

**Biomarker-Calibrated Energy and Protein Consumption
and Increased Cancer Risk among Postmenopausal Women**

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Abbreviations: BMI, body mass index; CI, confidence interval; DM-C, Dietary Modification trial comparison group; FFQ, food frequency questionnaire; NBS, Nutrient Biomarker Study; OS, observational study; WHI, Women's Health Initiative

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ABSTRACT

The authors have recently reported equations, derived from a Nutrient Biomarker Study within the Women's Health Initiative (WHI), that produce calibrated estimates of energy, protein, and % of energy from protein consumption estimates 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 WHI Dietary Modification trial comparison group, and 59,105 women enrolled in the Observational Study. These estimates were related prospectively to the total and site-specific invasive cancer incidence. 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 (HR) 1.18, 95% confidence interval (CI): 1.10, 1.27, for 20% consumption increase), as well with breast, colon, endometrial, and kidney cancer (respective HRs of 1.24, 1.35, 1.83, and 1.47). Calibrated protein was weakly associated, and calibrated % 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.

Keywords: bias (epidemiology); biological markers; cancer incidence; diet; energy intake; epidemiologic methods; nutrition assessment; protein

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, rectum, endometrium, ovary, and kidney cancer (1). Rodent feeding experiments indicate that underfeeding typically inhibits the development of site-specific and overall cancer (2, 3).

Analytic 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, 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' and 'In the view of the panel, the effect of energy intake on cancer is best assessed by examining the factors: rate of growth, body mass, and physical activity'. 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 (7) that protein consumption was not 'probably or convincingly' related to the risk of any cancer.

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

$$W = Z + e \quad (A)$$

where Z is the targeted (log-transformed) nutrient consumption, W is the (log-transformed) biomarker measured 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-report data typically needs to be more complex than the classical measurement model (A): 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 a measurement model (10, 11)

$$Q = S_0 + S_1Z + S_2V + S_3VZ + r + u \quad (B)$$

for the (log-transformed) self-report 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-report assessment for a study subject, u is an independent measurement error term. Also, S_0 , S_1 , S_2 , and S_3 are constants to be estimated, and all variables on the right sides of (A) and (B) are assumed to be independent, given V .

We have recently reported FFQ measurement error findings from a Nutritional Biomarker Study (NBS) among 544 women enrolled in the WHI Dietary Modification (DM) trial (12). FFQ estimates of energy, protein, and % 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 % of energy from protein for women in the DM trial comparison (control) group (DM-C), and for women in the WHI Observational Study

(OS). The two 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 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-C (n=29,294) and a subset of the OS cohort (n=93,676). Both cohorts included only women who were 50-79 years old at recruitment, were postmenopausal, and had no medical condition associated with less than three 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 OS women considered here were those remaining after imposing additional DM trial baseline exclusionary criteria as follows: prior history of breast or colorectal cancer, or other cancer (except non-melanoma skin) within the preceding 10 years; a stroke or

myocardial infarction in the preceding six 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 >5000 kcal).

WHI food frequency questionnaire

All DM trial and OS women completed FFQs at baseline. DM trial women repeated the FFQ at one year following enrollment and approximately every three years thereafter, while OS women repeated the FFQ at three 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, 19 adjustment items regarding fat intake, as well as summary questions, and the Nutrition Data System (Version 2005, University of Minnesota) was used to compute daily average nutrient consumption estimates (21, 22).

Nutritional Biomarker Study

The WHI Nutritional Biomarkers Study (NBS) 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 NBS 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 two-

week period, and 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 NBS protocol an average of six months later, to provide reliability data for measurement error component estimation (12). FFQ total energy and protein were found to be underestimated while % of energy from protein was overestimated. Women having high body mass index (BMI -- weight in kg/height in meters squared) and younger women underestimated energy consumption to a comparatively greater extent. Calibration equations were developed for each of energy, protein, and % 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 $7.61 + 0.062 (\log \text{ FFQ energy} - 7.27) + 0.013 (\text{BMI} - 28.2) - 0.005 (\text{age} - 70.9 \text{ years})$, 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 three calibration equations.

