



UNIVERSITAT DE
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The role of dietary patterns and inflammation in breast cancer risk and survival

Carlota Castro Espin

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UNIVERSITAT DE
BARCELONA

PHD THESIS

THE ROLE OF DIETARY PATTERNS AND INFLAMMATION IN BREAST CANCER RISK AND SURVIVAL

Doctoral thesis report submitted by

CARLOTA CASTRO ESPIN

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Supervised by **Antonio Agudo Trigueros**

Unit of Nutrition and Cancer. Cancer Epidemiology Research Program.
Catalan Institute of Oncology (ICO)

Nutrition and Cancer Group. Epidemiology, Public Health, Cancer
Prevention and Palliative Care Program. Bellvitge Biomedical Research
Institute (IDIBELL)

L'Hospitalet de Llobregat, Barcelona, Spain

Tutor: **Casimiro Francisco Javierre Garcés**, Department of Physiological
Sciences II, School of Medicine, University of Barcelona, Barcelona, Spain.

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GLOSSARY

AICR	American Institute for cancer research
arMED	Adapted relative Mediterranean diet
BMI	Body mass index
CRP	C-reactive protein
DII	Dietary inflammatory index
DRRD	Diabetes risk reduction diet
EPIC	European Prospective Investigation into Cancer and Nutrition
ERDP	Estrogen-related dietary pattern
IARC	International Agency for Research on Cancer
ISD	Inflammatory score of diet
RRR	Reduced rank regression
WCRF	World Cancer Research Fund
WHEL	Women's Healthy Eating and Living
WHO	World Health Organization
WINS	Women's Intervention Nutrition Study

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Thesis in the form of a collection of published articles.

This thesis comprises 4 objectives and 5 articles: 3 original research published, 1 original research unpublished, 1 systematic review and meta-analysis published.

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THESIS SUMMARIES IN ENGLISH AND CATALAN

ABSTRACT

Title The role of dietary patterns and inflammation in breast cancer risk and survival.

Introduction Factors like body fatness and physical activity, influenced by diet, are associated with both breast cancer and low-grade chronic inflammation. The direct link between breast cancer and inflammatory processes, as well as the impact of modulating these processes through diet, remains uncertain. Studying diet's potential to affect chronic inflammation and other biological processes can provide insights for better dietary strategies in breast cancer prevention and survival. Additionally, investigating the connection between inflammatory biomarkers and breast cancer survival complements dietary pattern research and enhances our understanding of molecular mechanisms, especially those related to inflammation.

Hypotheses We suggest that diets capable of modulating low-grade chronic inflammation may exert an impact on the risk and prognosis of breast cancer. In addition, we hypothesise that adherence to dietary patterns related to other underlying mechanisms associated with breast carcinogenesis, such as insulin resistance or oestrogen metabolism, can impact on breast cancer survival. We also hypothesise that the Mediterranean diet may underscore beneficial biological mechanisms that could impact on a better prognosis of breast cancer survivors. We suggest that elevated levels of inflammatory markers could influence the «latent» inflammation that precedes cancer and have an impact on breast cancer prognosis.

Objectives To evaluate the association between the inflammatory potential of the diet, by means of the inflammatory score of the diet (ISD),

and the risk and survival of breast cancer. To examine the association between other dietary patterns related to biological mechanism, such as the Diabetes Risk Reduction Diet (DRRD) and the Estrogen-Related Dietary Pattern (ERDP), and cancer mortality among breast cancer survivors. To assess the relationship with breast cancer survival with a more traditional dietary pattern, the Mediterranean diet. To investigate the association between pre-diagnosis inflammatory biomarkers and breast cancer survival. To examine all these associations according to menopausal status, hormone receptor status, and tumour stage.

Methods We used data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study to examine the associations between dietary patterns and inflammatory markers in relation to outcomes of breast cancer. In a sample of 318,686 women from nine European countries followed for an average 14 years, 13,270 incident breast cancer cases were identified. The ISD was assessed in relation to breast cancer risk. The DRRD score, the ERDP, the ISD, and the arMED score were assessed in relation to mortality among breast cancer survivors. All dietary patterns were computed using data from diet questionnaires collected at recruitment in EPIC. Finally, the relationship between pre-diagnostic plasma inflammatory biomarkers (interleukin (IL)-6, IL-8, IL-10, IL-13, IL-17D, IL-1RA, TNF- α , IFN- γ , CRP, leptin, and adiponectin) breast cancer survival was assessed in 1538 breast cancer cases. For associations between breast cancer risk or survival and dietary patterns or inflammatory markers, Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). For breast cancer incidence, cohort entry time was defined as age at recruitment, and exit time age at diagnosis, death, or end of follow-up. For survival, age at diagnosis was the entry time and date of death or end of follow-up the exit time.

Main results Pro-inflammatory diets were associated with higher risk of breast cancer (12% increased risk comparing higher to lower quintile of the ISD). Higher adherence to the DRRD score and the arMED score were associated with lower risk of overall mortality (HR_{1-SD} 0.92; 95%CI 0.87–0.96 and HR_{1-SD} 0.92; 95%CI 0.87–0.97, respectively). In addition,

the ISD was borderline associated with 6% higher risk of overall mortality (HR_{1-SD} 1.06; 95%CI 1.00–1.12), probably limited to postmenopausal survivors. No significant association was observed with the ERDP. None of the dietary patterns were associated with BC-specific mortality. Regarding pre-diagnostic inflammatory markers, IL-6 was associated with higher risk of all-cause and breast cancer-specific mortality. Furthermore, higher levels of IL-6, IL-10, and TNF α were associated with an increased risk of all-cause mortality among postmenopausal breast cancer survivors.

Conclusions Adherence to pro-inflammatory diets may represent a modest risk factor for breast cancer development, and its role might be limited to premenopausal women. Adherence to these diets before breast cancer diagnosis may also represent a determinant of poor prognosis, especially among postmenopausal women. Adherence to diets associated to a reduced risk of type 2 diabetes prior to a breast cancer diagnosis, primarily operating through mechanisms related to insulin resistance, may significantly contribute to improving overall survival for breast cancer patients. Specifically, when comparing the highest and lowest levels of adherence to these diets, the difference in overall survival seems substantial. Higher adherence to the traditional Mediterranean diet before diagnosis, with exclusion of alcohol, may improve long-term prognosis, especially among postmenopausal breast cancer survivors. The associations between dietary patterns and breast cancer outcomes seemed to not largely differ according to hormone receptor status. High levels of IL-6 before a breast cancer diagnosis could serve as a significant prognostic marker for long-term survival in breast cancer survivors. Elevated levels of IL-6, IL-10, and TNF α appears to be particularly relevant among postmenopausal women, predicting a higher risk of all-cause mortality.

RESUM

Títol El paper dels patrons alimentaris i la inflamació en el risc i la supervivència del càncer de mama

Introducció Factors com l'índex de massa corporal i l'activitat física, influïts per la dieta, estan associats tant al càncer de mama com a la inflamació crònica de baixa grau. La relació directa entre el càncer de mama i els processos inflamatoris, així com l'impacte de la modificació d'aquests processos mitjançant la dieta, roman incerta. L'estudi del potencial que té la dieta per afectar la inflamació crònica i altres processos biològics pot proporcionar idees per a millors estratègies dietètiques en la prevenció i la supervivència del càncer de mama. A més, investigar la connexió entre els biomarcadors inflamatoris i la supervivència del càncer de mama complementa la recerca sobre els patrons dietètics i millora la nostra comprensió dels mecanismes moleculars, especialment aquells relacionats amb la inflamació.

Hipòtesis Suggerim que les dietes capaces de modular la inflamació crònica de baix grau poden tenir un impacte en el risc i el pronòstic del càncer de mama. A més, hipotetitzem que l'adherència als patrons dietètics relacionats amb altres mecanismes subjacents associats a la carcinogènesi mamària, com la resistència a la insulina o el metabolisme d'estrògens, pot influir en la supervivència del càncer de mama. També suggerim que la dieta mediterrània pot subratllar mecanismes biològics beneficiosos que podrien tenir un impacte en un millor pronòstic per a les supervivents del càncer de mama. Tenim la hipòtesi que els nivells elevats de marcadors inflamatoris podrien influir en la «inflamació latent» que precedeix el càncer i tenir un impacte en el pronòstic del càncer de mama.

Objectius Avaluar l'associació entre el potencial inflamatori de la dieta, mitjançant un índex d'inflamació de la dieta anomenada ISD, i el risc i la supervivència del càncer de mama. Examinar l'associació entre altres

patrons dietètics relacionats amb mecanismes biològics, com la dieta associada a la reducció del risc de diabetis (DRRD) i el patró dietètic relacionat amb els estrògens (ERDP), i la mortalitat entre supervivents de mama. Avaluar la relació amb la supervivència del càncer de mama amb un patró dietètic més tradicional, la dieta Mediterrània. Investigar l'associació entre biomarcadors inflamatoris mesurats abans del diagnòstic i la supervivència del càncer de mama. Examinar totes aquestes associacions segons l'estat menopàusic, l'estat del receptor hormonal i l'estadi del tumor.

Mètodes Vam utilitzar dades de l'Estudi Prospectiu Europeu sobre Càncer i Nutrició (EPIC) per examinar les associacions entre els patrons dietètics i els marcadors inflamatoris en relació al càncer de mama. En una mostra de 318.686 dones procedents de nou països europeus seguides durant una mitjana de 14 anys, es van identificar 13.270 casos nous de càncer de mama. El patró d'inflamació (ISD) es va avaluar en relació amb el risc de càncer de mama. Els índexs DRRD, ERDP, ISD i arMED es van avaluar en relació amb la mortalitat entre supervivents de càncer de mama. Tots els patrons dietètics es van calcular utilitzant dades de qüestionaris alimentaris recollits en el moment de reclutament de l'estudi. Finalment, la relació entre els biomarcadors inflamatoris en plasma mesurats abans del diagnòstic (interleucina (IL)-6, IL-8, IL-10, IL-13, IL-17D, IL-1RA, TNF- α , IFN- γ , CRP, leptina i adiponectina) i la supervivència del càncer de mama es va avaluar en 1538 casos de càncer de mama. Per a les associacions entre el risc o la supervivència del càncer de mama i els patrons dietètics o els marcadors inflamatoris, es van utilitzar models de regressió de riscos proporcionals de Cox per calcular els ratios de risc (HRs) i els intervals de confiança del 95% (CI). Per a la incidència del càncer de mama, el temps d'entrada a la cohort va ser definit com l'edat de reclutament, i el temps de sortida com l'edat al diagnòstic, la mort o la fi del seguiment. Per a la supervivència, l'edat al diagnòstic va ser el temps d'entrada i la data de la mort o la fi del seguiment va ser el temps de sortida.

Resultats Les dietes pro-inflamatòries es van associar amb un major risc de càncer de mama (augment del 12% del risc comparant el quintil

superior amb el quintil inferior del ISD). Una major adherència als índexs DRRD i arMED es van associar amb un menor risc de mortalitat global (HR_{1-SD} 0,92; 95%CI 0,87-0,96 i HR_{1-SD} 0,92; 95%CI 0,87-0,97, respectivament). A més, l'ISD es va associar de forma limítrof amb un 6% més de risc de mortalitat global (HR_{1-SD} 1,06; 95%CI 1,00-1,12), probablement limitada a les supervivents post-menopàusiques.

No es va observar cap associació significativa amb l'ERDP. Cap dels patrons dietètics es va associar amb la mortalitat específica per a càncer de mama. Pel que fa als marcadors inflamatoris mesurats abans del diagnòstic, la IL-6 es va associar amb un major risc de mortalitat per totes les causes i de mortalitat específica per a càncer de mama. A més, els nivells elevats d'IL-6, IL-10 i TNF α es van associar amb un major risc de mortalitat per totes les causes entre les supervivents post-menopàusiques de càncer de mama.

Conclusions L'adherència a dietes pro-inflamatòries pot representar un modest factor de risc per al desenvolupament del càncer de mama, i el seu paper podria estar limitat a les dones pre-menopàusiques. L'adherència a aquestes dietes abans del diagnòstic de càncer de mama també pot representar un determinant de pitjor pronòstic, especialment entre les dones post-menopàusiques. Consumir dietes associades a un menor risc de diabetis tipus 2 abans del diagnòstic de càncer de mama, principalment influenciades per mecanismes relacionats amb la resistència a la insulina, pot contribuir significativament a millorar la supervivència global de les pacients amb càncer de mama. Concretament, en comparar els nivells més alts i més baixos d'adherència a aquestes dietes, la diferència en la supervivència global sembla ser substancial. Una major adherència a la dieta Mediterrània abans del diagnòstic, amb exclusió de l'alcohol, pot millorar el pronòstic a llarg termini, especialment entre les supervivents post-menopàusiques de càncer de mama. Les associacions entre els patrons dietètics i el risc o supervivència de càncer de mama no semblen diferir significativament segons l'estat dels receptors hormonals. Nivells elevats d'IL-6 abans del diagnòstic podrien servir com a marcador pronòstic significatiu per a la supervivència a llarg termini en les supervivents del càncer de mama.

Nivells elevats d'IL-6, IL-10 i TNF α semblen ser particularment rellevants entre les dones post-menopàusiques, ja que podrien predir un major risc de mortalitat per totes les causes.

CHAPTER I

INTRODUCTION

CHAPTER I. INTRODUCTION

1. BREAST CANCER

1.1. General aspects of the disease

Breast cancer is a heterogeneous disease, showing diversity in tumour morphology, molecular characteristics, and clinical outcomes. This disease is defined by the presence of malignant cancer cells form in the breast tissue, which are formed of lobes and ducts including smaller sections called lobules. The most common type of breast cancer is invasive ductal carcinoma, representing about 70% of tumours and 15-20% being invasive lobular carcinomas (1). The main symptoms of breast cancer include lump or thickening in the breast, changes in the shape or size of the breast, skin changes such as dimpling or puckering, discharge from the nipple, and pain or tenderness in the breast or nipple. Breast cancer in men, also known as male breast cancer, is considered rare representing only about 1% that of female breast cancer. Partly because of this, the aetiology of this type of breast cancer is poorly understood.

1.2. Aspects related to diagnostic and treatment

Among asymptomatic women, breast cancer screening looks for signs of disease through tests aimed at detecting cancer at an early stage, when it can be treated and possibly cured, with the primary goal of reducing breast cancer mortality. Factors such as age, family history, and certain exposures across lifetime are thought to help better understand which people are more likely to develop certain types of cancer. Mammography, ultrasound, or magnetic resonance imaging (MRI) are diagnostic imaging techniques that allow recognition of the morphological characteristics of normal and abnormal breast tissues. Mammography is the most common screening test for breast cancer currently, and MRI is usually used to screen women at a

higher risk of breast cancer (2). Screening mammography is associated with the reduction of breast cancer mortality by at least 20% (3). MRI screening shows high sensitivity of 90-93%, compared with 48-63% for conventional mammography and ultrasound combined, though the use of MRI has been limited to women at elevated risk of breast cancer in some countries (3).

Women with a strong family history of cancer may also be offered genetic testing. This method search changes in genes, gene expression, or chromosomes in cells or tissue of a person that could result in a sign of cancer or an increased risk of developing breast cancer. Genetic testing may also be used on tumour tissue to help characterization of diagnosis or the therapeutic approach. If a mammography turns abnormal, more tests may be done to diagnose breast cancer.

Following the diagnosis of breast cancer, the main goals of treatment for non-metastatic breast cancer are to eradicate the tumour from the breast and regional lymph nodes and to prevent the development of metastatic recurrence. Local therapy typically involves surgical resection to remove the tumour, along with the sampling or removal of axillary lymph nodes, with the consideration of postoperative radiation. Systemic therapy, which can be administered before surgery (neoadjuvant), after surgery (adjuvant), or both, is guided by the specific breast cancer subtype.

1.3. Molecular subtypes

Gene expression profiling enables the classification of breast cancers into distinct molecular subtypes with prognostic significance. The assessment of oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression is currently used in clinical decision-making for breast cancer. While the initial classification was based on the presence or absence of these markers, further advancements revealed four main molecular subtypes of breast cancer: Luminal A, Luminal B, HER2-enriched, and Basal-like classifications (4,5).

Luminal A subtype, characterized by hormone receptor positive (ER+PR+) and HER2 negative (-) represent approximately 70% of all breast cancer cases. HER2-enriched tumours, based on either ER or PR positive with HER2

positive, constitute 15-20% of cases, while triple-negative (ER- PR- HER2-) breast cancers account for about 15% (6,7). Luminal A subtype has a better outcome compared to the other subtypes. Although Basal-like and Triple-negative breast cancers (TNBC) subtypes share many similarities they are not biologically synonymous. The basal subtype is defined by a distinct gene expression signature and encompasses a diverse group of tumours. Both basal-like and TNBC are associated with poor clinical outcomes and show disproportionately higher prevalence in women of African descent. Moreover, TNBCs represent the most common subtype of invasive breast cancer observed in patients with BRCA1 germline mutations (8).

Overall, the vast majority of breast cancers are diagnosed at a non-metastatic stage, meaning the cancer has not spread beyond the breast at the time of diagnosis. Despite this, a routine clinical stratification of tumours has been established given the prognostic differences in breast cancer patient groups according to ER and PR status, as well as the level of HER2 expression.

1.4. Epidemiology

1.4.1. Descriptive epidemiology: incidence, mortality, and trends

In 2020, breast cancer became the most diagnosed cancer worldwide, accounting for 1 in 8 cancer diagnoses with more than 2.3 million new cases. Among women, breast cancer accounts for almost 1 in 4 cancer cases (24.5%) and for 1 in 6 cancer deaths (15.5%) (9). Breast cancer incidence rates are higher in countries that have undergone economic transition, with countries in transition carrying a higher burden of breast cancer deaths in contrast (**Figure 1**) (10). For instance, in the US, the incidence rates of female breast cancer have shown a gradual increase of approximately 0.5% per year since the mid-2000s. Furthermore, breast cancer now represents almost one-third of all new cancer diagnoses (11). In low- and middle-income countries, a greater proportion of cases are diagnosed at later stages, which are linked to poorer survival. Moreover, changes in reproductive patterns in these countries, such as delayed age at first birth, and lifestyle factors such as increased obesity, are contributing to the increasing burden of breast cancer (12).

