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Original Contribution

Biomarker-calibrated Energy and Protein Consumption and Increased Cancer Risk Among Postmenopausal Women

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The authors previously reported equations, derived from the Nutrient Biomarker Study within the Women's Health Initiative, that produce calibrated estimates of energy, protein, and percentage of energy from protein consumption from corresponding food frequency questionnaire estimates and data on other factors, such as body mass index, age, and ethnicity. Here, these equations were applied to yield calibrated consumption estimates for 21,711 women enrolled in the Women's Health Initiative dietary modification trial comparison group and 59,105 women enrolled in the observational study. These estimates were related prospectively to total and site-specific invasive cancer incidence (1993–2005). In combined cohort analyses that do not control for body mass, uncalibrated energy was not associated with total cancer incidence or site-specific cancer incidence for most sites, whereas biomarker-calibrated energy was positively associated with total cancer (hazard ratio = 1.18, 95% confidence interval: 1.10, 1.27, for 20% consumption increase), as well as with breast, colon, endometrial, and kidney cancer (respective hazard ratios of 1.24, 1.35, 1.83, and 1.47). Calibrated protein was weakly associated, and calibrated percentage of energy from protein was inversely associated, with total cancer. Calibrated energy and body mass index associations were highly interdependent. Implications for the interpretation of nutritional epidemiology studies are described.

bias (epidemiology); biological markers; diet; energy intake; epidemiologic methods; neoplasms; nutrition assessment; proteins

Abbreviations: CI, confidence interval; DM, dietary modification; FFQ, food frequency questionnaire; HR, hazard ratio; WHI, Women's Health Initiative.

Early international correlation studies reported a positive association between energy consumption and the incidence and mortality from cancer. Among women, associations were reported for breast, colon, rectal, endometrial, ovarian, and kidney cancer (1). Rodent feeding experiments indicate that underfeeding typically inhibits the development of site-specific and overall cancer (2, 3).

Analytical epidemiologic studies of diet, nutrition, and cancer date to the 1970s. Initial case-control studies used a range of dietary assessment procedures, including food records, recalls, and frequencies. Concern about dietary recall bias subsequently led to cohort studies as the predominant design for dietary association studies. Because these studies typically involve tens of thousands of enrollees, a self-administered, machine-readable food frequency questionnaire (FFQ) has been the principal dietary assessment tool in cohort studies.

However, like other dietary assessment methods, the measurement properties of FFQs remain substantially unknown. Comparison of FFQ assessments with food records reveals noteworthy differences (4) that imply an important error component to self-reported nutrient intake. Small-scale studies using a doubly labeled water biomarker (5) of energy consumption suggest important systematic biases also, as obese persons may systematically underreport energy consumption (6) in some populations. Measurement error,

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Table 1. Subject Characteristics for Women in the Women's Health Initiative Dietary Modification Trial Comparison Group and Observational Study, 1993–1998

Characteristic	Dietary Modification Trial Comparison Group (n = 21,711)[a]		Observational Study (n = 59,105)[a]	
	%	No.	%	No.
Age, years[b]				
50–59	30	6,421	19	11,135
60–69	48	10,495	43	25,257
70–79	21	4,667	35	20,555
80–89	1	128	4	2,158
Body mass index, kg/m^2				
Normal (<25.0)	26	5,704	42	24,938
Overweight (25.0–29.9)	36	7,767	34	20,361
Obese (≥30)	38	8,239	23	13,806
Race				
White	82	17,889	86	51,028
Black	10	2,161	6	3,661
Hispanic	3	725	3	1,736
Other[b]	4	936	5	2,680
Income (total yearly)				
<$20,000	15	3,218	14	8,159
$20,000–$34,999	25	5,335	23	13,605
$35,000–$49,999	21	4,593	21	12,214
$50,000–$74,999	21	4,546	21	12,407
≥$75,000	18	4,009	22	12,720
Education				
Less than high school diploma	4	893	4	2,196
High school diploma or equivalent	18	3,803	16	9,379
School after high school	40	8,593	36	21,421
College degree or higher	39	8,422	44	26,109
Smoking				
Current	6	1,392	6	3,307
Past	52	11,373	51	30,232
Never	41	8,946	43	25,566

Table continues

especially systematic biases, may substantially distort diet and cancer associations. It is important to examine nutrient and disease associations in a manner that appropriately accommodates FFQ measurement errors.

The accumulated data on diet and cancer were reviewed by an international panel of experts in 1997 (7). Rather few ''definite'' or ''probable'' dietary associations emerged. The authors wrote, ''The significance of the data on energy intake and cancer risk in humans remains unclear'' (7, p. 371), and ''In the view of the panel, the effect of energy intake on cancer is best assessed by examining the data on related factors: rate of growth, body mass, and physical activity'' (7, p. 371). This state of affairs has evidently not changed in the intervening decade (8) and reflects considerable uncertainty about energy consumption estimates and related association study findings. The 1997 panel also assessed that protein consumption was not ''probably or convincingly'' related to the risk of any cancer (7, p. 394).

Good-quality biomarkers of both total energy consumption (5) and protein consumption (9) have been developed but, for cost and logistics reasons, have received little use in epidemiologic research. These biomarkers involve urinary recovery of metabolites produced when these nutrients are expended. In weight-stable persons, they provide objective estimates of short-term energy and protein consumption. The associated measurement error plausibly adheres to a simple classical measurement model,

$$W = Z + e, \quad (1)$$

where Z is the targeted (log-transformed) nutrient consumption, W is the (log-transformed) biomarker-measured

Table 1. Continued

Characteristic	Dietary Modification Trial Comparison Group (n = 21,711)[a]		Observational Study (n = 59,105)[a]	
	%	No.	%	No.
Recreational physical activity, metabolic equivalents/week				
<1.5	25	5,335	16	9,508
1.5–6.2	25	5,378	20	11,715
6.3–14.7	26	5,541	27	15,708
≥14.8	25	5,457	38	22,174
Breast cancer family history, yes	18	3,729	19	10,631
Gail 5-year risk score, %				
<1.00	15	3,355	11	6,778
1.00–1.99	62	13,368	62	36,531
2.00–2.99	14	3,073	16	9,623
≥3.00	9	1,915	10	6,173
Colon cancer family history, yes	16	3,257	17	9,006
History of polyps, yes	8	1,780	9	5,275
Unopposed estrogen use ever, yes	37	8,084	38	22,736
Estrogen + progesterone use ever, yes	28	6,054	31	18,395
Diabetes, yes	6	1,313	5	2,664
Hypertension, yes	41	8,909	37	22,029
Alcohol use				
Nondrinker	10	2,086	10	6,063
Current drinker				
<1 drink/week	36	7,708	32	18,768
1–7 drinks/week	27	5,923	27	16,048
>7 drinks/week	10	2,116	14	8,010
Past drinker	18	3,878	17	10,216

[a] Number of subjects for whom there were no missing values for the energy regression calibration or for total cancer hazard ratio analysis.

