Diabetes Risk Reduction Diet and Survival after Breast Cancer Diagnosis

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ABSTRACT

Type II diabetes is associated with poor breast cancer prognosis. To study the association between a diabetes risk reduction diet (DRRD) and survival following breast cancer, we followed 8,482 women with breast cancer from two large cohort studies. Information on diet and other factors was repeatedly measured in validated questionnaires every two to four years. The DRRD includes 9 components: higher intakes of cereal fiber, coffee, nuts, whole fruits and polyunsaturated/saturated fat ratio; and lower glycemic index, trans fat, sugar-sweetened beverages, and red meat. Cumulative average DRRD score was calculated using repeated measures of postdiagnostic diet. Deaths were assessed by family members or via National Death Index. Multivariable-adjusted HRs and 95% confidence intervals (CI) were estimated using Cox proportional hazards models. During a median of 14 years of follow-up since diagnosis, 2,600 deaths occurred among participants, 1,042 of which were due to breast cancer. Women with higher postdiagnostic DRRD score had a 20% lower risk of breast cancer–specific mortality (top vs. bottom quintile HR = 0.80; 95% CI = 0.65–0.97; $P_{trend} = 0.02$) and 34% lower risk of all-cause mortality (HR = 0.66; 95% CI = 0.58–0.76; $P_{trend} < 0.0001$). Compared with women who consistently had lower score (≤median) before and after diagnosis, those whose score improved from low to high had a lower risk of breast cancer–specific mortality (HR = 0.77; 95% CI = 0.62–0.95) and overall mortality (HR = 0.85; 95% CI = 0.74–0.97). These findings demonstrate that greater adherence to DRRD was associated with better survival, suggesting postdiagnosis dietary modification consistent with type II diabetes prevention may be important for breast cancer survivors.

Significance: This study suggests that greater adherence to the diabetes risk reduction diet after diagnosis associates with improved survival outcomes among a large number of breast cancer survivors.

Introduction

Breast cancer remains the most common cause of cancer-related death for women worldwide (1). Currently, there are an estimated 4 million breast cancer survivors in the United States (2), a growing and aging population frequently burdened with multiple chronic conditions including type II diabetes (T2D; refs. 2, 3).

T2D has been associated with increased risk of breast cancer incidence and also poor progression through the mechanisms of insulin resistance, hyperinsulinemia, and metabolic disturbance (4–6). In previous studies, breast cancer survivors with T2D had 1.2- to 2.3-fold higher risks of breast cancer recurrence (7, 8) and breast cancer–specific mortality, compared with those without T2D (9–11). Moreover, having a breast cancer diagnosis may also increase the risk of developing T2D (12). Therefore, strategies for T2D prevention among breast cancer survivors may play a key role in improving survival outcomes. One approach may be through a diabetes risk reduction diet (DRRD), a dietary pattern comprised of 9 components that has been associated with 40% lower T2D risk (13). In Nurses' Health Study (NHS) and NHSII, we previously observed that four components of the DRRD [dietary glycemic index (14), red and processed meat (15), coffee (16), and sugar-sweetened beverages (SSB; ref. 17)] were associated with risk of mortality following breast cancer, while no association was found for whole fruit intake (18). However, no studies to date have evaluated the association between adherence to the whole DRRD [as measured by the DRRD score (13)] and survival outcomes after breast cancer. Most importantly, the current evidence on dietary changes after diagnosis in breast cancer survivorship care is very limited (3).

Herein, we examined the associations of adherence to DRRD and long-term breast cancer–specific and all-cause mortality among breast cancer survivors identified from two U.S. large prospective cohort studies, the NHS and NHSII. The rationale for studying all-cause mortality is that, in part because of treatment advances, a great number of breast cancer survivors do not die directly from breast cancer. For the majority of breast cancer survivors, noncancer conditions can be the driving causes of death (19). We hypothesized that greater adherence to the DRRD (a higher DRRD score) may be associated with better breast cancer survival outcomes.

Patients and Methods

Study population

The NHS was initiated in 1976 among 121,700 female registered nurses aged 30 to 55 years residing in 11 states in the United States (20), and the NHSII began in 1989 among 116,429 female registered nurses aged 25 to 42 years from 14 U.S. states (21). At baseline, all participants completed a mailed questionnaire describing demographics, lifestyle, and medical history. Corresponding information are updated through

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the ongoing biennial follow-up questionnaires. The study protocols of NHS and NHSII were approved by the Institutional Review Boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health (Boston, MA), and those of participating registries, as required. Return of the completed questionnaires was considered to imply written informed consent, and the two studies were conducted in accordance with recognized ethical guidelines (Declaration of Helsinki).