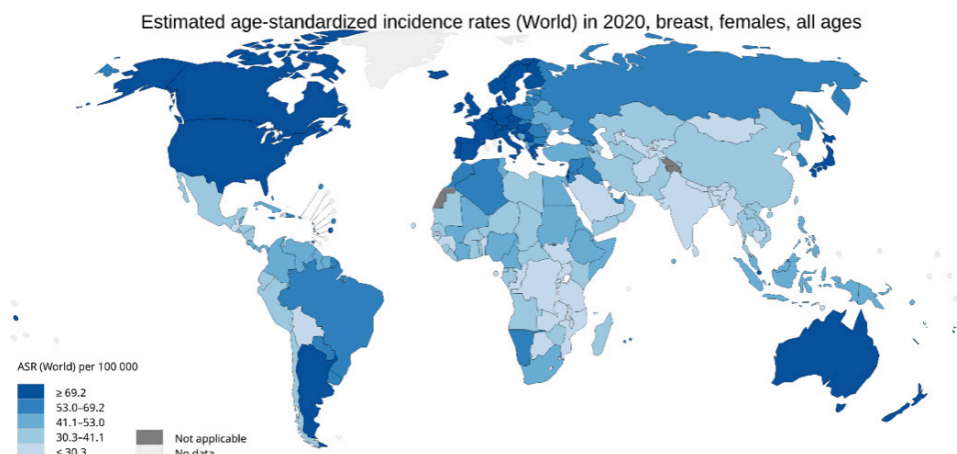


Figure 1. Estimated age-standardized incidence rates in 2020 worldwide of breast cancer among females of all ages.

Data source: GLOBOCAN 2020; IARC (<http://gco.iarc.fr/today>) World Health Organization

Almost 685,000 deaths from breast cancer worldwide were reported in 2020, although with large geographical variations across world regions.

While in most transitioned countries breast cancer mortality is decreasing, the burden of breast cancer mortality is increasing in low- and middle-income countries, attributable to the limited implementation of preventive measures and diagnosis at a later stage of cancer development. Around 70% of all cancer deaths occur in the least developed world regions (13) (**Figure 2**). Inequalities and disparities around cancer become barriers that people face when trying to access health care services (including screening and treatment). Understanding and define the inequalities within cancer should be one of the keys focuses of cancer research.

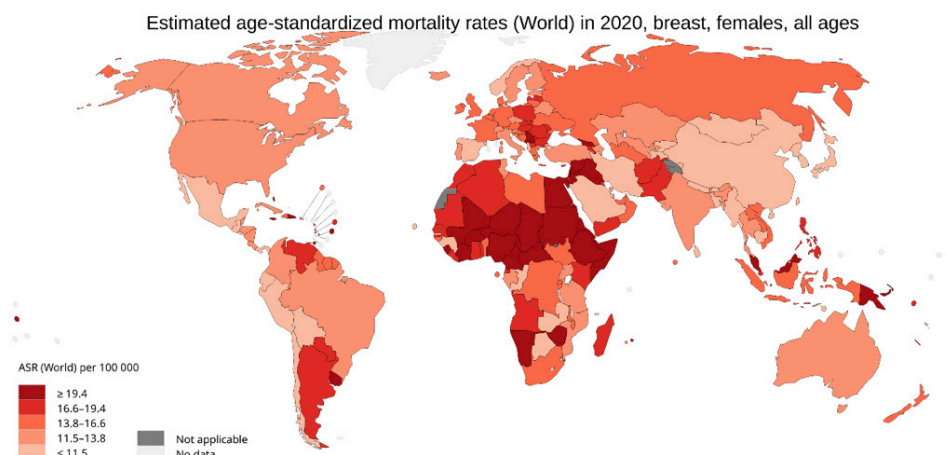


Figure 2. Estimated age-standardized mortality rates in 2020 worldwide of breast cancer among females of all ages.

Data source: GLOBOCAN 2020; IARC (<http://gco.iarc.fr/today>) World Health Organization

The International Agency for Research on Cancer (IARC) has predicted that the burden of this disease in 2040 will increase to more than 3 million new cases per year, which represents an increment of 40%, and more than 1 million deaths per year, which is an increase of 50% (10).

1.4.2. Pathogenesis and causes

Breast cancer is a complex and multifactorial disease influenced by a variety of risk factors. This disease primarily affects women over the age of 50, accounting for approximately 80% of cases. More than 40% of breast cancer patients are aged 65 or older. Thus, the risk of developing breast cancer progressively increases with age, with a 1.5% risk at age 40, a 3% risk at age 50, and a risk exceeding 4% at age 70 (14).

A high proportion of breast cancer cases can be attributed to specific risk factors, as shown in **Figure 3**. These factors fall into two main categories: non-modifiable and modifiable factors. Non-modifiable factors include genetic predisposition, medical conditions, family history of breast cancer, as well as some hormonal and reproductive factors. On the other hand, modifiable

factors encompass anthropometric, lifestyle, and environmental factors that can be altered or controlled. Among the well-established modifiable risk factors for breast cancer, alcohol consumption, obesity and insufficient physical activity have been identified as significant contributors. While there are suggestions that smoking and an unhealthy diet may influence breast cancer risk, the available data remain inconclusive (15).

- Older age
- Genetic mutations (eg, *BRCA1*, *BRCA2*, *PALB2*, *RAD51*, etc)
- Family history of cancer, especially breast, ovarian, pancreatic, and prostate
- Personal history of breast lesions
 - Non-proliferative lesions
 - Proliferative lesions without atypia
 - High-risk lesions (ie, atypical ductal hyperplasia and lobular intraepithelial neoplasia)
 - Breast cancer (ductal carcinoma in situ, invasive breast cancer)
- High breast density
- History of irradiation to the chest
- Type II diabetes
- High total lifetime number of menstrual cycles
- Late pregnancy factors
- Low number of births or no pregnancy
- Advanced age at first full-term delivery
- Short or no breastfeeding
- Obesity
- Diet content (eg, high fat and low fibre)
- Alcohol intake
- Smoking
- Exposure to steroid hormones
 - Hormonal therapy for climacteric symptoms
 - Recent oral contraceptives
- Low physical activity

Figure 3. Risk factors for breast cancer.

Reference: Lancet 2021; 397: 1750–69 (3).

1.4.2.1. *Genetics, susceptibility, and hereditary breast cancers*

Having a family history of breast cancer is linked to an increased risk of the disease. About 10% of all breast cancer cases are related to genetic predisposition or family history, with variation observed across countries and ethnicities (3).

Women with one first-degree relative affected by breast cancer face a nearly twofold increased risk compared to those without a family history. Moreover, women with multiple first-degree relatives affected have approximately three to four times higher risk than those without such a history (16).

Certain genetic mutations have been identified as associated with an elevated risk of developing breast cancer. The two main genes associated with a significant risk increase are BRCA1 and BRCA2. Women carriers of mutations in these genes are more susceptible to breast carcinogenesis (17). These mutations are usually inherited in an autosomal dominant manner, although sporadic mutations can also occur spontaneously without a family history. Although infrequent, germline mutations in BRCA1, BRCA2, and also gene p53 account for 2 to 5% of the cases and result in a substantially higher risk of breast cancer (16). Other breast cancer genes such as CDH1, PTEN, and STK11, are also considered highly penetrant, meaning that mutations in these genes are strongly associated with an increased risk of breast cancer. Additionally, carriers of these mutations are also more susceptible to ovarian cancer (14).

Furthermore, certain genetic syndromes, like Lynch syndrome, are also linked to an increased risk of breast cancer, although they have a low to moderate penetrance and are rare in the general population (18).

Mammographic breast density has been identified as a significant risk factor for breast cancer, irrespective of menopausal status. Studies have consistently shown that women with higher breast density have an increased risk of breast cancer representing a well-established and strong risk factor (19).

Being diagnosed with proliferative benign breast disease, with or without atypia, is associated with a significant increased risk of developing breast

cancer. Research suggests that individuals with benign breast disease showing atypia have a substantially higher risk of developing breast cancer, up to 4-5 times higher, compared to those with benign breast disease without atypia, who have a 1.5-2 times higher risk (20).

Moreover, women with type 2 diabetes (T2D) are at an increased risk of developing breast cancer. Research has revealed significant disparities according to specific ethnic groups, with white women showing a 20% increased risk, while African American women, who also have a higher prevalence of T2D, face a more substantial risk of about 40% for developing ER- breast cancer (21).

1.4.2.2. *Reproductive factors*

Hormonal and reproductive factors are widely acknowledged to play a crucial role in the aetiology of breast cancer. Endogenous oestrogens, in particular, are relevant predictors of breast cancer risk. Reproductive factors, which are characterized by different exposure to sex hormones, are also linked to the risk of developing breast cancer. For instance, parous women or women who have had a pregnancy that resulted in a live birth, have approximately half the risk compared to nulliparous women, with an even stronger protective effect observed in multiparous women. However, these relationships can vary according to specific breast cancer subtypes (6).

Moreover, a reduced risk of breast cancer is associated with early age at first birth. Additionally, if a woman breastfeeds after a full-term pregnancy, the protective effect related to parity is further enhanced, though this may depend on the duration of breastfeeding. It is important to note that the evidence for this association is somewhat limited in high-income countries with limited numbers of births and relatively short breastfeeding periods.

Menstrual factors, such as early age at menarche and late age at natural menopause are associated with higher risk of breast cancer, presumably influenced by ovulatory activity and the length of the ovulatory life period. In summary, reproductive factors, including late age at menarche, early age at menopause, parity, early age at first birth, and breastfeeding, are associated with a reduced risk of breast cancer (1).

Regarding external hormone exposure, the use of hormonal contraceptives has been a subject of debate for decades. Many studies have shown a small increased risk of breast cancer, particularly in current and recent users of oral contraceptives containing oestrogen plus progestogen (22,23).

On the other hand, menopausal hormone therapy (MHT) has been linked to an increased risk of postmenopausal breast cancer, although it remains challenging to determine how changes in prescribing patterns (such as the use of oestrogen plus progestin) impact this risk (1). The risk is greater with combined oestrogen plus progesterone, though hormone therapy without progesterone also has been linked to increased risk of breast cancer (24). The risk also increases substantially with duration of MHT use. Both, use of oral contraceptives containing oestrogen in combination with a progesterone and MHT combining oestrogen and progesterone have sufficient evidence suggesting a carcinogenic effect in humans (25).

Overall, evidence from epidemiological studies supports different effects of reproductive factors on the risk of developing hormone receptor-positive or -negative tumours, which explains the large heterogeneity among breast tumour subtypes.

1.4.2.3. *Environmental factors*

While the term «environmental factors» can encompass all non-genetic factors, in this section we refer to external exposures other than reproductive, medical, or nutritional factors. Some environmental risk factors include radiation, endocrine disruptors, air pollution, and night shift work.

Among these, only prolonged exposure to ionizing radiation, such as medical imaging or radiation therapy, has been established to increase breast cancer risk, even at low doses and particularly if received during puberty (26).

Within the European Study of Cohorts for Air Pollution Effects (ESCAPE) project, only suggestive but nonsignificant associations were observed between exposure to outdoor air pollution and risk of postmenopausal breast cancer (27).

In relation to endocrine disruptors, these are exogenous substances that interfere with the natural hormones' production, metabolism, action, or elimination, thereby leading to adverse health effects. Such compounds are commonly present in food packaging, fabrics, cosmetics, and other environmental sources. The evidence from animal and in vitro studies raises concerns about the negative health effects of these compounds, especially with polyfluoroalkyl substances (PFAS) and paraben exposures. However, more research is required in human populations to fully understand their impact. Additionally, genetic and ancestral factors may influence the physiological response to these environmental chemicals, which may not be evident in non-diverse epidemiological studies (28). The link between endocrine disrupting chemicals and risk of breast cancer has been mostly studied in animal models, limiting the conclusions in humans (29).

While avoiding tobacco exposure is a cancer prevention recommendation to reduce cancer risk, the relationship between tobacco smoking and breast cancer is not well-established. Previous epidemiological studies did not observe an association between active/passive tobacco smoking and breast cancer incidence and the relationship with this cancer site is considered suggestive but not conclusive (1). Pooled analysis have supported possible associations between smoking, particularly when initiated before first birth, and ER+ breast cancer (30).

1.4.2.4. *Nutritional factors*

The Continuous Update Project (CUP) is the ongoing program report of the World Cancer Research Fund International (WCRF) Network (16) that classifies evidence into different grades: «convincing,» «probable,» «limited-suggestive,» «limited-no conclusion,» and «substantial effect on risk unlikely.»

Body fatness

The impact of body fatness on breast cancer risk varies based on menopausal status. The CUP Panel within the WCRF considered BMI and measures of waist circumference and waist-hip ratio to assess the impact of body fatness and fat distribution. In young adulthood (between 18 and

30 years) or before menopause, the evidence is generally consistent, for a significant decreased risk with increasing BMI for premenopausal breast cancer. Across all ages, greater body fatness in premenopausal women (marked by BMI, waist circumference and waist-hip ratio) probably protects against premenopausal breast cancer.

Mechanisms through which body fatness may prevent premenopausal breast cancer are not well-established. A possible mechanism can be related with the increased adipose tissue influencing oestrogen concentrations or other endocrine factors in overweight children and adolescents leading to changes in breast tissue that reduces susceptibility to carcinogenesis (i.e., anovulation) (16).

Body fatness, assessed as not only BMI, but weight, waist circumference and waist-hip ratio, are associated with increased risk of postmenopausal breast cancer. Greater body fatness throughout adulthood is a convincing cause of postmenopausal breast cancer. Additionally, a comprehensive dose-response meta-analysis showed that the risk increases with weight gain through adulthood. Consequently, greater weight gain during adulthood is considered a convincing cause of postmenopausal breast cancer.

The developmental factors contributing to increase linear growth marked by adult attained height are a convincing cause of both, pre- and postmenopausal breast cancer. In this line, factors that lead to greater birthweight or its consequences are classified as probable cause of premenopausal breast cancer.

Physical activity

Physical activity has consistently shown a protective effect against breast cancer risk. Various hypothesized mechanisms contribute to this impact. Physical activity can decrease body fat, including subcutaneous, visceral, and liver fat, thereby altering hormonal and growth factors that could influence cancer susceptibility. Additionally, physical activity regulates insulin sensitivity, leading to reductions in fasting insulin and C-peptide levels, factors closely associated with reduced breast cancer risk. Exercise also

reduces oestrogens and androgens levels in postmenopausal women and among young women, high level of physical activity, increase menstrual cycle length and decrease ovulation (31).

The WCRF report concluded that overall physical activity is a probable protective factor of postmenopausal breast cancer, and vigorous physical activity (per 30 minutes a day) plays a role against both premenopausal and postmenopausal breast cancer.

Diet and breast cancer risk

Among dietary factors, alcohol consumption is a well-established cause of breast cancer. The evidence has been classified as «strong» indicating that consumption of alcoholic drinks is a probable cause of premenopausal breast cancer and a convincing cause of postmenopausal breast cancer. The result of a dose-response meta-analysis pointed out that per 10 grams of ethanol per day there was a statistically significant 5% increased risk for premenopausal breast cancer and 9% increased risk for postmenopausal breast cancer.

Although the mechanisms by which alcohol may influence breast cancer risk remain uncertain, it is possible that the phenomenon is partly explained because dietary patterns of alcohol consumers may differ from those who do not consume alcohol. For instance, the deprivation of essential nutrients intake in the first case (i.e., low folate intake) is likely influencing their susceptibility to carcinogenesis and thereby increasing their risk of breast cancer (32). Additionally, alcohol intake is associated with increased circulating levels of oestrogen which affect breast carcinogenesis. Based on breast cancer subtype, a few prospective cohort studies, including a pooled analysis, have reported a stronger positive association between alcohol intake above 15 grams per day and ER+ and PR+ breast cancer (32,33).

Other dietary factors, classified with limited-suggestive evidence, include non-starchy vegetables, foods containing carotenoids, dairy products, and diets high in calcium (16). Within vegetables, bioactive components like phytochemicals, have been suggested to reduce the risk of ER- breast cancer influencing the reduction of the epidermal growth factor receptor

(34). Further, specific compounds present in select fruits and vegetables, such as carotenoids, can be assessed both through diet and as circulating biomarkers. The existing evidence suggest a plausible anticarcinogenic role for carotenoids (i.e., antioxidant properties) for an inverse dose-response relationship for carotenoid exposure and reduced breast cancer risk. Despite the evidence is generally consistent it is still limited to draw more firm conclusions.

Dairy products represent an important source of calcium in the diet and are thought to have a protective effect against breast cancer, particularly premenopausal breast cancer, although evidence is limited and there are no conclusions on postmenopausal breast cancer. Related to this, it has also been suggested in laboratory studies that calcium intake and its metabolism have an impact on cancer, although evidence suggesting that calcium-rich diets decrease breast cancer risk remains limited (16).

1.4.3. Survival and prognosis

Efforts to reduce cancer mortality requires not only reducing incidence, but also the enhancement of survival. In recent decades, progress in early detection and treatment has led to an increase in cancer survivors.

Cancer survivors are considered all people who have a diagnosis of cancer, including before, during, and after treatment, and excludes people living with a benign tumour or premalignant conditions (26). The term «cancer survivor» covers a variety of circumstances starting at diagnosis through cancer treatment to the end of life. We talk about prognosis by the time the diagnosis has established, and factors such as the stage, the grade of differentiation of the tumour, the presence of hormone receptor status and especially treatment will strongly impact prognosis.

1.4.3.1. *Main outcomes*

Epidemiological studies assessing breast cancer prognosis include a wide range of outcomes. They may relate to the time to progression, including recurrence or metastasis, the occurrence of a second cancer, breast cancer-specific mortality, and mortality from all causes. Recurrence, which occurs when cells from the primary breast cancer move from the original tumour

to another part of the breast or outside the breast and eventually begin to grow again, is a major short- and medium-term concern among cancer survivors. This recurrence, which can be local or distant (metastasis), is a strong determinant of survival. Indicators of quality of life, which may include aspects of physical performance (e.g. fatigue) or mental well-being (e.g. depression), are also considered important outcomes.

