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Association of Dietary Carbohydrate Intake with Changes in Cardiometabolic Risk Markers During Breast Cancer Treatment: A Prospective Cohort Study

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Abstract

Background: Cardiovascular disease is the leading cause of death among breast cancer survivors, and chemotherapy is associated with adverse metabolic changes. Whether dietary carbohydrate intake during treatment independently tracks with cardiovascular risk factor changes remains unknown.

Methods: In this prospective cohort study, 100 women with histologically confirmed breast cancer were recruited before initiating chemotherapy and followed for six months. Dietary carbohydrate intake was assessed using nine 24-hour dietary records collected throughout treatment. Anthropometric, lipid, glycemic, and hepatic markers were measured at baseline and at six months. Linear regression models were used to examine associations between carbohydrate intake (% of total energy) and study outcomes. Model 1 used change scores (follow-up minus baseline) as the dependent variables, whereas Model 2 used follow-up values as the dependent variables and adjusted for age, tumor stage, physical activity, baseline BMI, and the corresponding baseline outcome value.

Results: Mean carbohydrate intake was 47 ± 4.71% of total energy. In the adjusted model, higher carbohydrate intake was independently associated with greater increases in waist circumference ($\beta = 0.123$, $P = 0.015$), fat mass ($\beta = 0.153$, $P = 0.015$), visceral adiposity index ($\beta = 0.053$, $P = 0.014$), triglycerides ($\beta = 0.637$, $P = 0.010$), fasting insulin ($\beta = 0.127$, $P = 0.014$), and AST ($\beta = 0.393$, $P = 0.001$). Associations with LDL-cholesterol, HDL-cholesterol, blood pressure, fasting blood glucose, HbA1c, HOMA-IR, and ALT were not statistically significant.

Conclusion: Dietary carbohydrate intake during chemotherapy was independently associated with unfavorable anthropometric, lipid, glycemic, and hepatic changes in women with breast cancer. These findings suggest that dietary carbohydrate intake may be relevant to cardiometabolic health during breast cancer treatment and warrants further investigation.

Keywords: breast cancer; chemotherapy; carbohydrate intake; cardiovascular risk factors; prospective cohort

Introduction

Breast cancer is the most commonly diagnosed cancer among women in most countries worldwide, causing an estimated 694,000 deaths in 2024 [1], and more than 4 million survivors are now living in the United States alone with the downstream consequences of diagnosis and treatment [2]. As breast-cancer-specific mortality has declined with therapeutic advances, cardiovascular disease has emerged as the leading cause of death among long-term survivors [3]: a large US study found that 14.67% of women developed clinically significant cardiovascular disease within a median of 5.8 years after diagnosis, with anthracycline- and trastuzumab-based regimens carrying particularly elevated risk [4]. This burden also carries real cost, unnecessary or overly frequent cardiac surveillance during HER2-targeted therapy has been identified as a substantial and avoidable contributor to US healthcare spending in this population [5].

Chemotherapy itself is associated with weight gain and altered body composition during treatment [6], and features of metabolic syndrome have been shown to worsen during chemotherapy, with whether these changes persist after treatment completion identified in the literature as an open question [7]. Reflecting this metabolic shift, breast cancer patients undergoing chemotherapy have been found to maintain carbohydrate and fibre intake at levels similar to women without cancer, even as their protein, fat, and alcohol intake falls [8], a pattern that may plausibly relate to chemotherapy's known effects on appetite, taste, and gastrointestinal tolerance, though this specific mechanism has not been directly tested. Consistent with a role for carbohydrate quantity in treatment-related morbidity more broadly, one study in breast cancer patients found that higher dietary carbohydrate intake increased the odds of acute radiation-induced skin toxicity, while protein intake appeared protective [9].

The epidemiological picture within breast cancer populations specifically, however, is far from settled. A meta-analysis pooling cohort studies found weak, largely non-significant associations between higher dietary carbohydrate intake and lower risk of breast cancer incidence, mortality, and recurrence [10], a finding seemingly at odds with a purely harmful framing of carbohydrate in this population. Yet subsequent work drawing on the Nurses' Health Study cohorts suggested the relationship is source-dependent rather than uniform: higher post-diagnostic intake of added sugar, sucrose, fructose, and carbohydrate from fruit juice was significantly associated with greater all-

cause mortality, and more tentatively with breast-cancer-specific mortality, while carbohydrate from vegetables was associated with lower mortality [11]. A Spanish cohort similarly found that high carbohydrate intake, specifically from monosaccharides, worsened prognosis, but only among normal-weight women [12], and a later analysis from the same Nurses' Health Study cohorts found that low-carbohydrate dietary patterns improved overall survival but not breast-cancer-specific survival, and only for plant-rich rather than animal-rich low-carbohydrate patterns [13]. These discrepancies indicate that carbohydrate's relationship to breast cancer outcomes remains incompletely understood.