[b] Age at food frequency questionnaire measurement (year 1 dietary modification trial comparison group and year 3 observational study).

consumption, and e is measurement error that is assumed to be independent of Z and of all other study subject characteristics. The cost to ascertain these biomarkers for each participant in a cohort study would be excessive. Instead, a substudy that includes both the biomarker and FFQ can be used to produce calibrated consumption estimates for all cohort members.

The measurement model for the self-reported data typically needs to be more complex than the classical measurement model (equation 1). Other factors, such as body mass, ethnicity, and age, may affect the assessment, and measurement errors may be correlated if the assessment is repeated for specific study subjects. Hence, we consider the measurement model (10, 11),

$$Q = S_0 + S_1 Z + S_2 V + S_3 VZ + r + u, \qquad (2)$$

for the (log-transformed) self-reported nutrient assessment Q, where V is a set of characteristics that may relate to systematic bias in the assessment, r is a person-specific error variable that will be present in each self-reported assessment for a study subject, and u is an independent measurement error term. In addition, S_0, S_1, S_2, and S_3 are constants to be estimated, and all variables on the right sides of equations 1 and 2 are assumed to be independent, given V.

We have recently reported (12) FFQ measurement error findings from the Nutritional Biomarker Study among 544 women enrolled in the Women's Health Initiative (WHI) dietary modification (DM) trial. FFQ estimates of energy, protein, and percentage of energy from protein were each found to incorporate important systematic bias, and corresponding calibration equations were developed. Here, we use these equations to produce calibrated estimates of energy, protein, and percentage of energy from protein for women in the DM trial comparison (control) group and for women in the WHI observational study. The 2 cohorts

will be used, separately and combined, to assess associations between calibrated nutrient consumption and cancer incidence as observed during WHI follow-up. Cancer risk among DM intervention group women may depend in a complex manner on baseline and follow-up dietary patterns, so that intervention group women were excluded from the present analyses.

MATERIALS AND METHODS

Study cohorts

Detailed accounts of the design of the WHI Clinical Trial and Observational Study and of the DM trial findings have been presented (13–18). This paper uses a subset of women assigned to the DM trial comparison group ($n = 29{,}294$) and a subset of the observational study cohort ($n = 93{,}676$). Both cohorts included only women who were 50–79 years of age at recruitment (1993–1998), were postmenopausal, and had no medical condition associated with less than 3 years' predicted survival. Both provided common core questionnaires at baseline on medical history, reproductive history, family history, personal habits, psychosocial attributes, and food frequency (19, 20).

DM trial women, who could be assigned to overlapping trials of postmenopausal hormone therapy and of calcium and vitamin D supplementation, also satisfied additional exclusionary criteria. To maximize commonality with the DM cohort, the 76,987 observational study women considered here were those remaining after imposing additional DM trial baseline exclusionary criteria as follows: prior history of breast cancer, colorectal cancer, or other cancer (except nonmelanoma skin cancer) within the preceding 10 years; a stroke or myocardial infarction in the preceding 6 months; severe hypertension (systolic blood pressure >200 mm or diastolic blood pressure >105 mm); already following a low-fat diet; underweight (body mass index <18); or FFQ-reported daily energy of <600 kcal or $>5{,}000$ kcal.

WHI food frequency questionnaire

All DM trial and observational study women completed FFQs at baseline. DM trial women repeated the FFQ at 1 year following enrollment and approximately every 3 years thereafter, while observational study women repeated the FFQ at 3 years following enrollment. FFQs were provided in connection with visits to the 40 participating clinical centers, where completeness and quality control checks were applied. The self-administered FFQ included 122 line items for individual foods/food groups and 19 adjustment items regarding fat intake, as well as summary questions. Nutrition Data System for Research, version 2005, software (University of Minnesota, Minneapolis, Minnesota) was used to compute daily average nutrient consumption estimates (21, 22).

Nutrient Biomarker Study

The WHI Nutrient Biomarker Study was conducted in 2004–2005 to assess measurement properties of this FFQ and to produce calibrated consumption estimates for energy and protein. The eligibility and recruitment methods for the Nutrient Biomarker Study have been described (12); 544 representative women from the DM trial cohort were enrolled (276 comparison group, 268 intervention group). These weight-stable women participated in a doubly labeled water protocol to estimate daily total energy expenditure over a 2-week period, as well as a urinary nitrogen protocol to estimate daily protein consumption over a 24-hour period, and also provided a concurrent FFQ and other questionnaire data. Twenty percent ($n = 111$) repeated the entire Nutrient Biomarker Study protocol an average of 6 months later to provide reliability data for measurement error component estimation (12). FFQ total energy and protein were found to be underestimated, while the percentage of energy from protein was overestimated. Women having high body mass index (weight (kg)/height $(m)^2$) and younger women underestimated energy consumption to a comparatively greater extent. Calibration equations were developed for each of energy, protein, and percentage of energy from protein by linear regression of log-biomarker estimates on corresponding log-FFQ estimates, body mass index, age, ethnicity, and other factors (12). For example, the calibrated log-energy consumption is given by $7.61 + 0.062$ (log-FFQ energy $- 7.27$) $+ 0.013$ (body mass index $- 28.2$) $- 0.005$ (age $- 70.9$ years), plus some less influential terms involving ethnicity, family income, and physical activity. DM intervention group assignment did not meet inclusion criteria for any of the 3 calibration equations.

