Circulating Carnitine Levels and Breast Cancer: A Matched Case-Control Study

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Abstract

Background: The existing epidemiologic studies on the association between carnitine and breast cancer development are scarce. This study examined the association between circulating carnitine levels and breast cancer in females.

Methods: This 1:1 age-matched case-control study identified 991 female breast cancer cases and 991 female controls without breast cancer. All cases and controls were confirmed with a pathological test. We measured 16 types of whole blood carnitine levels, such as free carnitine (C0) and octadecanoylcarnitine (C18), using targeted metabolomic technology.

Results: The average age for cases and controls were 50.0 years (SD: 8.7 years) and 49.5 years (SD: 8.7 years), respectively. After adjusting for covariates, each SD increase in malonylcarnitine (C3DC; OR 0.91; 95% CI 0.83-1.00), decenoylcarnitine (C10:1; OR 0.87; 95% CI 0.79-0.96) and decadienoylcarnitine (C10:2; OR 0.90; 95% CI 0.82-0.99) level was associated with decreased odds of breast cancer. However, higher butyrylcarnitine (C4) levels were associated with increased risk of breast cancer (OR 1.12; 95% CI 1.02-1.23). We observed no relationship between other carnitines with breast cancer. The false discovery rates for C3DC, C4, C10:1 and C10:2 were 0.172, 0.120, 0.064 and 0.139, respectively.

Conclusions: Higher levels of C3DC, C10:1, and C10:2 were protective factors for breast cancer, whereas increased C4 levels were a risk factor for breast cancer.

Background

Similar to other countries, breast cancer in China remains the most common type of malignancy among females [1]. The age-standardized incidence rate of breast cancer among females in China was 28.51 per 100,000 in 2014 [2]. The age standardized incidence rate for breast cancer among females aged 35–69 years in China was projected to increase to 85 per 100,000 females in 2021 [3]. Identifying specific metabolites contributing to breast cancer development may improve its prevention and treatment measures [4].

Carnitine is an amino acid derivative. The endogenous form of carnitine in the human body is comprised of free carnitine and various forms of short-, medium- and long-chain acylcarnitines. While carnitine has many metabolic functions, its primary role is in the transport of long-chain fatty acids into the mitochondrial matrix, thereby inducing fatty acid oxidation [5]. Carnitine is also able to preserve membrane integrity [6], stabilize the physiological coenzyme A (CoASH)/acetyl-CoA ratio in the mitochondria, and reduce lactate production [7, 8].

Carnitine may be involved in the pathogenesis of cancer development. There is evidence suggesting that carnitine-induced fatty acid oxidation plays a critical role in the production of NADH, FADH2, NADPH and ATP, factors which could contribute to the stimulation of the growth of tumors [9–11]. It has been

observed that carnitine palmitoyltransferase I (CPTI) is overexpressed in numerous tumors, and also plays an important role in tumor neovascularization [12].

Although carnitine may be related to breast cancer development, existing epidemiological studies are scarce and those that have examined this potential association are limited in their sample size [13, 14]. Previously, a Turkish case-control study, consisting of 58 breast cancer cases and 30 healthy controls, reported that serum carnitine levels were lower in breast cancer cases after radiotherapy than in controls [13]. In addition, a case-control study of 30 breast cancer cases and 16 healthy controls in Korean found that higher plasma l-octanoylcarnitine levels were associated with lower breast cancer risk [14]. Given that limited epidemiological studies have investigated this research question, we used a 1:1 matched case-control study with a relatively large same size to examine the association between circulating carnitine levels and breast cancer in females.

Methods

Study setting and subjects

Similar to our previous study [15], we recruited all study participants from The First Affiliated Hospital of Jinzhou Medical University, Jinzhou, Liaoning, China. This hospital provides medical services for approximately 11.2 million people in west Liaoning.

