

Dietary inflammatory index before diagnosis and survival in an Italian cohort of women with breast cancer

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Abstract

The dietary inflammatory indexTM (DII) has been shown to correlate with concentrations of several inflammatory markers and a variety of chronic disease endpoints, including cancers of various anatomic sites. We investigated whether the DII was associated with the risk for death among women with breast cancer (BrCa). This retrospective cohort study included 1453 women with BrCa, diagnosed between 1990 and 1994, and previously enrolled in a case–control study in northern Italy. With a median follow-up of 12.6 years, we observed 503 deaths, among which 398 were due to BrCa. The usual diet was assessed at BrCa diagnosis using a validated FFQ. DII scores were calculated using thirty-one foods/nutrients. Hazard ratios (HR) of death from all causes or from BrCa, with corresponding 95% CI, were calculated using the Cox models, adjusted for age at diagnosis, tumour stage, oestrogen/progesterone receptor status and other potential confounders. The median DII score of the study women was -1.23 , with a relatively narrow range (interquartile range -2.24 to -0.11), indicating a mainly anti-inflammatory diet. There was no difference in survival according to DII tertiles, neither considering all-cause mortality (HR_{tertile III v. I} 1.00; 95% CI 0.78, 1.28) nor BrCa-specific mortality (HR_{tertile III v. I} 0.97; 95% CI 0.73, 1.27). Study findings did not suggest an association between the inflammatory potential of diet, measured by the DII, and the survival of BrCa women. However, further studies are needed in populations reporting higher DII scores and a broader range of variability in the scores.

Key words: Breast cancer: Diets: Dietary inflammatory index: Inflammation: Survival

Breast cancer (BrCa) is, by far, the most common cancer among women worldwide and it still counts as the primary cause of cancer-related death among women in most regions, including Europe⁽¹⁾.

Current evidence indicates that different markers of systemic inflammatory status can be related to worse prognosis of several cancer types, including BrCa. Elevated levels of C-reactive protein (CRP) and serum amyloid A have been associated with lower all-cause and BrCa-specific survival among BrCa patients⁽²⁾. Inflammation measured by the Glasgow Prognostic Score, an index based on CRP and albumin levels, has been

shown to be associated with worse cancer prognosis among several cancer patients, including women with BrCa⁽³⁾. High concentrations of several inflammatory markers, including CRP, IL-6 and TNF- α , were also found to be associated with BrCa progression and prognosis^(4,5).

In addition, there is rising interest in a potential role of diet in modulating the inflammatory process, supported by increasing scientific evidence⁽⁶⁾. Specific foods and nutrients have been identified as pro- or anti-inflammatory agents, according to their association with levels of inflammatory biomarkers. On the basis of careful review and scoring of this evidence, the dietary

Abbreviations: BrCa, breast cancer; DII, dietary inflammatory index; ER, oestrogen receptor; HR, hazard ratios; PR, progesterone receptor.

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inflammatory indexTM (DII) has been derived by a review of the extensive literature on the topic⁽⁷⁾. By its design, the DII correlates with inflammatory markers such as CRP, IL-1 β , IL-6, IL-10 and TNF- α ⁽⁸⁾.

A cohort study on healthy US women reported that higher DII scores were associated with an increased risk for death from BrCa though not with its incidence⁽⁹⁾. Inconsistent results on the association between DII and risk for BrCa emerged from previous studies that reported positive^(10,11) or null associations^(12,13). In particular, a positive association emerged in the Italian case-control study⁽¹¹⁾ from which this cohort was derived, in which women in the highest DII quintile reported a 75% higher risk for BrCa than those in the lowest quintile. It is therefore possible that DII scores are associated with survival from BrCa, but, to our knowledge, no previous study has investigated this issue in a cohort of women with BrCa. Thus, we assessed whether the inflammatory potential of diet, measured at diagnosis using the DII score, could be associated with overall and BrCa-specific survival in a cohort of Italian women previously diagnosed with BrCa.