Nutrient Biomarker Study application to WHI cohorts

Here, we apply these calibration equations to FFQ data that were collected earlier in the WHI and relate the calibrated consumption estimates to subsequent cancer incidence. Doing so is complicated by the use of the FFQ in participant screening for the DM trial. The exclusion of about 50% of the women who had baseline FFQ percentage of energy from fat of less than 32, in conjunction with FFQ measurement error, implies that the baseline FFQ percentage of energy from fat is overestimated in the DM trial (by about 3% on average), with corresponding estimates of energy likewise distorted. Observational study baseline estimates are distorted in the opposite direction because many women screened out from the DM trial enrolled in the observational study. In terms of equation 2, these distortions arise because women tend to meet the FFQ inclusion criteria when the independent random error term (u) that attends a particular FFQ application is positive. Later FFQs for a woman, following a sufficient period of time (e.g., 6 months) to avoid carry-over effects on this measurement component, can be expected to be free of this measurement effect. Hence, our analyses rely on FFQs obtained at year 1 in the DM trial comparison group and at year 3 in the observational study, and only cancer diagnoses that follow these FFQ collections are included in analyses. These FFQs were collected an average 6.5 years (DM trial comparison group) and 4 years (observational study) prior to the Nutrient Biomarker Study data collection.

Table 2. Incidence of Invasive Cancer in the Women's Health Initiative Following Year 1 (Dietary Modification Trial Comparison Group) and Year 3 (Observational Study) Food Frequency Data Collection, 1993–2005

Cancer	Dietary Modification Trial Comparison Group (n = 21,711)[a]		Observational Study (n = 59,105)[a]		Total (N = 80,816)[a]	
	Incidence/1,000 Person-Years	No. of Cases	Incidence/1,000 Person-Years	No. of Cases	Incidence/1,000 Person-Years	No. of Cases
Total cancer[b]	12.34	1,807	11.06	3,234	11.48	5,041
Breast	4.98	685	4.73	1,018	4.83	1,703
Colon	0.89	123	0.87	240	0.88	363
Rectum	0.33	47	0.14	40	0.21	87
Ovary	0.63	72	0.57	131	0.59	203
Endometrium	1.32	115	1.21	220	1.25	335
Bladder	0.25	39	0.20	60	0.22	99
Kidney	0.28	42	0.27	81	0.27	123
Pancreas	0.26	40	0.23	71	0.24	111
Lung	0.95	146	0.91	275	0.92	421
Lymphoma	0.57	88	0.57	175	0.57	263
Leukemia	0.32	49	0.20	60	0.24	109

[a] The number of subjects in the cohort for whom there were no missing values for the energy calibration or for total cancer hazard ratio analysis. The number of subjects with no missing values varied slightly by cancer site and nutrient.
[b] Exclusive of nonmelanoma skin cancer.

Dietary consumption and disease risk associations were estimated for total invasive cancer, as well as for invasive cancers of the breast, colon, rectum, ovary, endometrium, bladder, kidney, pancreas, and lung, and for lymphoma and leukemia. The ovarian cancer analyses were restricted to women without bilateral oophorectomy at baseline, and the endometrial cancer analysis was restricted to women with a uterus at baseline.

DM comparison group women were queried twice per year, and observational study women annually, concerning diagnosis of any cancer other than nonmelanoma skin cancer. Cancer reports were verified by medical record and pathology report review by centrally trained physician adjudicators at participating clinical centers (23).

Statistical analyses

Log-consumption estimates were calibrated directly from the biomarker assessments (equation 1) for the few women included in the Nutrient Biomarker Study and for other women by using the calibration equations previously developed (12).

Hazard ratio estimates were based on Cox regression (24). Follow-up times extended from year 1 (DM trial comparison group) or year 3 (observational study) to the earliest of cancer occurrence, death, lost to follow-up, or March 31, 2005, when the intervention phase of WHI ended. To minimize mammographic screening influences on results, the breast cancer analyses censored the follow-up time for a woman the first time she exceeded 2 years without a mammogram. The Cox model baseline hazard rates for each cancer outcome were stratified on baseline age in 5-year categories and, for the DM trial comparison group, also on hormone therapy trial participation (active estrogen; estrogen placebo; active estrogen plus progestin; estrogen plus progestin placebo; not randomized). Analyses that combine the 2 cohorts stratify also on cohort. Analysis for specific cancer outcomes included standard risk factors in the Cox regression model to control confounding, as shown in Appendix Table 1. Women having missing confounding factors were excluded from analysis.

Principal analyses modeled the log-hazard ratio linearly on log-nutrient consumption, so that the hazard ratio for a fractional increase in the nutrient is independent of the consumption. For display purposes, we present hazard ratios for a 20% increase in consumption. For a woman with median consumption, a 20% increment corresponds to about 413 kcal of energy, 15 g of protein, or 2.9 units in percentage of energy from protein.

Usual Cox model standard error estimates were calculated for uncalibrated consumption regression coefficients. A more complex standard error estimation procedure is needed for the calibrated consumption coefficients to acknowledge uncertainty in the calibration parameter estimates, as well as in the ''regression calibration'' hazard ratio estimation procedure (11), which has been shown to be free of practically important biases in extensive simulation studies. A bootstrap procedure (500 bootstrap samples), with bootstrap sampling stratified on cohort and membership in the Nutrient Biomarker Study and in the Nutrient Biomarker Study reliability subset, was applied for calibrated standard error estimation. A bootstrap procedure

(500 samples) was also used to test the equality of hazard ratios in the DM trial comparison group and observational study cohorts.

Calibrated energy turns out to be strongly positively correlated with body mass index. The data analyzed here do not allow one to determine whether a high body mass should be regarded as a consequence of a high-energy diet, in which case body mass index should be excluded from the set of potential confounding factors to avoid overcorrection, or whether a high body mass may arise for other reasons (e.g., sedentary lifestyle), in which case energy consumption may be high as a result of related energy requirements, and body mass index control would be needed in regression analyses. Hence, we present hazard ratio estimates for energy and for body mass index separately and jointly. Two-sided *P* values are used throughout.

