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Association between dietary energy density and obesity-associated cancer: Results from the Women's Health Initiative

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Abstract

Background—Dietary energy density (DED) is the ratio of energy [kilocalories (kcal) or kilojoules (kJ)] intake to food weight (grams, g) and is a measure of diet quality. Consumption of foods high in DED has been associated with weight gain in adults.

Objective—To investigate the association between baseline DED and incident obesity-associated cancers in the Women's Health Initiative (WHI).

Design—Prospective cohort study of clinical trial and observational study participants.

Participants/setting—Postmenopausal women ages 50–79 years (n = 92,295) enrolled in the observational study or the calcium and vitamin D trial and hormone replacement therapy trials.

Main outcome measures—Incident, medical record-adjudicated, obesity-related cancers during follow-up. Exposure variable was DED (kcal/g for the total diet) from self-reported dietary intake at baseline using a food frequency questionnaire.

Statistical analyses performed—The associations between DED and each incident cancer, or any obesity-related cancer, were examined using competing-risks regression models, with death as a competing risk. Body mass index (BMI)-stratified models were generated to investigate BMI as a potential modifying factor.

Results—DED was associated with higher BMI (mean ± standard deviation: 28.9 ± 6.0 versus 26.3 ± 4.9 kg/m^2) and waist circumference (89.3 ± 14.2 versus 82.4 ± 12.4 cm) for DED quintiles 5 versus 1, respectively. DED was associated with a 10% increased risk of any obesity-related cancer (subhazard ratio$_{Q5\ vs\ Q1}$: 1.1; 95% confidence interval, 1.03–1.2; P = 0.004). This increased risk appeared limited to women who were normal-weight at enrollment.

Conclusions—Higher DED may be a contributing factor for obesity-related cancers, especially among normal-weight postmenopausal women and, as such, could serve as a modifiable behavior for dietary intervention to reduce obesity-associated cancer risk.

Keywords

Energy Density; Cancer; Obesity; Post-menopausal women

INTRODUCTION

It is estimated that over 30% of cancers could be prevented with dietary modification.[1,2] Select dietary components and patterns, particularly those that promote higher caloric intake, are associated with increased cancer risk, [3–5] especially for obesity-related cancers,[2,6] including breast, colorectal, ovarian, endometrial, kidney, gallbladder, esophageal, and pancreatic cancer.[7–9] Further, dietary patterns have also been associated with weight status and may therefore contribute to cancer risk.[10] For example, high energy-dense diets characterized by a high intake of saturated fat and a high glycemic load, among other factors, predicted weight and waist circumference gain in adults, whereas low energy-dense diets were protective.[11–13] Low energy-dense diets also have resulted in enhanced weight loss and less hunger compared to dietary fat restriction alone in a yearlong clinical trial.[14] Studies of dietary energy density (DED), defined as the ratio of energy [kilocalories (kcal) or kilojoules (kJ)] intake to food weight (grams, g),[15] and weight status have shown that regular consumption of foods high in DED contribute to weight gain in adults.[11,16,17] The mechanisms underlying the relationship between DED and chronic disease risk are not well described, but it has been postulated that foods high in DED may be associated with lower overall satiety resulting in greater overall energy intake.[18,19]

Self-reported energy intake can be calibrated using doubly labeled water as a comparator for energy balance to identify factors generally associated with under-reporting [e.g. age, body mass index (BMI)].[20] Previous evidence from the Women's Health Initiative (WHI) supported a role for calibrated, but not uncalibrated, self-reported energy consumption, in cancer risk, independent of BMI.[21] As calibration of energy intake is not feasible in large population studies due to cost and logistics, identifying other indicators of energy exposure that may be associated with cancer risk is an important objective. One such indicator is DED, which reflects the quality of energy consumed in the context of the dietary pattern, therefore enhancing the interpretation of total energy intake. Limited epidemiological data exist to describe the associations between high DED diets and cancer risk, as these relationships are postulated to be positively correlated. Experimental studies have demonstrated a rise in postprandial glucose and free fatty acid concentrations as well as decreased insulin response to consumption of a high DED meal.[22–24] Notably, a population-based case-control study found a positive association between DED and risk of pancreatic cancer.[25] Yet, no studies have prospectively investigated the relationship between DED and cancer risk.

The WHI provides a unique opportunity to prospectively explore the relationship between DED and cancer risk in a large sample of ethnically and racially diverse postmenopausal women in which cancer endpoints are well characterized. Further, the large number of obesity-related cancer cases and the variance in BMI afford ample opportunity to determine if associations between DED and obesity-associated cancers depend on a woman's BMI.