Potentially eligible participants for this analysis included women with confirmed breast cancer between 1980 and 2010 in the NHS ($n = 11{,}938$) and between 1991 and 2015 in the NHSII ($n = 5{,}843$). Breast cancer cases were identified by self-report from participant (or next of kin for decedents) on the biennial questionnaires and was further confirmed by pathologists/physicians via review of medical record or pathology reports. In the current analysis, we excluded participants who had stage IV or *in situ* tumor or missing information on stage ($n = 6{,}319$), died or were diagnosed with cancer before the baseline dietary intake assessment ($n = 433$), had missing information on the first postdiagnosis dietary intake or had implausible postdiagnosis total daily energy intake (i.e., <500 or >3,500 kcal/day; $n = 2{,}547$). After exclusions, 8,482 women with stage I–III breast cancer were included in the analysis.

Dietary assessment and derivation of DRRD score

The self-reported dietary information was collected via validated semiquantitative food-frequency questionnaires (FFQ) in 1980, 1984, 1986, and every 4 years thereafter from NHS participants, and from NHSII participants every 4 years starting in 1991. Questions included food portion size and the averaged frequency of consumption in the previous year. There were 9 response categories ranging from "never or less than once/month" to "6 or more times/day." Participants' nutrient intakes were calculated by multiplying the consumption frequency of each food item by the nutrient content of the specified portion size (22). The original DRRD score (13) assigned each participant a score for each dietary component between one (intake consistent with worst diet or highest T2D risk) and five (intake consistent with best diet or lowest T2D risk) that indicated the participant's quintile of intake for 8 dietary components. We additionally included whole fruits into this score given the more recent finding with T2D risk (23). Total vegetable intake was not included into the DRRD because it was not associated with the risk of T2D among our study population. Therefore, the final score (range = 9–45) was assigned in ascending order with higher intake of: cereal fiber, coffee (caffeinated and decaffeinated), nuts, polyunsaturated:saturated fat ratio, and whole fruits. In contrast, the score was assigned in descending order with higher intake/level of: glycemic index, trans-fat, SSBs/fruit juices, and red meat.

To avoid short-term dietary changes during active breast cancer treatment, the first postdiagnostic DRRD score was defined as dietary intake reported on the first FFQ collected at least 12 months after diagnosis date. To better reflect long-term dietary intake and reduce chance of random within-person error and reverse causation, we calculated cumulatively averaged DRRD score by updating the average of all postdiagnostic repeated FFQs throughout follow-up, as described elsewhere (24). In secondary analyses, we considered the prediagnostic DRRD score (using the last FFQ reported before diagnosis), the first postdiagnostic DRRD score, as well as a simple updated DRRD score (using time-varying FFQs measured at the latest postdiagnosis follow-up period).

Assessment of covariates

Information regarding participant demographic characteristics, reproductive history, medical history, smoking history, weight, height, and physical activity were self-reported and updated in the biennial follow-up questionnaires. Body mass index (BMI, kg/m^2) was calculated using height (m) reported at baseline for each cohort, and weight (kg) reported in the biennial questionnaires. We also collected the neighborhood socioeconomic status (nSES) information from census tract data (NHS 1986–2012 and NHSII 1989–2013) that applied to all NHS and NHSII participant geocoded addresses. The nSES information of median income, median home value, percent white, percent in poverty, percent with college degree, percent families with interest or dividends, percent occupied housing, and percent families headed by single female were included in calculating a summary nSES score using a standard method (25). Briefly, each of these measures was standardized based on *Z*-scores and then added together. Tumor stage was evaluated through pathologist review or extracted from medical records. Tumor markers [i.e., estrogen receptor (ER) and insulin receptor (IR) expression] were evaluated by immunohistochemistry assay on tumor microarrays from archived tumor tissue when possible (26), or extracted from medical records. Finally, information about breast cancer treatment was obtained from medical records when possible, or self-reported in a supplemental questionnaire from the breast cancer survivors in both cohorts.

Ascertainment of death

Deaths were first identified by family members or by US Postal Service or determined through the search of National Death Index (27). Once a death is reported, the specific causes of death are then determined through review of the medical records or death certificate. Study endpoints were defined as death or end of follow-up (June 1, 2016, for the NHS and June 1, 2017, for the NHSII), whichever came first.

Statistical analysis

We categorized the DRRD score into quintiles, with cutoffs determined separately within NHS and NHSII, and further combined the two cohorts' data for pooled analysis. Cox proportional hazards regression models were used to estimate HRs and 95% confidence intervals (CI) for the associations between DRRD score and breast cancer–specific and all-cause mortality. In the primary analysis, the person-time of follow-up was calculated from the return date of the first postdiagnostic FFQ to death or the end of the follow-up period. We used time since diagnosis as the analytic time scale, accounting for left truncation due to variations between participants in the timing of their first postdiagnostic FFQ. Tests for linear trend were performed using the median value for each quintile of the DRRD score as a continuous variable in the regression models. Furthermore, we also dichotomized the DRRD at the median (≤median was considered low level) and evaluated cross-classification changes of pre- and postdiagnosis DRRD score (low/high, high/low, high/high, compared with low/low) in relation to mortality.