This gap is notable given how little is known about carbohydrate intake's relationship to cardiovascular risk markers, as distinct from cancer recurrence or survival, specifically during chemotherapy, a period when metabolic vulnerability appears heightened [14] and when nutritional counseling could, in principle, be most actionable. Whether the quantity of carbohydrate consumed during treatment tracks with measurable changes in anthropometric, lipid, glycemic, or hepatic markers of cardiovascular risk in this population has not, to our knowledge, been directly examined.

We therefore aimed to evaluate the association between dietary carbohydrate intake and changes in cardiovascular disease risk factors among women with breast cancer undergoing chemotherapy. We hypothesized that higher carbohydrate intake, as a proportion of total energy, would be associated with unfavorable changes in anthropometric, lipid, glycemic, and hepatic markers of cardiovascular risk over the course of treatment.

1. Methods

Study design and participants

This study used a prospective cohort design and was conducted between 2023 and 2025 at selected oncology clinics in Tehran, Iran. A total of 100 women with histologically confirmed breast cancer were consecutively recruited before initiating systemic therapy. All were scheduled for chemotherapy and followed up for six months.

Treatment varied by clinical scenario. Participants on chemotherapy alone completed a 6-month protocol. Those on combined chemotherapy and HER2-targeted therapy received approximately 4.5 months of chemotherapy alongside HER2-targeted therapy planned for one year. Measurements including anthropometrics, laboratory values, and blood pressure were collected at two standard time points: at baseline and at 6 months. In the chemotherapy-only group, this 6-month assessment marked the end of treatment, while in the combined group it occurred during active HER2-targeted therapy. Tumor stage was obtained from the patients' medical records and was considered as a covariate in the adjusted regression analyses. Table 1 summarizes baseline clinical data, treatment regimens, and menopausal status.

The broader cohort study aimed to examine dietary carbohydrate intake during treatment and its relationship with changes in cardiometabolic and psychosocial outcomes throughout systemic treatment.

Measurements and ethical approval

Ethical approval for this study was obtained from the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.CRC.REC.1402.021). Prior to enrollment, all participants gave written informed consent.

Sample size

The sample size was determined a priori for the parent prospective cohort study, which was designed to investigate associations between dietary intake during breast cancer treatment and cardiometabolic outcomes using multivariable linear regression. Sample size estimation was performed using G*Power version 3.1.9.2 with an F-test for multiple linear regression, assuming an effect size of $f^2 = 0.20$, a two-sided significance level of 0.05, 80% statistical power, and seven predictors. Under these assumptions, a minimum sample size of 80 participants was required. The target sample size was increased to 100 participants to allow for an anticipated 20% loss to follow-up. All 100 participants completed the 6-month follow-up and were included in the final analyses.

The sample size was determined for the overall parent cohort based on a multivariable model including seven predictors. In the present analysis, total energy intake was not included as a covariate because carbohydrate intake was expressed as a percentage of total energy.

Eligibility Criteria

Women were considered eligible if they were 18 years of age or older, had a new histologically confirmed diagnosis of breast cancer, were planning to undergo chemotherapy, and had not previously received chemotherapy treatment.

Women were excluded if they had pre-existing conditions likely to interfere with metabolic or biochemical measurements specifically diabetes mellitus, cardiovascular disease, or clinically significant hepatic or renal impairment, as confirmed by medical records. Exclusion also applied to those following a highly restrictive or medically prescribed diet, anyone with a condition that would compromise reliable anthropometric or laboratory data collection, and those who withdrew consent or were lost to follow-up.

Treatment characteristics

The choice of chemotherapy regimen was left to the treating oncologist and guided by tumor-specific features and the protocols of the institution. Data on the clinical setting, tumor profile, hormone and HER2 receptor status, and systemic treatment type were extracted from medical records. Detailed characteristics of the study participants and their treatment courses are shown in Table 1. In cases where participants were receiving HER2-targeted agents, the six-month evaluation could occur following the completion of chemotherapy, provided that HER2-directed treatment remained ongoing at that time.

Dietary Intake Assessment

Dietary intake was evaluated using the nine 24-hour dietary records method throughout the chemotherapy period. Nine 24-hour dietary records were obtained from each participant, with three records collected during the early, three during the middle, and three during the late phase of chemotherapy. The recording days were selected separately from chemotherapy administration days to reduce the potential influence of the immediate effects of treatment on dietary intake. All dietary records were analyzed using Nutritionist IV software (The Hearst Corporation, San Bruno, CA, USA).