Thus, the purpose of this study was to investigate the association between baseline DED and risk of incident obesity-associated cancers in the WHI. It was hypothesized that higher baseline DED would be associated with increased risk of obesity-associated cancers and that these effects would be stronger among participants who were obese (BMI ≥ 30 kg/m^2) at study entry.

MATERIALS AND METHODS

Study Population

The analytical dataset for this study included healthy postmenopausal women ages 50–79 years enrolled between 1993 and 1998 in the WHI at one of 40 clinical centers across the U.S. The study sample includes women enrolled in the Observational Study and women from three of the four Clinical Trials: the calcium and vitamin D supplementation trial and the two hormone replacement therapy trials (estrogen alone or estrogen plus progesterone).[26] Women enrolled in the Dietary Modification (DM) trial were excluded given eligibility criteria specific to higher dietary fat intake, an exposure that would skew DED. Further, DED was quite stable in non-DM participants between baseline and year 3, whereas DED changed substantially for both arms of the DM trial in the first year of follow-up. The lack of change in DED in participants of the current study sample supports the theory that DED has potential stability over time and can be used in assessments of outcomes several years later. The total available sample size was 112,973 women. Exclusion criteria included personal history of cancer (n = 13,620), lack of dietary data (n = 150), reported energy intake < 600 kcal/day (n = 4105) or > 5000 kcal/day (n = 410), BMI < 18 kg/m^2 (n = 1244) or > 50 kg/m^2 (n = 589), missing BMI (n = 1214), and lack of follow-up data (n = 530). Additionally, one woman was excluded due to reported DED of over three standard deviations above mean, yielding a final analytical sample of 92,295 women. Written informed consent was obtained from all study participants prior to study enrollment, and each of the trials were approved by the Institutional Review Boards of the 40 participating institutions.

Identification of Cancer

Cancer at baseline screening was documented by self-report in which each woman was asked whether she had ever been told by a physician that she had cancer. Incident cancer during follow-up was documented by self-report at each semi-annual contact and then adjudicated using medical records and the centralized adjudication protocol at the WHI Clinical Coordinating Center. Obesity-associated cancers were defined according to the American Institute of Cancer Research (AICR) on-going epidemiological report of diet, physical activity, and cancer.[27] The numbers of AICR-defined obesity-associated cancers within the WHI sample (as of September 30, 2016) were: breast cancer (n = 5565), colorectal cancer (n = 1639), ovarian cancer (n = 662), endometrial cancer (n = 955), renal cancer (n = 347), gallbladder cancer (n = 61), esophageal cancer (n = 85), pancreatic cancer (n = 620), and any of the above (n = 9565). The mean follow-up period for the WHI sample evaluated here was 14.6 ± 5.6 years. Mean time-to-diagnosis (in years) for each cancer type are as follows: breast (8.2), colorectal (8.4), ovarian (8.6), endometrial (8.3), renal (8.9), pancreatic (10.0), and any obesity-related cancer (8.3). Mean time-to-death for women who died without any obesity-related cancer diagnosis was 11.8 years.

Dietary Assessment and Dietary Energy Density (DED)

Dietary intake was self-reported at baseline using a food frequency questionnaire (FFQ) designed for the WHI to estimate energy, nutrients, and food weight.[28] DED was the primary exposure of interest in the analysis. The DED of a single food is defined as the ratio of its energy content [kcal (kJ)] to its weight (g); this ratio remains constant regardless of the amount consumed. [15] DED for these analyses was derived from food only, with systematic exclusion of all beverages given the lack of information on water intake. DED for overall diet was calculated by dividing daily energy intake (kcal) from foods (solid foods and semi-solid or liquid foods such as soups) by the reported portion sizes and corresponding gram weights of these foods in the WHI FFQ database.

Statistical Analysis

This analysis included participants who completed the dietary assessment at baseline and who were followed until diagnosis of cancer, death, loss to follow-up, or end of study. Specific endpoints were any incident obesity-associated cancer as well as each individual cancer type: breast, colorectal, ovarian, endometrial, renal, and pancreatic. Gallbladder and esophageal cancers were not considered as their own endpoints due to the small number of cases (n < 100 each), but they were included in the sum of any obesity-associated cancer.