NBS 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 women having baseline FFQ % of energy from fat <32, in conjunction with FFQ measurement error, implies that baseline FFQ % energy from fat is overestimated in the DM trial (by about 3% on average), with corresponding

estimates of energy likewise distorted. OS baseline estimates are distorted in the opposite direction since many women screened out from the DM trial enrolled in the OS. In terms of Model B, 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-C, and at Year 3 in the OS, and only cancer diagnoses that follow these FFQ collections are included in analyses. These FFQs were collected an average 6.5 years (DM-C) and 4 years (OS) prior to the NBS data collection.

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 to women with uterus at baseline.

DM women were queried twice per year, and OS women annually, concerning diagnosis of any cancer other than non-melanoma 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 (Model A) for the few women included in the NBS, and for other women using the calibration equations previously developed (12).

Hazard ratio (HR) estimates were based on Cox regression (24). Follow-up times extended from the Year 1 (DM-C) or Year 3 (OS) 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 two 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-C also on hormone therapy trial participation (active estrogen; estrogen placebo; active estrogen plus progestin; estrogen plus progestin placebo; not randomized). Analyses that combine the two 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 A1. Women having missing confounding factors were excluded from analysis.

Principal analyses modeled the log-HR linearly on log-nutrient consumption, so that the HR for a fractional increase in the nutrient is independent of the consumption. For display purposes, we present HRs for a 20% increase in consumption. For a woman with median consumption, a 20% increment corresponds to about 413 kcal of energy, 15 grams of protein, or 2.9 units in % 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, and in the 'regression calibration' HR 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, membership in the NBS and in the NBS reliability subset, was applied for calibrated standard error estimation. A bootstrap procedure (500 samples) was also used to test equality of HRs in the DM-C and OS cohorts.

Calibrated energy turns out to be strongly positively correlated with BMI. 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 BMI 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 BMI control would be needed in regression analyses. Hence, we present HR estimates for energy and for BMI separately, and jointly. Two-sided p-values are used throughout.

RESULTS

A total of 26,531 (91%) of DM-C women and 66,788 (87%) of OS women provided FFQs (Year 1 DM, Year 3 OS) and were without a prior cancer diagnosis during WHI follow-up. Of these, 21,711 (82%) of DM-C and 59,105 (88%) of OS women had all 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, due to different confounding factors and, hence, missing data exclusions.

Table 2 shows incidence rates and number of invasive cancers through March 31, 2005, for calibrated energy analyses for each cancer site. Incidence rates are similar between the two cohorts. A total of 5041 invasive cancers contribute to the total cancer analyses, but the number of incident cancers is <300 for specific cancers other than breast, colon, endometrium, and lung.

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

Table 4 shows HR estimates for a 20% increase in total energy consumption under a linear log-HR model that excludes body mass index. A 20% increase corresponds to

about two standard deviations for calibrated energy and % 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 HR estimates (95% CIs) are given for the DM-C and OS cohorts, without and with biomarker calibration of consumption estimates. Biomarker calibration clearly has a major impact on HR estimates, with evidence for positive associations between calibrated energy and total cancer, as well as certain site-specific cancers, in both the DM-C and OS cohorts, but with little evidence of association for uncalibrated energy. There is also little evidence of difference in HRs between the two cohorts, with or without calibration, with the possible exception of leukemia.

The upper part of Figure 1 shows corresponding HR estimates and 95% confidence intervals from analysis of the two cohorts combined. Calibrated energy is positively related to total (HR=1.18, 95% 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), endometrium (HR=1.83, 95% CI: 1.49, 2.25), and kidney cancer (HR=1.47, 95% CI: 1.00, 2.16), 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 HRs reflects both uncertainty in the coefficients of the calibration equations, and de-attenuation that arises from acknowledging dietary assessment measurement error in the HR estimation procedure.