1.4.3.2. Main determinants of survival

Stage and grade of the tumour

The stage at which breast cancer is diagnosed stands as a pivotal factor influencing survival. Early-stage diagnoses (stage I or II) generally confer a better prognosis compared to advanced stages (stage III and especially stage IV). The stage denotes the tumour size and extent of spread to nearby lymph nodes or distant organs (metastasis), which can significantly impact survival. Moreover, the histological grade indicates how closely the cancer cells resemble normal cells. Well-differentiated tumours (low grade) often have a better prognosis compared to poorly differentiated tumours (high grade).

Geographical and social disparities

A greater proportion of cases are now diagnosed in low- and middle-income countries at later stages, which are linked to poorer survival. While the five-year net survival rate for breast cancer has been on a steady upward trend until 2014, specific regions such as India, Thailand and parts of Eastern Europe continue to face comparatively lower survival rates. According to the last CONCORD-3 update, a program dedicated to global cancer survival surveillance, worldwide breast cancer survival rates vary, ranging from 40% in Iran to 70% in certain Latin American countries, while North America and Oceania have survival rates surpassing 90% (35).

Comorbidities

Many elderly women who are diagnosed with breast cancer will die of other causes. Therefore, as breast cancer incidence increases with age,

concurrent chronic illnesses can occur and ultimately play a role on prognosis. A considerable number of breast cancer patients are diagnosed with one or more comorbidities, such as diabetes, hypertension, and cardiovascular diseases. In addition to that, cancer survivors are generally at an elevated risk of non-communicable diseases (26). These coexisting comorbidities can impact both the cancer treatment strategy and the subsequent short- and long-term survival outcomes. Specifically, certain breast cancer treatments, including chemotherapies, anti-HER2 therapy, and endocrine therapies, have been associated with cardiovascular toxicity, including hypertension and other related conditions (36). Moreover, diabetes mellitus diagnosed before or after a breast cancer diagnosis is associated with poor overall survival.

Hormone receptor status

Hormone receptor status of the tumour also determines prognosis and ultimately survival. Women with hormone receptor-positive cancers tend to have a better prognosis in the short-term, although these cancers can sometimes relapse many years after treatment. On the contrary, hormone receptor-negative breast cancers grow faster, generally among women before menopause, and it is more often to derive in a recurrence during first few years (37). Furthermore, triple-negative breast cancer, characterized by its biologically aggressive nature and rapid growth, presents a poor prognosis related to disease-free and overall survival. This is primarily attributed to the absence of effective therapeutic targets.

1.4.3.3. Lifestyle and survival

Improvements in cancer survival are driving the need to address the long-term health needs of cancer survivors. This involves not just cancer-related recommendations, but also looking at their general health status.

Ongoing efforts aim to comprehend the effects of lifestyle on breast cancer prognosis. The WCRF has reviewed how factors like excess body weight, physical activity, and diet, influence breast cancer prognosis. Moreover, a big proportion of evidence has focused on the role of these factors in

the capacity to improve cancer-related outcomes such as disease-specific survival, progression-free survival, and recurrence.

Obesity, body fatness

Elevated body fatness is considered a predictor of poor outcome in breast cancer survivors (26). Although the mechanisms of this association are unclear, chronic inflammation associated with obesity has been proposed to enhance the progression of the disease. Moreover, an overweight or obesity status have an impact on the risk of other chronic diseases such as diabetes and cardiovascular disease which can lead to poor survival among cancer patients. There is also evidence that women with obesity are less respondents to oncologic treatments maybe due to under-dosing of chemotherapy treatment (38).

Two randomized controlled trials (RCT) aimed to assess the effect of nutritional interventions on breast cancer recurrence have shown different results depending on the impact of the intervention in body weight. The Women's Healthy Eating and Living (WHEL) Study found no difference in recurrence-free survival between the intervention and control groups. The intervention group followed a low-fat diet which did not impact on weight (39). In contrast, breast cancer survivors in the Women's Intervention Nutrition Study (WINS) achieved a moderate weight loss after a dietary fat reduction and results pointed to an improvement in relapse-free survival compared to patients receiving usual care (40).

The WCRF/AICR Continuous Update Project (CUP) has conducted a comprehensive analysis encompassing systematic reviews and meta-analyses. These evaluations have assessed the quality of evidence of the association of postdiagnosis body fatness, physical activity, dietary factors, and breast cancer prognosis (41). The evidence on postdiagnosis body fatness in relation to all-cause mortality, breast cancer-specific mortality and second primary breast cancer was graded as strong (likelihood of causality: probable). Conversely, when considering breast cancer recurrence and non-breast cancer-related mortality, the report suggests that the evidence is only limited-suggestive. Overall, the findings from this report consistently

advocate for the adoption of a healthy lifestyle avoiding body fatness from breast cancer patients.

Physical activity

The last WCRF report on breast cancer survivors support the positive implications of physical activity on cancer patients. Specifically, various forms of exercise including cycling, weight training, walking, and aerobic exercise after treatment may confer benefits (26). These benefits encompass several healthy aspects such as aerobic fitness, reduced fatigue, reduced depressive symptoms, and improved quality of life. Additionally, engaging in exercise has shown advantages by reducing the therapeutic toxicity and improving tolerance (42,43). Importantly, the report strongly encourages breast cancer survivors to incorporate regular physical activity into their routines.

A recent review judged the evidence on the association between recreational physical activity and lower overall and breast cancer-specific mortality as limited-suggestive (41). This was due to limitations in the methodological quality of the included studies. Despite that, the conclusions from these systematic reviews and meta-analyses remains consistent – encouraging individuals affected by breast cancer to be physically active in the overall strategy to promote health and well-being of these patients.

Future research should focus on investigating the optimal types, amounts, and timing of physical activity that can positively influence quality of life outcomes with the goal of better developing specific guidelines for women with a breast cancer diagnosis.

Diet and breast cancer survival

During treatment, dietary advice for cancer patients aims to address both cancer- and treatment-related symptoms, to sustain adequate energy and nutrient levels while mitigating diverse symptoms, including gastrointestinal toxicity from systemic chemotherapy and radiotherapy. After completion of treatment, dietary interventions aim to improve prognosis in a broad sense, including overall and specific survival.

The role of diet in preventing recurrence or improving long-term outcomes in breast cancer is not well-established. Two randomized trials have examined the impact of diet on breast cancer recurrence, yielding conflicting results. In the WINS study, women who adhered to a low-fat diet (comprising less than 15% energy from lipids) experienced a 5-year cumulative recurrence rate of 9.8%, significantly lower than the 12.4% observed in the control group (40). Conversely, the WHEL study did not detect any effect of a diet rich in vegetables, fruit, and fibre, and low in fat. After a 6-year follow-up, the recurrence risk was 16.7% in the intervention group and 16.9% among the controls. Several factors have been proposed to explain these disparities, but one notable distinction is that in the WHEL study no significant changes in weight were observed in either the control or the intervention group, whereas the WINS study reported a substantial weight reduction in the intervention arm (39).

The WHEL and WINS clinical trials remain the cornerstone in this field. Although both trials employed similar dietary interventions focused on dietary fat reduction, they reached different conclusions regarding the risk of recurrences. This discrepancy has prompted the study of the effect of diet on factors such as body fat, composition or weight, and its possible relationship to prognosis.

Research into the optimal diet for breast cancer survivors is an ongoing field of investigation, but there are still many questions that have not been fully understood. For instance, the precise mechanisms through which diet influences breast cancer progression or the specific components of diet that may have a greater impact on this outcome are largely unknown.

In general, the influence of diet on breast cancer prognosis has been perceived as indirect, mainly through its impact on body fatness. Furthermore, some evidence has pointed to the synergistic effect of better-quality diets combined with physical activity in better survival outcomes independent of body fatness (44,45). Although dietary research for cancer survivorship is predominantly focused on breast cancer, the body of evidence remains insufficient to make concrete and specific recommendations (26).

At present, breast cancer survivors are still advised to adhere to the cancer prevention guidelines after completion of their treatment. However, it is important to note that cancer survivors have different features concerning health and cancer susceptibility than the general population and therefore may warrant different advice. To further enhance the evidence, well-designed RCT integrating dietary interventions and observational studies with extended follow-up periods, repeated dietary assessments and confounding factors are needed.

A recent systematic review and meta-analyses have sought to summarize the evidence on postdiagnosis dietary factors and breast cancer survival outcomes from evidence of RCT and longitudinal observational studies (46). The meta-analyses were only possible for dairy, isoflavone, carbohydrate, dietary fibre, alcohol intake and serum vitamin D with all-cause mortality, and for breast cancer-specific mortality with fruit, dairy, carbohydrate, protein, dietary fat, fibre, alcohol intake and serum vitamin D. Overall, results were null being classified as inconclusive to derive specific recommendations. In parallel to well-designed RCTs and large cohort studies, a conclusion reached in this review was that research into the underlying biological mechanisms can potentially strengthen the evidence for specific dietary recommendations for breast cancer survivors.

2. INFLAMMATION AND BREAST CANCER

2.1. Inflammation and cancer

During the past century an association has already been proposed between inflammation and cancer (47,48). Now, about 15% of all cancers are estimated to be linked to inflammation (1). Although inflammation may not lead directly to cancer, it interacts with other biological processes that are important contributors in the process of oncogenesis (49).

The immune response triggers acute inflammation by activating macrophages, monocytes, lymphocytes, neutrophils, and leukocytes. These cells migrate to the injured site with the aim of reducing inflammation. In instances of severe inflammation, these cells contribute to an excessive

production of pro-inflammatory molecules, including the cytokine tumour necrosis factor α (TNF- α), interleukin-1 β (IL-1 β) and IL-6, the chemokine receptor CXCR4 and its ligand CXCL12, cyclooxygenase 2 (COX-2), prostaglandins, nitric oxide, and leukotrienes. The cumulative effect of these molecules contributes to dysregulate signal transduction pathways that may be involved in the the development of cancer (49).

Furthermore, when inflammation is prolonged, the acute inflammation turns into a chronic stage, for instance in the case of chronic infection (i.e. *Helicobacter pylori* or *Human papillomavirus*), auto-immune diseases, or presence of overweight or obesity status. The chronic production, but a low-grade state, of inflammatory factors is often termed as low-grade inflammation. Research on factors linking chronic inflammation and cancer suggest that prolonged activation of pro-inflammatory transcription factors play a critical role in the sustained cell proliferation of carcinogenesis (50). Moreover, chronic inflammation is associated with production of pro-inflammatory cytokines and chemokines that activate pro-survival transcription factors that may act as key regulators of carcinogenesis (49).

In the clinical context, patients receiving chemotherapy or radiotherapy often experience tumour-associated inflammation induced by tumour necrosis, which contributes to resistance to therapy and/or induction of anti-tumour immunity (51). Additionally, the inflammation associated with obesity is proposed as another significant contributor influencing cancer-related mortality (1).

2.2. Inflammation and breast cancer

In some cancers, inflammatory conditions are present before a malignant change occurs (such as inflammatory bowel disease). Conversely, at times, an intrinsic pathway promoted by genetic alterations, such as oncogenes, promotes both inflammation and neoplasia (**Figure 4**).

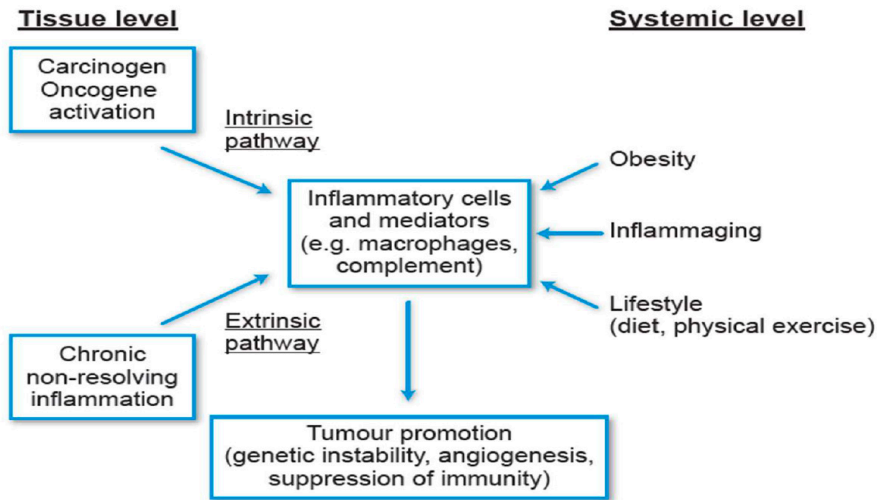


Figure 4. Pathways connecting inflammation and cancer.

Reference: World Cancer Report 2020 (1).

For breast cancer, a firm causal relationship to inflammation has not been established in relation to the underlying mechanisms of inflammation. However, low-grade chronic inflammation is often considered to play an indirect role in the development of breast cancer. Risk factors such as alcohol consumption, obesity, unhealthy diet, and physical activity (as an anti-inflammatory factor) may be associated with breast cancer mainly mediated by chronic inflammatory mechanisms. In addition, chronic inflammation might be one of the underlying pathways that may partially explain the causal associations with obesity and physical activity.

Inflammatory breast cancer (IBC) constitutes a rare and aggressive type of breast cancer, representing approximately 2 to 4% of all breast cancers. Although some regions of the Middle East and northern Africa exhibit a higher incidence of IBC, the histologic features of IBC might not always align with classical inflammation process (including immune cell infiltration, vasodilation, increased permeability, and the release of pro-inflammatory molecules). In addition, the molecular subtype is the most important factor that determines the treatment strategy. However, all IBC molecular subtypes are more aggressive with poorer disease-free survival and overall survival

compared to non-IBC. This type of breast cancer causes the 7-10% breast cancer-related deaths in Western countries (52). The underlying mechanisms leading to worse clinical outcomes for inflammatory breast cancer remain unclarified.

2.3. The potential role of inflammation in breast cancer risk and prognosis: main markers of inflammation

Inflammatory mediators are released as part of the inflammatory response. In recent years, research has focussed on the identification of cytokines as risk and prognostic factors. Cytokines, such as transforming growth factor- β (TGF- β), TNF- α , various interleukins like IL-1, IL-6, IL-10, and the interferons, hold significant influence in regulating the immune system's activity.

In breast cancer, inflammation might have a relevant role because elevated levels of some cytokines in the event of chronic inflammation, such as IL-6 and TNF- α , have been associated with upregulation of angiogenesis and stimulation of aromatase activity in breast tissues. TNF α also promotes oestrogen synthesis by inducing expression of aromatase and IL-6 in adipose tissue (53-55). Furthermore, TNF- α might also contribute to carcinogenesis by triggering the activation of NF- κ B, a key transcription factor that promotes cell migration and invasion. As a result, this activation leads to the upregulation of genes linked to cell proliferation, apoptosis, angiogenesis, and metastasis (56).

The tumour microenvironment also plays an essential role in disease progression through mechanisms of inflammation. Depending on cytokine interference, the microenvironment can enhance the pro- and antitumorigenic response, mediate inflammation and oncogenesis (57). Higher levels of inflammatory biomarkers, including IL-6, TNF- α , IL-8, and C-reactive protein may contribute to a pro-tumorigenic inflammatory environment.

Adipokines may contribute to the state of low-grade chronic inflammation related to obesity, while influencing energy expenditure, inflammation, cancer growth, progression, and metastasis. Among adipokines, leptin, primarily generated by adipocytes, may promote breast cancer development

by stimulating the conversion of androgens into oestradiol or inducing metabolic dysregulation stimulating insulin and IGF-1, which are hypothesized to increase risk of breast cancer (58,59). Conversely, adiponectin is an anti-inflammatory adipokine that might prevent carcinogenesis by inhibiting angiogenesis and promoting apoptosis.

2.4. Inflammation and diet

The role of diet has been extensively studied in relation to its potential to influence inflammatory processes. It has been hypothesised that some components of the diet may modulate levels of inflammation in the body, potentially influencing the risk, development, and prognosis of breast cancer. Despite this, the potential impact of diet and inflammation in the aetiology of breast cancer is unclear. Besides, with regard to diet in general, current cancer prevention guidelines, recommended for both people free of breast cancer and breast cancer survivors, do not provide strong evidence to support any dietary advice beyond avoiding alcohol consumption (16).

The relationship between diet and inflammatory mediators has mostly focused on individual components of the diet. Saturated fats, red and processed meat, and diets rich in processed foods may exert pro-inflammatory effects promoting chronic inflammation (60–62). Limiting consumption of these foods may help reduce inflammation and subsequently lower breast cancer risk. Conversely, higher-fibre or whole-grain diets with lower dietary glycemic index and glycemic load, may provide anti-inflammatory benefits (63). These foods can help reduce the production of pro-inflammatory molecules, potentially mitigating cancer-related inflammation. In addition, omega-3 fatty acids found in fatty fish like salmon, walnuts, and flaxseeds have anti-inflammatory effects (64). Also, adequate vitamin D levels have been linked to reduced inflammation and improved immune function. Some studies suggest that maintaining optimal vitamin D levels might play a role in lowering breast cancer risk (65).

3. DIETARY PATTERNS

3.1. The approach to analyse diet in relation to cancer

Diet stands out as a critical modifiable factor that has the potential to influence both the risk of developing cancer and the progression of the disease once it occurs. Various dietary elements such as nutrients, energy intake, phytochemicals, and alcohol, may play important roles. These dietary factors interact with a multitude of host factors (genetics, epigenetics, microbiome, metabolic and inflammatory state, and immune function), and other environmental elements, creating a complex combination that influences the cancer process. Apart from the well-established harmful effect of alcohol, there is evidence that some dietary factors decrease the risk of cancer. Vegetables and fruit intake that contributes with many micronutrients and phytochemicals, including dietary fibre, carotenoids, and flavonoids have demonstrated anti-cancer effects.

3.2. Overview of the relationship of diet and its components with breast cancer

Several foods, groups of foods and different dietary components have been considered with regard to breast cancer risk in a recent systematic review and meta-analyses conducted by the CUP, which is part of the WCRF Network (16). Evidence regarding non-starchy vegetable intake and breast cancer shows a trend towards a protective inverse association, although the evidence is considered limited with no evidence of a significant dose-response relationship. It appears that consumption of non-starchy vegetables may have a greater impact only in ER- breast cancers. Similarly, significant inverse associations were reported for dietary beta-carotene and other carotenoids, including circulating beta-carotene, in ER- breast cancers (66). Despite this, the evidence suggests that consumption of carotenoid-rich foods as a protective factor against breast cancer risk is limited.

