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Association of inflammatory dietary pattern with health-related quality of life among breast cancer survivors

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Abstract

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Chronic inflammation after cancer treatment may reduce the quality of life of cancer survivors and diet has been suggested to play a role in predisposition of chronic inflammatory condition. However, little is known about the association between inflammatory diet and the health-related quality of life (HRQOL) among breast cancer survivors. Thus, this study aimed to derive an inflammatory dietary pattern and examined its association with HRQOL among breast cancer survivors. This study included 454 female breast cancer survivors aged from 33 to 81 years. Information of food intakes were obtained using 3-day dietary records or food

frequency questionnaire (FFQ) for those who did not provide 3-day dietary records. Self-perceived HRQOL levels were assessed using the Short Form 36 (SF-36) Health Survey. The reduced rank regression (RRR) was used to derive the inflammatory dietary pattern among 158 breast cancer survivors that maximizes the explained variation of high-sensitivity C-reactive protein (hsCRP), interleukine-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels. A generalized linear model (GLM) was used to estimate the least square means (LS-means) and 95% confidence intervals (CIs) of the HRQOL levels according to the inflammatory dietary pattern scores. The inflammatory dietary pattern was characterized as a high intake of red meat, white rice and noodles and a low intake of seafood-based soup. Higher inflammatory dietary pattern scores were associated with lower levels of the physical component summary, role-physical and bodily pain domains in breast cancer survivors diagnosed with stage II or III breast cancer. For physical component summary domain, the LS-means (95% CIs) were 51.06 (49.07-53.06) in the bottom quartile and 47.09 (45.14-49.04) in the top quartile (*P* for trend=0.03). For role-physical domain, the LS-means (95% CIs) were 80.11 (72.90-87.32) in the bottom quartile and 64.06 (57.00-71.12) in the top quartile (*P* for trend=0.01). For bodily pain domain, the LS-means (95% CIs) were 79.42 (73.45-85.39) in the bottom quartile and 65.71 (59.87-71.56) in the top quartile (*P* for trend=0.01). However, higher inflammatory dietary pattern scores were associated with higher levels of role-emotional, social functioning and role-physical domains in breast cancer survivors diagnosed with stage I breast cancer. For role-emotional domain, the LS-means (95% CIs) was 75.56 (69.81-81.30) in the bottom quartile and 82.95 (77.05-88.85) in the top quartile (*P* for trend=0.03).

For social functioning domain, the LS-means (95% CIs) was 82.75 (78.16-87.34) in the bottom quartile and 89.48 (84.77-94.19) in the top quartile (*P* for trend=0.04). For role-physical domain, the LS-means and (95% CIs) was 72.83 (66.87-78.78) in the bottom quartile and 81.42 (75.27-87.58) in the top quartile (*P* for trend=0.02). In conclusion, inflammatory dietary pattern was characterized as high intakes of red meat, white rice and noodles, and low intakes of seafood-based soup. Increasing scores of inflammatory dietary pattern were associated with decreasing levels of the physical component summary, role-physical and bodily pain domains in breast cancer survivors diagnosed with stage II or III breast cancer. Although the present study did not infer a causal relationship between inflammatory dietary pattern and the HRQOL levels, breast cancer survivors and their caregivers may need to consider avoiding pro-inflammatory diet to improve HRQOL status. This study warrants further prospective investigation to elucidate whether the inflammatory dietary pattern worsens the HRQOL among breast cancer survivors and whether the association is differed by cancer stage.

Keyword: Breast cancer survivors, Inflammatory dietary pattern, Health-related quality of life (HRQOL), Reduced rank regression (RRR), High-sensitivity C-reactive protein (hsCRP), Interleukin-6 (IL-6), and Tumor necrosis factor-α (TNF-α)

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List of Abbreviations

HRQOL	Health-related quality of life
CRP	C-reactive protein
DII®	Dietary inflammatory index™
BMI	Body mass index
CIs	Confidence intervals
HR	Hazard ratio
TNF-α	Tumor necrosis factor-α
OR	Odds ratio
hsCRP	High-sensitivity C reactive protein
SF-36	Short-form 36
SD	Standard deviation
IL-6	Interleukin-6
FFQ	Food frequency questionnaire
CAN-pro	Computer Aided Nutritional Analysis Program
MET	Metabolic equivalent task
ER	Estrogen receptor status
RRR	Reduced rank regression
GLM	Generalized linear model
LS-means	Least square-means
FDR	False discovery rate

I. Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide (Bray et al.) and the second common cancer among women in South Korea with 55.9 per 100,000 of age-standardized incidence rate in 2015(Korea Central Cancer Registry., 2017). Because of the improvement in treatment and early detection of breast cancer, 5-year age-standardized relative survival rate has increased from 78% in 1993-1995 to 92% in 2011-2015 (Korea Central Cancer Registry., 2017), resulting in increasing attention to life after cancer treatment for breast cancer survivors.

Quality of life and physical and psychological well-being are important aspects of breast cancer survivorship. Evidences from prospective studies has suggested that a better health-related quality of life (HRQOL) has improved breast cancer survival (De Aguiar et al., 2014; Epplein et al., 2011; Montazeri, 2009). Several epidemiologic studies have reported that chronic inflammation is associated with poor mental health and physical fatigue (Alfano et al., 2012; Bower et al., 2011; Haapakoski et al., 2015; Schubert et al., 2007).

Several studies have reported that breast cancer patients had a higher inflammation status than the healthy general population (Jiang et al., 2000; Kozlowski et al., 2003). Pro-inflammatory cytokines may facilitate tumor progression and metastasis (Grivennikov et al., 2010). A recent meta-analysis also suggested that C-reactive protein (CRP), systematic marker of chronic

inflammation, was associated with poor survival among breast cancer patients (Guo et al., 2016).

Chronic inflammation may be driven by failure to resolve acute inflammation or by continuous exposure to factors that trigger or aggravate inflammation, and dietary components have the potential to modulate the predisposition of chronic inflammatory conditions (Calder et al., 2013).

When investigating the association of diet with health outcomes, the overall dietary pattern rather than single nutrients or foods had emerged in nutritional epidemiology due to several conceptual and methodological limitations (Hu, 2002). Recent studies have suggested that a dietary pattern associated with inflammation increases the risk of several cancers and cancer mortality. In a recent meta-analysis, the dietary inflammatory index™ (DII®), developed based on literature reviews (Shivappa et al., 2014), was associated with increasing risk of overall cancer incidence and mortality (Fowler et al., 2017), and increasing risk of breast cancer (Wang et al., 2018). The empirical dietary inflammatory index, developed from the Nurses' Health Study cohort (Tabung et al., 2016), was directly associated with the risk of colorectal cancer in the cohort study (Tabung et al., 2018). Those studies may imply that inflammation is a potential mediator between diet and health outcomes.

The aim of this study is to empirically derive the inflammatory dietary pattern among Korean breast cancer survivors and examined whether the inflammatory dietary pattern was associated with the HRQOL levels.

II. Literature Review

1. Statistics of breast cancer

Breast cancer is the second most common cancer worldwide. About 2.1 million cases were newly diagnosed with breast cancer and the incidence rate of breast cancer was 46.3% in 2018 (Bray et al., 2018). Lung cancer is the most commonly diagnosed cancer, followed by breast cancer, and the difference in number of cases of lung and breast cancer is only about 5,000 cases (Bray et al., 2018). Breast cancer incidence rates were relatively high in more developed countries including Australia/New Zealand, Northern Europe (e.g., the United Kingdom, Sweden, Finland and Denmark), Western Europe (Belgium, the Netherlands and France), Southern Europe (Italy), and North America (Bray et al., 2018). South Korea (hereafter, Korea) showed slightly higher incidence rates than Japan. Although breast cancer is the second most common cancer, it ranks fifth as a cause of death among cancers due to a relatively favorable prognosis worldwide. Still, breast cancer is the most frequent cause of death from cancer among women in 2018 worldwide (626,979 deaths) (Bray et al., 2018).

The incidence of breast cancer is also pronounced in Korea and breast cancer ranked second for common cancer among women. The age-standardized incidence rates from 1999 to 2015. The incidence rate of breast cancer among women in Korea has annually increased and was 55.9 per 100,000 in 2015 (Korea Central Cancer Registry., 2017). However, the 5-year relative survival rates reached to

92.3% in 2015 (Korea Central Cancer Registry., 2017). Both increase in incidence and survival rate resulted in an increased number of breast cancer survivors in Korea.

2. The role of diet in development and prognosis of breast cancer

Diet has been known to be related with various disease outcomes and prognosis. In a meta-analysis among studies that investigated the effect of diet quality on health outcomes, a healthy diet was associated with a reduced risk of all-cause mortality, cardiovascular disease, cancer, type 2 diabetes and neurodegenerative disease among cancer survivors (Schwingshackl et al., 2018). A review study summarized various potential mechanisms of dietary pattern including modulating breast density, sex hormones, body mass index (BMI), oxidative stress and inflammation. These mechanisms are suggested to impact the risk of breast cancer risk and prognosis (Thomson et al., 2009). In a meta-analysis, healthy dietary pattern was associated with a lower risk of breast cancer, while dietary pattern high in an alcoholic drink was associated with a higher risk of breast cancer (Brennan et al., 2010).

Breast cancer prognosis may also be affected by diet including fat, fiber and micronutrient or dietary pattern (Patterson et al., 2010). Breast cancer survivors may be motivated to change their lifestyle including diet after diagnosis (Song et al., 2016; Velentzis et al., 2011). Epidemiologic evidence have supported that changes in a pre- and post-diagnostic diet was associated with breast cancer prognosis. In the Women's Health Initiative cohort study of US postmenopausal women, those who changed their diet from pre to post-diagnosis showed a 66% higher risk of death from breast cancer (95% confidence intervals (CIs): 1.09-2.52) compared to those who did not change their diet (Sun et al., 2018). Also,

several prospective studies found that a post-diagnostic diet was associated with death from breast cancer. Multiethnic cohort study found that adherence to the Healthy Eating Index-2005 scores after breast cancer diagnosis was inversely associated with reduced risk of overall and breast cancer-specific mortality (overall mortality hazard ratio (HR) 0.40; 95% CIs 0.17-0.94 and breast cancer-specific mortality HR 0.12; 95% CIs 0.02-0.99) (George et al., 2011). In the Life After Cancer Epidemiology study, those who consumed larger amounts of high-fat dairy (≥1.0 servings/day) was associated with the increased risk of breast cancer-specific mortality (HR 1.49; 95% CIs 1-2.24) and risk of all-cause mortality (HR 1.64; 95% CIs 1.24-2.17) (Kroenke et al., 2013). Other prospective cohort studies also reported the healthy diet after diagnosis was associated with decreased risk of overall mortality, although they were not associated with breast cancer-specific mortality (George et al., 2014; Kwan et al., 2009)., a review of epidemiologic studies summarized that a healthy diet had the potential to improve the prognosis of breast cancer, while a 'Western' diet may be associated with poor breast cancer prognosis (Jochems et al., 2018).

3. Quality of life of breast cancer survivors

Because the incidence rates and the 5-year age-standardized relative survival rate of breast cancer increased in Korea (Korea Central Cancer Registry., 2017), the number of breast cancer survivors has increased rapidly (Ho et al., 2018). This has resulted in increasing attention to the quality of life after cancer treatment of breast cancer survivors.