Baseline characteristics of the analytical sample were described across quintiles of DED according to mean ± standard deviation (SD) for continuous variables or *n* (%) for categorical variables. The association between DED and each incident cancer, or any obesity-related cancer, was examined using competing-risk regression models, with death as a competing risk. Competing-risk models generate subhazard ratios (SHR) instead of the more familiar hazard ratio and treat deaths differently than other censoring, because participants who die can never have any subsequent outcome, unlike those who are lost to follow-up. Women who self-reported bilateral mastectomies before enrollment (*n* = 177) were excluded from breast cancer analyses. Women who self-reported bilateral oophorectomies (*n* = 16,375) were excluded from ovarian cancer analyses. Women who self-reported hysterectomies before enrollment (*n* = 36,037) were excluded from endometrial cancer analyses, and those with an adjudicated hysterectomy during follow-up (*n* = 549) were censored at the time of surgery. SHRs and 95% confidence intervals (CI) were calculated for each quintile of DED (categorical), with the lowest quintile as the reference group. To determine if there was a linear trend in the SHR across DED quintiles, the median of each interval was used to create a continuous variable in each competing-risk model.

Potential confounding variables were identified from the literature and prior WHI analysis of diet-cancer outcomes. These included baseline age (continuous), race/ethnicity [non-Hispanic white (NHW), black, Hispanic, Asian, Native American, other/unknown], neighborhood socioeconomic status (NSES; continuous),[29] smoking (never, former, current), physical activity (MET-hr/week; continuous), disease history [personal history of diabetes, family history of diabetes (with “don’t know” as own category), cardiovascular disease, and hypertension], weight change pattern during adulthood (self-report: weight had stayed about the same, steady gain in weight, lost weight as an adult and kept it off, or weight has gone up and down), alcohol (g/day), hormone use (never, former, current), and use of disease-related

medications [nonsteroidal anti-inflammatory drug (NSAID), metformin (an insulin regulator, increasing insulin sensitivity), and aspirin]. BMI was calculated from clinic-measured height and weight (continuous); waist circumference was also clinic measured (continuous). Variables were added stepwise to the age-adjusted model; those that changed the beta coefficient for any DED quintile by ≥10% were added to multivariable models. Initial screening for confounders was accomplished using Cox proportional hazards regression models because of the lengthy computation time required to run each competing-risk model in such a large sample.

Underreporting of energy intake is a recognized phenomenon in epidemiological studies investigating diet-disease relationships, and underreporting is more likely to occur in women who are overweight compared to normal weight.[20,30,31] Therefore, potential interactions between DED and BMI were investigated using likelihood ratio tests of nested Cox proportional hazards models (because likelihood ratio tests are not valid with competing-risk models), and models were BMI-stratified using standard cut points (< 25, 25–29.9, or ≥ 30 kg/m^2). Interactions of DED with race/ethnicity were also explored, although sample size limited robust testing (data not shown). All statistical analyses were conducted using Stata 14.2 (StataCorp, College Station, TX), and results were considered statistically significant at alpha < 0.05.

RESULTS

At baseline, higher DED was associated with younger age, lower NSES, lower alcohol intake, lower physical activity, and higher NSAID use (Table 1). In relation to body size, higher DED was associated with higher BMI (mean ± SD: 29.0 ± 6.0 kg/m^2 versus 26.3 ± 4.9 kg/m^2 for DED quintiles 5 and 1, respectively) as well as higher waist circumference (89.3 ± 14.2 cm versus 82.4 ± 12.4 cm for quintiles 5 and 1, respectively). Additionally, higher DED was associated with a self-reported increase in weight during adulthood.

Risk of any obesity-related cancer was 10% greater in women reporting intake within the highest quintile of DED compared to the lowest quintile: (SHR, 1.1; 95% CI, 1.03–1.2; P = 0.004; P_{trend} = 0.001 (Table 2). Associations between DED and each individual cancer type were not statistically significant after accounting for confounders. A test for interaction between BMI and DED on any obesity-related cancer was non-significant ($P_{interaction}$ = 0.07); however, BMI-stratified analysis showed that the positive association appeared limited to women who were normal weight (BMI < 25 kg/m^2) at the time of study entry (Figure 1). Normal-weight women in DED quintiles 3–5 had 10%, 18%, and 12% significantly higher risk of any-obesity related cancer than normal-weight women in DED quintile 1 (SHR_{trend}, 1.2; P = 0.006). There were no statistically significant associations between DED and any obesity-related cancer in overweight or obese women.