The participants for this case-control study were recruited from the Department of Breast Surgery from The First Affiliated Hospital of Jinzhou Medical University during the time frame of November 2015 to September 2020. All participants were female, had a clear diagnosis for either breast cancer or non-breast cancer, had a valid carnitine measurement, and had complete and valid data on covariates (age, body mass index [BMI], age at menarche, hypertension diagnosis, type 2 diabetes diagnosis, history of cancer, smoker, alcohol consumption, family history of cancer, postmenopausal status, and parity). We excluded participants with current or past carnitine related treatments (i.e., l-carnitine). This research was approved by the institutional review board (IRB; Project #: 202007) at The First Affiliated Hospital of Jinzhou Medical University. We obtained written informed consent from all participants for the present study.

Confirmation of breast cancer cases and non-breast cancer controls

Breast cancer cancers cases and non-breast cancer controls recruited between November 2015 and September 2020 were all confirmed with a pathological test. The pathological stage of diagnosis for all breast cancer cases were assessed according to the 7th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis (TNM) classification method [16]. Histological tumor grades for breast cancer cases were determined using the most recent Chinese guideline for breast cancer [17]. We also assessed molecular subtypes of breast cancer (e.g., human epidermal growth factor receptor-2 [HER2] –enriched [estrogen receptors [ER]–, progesterone receptors [PR]–, and HER2+], luminal A [ER + and/or PR+, and HER2–], luminal B [ER + and/or PR+, and HER2+], and basal-like [ER–, PR–, and HER2–]) based on

established methods [18]. All controls were confirmed to be free of breast cancer with a pathological test and were matched 1:1 by age (± 1 year) to cases.

Blood collection and processing

We collected the fasting blood samples (time of fasting > 8 hours) from all participants using vacutainer tubes (red cap) in the morning. These whole blood samples were made into dried blood spot samples using dried blood filter paper. All dried blood spot samples were stored at -80 ^{o}C until assays were completed.

Carnitine measurement

The carnitine compounds considered in this study were: free carnitine (C0), acetylcarnitine (C2), propionylcarnitine (C3), malonylcarnitine (C3DC), butyrylcarnitine (C4), isovalerylcarnitine (C5), tiglylcarnitine (C5:1), hexanoylcarnitine (C6), octanoylcarnitine (C8), decanoylcarnitine (C10), decenoylcarnitine (C10:1), decadienoylcarnitine (C10:2), dodecanoylcarnitine (C12), myristoylcarnitine (C14), palmitoylcarnitine (C16), and octadecanoylcarnitine (C18). Details regarding the measurement method for circulating levels of carnitine are described elsewhere [19]. Briefly, we punched the dried blood spot papers into 3-mm (diameter) discs. These discs were extracted with ethanol and centrifuged (2 min at 1500g) to collect the supernatant. The supernatant was filtered and moved to 96-well plates. Standard carnitine (catalog number: NSK-A; Cambridge Isotope Laboratory, Tewksbury, MA) solution samples served as quality controls. These plates were dried under 50 ^{o}C pure nitrogen flow, incubated with 1-butanol/acetyl chloride mixture, and dried again at 50 ^{o}C pure nitrogen flow. Finally, mobile phase solution (80% acetonitrile aqueous solution) was used to dissolve dried samples, which were measured with liquid chromatography coupled with mass spectrometry (high performance liquid chromatography detector LC-20A [Shimadze, Japan] and tandem mass spectrometry detection system AB Sciex 4000 QTrap [AB Sciex, Framinham MA]); this platform is suggested to be able to sensitively detect biomolecules [20].

Ascertainment of covariates

Demographics (age and BMI), lifestyle factors (smoker and alcohol consumption), and medical history (age at menarche, postmenopausal status, hypertension diagnosis, type II diabetes diagnosis, personal history of cancer, family history of cancer, and parity) were considered as covariates for this study. BMI was calculated using the formula: measured weight (kg) / (measured height [m])^2. An individual was considered to have a diagnosis of hypertension if the measured systolic blood pressure was ≥ 140 mmHg or if the measured diastolic blood pressure was ≥ 90 mmHg [21]. A type 2 diabetes diagnosis was determined based on fasting plasma glucose testing, glucose tolerance testing, and A1C testing results [22]. Self-reported information on age at menarche, history of cancer, smoker, alcohol consumption, family history of cancer, postmenopausal status, and parity (subsequently categorized as 0, 1, 2, and 3+) were extracted from medical records.