For premenopausal breast cancer, there is some indication that consuming dairy products might reduce the risk, although the available evidence is somewhat limited. It has been suggested that this possible protective

effect of dairy products is attributed to their high calcium content. However, it is important to note that while there is suggestive but limited evidence supporting this link for premenopausal breast cancer, the evidence remains inconclusive when it comes to postmenopausal breast cancer. Moreover, for both pre- and postmenopausal breast cancer, the evidence for diets with high-calcium content is limited but generally consistent pointing to a decreased risk of breast cancer with higher consumption of dietary calcium (16).

Evidence for other dietary exposures, including soy and soy products, red and processed meat, poultry, fish, coffee, tea, carbohydrates, glycaemic index, folate, vitamin D, isoflavones, dietary patterns, and energy intake remains limited and inconclusive. Reasons for grading the evidence as limited-inconclusive relate to a too low quality of data or too inconsistent or too limited number of studies to draw firm conclusions (16).

Consumption of alcoholic drinks is a probable cause of premenopausal breast cancer and a convincing cause of postmenopausal breast cancer. Thus, ethanol is the only dietary compound clearly established as a cause of breast cancer.

Data remains limited on the role of diet on breast cancer survival. Though classified as limited-suggestive evidence, the WCRF report indicated that maintaining a healthy body weight, engaging in regular physical activity, and adhering to a diet rich in fibre and soy after diagnosis were associated with improved overall survival (26).

A comprehensive systematic review and meta-analysis of the evidence on post-diagnosis diet and prognostic outcomes in breast cancer has recently been conducted (46), incorporating studies on foods, food groups, dietary patterns, food components, nutrients, and dietary supplements in relation to survival, recurrence, and secondary primary cancers. Overall, data regarding the relationship between dietary factors and breast cancer outcomes was considered limited and inconsistent for drawing conclusions. Only dietary patterns associated with lower risk of all-cause mortality and other causes of death, soy intake associated with lower risk of all-cause mortality, specific mortality and recurrence, dietary fibre associated with lower risk of all-cause

mortality, and serum 25(OH)D associated with lower risk of all-cause and specific mortality were judged as «limited-suggestive», while the remaining dietary exposures were judged as «limited-not conclusive».

3.3. The potential role of diet assessed by means of dietary patterns

Traditionally, dietary research has primarily focused on examining the impact of individual foods or nutrients on cancer risk and prognosis. Nevertheless, over the past decade, the need to be more specific in cancer prevention guidelines has prompted research on dietary patterns in relation to cancer. This shift is motivated by the understanding that dietary components are interconnected and can mutually influence each other, ultimately impacting the risk of developing diseases. Additionally, analyzing comprehensive dietary patterns provides valuable insights that could lead to more effective development of dietary guidelines.

3.4. Main dietary patterns evaluated in cancer risk or prognosis

In general, dietary patterns are usually divided into two groups: those determined empirically or derived from study data and those using predefined criteria. *A posteriori* dietary patterns are those derived from study data and determined by statistical techniques, whereas *a priori* dietary patterns are based on predefined criteria to capture adherence to a specific way of eating independently of data collection for a given population (67).

Data-driven, or a *posteriori* dietary pattern employ statistical techniques like principal component analysis (PCA), factor analysis, or cluster analysis to empirically identify dietary intake patterns that explain the variance in intake within a particular study population. The most common *a posteriori* dietary patterns include unhealthy and healthy dietary patterns, often labelled as «Western» and «prudent» diets. Western diet is usually characterized by high consumption of red and processed meats, sugary beverages, refined carbohydrates, and salty snacks, while the prudent is defined by higher intake of vegetables and fruits.

A priori dietary pattern scores can vary substantially between studies in the number of dietary components, the foods and beverages included (i.e.,

some scores will include refined grains, other whole grains, and others total grains), and the thresholds used to define adherence (i.e., the cut-points are based on population-specific ranking of intake values). Therefore, this score will be dependent or relative to the population being studied. Instead, other scores can have fixed cut-points.

3.5. Dietary patterns based on biological markers and mechanisms

In the epidemiological literature, some a priori dietary patterns have been developed based on the effect of various dietary factors on specific biological mechanisms or pathways. Notably, these dietary patterns relate to mechanisms of inflammation, insulin resistance and hyperinsulinemia, oxidative stress, and oestrogen metabolism to explore the potential association with cancer risk (68).

The dietary inflammatory index (DII) was developed to evaluate the inflammatory potential of diets by considering the intake of up to 45 dietary components, primarily macro- and micronutrients. These components were assigned inflammatory weights based on a comprehensive literature review that assessed their pro- or anti-inflammatory effects according to their correlations with the concentrations of inflammatory markers (69). The index combines the intake of each dietary component with its inflammatory weight, and the resulting values are added to obtain the index of each individual. High values of the DII score represent pro-inflammatory diets and low DII scores represent anti-inflammatory diets. Other dietary indexes related to inflammation have been developed and studied in relation to cancer outcomes. The inflammatory score of diet (ISD). In addition of some differences in the standardization of the intake, it excludes the total fat component, as the main fats subtypes are already included within the index, and excludes alcohol, specifically for the study of breast cancer outcomes (70).

The empirical dietary inflammatory pattern (EDIP), a food-based score derived using reduced rank regression (RRR) in a subsample of the Nurses' Health Study with data on serum inflammatory biomarkers (71). The technique of RRR commonly uses an intermediate marker or biomarker to

define a dietary pattern, primary based on the capacity of the components of the pattern to explain variations in that marker. Similar methods are employed to build the Empirical Dietary Index for Hyperinsulinemia (EDIH) and the Empirical Dietary Index for Insulin Resistance (EDIR). These indices are developed through multiple linear regression analysis to identify food group intakes that explain the most variation in C-peptide levels for EDIH, a marker of insulin secretion, and TAG:HDL-cholesterol ratio for EDIR, an indicator of insulin resistance (72). Both dietary patterns comprise 18 food groups. In the EDIH, 13 foods were positively associated with C-peptide and 5 were inversely associated; in the EDIR, 10 foods were positively associated with TAG:HDL-cholesterol and 8 were inversely associated.

The Estrogen-Related Dietary Pattern (ERDP) is another dietary pattern derived through RRR, specifically linked to plasma oestrogen metabolites (73). Initially, this pattern was based on the dietary pattern developed by Fung et al., which correlated with serum levels of oestradiol and estrone sulfate within the Nurses' Health Study (74). The ERDP is associated with oestrogen metabolites hypothesized to be associated with breast cancer risk, namely unconjugated oestradiol and the ratio of 2- and 16-hydroxylated oestrogen metabolites. This dietary pattern was developed and studied within patients of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (73).

Another mechanism associated with cancer risk is oxidative stress, which can lead to unrepaired DNA damage. The Oxidative Balance Score (OBS) comprises a variable number of components, typically ranging from 3 to 8, including both dietary and non-dietary lifestyle factors attributed to having antioxidant or pro-oxidant effects. However, data regarding the OBS's association with specific cancer sites remains limited (75).

3.6. Main dietary pattern studies in relation to breast cancer risk

Overall, dietary patterns that include vegetables and fruits, legumes, lean protein and whole grains are associated with a reduced risk of breast cancer (76). A comprehensive systematic review and meta-analyses of a posteriori dietary patterns grouped as «healthy» or «unhealthy», found that higher

adherence to a «healthy» diet was associated with a reduced risk of breast cancer (77). Similarly, another meta-analysis concluded that high adherence to a «prudent» diet was associated with decreased risk of breast cancer, whereas adherence to a «Western» pattern was associated with increased risk of breast cancer, although this last conclusion was limited to case-control studies and not cohort studies (78). Additionally, adherence to diets including a pattern of alcoholic beverage consumption, has been associated with increased risk of breast cancer (79). No association with breast cancer incidence has been observed with plant-based diets, diets excluding meat or animal products (80,81).

Among a priori dietary patterns, the following have been associated with decreased risk of breast cancer: the HEI-2005 (76), the aHEI (82), and the Mediterranean Diet score (83). The HEI has been included in several systematic reviews and meta-analyses to explore the association with cancer risk, whereas the aHEI was created to define diet quality according to the evidence for chronic disease prevention. Main differences between these dietary patterns include separate categories for alcohol and nuts and/or legumes, differentiation between types of meat, and inclusion of long-term multivitamin use (84). Furthermore, there is no consistent evidence for an association between the healthy Nordic food index (HNFI), and the vegetarian diet, and breast cancer.

Regarding dietary patterns based on biological processes, pro-inflammatory diets based on higher DII scores have been consistently associated with increased risk of breast cancer (85-87). Higher oxidative balance score (OBS) reflecting a predominance of antioxidant relative to pro-oxidant diets, has been associated with reduced risk of breast cancer (75). Finally, there were no consistent associations between a pro-estrogenic dietary pattern and increased risk of breast cancer (73,74).

3.7. Dietary patterns and breast cancer prognosis

We conducted a systematic review on prospective cohort studies focusing on dietary patterns and cancer survival outcomes (88). The primary outcomes of interest included all-cause and breast cancer-specific mortality. Among

these studies, thirteen were dedicated to investigating outcomes related to breast cancer, including predominantly studies on postmenopausal breast cancer patients.

The DASH diet exhibited inverse associations with both all-cause mortality and breast cancer-specific mortality (89). However, another study reported this protective association exclusively for non-breast cancer-related mortality (90). Higher adherence to pro-inflammatory diets, as measured by the DII, was associated with an increased risk of recurrence and all-cause mortality (91). Similarly, in a separate study focused only on postmenopausal survivors, anti-inflammatory diets were associated with a lower risk of all-cause mortality (92). The dietary pattern is the Diabetes Reduction Risk Diet (DRRD) comprises 9 dietary components associated with 40% lower risk of type II diabetes. Data limited to one study showed a reduced risk of all-cause and breast cancer-specific mortality when comparing highest to lowest category of adherence to the score (93). In contrast, the Mediterranean Diet score was not associated with all-cause mortality in two studies (94,95).

Studies utilizing scores developed from specific dietary guidelines included the Chinese Food Pagoda (CHFP), the American Cancer Society (ACS) recommendations, and the WCRF/AICR guidelines. Overall, adhering to the CHFP and the WCRF/AIRC recommendations was associated with a statistically significant reduction in the risk of all-cause mortality (89,96). In contrast, breast cancer survivors who achieved higher scores based on ACS recommendations exhibited improvements only concerning non-breast cancer causes of death (97).

The HEI and aHEI indices, dietary patterns indicative of diet quality, have been the most explored in relation to breast cancer survival and the number of studies available allowed for a meta-analysis (88). The results revealed a significant association between high diet quality indices and a reduced risk of all-cause mortality. However, in neither case there was evidence of an association between adherence to these indices and breast cancer-specific mortality.

4. AN OVERVIEW OF THE ROLE OF DIETARY PATTERNS ON BREAST CANCER RISK AND PROGNOSIS

Inflammation is now recognized as one of the hallmarks of cancer. Some types of cancer have traditionally been associated with chronic inflammation, which plays a role in their biology. However, it remains uncertain whether breast cancer is directly linked to these inflammatory processes and whether dietary choices that modulate these mechanisms can impact the development of this disease. Furthermore, limited knowledge exists regarding the connection between diet and breast cancer. Notably, factors such as body fatness and physical activity, which are influenced by or correlated with dietary habits, are associated with both breast cancer and chronic inflammation.

Examining the potential impact of diet in modulating chronic inflammation processes may provide valuable insights and help us derive more definitive conclusions regarding the optimal dietary strategies for breast cancer prevention. Additionally, assessing diet through dietary patterns offers a more practical approach, as it likely reflects the interactive, synergistic, and combined effects of various dietary components. In this context, a promising approach is to investigate dietary patterns that relate to underlying biological mechanisms of breast carcinogenesis, which in turn may be influenced by diet.

Of particular interest is the research focused on modifiable lifestyle factors, especially for breast cancer survivors who currently lack specific dietary recommendations. While adhering to general cancer prevention guidelines is advisable, specific dietary recommendations may hold even greater impact for improving their prognosis. Considering the established links between postmenopausal breast cancer risk and elevated oestrogen levels, as well as the associations between obesity (a strong predictor of mortality), insulin resistance, hyperinsulinemia, chronic low-grade inflammation, and sedentary behaviours with both breast cancer risk and prognosis, dietary patterns targeting these mechanisms may significantly impact the prognosis of breast cancer survivors.

Traditional dietary patterns, such as the Mediterranean diet, may also be related to some of the mechanisms and may support the feasibility of

following specific dietary recommendations after breast cancer diagnosis. In particular, this dietary pattern is consistent with some of the World Cancer Research Fund (WCRF) recommendations for cancer survivors and hence it is worth exploring its relevance for breast cancer survivors.

On the other hand, investigating the direct association between inflammatory biomarkers and breast cancer survival will complement studies focusing on the inflammatory potential of diet through dietary patterns. These biomarkers, independently measured and assessed in relation to breast cancer survival, are unrelated to the construction of the inflammatory dietary patterns. Exploring the association between inflammatory biomarkers and breast cancer survival provides crucial insights. It allows for comparisons with results obtained from dietary patterns and enhances our understanding of the potential molecular mechanisms involved, particularly those related to inflammation.

Finally, these studies are conducted in the same European context, which facilitates the pooling and complementarity of the results to draw conclusions regarding the role of dietary patterns in both breast cancer risk and prognosis.

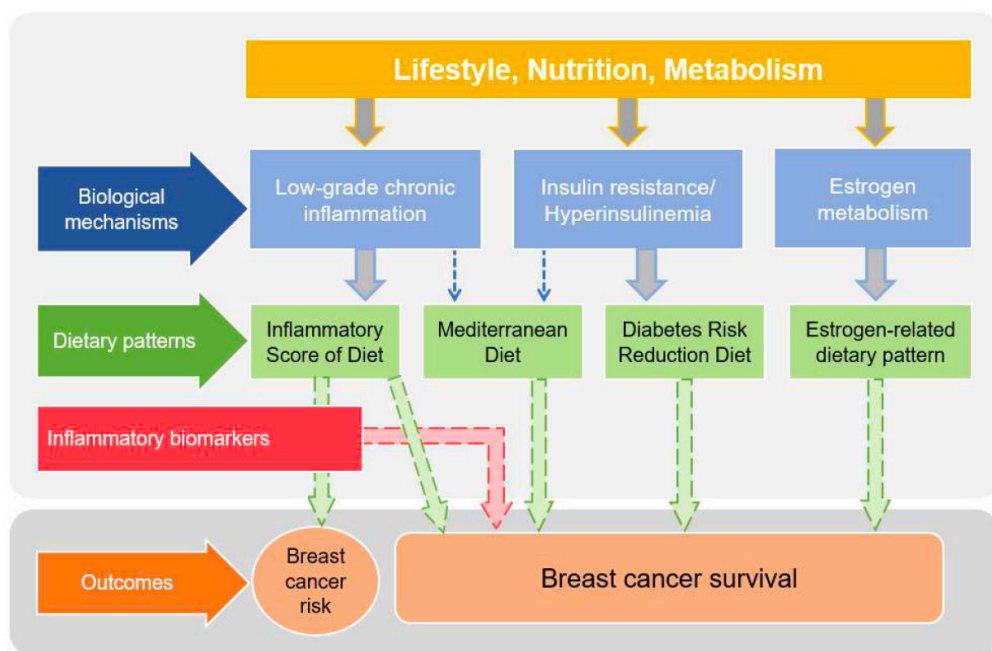


Figure 5. Diagram of the main hypotheses covered in the thesis.

Lifestyle factors, including nutrition and metabolism, can influence biological mechanisms relevant to breast carcinogenesis, such as low-grade chronic inflammation, insulin resistance, and estrogen metabolism. Previously established dietary patterns, now derived within the EPIC study, have been used to investigate their association with breast cancer outcomes. Initially, we explored the inflammatory potential of diet in relation to breast cancer risk, and subsequently, we assessed this same pattern along with three others in relation to survival. Moreover, pre-diagnosis circulating inflammatory markers have been examined regarding breast cancer survival. The dashed arrows in this diagram represent the hypotheses evaluated in the current thesis.

SYSTEMATIC REVIEW AND META-ANALYSIS



Review

The Role of Diet in Prognosis among Cancer Survivors: A Systematic Review and Meta-Analysis of Dietary Patterns and Diet Interventions

Carlota Castro-Espin ^{1,2}  and Antonio Agudo ^{1,2,*}

¹ Unit of Nutrition and Cancer, Catalan Institute of Oncology—ICO, L'Hospitalet de Llobregat, 08908 Barcelona, Spain; ccastro@idibell.cat

² Nutrition and Cancer Group, Epidemiology, Public Health, Cancer Prevention and Palliative Care Program, Bellvitge Biomedical Research Institute—IDIBELL, L'Hospitalet de Llobregat, 08908 Barcelona, Spain

* Correspondence: a.agudo@iconcologia.net; Tel.: +34-93-2607401

Abstract: Cancer survival continues to improve in high-income countries, partly explained by advances in screening and treatment. Previous studies have mainly examined the relationship between individual dietary components and cancer prognosis in tumours with good therapeutic response (breast, colon and prostate cancers). The aim of this review is to assess qualitatively (and quantitatively where appropriate) the associations of dietary patterns and cancer prognosis from published prospective cohort studies, as well as the effect of diet interventions by means of randomised controlled trials (RCT). A systematic search was conducted in PubMed, and a total of 35 prospective cohort studies and 14 RCT published between 2011 and 2021 were selected. Better overall diet quality was associated with improved survival among breast and colorectal cancer survivors; adherence to the Mediterranean diet was associated to lower risk of mortality in colorectal and prostate cancer survivors. A meta-analysis using a random-effects model showed that higher versus lower diet quality was associated with a 23% reduction in overall mortality in breast cancer survivors. There was evidence that dietary interventions, generally combined with physical activity, improved overall quality of life, though most studies were in breast cancer survivors. Further cohort and intervention studies in other cancers are needed to make more specific recommendations.