The strategy for choosing confounders was based on a change in the estimate of at least 10%. Smoking and alcohol, for example, were not included because they did not meet this threshold. As one illustration: The age-adjusted estimates for DED quintiles 2–5 for any obesity-related cancer were 1.00, 1.05, 1.05, and 1.10 (respectively). The same estimates

after further adjustment for smoking were 1.00, 1.06, 1.05, and 1.10 (respectively). Since these estimates are substantially unchanged, smoking was not included as a confounder.

DISCUSSION

In this large sample of postmenopausal, predominantly NHW women, DED was associated with higher risk of any obesity-related cancer. Of note, the higher risk was restricted to women of normal BMI. Further, in our sample, higher DED was associated with higher BMI and waist circumference as well as adult weight gain. Importantly, there was no interaction between unintentional adult weight gain and DED for risk of any obesity-related cancer. Suggesting weight gain does not explain these findings, even in normal-weight women. The results are also supported by the use of mortality as a competing risk in the analysis. The demonstrated effect in normal-weight women in relation to risk for obesity-related cancers is novel and contrary to our hypothesis. This finding suggests that weight management alone may not protect against obesity-related cancers should women favor a diet pattern indicative of high energy density. Thus, higher DED in normal-weight women may promote metabolic dysregulation independent of body weight, an exposure known to increase cancer risk.[32,33]

Several studies have evaluated the role of DED in weight management, although predominantly in cohorts that are largely represented by NHW participants.[34] A 2009 prospective cohort study of over 89,000 Europeans suggested a role of DED in relation to gains in central adiposity among adults of normal body weight at study entry,[17] an additional risk factor for select obesity-associated cancers.[35,36] A systematic review suggested a consistent relationship between DED and excess adiposity and adult weight gain, but not BMI or central obesity.[37] In our study, DED in the highest quintile was associated with higher BMI and waist circumference, with means of 82.4 ± 12.4 and 89.3 ±14.2 cm for quintile 1 and quintile 5, respectively. However, risk was demonstrated in women with normal BMI. Among normal-weight women, those in the highest and lowest DED quintiles had mean waist circumference of 75.8 and 74.0 cm, respectively. Few normal-weight WHI participants (< 2%) became obese during follow-up of the main WHI study period (~10 years); thus, weight gain alone does not explain the elevated cancer risk shown here (data not shown). Body composition data that could inform on adiposity and the role of lean mass are limited in numbers within WHI women, thereby precluding robust evaluation in relation to DED and obesity-related cancer risk.

Few studies have evaluated DED and obesity or obesity-related cancer risk across racial/ethnic groups, although cancer risk is known to vary in these populations. DED was associated with overweight status in the Hawaii-Los Angeles Multiethnic Cohort wherein higher DED conferred elevated risk for overweight status, with risk increase estimates ranging from 4–34%.[38] The elevation in risk was evident in all ethnic groups regardless of gender. WHI is another of the few large cohorts with diversity in enrollment to study diet-cancer associations. Nonetheless, WHI is a predominantly NHW, well-educated sample of postmenopausal women. As such, evaluating relationships within the WHI minority participants has limitations. In fact, the current findings suggested that black women were substantially more likely to report higher DED than NHWs (Table 1). Small sample size undermined our ability to robustly evaluate these associations for racial/ethnic groups, and

there was little evidence that DED and obesity-related cancer risk varied when comparing NHW women to all other racial/ethnic groups (data not shown).

Overall, studies evaluating the role of DED in cancer incidence are lacking. There are, however, some reports of DED being associated with diabetes, a known risk factor for select obesity-related cancers.[24] These reports include an analysis from the European Prospective Investigation of Cancer (EPIC)-Norfolk that reported an overall 60% higher risk for diabetes,[39] and a separate analysis from WHI that showed a 24% greater risk for diabetes in individuals in the highest versus lowest quintile of DED.[40] Among the few association studies specific to cancer is a case-control study in Shanghai that suggested high DED was associated with 72% greater risk for pancreatic cancer, one of several obesity-related cancers. [25] Contrary to these findings, here there was no elevation in pancreatic cancer risk. These differences can perhaps be explained by the high representation of men in the Shanghai study as compared to the WHI's female-only cohort.

An estimated 6% increase in risk for breast cancer, the most common obesity-related cancer in postmenopausal women, was identified, though it was not statistically significant (SHR, 1.06; 95% CI, 0.97–1.1; $P = 0.2$). In an analysis of 906 breast cancer cases and 1059 matched controls within the WHI, higher fat density was associated with a 19% increase in breast cancer risk based on 4-day food records.[41] Furthermore, novel work from Jones et al. using the Dietary Intervention Study in Children cohort demonstrated that each one-unit increase in food-only DED conferred 25.9% higher breast density.[42] Given appreciable evidence that breast density is a risk factor for breast cancer, these data, in combination with our findings, suggest that DED may influence breast cancer risk.