The HRQOL status tended to improve with time since diagnosis (Ho et al., 2018). However, evidence revealed that the HRQOL of breast cancer survivors were poorer than that of the general population (Ho et al., 2018; Lee et al., 2011). The HRQOL of breast cancer survivors includes physical and mental functioning as symptoms or conditions following cancer treatment. A study that investigated the occurrence of fatigue of breast cancer survivors found that about one third of the breast cancer survivors had severe fatigue, which was associated with higher levels of depression, pain, and sleep disturbance (Bower et al., 2000). The fatigue was more pronounced with menopausal symptoms and fatigued women were more likely to have been treated with chemotherapy (Bower et al., 2000). A prospective study reported that long-term and disease-free survivors had high levels of functioning and quality of life years after treatment. However, symptoms of vaginal dryness and urinary incontinence increased while sexual activity decreased (Ganz et al., 2002). Also, participants had systematic adjuvant therapy had poorer status in several domains of the quality of life compared to those who had no past systematic adjuvant therapy (Ganz et al., 2002). A systematic review study reported that most of the breast cancer survivors experienced specific symptoms that may

affect the HRQOL, and chemotherapy, widely used to treat breast cancer was the one of the negative predictors of the HRQOL (Mols et al., 2005). Another review of Asian studies concluded that the HRQOL improves overtime after diagnosis (Ho et al., 2018). However, patients with comorbidities, treated with chemotherapy, with less social support and with more unmet needs, had worse HRQOL while other factors including the type of surgery, radiotherapy, hormone therapy and unmet sexuality needs showed inconsistent associations with the HRQOL levels (Ho et al., 2018).

The HRQOL of cancer patients may have an impact on cancer survivorship. A review study on the quality of life as prognostic indicators of cancer survival concluded that several aspects of the quality of life predicted survival times in breast cancer patients (Montazeri, 2009). A prospective cohort study also found that women with a worse future perspective level had a higher risk of mortality than women with a better future perspective level (HR 3.46, 95% CIs 1.36-8.79) (De Aguiar et al., 2014). Another prospective study reported that women in the top tertile of social well-being quality of life score had a lower risk of mortality and recurrence of breast cancer than women in the bottom tertile (HR 0.62, 95% CIs 0.46-0.85 and HR 0.52, 95% CIs 0.38-0.71, respectively) (Epplein et al., 2011).

4. Inflammatory dietary pattern and health-related quality of life among breast cancer survivors

Evidence have shown that the levels of inflammatory biomarkers increased after cancer treatment among breast cancer patients (Bower et al., 2011; Pusztai et al., 2004). A quantitative review study that summarized the associations of inflammatory markers including circulating levels of inflammatory biomarkers in cancer patients, reported their associations with increasing cancer-related fatigue (Schubert et al., 2007). Similarly, several epidemiologic studies examined the associations between inflammatory biomarker levels and HRQOL. Another cross-sectional study found that clinical symptoms including fatigue and sleep disturbance elevated after the breast cancer treatment and fatigue was associated with high levels of soluble tumor necrosis factor (TNF) receptor II, particularly in the group treated with chemotherapy (Bower et al., 2011). Also, breast cancer survivors in the highest tertile of C-reactive protein CRP level had 1.8 times greater risk of fatigue compared to those in the lowest tertile (odds ratio (OR) 1.8, 95% CI 1.10-2.10) (Alfano et al., 2012). Similarly, among breast cancer patients after a year from radiotherapy, CRP, interleukin-1 receptor antagonist and soluble TNF receptor II were independent risk factors of fatigue (Xiao et al., 2017).

Dietary factors modulate inflammatory status through various mechanisms including decreasing inflammatory mediator (ω-3 fatty acids, vitamin E, plant flavonoids), reducing the production of harmful oxidants (vitamin E and other antioxidants), and enhancing gut barrier function and anti-inflammatory responses (prebiotics and probiotics) (Calder et al., 2009). Also, a review study that

summarized available evidence of human studies suggested that the intakes of magnesium, fiber, ω-3 polyunsaturated fatty acids, monounsaturated fatty acids, flavonoids, and carotenoids from food were associated with lower levels of inflammatory markers, whereas the intakes of saturated fatty acid, trans-fatty acid, high-glycemic index (GI) carbohydrates, and a high ω-6/ω-3 polyunsaturated fatty acids ratio were associated with high levels of inflammation (Bosma-den Boer et al., 2012; Galland, 2010).

As aforementioned, since a dietary pattern, rather than a single food or a nutrient, has emerged in nutritional epidemiology due to several conceptual and methodological limitations (Hu, 2002), the effects of dietary pattern on various disease endpoints have been studied. However, only a few studies considered inflammation as a biological pathway between dietary pattern and the HRQOL levels. In a cross-sectional pilot study of breast cancer survivors, the Healthy Eating Index-2010 diet score was inversely correlated with an inflammatory biomarker with marginal significance only in women with prior chemotherapy. However, no relationship was found with the HRQOL scores (Orchard et al., 2018). With regard to mental health, the Nurses' Health Study found that the inflammatory dietary pattern was associated with increased risk of depression among women (Lucas et al., 2014). Also, a recent meta-analysis reported that the lowest adherence to DII® in comparison to the highest adherence was associated with the lower risk of depressive outcomes (OR 0.71, 95% CIs 0.60-0.84) (Lassale et al., 2018).

III. Materials and Methods

1. Study population

The flow diagram of study population included in the present study is shown in Figure 1. Participants of this study comprised 638 female breast cancer survivors with stage I to III who answered structured questionnaires during 2015 to 2017 from 6 hospitals in Korea. Participants who had undergone surgery less than a year ago from the date of consent (n=8), who had recurrence of breast cancer or other cancers before enrollment (n=36), who had any missing data of the aforementioned criteria (n=1), who did not complete a dietary assessment (n =29), or who had levels of inflammatory biomarkers considered as an acute inflammation high-sensitivity C-reactive protein (hsCRP) level>10mg/L (Pearson et al., 2003) or had levels out of detectable range (n=76) were excluded from the analysis. Among those eligible participants (n=488), participants who did not complete the Short Form 36 (SF-36) health survey version 2.0 (n=31) or who reported an implausible level of energy intakes (±3 standard deviation (sd) from the mean value of the log transformed reported energy intake) (n=3) were further excluded. As a result, a total of 454 breast cancer survivors for inflammatory dietary pattern and HRQOL analysis were included.

To derive inflammatory dietary pattern, a total of 158 participants whose levels of hsCRP, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured

and who had a reasonable level of energy intake (within 3sd from the mean value of the log transformed reported energy intake) were included.

The National Cancer Center, Chonbuk National University Hospital, Soonchunhyang University Hospital, Keimyung University Dongsan Medical Center, Konkuk University Medical Center and Samsung Medical Center Institutional Review Boards approved the study protocol and all participants provided written informed consent at the date of consent.

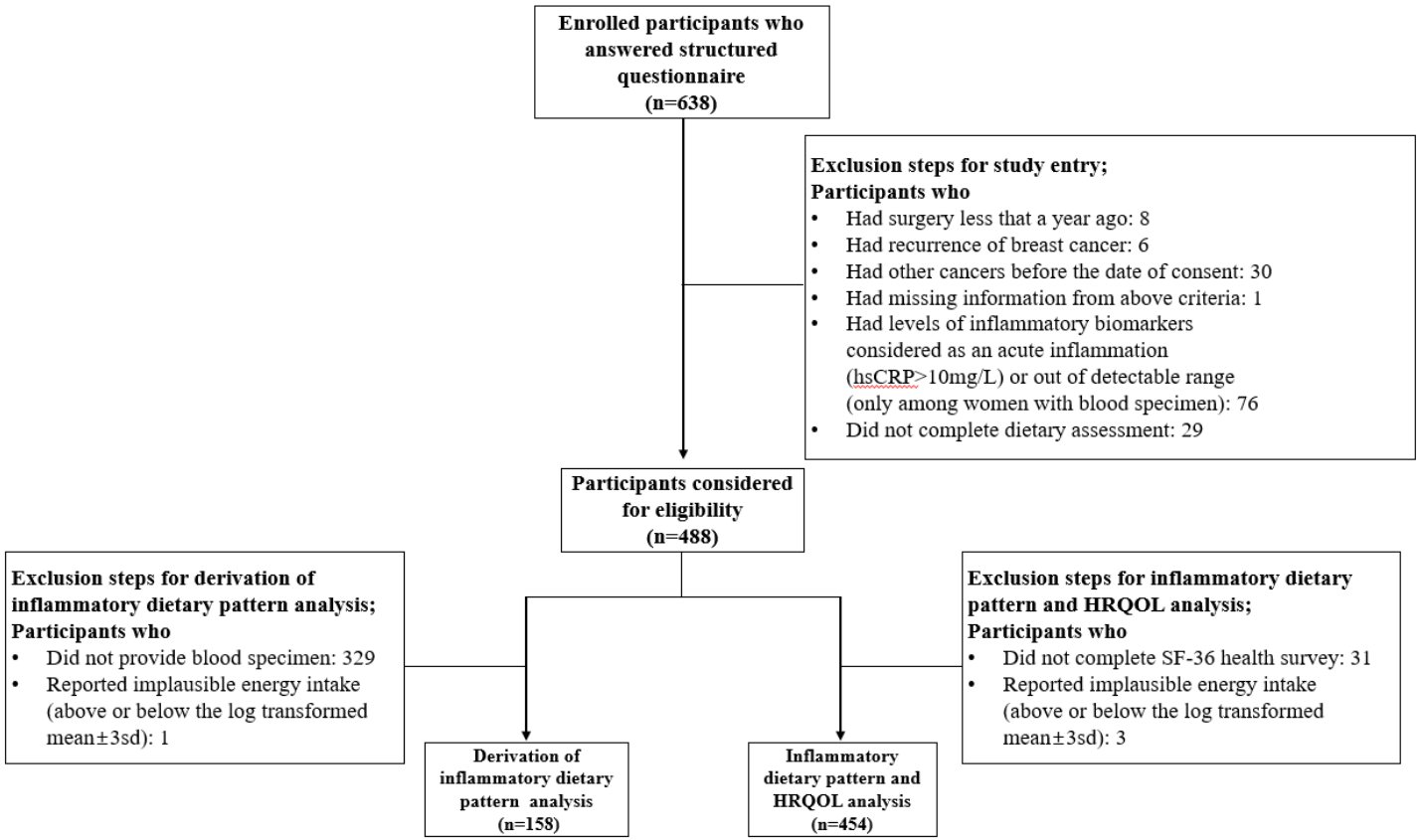

Figure 1. Flow diagram of study population included in the present study

2. Outcome assessment

The HRQOL levels were assessed using the SF-36 health survey version 2.0 (Maruish, 2011; Ware, 2000). Briefly, the SF-36 health survey is a multipurpose, short-form health survey with 36 questions that yields an eight-scale profile of functional health and well-being that includes; vitality, role-emotional, social functioning, mental health, physical functioning, role-physical, bodily pain and general health scales (Ware, 2000). The aggregates of the health domain scales are referred to as component summary measures and are divided into the mental component summary and physical component summary (Ware, 2000). Higher scores of all domains in the SF-36 health survey indicate better HRQOL levels.

