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ORIGINAL REPORT

Protein Intake and Breast Cancer Survival in the Nurses' Health Study

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ABSTRACT

Purpose

Greater protein intake has been associated with better breast cancer survival in several prospective studies, including among 1,982 women in the Nurses' Health Study. We proposed to extend this previous finding. We hypothesized that protein, essential amino acid, branched-chain amino acid, and leucine intakes are associated with improved survival and that these associations are stronger in tumors expressing insulin receptor (IR).

Patients and Methods

We included 6,348 women diagnosed with stage I to III breast cancer between 1976 and 2004. There were 1,046 distant recurrences. Relative risks (RRs) and 95% CIs were calculated according to quintiles of updated postdiagnostic diet using adjusted Cox proportional hazards models based on follow-up until 2010.

Results

There was an inverse association between energy-adjusted protein intake and recurrence. Multivariable RRs for increasing quintiles of intake compared with the lowest were 0.95 (95% CI, 0.79 to 1.15), 0.92 (95% CI, 0.76 to 1.11), 0.75 (95% CI, 0.61 to 0.91), and 0.84 (95% CI, 0.69 to 1.03; trend $P = .02$). For animal protein intake, the RRs were 0.88 (95% CI, 0.73 to 1.06), 0.85 (95% CI, 0.70 to 1.02), 0.75 (95% CI, 0.62 to 0.92), and 0.78 (95% CI, 0.63 to 0.95; trend $P = .003$). Neither essential amino acids, branched-chain amino acids, nor any individual amino acid stood out as being the source of the association. The association also did not differ by IR status. There was no clear association with any protein-containing foods.

Conclusion

We found a modest survival advantage with higher intake of protein, regardless of IR status. There was no clear mechanism for this association, although it is consistent with prior studies. Our data suggest that there is likely no advantage for women with a history of breast cancer in restricting protein intake or protein-containing foods.

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INTRODUCTION

Greater protein intake has been associated with better breast cancer survival in several prospective studies,[1-3] including a report of 1,982 women in the Nurses' Health Study (NHS), the largest to date.[4] Reasons for this association are unknown.

There has been recent interest in measures of protein quality and health effects.[5] In particular, the role of essential amino acids (lysine, threonine, valine, isoleucine, leucine, methionine, phenylalanine, tryptophan, and histidine) in preservation of lean body mass, cell signaling, glucose metabolism, bone health, and satiety is an area of active research.[6] The branched-chain amino acids (leucine, isoleucine, and valine) modulate muscle protein synthesis through the insulin-signaling pathway and are abundant in the food supply, particularly from dairy products.[7] Leucine in particular improves weight loss, inhibits skeletal muscle breakdown, and stimulates muscle protein synthesis by enhancing insulin sensitivity,[8,9] and glutamine improves insulin sensitivity in vivo.[10,11] The beneficial effects of protein on fat-free mass seem to be additive with physical activity.[7,12,13]

The NHS previously reported a decreased risk of death resulting from any cause with higher protein intake among 1,982 women (relative risk [RR], 0.65).[4] With an additional 16 years of follow-up and more than 4,000 additional patient cases,

ASSOCIATED CONTENT

Appendix
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we proposed to study breast cancer recurrence and death resulting from breast cancer as well as the association of survival with intake of total protein and type of protein. Protein types included that from vegetable and animal sources, including fish, dairy, red meat, poultry, and eggs. We also proposed to study essential amino acids, branched-chain amino acids, and individual food sources.

We hypothesized that total protein, essential amino acid, branch-chain amino acid, and leucine intakes are associated with improved survival after breast cancer. We also hypothesized that these associations are strongest in tumors expressing insulin receptor (IR) because of the associations of these amino acids with the insulin pathway.

PATIENTS AND METHODS

Study Population

The NHS is a cohort established in 1976, when 121,700 female nurses in the United States, then age 30 to 55 years, responded to a questionnaire regarding medical and lifestyle factors. Since then, follow-up questionnaires have been sent biannually. Beginning in 1980, participants completed a 61-item food frequency questionnaire (FFQ),[14] which was expanded to 116 items beginning in 1984.

The study was approved by the institutional review board of Brigham and Women's Hospital (Boston, MA), and all participants provided written informed consent. Our analysis included women diagnosed with stage I to III breast cancer between 1976 and 2004 (those with missing stage [n = 726] or stage IV at diagnosis [n = 180] were excluded), with diet data beginning in 1980 (N = 8,004). Women who had died or whose cancer had recurred within 1 year of primary diagnosis (n = 293) or who had missing diet information at least 12 months after diagnosis (n = 1,363) were excluded from analysis. After these exclusions, 6,348 participants were available for this analysis.

Assessment of Dietary Intake

Dietary assessments were administered in 1980, 1984, 1986, 1990, 1994, 1998, 2002, and 2006 using validated semiquantitative FFQs.[14] For each food or beverage, participants were asked how often, on average, they had consumed a specified amount over the past year. Mean daily intakes of dietary factors were calculated using US Department of Agriculture food composition sources, supplemented with data from manufacturers and other sources. The baseline diet was the one that most closely followed the diagnosis, with a minimum lag of 12 months. Previous validation studies have reported strong correlations between energy-adjusted nutrients assessed by the FFQ and food records completed over the previous year.[15]

End Point Ascertainment

Participants self-reported breast cancer diagnosis on the biennial questionnaires. We then obtained permission to view pathology records to confirm diagnosis and obtain information on staging and other relevant information. Participants were observed until death or June 1, 2010, whichever occurred first. Deaths were reported by family members or the postal service or determined through searches in the National Death Index for questionnaire nonresponders.[16] Cause of death was ascertained by physician review of the death certificate and medical record. Ascertainment of the cause of death in this cohort is estimated to be 98%.[16]

Women reported recurrence on supplemental biennial questionnaires. In a validation study, we found that self-reported recurrence had a sensitivity and specificity of 92% compared with medical records. In addition, women who died as a result of breast cancer and did not answer the supplemental questionnaire were considered to have experienced recurrence 2 years before death (ie, median survival time in stage IV breast cancer). We assumed breast cancer had recurred if a woman diagnosed with breast cancer reported a second cancer to a common site of breast cancer recurrence (liver, brain, or bone). Medical records of women who reported a second cancer to the lung were reviewed to distinguish between primary lung cancer and breast cancer metastasis.[17] The number of recurrences calculated in this manner was similar to the number expected from recurrence rates found in a large trial of women with early-stage breast cancer (N = 5,569).[18] Distant breast cancer recurrence was the primary end point. Death resulting from breast cancer and total mortality were secondary end points.

Assessment of IR and Estrogen Receptor Status

Tissue microarrays were constructed in the Dana-Farber Harvard Cancer Center Tissue Microarray Core Facility (Boston, MA) from 4,308 formalin-fixed, paraffin-embedded incident breast cancers from 1976 to 2008, using three 0.6-mm cores from each breast cancer.[19-21] IR expression (cytoplasmic and membranous) was quantified using Definiens image analysis software (http://www.definiens.com). We calculated an IR H score as a weighted sum of the intensity of immunohistochemical cytoplasmic and membranous expression as follows: H score = % of positively stained cells at weak intensity category X 1 + % of positively stained cells at median intensity category X 2 + % of positively stained cells at high intensity category X 3.[21] In a subset of 124 patient cases, we observed a sensitivity and specificity of 83% and 69%, respectively, with manual reading as the gold standard. Median H score was chosen as the cutoff for IR positivity. Immunohistochemical staining was performed for estrogen receptor (ER) using previously described methods.[19,20]

Covariates

Body mass index (BMI; five categories), weight change, menopausal status, hormone therapy use, age at first birth, parity, alcohol consumption, aspirin use, and oral contraceptive use were included, because these factors were previously shown to be associated with breast cancer survival in the NHS cohort.[4,22-24] In addition, we adjusted for breast cancer characteristics, including year of diagnosis, disease stage (I, II, or III), self-reported radiation therapy (yes or no), chemotherapy (yes or no), and hormonal treatment (yes or no). Smoking was also included because of its association with total mortality. Physical activity measured in total metabolic equivalent task hours per week was first assessed in 1986 and updated in 1988, 1992, 1996, 1998, 2000, 2004, and 2008. To avoid assessment during active treatment, only measurements taken at least 12 months after diagnosis were considered. Energy intake (five categories) and alcohol consumption (five categories) were first assessed using the questionnaire that most closely followed at least 12 months after breast cancer diagnosis. All other covariates were taken from the questionnaire preceding diagnosis.

Statistical Analyses

Baseline diet was ascertained using the first FFQ at least 12 months after breast cancer diagnosis. This was done to allow completion of active treatment, which may affect diet. To reduce random within-person variation and best represent the long-term effects of dietary intake, cumulative averages of the diet scores from repeated FFQs were computed and updated, as described elsewhere.[25] Women were categorized into quintiles of nutrient and food intakes. Two-tailed P values for linear trend tests across quintiles were computed by modeling the median value of each category as a continuous variable.

We used Cox proportional hazards models to assess the association between quintiles of energy-adjusted nutrient and food intakes and outcomes of interest. All Cox models were tested for proportionality of hazards by testing the statistical significance of time-varying covariates, created as interactions between each predictor and the log of the event time.[26] Distant breast cancer recurrence was the primary end point. Secondary analyses considered death resulting from breast cancer and total mortality. For each participant, breast cancer diagnosis marked the beginning of follow-up. Person-months were accumulated until the analysis end point or June 2010, whichever occurred first.

Because time since diagnosis is a strong predictor of breast cancer survival, all models were stratified by time since diagnosis. In addition, simple models were adjusted for age. Multivariate models were adjusted for the covariates listed in Covariates and are detailed in the table footnotes. In addition, we conducted analyses stratified by the ER or IR status of the tumor and by BMI at diagnosis (< 30 *v* ≥ 30 kg/m^2). Analyses stratified by IR or ER were performed using a statistical method for disease heterogeneity analysis for categorical subtypes in cohort studies, with a competing risk framework using a Cox proportional hazards model.[27] The analysis stratified by BMI was performed using a stratified Cox model, using the likelihood ratio test to determine the statistical significance of the interaction term. We used a nonparametric analysis (SAS PROC LIFETEST; SAS Institute, Cary, NC) to generate Kaplan-Meier survival curves by quintile of protein intake and calculate absolute unadjusted recurrence differences 5 and 10 years after diagnosis. Statistical analyses were performed using SAS software (version 9.3). *P* values of less than .05 were considered significant.

RESULTS

There were 6,348 participants included in the analysis and 1,046 distant recurrences, 919 deaths resulting from breast cancer, and 1,847 total deaths. The age-standardized summary of baseline characteristics according to quintiles of total protein intake is provided in Table 1. Of note, more physically active women seemed to consume more protein.