RESULTS

A total of 26,531 (91%) DM trial comparison group women and 66,788 (87%) observational study women provided FFQs (year 1 DM, year 3 observational study) and were without a prior cancer diagnosis during WHI follow-up. Of these, 21,711 (82%) DM trial comparison group and 59,105 (88%) observational study women had all the data needed for energy calibration and for confounding control for total cancer. Table 1 shows some demographic and lifestyle characteristics for these women. Analyses of other cancer outcomes or other nutrients involve a slightly different set of women, because of different confounding factors and, hence, missing data exclusions.

Table 2 shows incidence rates and the number of invasive cancers through March 31, 2005, for energy analyses for each cancer site. Incidence rates are similar between the 2 cohorts. A total of 5,041 invasive cancers contribute to the total cancer analyses, but the number of incident cancers is <300 for specific cancers other than breast, colon, endometrial, and lung.

Table 3 shows the geometric mean consumption and 95% confidence interval for the consumption of energy, protein, and percentage of energy from protein for both cohorts, with and without calibration. The distribution of calibrated consumption estimates is similar in the 2 cohorts. The narrower confidence intervals for the calibrated versus uncalibrated estimates reflect, in part, smaller variations in actual consumption compared with that assessed by the FFQ.

Table 4 shows hazard ratio estimates for a 20% increase in total energy consumption under a linear log-hazard ratio model that excludes body mass index. A 20% increase corresponds to about 2 standard deviations for calibrated energy and percentage of energy from protein and about 1.3 standard deviations for calibrated protein. For comparison, extreme quartile medians differ by about 2.3 standard deviations, and extreme tertile medians differ by about 1.9 standard deviations, for normally distributed exposures.

Separate hazard ratio estimates are given for the DM trial comparison group and observational study cohorts, without and with biomarker calibration of consumption estimates. Biomarker calibration clearly has a major impact on hazard

Table 3. Geometric Mean Consumption and 95% Confidence Intervals for Uncalibrated Dietary Consumption, as Estimated by the Women's Health Initiative Food Frequency Questionnaire, and for Calibrated Consumption Using Nutritional Biomarker Data, in the Women's Health Initiative Dietary Modification Trial Comparison Group and Observational Study, 1993–2005

	Energy (kcal/day)				Protein (g/day)				Percentage of Energy From Protein			
	Uncalibrated		Calibrated[a]		Uncalibrated		Calibrated		Uncalibrated		Calibrated	
	Mean	95% Confidence Interval	Mean	95% Confidence Interval	Mean	95% Confidence Interval	Mean	95% Confidence Interval	Mean	95% Confidence Interval	Mean	95% Confidence Interval
Dietary modification trial comparison group (n = 21,711)	1,477.2	676.6, 3,224.9	2,140.6	1,786.9, 2,564.2	61.2	26.3, 142.1	78.1	58.4, 104.4	16.6	11.5, 24.0	14.4	11.9, 17.3
Observational study (n = 59,105)	1,384.3	641.0, 2,989.4	2,055.8	1,722.3, 2,453.9	58.6	24.8, 138.1	74.2	54.8, 100.5	16.9	11.5, 25.0	14.4	11.8, 17.6

[a] Calibrated by using the measurement model (equation 1) for women in the Nutrition Biomarker Study and equation 2 otherwise.

Table 4. Hazard Ratio Estimates for a 20% Increase in Energy (kcal/day) Consumption in the Women's Health Initiative Dietary Modification Trial Comparison Group and Observational Study, Without and With Biomarker Calibration, 1993–2005

Cancer	Dietary Modification Trial Comparison Group				Observational Study				Test of Equality of Hazard Ratios	
	Uncalibrated		Calibrated		Uncalibrated		Calibrated			
	Hazard Ratio[b]	95% Confidence Interval	Hazard Ratio[b]	95% Confidence Interval[c]	Hazard Ratio[b]	95% Confidence Interval	Hazard Ratio[b]	95% Confidence Inerval[c]	Uncalibrated *P* Value[a]	Calibrated *P* Value[a]
Total cancer	1.00	0.98, 1.02	1.13	1.02, 1.26	1.01	0.99, 1.03	1.21	1.11, 1.32	0.52	0.30
Breast	0.99	0.95, 1.02	1.25	1.07, 1.47	1.02	0.99, 1.05	1.23	1.06, 1.41	0.20	0.85
Colon	0.93	0.86, 1.00	1.11	0.75, 1.66	0.96	0.91, 1.02	1.47	1.11, 1.94	0.44	0.26
Rectum	1.10	0.96, 1.26	1.00	0.49, 2.02	1.00	0.87, 1.14	1.52	0.94, 2.47	0.30	0.34
Ovary	0.98	0.89, 1.09	1.00	0.61, 1.63	1.04	0.96, 1.12	1.09	0.71, 1.65	0.42	0.80
Endometrium	1.00	0.92, 1.09	1.73	1.21, 2.49	1.07	1.00, 1.14	1.88	1.48, 2.39	0.21	0.69
Bladder	0.99	0.87, 1.13	1.07	0.58, 1.97	1.10	0.98, 1.23	1.27	0.82, 1.97	0.26	0.70
Kidney	1.14	1.00, 1.30	1.87	0.95, 3.68	1.00	0.90, 1.11	1.28	0.81, 2.05	0.11	0.42
Pancreas	1.02	0.90, 1.16	1.72	1.09, 2.73	1.01	0.91, 1.12	1.02	0.49, 2.10	0.88	0.22
Lung	0.99	0.93, 1.06	1.01	0.72, 1.42	0.97	0.93, 1.03	0.76	0.55, 1.06	0.73	0.26
Lymphoma	0.96	0.88, 1.04	0.75	0.47, 1.23	0.98	0.92, 1.05	0.75	0.53, 1.08	0.69	0.97
Leukemia	0.97	0.86, 1.10	0.90	0.52, 1.56	1.14	1.01, 1.28	1.93	1.15, 3.21	0.07	0.05

[a] *P* value based on the difference between log-hazard ratios from the dietary modification trial comparison group and observational study cohorts, with a bootstrap estimate of standard deviation for the difference between the calibrated log-hazard ratios.

[b] Hazard ratio associated with a 20% increase in daily consumption by considering the hazard ratio for log(1.2*x*) compared with log(*x*): $\exp(\text{beta})^{\log 1.2}$, where beta is the estimated coefficient in Cox regression.