The mean carbohydrate intake across the nine 24-hour dietary records was calculated for each participant and expressed as a percentage of total daily energy intake. This value was used as the primary measure of dietary carbohydrate intake in the analyses.

Physical Activity Assessment

Physical activity was assessed at the end of the study using the short form of the International Physical Activity Questionnaire (IPAQ-SF). Participants reported the frequency and duration of walking, moderate-intensity, and vigorous-intensity physical activities performed during the previous 7 days. Physical activity was expressed as metabolic equivalent of task minutes per week (MET-min/week) according to the standard IPAQ scoring protocol. Total physical activity was calculated by summing the MET-min/week values for walking, moderate-intensity, and vigorous-intensity activities. The final IPAQ-SF score obtained at the end of the study was used as the measure of physical activity in the adjusted regression analyses [15].

Anthropometric and cardiometabolic measurements

Anthropometric and clinical assessments were carried out at baseline and repeated at the 6-month follow-up visit. Standing height was recorded to the nearest 0.1 cm without shoes, using a wall-mounted stadiometer. Waist circumference was measured to the nearest 0.1 cm at the midpoint between the lower rib margin and the iliac crest, using a non-elastic tape measure. Body fat mass was determined by multi-frequency bioelectrical impedance analysis (InBody 230; Biospace Co., Ltd., Seoul, Republic of Korea), following the manufacturer's standardized protocol.

All measurements were taken in the morning after an 8- to 12-hour overnight fast and bladder emptying. Participants were asked to refrain from intense physical activity, caffeine, and alcohol for 24 hours prior to testing. Resting blood pressure (systolic and diastolic) was recorded in a seated position following 5 minutes of quiet rest, using a calibrated digital sphygmomanometer. Two readings taken 5 minutes apart were averaged.

Venous blood samples were drawn between 07:30 and 09:30 AM after an 8- to 12-hour overnight fast. Serum fasting blood glucose, HbA1c, total cholesterol, triglycerides, HDL-C, AST, and ALT were quantified using commercial enzymatic/colorimetric kits (Pars Azmun Diagnostics, Tehran,

Iran) on an automated clinical chemistry analyzer. Fasting insulin was measured with an enzyme-linked immunosorbent assay. LDL-C was derived using the Friedewald equation. HOMA-IR was calculated as:

$$HOMA - IR = \frac{\text{FBG (mg/dL)} \times \text{Fasting Insulin}(\mu\text{IU/mL})}{405}$$

Visceral Adiposity Index (VAI), sex-specific for females, was calculated using the formula defined by Amato et al. [16]:

$$\text{Visceral Adiposity Index (VAI)for women} = \left(\frac{\text{WC (cm)}}{(36.58 + (1.89 \times \text{BMI}))}\right) \times \left(\frac{\text{TG (mg/dL)}}{71.75}\right) \times \left(\frac{58.69}{\text{HDL} - C\ \text{(mg/dL)}}\right)$$

Body mass index (BMI) was calculated as follows:

$$BMI = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

All baseline and follow-up specimens were analyzed in the same accredited central laboratory, adhering to standard calibration procedures and daily multi-level internal quality controls. Intra- and inter-assay coefficients of variation were below 5% for all routine biochemical analytes.

Outcomes

The primary outcome was the change in visceral adiposity index (VAI) between pre-chemotherapy and the 6-month follow-up. The secondary outcomes were changes in triglycerides (TG), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), systolic and diastolic blood pressure, fasting blood glucose, HbA1c, fasting insulin, HOMA-IR, AST, and ALT.

For each outcome, the change score was calculated as the 6-month follow-up value minus the corresponding pre-chemotherapy value. Accordingly, positive values represented an increase, whereas negative values indicated a decrease over the chemotherapy period.

Statistical analysis

To evaluate the association between total carbohydrate intake (% of total energy) during chemotherapy and cardiometabolic outcomes, linear regression analyses were performed using two distinct models. In Model 1, the dependent variable was the change score for each outcome, calculated as the 6-month follow-up value minus the pre-treatment value. In Model 2, the 6-month follow-up value of each outcome served as the dependent variable, with adjustment for its baseline value, age, tumor stage, physical activity assessed at the 6-month follow-up, and baseline BMI.

Because carbohydrate intake was expressed as a percentage of total energy intake (% of total energy), total energy intake was not additionally included as a covariate in the present analysis. This approach was specific to the current exposure definition; in other analyses derived from the same cohort, total energy intake was included as an adjustment variable when dietary exposures were not expressed as a percentage of total energy.