We fitted three models as follows: model 1 included only age at diagnosis and calendar year of diagnosis. Model 2 was the multivariable-adjusted model and included multiple time-varying covariates: change in BMI from pre- to postdiagnosis, postdiagnosis smoking status, postdiagnosis recreational and leisure-time physical activity, postdiagnosis aspirin use, postdiagnosis alcohol, and calories consumption. Updating of all the time-varying covariates was consistent with DRRD being measured. Moreover, in model 2, we adjusted for fixed-time covariates measured prior to or at the time of diagnosis: age at menarche, menopausal status, parity, menopausal hormone therapy use, oral contraceptive use, history of benign breast disease, family history of breast cancer, and prediagnosis BMI. We also included disease stage, ER status, and self-reported radiotherapy,

Table 1. Characteristics of study participants from the pooled data of Nurses' Health Study (NHS; follow-up from 1980–2016) and NHS2 (follow-up from 1991–2017) cohorts according to first postdiagnostic diabetes risk reduction diet score ($N = 8,482$).

Characteristics	Quintile 1 ($n = 1,830$)	Quintile 2 ($n = 1,553$)	Quintile 3 ($n = 1,821$)	Quintile 4 ($n = 1,683$)	Quintile 5 ($n = 1,595$)
Age at diagnosis, mean (SD)*	57 (10)	57 (10)	56 (10)	58 (10)	58 (10)
White, %	96	97	96	97	97
Husband education, college and grad school, %	68	71	71	74	74
Census tract annual median individual income ($), mean (SD)	47,781 (27,718)	47,010 (29,400)	49,791 (31,255)	49,059 (31,895)	50,187 (33,818)
Postmenopausal, %[a]	63	64	62	62	64
Age at menarche <12 years, %	21	22	25	24	26
Parous, %	91	91	90	90	87
Family history of breast cancer (first degree), %	19	16	17	18	16
History of benign breast diseases, %	35	38	38	36	39
History of type II diabetes, %	5	5	6	6	5
Ever used oral contraceptive, %	42	44	45	45	42
Current users of postmenopausal hormone therapy[b]	46	48	46	49	54
Current users of aspirin, %	43	46	46	47	46
Ever smoker, %	50	53	52	55	54
BMI, kg/m^2	26.9 (5.6)	26.1 (5.2)	26.0 (5.1)	25.6 (4.7)	24.8 (4.3)
Physical activity, MET hours/week[c]	13 (18)	15 (27)	17 (26)	19 (23)	22 (23)
Total calories intake, kcal	1,764 (552)	1,714 (564)	1,724 (553)	1,723 (527)	1,764 (537)
Alcohol consumption, g/day	5.0 (10.5)	5.3 (9.6)	6.1 (10.7)	6.3 (10.7)	5.8 (9.2)
Stage I breast cancer, %	57	55	58	59	59
Estrogen receptor positive breast cancer, %	80	82	79	81	83
Chemotherapy, %	48	49	48	50	44
Radiation therapy, %	58	59	58	58	60
Hormone therapy, %	71	70	70	71	71
Diabetes risk reduction diet (DRRD) score	19.5 (2.3)	24.1 (0.8)	27.2 (0.9)	30.5 (1.1)	35.5 (2.3)
Components of DRRD score					
Polyunsaturated: saturated fat ratio[d]	0.5 (0.1)	0.5 (0.2)	0.6 (0.2)	0.7 (0.2)	0.8 (0.3)
Cereal fiber, g/day[d]	4.5 (2.0)	5.2 (2.5)	6.0 (3.2)	6.7 (3.8)	7.8 (4.2)
Total coffee intake, cups/day[d]	1.2 (1.3)	1.7 (1.6)	1.7 (1.5)	2.1 (1.7)	2.2 (1.7)
Total nut or peanut butter intake, serving/day[d]	0.2 (0.3)	0.3 (0.4)	0.4 (0.5)	0.5 (0.6)	0.7 (0.8)
Total whole fruit intake, serving/day[d]	1.0 (0.8)	1.2 (0.8)	1.5 (1.0)	1.9 (1.2)	2.4 (1.3)
Glycemic index of diet[d]	54.5 (3.3)	53.0 (3.7)	52.2 (4.4)	51.4 (3.9)	50.1 (3.4)
Trans fat intake, % of total kcal/day[d]	1.4 (0.5)	1.3 (0.6)	1.1 (0.5)	1.0 (0.5)	0.8 (0.4)
Sugar-sweetened beverage/fruit juice intake, serving/day[d]	1.5 (1.3)	1.1 (1.1)	1.0 (1.0)	0.9 (0.9)	0.6 (0.8)
Red and processed meat, serving/day[d]	1.2 (0.7)	1.0 (0.6)	0.8 (0.6)	0.7 (0.5)	0.4 (0.4)

Note: Values are means (SD) or percentages and are standardized to the age distribution of the study population. All factors were considered at first postdiagnosis assessment unless otherwise noted.

Abbreviation: BMI, body mass index.

[a]Among women with natural menopause or bilateral oophorectomy.

[b]Calculated among postmenopausal women in the last prediagnosis period.

[c]Metabolic-equivalent-of-task from recreational and leisure-time activities.