Analyses of calibrated protein and % of energy from protein similarly yielded little evidence of HR differences between the two cohorts (each $P > 0.05$). The middle and lower panels of Figure 1 show corresponding combined cohort HRs and 95% confidence intervals for a 20% increase in these nutritional factors. The HRs for a 20% increase in calibrated protein are above one 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 HR estimates for % energy from protein are less than one for total and most specific cancers, and the inverse association is significant for total cancer (HR=0.92, 95% CI: 0.85, 0.99 for a 20% increase in % of energy from protein). Results corresponding to Figure 1 by quartile of calibrated consumption are given in Appendix Table A2.

The correlation coefficients for BMI with log-transformed energy, protein and % 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 BMI associations, with total or site-specific cancer. Table 5 examines the effect of including BMI in the log-HR model on the calibrated energy HRs shown in Figure 1, and also shows the effect of including calibrated energy on the HR for BMI. HRs for both energy and BMI are not significant

for most cancer sites and may be unstable, in the presence of the other variable, and CIs are wide.

DISCUSSION

This report has both methodologic 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-report 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 % 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 % 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, endometrium, 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 1).

Measurement error has typically been acknowledged in epidemiology reporting through a simple de-attenuation factor, as befits measurement Model B in the absence of systematic bias (i.e., $S_2 = S_3 = 0$). Such de-attenuation typically has little effect on significance levels. The presence of systematic bias changes this feature, however, since 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, on 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 BMI imply that log FFQ energy does not adhere to a simple classical measurement model. A linear regression of BMI on log-calibrated energy gives a projected BMI 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 these diseases. Table 5 likewise suggests that much of the dependence of cancer incidence rates on BMI 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 OS. However, this extrapolation is under near optimal conditions as the two 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 (e.g., 27, 28) could be informative.

As noted above, the NBS was conducted in 2004-2005, an average of about 6.5 years after the 1-year FFQ data collection for the DM-C women, and about 4 years on average after the 3-year FFQ data collection for OS women. Our application assumes that the calibration equations developed from NBS data apply to FFQs at these earlier time points. Also, the biomarker data provide consumption estimates over a rather short period of time (e.g., six months between initial and repeat application in 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 % of energy from protein and bladder cancer (Figure 1) 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 mechanisms leading to elevated cancer risk with high

energy consumption. However, 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 BMI 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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Figure Legend:

Figure 1. Estimated Hazard Ratios and 95% Confidence Intervals for a 20% Increase in Energy, Protein, or % of Energy from Protein Consumption, from Combined Analysis of Data from the Women's Health Initiative Dietary Modification Trial Comparison Group (DM-C) and Observational Study (OS), Without and With Biomarker Calibration of Consumption: Open box – uncalibrated, Black circle – calibrated; A) Energy, kcal/day; B) Protein, g/day; C) Percent of energy from protein.

Table 1. Subject Characteristics for Women in the Women’s Health Initiative Dietary Modification Trial Comparison Group (DM-C) and Observational Study (OS).

Characteristic		DM-C (N=21711) [†] % (No.)	OS (N=59105) [†] % (No.)
Age (years) [‡]	50-59	30 (6421)	19 (11135)
	60-69	48 (10495)	43 (25257)
	70-79	21 (4667)	35 (20555)
	80-89	1 (128)	4 (2158)
BMI	Normal (<25.0)	26 (5704)	42 (24938)
	Overweight (25.0-29.9)	36 (7767)	34 (20361)
	Obese (≥ 30)	38 (8239)	23 (13806)
Race	White	82 (17889)	86 (51028)
	Black	10 (2161)	6 (3661)
	Hispanic	3 (725)	3 (1736)
	Other*	4 (936)	5 (2680)
Income (total yearly)	< \$20,000	15 (3218)	14 (8159)
	\$20,000-\$34,999	25 (5335)	23 (13605)
	\$35,000-\$49,999	21 (4593)	21 (12214)
	\$50,000-\$74,999	21 (4546)	21 (12407)
	\$75,000+	18 (4009)	22 (12720)
Education	< High school diploma	4 (893)	4 (2196)
	High school diploma/GED	18 (3803)	16 (9379)
	School after high school	40 (8593)	36 (21421)
	College degree or higher	39 (8422)	44 (26109)
Smoking	Current	6 (1392)	6 (3307)
	Past	52 (11373)	51 (30232)
	Never	41 (8946)	43 (25566)
Recreational Physical Activity (METs/week)	< 1.5	25 (5335)	16 (9508)
	1.5 – 6.2	25 (5378)	20 (11715)
	6.3 – 14.7	26 (5541)	27 (15708)
	> 14.8	25 (5457)	38 (22174)
Breast cancer family history	Yes	18 (3729)	19 (10631)
Gail 5-year risk score	< 1.00%	15 (3355)	11 (6778)
	1.00-1.99%	62 (13368)	62 (36531)
	2.00-2.99%	14 (3073)	16 (9623)
	≥ 3.00%	9 (1915)	10 (6173)