The primary analysis was conducted using an analysis-of-covariance approach, with the 6-month follow-up value of each outcome as the dependent variable and average carbohydrate intake during chemotherapy as the main exposure. Models were adjusted for the corresponding baseline outcome value and the prespecified covariates. This approach allowed the association between carbohydrate intake and follow-up outcomes to be evaluated while accounting for baseline levels. As a complementary analysis, linear regression models were performed using the change in each outcome from baseline to follow-up as the dependent variable.

Effect estimates are presented as unstandardized regression coefficients (β) with 95% confidence intervals (95% CI). All tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Participant characteristics

One hundred women with breast cancer were followed prospectively during chemotherapy. Mean age was 45.51 ± 10.30 years and mean BMI was 26.08 ± 3.30 kg/m². The majority were premenopausal (60%), estrogen receptor-positive (78%), and lymph node-positive (60%). The most common chemotherapy regimen was AC→T (50%), followed by TC+H (29%). HER2-positive status was present in 35% of participants. The characteristics of the participants are presented in **Table 1.**

Nutritional Intake During Chemotherapy

As shown in **Table 2**, Mean total energy intake during chemotherapy was 1360.9 ± 262.11 kcal/day (20.03 ± 4.43 kcal/kg/day). Mean carbohydrate intake was 161.6 ± 34.95 g/day (2.38 ± 0.59 g/kg/day), representing 47 ± 4.71% of total energy intake. Mean protein intake was 0.74 ± 0.15 g/kg/day (14% of energy) and fat intake was 0.89 ± 0.21 g/kg/day (39% of energy).

Participant Flow and Completeness of Follow-up

From 2023 to 2025, 100 women meeting the eligibility criteria were recruited prior to starting chemotherapy; those with predefined exclusion criteria were screened out at enrollment. All enrolled participants completed the planned 6-month follow-up assessment. No loss to follow-up or withdrawal occurred, and complete outcome data were available for all 100 participants (Figure 1).

Association between carbohydrate intake and CVD risk factors

Table 3 presents the linear regression results for the association between total carbohydrate intake (% of total energy intake) and changes in cardiovascular and metabolic risk factors.

In the crude model (Model 1), significant positive associations were observed for WC ($P = 0.013$), fat mass ($P = 0.028$), LDL ($P = 0.018$), HbA1c ($P = 0.020$), and AST ($P = 0.004$).

In the adjusted model (model 2), higher carbohydrate intake was significantly and positively associated with increases in waist circumference (β = 0.123, 95% CI: 0.025–0.221, $P = 0.015$), fat mass (β = 0.153, 95% CI: 0.031–0.276, $P = 0.015$), VAI (β = 0.053, 95% CI: 0.011–0.096, $P = 0.014$), triglycerides (β = 0.637, 95% CI: 0.153–1.121, $P = 0.010$), fasting insulin (β = 0.127, 95% CI: 0.026–0.228, $P = 0.014$), and AST (β = 0.393, 95% CI: 0.167–0.618, $P = 0.001$).

In contrast, associations with LDL (β = 0.381, $P = 0.208$), HDL (β = −0.113, $P = 0.174$), SBP (β = 0.197, $P = 0.127$), DBP (β = 0.045, $P = 0.596$), FBG (β = 0.058, $P = 0.681$), HbA1c (β = 0.013, $P = 0.085$), HOMA-IR (β = 0.032, $P = 0.055$), and ALT (β = 0.153, $P = 0.157$) did not reach statistical significance in the adjusted model.

Discussion

This cohort of 100 women with breast cancer showed that higher dietary carbohydrate intake during chemotherapy was independently associated with greater waist circumference, fat mass, visceral adiposity index, triglycerides, fasting insulin, and AST after adjustment for age, tumor stage, physical activity, baseline BMI and baseline values indicating an association spanning anthropometric, lipid, glycemic, and hepatic risk domains rather than a single pathway. Crude-model associations with LDL-cholesterol and HbA1c did not persist after adjustment, and HOMA-IR showed only a borderline adjusted association, while no associations emerged for blood pressure, fasting blood glucose, HDL-cholesterol, or ALT.

