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Energy Intake and Risk of Postmenopausal Breast Cancer: An Expanded Analysis in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) Cohort

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Abstract

Although animal experiments have consistently demonstrated a positive relationship between breast cancer and energy intake, evidence from human studies remains inconclusive. In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort, 29,170 women, aged 55–75 years, who successfully completed a food frequency questionnaire (FFQ) at entry (1993–2001), were followed through 2007; 1,319 incident breast cancers were ascertained (median time from FFQ completion to diagnosis, 4.4 y). Women in the highest quartile of energy intake, relative to the lowest, had modestly, but significantly, increased breast cancer risk [multivariate relative risk (RR), 1.21; 95% confidence interval (95% CI), 1.03–1.42; $P_{trend} = 0.03$]. Including body mass index and physical activity in the model reduced risk slightly (RR, 1.18; 95% CI, 1.00–1.39; $P_{trend} = 0.07$). However, in similar analyses using energy intake from a FFQ administered approximately 5 years after entry (27,428 women; 806 incident breast cancers; median time from FFQ completion to diagnosis, 2.7 y), women in the highest and lowest quartiles of energy intake had similar risk. When follow-up time after the first FFQ was divided into three four-year periods, the multivariate RRs for high versus low energy intake increased from 1.21 to 1.37 to 1.55 with increasing time since dietary assessment. Although the divergent results for the two FFQs could be due to subtle questionnaire differences, our findings suggest a modest positive association between energy intake and postmenopausal breast cancer that strengthens with time since dietary assessment.

Keywords

breast cancer; energy intake; energy balance; cohort

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INTRODUCTION

The potential influence of energy intake on risk of breast cancer has been studied in both observational and experimental settings (1). Animal studies have provided consistent evidence that energy restriction reduces breast cancer risk (2–4). Suggested mechanisms for the inhibition of mammary carcinogenesis include changes in cell cycle regulation, through decreased cell proliferation and increased apoptosis; reduced oxidative stress and strengthened antioxidant defense; and decreased angiogenesis, which is necessary for tumor growth (1,3). These mechanisms may be mediated by decreased insulin and insulin-like growth factor 1 (IGF-1) levels as well as increased corticosteroid production (3–6).

In contrast to strong evidence from animal studies, evidence from human populations exposed to famine and energy restriction has been mixed (7–10). Epidemiologic studies investigating the relationship between energy excess and breast cancer risk have also been inconclusive. Over the years, several retrospective (11–16) and prospective studies (17–19) observed increased risk of breast cancer with increased energy intake, but recent studies found no association (20–23). However, most epidemiologic studies of diet and breast cancer have not looked specifically at the influence of total energy intake; they have instead used estimates of energy intake to adjust the estimated intake of other macronutrients and micronutrients, thereby correcting for consistent over- or under-reporting of all food items.

In an earlier analysis of postmenopausal women in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), which included 764 incident breast cancer cases, a modest but statistically significant positive association between energy intake and breast cancer was found [relative risk (RR) for highest quartile relative to lowest, 1.25; 95% CI, 1.02–1.53] (24). This association persisted after adjustment for the other components of energy balance, specifically physical activity and body mass index (BMI), which suggested that energy intake had an independent effect on breast cancer risk that was not simply due to increasing BMI. In this analysis, breast cancer risk increased steadily over a 900 – 3,300 kcal/d range in reported energy intake with women consuming 3,300 kcal/d or more at nearly 50% higher risk for breast cancer compared to women consuming 1,500–1,799 kcal/d.

Given the scientific interest in the potential role of energy intake in breast carcinogenesis, the limited number of cohorts that have evaluated this relationship, and our earlier findings, in the current study we reanalyzed the association between energy intake and breast cancer risk in the PLCO cohort, including an additional four years of follow-up and a total of 1,319 incident breast cancer cases. In addition, we incorporated energy intake information from a second, somewhat different, food frequency questionnaire (FFQ) that was completed approximately five years after the initial FFQ.

MATERIALS AND METHODS

PLCO Study Design

The PLCO, coordinated by the National Cancer Institute in 10 U.S. centers, enrolled between November 1993 and September 2001 approximately 77,000 women and 78,000 men, aged 55–74, in a randomized, two-arm trial to determine if screening reduces the incidence and mortality of prostate, lung, colorectal, and ovarian cancer. Female participants randomized to the screening arm received a chest x-ray, flexible sigmoidoscopy and a digital rectal examination, and a CA-125 blood test and transvaginal ultrasound. Those participants randomized to the control arm received care by their usual physicians. A complete description of the PLCO study design has been published (25).

Those enrolled in the trial were asked to complete a baseline questionnaire. This self-administered questionnaire collected information about demographics, medical history, and cancer risk factors, including height and weight at baseline. In addition, those randomized to the screening arm were asked at baseline to complete a FFQ developed for the PLCO called the PLCO Dietary Questionnaire (DQx).[1] The DQx asked about typical frequency of intake during the past year for 137 food items and typical portion size for 77 of the food items. The DQx also assessed current physical activity with the question, "About how many hours do you spend in vigorous activities, such as swimming, brisk walking, etc.?" Possible responses were 0, <1, 1, 2, 3, and 4+ hours per week. A second FFQ, the National Institutes of Health Dietary History Questionnaire (DHQ),[2] which included typical frequency of intake questions for 114 food items and typical portion size questions for 109 items and also assessed diet during the preceding year, was distributed to participants in both the screening and control arms of the trial beginning in 1998 (26). Nearly all FFQs were fully completed, with 95.9% of the DQx and 94.5% of the DHQ returned by the women missing three or fewer food items. Response rates for the two FFQs were similar (84.3% and 82.0% for the DQx and DHQ, respectively) despite the longer time required to complete the DHQ (26).