Statistical analysis

All statistical analyses were performed using SPSS (version: 24.0; SPSS, Chicago, IL) and R (Version 3.5.3, R Foundation for Statistical Computing). Descriptive statistics were performed to characterize breast cancer cases and non-breast cancer controls. We used conditional logistic regression models to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the associations between 1 standard deviation (SD) increase in the various carnitine compound levels and breast cancer. The final conditional logistic regression models were adjusted for postmenopausal status and parity, because only these two factors were significantly associated with breast cancer at alpha = 0.05 under bivariate analysis with breast cancer. To address the issue of multiple testing, we also calculated the false discovery rates (FDRs) for all carnitines.

When certain carnitines were identified as significantly associated with breast cancer in the multivariable logistic regression models, the association of baseline characteristics with these carnitines in controls were analyzed in the multiple linear regression models. Subgroup analyses by pathological stage of diagnosis, tumor grades, and molecular subtypes were also performed. We tested for dose response by pathological stage of diagnosis and tumor grades in the associations between carnitine and breast cancer among cases using multiple linear regression models, in which continuous measures of carnitines were the independent variables, and pathological stages of diagnosis and tumor grades were dependent variables. *P* for interaction between molecular subtypes and carnitine levels were tested using the interaction term (molecular subtypes* carnitine levels [per 1-SD increase]) among cases in unconditional logistic regression models. All linear regression models were adjusted for age, BMI, age at menarche, hypertension diagnosis, type 2 diabetes diagnosis, history of cancer, smoker, alcohol consumption, family history of cancer, postmenopausal status, and parity.

Results

We identified 991 breast cancer cases and 991 non-breast cancer controls, with a mean age of 50.0 years (SD: 8.7 years) and 49.5 years (SD: 8.7 years), respectively (Table 1). A total of 332 (33.5%), 481 (48.5%), 164 (16.5%), and 14 (1.4%) breast cancer cases had pathologically confirmed diagnosis stages of I, II, III, and IV, respectively. There were 55 (5.5%), 609 (61.5%), and 128 (12.9%) cases with tumor grades of I, II, and III, respectively; 199 cases (20.1%) did not have information on tumor grades. There were 143 (14.4%), 192 (19.3%), 155 (15.6%), and 471 (47.5%) cases with basal-like, HER2-enriched, Luminal A, and Luminal B molecular subtypes, respectively; 30 (3.0%) cases did not have completed tests for molecular subtypes. A majority of the controls (96.5%) had a benign breast lump, while other controls had either a mastitis (2.1%), a benign accessory breast lump (0.7%), hyperplasia of mammary glands (0.5%), a benign axillary lump (0.1%), or a lipoma of the breast (0.1%).

Table 1
Characteristics for cases and controls

Variable	Breast Cancer Cases (N = 991)	Controls (N = 991)	*P*
Age (years)	50.0 (8.7)	49.5 (8.7)	0.217
Body mass index (kg/m^2)	24.3 (3.5)	24.2 (3.3)	0.553
Age at menarche (years)	15.2 (1.7)	15.1 (1.7)	0.340
Hypertension diagnosis (n, %)	110 (11.1)	130 (13.1)	0.169
Type 2 diabetes diagnosis (n, %)	38 (3.8)	26 (2.6)	0.127
History of cancer (n, %)	34 (3.4)	21 (2.1)	0.075
Smoker (n, %)	20 (2.0)	18 (1.8)	0.743
Alcohol consumption (n, %)	2 (0.2)	2 (0.2)	1.000
Family history of cancer (n, %)	44 (4.4)	49 (4.9)	0.595
Postmenopausal status (n, %)	407 (41.1)	355 (35.8)	0.016
Parity (n, %)			0.001
0	53 (5.4)	30 (3.0)	
1	645 (65.1)	670 (67.6)	
2	240 (24.2)	264 (26.6)	
3+	53 (5.4)	27 (2.7)	
Unless otherwise specified, variables are presented as the mean (standard deviation).			