Main results are listed in Table 2, summarizing the association between intake of protein, amino acids, and protein-containing food groups with distant breast cancer recurrence. The difference between simple (adjusted for age, total energy intake, and time

Table 1. Age-Standardized Summary of Baseline Characteristics

	Quintile of Total Protein Intake				
Characteristic	First (n = 1,238)	Second (n = 1,312)	Third (n = 1,294)	Fourth (n = 1,281)	Fifth (n = 1,223)
Weight change, %					
Same	32	33	33	31	28
Loss ($\geq$ 0.5 kg/m^2)	27	27	29	29	27
Gain ($\geq$ 0.5 kg/m^2)	40	41	38	40	45
Aspirin use, %					
Never	12	11	11	10	12
Past	43	40	42	39	38
Current, d/wk					
1	11	10	10	11	11
2-3	5	6	5	7	6
4-5	5	4	4	4	4
$\geq$ 6	23	29	28	28	29
Age at first birth and parity, %					
No births	6	7	7	6	6
< 25 years, 1 or 2 births	14	13	14	14	15
< 25 years, > 2 births	33	35	34	33	33
$\geq$ 25 years, 1 or 2 births	25	21	21	22	22
$\geq$ 25 years, > 2 births	23	23	24	25	24
Oral contraceptive use, %					
Never	56	55	53	52	52
Ever	44	45	47	48	48
Smoking status before diagnosis, %					
Never-smoker	40	39	43	42	46
Past	40	45	42	44	43
Current	21	16	14	14	11
Stage at diagnosis, %					
I	60	65	63	63	63
II	34	30	31	31	32
III	6	5	7	6	5
Menopausal status and hormone use before disease, %					
Premenopausal	18	18	18	19	19
Post, never	25	22	21	21	24
Post, current	32	35	35	35	34
Post, past	19	20	20	21	19
Unknown or missing	5	5	5	4	5
ER positive, %	80	81	80	83	81
Radiation therapy, %	53	56	55	56	53
Tamoxifen use, %	69	68	67	70	71
Chemotherapy, %	35	35	37	36	36
BMI one cycle before diagnosis, kg/m^2	24.9	25.3	25.9	26.2	27.4
Alcohol, g/d	10.2	8.2	6.1	5.8	4.1
Physical activity, MET hr/wk	14.4	15.6	16.4	16.3	16.9

NOTE. Values are standardized to the age distribution of the study population. Values of polytomous variables may not sum to 100% because of rounding.
Abbreviations: BMI, body mass index; ER, estrogen receptor; MET, metabolic equivalent of task.

Table 2. Protein, Amino Acids, and Animal Protein–Containing Food Groups and Distant Breast Cancer Recurrence in NHS

Type of Nutrient	Quintile of Nutrient Intake					P_{trend}
	First	Second	Third	Fourth	Fifth	
Total protein						
No. of recurrences	245	216	213	179	193	
Median value of quintile, g/d	61.5	71.9	76.4	80.9	88.3	
Simple model, RR (95% CI)*	1.00†	0.83 (0.69 to 1.00)	0.79 (0.66 to 0.95)	0.66 (0.55 to 0.81)	0.79 (0.65 to 0.95)	< .001
Multivariable model, RR (95% CI)‡	1.00†	0.95 (0.79 to 1.15)	0.92 (0.76 to 1.11)	0.75 (0.61 to 0.91)	0.84 (0.69 to 1.03)	.02
Animal protein						
No. of recurrences	262	210	207	187	190	
Median value of quintile, g/d	41.5	52.1	56.2	60.7	68.5	
Simple model, RR (95% CI)*	1.00†	0.80 (0.66 to 0.96)	0.75 (0.62 to 0.90)	0.71 (0.59 to 0.86)	0.75 (0.62 to 0.91)	< .001
Multivariable model, RR (95% CI)‡	1.00†	0.87 (0.73 to 1.05)	0.83 (0.69 to 1.00)	0.73 (0.60 to 0.89)	0.74 (0.61 to 0.91)	< .001
Multivariable model, RR (95% CI)§	1.00†	0.88 (0.73 to 1.06)	0.85 (0.70 to 1.02)	0.75 (0.62 to 0.92)	0.78 (0.63 to 0.95)	.003
Vegetable protein						
No. of recurrences	181	194	208	220	243	
Median value of quintile, g/d	14.3	17.7	19.8	21.6	25.0	
Simple model, RR (95% CI)*	1.00†	0.85 (0.69 to 1.04)	0.87 (0.71 to 1.06)	0.89 (0.73 to 1.08)	0.95 (0.78 to 1.15)	.91
Multivariable model, RR (95% CI)‡	1.00†	1.09 (0.88 to 1.34)	1.11 (0.90 to 1.37)	1.19 (0.96 to 1.47)	1.29 (1.05 to 1.59)	.01
Multivariable model, RR (95% CI)‖	1.00†	1.07 (0.87 to 1.32)	1.09 (0.88 to 1.34)	1.14 (0.92 to 1.41)	1.20 (0.97 to 1.49)	.08
Essential amino acids						
No. of recurrences	245	221	210	179	191	
Median value of quintile, g/d	4.1	8.5	12.7	16.5	19.9	
Simple model, RR (95% CI)*	1.00†	0.90 (0.75 to 1.08)	0.81 (0.67 to 0.97)	0.69 (0.57 to 0.84)	0.86 (0.71 to 1.04)	.005
Multivariable model, RR (95% CI)‡	1.00†	1.01 (0.84 to 1.21)	0.91 (0.76 to 1.10)	0.75 (0.61 to 0.91)	0.86 (0.71 to 1.05)	.008
Multivariable model, RR (95% CI)¶	1.00†	0.96 (0.67 to 1.38)	0.85 (0.53 to 1.36)	0.71 (0.39 to 1.26)	0.63 (0.31 to 1.30)	.20
Branched-chain amino acids						
No. of recurrences	251	223	201	180	191	
Median value of quintile, g/d	4.1	8.4	12.7	16.5	19.9	
Simple model, RR (95% CI)*	1.00†	0.87 (0.72 to 1.04)	0.76 (0.63 to 0.92)	0.69 (0.57 to 0.83)	0.81 (0.67 to 0.98)	.001
Multivariable model, RR (95% CI)‡	1.00†	0.99 (0.82 to 1.19)	0.87 (0.72 to 1.05)	0.77 (0.63 to 0.94)	0.82 (0.68 to 1.00)	.004
Multivariable model, RR (95% CI)#	1.00†	0.90 (0.65 to 1.24)	0.74 (0.48 to 1.12)	0.68 (0.41 to 1.12)	0.58 (0.32 to 1.05)	.06
Animal protein–containing food groups						
Red meat						
No. of recurrences	242	223	198	192	191	
Median value of quintile, serving/d	0.40	0.67	0.89	1.15	1.67	
Simple model, RR (95% CI)*	1.00†	1.04 (0.87 to 1.26)	0.95 (0.78 to 1.15)	0.99 (0.81 to 1.21)	1.31 (1.05 to 1.62)	.05
Multivariable model, RR (95% CI)‡	1.00†	1.02 (0.84 to 1.23)	0.91 (0.75 to 1.11)	0.92 (0.74 to 1.13)	1.03 (0.83 to 1.29)	.93
Poultry						
No. of recurrences	208	232	203	213	190	
Median value of quintile, serving/d	0.14	0.22	0.32	0.41	0.56	
Simple model, RR (95% CI)*	1.00†	0.83 (0.69 to 1.01)	0.83 (0.68 to 1.01)	0.81 (0.66 to 0.98)	0.76 (0.62 to 0.93)	.02
Multivariable model, RR (95% CI)‡	1.00†	0.87 (0.72 to 1.05)	0.94 (0.78 to 1.16)	0.96 (0.79 to 1.18)	0.85 (0.69 to 1.05)	.39
Fish						
No. of recurrences	207	205	215	221	198	
Median value of quintile, serving/d	0.07	0.14	0.20	0.29	0.46	
Simple model, RR (95% CI)*	1.00†	0.91 (0.75 to 1.11)	0.88 (0.73 to 1.07)	0.84 (0.69 to 1.01)	0.81 (0.66 to 0.99)	.03
Multivariable model, RR (95% CI)‡	1.00†	0.90 (0.74 to 1.10)	1.01 (0.82 to 1.23)	0.99 (0.81 to 1.21)	0.93 (0.76 to 1.15)	.87
High-fat dairy						
No. of recurrences	219	208	210	221	188	
Median value of quintile, serving/d	0.33	0.64	0.96	1.43	2.49	
Simple model, RR (95% CI)*	1.00†	1.04 (0.86 to 1.26)	1.13 (0.93 to 1.37)	1.18 (0.97 to 1.44)	1.13 (0.91 to 1.39)	.13
Multivariable model, RR (95% CI)‡	1.00†	1.10 (0.90 to 1.34)	1.09 (0.90 to 1.33)	1.20 (0.98 to 1.46)	1.09 (0.88 to 1.35)	.30
Low-fat dairy						
No. of recurrences	225	221	215	201	184	
Median value of quintile, serving/d	0.14	0.50	0.86	1.30	2.15	
Simple model, RR (95% CI)*	1.00†	0.92 (0.76 to 1.11)	0.85 (0.71 to 1.03)	0.78 (0.65 to 0.95)	0.72 (0.59 to 0.88)	< .001
Multivariable model, RR (95% CI)‡	1.00†	1.07 (0.89 to 1.30)	1.03 (0.85 to 1.25)	0.92 (0.75 to 1.12)	0.84 (0.69 to 1.04)	.04

Abbreviations: NHS, Nurses' Health Study; RR, relative risk.
*Adjusted for age at diagnosis, time since diagnosis, and energy intake (quintiles).
†Referent.
‡Adjusted for age at diagnosis, time since diagnosis, energy intake (quintiles), body mass index (< 21, 21 to < 23, 23 to < 25, 25 to < 30, or ≥ 30 kg/m^2), weight change (same, loss, or gain), age at first birth and parity (nulliparous, one to two children and age at first birth < 25 years, ≥ two children and age at first birth < 25 years, one to two children and age at first birth ≥ 25 years, or two children and age at first birth ≥ 25 years), oral contraceptive use (never or ever), menopausal status and hormone therapy use (premenopausal, postmenopausal and never use, post and current use, post and past use, or unknown or missing menopausal information), aspirin use (never, past, current one to two tablets/wk, current three to five tablets/wk, current six to 14 tablets/wk, current ≥ 15 tablets/wk, or current unknown quantity), alcohol (0, > 0-5, > 5-15, or > 15 g/d), smoking (never, past, or current), physical activity (< 3, 3 to < 9, 9 to < 18, 18 to < 27, > 27 metabolic equivalents of task/wk, or missing), tumor stage (I, II, or III), radiation treatment (yes, no), other treatment (no chemotherapy and no tamoxifen, chemotherapy but no tamoxifen, or chemotherapy and tamoxifen), and calendar year.
§Adjusted for same variables in (‡) and vegetable protein (quintiles).
‖Adjusted for same variables in (‡) and animal protein (quintiles).
¶Adjusted for same variables in (‡) and nonessential amino acids (quintiles).
#Adjusted for same variables in (‡) and non–branched-chain amino acids (quintiles).

since diagnosis) and multivariable models (also adjusted for stage, treatment, and other covariates) was largely accounted for by adjustment for physical activity. Additional multivariable models adjusted for types of protein and amino acids were constructed to show their independent effect.