3. Assessment of dietary, lifestyle and clinical information

Dietary intakes of participants were assessed using either 3-day dietary records or the food frequency questionnaire (FFQ), which was developed for Korean breast cancer survivors in 2016.(Shin et al., 2016) A total of 274 participants provided 3-day dietary records and 180 participants provided FFQs. Participants were asked to record all foods and beverages consumed in two weekdays and at least one weekend day using the 3-day dietary records. Food photograph booklets were provided to help participants estimate the portion size of foods. Food and nutrient intakes from 3-day dietary records were calculated using the Computer Aided Nutritional Analysis Program (CAN-pro) version 4.0 (The Korean Nutrition Society, Seoul, Korea). Participants answered questions about frequency and portion size of food items listed on the FFQ to report their usual intakes of 123

food and beverage items over the last 12 months with a 9-frequency scale ranging from ‘never or almost never’ to ‘three times per day’ (Shin et al., 2016). Daily intake (g/day) of each food was calculated by averaging the 3-day intakes for 3-day dietary records and by multiplying the daily frequency with portion size for FFQ.

Alcohol drinking status (current drinker, past drinker and never drinker), frequency (5 frequency scales from ‘less than once a month’ to ‘everyday’) and cups per serving of alcohol drinking (6 serving size scales from ‘less than a cup’ to ‘more than 10 cups’) was specifically asked among current and past drinkers. Ethanol intake (g/day) was calculated by multiplying the reported frequency with the portion size and 14g of pure ethanol contained in one alcoholic drink-equivalent (Bowman, 2014). Participants were asked to report their age and current weight and height. The body mass index (BMI) was calculated by dividing the weight (kg) by the height squared (m^2). Participants were also asked about education level, smoking status, and use of supplement. For physical activity, the type, duration (minutes) and frequency (times/week) of exercise were collected and then the metabolic equivalent of task (MET)-hours/week was calculated by multiplying the MET value of each specific type of activity with the frequency and duration (hours) of exercise, and then summing all the calculated MET-hours per week (Ainsworth et al., 2011).

Clinical information including the date of diagnosis and surgery, recurrence of breast cancer, other diagnosed cancers before enrollment, menopausal status at diagnosis, breast cancer stage, types of adjuvant therapy, and estrogen receptor (ER) status were obtained from medical records of each hospitals.

4. Assessment of inflammatory biomarkers

The plasma hsCRP levels (mg/L) were measured using the particle-enhanced immunoturbidimetric assay with Cobas 8000 C702 (Roche, Germany) and plasma IL-6 and TNF-α levels (pg/mL) were measured using the multiple cytokine assay with Bio-Plex Pro Human Cytokine 8-plex (Bio-Rad, USA). The overall inter-assay coefficients of variation was 2.99% for hsCRP and overall intra-coefficients of variation were 28.65% for IL-6 and 15.60% for TNF- α.

5. Statistical methods

5.1. Derivation of the inflammatory dietary pattern

To derive the inflammatory dietary pattern, foods from 3-day dietary records was combined into 43 food groups based on their nutrients composition and culinary methods. A reduced rank regression (RRR) (Hoffmann, Schulze, et al., 2004) was used to derive the inflammatory dietary pattern that identifies linear functions of independent variables that explain as much variation of dependent variables (levels of hsCRP, IL-6 and TNF-α) as possible. The 43 food groups and ethanol intakes were included into the RRR model. The levels of hsCRP and IL-6 were log-transformed to improve the normality of distribution. The levels of three biomarkers were adjusted for age using residual method (Willett, 1998). As a result, three dietary patterns were obtained because the number of dietary patterns extracted from the RRR is equal to the number of independent variables included.

The first factor extracted from the RRR was used for subsequent inflammatory dietary pattern and HRQOL analysis because it explains the largest variation of response variables (Hoffmann, Schulze, et al., 2004). To apply the inflammatory dietary pattern by generating inflammatory dietary pattern scores to whole population, food groups of obtained dietary pattern were selected by retaining food groups with absolute value of factor loading greater than 0.25, the level of factor loading considered to be reasonably high enough to construct robust scores in current analysis. Finally, an inflammatory dietary pattern score was calculated as following formula;

$$\text{Inflammatory dietary pattern score} = \sum(\text{standardized intake of food} \times \text{factor loading of food})$$

Higher inflammatory dietary pattern score indicates higher intakes of inflammatory dietary pattern.

5.2. Analysis of inflammatory dietary pattern score

A generalized linear model (GLM) was used to estimate the least squares-means (LS-means) and 95% CIs of levels of inflammatory biomarkers according to the quartiles of the inflammatory dietary pattern scores. Then, the relative concentrations and 95% CIs of the quartiles of the inflammatory dietary pattern scores were calculated as a ratio between the LS-means of each subsequent quartile of inflammatory dietary pattern scores and the lowest quartile. Linear trends between the inflammatory dietary pattern scores and levels of inflammatory

biomarkers were tested for significance by treating median value of each quartiles of the inflammatory dietary pattern scores as a continuous variable.

The LS-means and 95% CIs of HRQOL scores across the quartiles of inflammatory dietary pattern scores were estimated using the GLM. Linear trends between the inflammatory dietary pattern scores and HRQOL scores were tested for significance by treating median value of each quartile of the inflammatory dietary pattern scores as a continuous variable. Age (year, continuous), total energy intake (kcal/day, continuous), BMI at enrollment (kg/m², <23, 23-<25, ≥25), use of supplement (yes, no), chemotherapy (yes, no), time since surgery (years, <2, 2-<5, ≥5), breast cancer stage and center were adjusted in the multivariate models for HRQOL domains related to physical health dimensions, and further adjusted for physical activity (MET-hours/week, quartile) for HRQOL domains related to mental health dimensions. Data were further analyzed by cancer stage, menopausal status at diagnosis and estrogen receptor (ER) status. Interaction by time since surgery was tested among either stage I or stage II/III breast cancer survivors. Results were considered statistically significant if *P*-value<0.05. Multiple comparisons was additionally adjusted using false discovery rate (FDR) (Benjamini et al., 1995) and considered statistically significant if *P*-value<0.1. All analysis were performed using statistical analysis system (SAS) version 9.4 (SAS Institute, Cary, NC, USA).

IV. Results

1. Derivation of inflammatory dietary pattern

The inflammatory dietary pattern represented a diet in high intakes of red meat, white rice and noodle, and low intakes of seafood-based soup. Factor loadings of each food groups and explained variations of each inflammatory biomarkers and food groups are presented in Table 1.

The highest quartile of inflammatory dietary pattern score had 1.91 times higher levels of hsCRP compared to the lowest quartile of inflammatory dietary pattern score (*P* for trend <0.001). Also, the upward trends for IL-6 and TNF-α levels were observed, but they were not statistically significant (*P* for trend=0.12 for IL-6 and 0.07 for TNF-α) (Table 2).

Table 1. Factor loadings and explained variations of inflammatory dietary pattern

	Factor loading	Explained variation by extracted factor (%)
Food groups		2.65
Positive association		
Red meat	0.48	27.22
White rice	0.27	8.77
Noodles	0.26	7.77
Snack	0.23	5.95
Coffee	0.21	4.91
Salad	0.15	2.47
Confectionary / Desserts	0.15	2.47
Porridge	0.12	1.70
White bread	0.11	1.50
Other breads	0.11	1.49
Seaweeds	0.07	0.56
Cooked vegetables	0.03	0.09
Salted vegetables	0.02	0.06
Meat-based soup	0.02	0.04
Pizza	0.01	0.02
Carbonated / sweet beverages	<0.01	<0.01
Milk	<0.01	<0.01
Negative association		
Seafood-based soup	-0.25	7.53
Alcohol	-0.248	7.15
Soy products	-0.24	6.75
Eggs	-0.20	4.64
Nuts / Seeds	-0.18	3.87
Mushroom	-0.16	2.85
Dairy	-0.16	2.86
Fish	-0.14	2.19
Raw vegetables	-0.11	1.32
Fried food	-0.11	1.50
Mixed rice	-0.11	1.53
Salted seafood	-0.10	1.08
Korean pancake	-0.10	1.26
Whole / mixed grain rice	-0.09	0.95
Red meat byproducts	-0.09	0.96
Sandwiches	-0.09	1.00

(continued)

Table 1. Factor loadings and explained variations of inflammatory dietary pattern (continued)

	Factor loading	Explained variation by extracted factor (%)
Fruits	-0.08	0.71
Vegetable-based soup	-0.08	0.72
Poultry	-0.07	0.57
Sauces	-0.07	0.61
Whole / mixed grain bread	-0.06	0.39
Juices	-0.05	0.24
Other seafoods	-0.05	0.31
Tea	-0.05	0.34
Rice cake / dumpling	-0.04	0.19
Tubers / starch foods	-0.02	0.03
Processed meat	-0.02	0.04
Inflammatory biomarkers		10.67
hsCRP[a]		20.47
IL-6[a]		5.86
TNF-α[b]		5.69

Abbreviations: hsCRP: high-sensitivity C-reactive protein, IL-6: interleukine-6, TNF-α: tumor necrosis factor- α

[a]Log transformed and adjusted for age

[b]Adjusted for age

Table 2. Relative concentrations and 95% confidence intervals (CIs) of levels of hsCRP, IL-6 and TNF-α according to the quartiles of inflammatory dietary pattern scores

Inflammatory biomarkers	Quartiles of inflammatory dietary pattern scores (n=158)				
	Q1	Q2	Q3	Q4	*P* for trend
hsCRP[a]	1.00 (ref)	1.02 (0.59-1.76)	1.36 (0.79-2.35)	1.91 (1.10-3.31)	<0.001
IL-6[a]	1.00 (ref)	1.05 (0.65-1.69)	1.20 (0.74-1.93)	1.27 (0.79-2.06)	0.12
TNF-α[b]	1.00 (ref)	0.91 (0.65-1.28)	1.03 (0.75-1.41)	1.16 (0.86-1.57)	0.07

Abbreviations: hsCRP: high-sensitivity C-reactive protein, IL-6: interleukine-6, TNF-α: tumor necrosis factor- α
[a]Log transformed and adjusted for age
[b]Adjusted for age

2. Characteristics of participants

Table 3 shows the characteristics of participants according to the quartiles of inflammatory dietary pattern score. The mean age of the participants was 53 years.

Breast cancer survivors in the highest quartile of the inflammatory dietary pattern scores were more likely to be younger and were less likely to use supplement than those in the lowest quartile. Also, breast cancer survivors in the lowest quartile of the inflammatory dietary pattern scores tended to engage in more physical activity than those in the highest quartile. The proportion of premenopausal breast cancer was higher in the highest quartile of inflammatory dietary pattern scores than the lowest quartile.