Breast cancer cases were significantly associated with postmenopausal status and parity. Age, BMI, age at menarche, hypertension diagnosis, type 2 diabetes diagnosis, history of cancer, smoker, alcohol consumption, and family history of cancer were not significantly different between cases and controls.

Each SD increase in C3DC (OR 0.91; 95% CI 0.83-1.00), C10:1 (OR 0.87; 95% CI 0.79–0.96), and C10:2 (OR 0.90; 95% CI 0.82–0.99) level was associated with decreased odds of breast cancer (Table 2). However, higher C4 levels were associated increased risk of breast cancer (OR 1.12; 95% CI 1.02–1.23). No other carnitine compounds were associated with breast cancer. The FDRs for C3DC, C4, C10:1, and C10:2 were 0.172, 0.120, 0.064, and 0.139, respectively. The associations between C3DC, C4, C10:1, and C10:2 with breast cancer did not differ with stage of diagnosis or tumor grade (all *P* for trend > 0.1; Figs. 1–4). Subgroup analysis by molecular subtype suggests that the impact of C4 on breast cancer was higher for individuals with the luminal B subtype, but not for the other subtypes (*P* for interaction = 0.013; Fig. 1). However, we did not observe any evidence that molecular subtypes modified the associations of C4, C10:1, or C10:2 with breast cancer (Figs. 2–4).

Table 2

Multivariable logistic regression analysis[a] of the association between carnitine levels (per 1-SD increase) and breast cancer

Carnitine (Abbreviation)	Odds Ratio (95% Confidence Interval)	*P*	False Discovery Rate
Free carnitine (C0)	1.05 (0.96, 1.15)	0.298	0.659
Acetylcarnitine (C2)	1.04 (0.94, 1.16)	0.435	0.659
Propionylcarnitine (C3)	1.03 (0.94, 1.14)	0.494	0.659
Malonylcarnitine (C3DC)	0.91 (0.83, 1.00)	0.043	0.172
Butyrylcarnitine (C4)	1.12 (1.02, 1.23)	0.015	0.120
Isovalerylcarnitine (C5)	0.98 (0.89, 1.08)	0.722	0.825
Tiglylcarnitine (C5:1)	0.98 (0.89, 1.08)	0.680	0.825
Hexanoylcarnitine (C6)	0.99 (0.91, 1.09)	0.880	0.880
Octanoylcarnitine (C8)	0.94 (0.86, 1.03)	0.196	0.627
Decanoylcarnitine (C10)	0.99 (0.90, 1.08)	0.810	0.864
Decenoylcarnitine (C10:1)	0.87 (0.79, 0.96)	0.004	0.064
Decadienoylcarnitine (C10:2)	0.90 (0.82, 0.99)	0.026	0.139
Dodecanoylcarnitine (C12)	1.03 (0.94, 1.13)	0.483	0.659
Myristoylcarnitine (C14)	1.04 (0.94, 1.14)	0.448	0.659
Palmitoylcarnitine (C16)	1.06 (0.95, 1.17)	0.288	0.659
Octadecanoylcarnitine (C18)	1.04 (0.95, 1.14)	0.372	0.659

[a]Models were adjusted for postmenopausal status and parity.

In the multivariable model, C3DC and C10:1 were positively associated with greater number of parity, but not with other characteristics among controls (Additional file 1). There were no significant associations between C10:2 and baseline characteristics. C4 was only associated with age.

Discussion

This 1:1 individually matched case-control study found that C3DC, C4, C10:1, and C10:2 were significantly associated with increased risk of breast cancer. Stage of diagnosis, tumor grade, and molecular subtype did not modify the associations between C3DC, C10:1, and C10:2 with breast cancer. The relationship between C4 and breast cancer did not significantly differ across various stages of

diagnosis or tumor grades. Although, C4 was more strongly associated with breast cancer among individuals with a luminal B subtype than other molecular subtypes.