Keywords: systematic review; meta-analysis; dietary pattern; prospective cohort; randomised controlled trial; cancer prognosis; cancer survival; dietary intervention



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1. Introduction

The term cancer survivor is generically applied to people living with a cancer diagnosis, including those who have been cured or recovered from the disease [1]. Although this definition includes people who have been diagnosed but have not yet started treatment, as well as patients being treated, and those who are at an advanced stage of the disease, in the present review we refer specifically to people who have been treated and have had a satisfactory response to treatment. For cancer survivors the main threat to their health in the short and medium term is the reappearance of the disease (recurrence), which can be local or distant (metastasis); the latter is, in turn, a strong determinant of survival. According to the most recent estimates, there were 44 million persons living with cancer in 2020 who had been diagnosed within the last 5 years [2]. That is, the high prevalence of cancer survivors is becoming a major health and social problem.

The diagnosis and treatment of cancer have experienced important advances in recent decades. Especially in the most developed countries, the practice of screening for breast cancer, and to a lesser extent for colon and rectal cancer, has spread. In addition, opportunistic screening for prostate cancer and some other tumours (thyroid, lung) is assiduously practiced. Furthermore, there have been substantial advances in the management and

treatment of many tumours. As a result of these improvements, 5-year survival from colon, rectal and breast cancers has increased steadily in most developed countries for patients diagnosed during 2005–2009 [3]; survival for colon and rectal cancer reached 60% or more in 22 countries around the world, while for breast cancer, survival rose to 85% or higher in 17 countries worldwide. Striking increases in prostate cancer survival have occurred in many countries, reaching 95% in most developed countries, but trends vary widely.

Although the factors associated with higher or lower cancer incidence (risk or protective factors) do not necessarily must have prognostic value, it seems quite straightforward to think that determinants of the occurrence of a tumour may have some effect on the progression or recurrence of the disease, including the occurrence of a second tumour. Thus, the interest in the possible role of diet in cancer prognosis has been mostly focused on tumours for which diet is a widely recognised risk or protective factor. On the other hand, this area of research has been directed towards frequent tumours for which therapeutic alternatives with good response are available. Therefore, the results on the possible role of nutrition and related factors in the prognosis are concentrated mainly in breast, colon and prostate cancers [1].

Despite the apparent similarity or parallelism between the studies on the determinants of risk and prognosis, there are important differences in their research framework. First of all, the design option: although case-control studies are less and less used in nutritional epidemiology oriented to etiological research, in the case of prognostic determinants, where the outcome is often mortality, this option is not suitable. Only well-designed prospective cohorts are a suitable design for observational studies aimed to assess prognosis in this setting. On the other hand, intervention studies (i.e., randomised controlled trials, RCT) are needed and always preferred to establish the prognostic value of dietary factors with a high degree of evidence. The RCT are always complex and expensive; however, as they can be conducted in the clinical setting and the expected events are relatively common (at least compared with population studies looking for incidence), they should be, at least in theory, more prevalent than in etiological research. An additional problem has to do with the outcome, or rather, the variability in the possible outcomes. Indeed, while in the studies on risk factors the result is unique (diagnosis of an incident case of the disease), in the evaluation of the prognosis we can consider several outcomes: mortality (overall), death by a specific cause, recurrence, occurrence of a second tumour, a surrogate or marker of progression, or quality of life. Finally, there is the time frame of exposure (diet) assessment. Time-to-event analyses when the outcome is mortality (or recurrence) take the date at diagnosis as the entry time; therefore, ideally the dietary assessment should be as close to that date as possible. Two main time frames are considered when assessing prognosis: dietary factors collected pre- or post-diagnostic. Moreover, the time from dietary assessment to diagnosis, or conversely, from diagnosis to dietary assessment, must be considered. If this period is too long, it may call into question the validity of the study. Although there is not a clear consensus about this issue, most studies tend to restrict the dietary assessment to one year prior or after the date of diagnosis.

A comprehensive review [4] reported that physical activity after treatment may confer a number of health benefits to cancer patients, and that there is evidence to suggest that elevated body fatness is a predictor of poor outcome in breast cancer survivors. With regard to diet, this review reported that there is evidence of links between better survival after breast cancer and eating foods containing fibre, soya, and lower intakes of total and saturated fats. However, due to limitations of much of the existing research, the evidence is not strong enough to make specific recommendations. Several reviews summarising the observational evidence from prospective cohorts of cancer survivors have been published in the last ten years [5–7]. All of them reported associations between mortality and some foods or groups of foods among survivors of several common cancers. On the other hand, a recent review of the quality of five evidence-based nutrition guidelines for cancer survivors [8] reported that limited information on nutrition was available in these guidelines, with the focus being on the promotion of fruit, vegetables and wholegrains and reducing fat, red

meat and alcohol. There was also a tendency to recommend cancer prevention guidelines be used for cancer survivors rather than developing specific guidance for this group.

A couple of issues about the major conclusions of these reviews are worth considering. First, as already noted, most of the observational evidence summarised concerns individual foods, food groups or single nutrients. However, food consumption cannot be considered in isolation, but in combination with others. Therefore, examination of the survivor's diet as a whole, by means of dietary patterns, could be more readily translated into dietary guidelines. This seems particularly relevant for assessing protective effects: while there are several examples of dietary components that can increase the risk of cancer (e.g., alcohol) there are few (if any) examples of single nutrients or components that directly decrease cancer risk [9]. This can translate into disease progression, risk of recurrence or death. By means of dietary patterns assessment, studies may try to look at the whole diet, which is likely to have interactive, synergistic and combined effects on disease risk and progression [10].

On the other hand, in reviews discussed above [4,8], a claim was made that further research, mainly from intervention studies, is needed to make specific recommendations for cancer survivors. In fact, it is not entirely true that clinical trials on the effect of diet as a prognostic factor in cancer survivors are lacking: during the first decade of this century, results of two large RCT evaluating the effect of dietary intervention on the risk of recurrence of breast cancer were published [11,12]. However, they did not provide clear support for a role of diet owing to their discrepant results. The Women's Intervention Nutrition Study (WINS) [11] assigned 2437 women with early stage breast cancer to either a low-fat or standard diet. After approximately five years of follow up the intervention group had a significant 24% lower risk of recurrence compared to the control group. In contrast, the Women's Healthy Eating and Living Study (WHEL) [12], including 3088 breast cancer patients, found that an intervention diet rich in vegetables, fruit and fibre, and low in fat compared to a control diet did not reduce risk of recurrence or mortality after a 7-year follow up. Several reasons have been put forward to explain these discrepancies; however, the most remarkable difference is that in WHEL there was no significant weight modification in either the control or intervention group, whereas in WINS there was a significant, though unplanned, weight reduction in the intervention arm [13]. These results suggest that energy balance may play a significant role in breast cancer prognosis and may be more important than the modest effects of reducing total fat intake or modifying other dietary factors. The growing evidence suggesting the relevant role of weight control on breast cancer recurrence, together with evidence of the beneficial effects of physical activity among cancer patients [14,15], led to the development of lifestyle interventions combining dietary and physical activity components as the best strategy to improve prognosis and quality of life among survivors of breast and other cancers.

Keeping in mind the issues discussed above, the aim of this study was to conduct a systematic review and meta-analysis of prospective cohort studies and randomised controlled trials that investigated the effects of dietary patterns and dietary interventions on the prognosis among cancer survivors. We adopted a broad definition of prognosis, including all the events and outcomes with prognostic significance: overall and cancer-specific mortality, recurrence, markers of disease progression and quality of life.

2. Materials and Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16] and followed a pre-planned unpublished protocol that can be requested by contacting the corresponding author.

2.1. Search Strategy

The authors conducted a total of seven literature searches using combinations of several keywords related to diet and cancer prognosis in PubMed database, from 1 January 2011 until 31 August 2021. No restriction on language was made and only peer reviewed

sources limited to human adult studies were included. When articles were reviews and/or meta-analyses only those published on the previous five years were included to further explore other relevant references. The following search strategy was used: (cancer OR neoplasm) AND (dietary pattern OR food-stuff OR food nutrients OR diet) AND (mortality OR prognosis OR cancer mortality OR cancer survival OR cancer prognosis OR cancer outcomes OR cancer recurrence OR cancer survivors) AND intervention. Further exploration of the reference lists of the identified papers complemented these searches. Any disagreement was resolved through discussion between the two authors.

2.2. Study Selection

The authors reviewed the titles and abstracts of all articles and selected studies that met the following criteria: (1) prospective cohort or randomised controlled trial (RCT) design; (2) available in full-text; and (3) assessing the relationship between dietary patterns (in cohorts) or dietary intervention (in trials) and prognostic-related outcomes (i.e., all-cause mortality, cancer-specific mortality, recurrence and quality of life (QoL)). For RCT, studies including dietary interventions either alone or in combination with physical activity were considered. We excluded feasibility, cross-sectional, case-series or case-control studies, retrospective cohorts, studies focused on the rationale and design presenting no results, any study whose population is not clearly defined as cancer survivors, as well as reviews or meta-analysis published before 1 January 2016 and exposure considering only alcohol (Figure 1).

2.3. Data Extraction

The following information was extracted from each selected study: reference (author, year), country, population details (clinical features, sample size, age, and follow-up time of the cohort or trial), dietary assessment tool with its main relevant features, outcomes, results, and observations (e.g., adjustment for confounders). For the RCT we included a description of the intervention and the methods used for the assessment of quality of life, as many of them investigated this outcome. Where multivariable models were reported, the model including the set of potential confounders judged as the most adequate was selected.

2.4. Outcomes

The primary outcome usually was of time-to-event type. Survival was mostly measured as overall or cancer-specific mortality, as well as disease-free survival (or risk of recurrence). Other selected outcomes related to prognosis were different dimensions of quality of life.

2.5. Bias Assessment

The risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) for cohort studies [17]. The NOS contains eight items, categorised into three dimensions including selection, comparability and outcome (Table A1). For each item a series of response options is provided, and a star system is used, whereby the highest quality studies are awarded with a maximum of one star for each item with the exception of the item related to comparability, which allows the assignment of two stars. Therefore, the NOS score ranges from zero to nine.

2.6. Meta-Analysis

Eligible studies for meta-analysis were those that studied the same outcome, same exposure and same cancer type; a meta-analysis was performed only for sets of three or more studies that fulfilled the above-mentioned criteria. According to this, we conducted a meta-analysis of four cohort studies on breast cancer survivors, looking at overall and specific mortality in relation to dietary patterns reflecting diet quality [18–21].

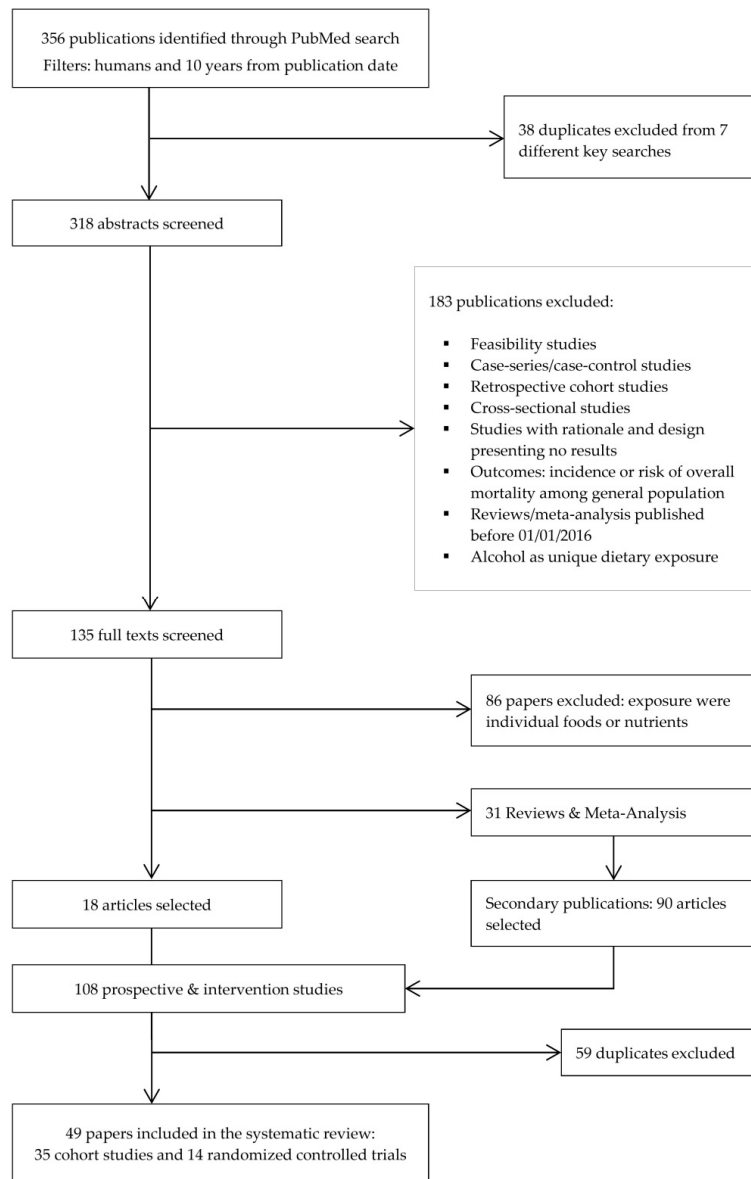


Figure 1. Flow diagram of literature search and selection process adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

We used the adjusted hazard ratio (HR) as an estimate of the relative risk of each study to calculate a summary effect estimate applying two different approaches. First, we used estimates for the fourth quartile [19–21] or the fifth quintile [18] as compared with the

reference (first quartile or quintile) to calculate the effect of the highest versus the lowest level of the diet quality index. On the other hand, we calculated an estimate of the effect (with its corresponding 95% confidence interval) associated with each 10-unit increase of the index using the mean or the midpoint of each category, by means of a method based upon generalised least squares [22]. The overall HRs were estimated by means of a random effect model [23,24]. Heterogeneity across studies was assessed by means of the I^2 statistic [25], together with a prediction interval [26]. All the data used to perform the meta-analysis can be found in Table A2.

3. Results

3.1. Identified Studies

From the initial search, 356 records were identified (Figure 1) of which 318 were selected for title and abstract screen after removing duplicates. Of these, 183 were excluded, leaving 135 full-text articles for review. Additionally, prospective cohort studies where exposure was a single food, nutrient or food group were excluded, leaving 18 articles. Moreover, 90 new articles were identified through the systematic screening of references in reviews and meta-analyses found in the previous step, resulting in 108 articles selected. After removing duplicates, 49 papers in total were ultimately retained for the present review.

3.2. Prospective Cohort Studies

A total of 35 prospective cohorts were identified. Details of these studies are shown in Table 1. The majority of studies were conducted in North America (26 in the US, including one that combined data from Mexico, and two from Canada); four were conducted in Europe, two in Asia, and one in Australia. Most cohorts included breast and colorectal cancer survivors (13 and 11 studies respectively), followed by three studies of survivors of prostate cancer, two studies of head and neck cancers, two studies of ovarian cancer, and one study each of bladder cancer and multiple myeloma. The two remaining studies included survivors of a combination of several tumours.

All but six studies used a food frequency questionnaire (FFQ) to assess diet intake. Ten studies collected dietary data before diagnosis, twenty after diagnosis and five assessed diet both before and after diagnosis. Six studies built a diet pattern by means of statistically derived methods (i.e., Prudent/Western pattern; Healthy/Unhealthy pattern); most of the remaining studies ($n = 26$) used *a priori* defined indices, for example, based on dietary guidelines (i.e., Healthy Eating Index [HEI]-2005; Alternative Healthy Eating Index [AHEI]-2010; Mediterranean Diet Score [MDS]), and three studies included both approaches.

Overall, the cohort studies had a good quality as measured by the NOS Quality Assessment Scale (Table A1), with an average score of 7.8 (scale with range 0–9). Seven studies graded the maximum 9 points of the scale, seventeen graded 8 points, seven graded 7 points and the remaining three graded 6 or 5 points.

3.2.1. Breast Cancer (BC)

Five out of thirteen prospective studies focused on postmenopausal BC patients and eleven studies included overall mortality and breast cancer-specific mortality as outcomes. Other outcomes of interest were recurrences [18,27–29] and breast cancer-specific events, defined as recurrence or metastasis of breast cancer and breast cancer deaths, which was only reported in one study [21].

A total of seven studies assessed diet using the HEI or AHEI indices. The HEI is a measure of diet quality in relation to the Dietary Guidelines for Americans (DGA) with different versions updated over the years; the AHEI captures evidence-based recommendations that incorporate additional food- and nutrient-focused components to predict chronic disease risk [30]. For instance, the DGA 2015 has moved in the direction of the AHEI and the HEI-2015 has included new components present in the AHEI. The different versions of HEI and the AHEI-2010 are similar in several aspects.

Table 1. Characteristics of the included prospective cohort studies (*n* = 35) examining the association between dietary patterns and prognosis in cancer survivors.