Table 3. Characteristics of whole study population according to the quartiles of inflammatory dietary pattern score

Characteristics	Quartiles of inflammatory dietary pattern scores (n=454)			
	Q1	Q2	Q3	Q4
Age, mean (sd), years	54.21 (7.90)	53.28 (8.60)	53.64 (8.73)	51.04 (8.81)
BMI, mean (sd), kg/m²	23.35 (2.33)	23.65 (2.94)	23.03 (2.97)	23.92 (3.55)
Smoking, n (%)				
Never	97 (91.51)	98 (89.91)	107 (95.54)	99 (90.83)
Ever	9 (8.49)	11 (10.09)	5 (4.46)	10 (9.17)
Supplement use, n (%)				
No	39 (35.14)	40 (35.40)	44 (39.29)	52 (46.02)
Yes	72 (64.86)	73 (64.60)	68 (60.71)	61 (53.98)
Physical activity, mean (sd), MET-hours/week	36.57 (33.02)	35.40 (35.22)	31.72 (44.55)	24.96 (20.90)
Menopausal status at diagnosis, n (%)				
Premenopause	67 (59.29)	75 (65.79)	70 (61.95)	79 (70.54)
Menopause	46 (40.71)	39 (34.21)	43 (38.05)	33 (29.46)
Cancer stage, n (%)				
Stage I	58 (51.33)	58 (50.88)	58 (50.88)	56 (49.56)
Stage II	41 (36.28)	43 (37.72)	47 (41.23)	47 (41.59)
Stage III	14 (12.39)	13 (11.40)	9 (7.89)	10 (8.85)
Chemotherapy, n (%)				
No	27 (23.89)	35 (30.70)	35 (30.70)	31 (27.43)
Yes	86 (76.11)	79 (69.30)	79 (69.30)	82 (72.57)
Time since surgery				
<2 years	35 (30.97)	35 (30.70)	31 (27.19)	42 (37.17)
2 -< 5 years	46 (40.71)	44 (38.60)	40 (35.09)	39 (34.51)
≥5 years	24 (21.24)	35 (30.70)	43 (37.72)	32 (28.32)

Abbreviations: BMI=body mass index, sd=standard deviation MET= Metabolic equivalent task

3. Association between inflammatory dietary pattern scores and health-related quality of life in whole study population

There were no significant associations between the inflammatory dietary pattern scores and HRQOL levels in all the participants (Table 4). When the analyses were stratified by stage I and stage II or III, the components of HRQOL associated with inflammatory dietary pattern scores differed by stage (Table 5). Among stage I breast cancer survivors, inflammatory dietary pattern scores were positively associated with the HRQOL scores of role-emotional, social functioning and role-physical domains (*P* for trend=0.03, 0.04 and 0.02, respectively). However, higher inflammatory dietary pattern scores were associated with lower scores of the physical component summary, role-physical and bodily pain domains among stage II or III breast cancer survivors (*P* for trend=0.03, 0.01 and 0.01, respectively). After adjusting for multiple comparisons using the FDR method, the associations were no longer significant at α=0.1 among stage I breast cancer survivors. Among stage II or III breast cancer survivors, adjustment for multiple comparisons resulted in *P* value for trend at a FDR of 0.09 for the physical component summary domain and 0.07 for each role-physical domain and bodily pain domain.

No significant association was found in the analyses stratified by menopausal status at diagnosis (Table 6), estrogen receptor status (Table 7), BMI (Table 8) or time since surgery (Table 9).

Among women with stage I breast cancer who underwent surgery 3.1 years or more before enrollment (median time since surgery), increasing scores of inflammatory dietary pattern were associated with increasing levels of role-

emotional, physical component summary, role-physical and general health domains with significance at FDR<0.1, whereas there were no associations for those who had shorter time since surgery (< 3.1 years, median time) (Table 10). Notably, among stage II or III breast cancer survivors, increasing scores of inflammatory dietary pattern were associated with decreasing levels of bodily pain domain among women who underwent surgery less than 3.1 years before enrollment and with decreasing levels of physical component summary, physical functioning and role-physical domains among women who underwent surgery 3.1 years or more before enrollment (Table 11). These inverse associations remained significant at α=0.1 after adjusting for multiple comparisons.

Table 4. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores

HRQOL scales		Quartiles of inflammatory dietary pattern scores (n=454)				
		Q1	Q2	Q3	Q4	*P* for trend
Mental health dimensions[a]						
Mental component summary	Age-adjusted	48.37 (46.56-50.18)	49.20 (47.40-50.99)	50.29 (48.49-52.08)	48.83 (47.01-50.64)	0.65
	Multivariate-adjusted	48.25 (46.37-50.13)	49.06 (47.25-50.86)	50.38 (48.56-52.20)	49.00 (47.10-50.89)	0.48
Vitality	Age-adjusted	59.21 (55.16-63.25)	57.41 (53.39-61.43)	56.91 (52.89-60.93)	57.80 (53.73-61.86)	0.67
	Multivariate-adjusted	59.17 (54.98-63.37)	56.79 (52.76-60.82)	57.23 (53.16-61.30)	58.13(53.90-62.37)	0.87
Role-emotional	Age-adjusted	75.96 (71.54-80.38)	78.55 (74.16-82.94)	86.08 (81.69-90.47)	77.97 (73.53-82.41)	0.29
	Multivariate-adjusted	76.45(71.92-80.99)	78.29 (73.93-82.66)	85.75(81.35-90.16)	78.07 (73.48-82.66)	0.32
Social functioning	Age-adjusted	83.06(79.45-86.67)	84.45 (80.86-88.04)	86.67(83.08-90.26)	84.13 (80.51-87.76)	0.59
	Multivariate-adjusted	82.77 (79.12-86.42)	84.21 (80.70-87.73)	86.70(83.15-90.24)	84.63 (80.94-88.32)	0.39
Mental health	Age-adjusted	70.44 (66.76-74.12)	70.79 (67.14-74.44)	71.72 (68.06-75.37)	69.92 (66.23-73.62)	0.89
	Multivariate-adjusted	70.14 (66.30-73.99)	70.60 (66.91-74.30)	71.82 (68.09-75.56)	70.30 (66.42-74.19)	0.88

(continued)

Table 4. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores (continued)

HRQOL scales		Quartiles of inflammatory dietary pattern scores (n=454)				
		Q1	Q2	Q3	Q4	*P* for trend
Physical health dimensions[b]						
Physical component summary	Age-adjusted	49.91 (48.57-51.25)	49.02 (47.69-50.35)	49.65 (48.32-50.98)	49.31 (47.97-50.66)	0.75
	Multivariate-adjusted	50.14 (48.79-51.48)	48.99 (47.69-50.29)	49.37 (48.06-50.67)	49.40 (48.04-50.76)	0.66
Physical functioning	Age-adjusted	76.24 (72.59-79.88)	74.65 (71.03-78.27)	78.14 (74.51-81.76)	75.66 (72.00-79.32)	0.85
	Multivariate-adjusted	77.36 (73.74-80.97)	74.45 (70.96-77.94)	77.34 (73.84-80.85)	75.54 (71.88-79.20)	0.85
Role-physical	Age-adjusted	75.59 (71.00-80.18)	74.19 (69.63-78.75)	81.68 (77.12-86.25)	72.75 (68.14-77.36)	0.79
	Multivariate-adjusted	76.40 (71.76-81.03)	74.25 (69.78-78.72)	80.67 (76.17-85.17)	72.89 (68.20-77.59)	0.70
Bodily pain	Age-adjusted	75.18 (70.92-79.44)	71.78 (67.56-76.01)	73.84 (69.61-78.07)	72.36 (68.08-76.63)	0.55
	Multivariate-adjusted	75.96 (71.61-80.31)	71.64 (67.44-75.84)	73.13 (68.90-77.35)	72.44 (68.03-76.84)	0.46
General health	Age-adjusted	60.20 (56.69-63.71)	62.41 (58.92-65.89)	58.85 (55.36-62.33)	63.12 (59.59-66.64)	0.49
	Multivariate-adjusted	59.46 (55.79-63.13)	62.42 (58.88-65.96)	58.70 (55.14-62.26)	63.99 (60.28-67.70)	0.27

[a]Age-adjusted model was adjusted for age (years, continuous); and Multivariate-adjusted model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), physical activity (MET-hours/week, quartile), adjuvant chemotherapy (yes, no), breast cancer stage and center

[b]Age-adjusted model was adjusted for age (years, continuous); and Multivariate-adjusted model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), adjuvant chemotherapy (yes, no), breast cancer stage and center

Table 5. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by breast cancer stage

Breast cancer stage I (n=230)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	48.65 (46.31-50.98)	48.95 (46.67-51.24)	49.58 (47.26-51.89)	50.82 (48.43-53.22)	0.18
Vitality	58.99 (53.43-64.55)	57.64 (52.19-63.09)	52.54 (47.02-58.05)	62.44 (56.72-68.15)	0.51
Role-emotional	75.56 (69.81-81.30)	77.82 (72.19-83.45)	88.66 (82.96-94.36)	82.95 (77.05-88.85)	0.03
Social functioning	82.75 (78.16-87.34)	86.09 (81.59-90.59)	89.16 (84.61-93.71)	89.48 (84.77-94.19)	0.04
Mental health	71.50 (66.33-76.68)	71.17 (66.09-76.25)	68.44 (63.31-73.58)	73.82 (68.50-79.14)	0.62
Physical health dimensions[b]					
Physical component summary	49.33 (47.53-51.13)	49.83 (48.05-51.61)	49.44 (47.66-51.21)	51.59 (49.72-53.45)	0.12
Physical functioning	77.86 (72.98-82.74)	78.74 (73.92-83.55)	78.01 (73.20-82.82)	79.26 (74.22-84.31)	0.76
Role-physical	72.83 (66.87-78.78)	75.05 (69.17-80.92)	84.50 (78.63-90.37)	81.42 (75.27-87.58)	0.02
Bodily pain	73.43 (67.15-79.70)	73.05 (66.87-79.24)	72.12 (65.94-78.30)	79.07 (72.59-85.56)	0.23
General health	59.64 (55.03-64.26)	61.79 (57.25-66.34)	53.90 (49.35-58.45)	67.54 (62.77-72.31)	0.10

(continued)

Table 5. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by breast cancer stage (continued)

Breast cancer stage II or III (n=224)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[c]					
Mental component summary	48.19 (45.18-51.20)	48.88 (45.93-51.82)	51.50 (48.63-54.36)	46.86 (43.90-49.83)	0.77
Vitality	59.69 (53.46-65.91)	56.56 (50.48-62.65)	62.20 (56.26-68.13)	52.85 (46.72-58.98)	0.31
Role-emotional	78.07 (70.90-85.24)	77.90 (70.88-84.91)	83.71 (76.88-90.54)	72.55 (65.48-79.62)	0.47
Social functioning	83.37 (77.56-89.18)	81.99 (76.31-87.68)	84.19 (78.65-89.73)	79.53 (73.81-85.26)	0.48
Mental health	69.31 (63.53-75.09)	69.33 (63.67-74.99)	75.94 (70.43-81.45)	66.34 (60.64-72.04)	0.81
Physical health dimensions[d]					
Physical component summary	51.06 (49.07-53.06)	48.19 (46.24-50.14)	49.31 (47.40-51.21)	47.09 (45.14-49.04)	0.03[†]
Physical functioning	77.28 (71.96-82.60)	70.06 (64.85-75.27)	76.81 (71.72-81.90)	71.25 (66.04-76.46)	0.46
Role-physical	80.11 (72.90-87.32)	73.43 (66.37-80.49)	77.22 (70.32-84.12)	64.06 (57.00-71.12)	0.01[†]
Bodily pain	79.42 (73.45-85.39)	69.48 (63.64-75.32)	74.31 (68.60-80.02)	65.71 (59.87-71.56)	0.01[†]
General health	59.96 (54.21-65.72)	62.74 (57.10-68.38)	63.76 (58.26-69.27)	60.07 (54.43-65.70)	0.98

[a]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), physical activity (MET-hours/week, quartile) adjuvant chemotherapy (yes, no) and center

[b]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), adjuvant chemotherapy (yes, no) and center

[c]Mltivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), physical activity (MET-hours/week, quartile), adjuvant chemotherapy (yes, no), breast cancer stage (stage II, stage III) and center

[d]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), adjuvant chemotherapy (yes, no), breast cancer (stage II, stage III) and center

[†]*P* value <0.1 after adjusting for multiple comparisons using false discovery rate (FDR) method

Table 6. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by menopausal status at diagnosis

