong></td>
<td>75.9 (15.4)</td>
<td>74.9 (11.9)</td>
</tr>
<tr>
<td><strong>Protein (grams/day)</strong></td>
<td>59.7 (12.4)</td>
<td>52.3 (9.6)</td>
</tr>
<tr>
<td><strong>Total fat (grams/day)</strong></td>
<td>17.7 (6.8)</td>
<td>18.8 (5.5)</td>
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<td>3</td>
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</tr>
<tr>
<td><strong>Family history of colon cancer, %</strong></td>
<td>13</td>
<td>15</td>
</tr>
</tbody>
</table>

**NOTE:** Values are mean (SD) or percentages and are standardized to the age distribution of the study population.

aValue is not age standardized.

bAmong ever OC users.

cAmong parous women.

dAmong postmenopausal women.
reduced risk among women who consumed high GL diets (RR, 0.63; 95% CI, 0.46–0.84 for highest vs. lowest quartile; ref. 25), most studies report nonsignificant elevations in endometrial cancer risk with GL or GI (26). Cohort studies observed elevated risks of 15% to 36% with high GL diets (pooled RR, 1.22; 95% CI, 1.09–1.37 for highest vs. lowest category), including the NHS (RR, 1.29; 95% CI, 0.99–1.67; ref. 41), but not with GI (pooled RR, 1.00; 95% CI, 0.87–1.14; ref. 26). In contrast, case–control studies observed significant increased endometrial cancer risk with GI (pooled OR, 1.56; 95% CI, 1.21–2.02), but the relationship with high GL diets was weaker (pooled OR, 1.14; 95% CI, 0.91–1.44) compared with cohort studies (26).

To address the insulin hypothesis more directly, we used novel dietary insulin scores to quantify the postprandial insulin response. The food II, on which the scores were based, was developed under highly standardized conditions (22). Dietary II accurately predicted insulin response to mixed meals in healthy volunteers, demonstrating validity of the index (33). Moreover, in the NHS and Health Professionals Follow-up Study cohorts, dietary insulin scores positively correlated with plasma glucose (GL).
Table 3. Cumulative average dietary IL, dietary II, and risk of endometrial cancer stratified by BMI and physical activity.

<table>
<thead>
<tr>
<th>BMI/C1</th>
<th>Dietary IL (tertiles) RRa (95% CI)</th>
<th>Dietary II (tertiles) RRa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases, N</td>
<td>RRa (95% CI)</td>
<td>RRa (95% CI)</td>
</tr>
<tr>
<td>&lt;30 kg/m²</td>
<td>100</td>
<td>1.00 (0.88–1.13)</td>
</tr>
<tr>
<td>30 kg/m²</td>
<td>298</td>
<td>1.01 (0.91–1.12)</td>
</tr>
<tr>
<td>30–40 kg/m²</td>
<td>341</td>
<td>1.01 (0.92–1.13)</td>
</tr>
<tr>
<td>&gt;40 kg/m²</td>
<td>414</td>
<td>1.01 (0.92–1.13)</td>
</tr>
<tr>
<td>BMI/C2</td>
<td>Dietary IL (tertiles) RRa (95% CI)</td>
<td>Dietary II (tertiles) RRa (95% CI)</td>
</tr>
<tr>
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<td>1.01 (0.92–1.13)</td>
</tr>
</tbody>
</table>

Abbreviation: PA, physical activity.

triglyceride levels, particularly among obese individuals (42), confirming the ability to predict an expected biologic response associated with insulin resistance. Contrary to our hypothesis, we did not find evidence of increased endometrial cancer risk associated with the dietary insulin scores. Given that imprecise FFQ assessments may have biased results toward the null, we examined long-term exposure using cumulative average dietary scores, which dampen variation due to measurement error. The scores remained unrelated to endometrial cancer risk.

Insulin resistance/metabolic syndrome is an emerging risk factor for endometrial cancer (14–19). Fasting insulin, a marker of insulin resistance (43), was associated with overall endometrial cancer risk in a Canadian population-based case–control study (44), and in subgroups of non-HT users and/or overweight/obese women in a Swedish population-based case–control study (45) and the Women’s Health Initiative Observational Study (12). Because excess energy is a major contributor to insulin resistance and sustained elevated insulin levels (39), we hypothesized that insulin-resistant individuals (obese/inactive) who consume an insulinogenic diet would be at highest risk for endometrial cancer. However, we did not observe significant associations between dietary insulin scores and endometrial cancer risk among these individuals ($P_{trend} \geq 0.17; P_{heterogeneity} \geq 0.19$).

Our study benefits from the large, prospective design in which dietary and risk factor information was updated every 2 to 4 years over follow-up. The prospective nature and high follow-up rate minimized recall and selection biases, whereas repeated assessments reduced measurement error. Known and suspected risk factors were controlled to minimize residual confounding, although confounding by unmeasured or unknown exposures cannot be ruled out. Given our extensive data, we conducted a number of sensitivity analyses to rule out chance findings or a potential effect of subclinical disease on dietary intake.

We recognize that our study has several limitations. Although dietary insulin scores were developed to assess total postprandial insulin response to food intake, the scores do not account for overall composition or frequency of food intake, which may affect insulin response. In developing the database, acute postprandial insulin responses were measured in young lean individuals (22), which may not reflect the absolute response in heavier, middle-aged women. However, the method is valid if the relative insulin response to each food is comparable between the two groups. It is important to consider that in addition to dietary factors that influence insulin secretion acutely, elevated insulin levels are determined by a host of factors including anthropometric characteristics throughout the lifecourse, physical activity, dietary factors that influence insulin resistance, and genetic predisposition (39, 46–50). Thus, the acute postprandial insulin response alone may not sufficiently reflect absolute exposure to insulin levels. Finally, our cohort is not representative of the general U.S. population. By design, the target population was chosen to maximize...
internal validity through enhanced reporting of exposures and health outcomes. As underlying biology is likely very similar across ethnic groups and social class, observations made in our cohort may apply more broadly.

In summary, our results do not support an association between dietary factors specifically related to the post-prandial insulin response and endometrial cancer risk. An integrated surrogate measure of hyperinsulinemia that incorporates dietary, lifestyle, and genetic factors may provide a more useful indicator for studies investigating the insulin hypothesis in disease risk.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Disclaimer
The opinions or assertions contained in this work are the private views of the authors and are not considered as official or reflecting the views of the NIH. Certain data used in this publication were obtained from the Connecticut Department of Public Health (DPH). The authors assume full responsibility for analyses and interpretation of these data.

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Acknowledgments
The authors thank the NHS participants and cohort staff for their valuable contributions as well as following the state regulations: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. This study was approved by the Human Investigations Committee of the DPH.

Grant Support
The NIH project, E.L. Giovannucci, and S.E. Hankinson are supported by the NIH (P01 CA57969). I. De Vivo (R01 CA82803) and J. Prescott (US5 CA15626) were supported by funds from the NIH.

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Received February 14, 2014; revised May 1, 2014; accepted May 6, 2014; published OnlineFirst May 23, 2014.

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Cancer Epidemiol Biomarkers Prev 2014;23:1512-1520. Published OnlineFirst May 23, 2014.

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