To the best of our knowledge, this is the first large epidemiologic study examining the impact of 16 types of carnitine on breast cancer in females. We identified four types of carnitine, including C3DC, C4, C10:1, and C10:2, to be significantly associated with breast cancer, though the relationship differed between the types of carnitine. We observed negative associations with breast cancer for C3DC, C10:1, and C10:2, which is partly consistent with a previous study where serum carnitine levels were lower in breast cancer cases than in controls after radiotherapy [13]. A previous case-control study identified l-octanoylcarnitine as a candidate biomarker for breast cancer [14]. This finding is not in line with our study, in which C8 was not related to breast cancer. The underlying reasons for this discrepancy are still unclear. However, it may be partially attributed to the differences in the study population (Korean vs. Chinese), sample sizes (40 cases and 30 controls vs. 991 cases and 991 controls) and study designs (unmatched case-control study vs. matched case-control study) between the previously published studies and present study.

We report mixed findings between various types of carnitine and breast cancer. The specific biological mechanisms for the relationship identified between C3DC, C4, C10:1, and C10:2 with breast cancer are still unclear. On the one hand, carnitine is able to transport long-chain fatty acid into the mitochondria. This induces fatty acid oxidation via the catalytic effects of CPTI [5, 12], which fuels breast cancer growth [9–11, 23]. This mechanism is likely responsible for the positive association between C4 and breast cancer. On the other hand, carnitine balances physiologic CoASH/acetyl-CoA ratio [7, 8]. A balanced CoASH/acetyl-CoA ratio removes excessive short- and medium-chain fatty acids, which can be potentially toxic, from the mitochondria [24]. This partially supports the protective effects of C3DC, C10:1, and C10:2 on breast cancer.

Our study had several strengths. This study has a relatively large sample size; this ensures the reliability and accuracy of our results. The individually 1:1 matched case-control study design would exclude the potential confounding factor of age. We excluded individuals with carnitine related treatments to rule out the influence of potential medical effects on circulating carnitine levels. We collected fasting blood samples to remove the influence of diet on carnitine measurements. Lastly, all blood samples were drawn in the morning to control for potential impacts that the circadian rhythm may have on carnitine levels [25].

Our findings should be interpreted within the context of a number of limitations. First, due to the case-control study design, we cannot make a causal inference about the relationships of C3DC, C4, C10:1, or C10:2 with the incidence of breast cancer. Second, this study did not have data on a number of risk factors that have been identified for breast cancer, such as physical activity, hormone replacement therapy, and diethylstilbestrol use. Potential residual confounding cannot be completely ruled out. Third, a majority of the controls (96.5%) in this study had a benign breast lump. It is unclear whether similar conclusions would have been found when healthy controls were used. Lastly, our findings may not be able to generalizable as we used a hospital-based population, which may be influenced by selection bias.

Conclusions

Higher levels of C3DC, C10:1, and C10:2 were found be protective factors for breast cancer. In contrast, higher C4 levels were identified as a risk factor for breast cancer. Circulating levels of C3DC, C4, C10:1, and C10:2 may have clinical implications for breast cancer risk assessment. Carnitine levels can be modified via the consumption of animal-based products and l-carnitine supplements [26, 27]. Therefore, a supplementation of specific carnitine compounds (e.g., C3DC, C10:1, and C10:2) can be potential therapeutic and/or prevention strategies for breast cancer following validation of our findings in human trials.

Abbreviations

Body mass index-BMI, Coenzyme A-CoASH, free carnitine-C0, acetylcarnitine-C2, propionylcarnitine-C3, malonylcarnitine-C3DC, butyrylcarnitine-C4, isovalerylcarnitine-C5, tiglylcarnitine-C5:1, hexanoylcarnitine-C6, octanoylcarnitine-C8, decanoylcarnitine-C10, decenoylcarnitine-C10:1, decadienoylcarnitine-C10:2, dodecanoylcarnitine-C12, myristoylcarnitine-C14, palmitoylcarnitine-C16, octadecanoylcarnitine-C18, false discovery rates-FDRs, odds ratio-OR, confidence interval-CI, human epidermal growth factor receptor-2-HER2, estrogen receptors-ER, progesterone receptors-PR, carnitine palmitoyltransferase I-CPTI

Declarations

Ethics approval and consent to participate: We acknowledge the institutional review board at The First Affiliated Hospital of Jinzhou for approving this research (Project #: 202007). Written informed consent was obtained from all participants in the study.