Methods

Study subjects

This study is part of a retrospective cohort investigation on the survival of women with BrCa, as described in detail elsewhere^(14,15). By the term retrospective, we define a cohort study that was conceived after the events of interest had already occurred. In brief, the study included 1453 women initially enrolled as cases, between 1990 and 1994, in a case-control study on the association between lifestyle factors and BrCa risk^(11,16). The original case-control study⁽¹⁶⁾ was conducted in six Italian centres, whereas this cohort investigation included only three areas (i.e. Aviano/Pordenone, the urban area of Genova, and the Forlì province in northern Italy) located within population-based cancer registry areas (i.e. the Friuli Venezia Giulia and Veneto regions, the Genova province and the Forlì province), which made it possible to retrieve vital status and cause of death data for cohort members.

Cases were women with histologically confirmed BrCa who had been diagnosed ≤ 1 year before the interview; they were between 23 and 74 years of age and had no previous diagnosis of any other cancer. These women had been consecutive cases identified in major local hospitals in the study areas. All cases had signed an informed consent, according to the rules of the internal Board of Ethics, which approved the study protocol.

Data collection and dietary assessment

BrCa cases had been interviewed during their hospital stay by trained personnel, using a structured questionnaire to collect information on sociodemographic characteristics and lifestyle factors (e.g. education, tobacco smoking, physical activity, anthropometric measures, anamnesis). The usual diet during the 2 years before BrCa diagnosis had been assessed using a FFQ that included seventy-eight foods and beverages. Women had been asked to indicate the average weekly frequency of consumption of each dietary item; intakes lower than once a

week, but at least once a month, were coded as 0.5/week. Serving size was defined either in a 'natural' unit (e.g. one apple, one egg) or as an average serving in the Italian diet (e.g. 80 g serving of pasta; 150 g of red meat). Women were provided with pictures of average serving sizes and were asked to report whether their usual servings were less or more in quantity. For fruit and vegetables subject to seasonal variation, consumption in season and the corresponding duration were determined. After allowance for variation in serving size and seasonal variation, nutrient and total energy intakes were determined using the Italian food composition database⁽¹⁷⁾. The FFQ showed satisfactory validity⁽¹⁸⁾ and reproducibility⁽¹⁹⁾. BrCa characteristics including TNM classification of tumour stage and oestrogen/progesterone receptor (ER/PR) status were gathered from the original medical records and centrally reviewed by a physician.

Dietary inflammatory index

The DII was calculated in the original case-control study⁽¹¹⁾ using forty-five parameters including foods, nutrients and other food components, which have been shown to be associated with inflammatory biomarkers in a literature review (i.e. from >6000 articles published between 1950 and 2010 of which 1943 qualifying studies were reviewed and scored)⁽⁷⁾. Robust estimates of the 'global' mean and the standard deviation of consumption of each of the forty-five parameters considered in the DII definition were derived from a comprehensive database, including data from eleven countries worldwide⁽⁷⁾. A higher DII score indicated a more pro-inflammatory diet and a lower DII score indicated a more anti-inflammatory diet.

The DII score for each woman was calculated by linking data collected using the FFQ to the previously described global database. In the present study, the DII computation considered only the following thirty-one parameters (available in our FFQ) among the forty-five possible parameters included in the original DII definition: carbohydrates, proteins, fats, alcohol, fibres, cholesterol, SFA, MUFA, PUFA, *n*-3, *n*-6, niacin, thiamin, riboflavin, vitamin B₆, Fe, Zn, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, β carotene, anthocyanidins, flavan-3-ols, flavonols, flavanones, flavones, isoflavones, caffeine and tea. The thirteen missing food parameters were pepper, saffron, turmeric, garlic, ginger, onion, eugenol, *trans*-fat, Se, Mg, vitamin B₁₂, thyme and rosemary.