Author, Year	Country	Population, Cohort	Dietary Assessment	Dietary Patterns	Outcomes	Results—Multivariate Adjusted RR/HR(95% CI)	Observations
Several tumour sites							
Inoue-Choi, 2013	USA	IWHS, 2017 cancer cases: breast (<i>n</i> = 938), colorectal (<i>n</i> = 380), gynaecologic (<i>n</i> = 262) and other cancer (<i>n</i> = 437), mean age 78.9 years, mean follow-up 5.4 years.	Post-diagnostic 127-items FFQ.	WCRF/AICR guidelines scores.	All-cause mortality, cancer-specific mortality, CVD-specific mortality.	Q4 vs. Q1. All survivors: All-cause mortality: HR = 0.67 (0.49–0.90), p-trend = 0.03; Cancer-specific mortality HR = 0.63 (0.39–1.04), p-trend = 0.21; CVD-specific mortality: HR = 0.92 (0.57–1.47), p-trend = 0.40. Gynaecological cancers: All-cause mortality: HR = 0.96 (0.34–2.69), p-trend = 0.94; Gynaecological cancer-specific mortality: NA; CVD-specific mortality: HR = 1.05 (0.27–4.15), p-trend = 0.83. Other cancer: All-cause mortality: HR = 0.55 (0.30–1.01), p-trend = 0.12.	Gynaecology included cervical, endometrial, ovarian and other female genital organ cancers. ‘Other cancer’ category was not further defined. Models adjusted for age, total number of comorbid conditions (accumulated, 1986–2004), perceived general health and current smoking, cancer stage, cancer type, cancer treatment (surgery, chemotherapy), subsequent cancer diagnosis before 2004, current cancer treatment and person-years since cancer diagnosis. Mean time since cancer diagnosis is 8.6 years (SD = 4.8 years).
Karavasiloglou, 2019	USA	120 gynaecological cancers: ovarian (<i>n</i> = 19), cervical cancer (<i>n</i> = 54), and uterine cancer (<i>n</i> = 47), NHANES III, mean follow-up 12.4 years.	Post-diagnostic 24-h dietary recall.	HEI and MDS.	All-cause mortality.	By 1-unit increase, HEI: HR = 0.92 (0.89–0.96). MDS; HR = 0.77 (0.57–1.04). Good (≥ 70) vs. Poor (< 70) HEI: 0.20 (0.10–0.43). Adheres (5–9) vs. Non-adheres (0–4) MDS; HR = 0.49 (0.18–1.37).	Usual variables of adjustment; alcohol was not included in the adjustment of the MDS model (it is one of the MDS items). Information regarding disease severity or treatment was not available. Important: mean time between diagnosis and completion of the questionnaire is 10.4 years; therefore, these associations refer to long-term survivors.

Table 1. Cont.

Author, Year	Country	Population, Cohort	Dietary Assessment	Dietary Patterns	Outcomes	Results—Multivariate Adjusted RR/HR (95% CI)	Observations
Breast cancer (BC)							
Kim, 2011	USA	2729 postmenopausal BC stage I–III, NHS study, follow-up 6 years.	Pre- and post-diagnosis FFQ every 4 years (initially 61-items, until 130-items).	Diet quality indices: AHEI, DQIR, RFS, aMED	All-cause mortality, BC-specific mortality and non-BC mortality, BC-recurrence	Q5 vs. Q1 (post-diagnostic diet): All-cause mortality: HEI, RR = 0.85 (0.63–1.17); DQIR, RR = 0.78 (0.58–1.07); RFS, RR = 1.03 (0.74–1.42); aMED, RR = 0.87 (0.64, 1.17). BC-specific mortality: RFS, RR = 1.54 (0.95–2.47) p-trend = 0.02. Distant recurrences: RFS, RR = 1.45 (0.94–2.23) p-trend = 0.001. Pre-diagnostic diet quality indices were not associated with outcomes.	For pre-diagnosis diet, diet quality indices based on a single dietary questionnaire were not associated with total mortality, breast cancer mortality, distant recurrences or non-breast cancer mortality (data not reported). Adjustment for relevant variables.
George, 2011	Mexico, USA	HEAL Study; 670 local or regional BC survivors, follow-up 6 years.	Post-diagnostic 122-items self-administered FFQ 6 and 30-month.	HEI-2005.	All-cause and BC-specific mortality.	Q4 vs. Q1: all-cause mortality HR = 0.40 (0.17–0.94). BC-specific mortality HR = 0.12 (0.02–0.99). All-cause mortality in active-higher HEI-2005 vs. inactive-lowest HEI-2005: HR = 0.11 (0.04–0.36). BC-specific mortality in active-higher vs. inactive-lowest HEI-2005: HR = 0.09 (0.01–0.89).	Adjusted for energy, physical activity, race, stage and tamoxifen use.
Vrieling, 2013	Germany	2522 postmenopausal BC stage I–IV, median follow-up 5.5 years, MARIE study.	1-year pre-diagnostic 176-item FFQ.	Dietary patterns: ‘healthy’ and ‘unhealthy’; defined by principal components and factor analysis.	Overall mortality, BC-specific and non-BC mortality; recurrence of breast cancer.	Q4 vs. Q1 ‘unhealthy’ pattern: HR = 3.69 (1.66–8.17) p-trend < 0.001 (non-BC mortality). HR = 1.34 (0.93–1.94) p-trend = 0.03 (overall mortality). HR = 0.99 (0.64–1.52) p-trend = 0.59 (BC-mortality). Within cases stage I–IIIa, ‘healthy’ pattern HR = 0.74 (0.47–1.15) p-trend = 0.02 (overall mortality), HR = 0.71 (0.48–1.06) p-trend = 0.02 (recurrence).	BMI and physical activity not included in multivariate models.

Table 1. Cont.

Author, Year	Country	Population, Cohort	Dietary Assessment	Dietary Patterns	Outcomes	Results—Multivariate Adjusted RR/HR(95% CI)	Observations
Inoue-Choi, 2013	USA	IWHS, 938 BC cases.	Post-diagnostic 127-items FFQ.	WCRF/AICR guidelines scores.	all-cause mortality, BC-specific mortality, CVD-specific mortality	Q4 vs. Q1. All-cause mortality: HR = 0.61 (0.39–0.96), p-trend = 0.01. BC-specific mortality: HR = 0.88 (0.41–1.91), p-trend = 0.65. CVD-specific mortality: HR = 0.67 (0.33–1.37), p-trend = 0.10.	Models adjusted for age, total number of comorbid conditions (accumulated, 1986–2004), perceived general health and current smoking, cancer stage, cancer type, cancer treatment (surgery, chemotherapy), subsequent cancer diagnosis before 2004, current cancer treatment and person-years since cancer diagnosis. No data on cancer stage, mean age of cases and mean/median follow-up time. See note in 'Several tumour sites' section for this article.
Izano, 2013	USA	NHS, 4103 BC cases stages I–III, median follow-up 9.3 years.	At least 12 months after diagnostic, FFQ	DASH, AHEI-2010.	Primary: BC-mortality; Secondary: distant BC recurrence, non-BC mortality, total mortality.	Q5 vs. Q1 dietary pattern; BC mortality, DASH RR = 0.85 (0.61–1.19) p-trend = 0.47; AHEI-2010 RR = 1.07 (0.77–1.49) p-trend = 0.95. Non-BC mortality, DASH RR = 0.72 (0.53–0.99) p-trend = 0.03; AHEI-2010 RR = 0.57 (0.42–0.77) p-trend < 0.0001.	No association with BC recurrence (data not shown) in multivariate models. Results for total mortality (one of the secondary endpoints) not reported, only mentioned in methods. Adjustment: age at diagnosis, energy intake, BMI, smoking and physical activity.
George, 2014	USA	2317 postmenopausal women invasive BC (localised, regional, distant, unknown), WHI (50–79 years), WHI Dietary Modification Trial (<i>n</i> = 1205) and Observational Study (<i>n</i> = 1112), follow-up 9.6 years.	Post-diagnostic, self-administered FFQ at baseline and at 3-year of follow-up.	HEI-2005 scores.	All-cause and cause-specific mortality.	Q4 vs. Q1 HEI score; all-cause mortality HR = 0.74 (0.55–0.99) p-trend = 0.04; non-BC mortality HR = 0.58 (0.38–0.87) p-trend = 0.01; BC mortality HR = 0.91 (0.60–1.40) p-trend = 0.63.	Multivariate model not adjusted for BMI and smoking status. Further adjustment for BMI did not modify HRs (data not reported).

Table 1. Cont.

Author, Year	Country	Population, Cohort	Dietary Assessment	Dietary Patterns	Outcomes	Results—Multivariate Adjusted RR/HR(95% CI)	Observations
McCullough, 2016	USA	4452 cases (40–93 years), CPS-II Nutrition Cohort, mean follow-up 9.8 years.	Pre- and post-diagnostic 68-item Block FFQ (baseline), 152-item Harvard FFQ twice during follow-up.	Dietary pattern scores based on ACS dietary guidelines.	All-cause mortality and deaths from BC, non-BC and CVD.	Highest vs. Lowest post-diagnostic dietary pattern: BC-mortality RR = 1.44 (0.90–2.30); CVD mortality RR = 0.81 (0.47–1.39); Non-BC mortality RR = 0.78 (0.56–1.07) p-trend = 0.03 & per 2-point increase RR = 0.88 (0.79–0.99). Pre-diagnostic diet score was not associated with all-cause mortality.	Adjustment for usual variables, alcohol not included in the final model since it did not change the estimated RRs.
Jang, 2018	Korea	511 cases (mean age 51.9 years), mean follow-up 69 months, Hanyang University Seoul Hospital.	Post-diagnostic 24-h diet recall.	DII (34 items).	BC recurrence and overall mortality.	Q4 vs. Q1; BC recurrence HR = 2.3 (1.17–4.71) p-trend = 0.019; overall mortality HR = 3.0 (1.08–8.83) p-trend = 0.041.	Not adjusted for physical activity, alcohol and smoking status. Associations were also significant among women < 50 y, premenopausal, BMI ≥ 25 kg/m ² , HR+ tumours, tumour size > 2 cm and lymph node metastasis (strata of prognostic factors).
Sun, 2018	USA	2295 postmenopausal women (50–79 years at recruitment), invasive BC, 12 years follow-up, WHI study.	Pre- and post-diagnostic FFQ, HEI-2010 based on 12 components.	HEI-2010 score.	All-cause mortality, BC-mortality, non-BC mortality.	Compared with women with stable diet quality, women who decreased ≥15% HEI-2010, HR = 1.66 (1.09–2.52) for BC-mortality. Women who increased ≥15% HEI-2010 vs. stable diet quality HR = 1.00 (0.81–1.23) for all-cause mortality; HR = 0.98 (0.67–1.44) for BC-mortality and HR = 0.96 (0.74–1.23) for other causes.	Adjustment for relevant variables.
Zheng, 2018	USA	2150 postmenopausal women (age 50–79 years), 13.3 years follow-up, WHI.	1.5 years post-diagnostic: FFQ 120-items plus other related questions.	E-DII (32 components).	All-cause, BC-specific, and CVD mortality.	Q1 vs. Q4 E-DII; HR = 0.96 (0.62–1.49) p-trend = 0.96 (BC mortality); HR = 0.82 (0.63–1.05) p-trend = 0.17 (all-cause mortality); HR = 0.44 (0.24–0.82) p-trend = 0.005 (CVD mortality).	Adjustment for usual variables except for alcohol (probably because alcohol is one of the DII's items). Stratified analyses for hormonal receptors (ER, PR and combined ER-PR status) with no significant interactions.

Table 1. Cont.

Author, Year	Country	Population, Cohort	Dietary Assessment	Dietary Patterns	Outcomes	Results—Multivariate Adjusted RR/HR(95% CI)	Observations
Karavasiloglou, 2019	USA	110 women, NHANES III, mean follow-up 8.6 years.	Post-diagnostic 24-h dietary recall.	HEI, MDS.	All-cause mortality.	By 1-unit increase, HEI: HR = 0.97 (0.95–0.99); MDS: HR = 0.97 (0.82–1.16). Good (≥ 70) vs. Poor (< 70) HEI: 0.49 (0.25–0.97). Adherers (5–9) vs. Non-adherers (0–4) MDS: HR = 0.78 (0.47–1.32).	Usual variables of adjustment; alcohol was not included in the adjustment of the MDS model (it is one of the MDS items). Information regarding disease severity or treatment was not available. See note in ‘Several tumour sites’ section for this article.
Wang, 2020	China	3450 cases stage I–IV SBCSS, follow-up time 8 years.	Post-diagnostic: 93-item semi-quantitative FFQ at 5 years.	CHFP-2007, CHFP-2016, modified DASH, HEI-2015.	All-cause mortality, BC-specific mortality, BC-specific events.	Q1 vs. Q4 dietary pattern; all-cause mortality: CHFP-2007 HR = 0.66 (0.48–0.89), CHFP-2016 HR = 0.75 (0.55–1.01), DASH HR = 0.66 (0.49–0.91). BC-specific events: CHFP-2007 HR = 0.64 (0.44–0.93), CHFP-2016 HR = 0.67 (0.45–0.99), DASH HR = 0.60 (0.40–0.90). Similar association patterns observed for BC-specific mortality.	BC-specific events defined as recurrence or metastasis of BC and deaths from BC. Usual variables of adjustment except for alcohol (not included). Information on outcomes collected during the 10-year post-diagnosis by means on in-person survey.
Wang, 2021	USA	8482 BC cases stage I–III, median follow-up 14 years, NHS and NHSII.	Post-diagnostic semi-quantitative FFQ every 4 years.	DRRD (9 components).	All-cause mortality, BC-specific mortality.	Q5 vs. Q1 DRRD: BC-mortality: HR = 0.80 (0.65–0.97) p-trend = 0.02; all-cause mortality HR = 0.66 (0.58–0.76) p-trend < 0.0001. Compared with lower score ($\leq$ median) before & after diagnosis, women whose score improved from low to high: HR = 0.77 (0.62–0.95) for BC-specific mortality; HR = 0.85 (0.74–0.97) for overall mortality.	Multivariate model adjusted for key confounders. Included change in BMI from pre- to post-diagnostic in adjustments.

Table 1. *Cont.*

Author, Year	Country	Population, Cohort	Dietary Assessment	Dietary Patterns	Outcomes	Results—Multivariate Adjusted RR/HR(95% CI)	Observations
Colorectal cancer (CRC)							
Inoue-Choi, 2013	USA	IWHS, 380 CRC cases, older female survivors (no age specified).	Post-diagnostic 127-items FFQ.	WCRF/AICR guidelines scores.	All-cause mortality. CRC-specific mortality.	Q4 vs. Q1. All-cause mortality: HR = 1.19 (0.59–2.43), p-trend = 0.64. CRC-specific mortality: HR = 1.16 (0.33–4.12), p-trend = 0.84. CVD-specific mortality: HR = 2.61 (0.78–8.71), p-trend = 0.19.	Models adjusted for age, total number of comorbid conditions (accumulated, 1986–2004), perceived general health and current smoking, cancer stage, cancer type, cancer treatment (surgery, chemotherapy), subsequent cancer diagnosis before 2004, current cancer treatment and person-years since cancer diagnosis. No data on cancer stage, mean age of cases and mean/median follow-up time. See note in 'Several tumour sites' section for this article.
Zhu, 2013	Canada	529 invasive CRC. Newfoundland Familial Colorectal Cancer Registry, median follow-up 6.4 years.	Pre-diagnostic semi-quantitative 170-items FFQ (including vitamin and dietary supplements). Principal factor analysis (39 food groups).	Dietary patterns extracted: 'processed meat pattern', 'prudent vegetable pattern' and 'high-sugar pattern'.	Disease-free survival (DFS) and overall survival (OS).	Q4 vs. Q1: processed meat pattern CRC HR = 1.82 (1.07–3.09), p-trend = 0.09 for DFS. Colon HR = 2.29 (1.19–4.40) & rectum HR = 0.97 (0.38–2.45) for DFS. Colon HR = 2.13 (1.03–4.43) for OS.	Physical activity, alcohol and smoking status not included in the adjustment.
Felszer, 2014	USA	NIH-AARP Diet and Health study, 4213 colon and 1514 rectal cancer cases, 5 years follow-up.	Pre-diagnostic 124-item FFQ.	HEI-2005.	All-cause, CRC-mortality and CVD-mortality.	Q5 vs. Q1: Colon cancer: all-cause mortality: RR = 0.95 (0.78–1.16), p-trend = 0.22; CRC-mortality RR = 0.99 (0.77–1.27), p-trend = 0.41; CVD-mortality RR = 0.45 (0.23–0.87), p-trend = 0.01. Rectal cancer: all-cause mortality: RR = 0.60 (0.42–0.86), p-trend = 0.04; CRC-mortality RR = 0.64 (0.41–0.99), p-trend = 0.05; CVD-mortality RR = 0.28 (0.06–1.43).	Variables of adjustment usually used except for socioeconomic status.

Table 1. Cont.

Author, Year	Country	Population, Cohort	Dietary Assessment	Dietary Patterns	Outcomes	Results—Multivariate Adjusted RR/HR(95% CI)	Observations
Fung, 2014	USA	1201 stage I–III CRC cases (women only), median follow-up 11.2 years, NHS.	Post-diagnostic: FFQ at least 6 months after diagnosis; principal component analysis.	AHEI-2010, aMED and DASH and 2 derived dietary patterns: western and prudent diet.	Overall and CRC-specific mortality.	Q5 vs. Q1; AHEI-2010: Overall mortality: HR = 0.71 (0.52–0.98), p-trend = 0.01; CRC mortality: HR = 0.72 (0.43–1.21), p-trend = 0.07.	No other diet quality score or dietary pattern was associated with overall or CRC-specific mortality.
Romaguera, 2015	Europe (10 countries)	EPIC, 3292 CRC cases, mean follow-up 4.2 years.	Pre-diagnostic country-specific validated dietary questionnaires and standardised EPIC Nutrient Data Base.	WCRF/AICR guidelines. Score range 0–6 in men, 0–7 in women; higher scores: greater adherence.	CRC-specific and overall mortality.	CRC-specific mortality: 2nd, 3rd and 4th concordance with recommendations vs. lowest concordance: HR _{2nd} = 0.87 (0.72–1.06), HR _{3rd} = 0.74 (0.61–0.90), HR _{4th} = 0.70 (0.56–0.89); p-trend < 0.0001. Similar results for overall survival (p-trend 0.004).	Adjusted by usual variables including smoking. Body fatness, PA and alcohol were part of the WCRF score, so these were not included in the adjustment.
Jacobs, 2016	USA	MEC study, 4204 cases (men and women aged 45–75 years), stage: localised, regional, distant or unknown, mean follow-up 6.0 years.	Pre-diagnostic FFQ (>180 food items).	4 diet quality indexes: HEI-2010, AHEI-2010, aMED and DASH.	CRC-specific and all-cause mortality.	African-American women: aMED, CRC-specific mortality: HR _{iso} = 0.86 (0.77–0.96); HR _{iso} = 0.88 (0.81–0.96). No significant for men in either case. HEI-2010, AHEI-2010, and DASH no significantly associated with CRC-specific or all-cause mortality.	Usual variables of adjustment used except for alcohol since it is part of some scores.
Yuan, 2017	USA	2006 cases from 2 cohorts: NHS, and HPS, 12.7 years median follow-up	Post-diagnostic FFQ every 4 years	Two dietary insulin (DI) scores: DI-index and DI-load.	CRC-specific mortality and overall mortality.	Q5 vs. Q1. CRC-specific mortality: DI-load HR = 1.82 (1.20–2.75), p-trend = 0.006 & DI-index HR = 1.66 (1.10–2.50), p-trend = 0.004. Overall mortality: HR = 1.33 (1.03–1.72), p-trend = 0.03 for DI-load & HR = 1.32 (1.02–1.71), p-trend = 0.02 for DI-index. In BMI ≥ 25 HR = 2.32 (1.21–4.46) for higher DI-index; BMI ≥ 25 kg vs. BMI < 25 (p-interaction = 0.01).	Usual variables of adjustment used (BMI, PA, alcohol, smoking status).