Our findings associating DED with colorectal cancer showed a 28% higher risk in age-adjusted models (SHR, 1.3; 95% CI, 1.1–1.5; $P = 0.001$), results that were attenuated after adjusting for confounders (SHR, 1.1; 95% CI, 0.9–1.3; $P = 0.2$). This finding is noteworthy in that a recent report from WHI demonstrated a marked 49% increase in colorectal cancer risk for normal-weight women with metabolic dysregulation as compared to women who were metabolically healthy.[43] While our findings did not specifically evaluate DED and metabolic health, higher energy intake could result in hyperinsulinemia in individuals with metabolic abnormalities. In fact, evidence suggests that among patients with colorectal cancer, energy intake is positively associated with metabolic syndrome.[44] Similar age-adjusted findings were also apparent for endometrial cancer in our analysis. Evidence supporting insulin resistance as a mechanism for endometrial cancer risk exists,[45] and a causal relationship has been postulated in a recent proteomics analysis.[46] Given the expanding attention to metformin as a cancer chemoprevention drug,[47,48] future studies should evaluate DED in relation to metabolic health, an approach beyond the scope of the current analysis.

Mechanistic explanations for the relationship between DED and obesity-related cancers include adiposity-induced inflammatory effects. While inflammation is more common in obese individuals, it is also positively associated with central body fat, independent of BMI. In our study, the DED-cancer risk findings were restricted to normal-weight women, who did show higher waist circumference across DED quintiles, suggesting that inflammation

and the related metabolic dysregulation may drive this risk. A recent meta-analysis found that individuals in the highest percentile of DED had 27% increased risk of excess adiposity as compared to subjects in the lowest percentile of DED, although the authors found no association specifically with central adiposity or BMI.[37] These data and other recent reports[49,50] suggest more attention to body composition beyond waist circumference, to include robust body composition analysis, is warranted to advance our understanding of DED and cancer risk. An alternative or complementary mechanism-based hypothesis could be that DED represents a higher requirement for food substrate metabolism and ultimately the production of postprandial oxidative stress response, an exposure that is an identified hallmark of cancer.[51]

While there is a question whether calculation of DED should include or exclude intake of water and other beverages, a standardized approach for calculating DED that excludes beverages was applied,[52] given the lack of information on water intake in the WHI FFQ. Another potential limitation is that the database may not have fully accounted for water loss during cooking or for cup weights that vary depending on how the food is measured and packed. Further, errors in dietary energy reporting, particularly underreporting in obese women, have been previously described in WHI.[53] Overall residual confounding cannot be ruled out. Of note, women within the lowest DED quintile demonstrated not only lower BMI, but also higher physical activity levels and less tobacco and alcohol use, suggesting a clustering of healthier behaviors.

Strengths of the analysis include the large sample of postmenopausal women for which detailed information on potential covariates is available, as well as the use of a competing-risk model that included mortality. Further, cancer outcomes were verified using a centrally adjudicated, physician-administered protocol. Importantly, efforts to qualify intake using DED estimated from the WHI FFQ afforded an opportunity to expand on existing evidence from WHI in regards to energy intake and cancer risk.[21,41]

CONCLUSION

Among normal-weight women, higher DED may be a contributing factor for obesity-related cancers. Importantly, DED is a modifiable risk factor. Nutritional intervention targeting energy density as well as other diet-related cancer preventive approaches are warranted to reduce cancer burden among postmenopausal women.