For each parameter, a woman's exposure relative to the global mean was expressed using a *z*-score (i.e. standardisation by subtracting the mean of the regionally representative subset included in the global database from the amount reported in the FFQ and dividing the result by the standard deviation of the parameter). *z*-Scores were converted into percentiles centred at 0 (by multiplying by 2 and subtracting 1) in order to minimise right skewing. The centred percentile score for each parameter and for each woman was then multiplied by the respective parameter's literature-derived effect score⁽⁷⁾. The overall DII score, for each study woman, was then calculated as a linear combination of all of the parameter-specific DII scores as follows⁽⁷⁾: $DII = b_1 \times n_1 + b_2 \times n_2, \dots, b_{31} \times n_{31}$, where *b* is the literature-derived effect score for each parameter and *n* the parameter-specific centred percentile derived from the current FFQ dietary data.

A description of the validation work, including both dietary recalls and a structured questionnaire similar to a FFQ, is also available⁽⁸⁾.

Statistical analysis

Considering the number of BrCa-related deaths, the exposure variable was categorised into tertiles to ensure a sufficient number of events in sub-group analyses. The associations between the DII tertiles and the main characteristics of the study women were evaluated using the Mantel–Haenszel χ^2 test for ordinal variables and the Pearson χ^2 test for nominal variables. Differences in the mean across DII tertiles of quantitative variables were evaluated by ANOVA.

Each woman accumulated person-time towards the risk for death in months from the date of BrCa diagnosis to the date of death or to the end of follow-up (i.e. 30 November 2006 in the Friuli Venezia Giulia region and 30 June 2005 for the other areas), whichever came first. Women who were lost at follow-up (1.7%) because of migration from the study areas were censored at the date of last follow-up information.

The overall survival probabilities according to DII tertiles were estimated by means of the Kaplan–Meier method. The log-rank test was used to assess survival differences between survival curves. In the analyses of cause-specific mortality, deaths from any other cause except the one under investigation were censored. Hazard ratios (HR) of death by any cause, BrCa, and by all cancers, with corresponding 95% CI, were estimated using the Cox proportional hazards models⁽²⁰⁾. The proportional hazards assumption was assessed using the Schoenfeld residuals and by including interactions with follow-up time⁽²¹⁾, but no violation was detected.

HR were adjusted for area of residence (Friuli Venezia Giulia, Veneto, Genova, Forlì), calendar year of diagnosis (1990–1992, 1993–1994), age at diagnosis (quinquennia), education (<7, 7–11, ≥ 12 years), menopausal status (premenopause, postmenopause), smoking habits at diagnosis (never, former, current <15 cigarettes/d, current ≥ 15 cigarettes/d), BMI 1 year before diagnosis (BMI, kg/m², calculated as weight divided by squared height: <25, 25–29, ≥ 30 kg/m²) total energy intake (kcal/d, continuous), ER/PR status (ER–/PR–, ER+ /PR–, ER–/PR+, ER +/PR+, unknown) and TNM classification of tumour stage (I, II, III–IV, unknown). The analyses were performed using SAS software 9.4 (SAS Institute Inc.).

Results

Among 1453 enrolled women with BrCa, the median length of follow-up was 12.6 years (interquartile range, IQR 8.0–13.6 years) for a total of 15 628 person-years of observation. Overall, 503 (34.6%, median follow-up 5.3 years, IQR 2.9–9.2 years) deaths were recorded, among which 398 (79.1% of all deaths, median follow-up 4.7 years, IQR 2.6–7.9 years) were due to BrCa. The crude overall survival probability at 10 years from BrCa diagnosis was 74 (95% CI 71, 77) %.