Our findings are consistent with an evaluation of nutritional status in breast cancer patients undergoing chemotherapy, in which patients who had completed chemotherapy showed impairments in lipids, glucose levels, and visceral fat distribution alongside unhealthy dietary patterns characterized by higher carbohydrate and caloric intake, relative to matched controls [17]. A comparable cohort study found that breast cancer patients undergoing chemotherapy consumed amounts of carbohydrate and dietary fibre similar to age-matched women without cancer, even though their protein, fat, and alcohol intakes were lower, suggesting that carbohydrate may constitute a relatively larger share of energy intake in this population during treatment [8]. Carbohydrate-related treatment morbidity specific to breast cancer patients was also reported by the ATHENA project, in which higher dietary carbohydrate intake increased the odds of acute radiation-induced skin toxicity while protein intake was protective [9], supporting the broader premise that carbohydrate quantity influences treatment-related outcomes in this population even though the endpoint differs from ours.

The triglyceride association we observed in the adjusted model is consistent with two independent cohorts describing chemotherapy-related dyslipidemia in breast cancer patients: a retrospective study of 805 patients found that (neo)adjuvant chemotherapy produced a temporary increase in triglycerides and LDL-cholesterol alongside a decrease in HDL-cholesterol [18], and a further retrospective cohort of 394 patients similarly reported significantly higher total cholesterol, triglycerides, LDL-cholesterol, and apolipoprotein B, with significantly lower HDL-cholesterol and apolipoprotein A1, after adjuvant chemotherapy compared with pre-chemotherapy levels [19].

A separate prospective study following patients through their first chemotherapy cycle found a more mixed short-term pattern, with total cholesterol rising by the end of the cycle while triglycerides fell between the cycle's early and late assessment points [20], suggesting that the direction of lipid change may depend on the chemotherapy phase and duration studied. Our fasting-insulin finding is broadly in line with a prospective cohort of women treated for early-stage breast cancer, in which HOMA-IR showed a non-significant overall trend toward increase six months after diagnosis, but this change was significantly greater specifically in patients who received chemotherapy compared with those who did not [14]. This is not entirely consistent across the literature, however: another study of adjuvant chemotherapy in breast cancer patients reported a numerical decrease in HOMA-IR after treatment that did not reach statistical significance [21], indicating that chemotherapy's short-term effect on insulin resistance is not uniformly in one direction across cohorts. The AST elevation we observed adds to limited existing evidence of liver-enzyme abnormalities occurring during adjuvant chemotherapy in breast cancer patients, reported in a study that specifically examined hepatotoxicity in relation to concurrent use of alternative/herbal remedies during treatment [22]; we did not identify any prior study specifically linking dietary carbohydrate intake to liver transaminases in this population, indicating a gap that our findings may begin to address. A related prospective cohort study protocol, still in progress, summarizes prior evidence suggesting that (neo)adjuvant chemotherapy is associated with deterioration in fasting insulin, HOMA-IR, HbA1c, triglycerides, and HDL-cholesterol [23], broadly consistent with the direction of the associations identified here, although this source itself reports background literature rather than new primary data.

Our results should also be read alongside literature on the broader cardiometabolic vulnerability of breast cancer patients during and after chemotherapy: a study of 5-year breast cancer survivors specifically examined changes in body composition in relation to subsequent cardiovascular disease risk in this population [24], chemotherapy-induced weight gain has been linked to systemic inflammation and gut dysbiosis [6], unfavorable shifts in metabolite and lipoprotein profiles have been examined as predictors of weight gain during breast cancer treatment [25], and components of metabolic syndrome have been reported to worsen after completion of chemotherapy [7]. Taken together, our findings extend this breast-cancer-specific literature by suggesting that dietary

carbohydrate intake may be associated with cardiometabolic changes observed during breast cancer treatment.

Several biologically plausible mechanisms, established primarily in general-population and experimental studies, may underlie the associations observed in this study. Diets higher in carbohydrate, particularly refined and rapidly absorbed forms, produce larger postprandial glucose and insulin excursions that, over time, promote insulin resistance; this is consistent with a large population-based analysis in which total carbohydrate intake was a significant, direct predictor of HOMA-IR after adjustment for covariates including waist circumference [26]. Excess carbohydrate substrate also drives hepatic de novo lipogenesis (DNL) through activation of the transcription factor SREBP-1c, a pathway particularly stimulated by fructose because its hepatic metabolism bypasses the rate-limiting step of glycolysis and does not require insulin, favoring conversion of carbohydrate-derived substrate into triglycerides [27-29]. This lipogenic flux increases hepatic and circulating triglyceride production and shifts LDL and HDL particles toward smaller, denser subfractions associated with atherogenic dyslipidemia [30, 31], offering a plausible explanation for the triglyceride association observed in our adjusted model. Increased hepatic lipogenesis and associated hepatocellular lipid accumulation can also manifest as mild elevations in aminotransferases such as AST, providing a possible mechanistic link between higher carbohydrate intake and the AST elevation observed in this cohort [27-29]. With respect to adiposity, chronic excess carbohydrate and energy intake favors triglyceride storage in visceral and subcutaneous depots; a randomized primary-care trial found that reducing dietary fructose specifically produced significantly greater reductions in waist circumference than a standard energy-restricted diet without a fructose-reduction component [32], consistent with a role for carbohydrate quality in adiposity change.