[c] The 95% confidence intervals for calibrated hazard ratios are based on the log-estimated hazard ratio $\pm$ 1.96 $\times$ the bootstrap standard error.

ratio estimates, with evidence for positive associations between calibrated energy and total cancer, as well as certain site-specific cancers, in both the DM trial comparison group and observational study cohorts, but with little evidence of association for uncalibrated energy. There is also little evidence of difference in hazard ratios between the 2 cohorts, with or without calibration, with the possible exception of leukemia.

Figure 1 shows corresponding hazard ratio estimates and 95% confidence intervals from the analysis of the 2 cohorts combined. Calibrated energy is positively related to total (hazard ratio (HR) = 1.18, 95% confidence interval (CI): 1.10, 1.27), breast (HR = 1.24, 95% CI: 1.11, 1.38), colon (HR = 1.35, 95% CI: 1.06, 1.71), endometrial (HR = 1.83, 95% CI: 1.49, 2.25), and kidney (HR = 1.47, 95% CI: 1.00, 2.16) cancer, while uncalibrated energy was not significantly related to total cancer or to any specific cancer, with the exception of an inverse association with colon cancer. The wider confidence intervals for calibrated versus uncalibrated energy hazard ratios reflect both uncertainty in the coefficients of the calibration equations and deattenuation that arises from acknowledging dietary assessment measurement error in the hazard ratio estimation procedure.

Analyses of calibrated protein and percentage of energy from protein similarly yielded little evidence of hazard ratio differences between the 2 cohorts (each $P > 0.05$). Figures 2 and 3 show corresponding combined cohort hazard ratios and 95% confidence intervals for a 20% increase in these nutritional factors. The hazard ratios for a 20% increase in calibrated protein are above 1 for total cancer (HR = 1.06, 95% CI: 1.01, 1.12), breast cancer (HR = 1.09, 95% CI: 1.01, 1.19), endometrial cancer (HR = 1.37, 95% CI: 1.16, 1.61), and leukemia (HR = 1.39, 95% CI: 1.05, 1.83). These positive associations may be substantially attributable to correlation between protein and energy consumption, since the hazard ratio estimates for percentage of energy from protein are less than 1 for total and most specific cancers, and the inverse association is significant for total cancer

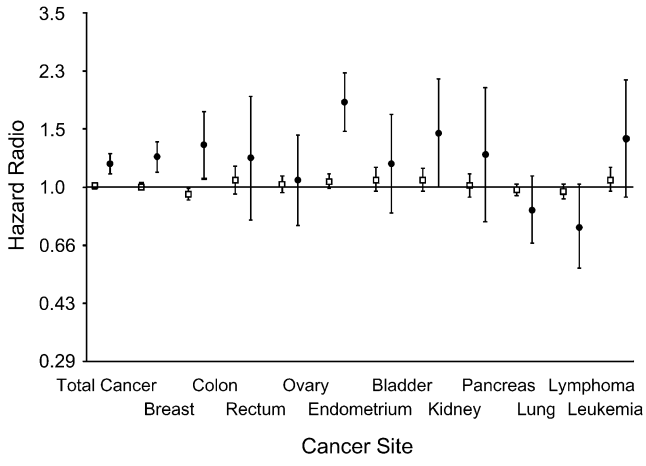

Figure 1. Estimated hazard ratios and 95% confidence intervals for a 20% increase in energy consumption (kcal/day), from combined analysis of data from the Women's Health Initiative dietary modification trial comparison group and observational study, without and with biomarker calibration of consumption, 1993–2005. Unfilled square, uncalibrated; filled circle, calibrated.

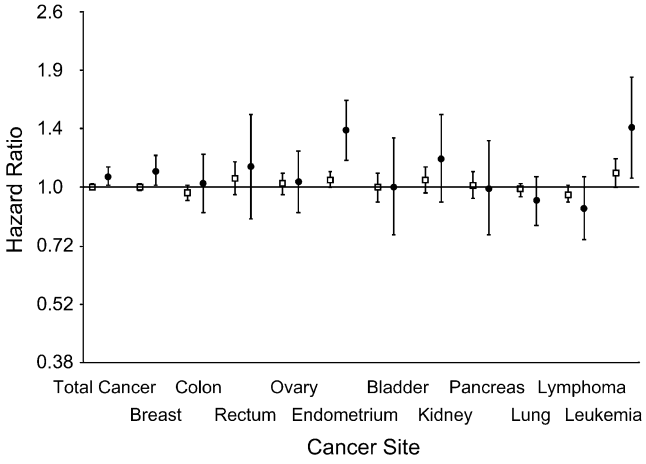

Figure 2. Estimated hazard ratios and 95% confidence intervals for a 20% increase in protein consumption (g/day), from combined analysis of data from the Women's Health Initiative dietary modification trial comparison group and observational study, without and with biomarker calibration of consumption, 1993–2005. Unfilled square, uncalibrated; filled circle, calibrated.

(HR = 0.92, 95% CI: 0.85, 0.99 for a 20% increase in percentage of energy from protein). Results corresponding to Figures 1–3 by quartile of calibrated consumption are given in Appendix Tables 2–4.

The correlation coefficients for body mass index with log-transformed energy, protein, and percentage of energy from protein in the combined cohorts were, respectively, 0.07, 0.10, and 0.07 without calibration and 0.81, 0.46, and −0.12 following calibration. Hence, it may be difficult to distinguish between total energy and body mass index associations, with total or site-specific cancer. Table 5 examines the effect of including body mass index in the log-hazard ratio model on the calibrated energy hazard ratios shown in Figure 1 and also shows the effect of including calibrated energy on the hazard ratio for body mass index. Hazard ratios for both energy and body mass index are not significant for most cancer sites and may be unstable in the presence of the other variable, and confidence intervals are wide.