[d]Intakes were adjusted for total energy intake.

chemotherapy, and hormonal therapy. Model 3 additionally included the postdiagnosis census tract nSES score, updated every two years. Detailed definitions of these covariates were listed in the footnote of **Table 2**. All models were stratified by cohort and follow-up period.

We carried out subgroup analyses by breast cancer ER status, IR status, stage, menopausal status at diagnosis, BMI at diagnosis, physical activity, and nSES score at diagnosis. We tested potential effect modification of DRRD score levels using a likelihood ratio test comparing models with versus without interaction terms (continuous median DRRD score across quintiles * effect modifier). We also performed mediation analyses (28, 29), to explore how much of the observed association is mediated by the relation of DRRD to the development of postdiagnostic T2D or changes in BMI.

To assess potential reverse causation from diet changes due to serious illness, we applied a 4-year lag (as dietary factors were updated every 4 years) to the postdiagnosis DRRD score. For example, we used the second to last post-diagnosis DRRD score as latest updated score in the lagged analysis. For the same purpose, we also repeated the main analyses after excluding participants who died within 5 years after diagnosis ($n = 320$). Another sensitivity analysis excluded women diagnosed with T2D before breast cancer ($n = 453$). We also additionally adjusted for total vegetable intake in a separate model. All statistical analyses were conducted with SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC). P values <0.05 were considered significant and all statistical tests were two-sided.

Results

During a median follow-up of 14 years since diagnosis, we documented 2,600 overall deaths among 8,482 breast cancer survivors,

Table 2. Multivariable HRs and 95% CIs for the association between quintiles of cumulative average postdiagnostic diabetes risk reduction diet score and mortality outcomes among breast cancer survivors using pooled data from NHS (follow-up from 1980–2016) and NHSII (follow-up from 1991–2017; $N = 8{,}482$).

Median (IQR)	Quintile 1 20 (19–22)	Quintile 2 24 (23–25)	Quintile 3 27 (26–28)	Quintile 4 30 (29–31)	Quintile 5 34 (33–37)	P_{trend}
Breast cancer–specific mortality						
No. of events ($n = 1{,}042$), 100,214 py	240	222	199	192	189	
Model 1[a]	1 (referent)	0.91 (0.76–1.10)	0.73 (0.61–0.89)	0.76 (0.63–0.92)	0.70 (0.58–0.85)	<0.0001
Model 2[b]	1 (referent)	0.84 (0.70–1.01)	0.74 (0.61–0.90)	0.80 (0.66–0.98)	0.79 (0.65–0.97)	0.02
Model 3[c]	1 (referent)	0.85 (0.71–1.03)	0.76 (0.63–0.92)	0.81 (0.67–0.99)	0.80 (0.65–0.97)	0.02
All-cause mortality						
No. of events ($n = 2{,}600$), 100,214 py	617	552	566	470	395	
Model 1[a]	1 (referent)	0.83 (0.74–0.93)	0.76 (0.68–0.86)	0.67 (0.59–0.76)	0.55 (0.48–0.62)	<0.0001
Model 2[b]	1 (referent)	0.82 (0.73–0.92)	0.83 (0.74–0.94)	0.78 (0.69–0.88)	0.66 (0.57–0.75)	<0.0001
Model 3[c]	1 (referent)	0.83 (0.74–0.93)	0.85 (0.76–0.96)	0.79 (0.70–0.90)	0.66 (0.58–0.76)	<0.0001

Abbreviations: IQR, interquartile range; py, person-years.

[a]Model 1: Adjusted for age at diagnosis (continuous) and calendar year of diagnosis (continuous).

[b]Model 2: Adjusted for age at diagnosis (continuous) and calendar year of diagnosis (continuous), prediagnostic menopausal status (premenopausal, postmenopausal), age at menarche (<12, 12, 13, 14, >14), prediagnostic parity (ever parous, never parous), prediagnostic family history of breast cancer in a first degree relative (yes, no), prediagnostic personal history of benign breast disease (yes, no), prediagnostic oral contraceptive use (ever, never), prediagnostic menopausal hormone therapy use (current, past, never), prediagnostic BMI (<25, 25 to <30, ≥30 kg/m^2, or unknown), cumulative average postdiagnostic BMI changes from pre- to postdiagnosis (lost >0.5 kg/m^2, stayed within 0.5 kg/m^2, gained 0.5–2 kg/m^2, gained >2 kg/m^2, or unknown), postdiagnostic cigarette smoking (never, former, current, or unknown), postdiagnostic aspirin use (never, former, current, or unknown), cumulative average postdiagnostic physical activity (by quintile), cumulative average postdiagnostic total energy intake (by quintile), cumulative average postdiagnostic alcohol intake (by quintile), disease stage (I, II, and III), tumor estrogen receptor status (positive, negative, or unknown), self-reported radiotherapy (yes, no, or unknown), chemotherapy (yes, no, or unknown), and hormonal treatment (yes, no, or unknown).