Premenopausal breast cancer (n=291)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	48.33 (45.93-50.74)	49.49 (47.33-51.66)	51.42 (49.13-53.71)	48.16 (45.91-50.42)	0.94
Vitality	59.77 (54.35-65.20)	57.16 (52.26-62.06)	61.06 (55.88-66.24)	55.39 (50.3-60.47)	0.47
Role-emotional	77.72 (71.89-83.56)	78.26 (72.99-83.52)	87.58 (82.02-93.15)	76.75 (71.29-82.22)	0.71
Social functioning	80.90 (76.27-85.53)	85.37 (81.19-89.55)	88.98 (84.56-93.40)	84.16 (79.82-88.5)	0.31
Mental health	70.46 (65.72-75.19)	71.98 (67.70-76.25)	73.86 (69.34-78.38)	70.29 (65.86-74.73)	0.99
Physical health dimensions[b]					
Physical component summary	50.74 (49.05-52.42)	48.81 (47.27-50.36)	50.69 (49.07-52.32)	49.88 (48.29-51.47)	0.96
Physical functioning	77.07 (72.61-81.52)	76.28 (72.20-80.35)	79.96 (75.66-84.25)	77.67 (73.46-81.87)	0.56
Role-physical	76.96 (71.08-82.85)	72.39 (67.00-77.77)	83.32 (77.64-89.00)	73.04 (67.48-78.59)	0.97
Bodily pain	77.91 (72.40-83.41)	70.77 (65.73-75.81)	76.74 (71.43-82.06)	73.25 (68.05-78.44)	0.69
General health	63.14 (58.65-67.62)	62.37 (58.26-66.47)	62.74 (58.42-67.07)	63.65 (59.41-67.88)	0.81

(continued)

Table 6. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by menopausal status at diagnosis (continued)

Postmenopausal breast cancer (n=161)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	48.25 (45.03-51.47)	48.24 (44.83-51.65)	49.08 (45.81-52.36)	49.77 (46.00-53.54)	0.50
Vitality	58.87 (52.14-65.60)	56.47 (49.34-63.60)	50.24 (43.40-57.09)	63.76 (55.88-71.64)	0.51
Role-emotional	75.26 (67.68-82.84)	78.39 (70.36-86.42)	84.05 (76.34-91.76)	77.77 (68.89-86.65)	0.56
Social functioning	86.06 (79.72-92.41)	81.61 (74.90-88.33)	83.17 (76.72-89.62)	84.30 (76.87-91.73)	0.87
Mental health	69.54 (62.48-76.61)	67.48 (60.00-74.97)	69.18 (62.00-76.37)	69.52 (61.25-77.80)	0.90
Physical health dimensions[b]					
Physical component summary	49.51 (47.26-51.75)	49.12 (46.76-51.47)	46.71 (44.45-48.97)	48.93 (46.30-51.56)	0.52
Physical functioning	77.86 (71.53-84.19)	70.41 (63.76-77.06)	72.13 (65.75-78.51)	71.85 (64.43-79.26)	0.36
Role-physical	75.84 (68.39-83.29)	77.23 (69.41-85.04)	77.38 (69.87-84.89)	72.83 (64.11-81.56)	0.60
Bodily pain	73.69 (66.41-80.96)	73.03 (65.40-80.66)	66.07 (58.74-73.40)	71.13 (62.62-79.65)	0.46
General health	54.68 (48.32-61.03)	62.61 (55.93-69.28)	50.62 (44.21-57.02)	65.39 (57.95-72.84)	0.21

Abbreviations: CIs = confidence intervals

[a]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), physical activity (MET-hours/week, quartile), adjuvant chemotherapy (yes, no), breast cancer stage and center

[b]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), adjuvant chemotherapy (yes, no), breast cancer stage and center

Table 7. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by estrogen (ER) status

Estrogen receptor-positive breast cancer (n=329)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	48.09 (45.88-50.31)	49.41 (47.33-51.49)	49.77 (47.62-51.91)	50.20 (47.92-52.47)	0.23
Vitality	58.80 (53.84-63.77)	58.45 (53.78-63.13)	56.75 (51.93-61.56)	59.12 (54.02-64.23)	0.99
Role-emotional	76.20 (70.78-81.63)	77.37 (72.26-82.47)	85.09 (79.84-90.35)	79.52 (73.95-85.10)	0.21
Social functioning	83.40 (79.14-87.66)	85.84 (81.83-89.85)	85.41 (81.28-89.53)	86.21 (81.83-90.59)	0.48
Mental health	69.64 (65.07-74.22)	70.99 (66.69-75.30)	70.29 (65.86-74.72)	73.05 (68.35-77.75)	0.37
Physical health dimensions[b]					
Physical component summary	50.26 (48.65-51.87)	49.05 (47.53-50.57)	49.10 (47.54-50.65)	49.25 (47.59-50.91)	0.52
Physical functioning	77.83 (73.47-82.18)	73.36 (69.24-77.47)	77.17 (72.96-81.38)	74.40 (69.91-78.89)	0.63
Role-physical	76.26 (70.69-81.82)	75.33 (70.07-80.59)	80.23 (74.85-85.61)	73.56 (67.82-79.30)	0.76
Bodily pain	75.82 (70.73-80.92)	71.45 (66.64-76.26)	71.58 (66.66-76.50)	74.83 (69.58-80.08)	0.98
General health	59.65 (55.23-64.07)	63.24 (59.06-67.41)	56.82 (52.55-61.10)	64.36 (59.81-68.92)	0.48

(continued)

Table 7. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by estrogen (ER) status (continued)

Estrogen receptor-negative breast cancer (n=125)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	48.72 (44.97-52.48)	49.05 (45.21-52.89)	51.57 (47.96-55.17)	45.66 (42.01-49.30)	0.43
Vitality	60.38 (51.90-68.87)	52.47 (43.79-61.14)	58.44 (50.29-66.60)	55.01 (46.77-63.24)	0.67
Role-emotional	76.49 (67.72-85.25)	82.59 (73.63-91.55)	87.80 (79.37-96.22)	73.82 (65.31-82.33)	0.84
Social functioning	81.93 (74.69-89.17)	81.38 (73.98-88.78)	89.97 (83.01-96.93)	78.62 (71.60-85.65)	0.95
Mental health	71.66 (64.19-79.14)	72.05 (64.41-79.69)	74.80 (67.62-81.98)	62.54 (55.29-69.79)	0.15
Physical health dimensions[b]					
Physical component summary	49.69 (47.10-52.28)	48.79 (46.11-51.47)	50.42 (47.92-52.93)	49.59 (47.06-52.11)	0.80
Physical functioning	76.35 (69.55-83.15)	78.70 (71.67-85.72)	78.04 (71.46-84.62)	77.07 (70.43-83.71)	0.95
Role-physical	75.93 (67.23-84.63)	72.70 (63.71-81.70)	81.79 (73.37-90.21)	70.74 (62.25-79.24)	0.78
Bodily pain	76.64 (67.92-85.37)	72.34 (63.32-81.35)	78.02 (69.58-86.45)	65.81 (57.29-74.33)	0.20
General health	58.14 (51.21-65.07)	59.87 (52.71-67.03)	63.54 (56.84-70.24)	64.13 (57.36-70.89)	0.17

Abbreviations: CIs = confidence intervals

[a]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), physical activity (MET-hours/week, quartile), adjuvant chemotherapy (yes, no), breast cancer stage and center

[b]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), adjuvant chemotherapy (yes, no), breast cancer stage and center

Table 8. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by body mass index (BMI)

BMI <23 (n=211)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	47.32 (44.53-50.12)	50.12 (47.32-52.91)	49.98 (47.64-52.33)	49.71 (46.95-52.47)	0.32
Vitality	58.31 (51.90-64.72)	58.35 (51.95-64.76)	59.05 (53.67-64.43)	56.96 (50.63-63.29)	0.81
Role-emotional	76.67 (69.99-83.35)	80.22 (73.55-86.89)	85.13 (79.53-90.74)	79.55 (72.96-86.14)	0.42
Social functioning	80.75 (75.41-86.09)	88.35 (83.01-93.68)	86.41 (81.93-90.89)	85.77 (80.50-91.04)	0.36
Mental health	68.04 (62.50-73.58)	74.32 (68.79-79.86)	71.68 (67.03-76.33)	73.40 (67.93-78.87)	0.34
Physical health dimensions[b]					
Physical component summary	50.56 (48.65-52.46)	50.59 (48.67-52.51)	50.55 (48.95-52.16)	49.94 (48.04-51.83)	0.65
Physical functioning	78.57 (73.66-83.48)	79.81 (74.86-84.77)	80.18 (76.04-84.32)	75.70 (70.81-80.59)	0.44
Role-physical	76.99 (70.75-83.23)	79.79 (73.49-86.09)	82.03 (76.77-87.29)	77.66 (71.45-83.87)	0.80
Bodily pain	76.21 (69.43-82.99)	75.20 (68.35-82.04)	75.3 (69.59-81.02)	75.36 (68.61-82.10)	0.88
General health	60.34 (54.85-65.83)	63.54 (57.99-69.08)	59.44 (54.81-64.07)	63.87 (58.40-69.34)	0.64

(continued)

Table 8. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by body mass index (BMI) (continued)

BMI ≥23 (n=221)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	48.58 (45.74-51.42)	47.82 (45.15-50.49)	51.38 (48.15-54.62)	48.27 (45.42-51.12)	0.84
Vitality	58.42 (52.41-64.43)	56.72 (51.08-62.37)	56.72 (49.89-63.56)	57.56 (51.54-63.57)	0.93
Role-emotional	75.14 (68.23-82.05)	75.12 (68.62-81.63)	87.52 (79.65-95.38)	76.35 (69.42-83.27)	0.54
Social functioning	85.09 (79.59-90.59)	80.45 (75.28-85.62)	85.37 (79.11-91.62)	82.61 (77.10-88.12)	0.90
Mental health	71.25 (65.30-77.20)	66.06 (60.46-71.65)	74.08 (67.31-80.85)	68.07 (62.11-74.04)	0.89
Physical health dimensions[b]					
Physical component summary	49.60 (47.54-51.66)	47.41 (45.47-49.35)	48.30 (45.96-50.65)	48.63 (46.56-50.69)	0.88
Physical functioning	76.67 (70.89-82.46)	69.37 (63.94-74.80)	75.07 (68.50-81.63)	74.03 (68.24-79.82)	0.95
Role-physical	75.95 (68.82-83.08)	67.81 (61.11-74.50)	79.87 (71.77-87.96)	68.31 (61.18-75.45)	0.46
Bodily pain	74.03 (67.93-80.13)	67.47 (61.74-73.19)	72.50 (65.58-79.43)	69.97 (63.87-76.08)	0.73
General health	58.35 (52.67-64.02)	60.61 (55.28-65.94)	58.30 (51.85-64.74)	63.82 (58.14-69.50)	0.25

Abbreviations: CIs = confidence intervals

[a]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², tertile), time since surgery (years, <2, 2-<5, ≥5), physical activity (MET-hours/week, quartile), adjuvant chemotherapy (yes, no), breast cancer stage and center

[b]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², tertile), time since surgery (years, <2, 2-<5, ≥5), adjuvant chemotherapy (yes, no), breast cancer stage and center

Table 9. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by time since surgery