There was an inverse association between total protein intake and distant breast cancer recurrence. Multivariable RRs for increasing quintiles of intake compared with the lowest intake were 0.95 (95% CI, 0.79 to 1.15), 0.92 (95% CI, 0.76 to 1.11), 0.75 (95% CI, 0.61 to 0.91), and 0.84 (95% CI, 0.69 to 1.03; linear trend *P* = .02). This inverse association was accounted for by animal protein intake; multivariable RRs for quintiles of animal protein intake adjusted for vegetable protein intake were 0.88 (95% CI, 0.73 to 1.06), 0.85 (95% CI, 0.70 to 1.02), 0.75 (95% CI, 0.62 to 0.92), and 0.78 (95% CI, 0.63 to 0.95; *P* = .003).

The association for higher intake of essential amino acids (adjusted for nonessential amino acids) and branched-chain amino acids (adjusted for nonbranched chain amino acids) tended toward the inverse, although it did not reach statistical significance. Among animal protein–containing food groups, only low-fat dairy showed a borderline inverse association between higher intake and recurrence. Multivariable RRs across quintiles of intake (compared with lowest intake) were 1.07 (95% CI, 0.89 to 1.30), 1.03 (95% CI, 0.85 to 1.25), 0.92 (95% CI, 0.75 to 1.12), and 0.84 (95% CI, 0.69 to 1.05; linear trend *P* = .04).

Point estimates were similar when participants who contributed to the 1999 NHS report[4] were excluded, but because of fewer outcomes, results were less likely to be statistically significant. For example, the multivariable RRs of recurrence for increasing quintiles of intake of total protein compared with the lowest intake were 1.03 (95% CI, 0.76 to 1.39), 0.92 (95% CI, 0.68 to 1.25), 0.78 (95% CI, 0.56 to 1.07), and 0.87 (95% CI, 0.63 to 1.20; linear trend *P* = .18).

The 5-year recurrence-free survival for women in the highest quintile of protein consumption was 94.0%, and for those in the lowest quintile of protein consumption, it was 92.1% (Appendix Fig A1, online only) The corresponding 10-year recurrence-free survival rates were 87.4% and 83.3%, respectively. The absolute unadjusted risk reduction for recurrence was 1.9% at 5 years and 4.1% at 10 years for women who in the highest quintile of protein consumption compared with the lowest.

Results for death resulting from breast cancer (Table 3) were similar to those for recurrence, although they were less robust because of fewer outcomes. Associations between intakes of protein, amino acids, and protein-containing food groups and breast cancer recurrence did not differ by tumor IR status (Table 4).

In addition, we examined the association between intakes of individual amino acids and individual animal protein–containing foods and risk of distant breast cancer recurrence (Appendix Table A1, online only). Although all amino acids had an inverse relationship with recurrence, and for many, the *P* value for the linear trend was statistically significant, no one amino acid stood out from the others. Because we found an inverse association between total death and poultry intake in the 1999 NHS report,[4] it is intriguing to examine the results on poultry intake. Among protein-containing foods, intake of poultry with skin was inversely associated with distant recurrence (highest *v* lowest quintile: RR, 0.72; 95% CI, 0.59 to 0.89; linear trend *P* = .008), whereas intake of poultry without skin was nearly associated with an increased risk of distant recurrence (highest *v* lowest quintile: RR, 1.15; 95% CI, 0.94 to 1.41; linear trend *P* = .08), thus accounting for the lack of association of poultry as a food group with distant recurrence. Results for death resulting from breast cancer (Appendix Table A2, online only) were similar. Results examining total death (Appendix Table A3, online only) showed similar results for poultry with and without skin and no association with protein, type of protein, or individual amino acids. Association between risk of distant recurrence and protein, amino acids, and protein-containing food groups did not differ either by ER status of the tumor (Appendix Table A4, online only) or by BMI at diagnosis (Appendix Table A5, online only).

DISCUSSION

Our large prospective study of more than 6,000 breast cancer survivors confirmed the modest inverse association with protein intake and breast cancer survival that the NHS first reported in 1999. This association did not vary by IR status, ER status, or BMI at diagnosis. Three other studies (N = 412, 477, and 603) produced similar findings.[1-3] A similar association was reported in 1989 for mammary cancer in dogs.[28]

In the 1999 NHS report, a survival advantage was found for intakes of poultry and dairy products, but not red meat.[4] Our study differed from the previous NHS report in both size and ability to examine breast cancer recurrence and death resulting from breast cancer. We again found a lower risk of recurrence and death resulting from breast cancer with higher intake of protein. This was particularly true for protein from animal sources (meat, poultry, fish, dairy, and eggs). However, although the *P* value for the linear trend for the association with animal protein was .003, it is of note that the values for quintiles two to five (RR, 0.88, 0.85, 0.75, and 0.78, respectively) did not vary much. Thus, the inverse association between animal protein and recurrence seems to be present for any intake above the lowest. In addition, the distributions of intake were different for animal and vegetable proteins. For example, the median of the highest quintile of vegetable protein intake (25.0 g per day) was less than the median of the lowest quintile of animal protein intake (41.5 g per day; Table 2). It may be that intake of vegetable protein was not high enough in our population to detect a benefit.

Although results should be interpreted cautiously because of multiple comparisons, the inverse association with protein intake did not seem to be a result of specific amino acids or groups of amino acids (essential or branched chain). Contrary to our hypothesis, this association was not confined to tumors expressing IR. Therefore, it is difficult to invoke the insulin pathway as a mechanism to explain these findings.

Among animal protein–containing foods, we found only a borderline inverse association with low-fat dairy intake and found no association with total dairy or high-fat dairy intake. In 2013, Kroenke et al[29] reported no association between low-fat dairy or total dairy intake and death resulting from breast cancer among 1,893 women in the LACE (Life After Cancer Epidemiology) cohort, but they did find a borderline increased risk of death resulting from breast cancer for high-fat dairy intake; compared

Table 3. Protein, Amino Acids, and Animal Protein–Containing Food Groups and Death Resulting From Breast Cancer in NHS

Type of Nutrient	Quintile of Nutrient Intake: First	Second	Third	Fourth	Fifth	P_{trend}
Total protein						
No. of deaths resulting from breast cancer	216	186	194	147	176	
Simple model, RR (95% CI)*	1.00†	0.81 (0.66 to 0.98)	0.81 (0.66 to 0.98)	0.62 (0.50 to 0.77)	0.83 (0.68 to 1.01)	.004
Multivariable model, RR (95% CI)‡	1.00†	1.00 (0.81 to 1.22)	0.97 (0.80 to 1.19)	0.74 (0.60 to 0.92)	0.95 (0.77 to 1.17)	.17
Animal protein						
No. of deaths resulting from breast cancer	232	178	179	164	166	
Simple model, RR (95% CI)*	1.00†	0.76 (0.62 to 0.92)	0.74 (0.60 to 0.89)	0.71 (0.58 to 0.87)	0.81 (0.66 to 0.99)	.008
Multivariable model, RR (95% CI)‡	1.00†	0.86 (0.71 to 1.06)	0.84 (0.69 to 1.03)	0.76 (0.62 to 0.93)	0.83 (0.68 to 1.03)	.03
Multivariable model, RR (95% CI)§	1.00†	0.87 (0.71 to 1.06)	0.85 (0.69 to 1.04)	0.77 (0.62 to 0.94)	0.85 (0.68 to 1.05)	.044
Vegetable protein						
No. of deaths resulting from breast cancer	166	173	187	184	209	
Simple model, RR (95% CI)*	1.00†	0.79 (0.64 to 0.98)	0.80 (0.65 to 0.99)	0.76 (0.62 to 0.94)	0.83 (0.68 to 1.02)	.13
Multivariable model, RR (95% CI)‡	1.00†	1.04 (0.83 to 1.30)	1.07 (0.86 to 1.34)	1.08 (0.87 to 1.36)	1.15 (0.92 to 1.44)	.18
Multivariable model, RR (95% CI)‖	1.00†	1.03 (0.82 to 1.28)	1.06 (0.85 to 1.32)	1.05 (0.84 to 1.32)	1.09 (0.87 to 1.37)	.44
Essential amino acids						
No. of deaths resulting from breast cancer	216	187	186	157	173	
Simple model, RR (95% CI)*	1.00†	0.86 (0.71 to 1.05)	0.81 (0.66 to 0.98)	0.70 (0.57 to 0.86)	0.90 (0.74 to 1.11)	.04
Multivariable model, RR (95% CI)‡	1.00†	1.02 (0.84 to 1.25)	0.94 (0.77 to 1.15)	0.80 (0.65 to 0.99)	0.96 (0.78 to 1.19)	.16
Multivariable model, RR (95% CI)¶	1.00†	0.91 (0.61 to 1.34)	0.85 (0.52 to 1.40)	0.77 (0.41 to 1.43)	0.75 (0.35 to 1.61)	.42
Branched-chain amino acids						
No. of deaths resulting from breast cancer	220	193	176	153	177	
Simple model, RR (95% CI)*	1.00†	0.86 (0.71 to 1.05)	0.76 (0.62 to 0.93)	0.67 (0.55 to 0.83)	0.88 (0.72 to 1.08)	.02
Multivariable model, RR (95% CI)‡	1.00†	1.05 (0.86 to 1.28)	0.90 (0.73 to 1.10)	0.80 (0.65 to 1.00)	0.95 (0.77 to 1.17)	.12
Multivariable model, RR (95% CI)#	1.00†	0.95 (0.67 to 1.35)	0.75 (0.48 to 1.18)	0.71 (0.41 to 1.21)	0.72 (0.38 to 1.35)	.18
Animal protein–containing food groups						
Red meat						
No. of deaths resulting from breast cancer	206	196	181	163	173	
Simple model, RR (95% CI)*	1.00†	1.11 (0.91 to 1.35)	1.05 (0.85 to 1.29)	1.03 (0.83 to 1.28)	1.47 (1.17 to 1.84)	.008
Multivariable model, RR (95% CI)‡	1.00†	1.03 (0.84 to 1.25)	0.97 (0.78 to 1.20)	0.91 (0.72 to 1.13)	1.08 (0.86 to 1.37)	.84
Poultry						
No. of deaths resulting from breast cancer	183	197	181	194	164	
Simple model, RR (95% CI)*	1.00†	0.83 (0.68 to 1.02)	0.85 (0.69 to 1.04)	0.85 (0.69 to 1.04)	0.75 (0.60 to 0.93)	.03
Multivariable model, RR (95% CI)‡	1.00†	0.89 (0.72 to 1.09)	1.00 (0.80 to 1.23)	1.05 (0.85 to 1.30)	0.88 (0.70 to 1.10)	.76
Fish						
No. of deaths resulting from breast cancer	183	176	197	192	171	
Simple model, RR (95% CI)*	1.00†	0.89 (0.72 to 1.09)	0.90 (0.74 to 1.11)	0.81 (0.66 to 0.99)	0.78 (0.63 to 0.97)	.02
Multivariable model, RR (95% CI)‡	1.00†	0.90 (0.73 to 1.11)	1.08 (0.88 to 1.34)	1.03 (0.83 to 1.28)	0.99 (0.80 to 1.24)	.64
High-fat dairy						
No. of deaths resulting from breast cancer	180	182	196	191	170	
Simple model, RR (95% CI)*	1.00†	1.12 (0.91 to 1.38)	1.28 (1.04 to 1.58)	1.28 (1.03 to 1.58)	1.29 (1.03 to 1.62)	.01
Multivariable model, RR (95% CI)‡	1.00†	1.17 (0.95 to 1.45)	1.22 (0.99 to 1.51)	1.29 (1.04 to 1.60)	1.24 (0.98 to 1.56)	.05
Low-fat dairy						
No. of deaths resulting from breast cancer	205	187	195	170	162	
Simple model, RR (95% CI)*	1.00†	0.85 (0.69 to 1.03)	0.84 (0.69 to 1.02)	0.72 (0.58 to 0.88)	0.68 (0.55 to 0.84)	< .001
Multivariable model, RR (95% CI)‡	1.00†	1.02 (0.83 to 1.25)	1.05 (0.86 to 1.29)	0.86 (0.70 to 1.07)	0.83 (0.67 to 1.04)	.03