[c]Model 3: Model 2+ postdiagnostic census tract neighborhood socioeconomic status score (by quintile).

including 1,042 deaths due to breast cancer and 345 deaths due to cardiovascular diseases. The median time between diagnosis and completing the first post-diagnosis FFQ questionnaire was 3.0 years. As shown in **Table 1**, women with highest first postdiagnostic DRRD score had higher income and were more likely to have husbands with higher education. These women also tended to be leaner, more physically active, and more likely to use postmenopausal hormone therapy. Approximately 5% of these women had T2D before or at breast cancer diagnosis and this was similar across the quintiles of DRRD score.

In our simple model and multivariable-adjusted model, we observed a statistically significant inverse association for cumulatively averaged postdiagnosis DRRD score and breast cancer–specific mortality (model 2: highest vs. lowest quintile HR = 0.79; 95% CI = 0.65–0.97; $P_{trend} = 0.02$; **Table 2**). This association was still evident in the model, which further adjusted for nSES score (HR = 0.80; 95% CI = 0.65–0.97; $P_{trend} = 0.02$). Women in the highest versus lowest quintile of DRRD score were at significantly lower risk of all-cause mortality in all the three models (model including nSES HR = 0.66; 95% CI = 0.58–0.76; $P_{trend} < 0.0001$). With further adjustment for total vegetable intake, the results were essentially unchanged. For breast cancer–specific mortality, the point estimate (highest vs. lowest quintile: HR = 0.80; 95% CI = 0.65–1.00) was identical but the P_{trend} slightly increased to 0.04. For all-cause mortality, the corresponding point estimate became less pronounced (HR = 0.69; 95% CI = 0.60–0.79) but P_{trend} was still significant ($P_{trend} < 0.0001$).

In secondary analyses of breast cancer–specific mortality examining other timings of exposure (Supplementary Table S1), we observed a similar statistically significant association for the simple updated DRRD score ($P_{trend} = 0.01$), although no significant associations were observed for the prediagnostic and first postdiagnostic DRRD score. The strong inverse association with all-cause mortality was consistent for DRRD measured at the other two timings/settings: first postdiagnosis ($HR_{Q5vsQ1} = 0.74$; 95% CI = 0.64–0.84; $P_{trend} < 0.0001$), and simple updated postdiagnosis ($HR_{Q5vsQ1} = 0.68$; 95% CI = 0.58– 0.80; $P_{trend} < 0.0001$). After further adjustment for the prediagnosis DRRD score, we observed less pronounced results for breast cancer mortality but similar associations for all-cause mortality.

Regarding changes in adherence to DRRD from before to after breast cancer diagnosis (**Table 3**), 14% of our study participants improved DRRD score from "low" to "high" and 15% decreased their adherence of DRRD from "high" to "low". Seventy-one percent of these women maintained in the same category of DRRD score level. Women with higher nSES score, gained less weight, and were nonobese and more physical active after breast cancer diagnosis were more likely to improve their DRRD adherence from low to high. Compared with women with consistent low DRRD score before and after diagnosis, those who improved their adherence to DRRD after diagnosis had a 23% lower risk of breast cancer–specific mortality (HR = 0.77; 95% CI = 0.62–0.95) and 15% lower risk of all-cause mortality (HR = 0.85; 95% CI = 0.74–0.97). All-cause mortality was also lower among women who maintained higher DRRD score after diagnosis (HR = 0.87; 95% CI = 0.79–0.96), although that was not observed for breast cancer–specific mortality. We also explored the interaction between pre- and postdiagnosis DRRD, although the interaction was not significant, the inverse association for breast cancer mortality was only apparent among those with low DRRD before diagnosis, and that there was no difference for all-cause mortality.

We did not identify statistically significant effect modification of the associations between postdiagnosis cumulative average DRRD score and breast cancer–specific mortality by: tumor ER or IR status, stage, menopausal status at diagnosis, BMI, or physical activity ($P_{interaction} \geq 0.23$; **Table 4**). However, we observed significant effect modification of the DRRD - breast cancer mortality association by nSES score at diagnosis. A higher DRRD score was strongly associated with a lower

Table 3. Multivariable HRs and 95% CIs for the association between cross-classified changes of diabetes risk reduction diet score before or after diagnosis and mortality among breast cancer survivors using pooled data from NHS (follow-up from 1980–2016) and NHSII (follow-up from 1991–2017; $N = 8{,}482$).

Characteristics	HR (95% CI)
Breast cancer–specific mortality	
Cross-classified changes	
No. of events ($n = 1{,}042$), 100,214 py	
Low to low ($n = 349$)	1 (referent)
Low to high ($n = 116$)	0.77 (0.62–0.95)
High to low ($n = 151$)	0.92 (0.76–1.12)
High to high ($n = 370$)	0.94 (0.81–1.10)
All-cause mortality	
Cross classified changes	
No. of events ($n = 2{,}600$), 100,214 py	
Low to low ($n = 872$)	1 (referent)
Low to high ($n = 281$)	0.85 (0.74–0.97)
High to low ($n = 431$)	0.99 (0.88–1.11)
High to high ($n = 883$)	0.87 (0.79–0.96)