Incident breast cancers were ascertained primarily from annual study update questionnaires mailed to PLCO participants and returned with a response rate of 95.7%. Women were asked if they had been diagnosed with cancer in the past year and if yes, to specify the type of cancer. This method accounted for more than 93% of case ascertainment in the study population. Other breast cancer cases were ascertained from reports by next-of-kin and personal physicians, death certificates, and other PLCO study forms. Cases were confirmed using hospital records and pathology reports. As more than 95% of self-reported breast cancer cases were positively confirmed, self-reported cases were included in our analyses.

Analytic Cohorts

The study population was limited to women randomized to the screening arm of the trial (n = 39,115). Women were excluded from the analysis if they did not complete a baseline questionnaire (n = 951), did not return at least one annual study update questionnaire (n = 387), reported a personal history of breast cancer on the baseline questionnaire (n = 1,334), or reported a personal history of cancer on the baseline questionnaire but did not specify the cancer site (n = 162). Therefore, a total of 36,281 women comprised the final study population. These women nearly all self-identified as White, non-Hispanic (88.7%) with the remaining women identifying as Black, non-Hispanic (5.7%), Hispanic (1.6%), Asian (3.3%), Pacific Islander (0.4%), or American Indian (0.3%).

Three analytic cohorts were created from this study population (Table 1). The first was limited to women who completed the DQx (n = 30,074). Further exclusions were made if women were not aged 55–75 years old at time of entry into the cohort (n = 8), missing quantitative responses to 8 or more food frequency questions (n = 332), or in the highest and lowest 1% for energy intake among all women who completed a baseline questionnaire and a DQx (n = 564) (energy intake range of remaining women: 606 – 3,995 kcal/d). Following these exclusions, there were 29,170 women (80.4% of study population) remaining for the DQx-based analyses. Among these women a total of 1,319 incident breast cancer cases were diagnosed during the follow-up period: 1,106 (83.9%) had been confirmed and 213 (16.1%) were awaiting confirmation. Among confirmed cases, there were 894 invasive (80.8%) and 212 *in situ* (19.2%) breast cancers.

[1]http://prevention.cancer.gov/files/programs-resources/dqx.pdf
[2]http://prevention.cancer.gov/files/programs-resources/dhq.pdf

The second analytic cohort was limited to women in the cohort who completed the DHQ (n = 28,591). Further exclusions were made if women were missing quantitative responses to 8 or more food frequency questions (n = 667) or were in the highest or lowest 1% for energy intake among all female DHQ respondents (n = 496) (energy intake range of remaining women: 464 – 3,663 kcal/d). Included in the DHQ-based analyses were thus 27,428 women (75.6% of study population). A total of 806 breast cancer cases were identified during follow-up: 610 cases (75.7%) had been confirmed (80.5% invasive and 19.5% *in situ*) and 196 (24.3%) were awaiting confirmation.

The third analytic cohort included 24,263 women (66.9% of study population) who completed an acceptable DQx and an acceptable DHQ. A total of 717 women developed breast cancer during the follow-up period.

Statistical Analysis

Entry date into the cohort was defined as the latest of the following dates: randomization, the baseline questionnaire, and the FFQ(s) of interest. Follow-up was terminated at the earliest of the following dates prior to March 31, 2007: for confirmed cases, breast cancer diagnosis date; for self-reported, but not yet confirmed, cases, the mid-point between the annual study update questionnaire that first reported breast cancer and the annual study update questionnaire that preceded it; and for non-cases, including those women lost to follow-up, the date of the most recent annual update questionnaire. Cox proportional hazards regression modeling was used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of breast cancer incidence by energy intake. Age, in months, was used as the time dependent variable.

Total energy intake was calculated as the summation across all foods of the frequency of consumption multiplied by both usual portion size (g) and energy content per gram (kcal/g). BMI was calculated by dividing current weight (kg) at baseline by the square of height (m) at baseline.

Analyses utilized three models. The age-adjusted model adjusted for age at entry date. The first multivariate model adjusted for age at entry date, study center (10 U.S. study centers), race (White, non-Hispanic; Black, non-Hispanic; Hispanic; Asian; Pacific Islander; American Indian/Alaskan Native), and accepted breast cancer risk factors: first-degree family history of breast cancer (yes/no), history of benign breast disease (yes/no), age at menarche (≤11, 12–13, 14–15, ≥16 y), age at first birth (≤19, 20–24, 25–29, ≥30 y, nulliparous), parity (0, 1, 2, 3, 4, ≥5 live births), age at last menses (<40, 40–44, 45–49, 50–54, ≥55 y), duration of menopausal hormone therapy use (0, 1–5 y, 6–9 y, ≥10 y), height (continuous), mammography in the last three years (0, 1, >1), and education (≤11 y, 12 y or completed high school, post-high school training, college graduate, or postgraduate). A second multivariate model adjusted for the covariates in the first multivariate model as well as for the other components of energy balance (in addition to energy intake): BMI (continuous) and physical activity (0, <1, 1, 2, 3, ≥ 4 h/wk of vigorous activity). Unless otherwise noted, values from the first multivariate model are presented in the results.

P for trend for energy intake was calculated in two ways using the Wald chi-square test: 1) using the median energy intake of each quartile as a continuous variable and 2) using energy intake as a continuous variable. Unless otherwise noted, p-values presented in the results are those from the first method. All correlation coefficients are Spearman's rank order correlations. Statistical analysis was done using SAS 9.1.3.

To examine the possible presence of a time lag effect, we divided follow-up in the DQx and DHQ analytic cohorts into four-year periods. The first four-year period of follow-up included all women in the FFQ-specific analytic cohort and truncated follow-up of each woman at four

years after her entry date. The second four-year period started four years after each woman's entry date and truncated follow-up eight years after her entry date. The third four-year period started eight years after the woman's original entry date and continued until the woman's original exit date. To test for statistical significance of the interaction between energy intake and four-year follow-up period, we utilized the p-value associated with the interaction term in the model. We also performed analyses in which the first year of follow-up for each analytic cohort was excluded from the analysis.