Colon cancer family history	yes	16 (3257)	17 (9006)
History of polyps	yes	8 (1780)	9 (5275)
Unopposed Estrogen use ever	yes	37 (8084)	38 (22736)
Estrogen + Progesterone use ever	yes	28 (6054)	31 (18395)
Diabetes	yes	6 (1313)	5 (2664)
Hypertension	yes	41 (8909)	37 (22029)
Alcohol use	Non drinker	10 (2086)	10 (6063)
	< 1 drink/week	36 (7708)	32 (18768)
	1-7 drinks/week	27 (5923)	27 (16048)
	7+ drinks/week	10 (2116)	14 (8010)
	Past drinker	18 (3878)	17 (10216)

*Age at FFQ measurement (Year 1 DM-C and Year 3 OS)

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

Table 2. Incidence of Invasive Cancer in the Women’s Health Initiative Dietary Modification Trial Comparison Group (DM-C) and Observational Study (OS) Following Year 1 (DM-C) and Year 3 (OS) Food Frequency Data Collection.

Cancer Site	Incidence per 1000 person-years (number of cases)		
	DM-C (N=21711) [†]	OS (N=59105) [†]	Total (N=80816) [†]
Total Cancer*	12.34 (1807)	11.06 (3234)	11.48 (5041)
Breast	4.98 (685)	4.73 (1018)	4.83 (1703)
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)

*Exclusive of non-melanoma skin cancer

[†]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.

Table 3. Geometric Mean Consumption and 95% Confidence Intervals for Uncalibrated Dietary Consumption as Estimated by the Women’s Health Initiative (WHI) Food Frequency Questionnaire, and for Calibrated Consumption Using Nutritional Biomarker Data, in the WHI Dietary Modification Trial Comparison Group (DM-C) and Observational Study (OS).

	Geometric Mean (95 % Confidence Interval)					
	Energy (kcal/day)		Protein (g/day)		% of Energy from Protein	
	Uncalibrated	Calibrated*	Uncalibrated	Calibrated	Uncalibrated	Calibrated
DM-C (N=21,711)	1477.2 (676.6, 3224.9)	2140.6 (1786.9, 2564.2)	61.2 (26.3, 142.1)	78.1 (58.4,104.4)	16.6 (11.5, 24.0)	14.4 (11.9, 17.3)
OS (N=59,105)	1384.3 (641.0, 2989.4)	2055.8 (1722.3, 2453.9)	58.6 (24.8, 138.1)	74.2 (54.8, 100.5)	16.9 (11.5, 25.0)	14.4 (11.8, 17.6)

*Calibrated using measurement model A for women in the Nutrition Biomarker Study, and model B otherwise.

Table 4. Hazard Ratio (HR) Estimates for a 20% Increase in Energy (kcal/day) Consumption in the WHI Dietary Modification Trial Comparison Group (DM-C) and the WHI Observational Study (OS), Without and With Biomarker Calibration.

Cancer Site	DM-C		OS		Test of Equality of HRs	
	Uncalibrated HR* (95%CI)	Calibrated HR* (95%CI) [†]	Uncalibrated HR* (95%CI)	Calibrated HR* (95%CI) [†]	Uncalibrated P-value [‡]	Calibrated P-value [‡]
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

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

[†]95% Confidence intervals for calibrated HRs are based on log-estimated HR \pm 1.96 x bootstrap standard error.