Abbreviations: NHS, Nurses' Health Study; RR, relative risk.
*Adjusted for age at diagnosis, time since diagnosis, and energy intake (quintiles).
†Referent.
‡Adjusted for age at diagnosis, time since diagnosis, energy intake (quintiles), body mass index (< 21, 21 to < 23, 23 to < 25, 25 to < 30, or ≥ 30 kg/m^2), weight change (same, loss, or gain), age at first birth and parity (nulliparous, one to two children and age at first birth < 25 years, ≥ two children and age at first birth < 25 years, one to two children and age at first birth ≥ 25 years, or two children and age at first birth ≥ 25 years), oral contraceptive use (never or ever), menopausal status and hormone therapy use (premenopausal, postmenopausal and never use, post and current use, post and past use, or unknown or missing menopausal information), aspirin use (never, past, current one to two tablets/wk, current three to five tablets/wk, current six to 14 tablets/wk, current ≥ 15 tablets/wk, or current unknown quantity), alcohol (0, > 0-5, > 5-15, or > 15 g/d), smoking (never, past, or current), physical activity (< 3, 3 to < 9, 9 to < 18, 18 to < 27, > 27 metabolic equivalents of task/wk, or missing), tumor stage (I, II, or III), radiation treatment (yes, no), other treatment (no chemotherapy and no tamoxifen, chemotherapy but no tamoxifen, or chemotherapy and tamoxifen), and calendar year.
§Adjusted for same variables in (‡) and vegetable protein (quintiles).
‖Adjusted for same variables in (‡) and animal protein (quintiles).
¶Adjusted for same variables in (‡) and nonessential amino acids (quintiles).
#Adjusted for same variables in (‡) and non–branched-chain amino acids (quintiles).

with the lowest number of servings per day (zero to < one half serving), the adjusted RR was 1.20 (95% CI, 0.82 to 1.77) for medium intake (half to < one serving) and 1.49 (95% CI, 1.00 to 2.24) for highest intake (≥ one serving; linear trend $P = .05$). The authors hypothesized that estrogenic hormones found in dairy fat may be detrimental to breast cancer survival. Our findings of an inverse association for poultry with skin and a nonstatistically significant positive association for poultry without skin are likely

Table 4. Protein, Amino Acids, and Animal Protein–Containing Food Groups and Distant Breast Cancer Recurrence According to IR Expression in NHS

Type of Nutrient	Quintile of Nutrient Intake: First	Second	Third	Fourth	Fifth	P_{trend}	$P_{interaction}$
Total protein							.60
IR positive							
No. of breast cancer recurrences	46	38	27	33	30		
Multivariable model, RR (95% CI)*	1.00†	0.91 (0.58 to 1.43)	0.56 (0.34 to 0.93)	0.68 (0.43 to 1.10)	0.72 (0.44 to 1.16)	.06	
IR negative							
No. of breast cancer recurrences	56	50	53	52	39		
Multivariable model, RR (95% CI)*	1.00†	0.91 (0.61 to 1.36)	0.88 (0.59 to 1.31)	0.87 (0.58 to 1.30)	0.76 (0.49 to 1.17)	.21	
Animal protein							.49
IR positive							
No. of breast cancer recurrences	44	41	30	32	27		
Multivariable model, RR (95% CI)*	1.00†	1.04 (0.67 to 1.62)	0.79 (0.49 to 1.28)	0.74 (0.46 to 1.19)	0.69 (0.42 to 1.14)	.08	
IR negative							
No. of breast cancer recurrences	61	49	61	44	35		
Multivariable model, RR (95% CI)*	1.00†	0.76 (0.51 to 1.12)	1.02 (0.70 to 1.49)	0.74 (0.49 to 1.10)	0.60 (0.39 to 0.93)	.03	
Vegetable protein							.15
IR positive							
No. of breast cancer recurrences	27	36	41	31	39		
Multivariable model, RR (95% CI)*	1.00†	1.32 (0.78 to 2.23)	1.25 (0.75 to 2.08)	0.99 (0.57 to 1.71)	1.40 (0.83 to 2.36)	.42	
IR negative							
No. of breast cancer recurrences	42	38	52	67	51		
Multivariable model, RR (95% CI)*	1.00†	0.89 (0.56 to 1.42)	1.07 (0.70 to 1.63)	1.47 (0.98 to 2.22)	1.16 (0.75 to 1.79)	.16	
Essential amino acids							.66
IR positive							
No. of breast cancer recurrences	47	36	31	33	27		
Multivariable model, RR (95% CI)*	1.00†	0.95 (0.60 to 1.49)	0.67 (0.42 to 1.07)	0.75 (0.47 to 1.20)	0.69 (0.42 to 1.14)	.07	
IR negative							
No. of breast cancer recurrences	58	50	60	46	36		
Multivariable model, RR (95% CI)*	1.00†	0.93 (0.63 to 1.38)	1.00 (0.68 to 1.46)	0.87 (0.58 to 1.30)	0.72 (0.46 to 1.11)	.17	
Branched-chain amino acids							.34
IR positive							
No. of breast cancer recurrences	45	38	31	35	25		
Multivariable model, RR (95% CI)*	1.00†	0.98 (0.63 to 1.54)	0.70 (0.43 to 1.12)	0.90 (0.56 to 1.43)	0.62 (0.37 to 1.03)	.07	
IR negative							
No. of breast cancer recurrences	63	45	60	42	40		
Multivariable model, RR (95% CI)*	1.00†	0.70 (0.47 to 1.05)	0.93 (0.64 to 1.35)	0.73 (0.49 to 1.10)	0.68 (0.45 to 1.04)	.13	
Animal protein–containing foods							.73
Red meat							
IR positive							
No. of breast cancer recurrences	41	32	26	40	35		
Multivariable model, RR (95% CI)*	1.00†	0.70 (0.43 to 1.14)	0.69 (0.41 to 1.15)	0.99 (0.62 to 1.59)	1.10 (0.66 to 1.83)	.31	
IR negative							
No. of breast cancer recurrences	55	51	53	49	42		
Multivariable model, RR (95% CI)*	1.00†	0.77 (0.52 to 1.15)	0.92 (0.62 to 1.38)	0.91 (0.60 to 1.39)	0.96 (0.61 to 1.50)	.82	
Poultry							.40
IR positive							
No. of breast cancer recurrences	41	41	35	28	29		
Multivariable model, RR (95% CI)*	1.00†	0.72 (0.46 to 1.14)	0.72 (0.45 to 1.15)	0.58 (0.35 to 0.95)	0.64 (0.39 to 1.06)	.06	
IR negative							
No. of breast cancer recurrences	41	57	56	51	45		
Multivariable model, RR (95% CI)*	1.00†	0.99 (0.65 to 1.50)	1.07 (0.70 to 1.64)	1.10 (0.72 to 1.70)	0.88 (0.56 to 1.38)	.74	
Fish							.98
IR positive							
No. of breast cancer recurrences	30	37	38	40	29		
Multivariable model, RR (95% CI)*	1.00†	1.03 (0.62 to 1.70)	1.09 (0.66 to 1.81)	1.02 (0.62 to 1.68)	0.87 (0.51 to 1.49)	.61	
IR negative							
No. of breast cancer recurrences	44	57	48	59	42		
Multivariable model, RR (95% CI)*	1.00†	1.08 (0.72 to 1.62)	0.97 (0.63 to 1.49)	1.10 (0.73 to 1.66)	0.88 (0.57 to 1.38)	.65	
High-fat diary							.80
IR positive							
No. of breast cancer recurrences	41	34	37	36	26		
Multivariable model, RR (95% CI)*	1.00†	0.99 (0.62 to 1.59)	1.42 (0.89 to 2.26)	1.12 (0.70 to 1.80)	0.89 (0.53 to 1.49)	.89	
IR negative							
No. of breast cancer recurrences	56	56	47	53	38		
Multivariable model, RR (95% CI)*	1.00†	1.17 (0.80 to 1.72)	1.17 (0.78 to 1.76)	1.32 (0.88 to 1.97)	0.92 (0.59 to 1.44)	.99	

(continued on following page)

Table 4. Protein, Amino Acids, and Animal Protein–Containing Food Groups and Distant Breast Cancer Recurrence According to IR Expression in NHS (continued)

Type of Nutrient	Quintile of Nutrient Intake: First	Second	Third	Fourth	Fifth	P_{trend}	$P_{interaction}$
Low-fat diary							.90
IR positive							
No. of breast cancer recurrences	35	33	37	37	32		
Multivariable model, RR (95% CI)*	1.00†	0.80 (0.49 to 1.31)	0.98 (0.60 to 1.59)	0.93 (0.57 to 1.52)	0.79 (0.48 to 1.32)	.60	
IR negative							
No. of breast cancer recurrences	48	53	45	53	51		
Multivariable model, RR (95% CI)*	1.00†	0.93 (0.62 to 1.40)	0.85 (0.55 to 1.29)	0.86 (0.57 to 1.31)	0.86 (0.56 to 1.31)	.47	

Abbreviations: IR, insulin receptor; NHS, Nurses' Health Study; RR, relative risk.
*Adjusted for age at diagnosis, time since diagnosis, energy intake (quintiles), body mass index (< 21, 21 to < 23, 23 to < 25, 25 to < 30, or ≥ 30 kg/m^2), weight change (same, loss, or gain), age at first birth and parity (nulliparous, one to two children and age at first birth < 25 years, ≥ two children and age at first birth < 25 years, one to two children and age at first birth ≥ 25 years, or two children and age at first birth ≥ 25 years), oral contraceptive use (never or ever), menopausal status and hormone therapy use (premenopausal, postmenopausal and never use, post and current use, post and past use, or unknown or missing menopausal information), aspirin use (never, past, current one to two tablets/wk, current three to five tablets/wk, current six to 14 tablets/wk, current ≥ 15 tablets/wk, or current unknown quantity), alcohol (0, > 0-5, > 5-15, or > 15 g/d), smoking (never, past, or current), physical activity (< 3, 3 to < 9, 9 to < 18, 18 to < 27, > 27 metabolic equivalents of task/wk, or missing), tumor stage (I, II, or III), radiation treatment (yes, no), other treatment (no chemotherapy and no tamoxifen, chemotherapy but no tamoxifen, or chemotherapy and tamoxifen), and calendar year.
†Referent.

the results of chance, particularly given the lack of association with poultry intake overall. In summary, no particular animal protein–containing food stood out as beneficial for breast cancer survival.