In addition, to approximate the previously published study (24), we divided the DQx analytic cohort into earlier and later periods of follow-up. The earlier period of follow-up created a cohort comparable to the previous analysis (29,170 women; 810 incident breast cancers; median follow-up = 5.0 y; median time between DQx and diagnosis = 2.8 y), and the later period of follow-up included only the additional follow-up since the previous study (27,223 women; 519 incident breast cancers; median follow-up = 3.7 y; median time between DQx and diagnosis = 7.2 y).

RESULTS

Characteristics of the analytic cohorts in this study are presented in Table 1. With 1,319 incident breast cancer cases, the DQx analytic cohort had 63% more cases than the DHQ analytic cohort and 84% more cases than the combined DQx/DHQ analytic cohort. Median follow-up time was 8.7 years for the DQx analytic cohort but approximately 5.5 years for the DHQ and combined DQx/DHQ analytic cohorts. Median time between FFQ completion and breast cancer diagnosis was 4.4 years in the DQx analytic cohort but only 2.7 years in the DHQ analytic cohort.

Figure 1 shows relative frequency distributions of daily energy intake for the women who completed both FFQs. The distribution curve for energy intake from the DQx is somewhat wider with a flatter peak than that from the DHQ. Median energy intake was 1,654 kcal/d (interdecile range: 1,041 – 2,551 kcal/d), based on the DQx, and 1,408 kcal/d (interdecile range: 851 – 2,217 kcal/d), based on the DHQ. More than 70% of the 24,263 women who answered both FFQs reported a higher energy intake on the DQx. Energy intake estimated by the two instruments was moderately correlated ($r = 0.56$) among all women completing both FFQs, and among these women stratified by age ($r = 0.56$ in each 5-year age group). The correlation between the two energy intake estimates did not differ by more than 0.03 across quartiles of BMI or by levels of physical activity. Sources of calories from the two instruments were similar: the mean percentages of calories from alcohol, carbohydrate, fat, and protein were 2.2%, 55.1%, 27.3%, and 15.5% for the DQx and 2.4%, 52.0%, 30.5%, and 15.1% for the DHQ.

Energy intake estimated by the DQx was positively, but weakly, associated with both BMI ($r = 0.08$) and physical activity ($r = 0.04$). Energy intake estimated by the DHQ was also positively, but even more modestly associated ($r = 0.03$ and 0.01 for BMI and physical activity, respectively). The women in the DQx and DHQ analytic cohorts who reported higher energy intake were more likely to be younger, heavier, taller, and more active compared to the women who reported lower energy intake (Table 2). Other breast cancer risk factors were not consistently associated with energy intake.

In the DQx analytic cohort (n = 29,170; 1,319 cases), energy intake was modestly, but statistically significantly, associated with increased risk of breast cancer (Table 3). Breast cancer risk, adjusted for accepted risk factors, was 21% higher (95% CI, 1.03–1.42) among women in the highest quartile of energy intake relative to women in the lowest quartile. The test for trend was also statistically significant (p = 0.03). After adjusting for BMI and physical activity, which may share a causal pathway with energy intake, the RR was reduced slightly

to 1.18 (95% CI, 1.00–1.39; P_{trend} = 0.07), but remained statistically significant. RRs were slightly reduced with the exclusion of the 213 self-reported cases (RR comparing highest to lowest quartiles of energy intake, 1.15; 95% CI, 0.96–1.33; P_{trend} = 0.14) and with the exclusion of both the 212 *in situ* and 213 self-reported cases (RR, 1.16; 95% CI, 0.96–1.41; P_{trend} = 0.04). Risk was also slightly reduced with the exclusion of the first year of follow-up after DQx administration (RR comparing highest to lowest quartiles of energy intake, 1.16; 95% CI, 0.98–1.38; P_{trend} = 0.10).

The association between energy intake and breast cancer risk was essentially unchanged with the addition of daily alcohol consumption (RR, 1.16; 95% CI, 0.99–1.37; P_{trend} = 0.07) or use of oral contraceptives (RR, 1.19; 95% CI, 1.02–1.40; P_{trend} = 0.03) to the multivariate model; therefore, these covariates were not included in the final model. Using World Health Organization BMI classifications of underweight, normal, overweight, and obese also did not alter estimates (RR, 1.18; 95% CI, 1.00–1.38; P_{trend} = 0.06).

In the DHQ analytic cohort (n = 27,428; 806 cases), however, energy intake was not associated with risk of breast cancer in the age-adjusted and multivariate models (Table 3). In this analytic cohort, women in the highest quartile of energy intake relative to those in the lowest quartile had a multivariate RR of 1.00, with similar results when BMI and physical activity were added to the model. The lack of association persisted with the exclusion of the self-reported cases, the exclusion of both *in situ* and self-reported cases, and the exclusion of the first year of follow-up after DHQ administration. As the DHQ was also administered in the control arm of the PLCO, we were able to look at the association between energy intake and breast cancer risk among these 27,197 women and again found no association.

The presence of a modest positive association with energy intake in the DQx analytic cohort, but not in the DHQ analytic cohort, could be explained by the different dietary instruments, the different populations, or the different follow-up times. The differences in the dietary instruments were summarized earlier in the Results. To evaluate whether the different populations influenced the results, we used DQx-based energy intake but excluded from the DQx analytic cohort those women not also in the DHQ analytic cohort. The DQx analytic cohort dropped from 29,170 women (1,319 cases) to 24,263 women (717 cases). The positive association between energy intake and breast cancer risk was somewhat stronger and more statistically significant than that observed in the DQx analytic cohort (RR for highest versus lowest quartiles of energy intake, 1.38; 95% CI, 1.11–1.73; P_{trend} = 0.01). This association was essentially unchanged after adjustment for BMI and physical activity but was reduced with the exclusion of the self-reported cases and the exclusion of both *in situ* and self-reported cases. The RR increased to 1.49 (95% CI, 1.16–1.92; P_{trend} = 0.004) with the exclusion of the first year of follow-up after DHQ administration. Among these women who completed both FFQs, using energy intake assessed several years later by the DHQ produced null results, similar to those found for the DHQ analytic cohort (data not shown).