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and/or analysed during the current study are not publicly available due to ethical reasons but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Conception, design, and analysis (WT, SY and JZ); interpretation of data (all authors); drafting the article (JZ); critically revising the article for important intellectual content (all authors); final approval of the version to be published (all authors); and agreement to be accountable for all aspects of the work (all authors).

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Figures

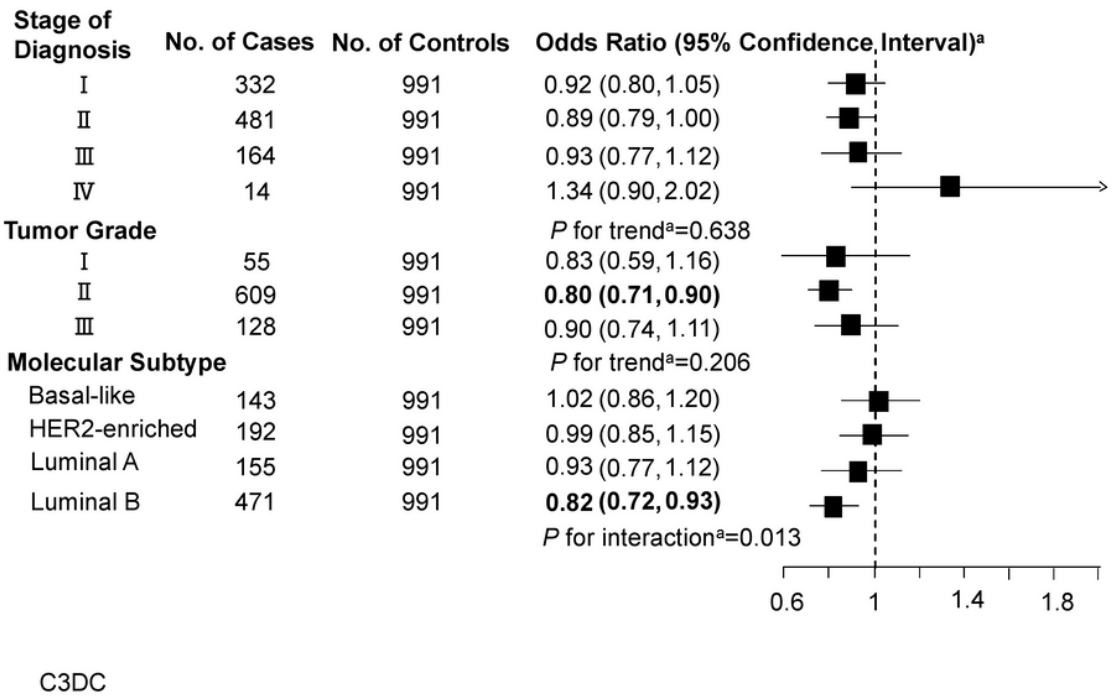

Figure 1

Association between malonylcarnitine (C3DC; per 1-SD increase) and breast cancer by pathological stage of diagnosis, tumor grade, and molecular subtype aAll models were adjusted for age, body mass index, age at menarche, hypertension diagnosis, type 2 diabetes diagnosis, history of cancer, smoker, alcohol consumption, family history of cancer, postmenopausal status, and parity. Bold values are statistically significant at α = 0.05.