Note: Adjusted for age at diagnosis (continuous) and calendar year of diagnosis (continuous), prediagnostic menopausal status (premenopausal, postmenopausal), age at menarche (<12, 12, 13, 14, >14), prediagnostic parity (ever parous, never parous), prediagnostic family history of breast cancer in a first-degree relative (yes, no), prediagnostic personal history of benign breast disease (yes, no), prediagnostic oral contraceptive use (ever, never), prediagnostic menopausal hormone therapy use (current, past, never), postdiagnostic census tract neighborhood socioeconomic status score (by quintile), prediagnostic BMI (<25, 25-<30, ≥30 kg/m^2, or unknown), cumulative average postdiagnostic BMI changes from pre- to postdiagnosis (lost >0.5 kg/m^2, stayed within 0.5 kg/m^2, gained 0.5–2 kg/m^2, gained >2 kg/m^2, or unknown), postdiagnostic cigarette smoking (never, former, current, or unknown), postdiagnostic aspirin use (never, former, current, or unknown), cumulative average postdiagnostic physical activity (by quintile), cumulative average postdiagnostic total energy intake (by quintile), cumulative average postdiagnostic alcohol intake (by quintile), disease stage (I, II, and III), tumor estrogen receptor status (positive, negative, or unknown), self-reported radiotherapy (yes, no, or unknown), chemotherapy (yes, no, or unknown), and hormonal treatment (yes, no, or unknown).
Abbreviation: py, person-years.

breast cancer–specific mortality only among women whose nSES score below median (HR = 0.54, 95% CI = 0.35–0.81), but not among those who are equal to or above median (HR = 0.81, 95% CI = 0.54–1.20, $P_{\text{interaction}} < 0.001$). After further stratifying by prediagnosis DRRD, the interaction of nSES and postdiagnosis cumulative DRRD became less pronounced.

Because dietary behaviors may be influenced by deteriorating health preceding death, we conducted a lagged analysis to address the concern for reverse causation (Supplementary Table S2). For breast cancer mortality, the effect estimates were less pronounced, particularly in the fifth quintile (HR = 1.01; 95% CI = 0.83–1.23; $P_{\text{trend}} = 0.68$), although HRs for other quintiles were similar. For all-cause mortality, the association with lagged DRRD was slightly attenuated, but still statistically significant ($HR_{Q5vsQ1} = 0.82$; 95% CI = 0.72–0.93; $P_{\text{trend}} = 0.002$).

In analyses excluding women who died within first five years of diagnosis or women with T2D before or at breast cancer diagnosis, we observed similar associations. Moreover, we found that "lower post-diagnosis T2D prevalence" and "less BMI changes" were not the mediating factors for the inverse association between DRRD and mortality outcomes, the mediation proportions were all below 1%.

Discussion

In this current study of 8,482 breast cancer survivors followed for a median of 14 years since diagnosis, we found that women with greatest adherence to the DRRD (highest DRRD score) after diagnosis had lower risk of both breast cancer–specific and all-cause mortality. An improved adherence to DRRD or a maintenance of high DRRD score after diagnosis was also associated with lower risk of breast cancer and overall mortality.

T2D has been associated with poor prognosis of breast cancer (8–10). We recently reported that dietary glycemic index, one of the components of DRRD, was statistically significantly associated with higher risk of breast cancer mortality (14). Metformin, the most commonly used therapy for patients with T2D, had been associated with decreased breast cancer mortality in some studies (11, 30) by reducing levels of insulin and insulin resistance, sex hormones, C-reactive protein, blood glucose, and improving lipid profile (31, 32). Therefore, it is biologically plausible to hypothesize that greater adherence to the DRRD may be a potential strategy in reducing risk of mortality after breast cancer. We observed that greater adherence to the DDRD was associated with 11% lower risk of breast cancer incidence in the same cohorts (33), and 20% lower risk of breast cancer–specific mortality in the current analysis. In our previous breast tumor tissue gene expression analyses (33), two immune-regulatory pathways (IFNα response and IFNγ response) and three pathways related to proliferation (mTOR signaling, E2F, and allograft rejection) were significantly downregulated with higher DRRD score. It is possible that these five pathways are also important for breast cancer prognosis. Further studies are needed to understand how the DRRD [a dietary pattern including both nutrients and food items that may or may not be contributing to calories (e.g., coffee)] influences insulinemic and glycemic responses and how such responses further influence breast tumor progression. In addition, we observed a stronger inverse association among women with lower nSES score (<median). This suggests diet after breast cancer diagnosis may be more important among more disadvantaged women. However, we cannot rule out that this finding on nSES could be due to chance. It is also notable that an inverse association was limited to ER-negative breast cancer ($P_{\text{trend}} = 0.02$). Although the interaction was not statistically significant, likely due to limited numbers of ER-negative breast cancers in our study, there is other evidence, including from our previous DRRD-breast cancer incidence publication (33), suggesting that dietary factors may be strongly associated with ER-negative breast cancer only. This finding may need to be replicated in populations with a higher incidence of ER-negative breast cancer (e.g., among African American women).