The different results observed for the DQx and DHQ analytic cohorts could also be explained by the different follow-up times, as the DQx analytic cohort had longer follow-up time and, therefore, longer time elapsed from FFQ completion to breast cancer diagnosis (Table 1). To explore the possible importance of follow-up time, we performed analyses on the DQx and DHQ analytic cohorts divided into four-year periods of follow-up (Table 4). In the DQx, the positive association between risk of breast cancer and energy intake increased with time elapsed since energy intake assessment. Women in the highest versus lowest quartiles of energy intake had a RR of 1.21 (95% CI, 1.02–1.43; P_{trend} = 0.04) in the first four years of follow-up, 1.37 (95% CI, 1.09–1.73; P_{trend} = 0.007) in the second four years of follow-up, and 1.55 (95% CI, 0.89–2.70; P_{trend} = 0.17) in the last years of follow-up. When comparable analyses were performed for the DHQ analytic cohort, no association was seen for the first four years of

follow-up (RR, 1.00; 95% CI, 0.80–1.24; P_{trend} = 0.95). However, energy intake was weakly, though not statistically significantly, associated with increased breast cancer risk during the remaining years of follow-up (RR, 1.23; 95% CI, 0.77–1.98; P_{trend} = 0.47). The interaction between energy intake and DQx four-year period of follow-up was of borderline statistical significance (p = 0.06); the interaction was not statistically significant in the DHQ analytic cohort (p = 0.48).

To determine whether the positive association between energy intake and breast cancer risk in the expanded DQx analytic cohort was attributable to our previously published findings for the same cohort with shorter follow-up time (24), we examined the DQx analytic cohort divided into earlier and later periods of follow-up (see Methods). In both periods of follow-up, energy intake was positively, but not significantly, associated with breast cancer risk (data not shown). For women in the highest quartile of energy intake relative to those in the lowest quartile, breast cancer risk was increased 15% (95% CI, 0.94–1.41; P_{trend} = 0.18) in the earlier period of follow-up and 25% (95% CI, 0.96–1.63; P_{trend} = 0.13) in the later period of follow-up. The stronger associations during the later period of follow-up indicate that the results of our current analysis extend, and do not simply repeat, our previously published findings (24). In addition, the increased risk lends support to the idea that time elapsed from energy intake assessment to diagnosis may be relevant. However, the interaction between energy intake and period of follow-up was not statistically significant (p = 0.70).

In addition, among women who completed both the DQx and the DHQ (n = 24,263; 717 cases), we integrated energy intake from both FFQs in several ways (data not shown). First, we averaged the energy intake percentiles of the two FFQs for each woman and compared women in the highest quartile of mean percentile energy intake to those in the lowest quartile. Second, we averaged the absolute energy intakes of the two FFQs for each woman and compared women in the highest quartile of mean absolute energy intake to those in the lowest. Finally, we ranked women by the quartile of energy intake in each FFQ and compared women jointly in the highest quartile of energy intake for each FFQ to women jointly in the lowest quartile of energy intake for each FFQ. The multivariate RRs of women in the highest level of integrated energy intake, relative to women in the lowest, ranged from 1.16 to 1.22; none of the confidence intervals excluded 1.0; and none of the various tests for trend were statistically significant.

DISCUSSION

In an expanded analysis of a previously published study of energy intake and risk of postmenopausal breast cancer in the PLCO cohort (24), we again observed a modest, but statistically significant, positive association between energy intake and risk of subsequent breast cancer. With four additional years of follow-up time and nearly 75% more breast cancer cases, we found a 20% increase in breast cancer risk comparing extreme quartiles of energy intake. This increase was minimally confounded by BMI and physical activity and strengthened noticeably with time elapsed since energy intake assessment. Results among women in the most recent four years of follow-up appeared stronger than those in the earlier years of follow-up, which indicates that our overall findings were not driven by the results we have already published.

Energy intake estimated from the second FFQ administered in the study, the DHQ, which was given, on average, 3.3 years after the DQx, provided another opportunity to expand upon the previous study. While energy intake was positively and significantly associated with increased breast cancer risk when using DQx-based energy intake, there was no evidence of an overall association when using DHQ-based energy intake.

The difference in results by FFQ could be explained by the different analytic populations, the different follow-up times, or the different dietary assessment instruments. While 1,742 fewer women were included in the DHQ analytic cohort than in the DQx analytic cohort, the two analytic cohorts were very similar, with more than 24,000 women completing both FFQs and, therefore, in both cohorts. Analyses among the 24,263 women who completed both FFQs demonstrated a positive association between DQx-based energy intake and breast cancer risk comparable to that in the DQx analytic cohort; therefore, the difference in analytic populations is not likely the reason for the difference in results by FFQ.

Secondly, the difference in results by FFQ could be explained by the different follow-up times. Each FFQ quantified energy intake, but the DHQ measured energy intake at a later point in time for each woman: the DHQ was administered, on average, 3.3 years after the DQx. Mean and median follow-up times were 3.1 and 3.3 years longer, respectively, in the DQx analytic cohort than in the DHQ analytic cohort. It is possible that several years need to elapse before the full influence of an increased or decreased energy intake on breast cancer incidence becomes apparent. Given more follow-up time, energy intake assessed by the DHQ may also show positive associations with risk, as a statistically significant 38% increase in risk, comparing extreme quartiles, did appear when using DQx-based energy intake among the women completing the DHQ.

Evidence for the importance of elapsed time also came from time lag analyses in the DQx and DHQ analytic cohorts. In four-year periods of follow-up created from the DQx analytic cohort, the relative risk of breast cancer increased from 1.21 to 1.37 to 1.55 with time elapsed since energy intake assessment. A similar, but weaker, relationship, with relative risk increasing from 1.00 to 1.23 with elapsed time since energy intake assessment, was detected in four-year periods of follow-up created from the DHQ analytic cohort.