The median DII score in the study population was –1.23 (IQR –2.24 to –0.11). No significant associations emerged between DII tertiles and age at diagnosis, years of education,

Table 1. Distribution of 1453 women with breast cancer according to dietary inflammatory index and selected variables at diagnosis (Italy, 1990–1994) (Numbers and percentages)

	Dietary inflammatory index (tertiles)						P
	I (<–1.87)		II (–1.87 to <–0.54)		III (\geq –0.54)		
	n	%	n	%	n	%	
Age at diagnosis (years)							
<45	88	33.9	94	36.2	78	30.0	0.06*
45–54	157	36.5	135	31.4	138	32.1	
55–64	148	32.8	146	32.4	157	34.8	
≥ 65	92	29.5	108	34.6	112	35.9	
Education (years)							
<7	256	34.9	221	30.1	257	35.0	0.55*
7–11	143	34.4	153	36.8	120	28.8	
≥ 12	86	28.9	109	36.6	103	34.6	
Menopausal status							
Premenopause	199	36.0	182	32.9	172	31.1	0.07*
Postmenopause	286	31.8	301	33.4	313	34.8	
Smoking habit							
Never smoker	327	35.0	299	32.0	308	33.0	0.33*
Former smoker	66	28.8	78	34.1	85	37.1	
Current smoker							
<15 cigarettes/d	63	34.6	66	36.3	53	29.1	
≥ 15 cigarettes/d	29	26.9	40	37.0	39	36.1	
BMI at diagnosis (kg/m ²)							
<25	274	33.7	274	33.7	266	32.7	0.38*
25–29	155	33.4	157	33.8	152	32.8	
≥ 30	55	32.0	51	29.7	66	38.4	
Receptor status							
ER–/PR–	44	29.9	50	34.0	53	36.1	<0.01†
ER–/PR+	13	25.0	17	32.7	22	42.3	
ER+ /PR–	45	48.9	22	23.9	25	27.2	
ER+ /PR+	235	39.0	178	29.5	190	31.5	
Unknown	148	26.5	216	38.6	195	34.9	
Tumour stage (TNM classification)							
I	154	32.4	153	32.2	168	35.4	0.78*
II	216	33.6	221	34.4	205	31.9	
III–IV	72	37.3	61	31.6	60	31.1	
Unknown	43	30.1	48	33.6	52	36.4	

ER, oestrogen receptor; PR, progesterone receptor.

* Mantel–Haenszel χ^2 test (unknown excluded).

† Pearson's χ^2 test (unknown excluded).

menopausal status, smoking habit, BMI and TNM tumour stage (Table 1). Conversely, a statistically significant association was found between DII and hormone receptor status ($P < 0.01$), with ER– BrCa women reporting lower values of DII. The consumption of main food groups across DII tertiles, reported in Table 2, showed reduced mean intakes of pasta, white meat, cheese, fruit, vegetables and coffee among women in the highest DII tertile.

No differences emerged in crude overall survival probabilities according to DII tertiles (Fig. 1). In the multivariate survival analysis, BrCa women with a more elevated DII were not observed to be at an increased risk for death from all causes (HR_{tertile III v. I} 1.00; 95% CI 0.78, 1.28) or from BrCa-specific causes (HR_{tertile III v. I} 0.97; 95% CI 0.73, 1.27) (Table 3). Similarly, no association emerged between DII and overall cancer-related mortality (HR_{tertile III v. I} 0.95; 95% CI 0.73, 1.24). No heterogeneity emerged in stratified analyses according to ER/PR status, or according to menopausal status, BMI, tumour

Table 2. Food groups (servings/week) across tertiles of dietary inflammatory index among 1453 women with breast cancer (Italy, 1990–1994) (Mean values and standard deviations)