We also observed that greater adherence to the DRRD was strongly inversely associated with all-cause mortality. Our findings here are consistent with previous studies conducted in the general population, which reported that dietary modifications to reduce the risk of developing insulin resistance and hyperinsulinemia was associated with lower overall mortality (34–40). Our findings are also consistent with the Women's Health Initiative Randomized Controlled Trial, which observed a reduced mortality after breast cancer for both all-cause and breast cancer–specific in the low-fat diet intervention group (41). However, a recent meta-analysis reported that a healthy dietary pattern or better dietary quality was found to be associated with improved overall mortality, but not breast cancer–specific mortality (42, 43). This suggests that although adherence to a healthy dietary pattern may not directly inhibit breast tumor progression, it could still play a key role in improving overall health among breast cancer survivors (42). For example, hyperinsulinemia and insulin resistance

Table 4. Subgroup analyses for the association between quintiles of cumulative average postdiagnostic diabetes risk reduction diet score and breast cancer mortality among breast cancer survivors using pooled data from NHS (follow-up from 1980–2016) and NHSII (follow-up from 1991–2017; $N = 8{,}482$).

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}	$P_{interaction}$
By menopausal status at diagnosis							
Premenopausal breast cancer ($n = 301$[a])	1 (referent)	0.59 (0.41–0.85)	0.72 (0.51–1.02)	0.70 (0.49–1.01)	0.68 (0.47–0.99)	0.10	0.97
Postmenopausal breast cancer ($n = 678$[a])	1 (referent)	0.96 (0.76–1.21)	0.73 (0.57–0.93)	0.82 (0.64–1.05)	0.81 (0.63–1.04)	0.04	
By estrogen receptor (ER) status							
ER positive ($n = 779$[a])	1 (referent)	0.89 (0.72–1.11)	0.83 (0.66–1.05)	0.93 (0.74–1.17)	0.85 (0.67–1.08)	0.27	0.23
ER negative ($n = 205$[a])	1 (referent)	0.67 (0.44–1.01)	0.67 (0.44–1.01)	0.57 (0.35–0.91)	0.63 (0.40–0.99)	0.02	
By insulin receptor (IR) status							
IR positive ($n = 170$[a])	1 (referent)	0.95 (0.58–1.56)	0.85 (0.51–1.43)	0.84 (0.50–1.41)	0.82 (0.45–1.47)	0.40	0.52
IR negative ($n = 208$[a])	1 (referent)	1.05 (0.67–1.64)	0.86 (0.54–1.35)	0.81 (0.49–1.33)	1.28 (0.80–2.04)	0.50	
By breast cancer stage							
Stage I ($n = 294$[a])	1 (referent)	0.92 (0.64–1.32)	0.85 (0.58–1.24)	1.03 (0.71–1.48)	0.85 (0.58–1.26)	0.61	0.79
Stage II ($n = 406$[a])	1 (referent)	0.96 (0.71–1.29)	0.80 (0.59–1.08)	0.67 (0.48–0.94)	0.76 (0.55–1.05)	0.02	
Stage III ($n = 342$[a])	1 (referent)	0.69 (0.50–0.97)	0.67 (0.47–0.96)	0.72 (0.51–1.03)	0.77 (0.53–1.11)	0.22	
By BMI at diagnosis							
<25 kg/m^2 ($n = 479$[a])	1 (referent)	0.75 (0.56–1.01)	0.86 (0.64–1.16)	0.93 (0.69–1.26)	0.77 (0.56–1.04)	0.29	0.36
25–30 kg/m^2 ($n = 316$[a])	1 (referent)	0.89 (0.64–1.24)	0.68 (0.47–0.99)	0.78 (0.55–1.12)	0.84 (0.57–1.22)	0.21	
≥30 kg/m^2 ($n = 201$[a])	1 (referent)	0.77 (0.52–1.14)	0.51 (0.33–0.80)	0.51 (0.31–0.83)	0.83 (0.51–1.33)	0.05	
By physical activity at diagnosis							
<9 MET h/week ($n = 671$[a])	1 (referent)	0.83 (0.66–1.03)	0.77 (0.61–0.98)	0.75 (0.59–0.97)	0.82 (0.63–1.05)	0.06	0.85
≥9 MET h/week ($n = 275$[a])	1 (referent)	0.67 (0.45–1.01)	0.62 (0.40–0.94)	0.89 (0.60–1.31)	0.73 (0.48–1.10)	0.54	
nSES at diagnosis							
<0.05 ($n = 355$[a])	1 (referent)	0.80 (0.59–1.09)	0.56 (0.40–0.80)	0.68 (0.47–0.98)	0.54 (0.35–0.81)	0.002	<0.001
≥0.05 ($n = 343$[a])	1 (referent)	0.60 (0.42–0.87)	0.69 (0.48–0.99)	0.75 (0.51–1.09)	0.81 (0.54–1.20)	0.65	