Lastly, differences in the dietary assessment instruments could explain the differential results by FFQ. The DQx[3] is similar to earlier FFQs in its grid format and inclusion of typical foods in the U.S. diet (26). However, it also incorporated the results of extensive cognitive research with volunteers on how to improve dietary assessment methodology (27, 28). Thus, the DQx includes an empirically derived comprehensive food list, rational categories for frequency of intake and portion size, and optimized wording and formatting. The DHQ,[4] finalized later in time, incorporated the continuing cognitive research (26). It is substantially longer and more comparable to a dietary history with a series of questions after specific food items eliciting additional detail. It does not rely on a conventional grid format and includes somewhat different food items, frequency of intake categories, and portion size definitions than the DQx. The DHQ has been compared to the Block and Willett FFQs in a calibration study using four 24-hour recalls, one in each season, conducted by telephone (29). The DHQ performed best overall; with a standard measurement error model, the correlation for energy between estimated truth and the DHQ was 0.48 for women. The DQx has never been compared with 24-hour dietary recalls or food records so it is not possible to use calibration studies to compare the two FFQs. However, in the PLCO cohort, energy intake estimated by the DQx was, as would be expected, positively, but weakly, associated with both BMI ($r = 0.08$) and physical activity ($r = 0.04$). Energy intake estimated by the DHQ was barely associated with these two determinants ($r = 0.03$ for BMI and 0.01 for physical activity), which suggests that the DQx may be modestly better at estimating energy intake.

In the PLCO cohort, the frequency distributions for energy intake estimated by the two FFQs only partially overlapped, the correlation between the energy estimates was only 0.56, and

[3]http://prevention.cancer.gov/files/programs-resources/dqx.pdf
[4]http://prevention.cancer.gov/files/programsresources/dhq.pdf

absolute energy intake estimated by the DHQ was lower than energy intake estimated by the DQx for approximately 70% of the women. It is conceivable, therefore, that the FFQs differ in their ability to assess true energy intake and the DQx is more accurate though the two instruments have not been compared side-by-side. When we compared sources of calories, the percent of calories from carbohydrate, fat, protein, and alcohol were similar for the two FFQs. Possible explanations for the different performance of the two FFQs include differences in design and respondent burden.

Three other prospective studies have reported positive associations between energy intake and breast cancer risk (17–19). In a large Canadian study of pre- and postmenopausal women (with 327,994 and 244,616 person-years of follow-up, respectively), multivariate HRs for highest to lowest quartiles of energy intake, in models including physical activity and BMI, were similar in magnitude to those found in our study and a significant trend was seen (19). After stratification by menopausal status at baseline, the association with energy intake was relatively strong among premenopausal women (multivariate HR, 1.45; 95% CI, 1.13–1.85; P_{trend} = 0.001) but null among postmenopausal women (multivariate HR, 0.94; 95% CI, 0.72–1.23; P_{trend} = 0.86) with a marginally significant p-value for interaction by menopausal status (p = 0.06) (19). Additionally, a small U.S. study of 590 postmenopausal women found increased breast cancer risk with each 500-kilocalorie increase in total energy intake (RR, 2.72; 95% CI, 1.51–4.89) (17) and a Norwegian study of pre- and postmenopausal women found evidence of an energy intake-breast cancer association (RR, 1.50; 95% CI, 1.05–2.15) though the association lost statistical significance when BMI was added to the model (18). Case-control studies in Argentina, China, Italy, and Switzerland have provided further evidence supporting a positive association between energy intake and risk of breast cancer (12–16), as have international correlation studies of total calories and breast cancer incidence (r = 0.70) and breast cancer mortality (r = 0.60) (30).

Surprisingly few epidemiologic studies have assessed the relationship between total energy consumption and breast cancer risk. The vast majority of studies of diet and breast cancer adjust nutrient estimates for total caloric intake by one of several accepted methods. Justifications include correcting for systematic underestimation and overestimation of consumption, reducing measurement error by controlling for variation in energy intake, controlling for confounding by total energy intake, and focusing on dietary composition rather than absolute nutrient intake (31). Therefore, most studies, by adjusting for energy, have not been able to evaluate its independent role.

However, our findings do differ from those of three recent cohort studies and one recent case-control study (20–23). Energy intake was not associated with risk among postmenopausal women in the Breast Cancer Detection Demonstration Project Follow-up Cohort Study (20) nor among pre-and postmenopausal women in the Nurses' Health Study cohort (21); both studies presented results controlled for BMI but not physical activity. There was also no association among pre- and postmenopausal women in the California Teachers Study cohort (22) nor among pre- and postmenopausal women in the case-control Shanghai Breast Cancer Study, which did not adjust for BMI or physical activity (23).

The evidence from studies of populations exposed to severe energy restriction has been mixed (7–10). A retrospective cohort study in Sweden found that in a group of women hospitalized for anorexia nervosa before age 40, calorie restriction was associated with a statistically significant 53% decreased risk of breast cancer, compared to the general female Swedish population (7). In a Norwegian study, those women who had undergone puberty during World War II experienced lower breast cancer incidence than those who were older or younger during the same time period. As daily energy intake was 22% lower during the war, caloric restriction may have contributed to the lower incidence (8). In contrast, a case-cohort study of women

exposed to the briefer, but more severe famine conditions in the Netherlands at the end of World War II reported that caloric restriction early in life increased later breast cancer risk (10). HRs, adjusted for adult BMI, were 1.13 (95% CI, 0.92–1.38) and 1.48 (95% CI, 1.09–2.01) for women moderately and severely exposed to the 1944–1945 Dutch famine, respectively. However, another study reported no association between place of residence in the Netherlands, which determined exposure to World War II famine, and risk of breast cancer (9).