Any observational study such as this is subject to the limitations of chance, confounding, and bias. Three previous cohort studies reported similar improved survival with higher protein intake, and our study is larger than the other three combined, making chance unlikely. Also, there are no published reports to date of worse breast cancer survival with increased protein intake. We adjusted for the key covariates; the fact that estimates for animal protein did not change much provides some reassurance against confounding to explain the results. Bias is a concern, particularly if women changed their diets as they approached death or developed metastatic disease. However, we used diet assessments updated approximately every 4 years over time. Also, results were similar for death resulting from breast cancer and breast cancer recurrence.

In summary, we found a modest survival advantage with higher protein intake that was not associated with any particular foods. There is no clear mechanism for this surprising finding. Our hypothesis that the effect might be mediated by the IR was not borne out in this study. Given the modest effect and the challenges involved in randomized trials of diet, this association is unlikely to ever be definitively tested in a randomized trial. However, the modest survival advantage with higher protein intake has been found in several studies, and we feel it is important that patients with breast cancer and their clinicians know this. At the least, it may provide reassurance that consuming protein-containing foods is not likely to increase the risk of breast cancer recurrence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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Data analysis and interpretation: All authors
Manuscript writing: All authors
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Protein Intake and Breast Cancer Survival in the Nurses' Health Study

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Appendix

Table A1. Multivariable Analysis of Animal Protein–Containing Foods and Individual Amino Acids and Breast Cancer Recurrence in NHS

	RR (95% CI)					
	Quintile of Nutrient Intake					
Type of Nutrient	First	Second	Third	Fourth	Fifth	P_{trend}
Animal protein–containing foods						
Meat	1.00*	1.06 (0.88 to 1.28)	0.88 (0.72 to 1.08)	0.90 (0.73 to 1.11)	0.87 (0.69 to 1.09)	.10
Processed meat	1.00*	0.98 (0.81 to 1.20)	0.91 (0.75 to 1.10)	1.10 (0.91 to 1.34)	0.97 (0.79 to 1.20)	.80
Bacon	1.00*	1.05 (0.87 to 1.28)	0.97 (0.80 to 1.18)	1.02 (0.84 to 1.24)	1.01 (0.83 to 1.24)	.99
Hamburger	1.00*	1.00 (0.82 to 1.22)	1.07 (0.89 to 1.29)	1.12 (0.92 to 1.38)	1.06 (0.87 to 1.30)	.34
Poultry without skin	1.00*	1.09 (0.89 to 1.34)	1.10 (0.90 to 1.35)	1.24 (1.02 to 1.51)	1.15 (0.94 to 1.41)	.08
Poultry with skin	1.00*	0.88 (0.73 to 1.06)	0.91 (0.75 to 1.10)	0.89 (0.74 to 1.08)	0.72 (0.59 to 0.89)	.008
Dairy	1.00*	0.95 (0.78 to 1.15)	0.86 (0.70 to 1.05)	0.92 (0.75 to 1.13)	0.91 (0.73 to 1.14)	.45
Cottage cheese	1.00*	1.07 (0.88 to 1.30)	1.11 (0.91 to 1.35)	1.06 (0.87 to 1.29)	0.93 (0.76 to 1.13)	.44
Skim milk	1.00*	1.01 (0.84 to 1.23)	0.94 (0.77 to 1.14)	0.93 (0.77 to 1.14)	0.85 (0.69 to 1.05)	.08
Ice cream	1.00*	1.04 (0.86 to 1.26)	1.06 (0.87 to 1.30)	1.01 (0.83 to 1.23)	1.04 (0.85 to 1.27)	.81
Eggs	1.00*	0.96 (0.79 to 1.16)	0.79 (0.65 to 0.97)	0.85 (0.70 to 1.04)	0.89 (0.73 to 1.10)	.17
Amino acids						
Alanine	1.00*	0.82 (0.68 to 0.99)	0.84 (0.70 to 1.02)	0.74 (0.61 to 0.90)	0.85 (0.70 to 1.04)	.03
Arginine	1.00*	0.87 (0.72 to 1.06)	0.85 (0.70 to 1.03)	0.87 (0.72 to 1.05)	0.92 (0.75 to 1.12)	.33
Asparagine	1.00*	0.97 (0.80 to 1.17)	0.94 (0.78 to 1.13)	0.78 (0.64 to 0.95)	0.86 (0.71 to 1.05)	.02
Aspartic acid	1.00*	0.82 (0.68 to 0.99)	0.88 (0.73 to 1.06)	0.81 (0.66 to 0.98)	0.90 (0.74 to 1.10)	.23
Cysteine	1.00*	1.03 (0.85 to 1.25)	0.86 (0.71 to 1.04)	0.94 (0.77 to 1.14)	0.91 (0.74 to 1.11)	.19
Glutamic acid	1.00*	0.94 (0.78 to 1.14)	0.90 (0.74 to 1.08)	0.73 (0.60 to 0.89)	0.82 (0.68 to 1.01)	.003
Glutamine	1.00*	0.85 (0.70 to 1.04)	0.87 (0.72 to 1.07)	0.85 (0.70 to 1.04)	0.82 (0.67 to 1.01)	.09
Glycine	1.00*	0.89 (0.73 to 1.07)	0.80 (0.66 to 0.98)	0.88 (0.73 to 1.06)	0.91 (0.74 to 1.11)	.24
Histidine†	1.00*	0.92 (0.76 to 1.11)	0.86 (0.71 to 1.04)	0.76 (0.62 to 0.92)	0.87 (0.71 to 1.06)	.02
Isoleucine‡	1.00*	1.01 (0.84 to 1.21)	0.85 (0.71 to 1.03)	0.78 (0.64 to 0.96)	0.82 (0.68 to 1.01)	.004
Leucine‡	1.00*	0.99 (0.82 to 1.19)	0.88 (0.73 to 1.06)	0.79 (0.65 to 0.96)	0.81 (0.67 to 0.99)	.005
Lysine†	1.00*	0.85 (0.70 to 1.03)	0.88 (0.72 to 1.07)	0.74 (0.61 to 0.90)	0.86 (0.70 to 1.04)	.03
Methionine†	1.00*	0.98 (0.81 to 1.18)	0.87 (0.72 to 1.06)	0.75 (0.61 to 0.91)	0.85 (0.70 to 1.03)	.007
Phenylalanine†	1.00*	0.98 (0.82 to 1.18)	0.89 (0.73 to 1.07)	0.78 (0.64 to 0.96)	0.86 (0.71 to 1.05)	.02
Proline	1.00*	0.98 (0.82 to 1.19)	0.87 (0.72 to 1.06)	0.86 (0.71 to 1.05)	0.78 (0.64 to 0.96)	.007
Serine	1.00*	1.01 (0.84 to 1.22)	0.90 (0.74 to 1.09)	0.73 (0.59 to 0.89)	0.89 (0.73 to 1.08)	.009
Threonine†	1.00*	0.99 (0.83 to 1.20)	0.85 (0.70 to 1.02)	0.74 (0.61 to 0.90)	0.87 (0.71 to 1.06)	.008
Tryptophan†	1.00*	0.88 (0.73 to 1.07)	0.89 (0.73 to 1.07)	0.68 (0.55 to 0.82)	0.85 (0.70 to 1.03)	.004
Tyrosine	1.00*	1.06 (0.88 to 1.28)	0.88 (0.73 to 1.07)	0.81 (0.67 to 0.99)	0.85 (0.70 to 1.04)	.009
Valine‡	1.00*	1.00 (0.83 to 1.21)	0.89 (0.73 to 1.07)	0.78 (0.64 to 0.95)	0.85 (0.70 to 1.04)	.01

NOTE. Multivariable analysis adjusted for age at diagnosis, time since diagnosis, energy intake (quintiles), body mass index (< 21, 21 to < 23, 23 to < 25, 25 to < 30, or ≥ 30 kg/m^2), weight change (same, loss, or gain), age at first birth and parity (nulliparous, one to two children and age at first birth < 25 years, ≥ two children and age at first birth < 25 years, one to two children and age at first birth ≥ 25 years, or two children and age at first birth ≥ 25 years), oral contraceptive use (never or ever), menopausal status and hormone therapy use (premenopausal, postmenopausal and never use, post and current use, post and past use, or unknown or missing menopausal information), aspirin use (never, past, current one to two tablets/wk, current three to five tablets/wk, current six to 14 tablets/wk, current ≥ 15 tablets/wk, or current unknown quantity), alcohol (0, > 0-5, > 5-15, or > 15 g/d), smoking (never, past, or current), physical activity (< 3, 3 to < 9, 9 to < 18, 18 to < 27, > 27 metabolic equivalents of task/wk, or missing), tumor stage (I, II, or III), radiation treatment (yes, no), other treatment (no chemotherapy and no tamoxifen, chemotherapy but no tamoxifen, or chemotherapy and tamoxifen), and calendar year.
Abbreviations: NHS, Nurses' Health Study; RR, relative risk.
*Referent.
†Essential amino acid.
‡Essential as well as branched-chain amino acid.

Table A2. Multivariable Analysis of Animal Protein–Containing Foods and Individual Amino Acids and Death Resulting From Breast Cancer in NHS