Food groups (servings/week)	Dietary inflammatory index (tertiles)						ANOVA (<i>P</i>)
	I (<-1.87)		II (-1.87 to <-0.54)		III (≥-0.54)		
	Mean	SD	Mean	SD	Mean	SD	
Bread	17.87	11.70	17.64	10.78	17.82	11.68	0.95
Pasta	5.21	2.01	4.93	1.91	4.54	1.97	<0.01
Red meat	4.02	2.03	3.77	1.94	3.85	2.14	0.19
White meat	2.23	1.38	2.09	1.37	2.04	1.40	0.03
Pork	2.82	1.84	2.97	2.10	3.06	2.23	0.07
Fish	1.65	1.08	1.71	1.00	1.68	1.10	0.56
Milk	6.15	7.38	4.65	4.57	5.36	6.19	0.05
Cheese	5.09	3.54	4.64	2.83	4.21	2.53	<0.01
Fruit	25.15	12.32	20.82	11.20	18.38	10.34	<0.01
Vegetables	15.28	6.55	13.40	5.46	12.71	5.25	<0.01
Pulses	0.81	0.82	0.81	0.73	0.86	0.92	0.40
Potatoes	1.80	1.33	1.76	1.31	1.68	1.26	0.14
Coffee	18.75	11.63	17.12	10.77	16.49	12.01	<0.01
Dessert	5.68	5.74	6.08	6.44	5.78	6.35	0.79

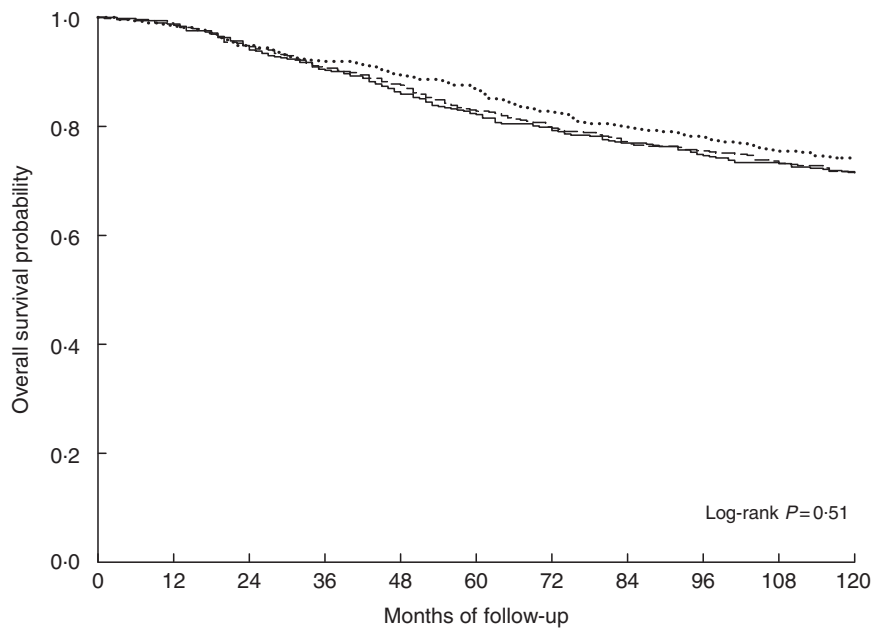


Fig. 1. All-cause survival curves among 1453 women with breast cancer, according to tertiles of dietary inflammation index (DII) (Italy, 1990–1994). —, DII – first tertile; ·····, DII – second tertile; - - -, DII – third tertile.

stage (Table 3) or other potential confounders (e.g. age at diagnosis, education; data not shown).

Discussion

These study findings did not support an association between the DII score and the prognosis for women with BrCa, neither considering overall mortality nor considering BrCa-specific mortality. These results seemed to be in contrast with those reported in a US cohort of healthy women showing a direct association between the DII score and BrCa mortality (HR 1.33; 95% CI 1.01, 1.76, for the highest *v.* the lowest quintile of DII), though not with BrCa incidence (HR 0.99; 95% CI 0.91, 1.07)⁽⁹⁾.