Strengths and Limitations

This study has several strengths. Dietary intake was estimated using nine 24-hour dietary records collected throughout chemotherapy rather than a single assessment, which may reduce day-to-day variability and provide a more representative estimate of usual carbohydrate intake during treatment. The study also assessed a broad range of anthropometric, glycemic, lipid, vascular, and hepatic outcomes, allowing a comprehensive evaluation of cardiometabolic changes. In addition,

the regression analyses accounted for several prespecified covariates, including age, tumor stage, physical activity, baseline BMI, and the baseline value of each outcome.

Several limitations should nevertheless be considered. First, the relatively modest sample size (n = 100) limits statistical power, particularly for outcomes with borderline associations, and increases the possibility of both type II error and unstable estimates. Second, the observational design precludes causal inference, and residual confounding from unmeasured factors cannot be excluded. Reverse causation is also possible because changes in health status and treatment-related symptoms may have influenced dietary intake during chemotherapy. Moreover, physical activity was assessed at the 6-month follow-up using the IPAQ-SF and therefore reflected activity during the previous 7 days rather than physical activity across the entire treatment period.

Third, dietary intake was self-reported and may therefore be affected by recall and reporting errors. Although intake was assessed repeatedly, the study focused on total carbohydrate intake as a proportion of total energy and did not evaluate carbohydrate quality, including glycemic index, glycemic load, fiber, added sugars, or specific carbohydrate sources. Because carbohydrate expressed as a percentage of total energy is inherently related to the proportions of other macronutrients, the observed associations may also reflect differences in macronutrient substitution rather than an isolated effect of carbohydrate intake. Protein, fat, and carbohydrate sources and their detailed dietary substitution patterns were not specifically examined.

Fourth, the cohort included patients receiving different chemotherapy regimens and, in some cases, targeted or HER2-targeted therapy, and treatment-related heterogeneity may have influenced metabolic and hepatic outcomes. Although tumor stage and other prespecified covariates were included in the models, the sample size limited the extent to which treatment-related factors could be fully controlled. The absence of a comparison group also limits the ability to distinguish changes related to chemotherapy from changes that may occur over time independently of treatment.

Finally, multiple outcomes were examined without formal adjustment for multiple comparisons, which may have increased the likelihood of chance findings. In addition, VAI is mathematically derived from waist circumference, BMI, triglycerides, and HDL-cholesterol; therefore, associations involving VAI and its individual components are not statistically independent. These

findings should consequently be interpreted as longitudinal associations rather than evidence of a causal or therapeutic effect. Future studies with larger samples, longer follow-up, appropriate comparison groups, and detailed assessment of carbohydrate quality and macronutrient substitution are needed to determine which aspects of carbohydrate intake are most strongly related to cardiometabolic outcomes during breast cancer treatment.

Conclusion

In conclusion, higher dietary carbohydrate intake during chemotherapy was associated with unfavorable changes in several anthropometric, lipid, glycemic, and hepatic markers among women with breast cancer. These associations remained after adjustment for prespecified covariates and baseline values, although no causal relationship can be established because of the observational design. The findings suggest that dietary carbohydrate intake may be relevant to cardiometabolic health during breast cancer treatment. Further prospective and randomized studies with larger samples, longer follow-up, and detailed assessment of carbohydrate quality and macronutrient substitution are needed to determine whether carbohydrate quantity or quality influences cardiometabolic outcomes in this population.

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Ethical Approval: The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Shahid Beheshti University

of Medical Sciences (IR.SBMU.CRC.REC.1402.021). Written informed consent was obtained from all participants before enrollment.

Conflict of Interest: The authors declare no competing interests.

Authors' Contributions: O.A. and S.H.D. conceived and designed the study. O.A., M.D.G, and C.A., contributed to study development and manuscript drafting. S.H.D. supervised the study, contributed to study design, and critically revised the manuscript. H.R.M. provided clinical expertise and contributed to patient identification and referral. B.N. provided statistical and methodological consultation. All authors reviewed, revised, and approved the final manuscript.

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Figure 1. Flow diagram of participant enrollment, follow-up completion, and final paired analysis.