Type of Nutrient	RR (95% CI)					P_{trend}
	Quintile of Nutrient Intake					
	First	Second	Third	Fourth	Fifth	
Animal protein–containing foods						
Meat	1.00*	1.08 (0.88 to 1.32)	0.93 (0.75 to 1.16)	0.90 (0.72 to 1.13)	0.90 (0.70 to 1.15)	.18
Processed meat	1.00*	0.99 (0.80 to 1.21)	0.85 (0.69 to 1.05)	1.11 (0.90 to 1.35)	0.91 (0.73 to 1.14)	.83
Bacon	1.00*	1.05 (0.85 to 1.30)	0.99 (0.81 to 1.22)	0.98 (0.80 to 1.21)	1.04 (0.84 to 1.29)	.94
Hamburger	1.00*	1.07 (0.86 to 1.32)	1.11 (0.91 to 1.36)	1.19 (0.96 to 1.47)	1.07 (0.86 to 1.33)	.39
Poultry without skin	1.00*	1.07 (0.87 to 1.33)	1.03 (0.83 to 1.28)	1.27 (1.03 to 1.56)	1.16 (0.93 to 1.43)	.06
Poultry with skin	1.00*	0.85 (0.70 to 1.05)	0.89 (0.73 to 1.09)	0.88 (0.72 to 1.08)	0.73 (0.59 to 0.91)	.02
Dairy	1.00*	0.97 (0.79 to 1.19)	0.86 (0.69 to 1.06)	0.96 (0.78 to 1.20)	1.01 (0.80 to 1.28)	.87
Dairy protein	1.00*	1.02 (0.83 to 1.25)	1.14 (0.93 to 1.39)	0.94 (0.76 to 1.17)	0.88 (0.71 to 1.08)	.15
Cottage cheese	1.00*	1.06 (0.86 to 1.30)	1.17 (0.95 to 1.43)	0.94 (0.76 to 1.17)	0.92 (0.74 to 1.14)	.25
Skim milk	1.00*	1.03 (0.84 to 1.27)	0.92 (0.75 to 1.14)	0.93 (0.75 to 1.15)	0.88 (0.71 to 1.10)	.15
Ice cream	1.00*	0.95 (0.77 to 1.16)	1.00 (0.81 to 1.24)	0.97 (0.79 to 1.20)	1.03 (0.83 to 1.27)	.74
Eggs	1.00*	0.95 (0.77 to 1.16)	0.83 (0.66 to 1.02)	0.88 (0.71 to 1.09)	0.98 (0.79 to 1.22)	.71
Amino acids						
Alanine	1.00*	0.88 (0.72 to 1.08)	0.88 (0.72 to 1.08)	0.82 (0.67 to 1.01)	0.94 (0.76 to 1.16)	.29
Arginine	1.00*	0.87 (0.71 to 1.06)	0.93 (0.76 to 1.14)	0.90 (0.73 to 1.10)	1.02 (0.83 to 1.26)	.92
Asparagine	1.00*	1.03 (0.84 to 1.27)	1.00 (0.82 to 1.23)	0.84 (0.68 to 1.04)	1.00 (0.81 to 1.23)	.37
Aspartic acid	1.00*	0.89 (0.72 to 1.09)	0.96 (0.79 to 1.18)	0.87 (0.70 to 1.07)	1.04 (0.85 to 1.29)	.94
Cysteine	1.00*	1.13 (0.92 to 1.39)	0.96 (0.78 to 1.18)	1.00 (0.81 to 1.24)	1.07 (0.87 to 1.33)	.97
Glutamic acid	1.00*	0.97 (0.79 to 1.18)	0.91 (0.75 to 1.11)	0.78 (0.63 to 0.96)	0.94 (0.76 to 1.15)	.11
Glutamine	1.00*	0.90 (0.73 to 1.11)	0.91 (0.74 to 1.12)	0.87 (0.70 to 1.08)	0.86 (0.70 to 1.07)	.19
Glycine	1.00*	0.86 (0.70 to 1.06)	0.81 (0.66 to 1.00)	0.92 (0.76 to 1.13)	0.97 (0.79 to 1.20)	.81
Histidine†	1.00*	0.96 (0.78 to 1.17)	0.89 (0.73 to 1.09)	0.83 (0.67 to 1.02)	0.98 (0.79 to 1.20)	.31
Isoleucine‡	1.00*	1.03 (0.85 to 1.26)	0.89 (0.73 to 1.09)	0.79 (0.64 to 0.98)	0.94 (0.76 to 1.15)	.08
Leucine‡	1.00*	1.03 (0.84 to 1.25)	0.88 (0.72 to 1.08)	0.82 (0.67 to 1.02)	0.93 (0.75 to 1.14)	.11
Lysine†	1.00*	0.86 (0.70 to 1.06)	0.93 (0.76 to 1.14)	0.80 (0.65 to 0.99)	0.94 (0.75 to 1.16)	.30
Methionine†	1.00*	0.99 (0.81 to 1.21)	0.89 (0.73 to 1.09)	0.80 (0.65 to 0.99)	0.95 (0.77 to 1.17)	.15
Phenylalanine†	1.00*	0.99 (0.81 to 1.21)	0.93 (0.76 to 1.14)	0.81 (0.65 to 1.00)	0.96 (0.78 to 1.19)	.22
Proline	1.00*	1.07 (0.87 to 1.30)	0.90 (0.73 to 1.10)	0.91 (0.73 to 1.12)	0.91 (0.74 to 1.13)	.15
Serine	1.00*	1.04 (0.85 to 1.26)	0.93 (0.76 to 1.14)	0.78 (0.63 to 0.97)	0.99 (0.81 to 1.23)	.19
Threonine†	1.00*	0.99 (0.81 to 1.21)	0.89 (0.72 to 1.08)	0.80 (0.65 to 0.99)	0.97 (0.78 to 1.19)	.19
Tryptophan†	1.00*	0.86 (0.71 to 1.06)	0.91 (0.75 to 1.11)	0.73 (0.59 to 0.90)	0.93 (0.76 to 1.15)	.13
Tyrosine	1.00*	1.09 (0.89 to 1.32)	0.90 (0.73 to 1.10)	0.84 (0.68 to 1.04)	0.94 (0.77 to 1.16)	.12
Valine‡	1.00*	1.05 (0.86 to 1.28)	0.89 (0.72 to 1.09)	0.81 (0.66 to 1.00)	0.98 (0.79 to 1.20)	.18

NOTE. Multivariable analysis adjusted for age at diagnosis, time since diagnosis, energy intake (quintiles), body mass index (< 21, 21 to < 23, 23 to < 25, 25 to < 30, or ≥ 30 kg/m^2), weight change (same, loss, or gain), age at first birth and parity (nulliparous, one to two children and age at first birth < 25 years, ≥ two children and age at first birth < 25 years, one to two children and age at first birth ≥ 25 years, or two children and age at first birth ≥ 25 years), oral contraceptive use (never or ever), menopausal status and hormone therapy use (premenopausal, postmenopausal and never use, post and current use, post and past use, or unknown or missing menopausal information), aspirin use (never, past, current one to two tablets/wk, current three to five tablets/wk, current six to 14 tablets/wk, current ≥ 15 tablets/wk, or current unknown quantity), alcohol (0, > 0-5, > 5-15, or > 15 g/d), smoking (never, past, or current), physical activity (< 3, 3 to < 9, 9 to < 18, 18 to < 27, > 27 metabolic equivalents of task/wk, or missing), tumor stage (I, II, or III), radiation treatment (yes, no), other treatment (no chemotherapy and no tamoxifen, chemotherapy but no tamoxifen, or chemotherapy and tamoxifen), and calendar year.

Abbreviations: NHS, Nurses' Health Study; RR, relative risk.

*Referent.

†Essential amino acid.

‡Essential as well as branched-chain amino acid.

Table A3. Multivariable Analysis of Animal Protein–Containing Foods and Individual Amino Acids and All Deaths in NHS

	RR (95% CI)					
	Quintile of Nutrient Intake					
Type of Nutrient	First	Second	Third	Fourth	Fifth	P_{trend}
Total protein	1.00*	0.93 (0.80 to 1.07)	0.97 (0.84 to 1.12)	0.87 (0.75 to 1.01)	0.98 (0.85 to 1.14)	.50
Animal	1.00*	0.91 (0.78 to 1.05)	0.96 (0.83 to 1.11)	0.89 (0.77 to 1.03)	0.99 (0.85 to 1.15)	.60
Vegetable	1.00*	0.98 (0.84 to 1.14)	0.98 (0.84 to 1.15)	0.93 (0.79 to 1.09)	0.97 (0.83 to 1.14)	.59
Animal protein–containing foods						
Meat	1.00*	0.97 (0.84 to 1.12)	0.94 (0.81 to 1.10)	0.90 (0.77 to 1.05)	0.94 (0.79 to 1.11)	.31
Red meat	1.00*	1.04 (0.90 to 1.20)	1.03 (0.88 to 1.19)	0.99 (0.85 to 1.16)	1.13 (0.96 to 1.33)	.28
Poultry	1.00*	0.99 (0.85 to 1.14)	1.08 (0.93 to 1.25)	1.02 (0.87 to 1.18)	0.93 (0.79 to 1.08)	.48
Fish	1.00*	0.98 (0.84 to 1.13)	1.09 (0.94 to 1.26)	1.10 (0.95 to 1.28)	0.96 (0.82 to 1.13)	.82
Processed meat	1.00*	1.04 (0.90 to 1.21)	0.93 (0.81 to 1.08)	1.17 (1.02 to 1.36)	0.99 (0.84 to 1.16)	.60
Bacon	1.00*	1.13 (0.97 to 1.31)	1.04 (0.89 to 1.20)	1.06 (0.91 to 1.23)	1.09 (0.94 to 1.27)	.51
Hamburger	1.00*	1.17 (1.01 to 1.36)	1.13 (0.98 to 1.31)	1.14 (0.98 to 1.32)	1.08 (0.93 to 1.27)	.47
Poultry without skin	1.00*	1.00 (0.86 to 1.16)	0.92 (0.79 to 1.08)	1.19 (1.02 to 1.37)	1.06 (0.91 to 1.23)	.08
Poultry with skin	1.00*	1.05 (0.92 to 1.21)	1.01 (0.87 to 1.16)	0.99 (0.86 to 1.14)	0.87 (0.74 to 1.01)	.06
Dairy	1.00*	0.89 (0.77 to 1.04)	0.90 (0.77 to 1.05)	0.98 (0.84 to 1.14)	1.01 (0.86 to 1.19)	.46
Cottage cheese	1.00*	0.99 (0.85 to 1.15)	1.08 (0.94 to 1.26)	0.94 (0.81 to 1.09)	0.95 (0.82 to 1.10)	.35
High-fat dairy	1.00*	1.09 (0.94 to 1.26)	1.10 (0.95 to 1.28)	1.04 (0.89 to 1.21)	1.12 (0.96 to 1.31)	.32
Low-fat dairy	1.00*	0.99 (0.86 to 1.15)	1.03 (0.89 to 1.19)	0.87 (0.75 to 1.01)	0.92 (0.79 to 1.07)	.10
Skim milk	1.00*	1.01 (0.87 to 1.17)	0.90 (0.77 to 1.04)	0.97 (0.83 to 1.12)	0.92 (0.79 to 1.08)	.25
Ice cream	1.00*	0.95 (0.82 to 1.10)	0.98 (0.85 to 1.14)	0.99 (0.85 to 1.15)	0.99 (0.85 to 1.15)	.94
Eggs	1.00*	1.07 (0.93 to 1.24)	0.91 (0.79 to 1.07)	0.96 (0.82 to 1.11)	0.96 (0.83 to 1.13)	.27
Essential amino acids	1.00*	0.98 (0.85 to 1.13)	0.92 (0.80 to 1.06)	0.95 (0.82 to 1.09)	0.97 (0.84 to 1.13)	.54
Branched-chain amino acids	1.00*	1.01 (0.88 to 1.17)	0.95 (0.82 to 1.10)	0.92 (0.80 to 1.07)	1.00 (0.86 to 1.16)	.54
Individual amino acids						
Alanine	1.00*	0.91 (0.79 to 1.05)	0.94 (0.82 to 1.08)	0.92 (0.80 to 1.06)	1.00 (0.86 to 1.17)	.89
Arginine	1.00*	0.90 (0.78 to 1.04)	0.96 (0.83 to 1.11)	0.94 (0.81 to 1.08)	1.01 (0.87 to 1.18)	.91
Asparagine	1.00*	1.08 (0.93 to 1.24)	0.99 (0.85 to 1.14)	0.97 (0.84 to 1.12)	1.04 (0.89 to 1.20)	.81
Aspartic acid	1.00*	0.94 (0.81 to 1.08)	1.02 (0.88 to 1.18)	0.95 (0.82 to 1.10)	1.06 (0.91 to 1.23)	.56
Cysteine	1.00*	1.03 (0.89 to 1.19)	0.96 (0.83 to 1.11)	1.01 (0.87 to 1.17)	1.04 (0.89 to 1.21)	.81
Glutamic acid	1.00*	0.96 (0.84 to 1.11)	0.96 (0.83 to 1.11)	0.92 (0.79 to 1.06)	0.98 (0.84 to 1.14)	.51
Glutamine	1.00*	1.06 (0.92 to 1.23)	0.96 (0.83 to 1.12)	0.99 (0.85 to 1.15)	0.94 (0.80 to 1.09)	.27
Glycine	1.00*	0.90 (0.78 to 1.04)	0.90 (0.78 to 1.04)	0.94 (0.81 to 1.08)	0.99 (0.86 to 1.16)	.89
Histidine†	1.00*	0.91 (0.79 to 1.05)	0.90 (0.78 to 1.04)	0.93 (0.81 to 1.08)	0.98 (0.84 to 1.14)	.71
Isoleucine‡	1.00*	1.01 (0.88 to 1.17)	0.94 (0.81 to 1.08)	0.92 (0.79 to 1.06)	0.98 (0.85 to 1.14)	.38
Leucine‡	1.00*	1.02 (0.88 to 1.17)	0.95 (0.82 to 1.10)	0.93 (0.80 to 1.07)	0.99 (0.86 to 1.15)	.48
Lysine†	1.00*	0.94 (0.81 to 1.08)	0.96 (0.83 to 1.11)	0.92 (0.80 to 1.07)	1.02 (0.88 to 1.19)	.93
Methionine†	1.00*	0.95 (0.82 to 1.10)	0.91 (0.79 to 1.05)	0.95 (0.82 to 1.10)	0.98 (0.84 to 1.14)	.66
Phenylalanine†	1.00*	1.00 (0.86 to 1.15)	0.94 (0.81 to 1.09)	0.99 (0.86 to 1.15)	0.97 (0.83 to 1.13)	.69
Proline	1.00*	0.95 (0.83 to 1.10)	0.94 (0.81 to 1.09)	0.99 (0.86 to 1.14)	0.98 (0.84 to 1.14)	.91
Serine	1.00*	1.00 (0.87 to 1.15)	0.92 (0.80 to 1.07)	0.90 (0.78 to 1.04)	1.03 (0.89 to 1.20)	.65
Threonine†	1.00*	0.99 (0.86 to 1.15)	0.94 (0.81 to 1.08)	0.94 (0.81 to 1.09)	1.03 (0.88 to 1.19)	.86
Tryptophan†	1.00*	0.86 (0.75 to 1.00)	0.96 (0.83 to 1.10)	0.90 (0.77 to 1.03)	0.98 (0.84 to 1.14)	.79
Tyrosine	1.00*	1.02 (0.89 to 1.18)	0.96 (0.83 to 1.11)	0.91 (0.79 to 1.06)	1.00 (0.86 to 1.16)	.44
Valine‡	1.00*	0.97 (0.84 to 1.12)	0.95 (0.83 to 1.11)	0.90 (0.78 to 1.04)	1.00 (0.86 to 1.16)	.55