Strengths of our study include the prospective design, which minimized selection and participation bias. The large number of women in the cohort provided stable estimates of risk. Cancer ascertainment from the annual study update questionnaires was excellent, with 96% of the questionnaires returned, on average, and 96% of self-reports of breast cancer subsequently confirmed by hospital reports. In addition, prospective ascertainment of diet and breast cancer risk factors prevented recall bias. Diet was assessed with detailed, comprehensive, cognitively-designed FFQs. The FFQs were carefully completed with nearly all missing three food items or fewer. Weaknesses of our study include the difficulties inherent in measuring diet using FFQs, with energy intake being particularly challenging to assess, which leads to measurement error and, frequently, attenuation of RR estimates (32,33). In addition, diet was assessed at only one point in time though each FFQ did ask the respondent to recall and integrate diet over the past year. At the time of our analyses, hormone receptor status information was being collected and available for only a portion of the confirmed breast cancer cases in our study population, which precluded additional analyses by breast cancer subtype.

In conclusion, findings from this extended analysis continue to suggest a modest positive association between total energy intake and risk of postmenopausal breast cancer, an association which was largely independent of BMI and physical activity. In this large cohort, breast cancer risk was increased 21% (95% CI, 3–42%) among women in the highest quartile of energy intake compared to those in the lowest. When follow-up time was divided into four-year periods, the RRs for high versus low energy intake increased from 1.21 to 1.37 to 1.55, with increasing time since dietary assessment. Our findings suggest a modest positive association between energy intake and postmenopausal breast cancer that strengthens with time since dietary assessment.

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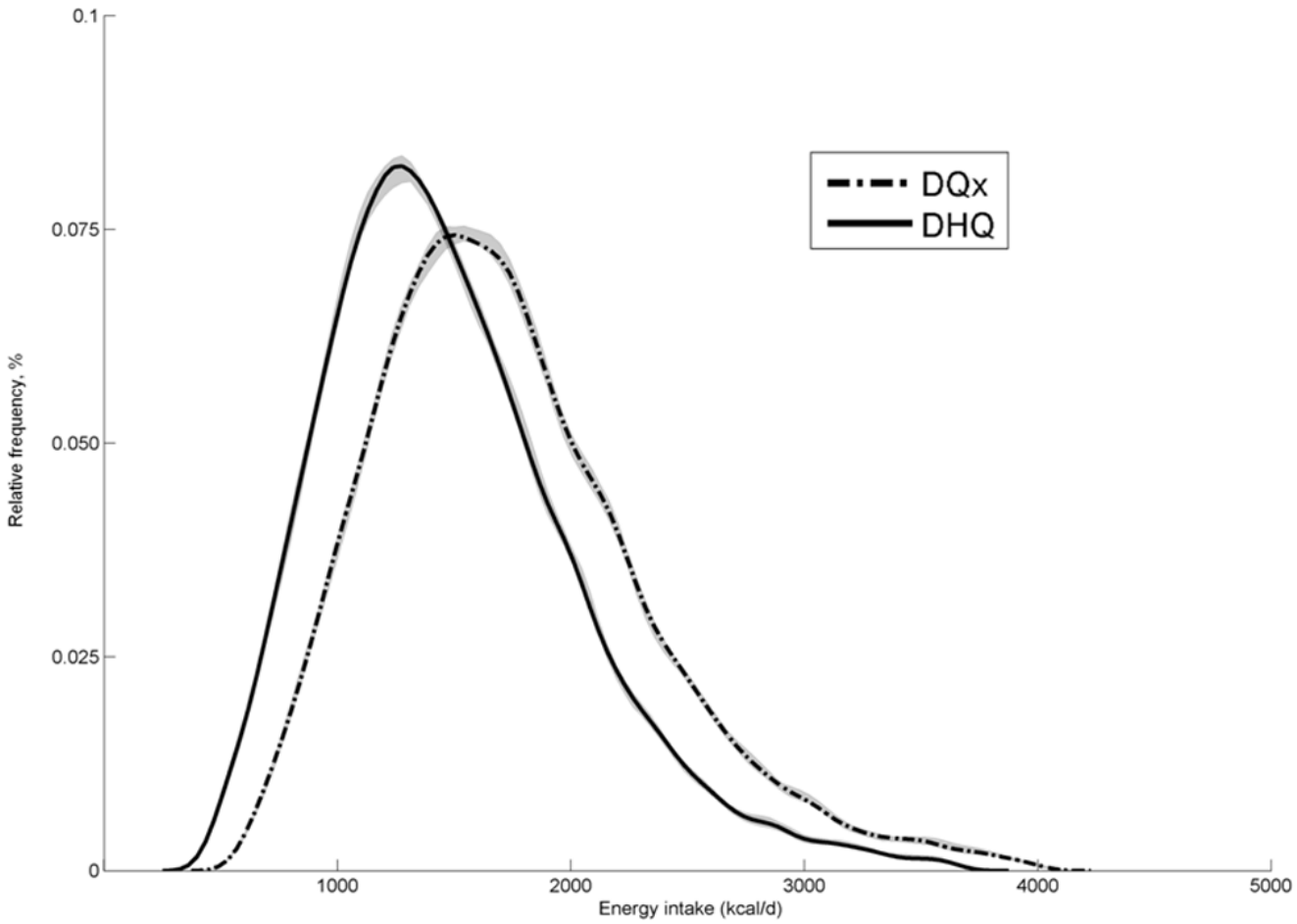

Figure 1.
Frequency distributions of daily energy intake (kcal/d) for women who completed both the DQx and DHQ food frequency questionnaires (n = 24,263).