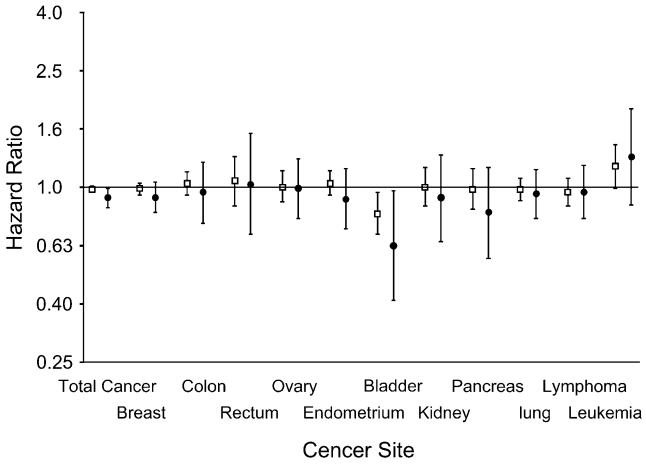

Figure 3. Estimated hazard ratios and 95% confidence intervals for a 20% increase in percentage of energy from protein, from combined analysis of data from the Women's Health Initiative dietary modification trial comparison group and observational study, without and with biomarker calibration of consumption, 1993–2005. Unfilled square, uncalibrated; filled circle, calibrated.

DISCUSSION

This report has both methodological and substantive implications. On the methodology side, it provides a first application of the use of urinary recovery markers to correct for systematic bias in dietary self-reported data, in an epidemiologic cohort setting. In analyses that control for standard confounding factors but not body mass index, FFQ estimates of energy, protein, or percentage of energy from protein were not significantly associated with total invasive cancer incidence. In contrast, following biomarker calibration, the associations with total cancer incidence were strong for energy ($P < 0.0001$), moderate for protein ($P = 0.01$), and inverse for percentage of energy from protein ($P = 0.03$), suggesting that macronutrients other than protein drive the positive energy association. Likewise, calibrated energy consumption was found to be positively associated with the risk of breast, colon, endometrial, and kidney cancer, whereas uncalibrated energy was not.

These comparisons suggest that systematic bias in dietary assessment could have a profound effect on nutritional epidemiology findings. Total energy assessment is a recognized weak aspect of FFQs. Uncalibrated FFQs are generally believed to be more reliable for nutrient density than for absolute consumption estimates. However, biomarker calibration also qualitatively affected the findings for protein density in relation to total cancer (Figure 3).

Measurement error has typically been acknowledged in epidemiology reporting through a simple deattenuation factor, as befits measurement equation 2 in the absence of systematic bias (i.e., $S_2 = S_3 = 0$). Such deattenuation typically has little effect on significance levels. The presence of systematic bias changes this feature, however, because regression coefficients are corrected for distortions beyond simple attenuation, possibly leading to substantially altered P values.

To help interpret the calibrated energy variable defined here, we note that calibrated energy can be viewed as estimated actual short-term energy consumption, as determined by FFQ energy, body mass index, age, and other factors. The correlations of calibrated energy, in our combined cohorts, with log-FFQ energy, body mass index, and age are, respectively, 0.35, 0.81, and −0.44. The strong associations with age and especially with body mass index imply that log-FFQ energy does not adhere to a simple classical measurement model. A linear regression of body mass index on log-calibrated energy gives a projected body mass index increase of 9.2 units corresponding to a 20% increase in calibrated energy, suggesting, in conjunction with Table 5, that much of the observed dependence of cancer incidence rates on total energy can be explained by body mass associations with

Table 5. Hazard Ratio Estimates for a 20% Increase in Calibrated Energy (kcal/day) Consumption and for a 10-Unit Increase in Body Mass Index, in Analyses That Either Exclude (Unadjusted) or Include (Adjusted) the Other Variable, Using Data from the Women's Health Initiative Dietary Modification Trial Comparison Group and Observational Study, 1993–2005

Cancer	Calibrated Energy				Body Mass Index			
	Body Mass Index Unadjusted		Body Mass Index Adjusted		Energy Unadjusted		Energy Adjusted	
	Hazard Ratio	95% Confidence Interval[a]	Hazard Ratio	95% Confidence Interval[a]	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval[a]
Total cancer	1.18	1.10, 1.27	0.90	0.76, 1.06	1.17	1.12, 1.23	1.27	1.11, 1.44
Breast	1.24	1.11, 1.38	1.11	0.81, 1.53	1.20	1.10, 1.30	1.10	0.86, 1.40
Colon	1.35	1.06, 1.71	0.70	0.41, 1.18	1.36	1.16, 1.61	1.81	1.19, 2.76
Rectum	1.23	0.79, 1.91	2.09	0.67, 6.50	1.15	0.81, 1.63	0.62	0.26, 1.52
Ovary	1.05	0.76, 1.45	1.12	0.61, 2.04	1.00	0.79, 1.28	0.95	0.58, 1.56
Endometrium	1.83	1.49, 2.25	1.40	0.83, 2.35	1.60	1.37, 1.87	1.26	0.84, 1.88
Bladder	1.18	0.83, 1.68	1.64	0.63, 4.25	1.08	0.77, 1.51	0.74	0.34, 1.60
Kidney	1.47	1.00, 2.16	1.27	0.52, 3.11	1.41	1.08, 1.83	1.14	0.59, 2.20
Pancreas	1.26	0.78, 2.03	0.88	0.41, 1.91	1.17	0.86, 1.59	1.37	0.76, 2.50
Lung	0.85	0.67, 1.08	0.58	0.37, 0.92	0.98	0.83, 1.16	1.44	0.99, 2.11
Lymphoma	0.75	0.56, 1.02	0.60	0.34, 1.04	0.87	0.70, 1.08	1.26	0.83, 1.90
Leukemia	1.41	0.93, 2.14	1.88	0.76, 4.60	1.22	0.90, 1.65	0.78	0.40, 1.51

[a] The 95% confidence intervals for analyses that include calibrated energy are based on the log-estimated hazard ratio $\pm 1.96 \times$ the bootstrap standard error.

these diseases. Table 5 likewise suggests that much of the dependence of cancer incidence rates on body mass index can be explained by energy consumption associations with these diseases.

Our analyses yielded similar results when calibration equations were applied in the DM cohort where they were derived and when exported to the observational study. However, this extrapolation is under near-optimal conditions as the 2 cohorts were drawn from essentially the same populations, with much commonality in eligibility and exclusionary criteria. Comparison with calibration equations from nutritional biomarker studies in other populations (25, 26) could be informative.