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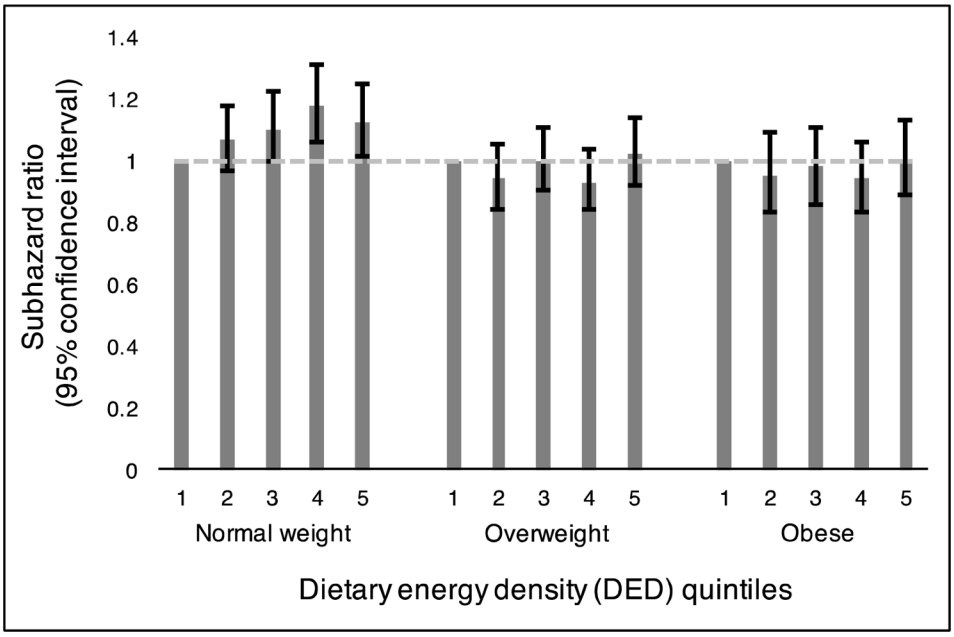

Figure 1.

Subhazard ratios for the association between dietary energy density (DED) and any obesity-related cancer in postmenopausal women enrolled in the Women's Health Initiative, stratified by BMI, using competing-risk regression (n = 92,295). Error bars depict 95% confidence intervals. Gray dashed horizontal line depicts the null value of 1.0, and the lowest quintile of DED was the reference group. The interaction between BMI and DED on breast any obesity-related cancer ($P_{\text{interaction}}$ = 0.07) was tested using a likelihood ratio test of nested Cox proportional hazards regression models.

Table 1

Baseline characteristics of postmenopausal women enrolled in the Women's Health Initiative (n = 92,295), across quintiles of dietary energy density (DED): mean ± SD or n (%)

Characteristic	Overall n = 92,295 (0.46–3.76)	Q1 n = 18,459 (0.46–1.09)	Q2 n = 18,459 (1.10–1.25)	Q3 n = 18,459 (1.26–1.42)	Q4 n = 18,459 (1.43–1.66)	Q5 n = 18,459 (1.67–3.76)
Age (years)	63.5 ± 7.3	64.5 ± 7.3	63.7 ± 7.3	63.5 ± 7.3	63.2 ± 7.3	62.4 ± 7.2
Race/ethnicity (%)						
Non-Hispanic white	77,505 (84.0)	15,659 (84.8)	16,022 (86.8)	15,746 (85.3)	15,514 (84.1)	14,564 (78.9)
Black	7003 (7.6)	1148 (6.2)	964 (5.2)	1232 (6.7)	1425 (7.7)	2234 (12.1)
Hispanic	3609 (3.9)	638 (3.5)	569 (3.1)	636 (3.5)	759 (4.1)	1007 (5.5)
Asian or Pacific Islander	2520 (2.7)	661 (3.6)	600 (3.3)	525 (2.8)	428 (2.3)	306 (1.7)
American Indian or Alaska Native	379 (0.4)	62 (0.3)	58 (0.3)	67 (0.4)	85 (0.5)	107 (0.6)
Other or unknown	1279 (1.4)	291 (1.6)	246 (1.3)	253 (1.4)	248 (1.3)	241 (1.3)
Neighborhood socioeconomic status[a]	75.9 ± 8.4	76.9 ± 8.0	76.9 ± 7.8	76.3 ± 8.2	75.6 ± 8.6	73.8 ± 9.2
Waist circumference (cm) [a]	85.3 ± 13.3	82.4 ± 12.4	83.5 ± 12.5	84.8 ± 12.7	86.4 ± 13.4	89.3 ± 14.2
Weight (kg)	71.7 ± 14.8	68.4 ± 13.4	69.8 ± 13.7	71.2 ± 14.1	72.9 ± 15.0	76.0 ± 16.6
Body mass index (kg/m^2)	27.4 ± 5.4	26.3 ± 4.9	26.7 ± 5.0	27.2 ± 5.2	27.8 ± 5.5	28.9 ± 6.0
Physical activity (MET[b]-hour/week) [a]	13.5 ± 14.3	18.8 ± 16.6	15.8 ± 14.5	13.5 ± 13.4	11.3 ± 12.7	8.1 ± 11.2
Smoking[a]						
Never smoker	46,377 (50.9)	9548 (52.5)	9478 (52.0)	9492 (52.1)	9223 (50.5)	8636 (47.3)
Former	38,499 (42.2)	8055 (44.3)	8018 (44.0)	7809 (42.8)	7590 (41.6)	7027 (38.5)
Current	6300 (6.9)	597 (3.3)	739 (4.1)	932 (5.1)	1437 (7.9)	2595 (14.2)
Alcohol intake[a]						
< 1 drink/week	56,144 (61.2)	11,584 (63.2)	10,576 (57.6)	10,674 (58.1)	10,985 (59.8)	12,325 (67.2)
1 to < 7 drink/week	23,744 (25.9)	4788 (26.1)	5295 (28.8)	5107 (27.8)	4751 (25.8)	3803 (20.7)
≥ 7 drink/week	11,921 (13.0)	1973 (10.8)	2498 (13.6)	2582 (14.1)	2647 (14.4)	2221 (12.1)
Personal history of diabetes[a]	3806 (4.1)	795 (4.3)	716 (3.9)	709 (3.8)	766 (4.2)	820 (4.5)
Family history of diabetes[a]						
No	58,578 (63.7)	11,913 (64.9)	12,070 (65.6)	11,828 (64.3)	11,668 (63.5)	11,099 (60.4)
Yes	29,219 (31.8)	5655 (30.8)	5636 (30.6)	5806 (31.6)	5902 (32.1)	6220 (33.9)