[‡]P-value based on difference between log-HRs from DM-C and OS cohorts, with bootstrap estimate of standard deviation for the difference between the calibrated log-HRs.

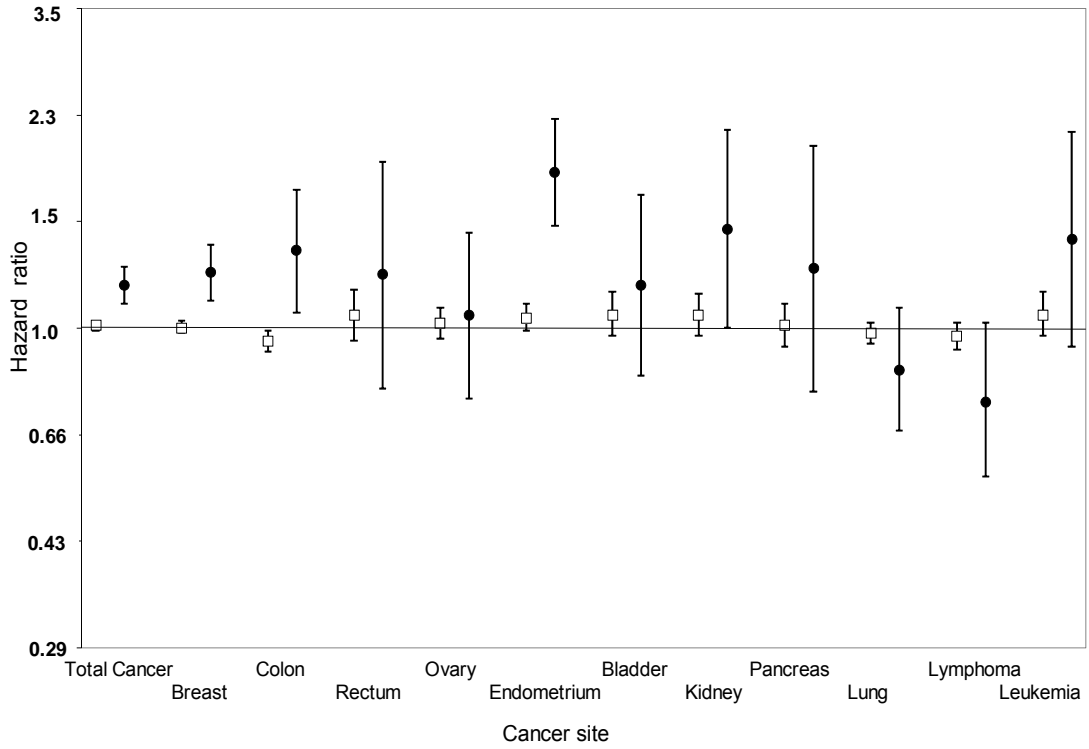
Table 5. Hazard Ratio (HR) Estimates for a 20% Increase in Calibrated Energy (kcal/day) Consumption and for a 10-unit Increase in Body Mass Index (BMI), in Analyses that Either Exclude (Unadjusted) or Include (Adjusted) the Other Variable, Using Data from WHI Dietary Modification Trial Comparison Group and Observational Study.

Cancer Site	Calibrated Energy		BMI	
	BMI Unadjusted HR (95%CI)*	BMI Adjusted HR (95%CI)*	Energy Unadjusted HR (95%CI)	Energy Adjusted HR (95%CI)*
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)