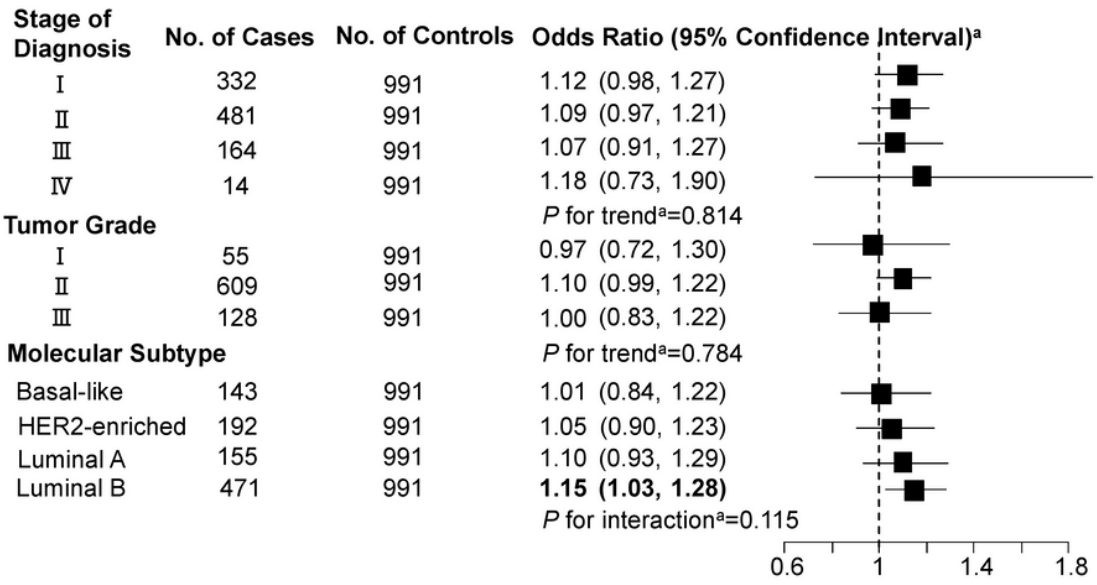

Figure 2

Association between butyrylcarnitine (C4; per 1-SD increase) and breast cancer by pathological stage of diagnosis, tumor grade, and molecular subtype aAll models were adjusted for age, body mass index, age at menarche, hypertension diagnosis, type 2 diabetes diagnosis, history of cancer, smoker, alcohol consumption, family history of cancer, postmenopausal status, and parity. Bold values are statistically significant at α = 0.05.