Table 1

Characteristics of the analytic cohorts used in this study

	Analytic cohort		
	DQx	**DHQ**	**Combined DQx/DHQ**
Cohort participants	29,170	27,428	24,263
Incident breast cancer cases	1,319	807	717
Person-years	245,160	145,474	129,742
Median age at entry, y	62.0	65.0	65.0
Median follow-up time (interdecile range), y	8.7 (5.8–11.2)	5.4 (3.0–7.2)	5.6 (3.0–7.2)
Median time between FFQ completion and breast cancer diagnosis (interdecile range), y	4.4 (1.0–8.6)	2.7 (0.5–5.5)	DQx: 6.0 (3.6–9.4) DHQ: 2.6 (0.4–5.6)

Table 2

Age-standardized[†] baseline characteristics of the DQx and DHQ analytic cohorts by quartiles of energy intake[*]

	DQx analytic cohort (n = 29,170)				DHQ analytic cohort (n = 27,428)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Range of energy intake (kcal/d)	≤1,311	1,312–1,653	1,654–2,080	≥2,081	≤1,095	1,096–1,407	1,408–1,796	≥1,797
Age at entry, y[**]	62.8 ± 5.3	62.7 ± 5.4	62.7 ± 5.4	62.2 ± 5.3	66.1 ± 5.6	65.9 ± 5.5	65.5 ± 5.5	65.1 ± 5.4
BMI, kg/m^2[**]	26.5 ± 0.07	26.7 ± 0.07	26.9 ± 0.07	27.6 ± 0.07	27.0 ± 0.07	26.8 ± 0.06	26.9 ± 0.07	27.5 ± 0.07
Height, m[**]	1.62 ± 0.09	1.63 ± 0.08	1.63 ± 0.09	1.64 ± 0.09	1.63 ± 0.08	1.63 ± 0.08	1.63 ± 0.08	1.64 ± 0.08
Vigorous physical activity (%), h/wk								
0	18.3	14.8	14.1	15.0	15.1	13.3	13.8	15.5
<1	19.1	17.7	17.2	17.3	19.8	18.2	18.1	17.8
1–2	27.8	29.0	29.7	27.6	28.8	29.9	29.1	28.3
≥3	34.8	38.6	39.1	40.1	36.3	38.7	39.0	38.4
Family history of breast cancer (%)	15.0	15.6	14.8	15.2	14.2	13.5	14.3	14.0
History of benign breast disease (%)	25.1	26.7	27.6	26.3	26.8	28.3	29.8	27.9
Mammography in last 3 y (%)								
More than once	71.3	72.5	72.6	69.8	72.0	74.0	75.0	71.1
Once	19.9	19.6	19.3	20.8	19.7	18.1	17.7	19.7
No	8.8	7.9	8.1	9.5	8.3	7.9	7.4	9.3
Age at menarche (%), y								
≤11	22.1	21.1	22.5	22.9	21.2	20.6	20.8	22.3
12–13	53.8	56.5	54.0	53.1	53.8	55.9	56.0	53.3
14–15	19.1	18.1	19.4	19.3	20.5	19.8	18.9	19.8
≥16	4.9	4.3	4.2	4.7	4.5	3.8	4.2	4.6
Age at first birth (%), y								
≤19	19.2	15.4	15.0	16.1	19.4	17.1	16.8	19.1
20–24	51.8	53.6	52.3	52.3	52.9	52.2	52.8	52.4
25–29	22.4	23.7	24.0	23.3	20.9	23.6	22.6	21.4
≥30	6.7	7.4	8.7	8.3	6.8	7.2	7.8	7.2
Parity (%)								
0	8.3	8.9	8.8	8.9	9.1	8.4	9.1	8.9
1	6.4	6.4	6.8	7.0	7.3	7.4	6.8	6.8
2	22.1	21.6	21.8	19.6	24.6	23.9	23.5	22.9
3	25.9	24.8	24.5	23.9	26.3	25.3	24.7	24.8
4	17.5	17.9	17.9	18.7	16.0	17.3	17.9	17.0
≥5	19.8	20.4	20.3	22.0	16.6	17.7	18.1	19.7
Age at last menses (%), y								
<40	15.1	12.9	12.7	12.6	15.9	13.7	13.7	14.5
40–44	14.6	15.5	14.2	14.2	14.5	14.1	13.8	13.8
45–49	24.7	24.1	23.1	25.0	23.9	23.8	23.7	23.0
≥50	45.7	47.6	50.0	48.2	45.7	48.4	48.8	48.6
Menopausal hormone therapy (%)								
Current user	47.4	48.4	47.9	45.3	52.4	53.9	53.4	51.2
Past user	17.0	17.3	18.3	17.6	17.1	15.5	16.4	16.2
Education (%)								
High school graduate or less	40.6	35.2	33.0	34.0	36.3	31.9	32.0	33.1
Post high school	34.9	36.4	35.8	36.0	36.6	36.5	35.5	36.3
College graduate	13.0	15.1	16.3	15.3	14.2	16.2	17.3	15.9
Postgraduate	11.5	13.3	14.9	14.8	12.9	15.4	15.3	14.7

[†] All values were standardized to the age distribution (by 5-year categories) of the DQx or DHQ analytic cohorts. Percents may not sum to 100% due to rounding.

[*] The DQx analytic cohort included all women in the study population (see Materials and Methods) who completed the DQx food frequency questionnaire (FFQ), were aged 55–75 at entry into the cohort, did not have 8+ missing responses on the DQx, and did not have extreme energy intakes (top or bottom 1% of energy intake among all female DQx respondents). The DHQ analytic cohort included all women in the study population who completed the DHQ FFQ, did not have 8+ missing responses on the DHQ, and did not have extreme energy intakes (top or bottom 1% of energy intake among all female DHQ respondents).

[**] Mean ± SD.