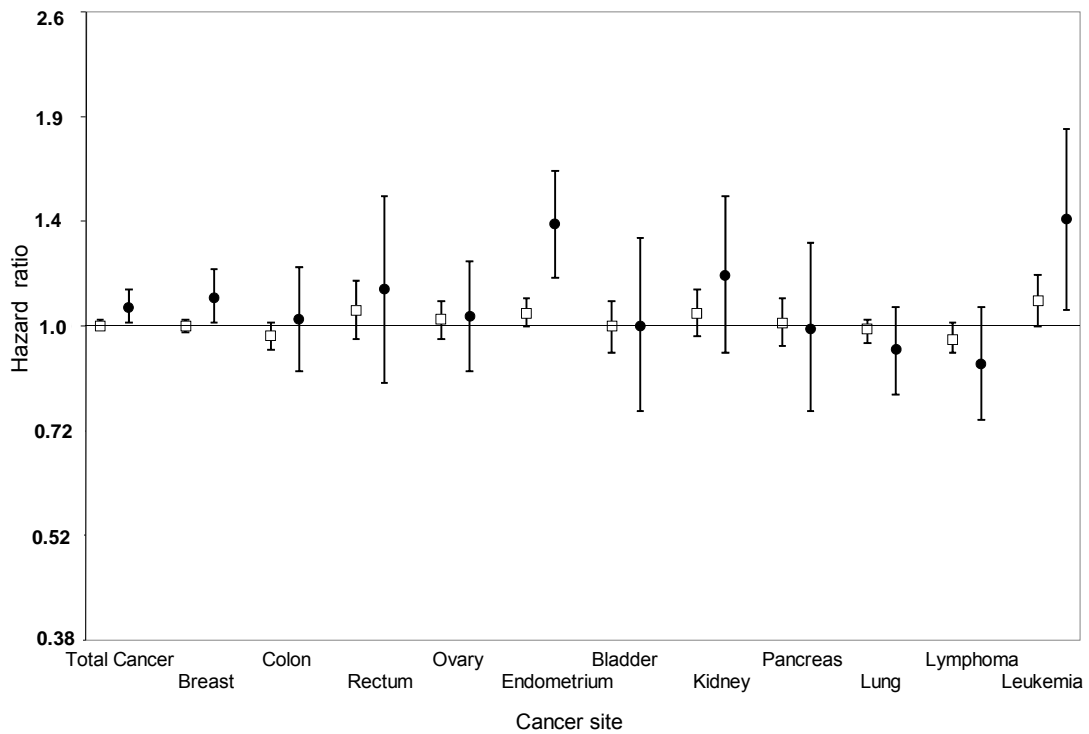
*95% confidence intervals for analyses that include calibrated energy are based on log-estimated HR $\pm 1.96 \times$ bootstrap standard error.

Figure 1.

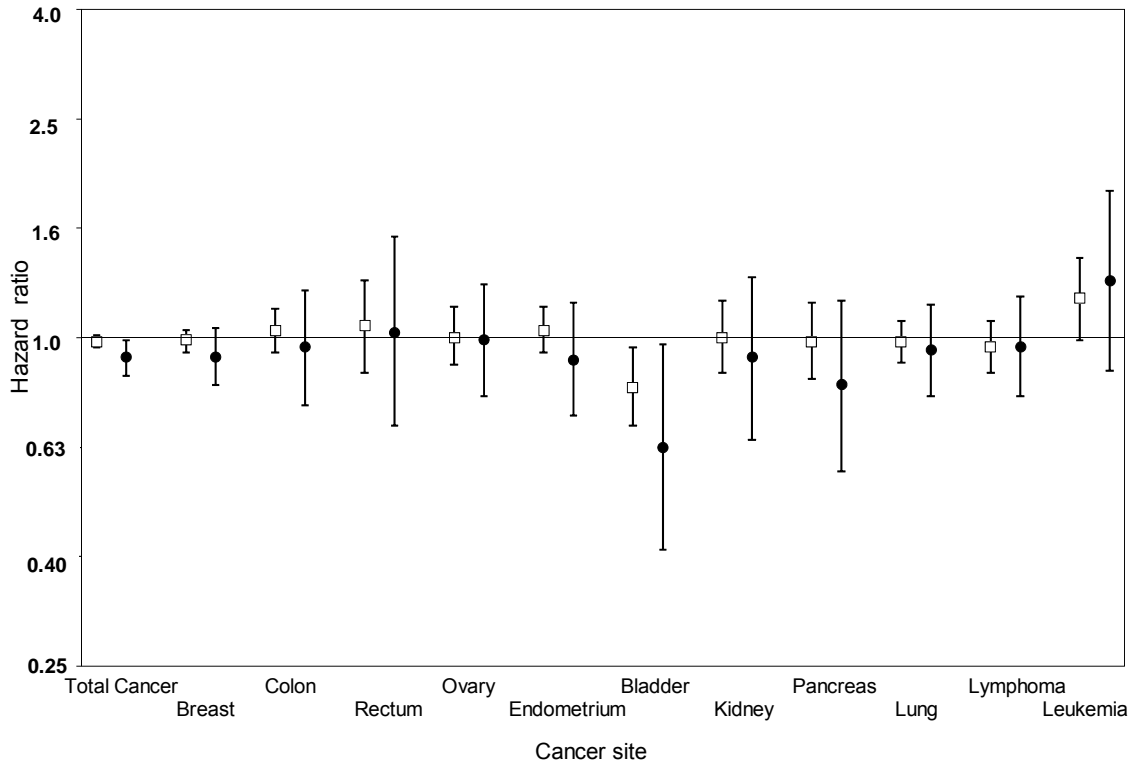
A)