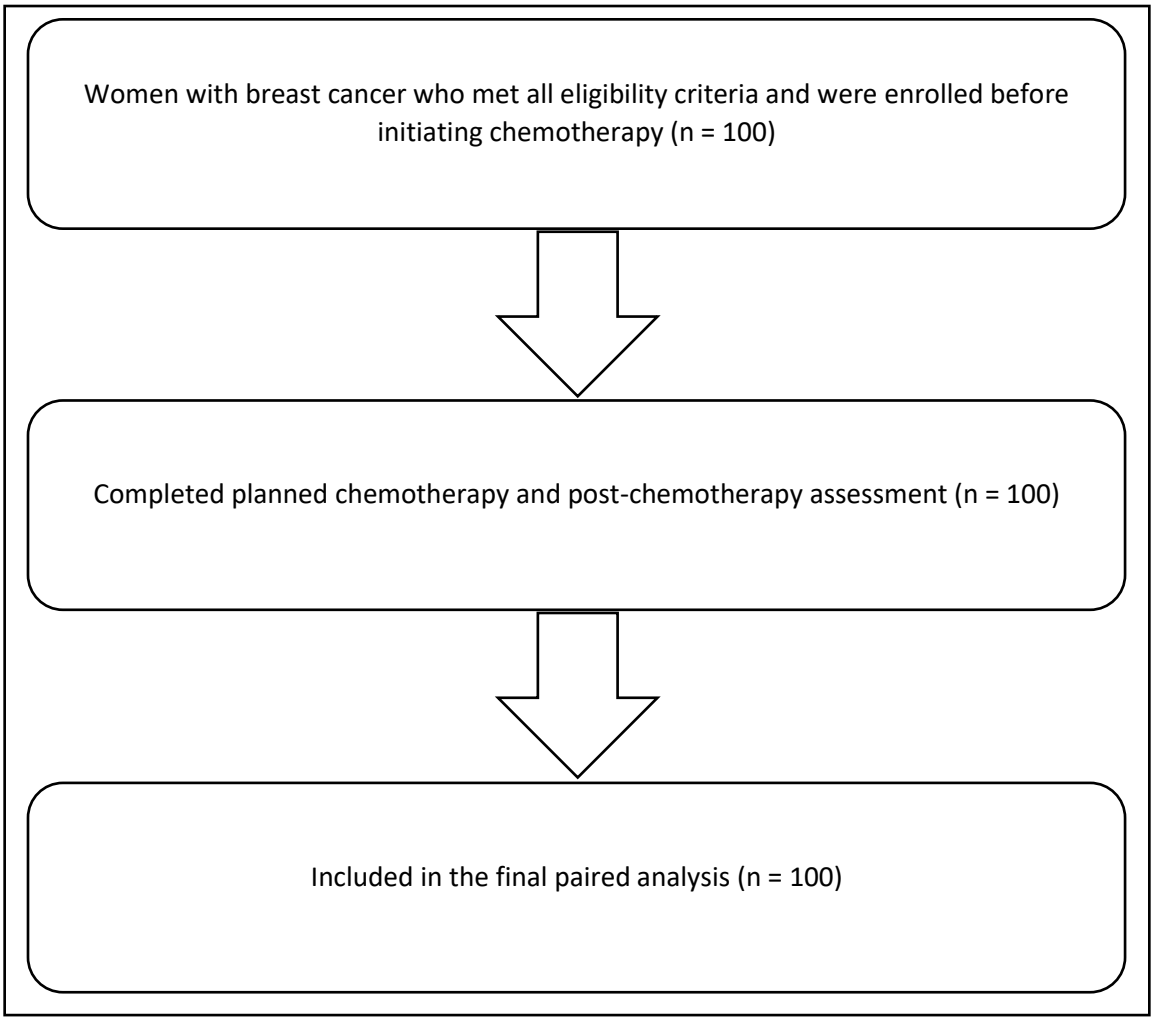


Table 1. Baseline patient characteristics (n=100)