As noted above, the Nutrient Biomarker Study was conducted in 2004–2005, an average of about 6.5 years after the 1-year FFQ data collection for the DM trial comparison group women and about 4 years on average after the 3-year FFQ data collection for observational study women. Our application assumes that the calibration equations developed from Nutrient Biomarker Study data apply to FFQs at these earlier time points. Moreover, the biomarker data provide consumption estimates over a rather short period of time (e.g., 6 months between initial and repeat applications in the 20% subsample). However, dietary patterns are expected to track over longer time periods for most women in these cohorts.

On the substantive side, we observe strong positive associations between calibrated energy consumption and the risk of total and certain site-specific cancers. There are also suggestions of a positive association between protein consumption and leukemia and an inverse association between percentage of energy from protein and bladder cancer (Figures 2 and 3) that would be worth examining in other settings. More comprehensive temporal data on the interplay between a high-energy diet and body fat accumulation will be needed to understand the mechanisms leading to elevated cancer risk with a high level of energy consumption. However, regardless of whether body fat accumulation results from a history of high-energy consumption, or whether a high body mass leads to increased energy requirements, or both, it is evident that a high body mass index is an important aspect of total and site-specific cancer risk, and efforts to prevent obesity deserve a continued high priority in national cancer control efforts.

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REFERENCES

1. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer.* 1975;15(4):617–631.
2. Kritchevsky D, Klurfeld DM. Influence of caloric intake on experimental carcinogenesis: a review. *Adv Exp Med Biol.* 1986;206:55–68.
3. Freedman LS, Clifford C, Messina M. Analysis of dietary fat, calories, body weight, and the development of mammary tumors in rats and mice: a review. *Cancer Res.* 1990;50(18):5710–5719.
4. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122(1):51–65.
5. Schoeller DA. Recent advances from application of doubly-labeled water to measurement of human energy expenditure. *J Nutr.* 1999;129(10):1765–1768.
6. Heitmann BL, Lissner L. Dietary underreporting by obese individuals—is it specific or non-specific? *BMJ*. 1995;311(7011):986–989.
7. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition and the Prevention of Cancer: A Global Perspective*. Washington, DC: American Institute for Cancer Research; 1997.
8. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: American Institute for Cancer Research; 2007.
9. Bingham SA. Urine nitrogen as a biomarker for the validation of dietary protein intake. *J Nutr.* 2003;133(suppl 3):921S–924S.
10. Prentice RL, Sugar E, Wang CY, et al. Research strategies and the use of nutrient biomarkers in studies of diet and chronic disease. *Public Health Nutr.* 2002;5(6A):977–984.

11. Sugar EA, Wang CY, Prentice RL. Logistic regression with exposure biomarkers and flexible measurement error. *Biometrics*. 2007;63(1):143–151.
12. Neuhouser ML, Tinker L, Shaw PA, et al. Use of recovery biomarkers to calibrate nutrient consumption self-reports in the Women's Health Initiative. *Am J Epidemiol*. 2008; 167(10):1247–1259.
13. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19(1):61–109.
14. Women's Health Initiative Study Group. Dietary adherence in the Women's Health Initiative dietary modification trial. *J Am Diet Assoc*. 2004;104(4):654–658.
15. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295(6):629–642.
16. Beresford SA, Johnson KC, Ritenbaugh C, et al. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295(6):643–654.
17. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295(6):655–666.
18. Prentice RL, Thomson CA, Caan B, et al. Low-fat dietary pattern and cancer incidence in the Women' s Health Initiative dietary modification randomized controlled trial. *J Natl Cancer Inst*. 2007;99(20):1534–1543.
19. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13(9 suppl):S18–S77.
20. Langer RD, White E, Lewis CE, et al. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol*. 2003;13(9 suppl):S107–S121.
21. Kristal AK, Shattuck AL, Williams ME. Food frequency questionnaires for diet intervention research. In: *17th National Nutrient Databank Conference Proceedings*. Baltimore, MD: International Life Sciences Institute; 1992:110–125.
22. Schakel SF, Buzzard IM, Gebhardt SE. Procedures for estimating nutrient values for food composition databases. *J Food Compost Anal*. 1997;10(2):102–114.
23. Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13(9 suppl):S122–S128.
24. Cox DR. Regression analysis and life tables (with discussion). *J R Stat Soc (B)*. 1972;34:187–220.
25. Subar AF, Kipnis V, Troiano RP, et al. Using intake biomarkers to evaluate the extent of dietary misreporting in a large sample of adults: the OPEN study. *Am J Epidemiol*. 2003;158(1):1–13.
26. Kipnis V, Subar AF, Midthune D, et al. Structure of dietary measurement error: results of the OPEN biomarker study. *Am J Epidemiol*. 2003;158(1):14–21; discussion 22–26.

APPENDIX

Appendix Table 1. Baseline Factors Included in Cox Model Hazard Ratio Analyses to Control Confounding, in the Dietary Modification Trial Comparison Group and Observational Study Components of the Women's Health Initiative, 1993–2005[a]

	Total Cancer	Cancer Site					Lymphoma, Leukemia
		Breast	Colon, Rectum	Ovary	Endometrium	Bladder, Kidney, Pancreas, Lung	
Race[b] (white/other, black, Hispanic)	x	x	x[c]		x	x[d]	
Education (high school or less, beyond high school, college degree)	x	x					
Exercise (METs/week)	x	x	x				
Smoking[b] (never, past, current)	x	x	x			x	x[e]
Alcohol[b] (never, past, <1/week, 1–7/week, >7/week)	x	x	x			x	
Breast cancer family history (no, yes)		x		x			
Gail 5-year risk (5-year absolute risk %)		x					
Unopposed estrogen use ever (no, yes)	x	x	x[c]	x	x		
Estrogen plus progesterone use ever (no, yes)	x	x	x[c]	x	x		
Colon cancer family history (no, yes)			x				
History of colorectal polyps (no, yes)			x[c]				
History of diabetes (no, yes)	x						
Hypertension (no, yes)	x				x	x[f]	

Abbreviation: MET, metabolic equivalent.

[a] The same factors were used for the dietary modification comparison group and observational study cohorts.