B)



C)



Appendix Table A1. Factors Included in Cox Model Hazard Ratio Analyses to Control Confounding, for Each Cancer Outcome. (The same factors were used for the Dietary Modification comparison group (DM-C) and Observational Study (OS) cohorts.)

Cancer Site	Total Cancer	Breast	Colon Rectum	Ovary	Endo- metrium	Bladder Kidney Pancreas Lung	Lymphoma Leukemia
Race* (white/other, black, Hispanic)	x	x	x [†]		x	x [§]	
Education (high school or less, beyond H.S, college degree)	x	x					
Exercise (METs/week)	x	x	x				
Smoking* (never, past, current)	x	x	x			x	x ^{††}
Alcohol* (never, past, <1/wk, 1-7/wk, >7/wk)	x	x	x			x	
Breast cancer family history (no, yes)		x		x			
Gail 5-yr risk (5-yr absolute risk %)		x					
Unopposed Estrogen use ever (no, yes)	x	x	x [†]	x	x		
Estrogen plus Progesterone use ever (no, yes)	x	x	x [†]	x	x		
Colon cancer family history (no, yes)			x				

Appendix Table A1 (continued).

Cancer Site	Total Cancer	Breast	Colon Rectum	Ovary	Endo- metrium	Bladder Kidney Pancreas Lung	Lymphoma Leukemia
History of colorectal polyps (no, yes)			x [†]				
History of diabetes (no, yes)	x						
Hypertension (no, yes)	x				x	x [‡]	

*For rare cancers: race: black/Hispanic (yes/no); smoking: ever (yes/no); alcohol: nondrinker (past/never), light drinker (<1 drink/wk), moderate/heavy (1+ drinks/wk).

[†]Colon cancer only

[§]Lung only

[‡]Kidney only

[¶]Leukemia only

Appendix Table A2. Hazard Ratios by Quartile of Biomarker-calibrated Nutrition Consumption from the Analyses of Combined Data from the WHI Dietary Modification Trial Comparison Group (DM-C) and Observational Study (OS).