However, it should be noted that the mean value of the DII score in this Italian study was lower (-1.05 (SD 1.64)) and had a generally narrower range than that reported in the USA (-0.78 (SD 2.61))⁽⁹⁾. DII scores in Germany (0.86 (SD 1.30)) also were higher⁽¹²⁾, and those in Sweden were much higher (2.67 (SD 1.47))⁽¹⁰⁾ than those in our study. This was not unexpected, because the Italian women enrolled in the present study were, by culture, probably more adherent to a Mediterranean diet, which has been shown to be inversely related to the DII score⁽²²⁾, than women living in USA or northern Europe. Indeed, the boundary of the highest tertile of DII score (-0.54) was clearly anti-inflammatory in our study population. Given this context, it is possible that the range of DII values reported

Table 3. All-cause death and breast cancer death in 1453 women with breast cancer, according to tertiles of dietary inflammatory index and in strata of selected variables (Italy, 1990–1994) (Numbers and percentages; hazard ratios (HR) and 95% confidence intervals)

	Dietary inflammatory index (tertiles)											χ^2 trend
	I (<-1.87)			II (-1.87 to <-0.54)				III (\geq -0.54)				
	n	%	HR	n	%	HR*	95% CI	n	%	HR*	95% CI	
Total cases	485			483				485				
All-cause deaths	177	36.5	1†	155	32.1	0.90	0.71, 1.13	171	35.3	1.00	0.78, 1.28	<0.01, P=0.95
Breast cancer deaths	145	29.9	1†	119	24.6	0.83	0.63, 1.08	134	27.6	0.97	0.73, 1.27	0.03, P=0.86
Premenopause	199			182				172				
All-cause deaths	59	29.6	1†	49	26.9	0.90	0.58, 1.39	44	25.6	0.84	0.52, 1.34	0.54, P=0.46
Breast cancer deaths	53	26.6	1†	44	24.2	0.82	0.51, 1.30	40	23.3	0.76	0.46, 1.26	1.05, P=0.31
Postmenopause	286			301				313				
All-cause deaths	118	41.3	1†	106	35.2	0.88	0.66, 1.17	127	40.6	1.05	0.78, 1.40	0.15, P=0.70
Breast cancer deaths	92	32.2	1†	75	24.9	0.81	0.58, 1.13	94	30.0	1.07	0.77, 1.51	0.23, P=0.63
BMI < 25 kg/m ²	274			274				266				
All-cause deaths	92	33.6	1†	84	30.7	0.98	0.71, 1.36	89	33.5	1.02	0.72, 1.43	0.01, P=0.92
Breast cancer deaths	76	27.7	1†	65	23.7	0.87	0.60, 1.26	69	25.9	0.95	0.65, 1.39	0.05, P=0.83
BMI \geq 25 kg/m ²	210			208				218				
All-cause deaths	84	40.0	1†	71	34.1	0.84	0.59, 1.19	81	37.2	1.01	0.70, 1.44	<0.01, P=0.94
Breast cancer deaths	68	32.4	1†	54	26.0	0.82	0.55, 1.21	64	29.4	1.00	0.67, 1.50	<0.01, P=0.97
ER-	57			67				75				
All-cause deaths	29	50.9	1†	23	34.3	0.62	0.30, 1.28	25	33.3	0.70	0.36, 1.28	0.84, P=0.36
Breast cancer deaths	28	49.1	1†	21	31.3	0.65	0.31, 1.38	23	30.7	0.76	0.38, 1.52	0.41, P=0.52
ER+	280			200				215				
All-cause deaths	103	36.8	1†	69	34.5	0.92	0.66, 1.29	86	40.0	1.08	0.77, 1.52	0.21, P=0.65
Breast cancer deaths	82	29.3	1†	55	27.5	0.91	0.63, 1.33	66	30.7	1.05	0.71, 1.54	0.05, P=0.82
I-II TNM stage	370			374				373				
All-cause deaths	117	31.6	1†	104	27.8	0.87	0.65, 1.17	117	31.4	1.01	0.76, 1.35	<0.01, P=0.92
Breast cancer deaths	94	25.4	1†	74	19.8	0.76	0.54, 1.06	88	23.6	0.97	0.69, 1.35	<0.01, P=0.95
III-IV TNM stage	72			61				60				
All-cause deaths	45	62.5	1†	37	60.7	0.95	0.59, 1.56	39	65.0	1.04	0.64, 1.71	0.02, P=0.88
Breast cancer deaths	41	56.9	1†	33	54.1	0.90	0.54, 1.53	34	56.7	0.91	0.54, 1.53	0.14, P=0.71

ER, oestrogen receptor; PR, progesterone receptor.