Table 3

RRs (95% CIs) of breast cancer by quartile of energy intake (kcal/d) in the DQx and DHQ analytic cohorts

Quartile of energy intake (kcal/d)	Cases	Person-years	Age-adjusted model	Multivariate model*
DQx (n=29,170)				
Q1 (<1,311)	281	60,770	1.00	1.00
Q2 (1,312–1,653)	335	61,267	1.18 (1.01–1.39)	1.12 (0.95–1.32)
Q3 (1,654–2,080)	339	61,794	1.19 (1.01–1.39)	1.09 (0.93–1.28)
Q4 (≥2,081)	364	61,329	1.29 (1.10–1.50)	1.21 (1.03–1.42)
$P_{trend\ by\ median\ of\ quartile}$			0.004	0.03
$P_{trend\ by\ continuous\ kcal/d}$			0.003	0.03
DHQ (n=27,428)				
Q1 (<1,095)	191	36,161	1.00	1.00
Q2 (1,096–1,407)	202	36,658	1.05 (0.86–1.28)	0.98 (0.80–1.21)
Q3 (1,408–1,796)	210	36,654	1.09 (0.90–1.33)	1.01 (0.82–1.23)
Q4 (≥1,797)	203	36,029	1.08 (0.88–1.31)	1.00 (0.81–1.22)
$P_{trend\ by\ median\ of\ quartile}$			0.50	0.99
$P_{trend\ by\ continuous\ kcal/d}$			0.56	0.93

$P_{trend\ by\ median\ of\ quartile}$ values were calculated using the median energy intake of each quartile as a continuous variable in the model.

$P_{trend\ by\ continuous\ kcal/d}$ values were calculated using kcal/d as a continuous variable in the model.

*Adjusted for age at entry, study center (10 PLCO study centers), race (White, non-Hispanic; Black, non-Hispanic; Hispanic; Asian; Pacific Islander; American Indian/Alaskan Native), family history of breast cancer (yes/no), history of benign breast disease (yes/no), age at menarche (≤11, 12–13, 14–15, ≥16 y), age at first birth (≤19, 20–24, 25–29, ≥30 y, nulliparous), number of live births (0, 1, 2, 3, 4, ≥5), age at last menses (<40, 40–44, 45–49, 50–54, ≥55 y), duration of menopausal hormone therapy use (0, 1–5 y, 6–9 y, ≥10 y), and education (≤ 11 y, 12 y or completed high school, post-high school training, college graduate, or postgraduate), height (continuous), and mammography in the last three years (0, 1, >1 times).

Table 4

RRs (95% CIs) of breast cancer by quartile of energy intake (kcal/d) in the DQx and DHQ analytic cohorts divided into 4-year periods of follow-up

DQx Quartile of energy intake (kcal/d)	Cases	Person-years	Multivariate model*	DHQ Quartile of energy intake (kcal/d)	Cases	Person-years	Multivariate model*
First four years of follow-up (n=29,170)				First four years of follow-up (n=27,428)			
Q1 (<1,311)	141	28,478	1.00	Q1 (<1,095)	144	25,758	1.00
Q2 (1,312–1,653)	157	28,467	1.13 (0.96–1.34)	Q2 (1,096–1,407)	143	25,871	0.98 (0.79–1.21)
Q3 (1,654–2,080)	144	28,585	1.11 (0.94–1.31)	Q3 (1,408–1,796)	152	25,919	1.04 (0.84–1.29)
Q4 (≥2,081)	157	28,571	1.21 (1.02–1.43)	Q4 (≥1,797)	150	25,785	1.00 (0.80–1.24)
$P_{trend\ by\ median\ of\ quartile}$			0.041	$P_{trend\ by\ median\ of\ quartile}$			0.95
$P_{trend\ by\ continuous\ kcal/d}$			0.026	$P_{trend\ by\ continuous\ kcal/d}$			0.97
Second four years of follow-up† (n=27,746)				Last years of follow-up† (n=20,509)			
Q1 (<1,311)	104	24,278	1.00	Q1 (<1,095)	47	10,404	1.00
Q2 (1,312–1,653)	135	24,443	1.14 (0.90–1.46)	Q2 (1,096–1,407)	59	10,786	1.19 (0.75–1.90)
Q3 (1,654–2,080)	132	24,677	1.17 (0.92–1.49)	Q3 (1,408–1,796)	58	10,734	1.39 (0.88–2.19)
Q4 (≥2,081)	146	24,545	1.37 (1.09–1.73)	Q4 (≥1,797)	53	10,244	1.23 (0.77–1.98)
$P_{trend\ by\ median\ of\ quartile}$			0.007	$P_{trend\ by\ median\ of\ quartile}$			0.47
$P_{trend\ by\ continuous\ kcal/d}$			0.009	$P_{trend\ by\ continuous\ kcal/d}$			0.43
Last years of follow-up** (n=15,864)							
Q1 (<1,311)	36	8,014	1.00				
Q2 (1,312–1,653)	43	8,358	1.36 (0.77–2.37)				
Q3 (1,654–2,080)	63	8,532	1.80 (1.06–3.07)				
Q4 (≥2,081)	61	8,212	1.55 (0.89–2.70)				
$P_{trend\ by\ median\ of\ quartile}$			0.17				
$P_{trend\ by\ continuous\ kcal/d}$			0.21				

$P_{trend\ by\ median\ of\ quartile}$ values were calculated using the median energy intake of each quartile as a continuous variable in the model.

$P_{trend\ by\ continuous\ kcal}$ values were calculated using kcal/d as a continuous variable in the model.

*Adjusted for age at entry date, study center (10 PLCO study centers), race (White, non-Hispanic; Black, non-Hispanic; Hispanic; Asian; Pacific Islander; American Indian/Alaskan Native), family history of breast cancer (yes/no), history of benign breast disease (yes/no), age at menarche (≤11, 12–13, 14–15, ≥16 y), age at first birth (≤19, 20–24, 25–29, ≥30 y, nulliparous), number of live births (0, 1, 2, 3, 4, ≥5), age at last menses (<40, 40–44, 45–49, 50–54, ≥55 y), duration of menopausal hormone therapy use (0, 1–5 y, 6–9 y, ≥10 y), and education (≤11 y, 12 y or completed high school, post-high school training, college graduate, or postgraduate), height (continuous), and mammography in the last three years (0, 1, >1 times).

**Follow-up for this period began eight years after the entry date for each woman and continued through her final exit date from the cohort.

†Follow-up for this period began four years after the entry date for each woman and continued through her final exit date from the cohort.