Cancer Site	Energy (kcal/day) HR (95% CI)*			Protein (g/day) HR (95% CI)*			% of Energy from Protein HR (95% CI)*		
	Quartile 2	Quartile 3	Quartile 4	Quartile 2	Quartile 3	Quartile 4	Quartile 2	Quartile 3	Quartile 4
Total Cancer	1.07 (0.97, 1.17)	1.07 (0.97, 1.19)	1.18 (1.07, 1.31)	1.07 (0.97, 1.18)	1.10 (0.99, 1.22)	1.09 (0.98, 1.22)	0.94 (0.85,1.04)	0.94 (0.85,1.04)	0.92 (0.82,1.04)
Breast	1.07 (0.90, 1.28)	1.17 (0.98, 1.40)	1.33 (1.12, 1.58)	1.15 (0.97, 1.36)	1.07 (0.90, 1.28)	1.22 (0.99, 1.49)	0.97 (0.83,1.13)	0.92 (0.78,1.09)	0.94 (0.78,1.12)
Colon	1.27 (0.88, 1.85)	1.12 (0.78, 1.60)	1.51 (1.03, 2.21)	0.97 (0.70, 1.34)	1.11 (0.76, 1.61)	0.96 (0.64, 1.44)	0.83 (0.58,1.2)	0.98 (0.71,1.35)	1.06 (0.74,1.51)
Rectum	1.82 (0.81, 4.08)	2.34 (1.04, 5.26)	1.51 (0.64, 3.58)	1.22 (0.56, 2.65)	1.57 (0.72, 3.41)	1.08 (0.48, 2.41)	0.85 (0.43,1.67)	1.24 (0.63,2.44)	1.01 (0.52,1.96)
Ovary	1.23 (0.78, 1.93)	1.19 (0.75, 1.89)	0.91 (0.58, 1.43)	0.68 (0.42, 1.10)	1.10 (0.73, 1.66)	0.85 (0.55, 1.31)	1.16 (0.76,1.77)	1.13 (0.72,1.8)	1.08 (0.69,1.69)
Endometrium	1.02 (0.66, 1.57)	1.26 (0.81, 1.96)	2.03 (1.38, 3.00)	1.36 (0.91, 2.04)	1.59 (1.08, 2.35)	1.85 (1.26, 2.70)	0.92 (0.65,1.29)	0.99 (0.71,1.39)	0.92 (0.63,1.35)
Bladder	1.76 (0.89, 3.46)	2.14 (1.02, 4.51)	1.05 (0.47, 2.39)	1.11 (0.54, 2.28)	1.25 (0.64, 2.45)	0.96 (0.45, 2.05)	0.72 (0.39,1.33)	0.84 (0.44,1.58)	0.58 (0.28,1.22)
Kidney	1.42 (0.77, 2.62)	1.31 (0.71, 2.43)	1.44 (0.80, 2.61)	1.12 (0.62, 2.03)	0.98 (0.53, 1.80)	1.31 (0.73, 2.36)	0.8 (0.44,1.48)	1.1 (0.63,1.92)	0.86 (0.48,1.53)
Pancreas	0.94 (0.49, 1.79)	1.24 (0.67, 2.32)	1.33 (0.68, 2.60)	1.41 (0.82, 2.41)	0.95 (0.47, 1.92)	1.19 (0.60, 2.37)	0.89 (0.54,1.44)	0.65 (0.36,1.17)	0.92 (0.56,1.53)
Lung	0.90 (0.68, 1.19)	0.75 (0.53, 1.07)	0.79 (0.58, 1.08)	1.00 (0.75, 1.34)	1.05 (0.76, 1.43)	0.78 (0.55, 1.10)	0.99 (0.73,1.33)	0.9 (0.66,1.23)	0.92 (0.67,1.26)

Appendix Table A2 (continued).

Cancer Site	Energy (kcal/day) HR (95% CI)*			Protein (g/day) HR (95% CI)*			% of Energy from Protein HR (95% CI)*		
	Quartile 2	Quartile 3	Quartile 4	Quartile 2	Quartile 3	Quartile 4	Quartile 2	Quartile 3	Quartile 4
Lymphoma	0.99 (0.70, 1.42)	0.81 (0.54, 1.21)	0.66 (0.42, 1.03)	0.88 (0.59, 1.30)	0.96 (0.63, 1.44)	0.68 (0.41, 1.11)	1.11 (0.77,1.59)	0.89 (0.61,1.28)	0.93 (0.61,1.4)
Leukemia	1.46 (0.71, 3.03)	1.63 (0.84, 3.18)	1.46 (0.69, 3.10)	1.38 (0.64, 2.99)	2.05 (1.02, 4.09)	1.77 (0.82, 3.81)	1.29 (0.74,2.24)	1.28 (0.73,2.25)	1.39 (0.76,2.54)

*Estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for second, third, and fourth quartiles relative to the first of biomarker-calibrated nutrient consumption. Confidence intervals for log-HRs derive from log-HR estimate ± 1.96 times the corresponding bootstrapped standard deviation estimate.