Characteristic	Overall *n* = 92,295 (0.46–3.76)	Q1 *n* = 18,459 (0.46–1.09)	Q2 *n* = 18,459 (1.10–1.25)	Q3 *n* = 18,459 (1.26–1.42)	Q4 *n* = 18,459 (1.43–1.66)	Q5 *n* = 18,459 (1.67–3.76)
Don't know	4119 (4.5)	796 (4.3)	701 (3.8)	756 (4.1)	810 (4.4)	1056 (5.8)
Cardiovascular disease[a,c]	15,763 (17.6)	3265 (18.2)	3232 (18.0)	3145 (17.5)	3076 (17.2)	3045 (17.1)
Hypertension[a]						
Never	60,449 (67.3)	12,323 (68.3)	12,256 (68.1)	12,253 (68.1)	12,013 (66.9)	11,604 (64.8)
Untreated hypertensive	7216 (8.0)	1417 (7.9)	1426 (7.9)	1373 (7.6)	1443 (8.0)	1557 (8.7)
Treated hypertensive	22,223 (24.7)	4304 (23.9)	4316 (24.0)	4376 (24.3)	4493 (25.0)	4734 (26.5)
Hormone therapy use[a]						
Never	29,875 (33.1)	5827 (32.3)	5566 (30.9)	5650 (31.3)	6065 (33.5)	6767 (37.4)
Former	21,118 (23.4)	4035 (22.4)	3933 (21.8)	4209 (23.3)	4353 (24.1)	4588 (25.3)
Current	39,298 (43.5)	8168 (45.3)	8510 (47.3)	8184 (45.4)	7682 (42.4)	6754 (37.3)
NSAID[d] use at baseline[a]	17,381 (18.8)	2983 (16.2)	3227 (17.5)	3510 (19.0)	3629 (19.7)	4032 (21.8)
Aspirin use at baseline[a]	19,384 (21.0)	4051 (22.0)	4067 (22.0)	3917 (21.2)	3892 (21.1)	3457 (18.7)
Metformin use at baseline[a]	686 (0.7)	125 (0.7)	153 (0.8)	126 (0.7)	132 (0.7)	150 (0.8)
History of weight change in adulthood[a]						
Stayed about the same	29,358 (32.1)	6681 (36.6)	6187 (33.9)	5809 (31.8)	5563 (30.4)	5118 (28.0)
Unintentional gain in weight	28,526 (31.2)	4181 (22.9)	5246 (28.7)	5954 (32.6)	6334 (34.7)	6811 (37.2)
Weight loss	2660 (2.9)	824 (4.5)	614 (3.4)	487 (2.7)	399 (2.2)	336 (1.8)
Weight fluctuations	30,833 (33.7)	6569 (36.0)	6232 (34.1)	6018 (32.9)	5983 (32.7)	6031 (33.0)
Diet						
Total energy, except beverages (kcal[e]/day)	1380 ± 554	1138 ± 383	1298 ± 450	1378 ± 506	1454 ± 570	1633 ± 687
Total protein, except beverages (grams/day)	60.1 ± 25.4	52.3 ± 20.4	58.9 ± 22.8	61.2 ± 24.4	62.8 ± 26.8	65.1 ± 29.9