Below median time of time since surgery (3.1 years) (n=226)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	48.39 (46.01-50.78)	46.59 (43.94-49.24)	50.35 (47.68-53.02)	49.16 (46.35-51.98)	0.27
Vitality	57.36 (52.30-62.42)	51.85 (46.23-57.47)	57.92 (52.25-63.58)	59.91 (53.94-65.87)	0.25
Role-emotional	76.51 (70.52-82.49)	71.49 (64.83-78.14)	84.44 (77.73-91.14)	75.51 (68.45-82.56)	0.42
Social functioning	81.49 (76.78-86.20)	79.48 (74.24-84.72)	87.04 (81.77-92.32)	82.76 (77.20-88.31)	0.29
Mental health	70.88 (66.20-75.56)	66.59 (61.39-71.80)	72.74 (67.50-77.98)	71.08 (65.56-76.59)	0.51
Physical health dimensions[b]					
Physical component summary	49.48 (47.74-51.22)	47.42 (45.48-49.35)	49.70 (47.75-51.65)	48.39 (46.35-50.44)	0.90
Physical functioning	74.94 (70.08-79.80)	70.93 (65.52-76.33)	79.03 (73.58-84.47)	73.82 (68.09-79.55)	0.62
Role-physical	74.12 (68.23-80.01)	65.10 (58.54-71.65)	79.77 (73.17-86.38)	71.45 (64.51-78.40)	0.55
Bodily pain	76.20 (70.65-81.75)	67.57 (61.39-73.75)	73.07 (66.85-79.29)	68.91 (62.36-75.45)	0.29
General health	59.97 (55.44-64.50)	59.79 (54.75-64.83)	60.17 (55.09-65.25)	62.54 (57.20-67.88)	0.48

(continued)

Table 9. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by time since surgery (continued)

At or above median time of time since surgery (3.1 years) (n=228)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	48.03 (45.07-50.99)	50.95 (48.45-53.45)	50.99 (48.51-53.48)	48.44 (45.85-51.03)	0.83
Vitality	60.64 (53.66-67.61)	61.15 (55.27-67.04)	57.36 (51.50-63.23)	56.45 (50.34-62.56)	0.25
Role-emotional	76.94 (69.92-83.96)	83.64 (77.72-89.57)	87.73 (81.83-93.63)	79.49 (73.35-85.64)	0.75
Social functioning	85.11 (79.41-90.81)	87.15 (82.34-91.96)	87.37 (82.58-92.16)	86.05 (81.06-91.04)	0.91
Mental health	69.64 (63.37-75.91)	73.34 (68.05-78.63)	72.94 (67.67-78.21)	67.84 (62.35-73.33)	0.46
Physical health dimensions[b]					
Physical component summary	51.28 (49.12-53.44)	49.89 (48.06-51.71)	49.53 (47.71-51.35)	50.15 (48.25-52.04)	0.54
Physical functioning	81.31 (75.72-86.90)	77.11 (72.38-81.83)	77.20 (72.49-81.92)	75.72 (70.81-80.63)	0.21
Role-physical	80.41 (73.04-87.78)	80.72 (74.49-86.95)	82.61 (76.39-88.82)	73.75 (67.27-80.23)	0.17
Bodily pain	76.92 (69.86-83.98)	73.04 (67.07-79.01)	75.03 (69.07-80.98)	74.85 (68.65-81.06)	0.89
General health	58.68 (52.77-64.59)	63.75 (58.75-68.74)	58.81 (53.82-63.79)	64.85 (59.65-70.04)	0.31

[a]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no),), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, tertile), physical activity (MET-hours/week, quartile), adjuvant chemotherapy (yes, no), breast cancer stage and center

[b]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, tertile), adjuvant chemotherapy (yes, no), breast cancer stage and center

Table 10. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores among breast cancer survivors diagnosed with stage I by time since surgery

Below median time of time since surgery (3.1 years) (n=126)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	49.70 (46.98-52.43)	48.24 (45.18-51.31)	50.28 (47.09-53.47)	52.71 (49.39-56.04)	0.12
Vitality	58.60 (51.71-65.50)	57.27 (49.52-65.03)	57.86 (49.79-65.93)	66.25 (57.84-74.66)	0.19
Role-emotional	80.51 (73.66-87.37)	73.15 (65.45-80.86)	88.09 (80.07-96.11)	81.83 (73.47-90.19)	0.27
Social functioning	86.20 (81.09-91.31)	83.97 (78.22-89.71)	91.55 (85.57-97.53)	89.94 (83.71-96.18)	0.14
Mental health	72.62 (66.65-78.58)	71.19 (64.49-77.89)	71.27 (64.29-78.24)	78.39 (71.12-85.66)	0.27
Physical health dimensions[b]					
Physical component summary	50.04 (48.02-52.06)	49.41 (47.16-51.65)	51.44 (49.08-53.80)	49.73 (47.25-52.21)	0.79
Physical functioning	79.78 (73.90-85.65)	78.02 (71.49-84.56)	83.57 (76.70-90.45)	76.10 (68.89-83.31)	0.76
Role-physical	75.82 (68.56-83.07)	69.58 (61.50-77.65)	86.16 (77.66-94.65)	79.73 (70.82-88.64)	0.12
Bodily pain	75.54 (68.41-82.66)	71.91 (63.98-79.84)	75.97 (67.63-84.31)	76.52 (67.78-85.27)	0.69
General health	61.52 (55.84-67.19)	62.94 (56.63-69.26)	59.68 (53.04-66.32)	64.00 (57.04-70.97)	0.80

(continued)

Table 10. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores among breast cancer survivors diagnosed with stage Ⅰ by time since surgery (continued)

At or above median time of time since surgery(3.1 years) (n=104)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	45.31 (40.74-49.89)	50.06 (46.29-53.84)	49.20 (45.55-52.85)	49.16 (45.47-52.86)	0.46
Vitality	56.39 (45.53-67.25)	59.41 (50.45-68.37)	48.44 (39.77-57.10)	58.51 (49.74-67.28)	0.94
Role-emotional	64.31 (53.51-75.12)	81.87 (72.95-90.79)	89.27 (80.65-97.89)	86.73 (78.00-95.46)	0.01[†]
Social functioning	76.57 (67.33-85.80)	88.03 (80.41-95.65)	87.48 (80.11-94.84)	88.61 (81.15-96.07)	0.15
Mental health	66.78 (56.47-77.09)	72.03 (63.52-80.54)	66.37 (58.14-74.60)	69.34 (61.01-77.68)	0.97
Physical health dimensions[b]					
Physical component summary	48.03 (44.49-51.58)	50.37 (47.40-53.34)	47.61 (44.77-50.46)	53.44 (50.52-56.37)	0.04[†]
Physical functioning	73.24 (63.88-82.60)	79.55 (71.70-87.39)	72.57 (65.05-80.09)	83.65 (75.93-91.38)	0.16
Role-physical	67.46 (56.60-78.32)	79.51 (70.41-88.61)	82.47 (73.75-91.20)	85.36 (76.41-94.32)	0.03[†]
Bodily pain	69.80 (57.21-82.39)	73.76 (63.21-84.31)	69.65 (59.53-79.76)	80.89 (70.50-91.27)	0.19
General health	54.09 (45.48-62.70)	62.32 (55.10-69.53)	49.49 (42.57-56.41)	69.88 (62.78-76.99)	0.02[†]

[a]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, tertile), physical activity (MET-hours/week, quartile), adjuvant chemotherapy (yes, no) and center

[b]Multivariate model was further adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, tertile), adjuvant chemotherapy (yes, no) and center

[†]*P* value <0.1 after adjusting for multiple comparisons using false discovery rate (FDR) method

Table 11. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores among breast cancer survivors diagnosed with stage II or III by time since surgery

Below median time of time since surgery (3.1 years) (n=100)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	46.33 (41.68-50.98)	45.06 (39.66-50.46)	49.91 (45.09-54.72)	45.19 (40.17-50.22)	0.82
Vitality	55.61 (47.31-63.92)	48.65 (39.01-58.30)	55.30 (46.71-63.90)	51.31 (42.34-60.29)	0.87
Role-emotional	71.18 (59.62-82.73)	70.11 (56.70-83.53)	76.63 (64.66-88.59)	71.08 (58.60-83.57)	0.78
Social functioning	75.49 (66.08-84.89)	76.89 (65.97-87.81)	78.46 (68.72-88.20)	74.39 (64.23-84.55)	0.94
Mental health	67.00 (58.79-75.21)	62.17 (52.64-71.71)	74.02 (65.52-82.52)	62.84 (53.96-71.71)	0.90
Physical health dimensions[b]					
Physicalcomponent summary	48.85 (45.67-52.03)	46.46 (42.79-50.14)	46.17 (42.87-49.46)	46.64 (43.26-50.02)	0.41
Physical functioning	67.60 (58.88-76.32)	64.05 (53.98-74.12)	69.36 (60.34-78.39)	73.89 (64.62-83.16)	0.21
Role-physical	73.28 (62.53-84.03)	61.73 (49.31-74.14)	67.65 (56.52-78.77)	62.50 (51.07-73.93)	0.38
Bodily pain	78.49(69.53-87.44)	66.25 (55.91-76.59)	64.88 (55.61-74.15)	59.11 (49.58-68.63)	0.01[†]
General health	56.29 (48.25-64.33)	59.66 (50.37-68.94)	61.41 (53.09-69.72)	58.27 (49.71-66.82)	0.73

(continued)

Table 11. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores among breast cancer survivors diagnosed with stage II or III by time since surgery (continued)

At or above median time of time since surgery (3.1 years) (n=124)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	48.73 (44.68-52.78)	53.40 (49.75-57.06)	53.32 (49.70-56.95)	46.45 (42.55-50.34)	0.32
Vitality	61.27 (51.99-70.55)	66.82 (58.46-75.19)	67.12 (58.82-75.42)	51.04 (42.12-59.95)	0.10
Role-emotional	82.82 (73.36-92.29)	86.40 (77.87-94.92)	88.88 (80.42-97.35)	72.42 (63.33-81.51)	0.13
Social functioning	89.05 (81.55-96.56)	89.45 (82.69-96.21)	89.12 (82.41-95.84)	80.97 (73.76-88.17)	0.12
Mental health	68.87 (60.60-77.14)	78.03 (70.58-85.49)	79.52 (72.12-86.92)	64.73 (56.79-72.67)	0.41
Physical health dimensions[b]					
Physical component summary	52.78 (50.22-55.35)	49.70 (47.4-52.01)	51.80 (49.50-54.10)	47.57 (45.13-50.01)	0.02[†]
Physical functioning	84.47 (77.73-91.21)	75.58 (69.53-81.64)	82.22 (76.18-88.26)	70.60 (64.18-77.01)	0.02[†]
Role-physical	85.42 (75.60-95.23)	82.92 (74.10-91.74)	84.18 (75.38-92.98)	65.19 (55.85-74.53)	<0.01[†]
Bodily pain	79.28 (71.16-87.40)	73.99 (66.69-81.28)	81.99 (74.70-89.27)	68.96 (61.23-76.69)	0.19
General health	61.36 (53.24-69.48)	65.96 (58.66-73.25)	68.30 (61.02-75.58)	59.62 (51.90-67.35)	0.75

[a]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, tertile), physical activity (MET-hours/week, quartile), adjuvant chemotherapy (yes, no), breast cancer stage (stage II, stage III) and center

[b]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, tertile), adjuvant chemotherapy (yes, no), breast cancer stage (stage II, stage III) and center

[†]*P* value <0.1 after adjusting for multiple comparisons using false discovery rate (FDR) method

4. Association between inflammatory dietary pattern scores and health-related quality of life among participants whose plasma inflammatory biomarkers were measured

Among participants whose plasma inflammatory biomarkers were measured (n=147), inflammatory dietary pattern scores were inversely associated with bodily pain scores (*P* for trend=0.01) (Table 12). The association remained significant at α=0.1 after controlling for multiple comparisons.