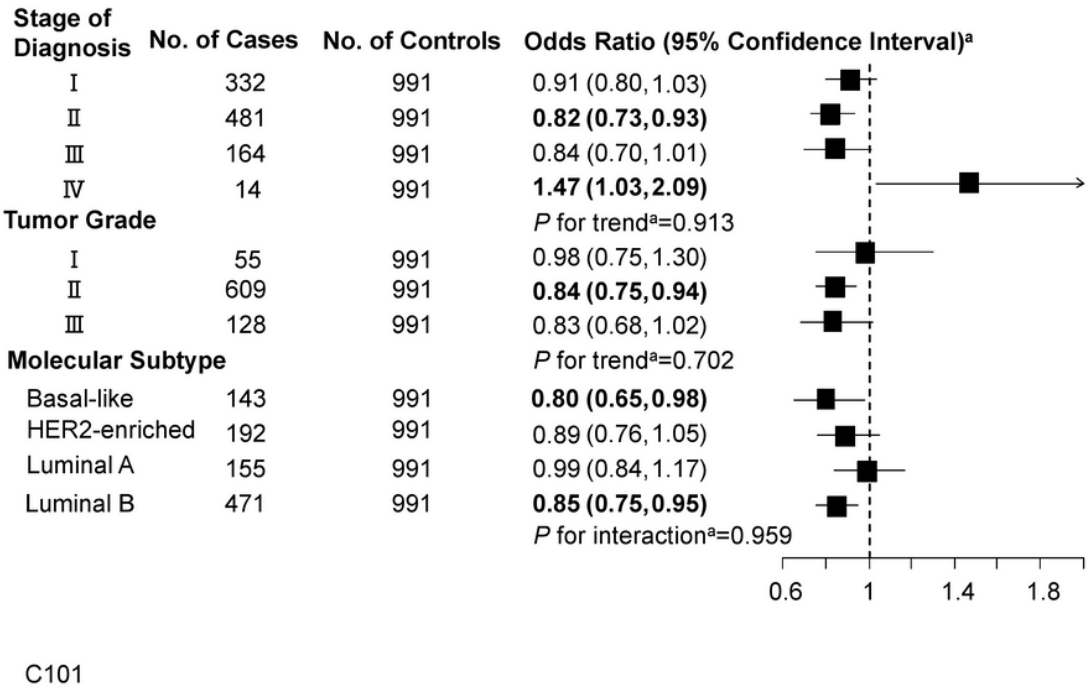

Figure 3

Association between decenoylcarnitine (C10:1; per 1-SD increase) and breast cancer by pathological stage of diagnosis, tumor grade, and molecular subtype aAll models were adjusted for age, body mass index, age at menarche, hypertension diagnosis, type 2 diabetes diagnosis, history of cancer, smoker, alcohol consumption, family history of cancer, postmenopausal status, and parity. Bold values are statistically significant at α = 0.05.

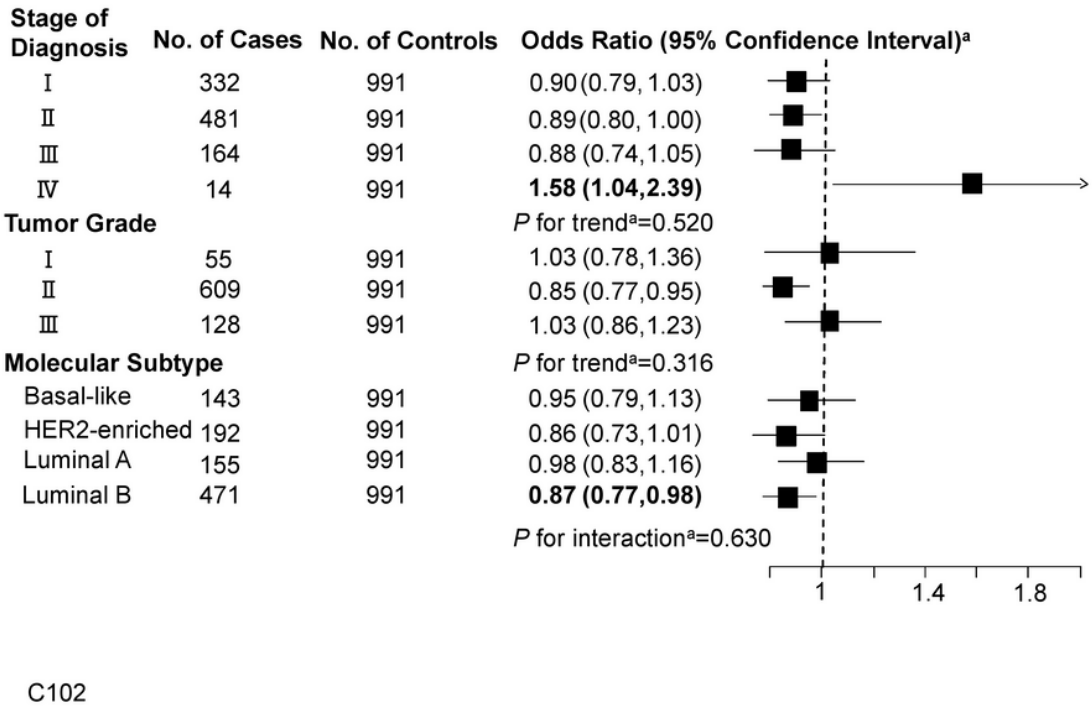

Figure 4

Association between decadienoylcarnitine (C10:2; per 1-SD increase) and breast cancer by pathological stage of diagnosis, tumor grade, and molecular subtype aAll models were adjusted for age, body mass index, age at menarche, hypertension diagnosis, type 2 diabetes diagnosis, history of cancer, smoker, alcohol consumption, family history of cancer, postmenopausal status, and parity. Bold values are statistically significant at α = 0.05.

Supplementary Files

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- Additionalfile1.docx