[a]Missing data: Neighborhood socioeconomic status (8999), waist circumference (272), physical activity (1927), smoking (1119), alcohol intake (486), personal history of diabetes (105), family history of diabetes (379), cardiovascular disease (2755), hypertension (2407), hormone therapy use (2004), NSAID (1), aspirin (1), metformin (1), history of weight change in adulthood (918)

[b]Metabolic equivalents

[c]Self-reported cardiovascular disease, including hypertension

[d]Nonsteroidal anti-inflammatory drug

[e]Kilocalories

Table 2

Association between dietary energy density (DED) and cancer incidence among postmenopausal women enrolled in the Women's Health Initiative (n = 92,295)

Cancer site	DED quintile	n (%)	Age-adjusted SHR (95% CI)[a]	Multivariable-adjusted SHR (95% CI)[a]
Breast				
	1	1105 (6.0)	1.00	(no confounders)
	2	1129 (6.1)	1.0 (0.9–1.1)	
	3	1121 (6.1)	1.0 (0.9–1.1)	
	4	1092 (5.9)	1.0 (0.9–1.1)	
	5	1117 (6.1)	1.06 (0.97–1.1)	
	Trend		1.05 (0.97–1.2)	
Colorectal[b]				
	1	311 (1.7)	1.00	1.00
	2	315 (1.7)	1.0 (0.9–1.2)	1.0 (0.8–1.2)
	3	325 (1.8)	1.1 (0.9–1.3)	1.0 (0.9–1.2)
	4	342 (1.9)	1.2 (1.02–1.4)*	1.1 (0.9–1.3)
	5	346 (1.9)	1.3 (1.1–1.5)**	1.1 (0.9–1.3)
	Trend		1.3 (1.2–1.6)***	1.1 (0.97–1.4)
Ovary				
	1	140 (0.9)	1.00	(no confounders)
	2	132 (0.9)	0.9 (0.7–1.2)	
	3	142 (0.9)	1.0 (0.8–1.3)	
	4	117 (0.8)	0.9 (0.7–1.1)	
	5	113 (0.8)	0.9 (0.7–1.1)	
	Trend		0.8 (0.6–1.1)	
Endometrium[c]				
	1	177 (1.6)	1.00	1.00
	2	183 (1.6)	1.0 (0.8–1.2)	1.0 (0.8–1.2)
	3	197 (1.7)	1.1 (0.9–1.4)	1.1 (0.9–1.3)
	4	190 (1.7)	1.1 (0.9–1.4)	1.0 (0.8–1.3)
	5	203 (1.9)	1.3 (1.1–1.6)*	1.1 (0.9–1.4)
	Trend		1.3 (1.1–1.7)**	1.1 (0.9–1.4)
Renal[c]				
	1	57 (0.3)	1.00	1.00
	2	68 (0.4)	1.2 (0.8–1.7)	1.2 (0.8–1.7)
	3	71 (0.4)	1.3 (0.9–1.8)	1.2 (0.8–1.7)
	4	80 (0.4)	1.5 (1.04–2.1)*	1.3 (0.9–1.9)
	5	71 (0.4)	1.4 (0.96–1.9)	1.2 (0.8–1.6)
	Trend		1.4 (1.01–2.0)*	1.2 (0.8–1.6)
Pancreas				

Cancer site	DED quintile	*n* (%)	Age-adjusted SHR (95% CI)[a]	Multivariable-adjusted SHR (95% CI)[a]
	1	132 (0.7)	1.00	(no confounders)
	2	120 (0.7)	0.9 (0.7–1.2)	
	3	145 (0.8)	1.1 (0.9–1.5)	
	4	112 (0.6)	0.9 (0.7–1.2)	
	5	111 (0.6)	1.0 (0.8–1.3)	
	Trend		1.0 (0.8–1.3)	
Any obesity-related cancer[d]				
	1	1882 (10.2)	1.00	(no confounders)
	2	1894 (10.3)	1.0 (0.9–1.1)	
	3	1961 (10.6)	1.05 (0.99–1.1)	
	4	1911 (10.4)	1.05 (0.98–1.1)	
	5	1917 (10.4)	1.1 (1.03–1.2)**	
	Trend		1.1 (1.04–1.2)**	

*$P < 0.05$;

**$P < 0.01$;

***$P < 0.001$

[a] Subhazard ratio and confidence interval

[b] Multivariate model further adjusted for waist and physical activity

[c] Multivariate model further adjusted for waist and body mass index

[d] Includes cancers of the breast, colorectum, ovary, endometrium, kidney, pancreas, gallbladder, and esophagus