Table 1. Cont.

Author, Year	Country	Population, Cohort	Dietary Assessment	Dietary Patterns	Outcomes	Results—Multivariate Adjusted RR/HR(95% CI)	Observations
Ratjen, 2017	Northern Germany	1404 CRC cases, median follow-up 7 years, median age 69 years, 56% men, PopGen biobank.	Post-diagnostic, 112-item semi-quantitative FFQ.	Two a priori-defined dietary patterns: MMDS and HNFI.	All-cause mortality.	MMDS: HR _{Q4-Q1} = 0.48 (0.32–0.74) & HR _{1-point-increment} = 0.88 (0.81–0.96), p-trend = 0.003, HNFI: HR _{Q4-Q1} = 0.63 (0.39–1.04) and HR _{1-point-increment} = 0.90 (0.82–0.99), p-trend = 0.04.	Usual variables of adjustment used. No information available for CRC-specific mortality.
Sharma, 2018	Canada	532 CRC (mean age 60 years), mean follow-up 6.27 years, Newfoundland Familial Colorectal Cancer Registry (NFCRC).	Pre-diagnostic 169-item FFQ.	Cluster Analysis (CA), Principal Component Analysis (PCA), aIMED, RFS and DII scores.	Overall mortality (OM) and combined Mortality, Recurrence or Metastasis (cMRM).	For cMRM: PCA-processed meats HR = 1.82 (1.07–3.09); CA-meat & dairy products HR = 2.19 (1.03–4.67); CA-total grains, sugar, soft drinks HR = 1.95 (1.13–3.37). For OM: Poor adherence aMED HR = 1.62 (1.04–2.56). No association with OM/cMRM with prudent vegetable, high sugar pattern, RFS and DII.	Usual variables of adjustment used.
Zheng, 2020	USA	WHI, 463 CRC cases postmenopausal women (aged 50–79 years), 11.6 years follow-up	Post-diagnostic FFQ (number of items not reported).	E-DII (31 components); DII calculated from diet plus supplements and from diet only.	All-cause, total cancer, and CRC-specific mortality.	T1 vs.T3: E-DII (diet + supplements) HR = 0.49 (0.31–0.79) for all-cause mortality; HR = 0.57 (0.29–1.10) for total cancer mortality; HR = 0.58 (0.28–1.22) for CRC-specific mortality. E-DII (diet only) HR = 0.72 (0.46–1.12) for all-cause mortality.	Most pro-inflammatory E-DII (T3) as ref. E-DII score from diet plus supplements and from diet only were both examined. Models not adjusted for alcohol consumption probably because alcohol is one of the items of DII.
Tabung, 2020	USA	1718 stage I–III CRC, NHS and HPFS cohorts, follow-up 9.9 years.	Pre- and post-diagnostic FFQ (number of items not reported).	EDIH score.	CRC-specific mortality and all-cause mortality.	Q5 vs. Q1: Pre-diagnostic EDIH: HR = 1.66 (1.03–2.69) for CRC-mortality & HR = 1.24 (0.97–1.58) for all-cause mortality. Higher EDIH pre- & post-diagnostic HR = 1.51 (0.98–2.32) for CRC-mortality & HR = 1.31 (1.04, 1.64) for all-cause mortality.	Usual variables of adjustment used.

Table 1. Cont.

Author, Year	Country	Population, Cohort	Dietary Assessment	Dietary Patterns	Outcomes	Results—Multivariate Adjusted RR/HR(95% CI)	Observations
Prostate cancer (PC)							
Kenfield, 2014	USA	4538 non-metastatic PC, HPFS, median follow-up (8.9 years for lethal and 9.1 years for fatal outcomes).	Post-diagnostic 130-items FFQ.	Med-Diet adherence.	PC-specific and overall mortality.	High vs. low adherence: HR = 0.98 (0.75–1.29) for lethal disease; HE = 1.01 (0.75–1.38) for fatal disease; HR = 0.78 (0.67–0.90), p-trend = 0.0007 for overall survival.	Assessed traditional and alternative Mediterranean diet pattern. Usual variables of adjustment used.
Yang M, 2015	USA	926 cases non-metastatic PC, PHS I or II, follow-up median 13.8 years.	Post-diagnostic FFQ (number of items not reported).	Prudent and Western pattern.	PC-specific and overall mortality.	Q4 vs. Q1: Western HR = 2.53 (1.00–6.42), p-trend = 0.02 for PC-mortality & HR = 1.67 (1.16–2.42), p-trend = 0.01 for all-cause mortality. Prudent HR = 0.64 (0.44–0.93) p-trend = 0.02 for all cause-mortality.	Usual variables of adjustment used.
Zucchetto, 2016	Italy	726 cases (median age 66 years), median follow-up 12.7 years, cohort study from a case-control study.	Pre-diagnostic 78-items + common Italian recipes FFQ.	DII (31 items).	All-cause and PC-specific survival.	T3 vs. T1: DII HR = 1.25 (0.86–1.83) for all-cause mortality. Heterogeneity to Gleason score $p < 0.01$. Gleason score 7–10 Pca, DII HR = 2.78 (1.41–5.48) for all-cause & HR = 4.01 (1.25–12.86) for PC-specific mortality.	Model adjusted for area of residence, calendar period of diagnosis, age at diagnosis, education, smoking habits, abdominal obesity, alcohol intake and energy intake.
Head and Neck cancer							
Arthur, 2013	USA	542 cases head and neck squamous cell carcinoma (HNSCC); mean age 59 years, mean follow-up ~6 years.	Pre-treatment self-administered, semi quantitative Harvard FFQ (131-item); principal component analysis.	Two dietary patterns: whole-foods pattern, western pattern.	Recurrence and all-cause survival.	Most adherence to the whole-foods pattern HR _{95%CI} = 0.56 (0.34–0.92), p-trend = 0.01.	Limitation: the heterogeneous nature of the study population regarding tumour site. Multivariate models adjusted for age, sex, tumour site, cancer stage, treatment, ACE-27 comorbidities, smoking, BMI and total energy intake.

Table 1. Cont.

Author, Year	Country	Population, Cohort	Dietary Assessment	Dietary Patterns	Outcomes	Results—Multivariate Adjusted RR/HR(95% CI)	Observations
Crowder, 2019	USA	336 cases, University of Michigan Head and Neck Specialised Program of Research Excellence, follow-up 1 year.	Pre-treatment self-administered 2007 Harvard FFQ.	Principal component analysis, 2 dietary patterns: prudent and western.	Nutrition impact symptoms (NIS) 1-year post-diagnostic difficulty chewing, dysphagia-liquids, dysphagia-solids foods, mucositis.	Prudent pattern: difficulty chewing OR = 0.44 (0.21–0.93), p-trend = 0.03; dysphagia liquids OR = 0.38 (0.18–0.79), p-trend = 0.009; dysphagia solid foods OR = 0.46 (0.22–0.96), p-trend = 0.03; mucositis OR = 0.48 (0.24–0.96), p-trend = 0.03, NIS summary score OR = 0.45 (0.22–0.94), p-trend = 0.03.	NIS were measured using the UM Head and Neck Quality of Life questionnaire. Final multivariable models not adjusted for PA or alcohol.
Ovarian cancer (OC)							
Thomson, 2014	USA	636 cases (postmenopausal, mean age 63 years) WHI, follow-up time not found or not clear.	Pre-diagnostic FFQ (number of items unknown).	HEI-2005 score.	Overall and OC-specific mortality.	For all-cause mortality: HEI-2005 HR _{3-T1} = 0.73 (0.55–0.97), p-trend = 0.03. For OC-mortality: HEI-2005 HR _{3-T1} = 0.75 (0.55–1.01), p-trend = 0.06. Women with waist ≤88 cm and no history of diabetes: HR = 0.73 (0.54–0.98).	No adjustments for smoking status, alcohol and BMI.
Hansen, 2020	Australia	OPAL study, 958 cases before diagnosis (n = 678) median follow-up 3.9 years and post-diagnosis (n = 512), median follow-up 3.5 years.	Collected at baseline, 12 and 24 months using a validated semi quantitative FFQ.	Pre- and post-diagnostic Healthy lifestyle index (HLI): including smoking status, physical activity, BMI, alcohol, diet quality score.	Overall survival.	HLI pre-diagnostic: HR most vs. least healthy HR = 0.79 (0.59–1.04). HLI Post-diagnosis most vs. least healthy HR = 0.61 (0.40–0.93). Diet quality score Pre-diagnostic HR _{3-T1} = 0.99 (0.76–1.31) p-trend = 0.9. Post-diagnostic diet quality score HR _{3-T1} (best quality vs. worst) = 1.01 (0.63–1.60), p-trend = 0.9.	Pre-diagnostic models: adjusted for age, education and comorbidities. Post-diagnostic models: adjusted for age, education, comorbidities, stage of disease at diagnosis, histological subgroup and residual disease remaining after surgery. Diet quality score based on WCRF/AICR guidelines (excluding alcohol).

Table 1. Cont.

Author, Year	Country	Population, Cohort	Dietary Assessment	Dietary Patterns	Outcomes	Results—Multivariate Adjusted RR/HR(95% CI)	Observations
Bladder cancer							
Westhoff, 2018	USA	595 non-muscle-invasive cancer (non-Hispanic white) University of Texas M.D. Anderson Cancer Center, Scott Department of Urology; median follow-up 65.7 months.	Pre-diagnostic semi-quantitative 181-items FFQ; exploratory factor analysis (included 135 items).	4 dietary patterns derived: fruits and vegetables, western, low-fat, and Tex-Mex.	Recurrence or progression to muscle-invasive bladder cancer or metastatic tumours.	T3 vs. T1; Recurrence, Western HR = 1.48 (1.06–2.06), p-trend = 0.03. Progression, Western HR = 1.56 (0.91–2.65) p-trend = 0.10. No significant associations with risk of recurrence or progression found for the other patterns.	Models adjusted for age, sex, education, income, BMI, smoking status and intensity, total energy intake, grade, tumour multiplicity, concomitant carcinoma in situ and treatment.
Multiple myeloma							
Lee, 2020	USA	423 cases (mean age 70–72 years women-men), NHS and HPFS, follow-up median 3.5 years.	Pre-diagnostic 130-items FFQ.	AHEI-2010, aMED, DASH, Prudent, Western and EDIP/EDIP/ EDIH.	Multiple myeloma-specific mortality, all-cause mortality.	1-SD increase; Specific mortality: AHEI-2010 HR = 0.76 (0.67–0.87), $p < 0.001$; aMED HR = 0.85 (0.75–0.97), $p = 0.01$; DASH HR = 0.85 (0.76–0.95), $p = 0.006$; Prudent pattern HR = 0.76 (0.66–0.87), $p < 0.001$; Western pattern HR = 1.24 (1.07–1.44), $p = 0.005$; EDIP HR = 1.16 (1.02–1.33), $p = 0.03$; EDIH HR = 1.17 (1.01–1.35), $p = 0.03$. Similar results for all-cause mortality.	No adjustments for smoking status, alcohol and physical activity.

Abbreviations: CI, confidence interval; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; ACS, American Cancer Society; RR, relative risk; HR, hazard ratio; ER, oestrogen receptor; PR, progesterone receptor; CVD, cardiovascular; Study names: WHI, Women's Health Initiative; UM HN-SPORE, University of Michigan Head and Neck Specialised Program of Research Excellence; CPS-II, Cancer Prevention Study II; CALGB, National Cancer Institute-sponsored Cancer and Leukaemia Group B; SBCSS, Shanghai Breast Cancer Survival Study; LACE, Life After Cancer Epidemiology; NHS, Nurses' Health Study; MEC, Multiethnic Cohort; IWHS, Iowa Women's Health Study; WHS, Women's Health Study; HPTs, Health Professionals Follow-up Study; NCI, National Cancer Institute; CWLS, Collaborative Women's Longevity Study; HEAL, Health, Eating Activity, and Lifestyle; LIBCSF, Long Island Breast Cancer Study Project; CBCS, Carolina Breast Cancer Study; AOCs, Australian Ovarian Cancer Study; CapSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; RFS, Recommended Food Score; OPAL, Ovarian cancer Prognosis And Lifestyle; NSHD, Northern Sweden Health and Disease Study; DDCB, Danish Diet, Cancer and Health Study; NOWAC, Norwegian Women and Cancer; PHS, Physicians' Health Study; DACHS, Darmkrebs: Chancen der Verhütung durch Screening; BCPP, Bladder Cancer Prognosis Programme. Dietary patterns: HEI, Healthy Eating Index; DASH, Dietary Approaches to Stop Hypertension; AHEI, Alternative Healthy Eating Index; DII, Dietary Inflammatory Index; E-DII, Energy-Adjusted Dietary Inflammatory Index; DQIR, Diet Quality Index-Revised; RFS, Recommended Food Score; EDIP, Empirical Dietary Inflammatory Index for Insulin Resistance; EDIP, Empirical Dietary Inflammatory Pattern; EDIH, Empirical Dietary Index for Hyperinsulinemia; MMDS, Modified Mediterranean Diet Score; HNFI, Healthy Nordic Food Index; CHFP, Chinese Food Pagoda.

A study based on the Nurses' Health Study (NHS) [18] found no association between four different diet quality indices, including the AHEI, and breast cancer survival among postmenopausal survivors. The same cohort examined the association with AHEI for all survivors with an extended follow-up, and only found a significant reduced risk (43%) of non-breast cancer-related mortality [28]. In contrast, the remaining two studies that assessed different versions of the HEI index, reported significant lower risk for all-cause mortality with higher adherence to the score [19,31] though the smaller sample size. When restricted to postmenopausal women, the Women's Health Initiative (WHI) study also observed a reduction in risk (36%) of all-cause and (42%) non-breast cancer-related mortality according to greater HEI-2005 scores [20]. Updated versions of the HEI score in more recent publications showed an increased risk (66%) of breast cancer mortality for women who decreased their diet quality compared to women with stable diet quality [32], however increased adherence to the HEI-2015 in a large Chinese cohort showed no significant association with breast cancer mortality.

For the two studies that assessed the DASH diet in relation to breast cancer survival, only one reported a significant protective effect (34% reduction) against all-cause mortality and breast cancer-specific events (40% reduction), although the cohort included survivors with I to IV stages [21]. By contrast, previous findings in the NHS only observed a significant protective effect for non-breast cancer-related mortality [28].

Two different cohorts assessed the inflammatory potential of the diet. One cohort based in Korea found that greater adherence to a more inflammatory diet as measured by the Dietary Inflammatory Index (DII) was associated with an increased risk of recurrence and all-cause mortality [29]. In the same direction, restricted to postmenopausal survivors in a larger US cohort, adherence to a more anti-inflammatory diet was associated with a protective effect (66% reduction) against all-cause mortality [33].

The Diabetes Reduction Risk Diet (DRRD), which comprises 9 dietary components associated with 40% lower type II diabetes risk, showed a significant reduced BC-specific mortality (20%) and all-cause mortality (34%) comparing highest versus lowest quintile of adherence from a large US cohort study [34]. Conversely, two different versions of the Mediterranean Diet Score were found to be not significantly associated with all-cause mortality [18,31].

Among data-driven dietary patterns, only the 'Unhealthy' pattern assessed before diagnosis was associated with an increased risk of non-breast cancer-related mortality among postmenopausal women [27]. This study included survivors with advanced (stage IV) tumours; furthermore, multivariable models were not adjusted for body mass index and physical activity.

For scores based on dietary guidelines for health across different populations, adherence scores to the Chinese Food Pagoda (CHFP) in a large Chinese cohort showed decreased risk of all-cause mortality (34%) according to the CHFP-2007 version and a 33–36% reduced risk of breast cancer-specific events (i.e., recurrence, metastasis, or death related to breast cancer) according to CHFP-2007 and CHFP-2016 [21]. Conversely, dietary scores based on the American Cancer Society (ACS) recommendations were not significantly associated with better breast cancer survival [35] but scores that underline the WCRF/AICR guidelines showed a significant lower risk (39%) of all-cause mortality among breast cancer survivors [36].

Meta-Analysis of Cohort Studies on Breast Cancer Survivors

Candidate studies for meta-analysis were those assessing common outcomes (i.e., all-cause mortality and breast cancer-specific mortality) in relation to a dietary pattern reflecting the quality of diet. The diet quality indices selected were the HEI-2005 [19,20], the HEI-2015 [21], and the AHEI [18]. They have a common background, are close to each other and are similarly associated with chronic disease risk [37]. All of them have a scale from 0 to 100.

Regarding all-cause mortality, the summary HR of the highest quality diet versus the lowest was 0.77 (95% CI, 0.64 to 0.91), based on estimates from four studies (Figure 2). Similarly, each 10-points increase in the score (increasing overall diet quality), which is equivalent to a jump from one quartile to the next, was associated with a significant 9% reduction of mortality (HR 0.91, 95% CI, 0.85 to 0.98). In neither case was there evidence of heterogeneity. For breast cancer-specific mortality (Figure 3) the summary HR was 0.82 (95% CI, 0.36 to 1.90) when comparing the highest versus lowest categories of diet quality, whereas no significant decrease in BC-mortality was found for each 10-point increase in the score. Potential heterogeneity was present ($I^2 = 66\%$, $p = 0.03$) for the highest versus lowest diet quality score. This is also reflected in the wide prediction interval, which indicates the uncertainty we could expect in the summary effect if a new study is included. Indeed, a meta-analysis with few studies is usually expected to report an imprecise prediction interval [38].