	Mean (SD)		Mean (SD)
Age (years)	45.51 (10.30)	Progesterone (ng/mL)	5.84 (6.23)
Height (cm)	162.61 (5.12)	Estrogen (pg/mL)	129.34 (108.03)
BMI (kg/m^2)	26.08 (3.30)	WBC (10^3/μL)	6.97 (0.94)
Body weight (kg)	68.91 (8.52)	RBC (10^6/μL)	4.60 (0.36)
WC (cm)	84.39 (7.35)	Platelets (10^3/μL)	283.58 (59.12)
Tumor size (cm)	3.39 (1.73)		
	Percent (%)		Percent (%)
Menopause status		Estrogen receptor expression	
Premenopausal	60	-	22
Postmenopausal	40	+	78
Education		Progesterone receptor expression	
High school diploma	47	-	49
University degree	53	+	51
Family history of cancer		HER2 receptor expression	
No	62	-	65
Yes	38	+	35
Marital status		Histological grade	
Single	29	1	6
Married	54	2	58
Divorced/widowed	17	3	36
Employment status		Lymph node involvement	
Unemployed	43	No	40
Employed	57	Yes	60
Smoking status		Metastatic status	
Smoker	13	Non-metastatic	73
Non-smoker	87	Metastatic	27
Number of children		Tumor stage	
0	35	IA	7
1	23	IB	11
2	30	IIA	18
3	12	IIB	22
Chemotherapy regimens		IIIA	18
AC→T	50	IIIB	13
TC→AC	15	IV	11
TC+P (targeted therapy)	6	Treatment type	
TC+H (targeted therapy)	29	Adjuvant	79
		Neoadjuvant	21

Footnote: AC: Doxorubicin + Cyclophosphamide, 4 cycles every 3 weeks; T: Docetaxel, 4 cycles every 3 weeks; TC: Docetaxel + Cyclophosphamide, 6 cycles every 3 weeks; P: Pertuzumab, 17 cycles; H: Trastuzumab, 17 cycles.

Table 2. Mean nutritional intake during chemotherapy.

	Mean	SD
Energy intake (kcal)	1360.9	262.11
Energy intake (kcal/kg)	20.03	4.43
Protein (g/day)	50.1	8.60
Protein (g/kg/day)	0.74	0.15
Protein (%)	14	1.86
Carbohydrate (g/day)	161.6	34.95
Carbohydrate (g/kg/day)	2.38	0.59
Carbohydrate (%)	47	4.71
Fat (g/day)	60.3	13.58
Fat (g/kg/day)	0.89	0.21
Fat (%)	39	3.99

Data are presented as mean ± SD. Values represent the average of nine 24-hour dietary records collected during chemotherapy. Dietary data were analyzed using Nutritionist IV software.

Table 3. association between **total carbohydrate intake (% from calorie intake)** and change in CVD risk factors among women with breast cancer.

Variables	Crude model					Adjusted model				
	Adjusted R Square	β	95% CI		P-value	Adjusted R Square	β	95% CI		P-value
			LL	UL				LL	UL	
WC (cm)	0.052	0.118	0.026	0.210	**0.013**	0.915	0.123	0.025	0.221	**0.015**
FM (kg)	0.039	0.133	0.015	0.250	**0.028**	0.713	0.153	0.031	0.276	**0.015**
VAI	0.023	0.038	-0.003	0.080	0.070	0.805	0.053	0.011	0.096	**0.014**
TG (mg/dL)	0.003	0.302	-0.219	0.822	0.253	0.857	0.637	0.153	1.121	**0.010**
LDL (mg/dL)	0.046	0.677	0.119	1.234	**0.018**	0.648	0.381	-0.215	0.977	0.208
HDL (mg/dL)	0.001	-0.084	-0.245	0.077	0.304	0.768	-0.113	-0.276	0.051	0.174
SBP (mmHg)	0.016	0.199	-0.044	0.441	0.108	0.416	0.197	-0.057	0.450	0.127
DBP (mmHg)	-0.008	0.035	-0.136	0.207	0.684	0.414	0.045	-0.124	0.215	0.596
FBG (mg/dL)	0.008	0.169	-0.080	0.418	0.180	0.447	0.058	-0.222	0.338	0.681
HbA1C (%)	0.044	0.017	0.003	0.031	**0.020**	0.328	0.013	-0.002	0.028	0.085
Fasting insulin (µIU/mL)	-0.007	-0.030	-0.131	0.071	0.558	0.803	0.127	0.026	0.228	**0.014**
HOMA-IR	-0.006	-0.010	-0.040	0.020	0.522	0.724	0.032	-0.001	0.065	0.055
AST (U/L)	0.071	0.363	0.118	0.609	**0.004**	0.489	0.393	0.167	0.618	**0.001**
ALT (U/L)	-0.004	0.080	-0.123	0.282	0.437	0.559	0.153	-0.060	0.367	0.157

Note: Model 1: unadjusted linear regression of total carbohydrate intake with change in outcomes (follow-up − baseline). Model 2: adjusted ANCOVA of follow-up outcomes for total carbohydrate intake, adjusted for the baseline value of the corresponding outcome, age, energy intake, tumor stage, physical activity, and baseline BMI. β, unstandardized regression coefficient; 95% CI, 95% confidence interval; R^2, coefficient of determination. $P < 0.05$ was considered statistically significant.