When the analyses were stratified by breast cancer stage, inverse associations with scores of physical component summary and bodily pain domain were observed among stage II or III breast cancer survivors (*P* for trend=0.04 and <0.001, respectively) (Table 13). The association with physical component summary score was not statistically significant while that with bodily pain score remained significant at α=0.1 after adjusting for multiple comparisons.

Table 12. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern score among breast cancer survivors whose plasma inflammatory biomarkers were measured

HRQOL scales		Quartiles of inflammatory dietary pattern scores (n=147)				
		Q1	Q2	Q3	Q4	*P* for trend
Mental health dimensions[a]						
Mental component summary	Age-adjusted	48.86 (45.77-51.96)	50.35 (47.31-53.4)	50.57 (47.52-53.62)	49.02 (45.95-52.09)	0.94
	Multivariate-adjusted	48.75 (45.41-52.09)	49.63 (46.38-52.88)	50.66 (47.36-53.96)	49.77 (46.30-53.23)	0.65
Vitality	Age-adjusted	59.10 (52.48-65.72)	61.36 (54.85-67.88)	56.06 (49.55-62.58)	56.89 (50.32-63.45)	0.40
	Multivariate-adjusted	58.94 (51.90-65.98)	59.90 (53.05-66.74)	55.90 (48.95-62.86)	58.66 (51.36-65.96)	0.78
Role-emotional	Age-adjusted	77.46 (69.55-85.37)	78.12 (70.33-85.91)	83.73 (75.94-91.52)	78.66 (70.81-86.51)	0.70
	Multivariate-adjusted	77.75 (69.51-86.00)	76.37 (68.36-84.39)	83.19 (75.04-91.34)	80.66 (72.10-89.22)	0.42
Social functioning	Age-adjusted	85.00 (78.59-91.40)	86.46 (80.16-92.76)	87.46 (81.16-93.76)	84.26 (77.91-90.62)	0.83
	Multivariate-adjusted	84.96 (78.33-91.59)	85.50 (79.06-91.95)	87.02 (80.47-93.58)	85.68 (78.80-92.56)	0.84
Mental health	Age-adjusted	71.16 (64.93-77.39)	74.70 (68.56-80.83)	72.47 (66.33-78.61)	68.42 (62.24-74.60)	0.34
	Multivariate-adjusted	71.15 (64.30-77.99)	74.04 (67.38-80.69)	71.83 (65.07-78.60)	69.72 (62.62-76.83)	0.61

(continued)

Table 12. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores among breast cancer survivors whose plasma inflammatory biomarkers were measured (continued)

HRQOL scales		Quartiles of inflammatory dietary pattern scores (n=147)				
		Q1	Q2	Q3	Q4	*P* for trend
Physical health dimensions[b]						
Physical component summary	Age-adjusted	50.26 (47.87-52.66)	50.16 (47.80-52.52)	48.57 (46.21-50.93)	47.71 (45.33-50.09)	0.08
	Multivariate-adjusted	50.75 (48.35-53.16)	50.40 (48.06-52.73)	47.35 (45.01-49.69)	48.22 (45.72-50.71)	0.06
Physical functioning	Age-adjusted	76.58 (70.38-82.77)	74.26 (68.16-80.35)	73.89 (67.79-79.99)	73.76 (67.61-79.90)	0.58
	Multivariate-adjusted	77.77 (71.67-83.87)	74.68 (68.77-80.59)	70.37 (64.44-76.31)	75.68 (69.36-82.01)	0.54
Role-physical	Age-adjusted	75.42 (67.34-83.50)	78.57 (70.62-86.53)	77.57 (69.61-85.53)	69.29 (61.27-77.31)	0.20
	Multivariate-adjusted	76.06 (67.78-84.35)	78.28 (70.25-86.31)	74.56 (66.49-82.63)	71.97 (63.38-80.57)	0.36
Bodily pain	Age-adjusted	78.49 (71.14-85.84)	77.97 (70.74-85.21)	74.75 (67.52-81.99)	67.39 (60.10-74.69)	0.02
	Multivariate-adjusted	80.28 (72.90-87.65)	78.49 (71.34-85.64)	72.60 (65.42-79.78)	67.29 (59.64-74.94)	0.01[†]
General health	Age-adjusted	61.14 (55.17-67.10)	64.29 (58.41-70.16)	58.23 (52.35-64.10)	60.37 (54.45-66.29)	0.51
	Multivariate-adjusted	61.88 (55.70-68.06)	64.83 (58.84-70.82)	56.63 (50.61-62.66)	60.70 (54.29-67.11)	0.37

[a]Age-adjusted model was adjusted for age (years, continuous); and Multivariate-adjusted model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), physical activity (MET-hours/week, quartile), adjuvant chemotherapy (yes, no), breast cancer stage and center

[b]Age-adjusted model was adjusted for age (years, continuous); and Multivariate-adjusted model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-<25, ≥25), time since surgery (years, <2, 2-<5, ≥5), adjuvant chemotherapy (yes, no), breast cancer stage and center; [†]*P* value <0.1 after adjusting for multiple comparisons using false discovery rate (FDR) method

Table 13. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by breast cancer stage among breast cancer survivors whose plasma inflammatory biomarkers were measured

Breast cancer stage I (n=75)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[a]					
Mental component summary	51.32 (47.02-55.62)	47.61 (43.50-51.72)	48.99 (44.63-53.35)	52.85 (47.45-58.25)	0.61
Vitality	62.08 (51.88-72.28)	57.69 (47.95-67.42)	54.53 (44.20-64.85)	65.60 (52.81-78.40)	0.84
Role-emotional	82.29 (71.00-93.57)	69.70 (58.93-80.48)	83.45 (72.02-94.87)	84.50 (70.33-98.66)	0.43
Social functioning	88.38 (80.27-96.49)	86.07 (78.33-93.81)	86.68 (78.47-94.89)	94.32 (84.14-104.49)	0.40
Mental health	73.99 (64.18-83.80)	71.93 (62.57-81.29)	69.95 (60.02-79.88)	75.49 (63.18-87.79)	0.96
Physical health dimensions[b]					
Physical component summary	49.03 (45.76-52.30)	50.96 (47.86-54.07)	49.60 (46.50-52.70)	49.43 (45.44-53.43)	0.94
Physical functioning	78.05 (69.90-86.20)	78.68 (70.93-86.43)	75.69 (67.95-83.43)	77.20 (67.22-87.17)	0.74
Role-physical	73.00 (61.94-84.06)	74.63 (64.11-85.15)	79.26 (68.76-89.76)	81.13 (67.60-94.67)	0.28
Bodily pain	76.84 (65.33-88.36)	78.58 (67.63-89.53)	79.35 (68.42-90.28)	73.56 (59.47-87.65)	0.78
General health	59.54 (51.59-67.49)	61.88 (54.33-69.44)	53.98 (46.43-61.52)	59.86 (50.14-69.59)	0.61

(continued)

Table 13. Least square means (LS-means) and 95% confidence intervals (CIs) of health-related quality of life (HRQOL) levels according to the quartiles of inflammatory dietary pattern scores by breast cancer stage among breast cancer survivors whose plasma inflammatory biomarkers were measured (continued)

Breast cancer stage II or III (n=72)	Quartiles of inflammatory dietary pattern scores				
HRQOL scales	**Q1**	**Q2**	**Q3**	**Q4**	***P* for trend**
Mental health dimensions[c]					
Mental component summary	46.90 (41.49-52.30)	51.80 (46.16-57.45)	53.46 (47.83-59.09)	47.41 (42.56-52.26)	0.82
Vitality	58.76 (48.78-68.74)	57.40 (46.97-67.83)	60.73 (50.34-71.12)	53.77 (44.82-62.73)	0.52
Role-emotional	72.50 (59.36-85.64)	85.14 (71.41-98.87)	84.96 (71.28-98.64)	78.09 (66.29-89.88)	0.86
Social functioning	83.06 (71.57-94.56)	83.55 (71.54-95.55)	89.21 (77.24-101.18)	78.78 (68.46-89.09)	0.62
Mental health	70.44 (60.17-80.71)	74.89 (64.16-85.62)	75.51 (64.82-86.20)	65.17(55.95-74.39)	0.31
Physical health dimensions[d]					
Physical component summary	53.13 (49.54-56.73)	47.99 (44.32-51.67)	45.80 (42.07-49.52)	47.02 (43.86-50.18)	0.04
Physical functioning	78.91 (69.18-88.64)	66.38 (56.43-76.34)	66.95 (56.87-77.03)	72.77 (64.21-81.33)	0.79
Role-physical	80.39 (67.44-93.33)	78.82 (65.57-92.06)	71.40 (57.99-84.82)	66.45 (55.06-77.84)	0.06
Bodily pain	84.87 (75.05-94.69)	75.09 (65.04-85.14)	68.21 (58.04-78.39)	61.59 (52.95-70.23)	<0.001[†]
General health	65.33 (55.65-75.02)	65.52 (55.60-75.43)	61.63 (51.59-71.66)	61.66 (53.14-70.19)	0.45

[a]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-≤25, >25), time since surgery (years, <2, 2-≤5, >5), physical activity (MET-hours/week, quartile), and adjuvant chemotherapy (yes, no) and center

[b]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-≤25, >25), time since surgery (years, <2, 2-≤5, >5), adjuvant chemotherapy (yes, no) and center

[c]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-≤25, >25), time since surgery (years, <2, 2-≤5, >5), physical activity (MET-hours/week, quartile), breast cancer stage (stage II, stage III) and center

[d]Multivariate model was adjusted for age (years, continuous), total energy intake (kcal/day, continuous), use of supplement (yes, no), BMI (kg/m², <23, 23-≤25, >25), time since surgery (years, <2, 2-≤5, >5), breast cancer stage (stage II, stage III) and center

[†]*P* value <0.1 after adjusting for multiple comparisons using false discovery rate (FDR) method

V. Discussion

In this cross-sectional study, dietary pattern associated with inflammatory biomarkers among Korean breast cancer survivors was empirically derived and it was characterized by high intakes of red meat, white rice, and noodles and low intakes of seafood-based soup.

Higher inflammatory dietary pattern scores were inversely associated with lower scores of physical component summary, role-physical and bodily pain domains among stage II or III breast cancer survivors, whereas higher scores of the inflammatory dietary pattern were associated with higher levels of role-emotional, social-functioning and role-physical domains among those with stage I breast cancer. The inverse associations of inflammatory dietary pattern scores with HRQOL levels were more pronounced in stage II or III breast cancer survivors with longer time since surgery (≥3.1 years, median time), where the higher inflammatory dietary pattern scores were associated with lower scores of physical component summary, physical functioning and role-physical domain. Among stage II or III breast cancer survivors with shorter time since surgery (<3.1 years), the inflammatory dietary pattern scores were inversely associated with the scores of bodily pain domain.