NOTE. Multivariable analysis adjusted for age at diagnosis, time since diagnosis, energy intake (quintiles), body mass index (< 21, 21 to < 23, 23 to < 25, 25 to < 30, or ≥ 30 kg/m^2), weight change (same, loss, or gain), age at first birth and parity (nulliparous, one to two children and age at first birth < 25 years, ≥ two children and age at first birth < 25 years, one to two children and age at first birth ≥ 25 years, or two children and age at first birth ≥ 25 years), oral contraceptive use (never or ever), menopausal status and hormone therapy use (premenopausal, postmenopausal and never use, post and current use, post and past use, or unknown or missing menopausal information), aspirin use (never, past, current one to two tablets/wk, current three to five tablets/wk, current six to 14 tablets/wk, current ≥ 15 tablets/wk, or current unknown quantity), alcohol (0, > 0-5, > 5-15, or > 15 g/d), smoking (never, past, or current), physical activity (< 3, 3 to < 9, 9 to < 18, 18 to < 27, > 27 metabolic equivalents of task/wk, or missing), tumor stage (I, II, or III), radiation treatment (yes, no), other treatment (no chemotherapy and no tamoxifen, chemotherapy but no tamoxifen, or chemotherapy and tamoxifen), and calendar year.
Abbreviations: NHS, Nurses' Health Study; RR, relative risk.
*Referent.
†Essential amino acid.
‡Essential as well as branched-chain amino acid.

Table A4. Protein, Amino Acids, and Animal Protein–Containing Foods and Distant Breast Cancer Recurrence According to ER Expression

	Quintile of Nutrient Intake						
Type of Nutrient	First	Second	Third	Fourth	Fifth	P_{trend}	$P_{interaction}$
Total protein							.08
ER positive							
No. of breast cancer recurrences	142	120	114	118	110		
Multivariable model, RR (95% CI)*	1.00†	0.84 (0.65 to 1.08)	0.78 (0.60 to 1.00)	0.83 (0.64 to 1.07)	0.83 (0.64 to 1.08)	.12	
ER negative							
No. of breast cancer recurrences	55	53	50	31	39		
Multivariable model, RR (95% CI)*	1.00†	1.00 (0.68 to 1.48)	1.01 (0.68 to 1.49)	0.54 (0.34 to 0.84)	0.77 (0.51 to 1.18)	.04	
Animal protein							.77
ER positive							
No. of breast cancer recurrences	152	118	120	112	102		
Multivariable model, RR (95% CI)*	1.00†	0.84 (0.65 to 1.07)	0.82 (0.64 to 1.05)	0.77 (0.60 to 0.99)	0.78 (0.55 to 1.00)	.02	
ER negative							
No. of breast cancer recurrences	61	43	50	36	38		
Multivariable model, RR (95% CI)*	1.00†	0.79 (0.53 to 1.17)	0.88 (0.60 to 1.29)	0.60 (0.40 to 0.91)	0.68 (0.44 to 1.03)	.02	
Vegetable protein							.12
ER positive							
No. of breast cancer recurrences	87	110	134	130	143		
Multivariable model, RR (95% CI)*	1.00†	1.16 (0.87 to 1.55)	1.33 (1.00 to 1.76)	1.29 (0.97 to 1.72)	1.41 (1.06 to 1.87)	.01	
ER negative							
No. of breast cancer recurrences	53	46	39	43	47		
Multivariable model, RR (95% CI)*	1.00†	0.83 (0.55 to 1.25)	0.68 (0.44 to 1.04)	0.84 (0.55 to 1.28)	0.87 (0.63 to 1.31)	.53	
Essential amino acids							.48
ER positive							
No. of breast cancer recurrences	141	122	123	110	108		
Multivariable model, RR (95% CI)*	1.00†	0.91 (0.71 to 1.16)	0.89 (0.69 to 1.14)	0.80 (0.62 to 1.03)	0.87 (0.67 to 1.13)	.15	
ER negative							
No. of breast cancer recurrences	59	53	46	32	38		
Multivariable model, RR (95% CI)*	1.00†	0.97 (0.66 to 1.41)	0.87 (0.58 to 1.28)	0.56 (0.36 to 0.87)	0.71 (0.46 to 1.08)	.01	
Branched-chain amino acids							.44
ER positive							
No. of breast cancer recurrences	144	122	118	110	110		
Multivariable model, RR (95% CI)*	1.00†	0.88 (0.68 to 1.12)	0.87 (0.68 to 1.12)	0.80 (0.62 to 1.04)	0.85 (0.66 to 1.11)	.14	
ER negative							
No. of breast cancer recurrences	61	55	41	33	38		
Multivariable model, RR (95% CI)*	1.00†	0.96 (0.66 to 1.39)	0.76 (0.51 to 1.14)	0.56 (0.36 to 0.86)	0.69 (0.46 to 1.05)	.01	
Animal protein–containing foods							.47
Red meat							
ER positive							
No. of breast cancer recurrences	149	136	117	101	101		
Multivariable model, RR (95% CI)*	1.00†	0.96 (0.76 to 1.22)	0.86 (0.66 to 1.11)	0.80 (0.61 to 1.05)	0.96 (0.72 to 1.28)	.45	
ER negative							
No. of breast cancer recurrences	48	47	36	46	51		
Multivariable model, RR (95% CI)*	1.00†	1.07 (0.71 to 1.62)	0.86 (0.55 to 1.34)	1.13 (0.74 to 1.71)	1.33 (0.87 to 2.04)	.17	
Poultry							.29
ER positive							
No. of breast cancer recurrences	114	126	119	125	120		
Multivariable model, RR (95% CI)*	1.00†	0.88 (0.68 to 1.14)	0.98 (0.75 to 1.27)	0.95 (0.73 to 1.24)	1.00 (0.76 to 1.31)	.73	
ER negative							
No. of breast cancer recurrences	51	55	47	42	33		
Multivariable model, RR (95% CI)*	1.00†	0.83 (0.56 to 1.23)	0.85 (0.56 to 1.27)	0.71 (0.47 to 1.08)	0.60 (0.38 to 0.94)	.02	
Fish							.35
ER positive							
No. of breast cancer recurrences	114	116	117	134	123		
Multivariable model, RR (95% CI)*	1.00†	0.94 (0.72 to 1.22)	0.89 (0.68 to 1.16)	1.02 (0.79 to 1.32)	1.06 (0.81 to 1.38)	.47	
ER negative							
No. of breast cancer recurrences	49	48	49	45	37		
Multivariable model, RR (95% CI)*	1.00†	0.90 (0.60 to 1.35)	0.93 (0.62 to 1.40)	0.76 (0.50 to 1.16)	0.72 (0.47 to 1.12)	.10	
High-fat diary							.95
ER positive							
No. of breast cancer recurrences	128	125	122	119	110		
Multivariable model, RR (95% CI)*	1.00†	1.18 (0.91 to 1.52)	1.12 (0.86 to 1.45)	1.15 (0.88 to 1.50)	1.14 (0.87 to 1.52)	.44	
ER negative							
No. of breast cancer recurrences	43	45	51	48	41		
Multivariable model, RR (95% CI)*	1.00†	1.28 (0.84 to 1.96)	1.35 (0.89 to 2.04)	1.32 (0.87 to 2.02)	1.23 (0.79 to 1.92)	.40	

(continued on following page)

Table A4. Protein, Amino Acids, and Animal Protein–Containing Foods and Distant Breast Cancer Recurrence According to ER Expression (continued)

Type of Nutrient	Quintile of Nutrient Intake: First	Second	Third	Fourth	Fifth	P_{trend}	$P_{interaction}$
Low-fat diary							.64
ER positive							
No. of breast cancer recurrences	123	141	121	109	110		
Multivariable model, RR (95% CI)*	1.00†	1.14 (0.89 to 1.46)	1.00 (0.77 to 1.29)	0.82 (0.62 to 1.07)	0.91 (0.69 to 1.19)	.08	
ER negative							
No. of breast cancer recurrences	55	47	45	46	35		
Multivariable model, RR (95% CI)*	1.00†	0.91 (0.61 to 1.36)	0.92 (0.61 to 1.37)	0.88 (0.59 to 1.31)	0.69 (0.45 to 1.07)	.12	

Abbreviations: ER, estrogen receptor; NHS, Nurses' Health Study; RR, relative risk.