* Estimated from the Cox proportional hazards models adjusted for: area of residence, calendar year of diagnosis, age at diagnosis, education, menopausal status, smoking habit, BMI, total energy intake, hormone receptor status and TNM tumour stage, as appropriate.

† Reference category.

in our study population precluded an estimation of the effect of an actual pro-inflammatory diet compared with an anti-inflammatory one. Although a significant association with BrCa risk has been reported in the original case-control study⁽¹¹⁾, the mean DII score in that study was different (-0.39 (sd 1.86)) as it also included other areas where no follow-up information was available.

The unavailability of postdiagnosis changes in dietary habits was the major limitation of our study as it could have impacted BrCa survival. However, in Italy, at the time during which the original case-control study was conducted (i.e. 1990–1994), the general population was unaware of any presumed association between diet and BrCa risk, and no guidelines for dietary intervention in women with BrCa were in force. The lack of information on treatments after BrCa diagnosis also ought to be acknowledged as a study weakness. Another limitation was the use of thirty-one instead of forty-five parameters in the overall DII score computation. However, it has been shown that the inclusion of a subset of parameters (from seventeen up to forty-four) did not affect the validity of the association between DII and biomarkers of inflammation⁽⁸⁾. Finally, the original case-control study^(11,16) was not specifically designed to estimate HR, in particular, with regard to statistical power. However, given the large sample size and the very long follow-up time of the study women, which allowed the observation of a large number of events of interest, the null findings of the present study were unlikely due to lack of study power.

The use of the DII made it possible to evaluate the diet-associated inflammatory potential for the diet as a whole, that is, in contrast to considering specific foods or nutrients that have a known, specific effect on inflammation⁽⁸⁾. Among the strengths of our study were the long follow-up of BrCa cases, which allowed assessing long-term survival. Accurate evaluation of mortality outcomes was made possible by the local availability of high-quality population-based cancer registries⁽²³⁾. However, some misclassification on the specific cause of death cannot be totally excluded. Although enrolled as cases in a previous hospital-based case-control study, BrCa women included in this study are representative of the population of women with BrCa living in the study areas. Indeed, selection bias was minimised in the original case-control study⁽¹⁶⁾ by including all newly diagnosed BrCa women consecutively admitted to the major local hospitals in the study areas; no selection was made according to clinical characteristics or treatments. Further, refusal rate in the original case-control study was below 4% and only 1.7% of women had been lost at follow-up because of migration from the study areas.

Further adjustment for other potential confounders (e.g. alcohol intake, fruit and vegetables consumption) did not substantially modify the risk estimates. In addition, there were no BrCa patients who had reported regular use of aspirin (some anti-inflammatory medications that could confound the association between DII and inflammatory status) at the time of cancer diagnosis.

To conclude, this Italian study did not support a role for the inflammatory potential of diet, assessed at BrCa diagnosis using the DII score, on the survival of women with BrCa. However, further studies are needed in populations reporting higher DII scores and a broader range of variability.

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A. Z. and J. P. conceived and designed the study and drafted the manuscript; A. Z. performed statistical analyses; D. S. and L. D. M. conceived the study and contributed to data interpretation; N. S. and J. R. H. conceived the dietary inflammatory index (DII) and contributed to data interpretation; C. S., A. P., F. F. were responsible for cancer registry data and record linkage; C. P. assembled data and performed quality checks; all the authors have critically reviewed the manuscript for intellectual content.

J. R. H. owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the DII from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. N. S. is an employee of CHI. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project. None of the authors has any conflicts of interest to declare.

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