Food components included in the inflammatory dietary pattern in this study were comparable to other studies that explored the inflammatory dietary pattern that comprised meat (red meat or processed meat), low-fiber foods (e.g., white rice or bread) and alcohol intakes (Barbaresko et al., 2013; Centritto et al., 2009;

Hoffmann, Zyriax, et al., 2004; Liese et al., 2009; Nettleton et al., 2007; Schulze et al., 2005; Tabung et al., 2016). Higher red meat intake was associated with higher levels of CRP and IL-6 and TNF-α receptor 2 (Azadbakht et al., 2009; Ley et al., 2014; Montonen et al., 2013; Tabung et al., 2016) and some of those associations were no longer significant after adjusting for BMI (Chai et al., 2017; Ley et al., 2014; Montonen et al., 2013). Additionally, *N*-glycolylneuraminic acid, rich in red meat, has been suggested to cause chronic inflammation and inflammatory disease (Samraj et al., 2015). White rice and noodles were selected as an inflammatory dietary pattern component in other studies (Centritto et al., 2009; Tabung et al., 2016). It has been proposed that high glucose may lead to an inflammatory response accompanied by hyperinsulinemia and insulin resistance, thereby causing low-grade chronic inflammation (Bosma-den Boer et al., 2012). A low intake of seafood-based soup associated with high hsCRP levels may be partly explained by ω-3 fatty acids. A higher intake of ω-3 fatty acids in the form of eicosapentaenoic acid and docosahexaenoic acid has been known to regulate the production of pro-inflammatory cytokines (Shivappa et al., 2014; Simopoulos, 2002). The polyunsaturated fatty acids from fish intakes including eicosapentaenoic acid and docosahexaenoic acid were inversely associated with the levels of soluble TNF receptors 1 and 2 and CRP among US men and women (Pischon et al., 2003). The effect of diet on inflammation may be partly mediated by obesity (Galland, 2010; Oddy et al., 2018) or the diet itself may directly modulate the inflammatory status (Barbaresko et al., 2013; Bosma-den Boer et al., 2012; Galland, 2010; Giugliano et al., 2006).

Several mechanisms have been introduced in developing mental and physical fatigue in relation to inflammation. Evidence has shown the link between inflammation and sickness behavior or fatigue in both animal and human studies (Bower, 2007; Dantzer, 2001; Schubert et al., 2007). Regarding neuroinflammation, pro-inflammatory cytokines may alter the central nervous system neurotransmission and brain serotonin metabolism (Clement et al., 1997) or increase neurotoxic metabolites within the brain, leading to depression (Capuron et al., 2003; Heyes et al., 1996). In addition, increased levels of pro-inflammatory cytokines may directly or indirectly elevate pain sensitivity (Cui et al., 2000; Obreja et al., 2002; Parada et al., 2003). Increased levels of inflammatory cytokines, including CRP and IL-6, were associated with physical performance (Cesari et al., 2004; Taaffe et al., 2000).

However, despite the evidences indicating the link between inflammation and symptoms related with HRQOL, studies on the associations between the inflammatory dietary pattern and overall HRQOL, particularly in cancer survivors, are scarce. The majority of previous studies that investigated the association of dietary pattern with HRQOL used predefined dietary pattern, or derived using PCA or factor analysis. A pilot study of 44 US postmenopausal breast cancer survivors investigated the relationship of Health Eating Index-2010 diet with inflammation and then examined the association between the Health Eating Index-2010 and HRQOL scores (Orchard et al., 2018). That study found inverse correlations of adherence to the Healthy Eating Index-2010 diet with the levels of IL-6 and TNF-α receptor 2 among women who had chemotherapy treatment but no association between adherence to Healthy Eating Index-2010 diet and the HRQOL scores.

The stage I breast cancer survivors had a worse status of HRQOL, while stage I breast cancer survivors had a better status of HRQOL with inflammatory dietary pattern scores. It remains unclear why the associations differed by stage status. Because breast cancer patients diagnosed with advanced cancer stage were more likely to receive chemotherapy and other therapies (Ho et al., 2018), it is possible that the increased inflammation was partly due to chemotherapy, and other adjuvant therapy could be more pronounced among stage II or III breast cancer survivors than stage I breast cancer survivors; inverse associations with better HRQOL levels were observed only among stage II or III breast cancer survivors. In this study, 90.18% of stage II to III breast cancer survivors received chemotherapy, and 53.91% of those with stage I breast cancer received chemotherapy. Given that chemotherapy has been known to elevate the inflammatory cytokine levels (Grivennikov et al., 2010; Zong et al., 2006) and is associated with a poor HRQOL status (Bower et al., 2011; Ganz et al., 2002; Ho et al., 2018; Pusztai et al., 2004), inflammatory potential diet could be associated with a worse HRQOL among cancer patients with an advanced disease status. Further studies regarding an inflammatory potential diet and HRQOL are warranted.

Applying the empirically derived dietary pattern from one population to another is another issue in investigating the association between dietary pattern and health outcome (Schulze et al., 2003). A variation of inflammatory biomarker levels and food groups correlated with those variations may differ among the population. Thus, food groups that loaded high at the extracted factor were selected as an inflammatory dietary pattern and were applied to participants without a blood specimen, thereby the dietary pattern reflects the inflammatory status of the whole

population. When the data were separately examined the association of inflammatory dietary pattern score with HRQOL status in breast cancer survivors whose inflammatory biomarkers were measured, the stronger inverse associations with several domains of HRQOL were not observed in the whole population. This might be natural considering the difference in correlation of derived dietary pattern with the variation of inflammatory biomarker levels between women who were and were not included in the derivation of inflammatory dietary pattern analysis. Nevertheless, inverse associations with physical component summary, role-physical and bodily pain scores in stage II or III breast cancer survivors were consistent in both whole participants and those with a blood specimen. This may indicate that extracted inflammatory dietary pattern may be able to reflect HRQOL status through inflammatory dietary pattern.

This is the first study of breast cancer survivors that empirically explored inflammatory dietary pattern and examined its association with quality of life of breast cancer survivors. However, cautious interpretation is required because several limitations might exist in the present study. First, the FFQs and 3-day dietary records were used to calculate the food intakes. This difference in dietary measurement could be an effect modifier, but the trends were similar when the analyses were limited to women whose dietary intakes were assessed using 3-day dietary records. Additionally, the characteristics of women who filled out the FFQs and who recorded their food intake using dietary records were not substantially different. Second, the sample size of the study was relatively small. However, a significant association even at FDR<0.1 was observed. Third, the unmeasured or residual confounding factors could be remained. Finally, given that the current

study design was cross-sectional, the causal relationship between the inflammatory dietary pattern and HRQOL could not be examined.

In conclusion, inflammatory dietary pattern was characterized as high intakes of red meat, white rice and noodles, and low intakes of seafood-based soup. Although the present study did not infer a causal relationship between inflammatory dietary pattern and the HRQOL levels, breast cancer survivors and their caregivers may need to consider avoiding pro-inflammatory diet to improve HRQOL status. This study warrants further prospective investigation to elucidate whether the inflammatory dietary pattern worsens the HRQOL among breast cancer survivors and whether the association is differed by cancer stage.

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국문초록

유방암 경험자의 염증식이패턴과 삶의 질과의 연관성

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문상은

암 경험자들에 있어 만성 염증은 삶의 질을 떨어뜨리며 식이요인은 염증상태에 영향을 미치는 것으로 알려져 왔다. 그러나 현재까지 유방암 경험자와 염증과 연관된 식이와 삶의 질과의 연관성에 대한 근거는 부족하였다. 따라서 본 연구는 한국에 있는 유방암 경험자의 염증식이패턴을 도출하고, 염증식이패턴과 삶의 질과의 연관성을 파악하고자 하였다. 본 연구에는 총 454 명의 33 세부터 81 세까지의 여성 유방암 경험자들을 포함하였다. 연구 참가자들의 식이조사는 3 일치

식사기록지 혹은, 3 일치 식사기록지를 수행하지 않은 대상자의 경우 식사섭취빈도설문지를 통해 조사되었다. 또한, 삶의 질은 Short Form 36 (SF-36) Health Survey 의 자가기록을 통해 조사되었다. 염증식이패턴은 연구 참여자의 일부 (158 명) 가 제공한 혈장 고감도 C-반응성 단백질, interleukin-6 (IL-6) 그리고 종양괴사인자-알파 수치와 식사 섭취량으로 축소랭크회귀모델을 이용하여 염증지표의 변이를 최대로 설명하는 패턴을 도출하였다. 염증식이패턴 점수에 따른 삶의 질 점수의 연관성은 일반화 선형모델을 이용하여 분석되었고, 이를 통해 최소 제곱 평균과 95% 신뢰구간을 추정하였다. 분석 결과, 염증식이패턴은 높은 적색육, 흰 쌀밥, 국수 섭취와 낮은 해산물 국 및 탕 섭취로 구성되었다. 유방암 병기가 II 혹은 III인 대상자들에서 염증식이패턴 점수가 높을수록 신체 건강 요약, 신체적 역할 제한과 통증 점수가 감소하는 것으로 나타났다. 신체 건강 요약 점수의 경우, 최소 제곱 평균 (95% 신뢰구간)은 최하위 사분위수에서 51.06 (49.07-53.06) 이고 최상위 사분위수에서 47.09 (45.14-49.04) 였다 (*P* for trend=0.03). 신체적 역할 제한 점수의 경우, 최소제곱평균과 (95% 신뢰구간)은 최하위 사분위수에서 80.11 (72.90-87.32) 이고 최상위 사분위수에서 64.06 (57.00-71.12) 이었다 (*P* for trend=0.01). 통증 점수의 경우 최소 제곱 평균 (95% 신뢰구간)은 최하위 사분위수에서 79.42 (73.45-85.39) 이고 최상위 사분위수에서 65.71 (59.87-71.56) 이었다 (*P* for trend=0.01). 반면, 유방암 병기가 I 인

대상자들의 경우 감정적 역할 제한, 사회적 기능과 신체적 역할 제한 점수가 염증식이패턴 점수가 높아짐에 따라 증가하는 것으로 나타났다. 감정적 역할제한 점수의 경우 최소제곱평균과 (95% 신뢰구간)은 최하위 사분위수에서 75.56 (69.81-81.30) 이고 최상위 사분위수에서 82.95 (77.05-88.85) 였다 (*P* for trend=0.03). 사회적 기능 점수의 경우, 최소제곱평균과 (95% 신뢰구간)은 최하위 사분위수에서 82.75 (78.16-87.34) 이고 최상위 사분위수에서 89.48 (84.77-94.19) 이었다 (*P* for trend=0.04). 신체적 역할 제한 점수의 경우, 최소제곱평균과 (95% 신뢰구간)은 최하위 사분위수에서 72.83 (66.87-78.78) 이고 최상위 사분위수에서 81.42 (75.27-87.58) 였다 (*P* for trend=0.02). 결론적으로, 본 연구에서 도출한 염증식이패턴은 높은 적색육, 흰 쌀밥, 국수 섭취와 낮은 해산물 국 및 탕 섭취로 구성되었다. 이 염증식이패턴은 유방암 병기가 Ⅱ 혹은 Ⅲ인 대상자에서 낮은 신체 건강 관련 삶의 질과 연관이 있는 것으로 나타났다. 본 연구는 염증식이패턴과 삶의 질 간의 인과성을 제시할 수 없지만, 유방암 경험자나 그들의 보호자 및 간병인은 삶의 질을 증진시키기 위해 염증식이패턴의 섭취를 낮추는 것을 고려해 볼 수 있다. 본 연구는 후의 전향적 연구들을 통해 염증식이패턴이 유방암 경험자의 삶의 질에 미치는 부정적인 효과와 유방암 병기에 따른 효과의 차이 여부를 밝힐 필요성을 제시하고 있다.

주요어: 유방암 경험자, 염증식이패턴, 삶의 질, 축소랭크회귀모델, 고감도 C-반응성 단백질, Interleukin-6 (IL-6), 종양괴사인자-알파

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