*Adjusted for age at diagnosis, time since diagnosis, energy intake (quintiles), body mass index (< 21, 21 to < 23, 23 to < 25, 25 to < 30, or ≥ 30 kg/m^2), weight change (same, loss, or gain), age at first birth and parity (nulliparous, one to two children and age at first birth < 25 years, ≥ two children and age at first birth < 25 years, one to two children and age at first birth ≥ 25 years, or two children and age at first birth ≥ 25 years), oral contraceptive use (never or ever), menopausal status and hormone therapy use (premenopausal, postmenopausal and never use, post and current use, post and past use, or unknown or missing menopausal information), aspirin use (never, past, current one to two tablets/wk, current three to five tablets/wk, current six to 14 tablets/wk, current ≥ 15 tablets/wk, or current unknown quantity), alcohol (0, > 0-5, > 5-15, or > 15 g/d), smoking (never, past, or current), physical activity (< 3, 3 to < 9, 9 to < 18, 18 to < 27, > 27 metabolic equivalents of task/wk, or missing), tumor stage (I, II, or III), radiation treatment (yes, no), other treatment (no chemotherapy and no tamoxifen, chemotherapy but no tamoxifen, or chemotherapy and tamoxifen), and calendar year.

†Referent.

Table A5. Protein, Amino Acids, and Animal Protein–Containing Foods and Distant Breast Cancer Recurrence According to BMI at Diagnosis

Type of Nutrient	Quintile of Nutrient Intake						
	First	Second	Third	Fourth	Fifth	P_{trend}	$P_{interaction}$
Total protein							.63
BMI < 30 kg/m²							
No. of breast cancer recurrences	214	186	184	154	145		
Multivariable model, RR (95% CI)*	1.00†	0.95 (0.78 to 1.16)	0.95 (0.78 to 1.17)	0.76 (0.62 to 0.95)	0.82 (0.66 to 1.03)	.02	
BMI ≥ 30 kg/m²							
No. of breast cancer recurrences	31	30	29	25	48		
Multivariable model, RR (95% CI)*	1.00†	1.10 (0.61 to 2.00)	0.76 (0.42 to 1.36)	0.68 (0.36 to 1.26)	0.91 (0.53 to 1.55)	.48	
Animal protein							.76
BMI < 30 kg/m²							
No. of breast cancer recurrences	234	178	178	153	140		
Multivariable model, RR (95% CI)*	1.00†	0.86 (0.71 to 1.05)	0.86 (0.71 to 1.06)	0.72 (0.58 to 0.89)	0.75 (0.60 to 0.93)	.002	
BMI ≥ 30 kg/m²							
No. of breast cancer recurrences	28	32	29	34	40		
Multivariable model, RR (95% CI)*	1.00†	1.12 (0.61 to 2.03)	0.81 (0.44 to 1.48)	0.81 (0.45 to 1.45)	0.81 (0.46 to 1.42)	.30	
Vegetable protein							.25
BMI < 30 kg/m²							
No. of breast cancer recurrences	148	165	171	187	212		
Multivariable model, RR (95% CI)*	1.00†	1.15 (0.91 to 1.45)	1.10 (0.87 to 1.39)	1.23 (0.98 to 1.55)	1.29 (1.03 to 1.63)	.03	
BMI ≥ 30 kg/m²							
No. of breast cancer recurrences	33	29	37	33	31		
Multivariable model, RR (95% CI)*	1.00†	0.69 (0.38 to 1.25)	0.94 (0.53 to 1.63)	0.77 (0.43 to 1.40)	1.10 (0.62 to 1.96)	.59	
Essential amino acids							.32
BMI < 30 kg/m²							
No. of breast cancer recurrences	215	185	183	152	148		
Multivariable model, RR (95% CI)*	1.00†	0.98 (0.80 to 1.20)	0.98 (0.80 to 1.20)	0.75 (0.61 to 0.93)	0.87 (0.70 to 1.09)	.03	
BMI ≥ 30 kg/m²							
No. of breast cancer recurrences	30	36	27	27	43		
Multivariable model, RR (95% CI)*	1.00†	1.12 (0.63 to 2.00)	0.68 (0.37 to 1.23)	0.72 (0.39 to 1.31)	0.79 (0.45 to 1.36)	.14	
Branched-chain amino acids							.56
BMI < 30 kg/m²							
No. of breast cancer recurrences	220	188	176	150	149		
Multivariable model, RR (95% CI)*	1.00†	0.98 (0.80 to 1.19)	0.92 (0.75 to 1.13)	0.77 (0.62 to 0.95)	0.84 (0.67 to 1.04)	.02	
BMI ≥ 30 kg/m²							
No. of breast cancer recurrences	31	35	25	30	42		
Multivariable model, RR (95% CI)*	1.00†	0.92 (0.52 to 1.64)	0.67 (0.36 to 1.24)	0.74 (0.41 to 1.33)	0.74 (0.43 to 1.28)	.21	
Animal protein–containing foods							.58
Red meat							
BMI < 30 kg/m²							
No. of breast cancer recurrences	212	197	160	161	153		
Multivariable model, RR (95% CI)*	1.00†	1.05 (0.86 to 1.28)	0.90 (0.72 to 1.12)	0.91 (0.73 to 1.14)	1.02 (0.80 to 1.30)	.75	
BMI ≥ 30 kg/m²							
No. of breast cancer recurrences	30	26	38	31	38		
Multivariable model, RR (95% CI)*	1.00†	0.64 (0.35 to 1.17)	0.75 (0.42 to 1.34)	0.73 (0.40 to 1.32)	0.77 (0.41 to 1.44)	.70	
Poultry							.14
BMI < 30 kg/m²							
No. of breast cancer recurrences	179	205	156	181	162		
Multivariable model, RR (95% CI)*	1.00†	0.89 (0.72 to 1.09)	0.89 (0.71 to 1.1)	1.00 (0.80 to 1.24)	0.88 (0.70 to 1.10)	.62	
BMI ≥ 30 kg/m²							
No. of breast cancer recurrences	29	27	47	32	28		
Multivariable model, RR (95% CI)*	1.00†	0.72 (0.40 to 1.31)	1.24 (0.72 to 2.14)	0.94 (0.53 to 1.69)	0.72 (0.39 to 1.31)	.50	
Fish							.10
BMI < 30 kg/m²							
No. of breast cancer recurrences	173	169	189	186	166		
Multivariable model, RR (95% CI)*	1.00†	0.90 (0.72 to 1.12)	1.09 (0.88 to 1.35)	1.03 (0.82 to 1.28)	1.00 (0.80 to 1.25)	.61	
BMI ≥ 30 kg/m²							
No. of breast cancer recurrences	34	36	26	35	32		
Multivariable model, RR (95% CI)*	1.00†	1.06 (0.62 to 1.82)	0.67 (0.38 to 1.20)	0.80 (0.47 to 1.38)	0.71 (0.41 to 1.24)	.14	
High-fat diary							.60
BMI < 30 kg/m²							
No. of breast cancer recurrences	188	174	176	187	158		
Multivariable model, RR (95% CI)*	1.00†	1.08 (0.87 to 1.33)	1.09 (0.88 to 1.35)	1.22 (0.98 to 1.52)	1.09 (0.87 to 1.38)	.25	
BMI ≥ 30 kg/m²							
No. of breast cancer recurrences	31	34	34	34	30		
Multivariable model, RR (95% CI)*	1.00†	1.36 (0.79 to 2.36)	1.22 (0.70 to 2.14)	1.13 (0.63 to 2.02)	0.91 (0.49 to 1.68)	.54	

(continued on following page)

Table A5. Protein, Amino Acids, and Animal Protein–Containing Foods and Distant Breast Cancer Recurrence According to BMI at Diagnosis (continued)

Type of Nutrient	Quintile of Nutrient Intake: First	Second	Third	Fourth	Fifth	P_{trend}	$P_{interaction}$
Low-fat diary							.43
BMI < 30 kg/m^2							
No. of breast cancer recurrences	193	181	182	174	153		
Multivariable model, RR (95% CI)*	1.00†	1.08 (0.88 to 1.34)	1.03 (0.84 to 1.27)	0.98 (0.79 to 1.22)	0.86 (0.69 to 1.08)	.12	
BMI ≥ 30 kg/m^2							
No. of breast cancer recurrences	32	40	33	27	31		
Multivariable model, RR (95% CI)*	1.00†	1.29 (0.75 to 2.21)	1.28 (0.72 to 2.27)	0.76 (0.42 to 1.38)	0.90 (0.50 to 1.63)	.25	

Abbreviations: BMI, body mass index; NHS, Nurses' Health Study; RR, relative risk.
*Adjusted for age at diagnosis, time since diagnosis, energy intake (quintiles), BMI (< 21, 21 to < 23, 23 to < 25, 25 to < 30, or ≥ 30 kg/m^2), weight change (same, loss, or gain), age at first birth and parity (nulliparous, one to two children and age at first birth < 25 years, ≥ two children and age at first birth < 25 years, one to two children and age at first birth ≥ 25 years, or two children and age at first birth ≥ 25 years), oral contraceptive use (never or ever), menopausal status and hormone therapy use (premenopausal, postmenopausal and never use, post and current use, post and past use, or unknown or missing menopausal information), aspirin use (never, past, current one to two tablets/wk, current three to five tablets/wk, current six to 14 tablets/wk, current ≥ 15 tablets/wk, or current unknown quantity), alcohol (0, > 0-5, > 5-15, or > 15 g/d), smoking (never, past, or current), physical activity (< 3, 3 to < 9, 9 to < 18, 18 to < 27, > 27 metabolic equivalents of task/wk, or missing), tumor stage (I, II, or III), radiation treatment (yes, no), other treatment (no chemotherapy and no tamoxifen, chemotherapy but no tamoxifen, or chemotherapy and tamoxifen), and calendar year.
†Referent.

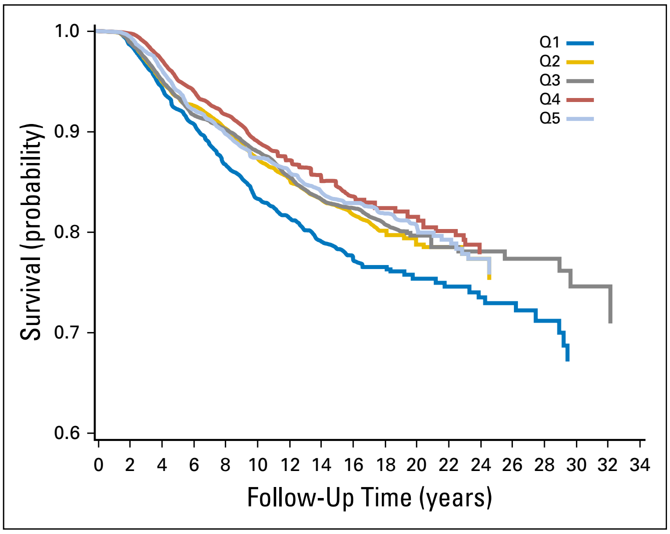

Fig A1. Kaplan-Meier survival curves of probability of recurrence by quintile (Q) of protein intake.