[b] For rare cancers: race: black/Hispanic (yes/no); smoking: ever (yes/no); alcohol: nondrinker (past/never), light drinker (<1 drink/week), moderate/heavy (≥1 drinks/week).

[c] Colon cancer only.

[d] Lung only.

[e] Leukemia only.

[f] Kidney only.

Appendix Table 2. Hazard Ratios by Quartile of Biomarker-calibrated Energy Consumption From the Analyses of Combined Data From the Women's Health Initiative Dietary Modification Trial Comparison Group and Observational Study, 1993–2005[a]

Cancer	Energy (kcal/day)					
	Quartile 2		Quartile 3		Quartile 4	
	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Total cancer	1.07	0.97, 1.17	1.07	0.97, 1.19	1.18	1.07, 1.31
Breast	1.07	0.90, 1.28	1.17	0.98, 1.40	1.33	1.12, 1.58
Colon	1.27	0.88, 1.85	1.12	0.78, 1.60	1.51	1.03, 2.21
Rectum	1.82	0.81, 4.08	2.34	1.04, 5.26	1.51	0.64, 3.58
Ovary	1.23	0.78, 1.93	1.19	0.75, 1.89	0.91	0.58, 1.43
Endometrium	1.02	0.66, 1.57	1.26	0.81, 1.96	2.03	1.38, 3.00
Bladder	1.76	0.89, 3.46	2.14	1.02, 4.51	1.05	0.47, 2.39
Kidney	1.42	0.77, 2.62	1.31	0.71, 2.43	1.44	0.80, 2.61
Pancreas	0.94	0.49, 1.79	1.24	0.67, 2.32	1.33	0.68, 2.60
Lung	0.90	0.68, 1.19	0.75	0.53, 1.07	0.79	0.58, 1.08
Lymphoma	0.99	0.70, 1.42	0.81	0.54, 1.21	0.66	0.42, 1.03
Leukemia	1.46	0.71, 3.03	1.63	0.84, 3.18	1.46	0.69, 3.10

[a] Estimated hazard ratios and 95% confidence intervals for the second, third, and fourth quartiles relative to the first quartile of biomarker-calibrated energy consumption. Confidence intervals for log-hazard ratios derive from the log-hazard ratio estimate ±1.96 times the corresponding bootstrapped standard deviation estimate.

Appendix Table 3. Hazard Ratios by Quartile of Biomarker-calibrated Protein Consumption From the Analyses of Combined Data From the Women's Health Initiative Dietary Modification Trial Comparison Group and Observational Study, 1993–2005[a]

Cancer	Protein (g/day)					
	Quartile 2		Quartile 3		Quartile 4	
	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Total cancer	1.07	0.97, 1.18	1.10	0.99, 1.22	1.09	0.98, 1.22
Breast	1.15	0.97, 1.36	1.07	0.90, 1.28	1.22	0.99, 1.49
Colon	0.97	0.70, 1.34	1.11	0.76, 1.61	0.96	0.64, 1.44
Rectum	1.22	0.56, 2.65	1.57	0.72, 3.41	1.08	0.48, 2.41
Ovary	0.68	0.42, 1.10	1.10	0.73, 1.66	0.85	0.55, 1.31
Endometrium	1.36	0.91, 2.04	1.59	1.08, 2.35	1.85	1.26, 2.70
Bladder	1.11	0.54, 2.28	1.25	0.64, 2.45	0.96	0.45, 2.05
Kidney	1.12	0.62, 2.03	0.98	0.53, 1.80	1.31	0.73, 2.36
Pancreas	1.41	0.82, 2.41	0.95	0.47, 1.92	1.19	0.60, 2.37
Lung	1.00	0.75, 1.34	1.05	0.76, 1.43	0.78	0.55, 1.10
Lymphoma	0.88	0.59, 1.30	0.96	0.63, 1.44	0.68	0.41, 1.11
Leukemia	1.38	0.64, 2.99	2.05	1.02, 4.09	1.77	0.82, 3.81

[a] Estimated hazard ratios and 95% confidence intervals for the second, third, and fourth quartiles relative to the first quartile of biomarker-calibrated protein consumption. Confidence intervals for log-hazard ratios derive from the log-hazard ratio estimate ±1.96 times the corresponding bootstrapped standard deviation estimate.

Appendix Table 4. Hazard Ratios by Quartile of Biomarker-calibrated Percentage of Energy From Protein Consumption From the Analyses of Combined Data From the Women's Health Initiative Dietary Modification Trial Comparison Group and Observational Study, 1993–2005[a]

Cancer	Percentage of Energy From Protein					
	Quartile 2		Quartile 3		Quartile 4	
	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Total cancer	0.94	0.85, 1.04	0.94	0.85, 1.04	0.92	0.82, 1.04
Breast	0.97	0.83, 1.13	0.92	0.78, 1.09	0.94	0.78, 1.12
Colon	0.83	0.58, 1.2	0.98	0.71, 1.35	1.06	0.74, 1.51
Rectum	0.85	0.43, 1.67	1.24	0.63, 2.44	1.01	0.52, 1.96
Ovary	1.16	0.76, 1.77	1.13	0.72, 1.8	1.08	0.69, 1.69
Endometrium	0.92	0.65, 1.29	0.99	0.71, 1.39	0.92	0.63, 1.35
Bladder	0.72	0.39, 1.33	0.84	0.44, 1.58	0.58	0.28, 1.22
Kidney	0.80	0.44, 1.48	1.10	0.63, 1.92	0.86	0.48, 1.53
Pancreas	0.89	0.54, 1.44	0.65	0.36, 1.17	0.92	0.56, 1.53
Lung	0.99	0.73, 1.33	0.90	0.66, 1.23	0.92	0.67, 1.26
Lymphoma	1.11	0.77, 1.59	0.89	0.61, 1.28	0.93	0.61, 1.40
Leukemia	1.29	0.74, 2.24	1.28	0.73, 2.25	1.39	0.76, 2.54

[a] Estimated hazard ratios and 95% confidence intervals for the second, third, and fourth quartiles relative to the first quartile of biomarker-calibrated percentage of energy from protein consumption. Confidence intervals for log-hazard ratios derive from the log-hazard ratio estimate ± 1.96 times the corresponding bootstrapped standard deviation estimate.