Note: Model adjusted for age at diagnosis (continuous) and calendar year of diagnosis (continuous), prediagnostic menopausal status (premenopausal, postmenopausal), age at menarche (<12, 12, 13, 14, >14), prediagnostic parity (ever parous, never parous), prediagnostic family history of breast cancer in a first-degree relative (yes, no), prediagnostic personal history of benign breast disease (yes, no), prediagnostic oral contraceptive use (ever, never), prediagnostic menopausal hormone therapy use (current, past, never), postdiagnostic census tract neighborhood socioeconomic status score (by quintile), prediagnostic BMI (<25, 25–<30, ≥30 kg/m^2, or unknown), cumulative average postdiagnostic BMI changes from pre- to postdiagnosis (lost >0.5 kg/m^2, stayed within 0.5 kg/m^2, gained 0.5–2 kg/m^2, gained >2 kg/m^2, or unknown), postdiagnostic cigarette smoking (never, former, current, or unknown), postdiagnostic aspirin use (never, former, current, or unknown), cumulative average postdiagnostic physical activity (by quintile), cumulative average postdiagnostic total energy intake (by quintile), cumulative average postdiagnostic alcohol intake (by quintile), disease stage (I, II, and III), tumor estrogen receptor status (positive, negative, or unknown), self-reported radiotherapy (yes, no, or unknown), chemotherapy (yes, no, or unknown), and hormonal treatment (yes, no, or unknown). For nSES subgroup analysis, model additionally adjusted for prediagnosis DRRD.

Abbreviations: MET, metabolic-equivalent-of-task; nSES, neighborhood socioeconomic status.

[a]Breast cancer death number.

are considered important underlying mechanisms linking poor lifestyle behaviors and quality of life (44), and to the development of multiple chronic diseases and conditions (45, 46). The particularly strong inverse association between DRRD and overall mortality in this analysis may also be due to adult weight gain and physical inactivity, which both increase insulin resistance, being risk factors for breast cancer. Thus, women with breast cancer could be enriched with those who would most benefit from this dietary pattern.

The strengths of our study include the large number of breast cancer survivors, long follow-up, detailed and multiple assessments of the exposures and potential confounders information both before and after diagnosis. We focused on using the cumulative average of repeated dietary measures rather than a single dietary assessment because this reduces random within-person error, better represents true long-term diet, and reduces the influence of reverse causation (13).

With regard to limitations, the inevitable measurement errors in dietary assessment may have resulted in exposure misclassification, biasing our results toward the null. However, we used a validated self-reported FFQ and the DRRD had been strongly linked with a reduced risk of developing T2D (13), suggesting that the score is well designed and measured. Second, we had limited power to evaluate the association between DRRD and breast cancer mortality by tumor IR status. Third, the possibility of residual confounding cannot be ruled out. Overall "healthy lifestyle" factors are cause for concern regarding residual confounding, but they are difficult to quantify. However, we controlled for a wide variety of predictors of DRRD and breast cancer mortality, including socioeconomic indicators. Moreover, our findings may not be generalizable to overall U.S. breast cancer patients because all the women in our study were health care professionals and they were predominately white. Finally, there was a potential concern of reverse causation for the observed inverse associations with mortality. It is unclear whether this could represent reverse causation or that more recent diet is most important. However, our use of the cumulative average exposure decreases the chances of this, and the effect estimates remained similar for the lagged analysis and the sensitivity analysis after excluding subjects who died within 5 years after diagnosis. Future studies should explore further the potential for reverse causation due to other factors that might cause changes in DRRD that

we lack data on in our current study (e.g., treatment nonadherence or complications; recurrence, chemotherapy resistance, treatment side effects, etc.). These factors could potentially significantly influence short-term survival.

In conclusion, our findings provide evidence that greater adherence to a DRRD is associated with reduced mortality after breast cancer diagnosis. This dietary pattern is rich in cereal fiber, nut/peanut butter, polyunsaturated fat, and whole fruits and includes coffee (both caffeinated and decaffeinated), but has limited amount of carbohydrates with a high GI value, saturated fat, trans-fat, SSBs/fruit juices, and red meat. Further investigation is needed to better understand the mechanism between the T2D prevention diet and breast cancer survival, especially by integrating circulating or tumor markers (i.e., C-peptide concentration, *PIK3CA* mutation) related to the insulin signaling pathway. In the meantime, our results are consistent with prevention of diabetes and overall good health and may benefit breast cancer survivors.

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Authors' Contributions

T. Wang: Formal analysis, investigation, methodology, writing–original draft. **M.S. Farvid:** Resources, formal analysis, writing–review and editing. **J.H. Kang:** Resources, formal analysis, writing–review and editing. **M.D. Holmes:** Methodology, writing–review and editing. **B.A. Rosner:** Investigation, methodology, writing–review and editing. **R.M. Tamimi:** Funding acquisition, investigation, methodology, writing–review and editing. **W.C. Willett:** Conceptualization, funding acquisition, investigation, methodology, writing–review and editing. **A.H. Eliassen:** Conceptualization, resources, supervision, funding acquisition, investigation, methodology, project administration, writing–review and editing.

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