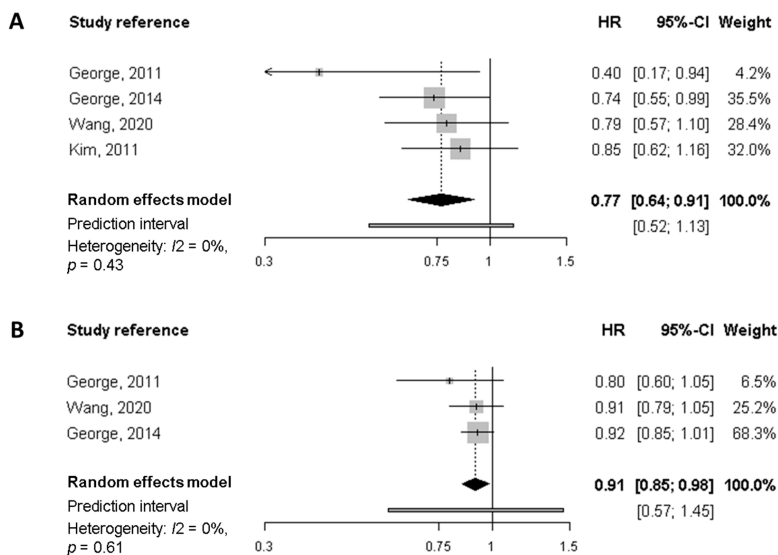


Figure 2. Meta-analysis of prospective cohort studies on the association between quality diet score and overall mortality among breast cancer survivors. **(A)** Forest plot showing pooled hazard ratios (HRs) with 95% CI for the highest diet quality (Healthy Eating Index [HEI], Alternate Health Eating Index [AHEI]) vs lowest diet quality category for overall mortality. **(B)** Forest plot showing pooled HRs with 95% CI for 10-point increase in the quality diet score and overall mortality.

3.2.2. Colorectal Cancer (CRC)

Most of the eleven studies selected used *a priori* dietary indices based on literature or derived from guidelines (e.g., WCRF/AICR guidelines, HEI score) to assess overall dietary intake. Only three studies, two from Canada [39,40] and one from the US [41], examined data-driven dietary patterns. A higher adherence to the pre-diagnosis ‘processed meat pattern’, characterised by a high intake of processed meat, red meat, fish and processed fish, was associated with worse disease-free survival (defined as first occurrence of death, recurrence or metastasis) among all CRC survivors, especially for colon cancers, and with an increased risk of overall mortality in colon cancer survivors [39]. Further analyses in the same cohort [40] found that clusters characterised by high intake of meat and dairy products and high intake of refined grains, sugar and soft drinks, compared with a reference

cluster characterised by higher intake of fruits, vegetables, whole grains and wine, showed poorer survival (higher risk of mortality, recurrence and metastasis). On the other hand, a pattern high in refined grains and sugar/soft drinks was also associated with an increased risk of overall mortality. In contrast, the ‘Prudent’ (healthy) and ‘Western’ (unhealthy) patterns were not associated with the overall or CRC-specific mortality in women in a different study [41].

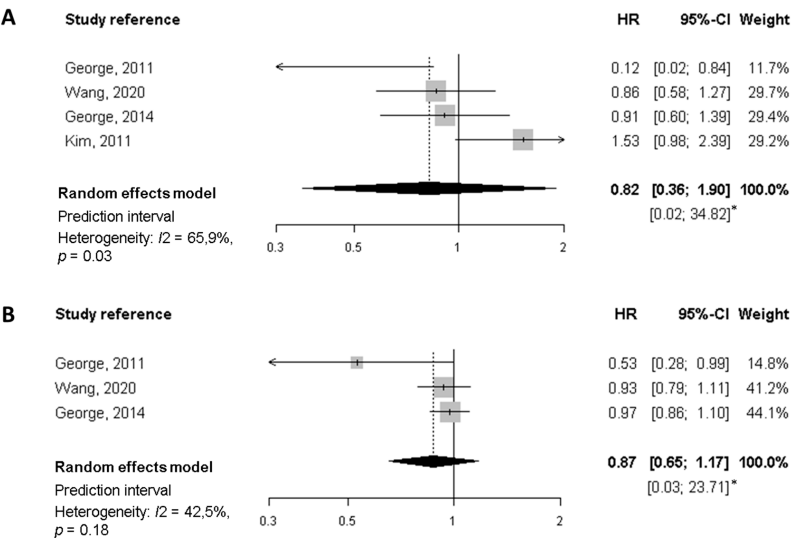


Figure 3. Meta-analysis of prospective cohort studies on the association between quality diet score and breast cancer-specific mortality among breast cancer survivors. (A) Forest plot showing pooled hazard ratios (HRs) with 95% CI for the highest diet quality (Healthy Eating Index [HEI], Alternate Health Eating Index [AHEI]) vs. lowest diet quality category for breast cancer-specific mortality. (B) Forest plot showing pooled HRs with 95% CI for 10-point increase in the quality diet score and breast cancer-specific mortality. * Prediction interval lines are not represented in this figure because intervals are too wide.

The most common *a priori* pattern used to study the overall and CRC-specific mortality was the Mediterranean Diet, present in a total of four studies. For pre-diagnosis assessments, lower adherence to the Alternate Mediterranean Diet Score (altMED) was significantly associated with 62% increase in overall mortality [40]. In addition, results from the large Multiethnic Cohort study (MEC) also reported a protective effect when moving from lower adherence to higher in the score for both CRC and all-cause deaths but limited to African-American women [42]. Similarly, in post-diagnosis assessment in a large German cohort, a lower overall mortality risk was found among men and women comparing extreme quartiles for higher adherence to the Modified Mediterranean Diet (MDD) score (adapted to non-Mediterranean countries) and also for a 1-point increase in score [43]. These findings, however, were not supported by results in other large cohort and no association was found for overall or specific mortality in women survivors of CRC [41].

Higher compared to lower adherence to the HEI-2005 dietary pattern before diagnosis showed a significant protective effect both for CRC-specific and overall mortality (36 and 40% reduction respectively, limited to rectal cancer survivors) [44]. Conversely, results from the MEC study found no association when all CRC survivors were analysed [42]. Among women CRC survivors from the NHS, a significant inverse association was found between

the highest versus lowest quintiles of the AHEI-2010 assessed after diagnosis and overall mortality [41].

Two studies reported no association between the DASH diet and overall and specific CRC mortality [41,42]. On the other hand, higher adherence to the Healthy Nordic Food Index (HNFI) was inversely associated with all-cause mortality (37% reduction as compared to lower adherence) and a significant 10% reduction for each 1-point increase in the score [43].

A Canadian study [40] examined the association between the inflammatory potential of diet after diagnosis and all-cause and specific mortality, but no association was found. However, the WHI cohort, including only women, using a modified version of the same index (E-DII) taking into account diet plus supplements intake, reported a lower all-cause mortality for those following the most anti-inflammatory diets (51% significant reduction compared to the most pro-inflammatory diets) [45].

Another study conducted within the NHS and Health Professionals Follow-up Study (HPFS) cohorts revealed that higher adherence to the empirical dietary index for hyperinulinaemia (EDIH) had a 66% increased risk of dying from CRC and a 24% increased risk of death from all causes [46].

Finally, results from the European Prospective Investigation into Cancer and Nutrition (EPIC) study indicated that higher concordance with the WCRF/AICR recommendations on diet, physical activity and body fatness prior CRC diagnosis was associated with improved overall and specific survival among CRC patients [47]. A previous study with a much smaller number of survivors who were asked to follow the same recommendations after diagnosis reported non-significant results [36]. It is worth mentioning, however, that this study did not report details of cancer stage of participants and did not include specific adjustment for lifestyle confounders.

3.2.3. Other Cancers

This section includes studies that examine several types of cancers together, as well as studies dealing with survivors of cancers of the prostate, head and neck, ovary, urinary bladder and multiple myeloma.

Two studies included several cancers, both conducted in two large cohorts of women [31,36]. The first one, from the Iowa Women's Health Study (IWHS), examined adherence to the WCRF/AICR guidelines among older women survivors of breast cancer, colorectal cancer, gynaecologic cancers (including cervical, endometrial, ovarian and related cancers) and other cancers [36]. The results showed that women with the highest versus the lowest adherence to guidelines of WCRF/AICR after diagnosis had a significantly better overall survival. The second analysed the HEI and Mediterranean Diet scores on the following gynaecological cancers: ovarian, cervical and uterine cancer [31]. Of the two dietary patterns assessed, only the HEI score was significantly associated with all-cause mortality, both for each unit increase in the score and also comparing good versus poor adherence.

Three cohorts examined different dietary patterns in relation to prostate cancer prognosis, two based in the US [48,49] and one in Italy [50]. All but one [50] accounted for key variables of adjustment (obesity, physical activity, alcohol consumption and smoking habit). Only one of the three studies used data-driven dietary patterns and found that higher adherence to a 'Western' dietary pattern was borderline associated with higher prostate-specific mortality and significantly associated with all-cause mortality, while a 'Prudent' dietary pattern was significantly related to lower all-cause mortality [49]. In a large cohort of prostate cancer survivors a higher adherence to a Mediterranean diet score was significantly associated with a 22% lower risk of overall survival [48]. On the other hand, a strong (and significant) relationship was observed in patients with Gleason 7–10 (more aggressive, poor-prognosis cancers) following more pro-inflammatory diets for prostate cancer-specific mortality [50].

Two studies on head and neck cancers survivors from the US used pre-treatment data-derived dietary patterns [51,52]. There was a significant inverse association between better

adherence to a ‘whole-foods’ pattern (characterised by high intakes of vegetables, fruit, fish, poultry and whole grains) and a decrease (44%) in overall mortality [51]. The second study, which examined the nutrition impact symptoms burden among head and neck cancer survivors, reported that a ‘Prudent’ pattern was significantly associated with a reduction in these symptoms (i.e., difficulty chewing, dysphagia of liquids and solid foods, and mucositis) [52]. The assessment of potential confounders was incomplete and inconsistent in both studies.

For ovarian cancer, two studies assessed the effect of different diet patterns in relation to cancer survival. In a study based in the US [53], survivors with a higher quality diet prior to diagnosis according to the HEI-2005 score presented a significantly lower risk (27%) of all-cause mortality, not significant for ovarian cancer-specific mortality. On the other hand, in a study conducted in Australia [54], the Healthy Lifestyle Index (HLI) (that included smoking status, height, weight, physical activity, diet quality score and alcohol) after diagnosis was inversely associated with lower overall mortality; however, when its components were analysed individually, a higher adherence to the diet quality score (defined and quantified using the WCRF/AICR score) was not associated with overall better survival.

Finally, a significant association was observed between the data-driven ‘Western’ pattern and risk of recurrence (48% increased risk) compared to the lowest adherence for urinary bladder cancer survivors [55]. Similarly for multiple myeloma survivors, a study within the NHS and HPFS cohorts found that the ‘Western’ dietary pattern was significantly associated with an increased risk of specific and overall mortality. In addition, survivors with healthier pre-diagnosis dietary patterns, specifically AHEI-2010, aMED, DASH and the ‘Prudent’ pattern, reported better overall and specific survival [56].

3.3. Randomised Controlled Trials (RCT)

A total of fourteen RCT were identified; the details and main features of these studies are shown in Table 2. Clinical trials were mostly from Europe (six studies) and the US (six studies, including a RCT conducted in the US and Canada); the remaining two RCT were carried out in Asia (South Korea and China). Eight studies focused on breast cancer survivors, three on colorectal cancers (including one exclusively on colon cancer), one on prostate cancer survivors, one study on endometrial cancer survivors and finally one study targeted survivors from several cancer subtypes (i.e., breast, stomach, colon, and lung cancer). Three of the fourteen studies were randomised controlled pilot trials [57–59] and hence included a small number of participants. The remaining RCT included a number of participants on the order of a few hundred, with a range from 38 to 3374. The primary outcome of three RCT was survival or cancer progression, but the most common outcomes were quality of life dimensions (i.e., fatigue, sleep quality, physical and mental function).

3.3.1. Randomised Controlled Trials on Breast Cancer Survivors

Two out of the eight RCT included only breast cancer survivors who were overweight or obese at start of the intervention [60,61] and one study focused exclusively on triple-negative BC survivors [62]. A total of four studies included interventions combining nutritional counselling and physical activity programme, targeting participants in the intervention groups generally with the primary goal of reducing energy intake [63,64], dietary fat [62] or weight change [65]. All but two studies [60,66] had as primary or secondary outcomes changes in quality of life assessed by means of different questionnaires (i.e., Function After Cancer Therapy [FACT], European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30], Short Form Health Survey [SF-36]). Some RCT defined outcomes as changes in the lifestyle components of the intervention (i.e., foods, groups of foods or nutrients, physical activity) or intervention-related parameters (i.e., weight, body mass index). We did not take into account these outcomes in our review as they do not have a clear prognostic meaning or cannot be considered as surrogates or prognosis.

Table 2. Characteristics of the included randomised controlled trials (*n* = 14) examining the association between dietary interventions and prognosis in cancer survivors.

Author, Year	Country	Population (Clinical Features, Sample Size, Age, Follow-Up)	Intervention Description	Outcome (Primary, Secondary)	QoL Assessment	Results: Effect Parameter (CI or <i>p</i> -Value)	Observations
Several cancers							
Yun, 2017	South Korea	Cancer survivors who had completed primary cancer treatment within the last 18–24 months. 248 participants randomised: 88 allocated to usual care, 166 to intervention.	LEACH program: first 1-h health education workshop (physical activity, dietary habits, and distress management) and a 3-h leadership workshop. Next individual coaching by telephone for a 24-week period; overall 16 sessions of tele-coaching were conducted: 30 min per week for 12 sessions, 30 min per 2 weeks for 2 sessions and 30 min per month for 2 sessions. Total duration: 1 year.	Primary: changes in physical activity, diet and in PTGI. Secondary: quality of life (QoL).	HADS, EORTC QLQ-C30.	Assessment at 12-month, adjusted means intervention group vs. control group (<i>p</i> -value); PTGI: 66.3 vs. 61.2 (<i>p</i> = 0.065); HADS: 5.2 vs. 5.7 (<i>p</i> = 0.23). EORTC (global health): 69.0 vs. 66.0 (<i>p</i> = 0.27). EORTC (fatigue): 34.8 vs. 41.9 (<i>p</i> = 0.01).	Included in situ, localised or regional with a favourable prognosis of cancers of the breast, stomach, colon and lung. The assessment at 12-months was carried out over 72 subjects (control group) and 134 (intervention group).
Breast cancer (BC)							
Scott, 2013	UK	90 women with early stage cancer (stage I–III), treated within the previous 3–18 months; mean age 56 years. 47 intervention, 43 controls, completed assessment at 6-month: 41 and 48.	6-month lifestyle intervention: exercise + hypocaloric healthy eating program: 3 supervised exercise sessions/week and individualised dietary advice + weekly nutrition seminars. Diet sessions: information on portion sizes from common foods and healthy eating plan. Goal: to reduce 600 kcal of daily calorie intake of their calculated energy requirements.	Primary: body weight, body composition. Secondary: quality of life (QoL).	FACT-B assessed at baseline and at 6-month.	FACT-B QoL: significant improvement in the intervention group: >6 points (<i>p</i> = 0.004) in FACT-B score and >2 points (<i>p</i> = 0.007) in the breast cancer subscale. Moreover, reduction in the intervention group of waist circumference (<i>p</i> < 0.001) and waist-to-hip ratio (<i>p</i> < 0.005).	

Table 2. Cont.

Author, Year	Country	Population (Clinical Features, Sample Size, Age, Follow-Up)	Intervention Description	Outcome (Primary, Secondary)	QoL Assessment	Results: Effect Parameter (CI or p-Value)	Observations
Goodwin, 2014	USA and Canada	LISA Study. Multicentre randomised trial in postmenopausal women with tumours stage T1–3N0–3M0, BMI ≥ 24 . Lifestyle intervention (up to 24 mo) diet + physical activity counselling, evaluating secondary outcomes. Groups: ($n = 167$) mail-based intervention and ($n = 171$) individual lifestyle intervention (LI).	Both arms received information on healthy lifestyle at baseline and at 1-year. Individualised LI: 2-year telephone-based intervention on the diabetes prevention program. Goal: 10% weight loss to a BMI not less than 21; calorie reduction to attain 500–1000 kcal daily deficit, and reduction in fat to 20% of kcal, and increased intake of fruits, vegetables, and grains; gradual increase in moderate-intensity aerobic physical activity to 150–200 min/week.	Primary: disease-free survival. Secondary: overall survival, distant-disease-free survival, weight loss, quality of life (QoL).	QoL: EORTC QLQ-C30 (physical condition and overall QoL score); SF-36 (PCS and MCS); Fatigue Symptom Inventory; Breast Symptom Checklist.	Weight: mean weight loss was significantly ($p < 0.001$) greater in the LI arm vs. comparison arm: 5.3% vs. 0.7% at 6 months; 3.6% vs. 0.4% at 24 months. QoL: mean change in SF36-PCS from baseline, LI arm vs. comparison arm: 4.2 vs. 2.3 at 6 months; 4.4 vs. 2.9 at 12 months; 4.1 vs. 4.4 at 24 months; $p = 0.005$. No significant changes in SF36-MCS, EORTC QLQ-C30 physical condition score ($p < 0.001$). No significant improvement in EORTC QLQ-C30 Quality of Life Score ($p = 0.062$). All p -values are adjusted for time period of assessment.	Accrual was terminated at 338 of 2150 planned patients because of loss of funding. Therefore, only intermediate (24-month) secondary outcomes are presented.
Swisher, 2015	USA	Survivors triple-negative BC (stage I–III), BMI > 25 , age < 80 years, average time at enrolment in the study after diagnosis 4–5 years. 28 women enrolled: 20 allocated to control group, 18 to the intervention.	Moderate-intensity aerobic exercise (150 min per week, for 12 weeks) and diet counselling, compared to usual care. Dietary counselling based on 2 individual sessions with the study dietitian; goal: to decrease dietary fat intake by 200 kcal per week.	Primary outcome: weight loss. Secondary: physical function, quality of life (QoL).	FACT-B.	Weight: subject in the intervention lost more body fat (2.4% loss vs. 0.4% gain, $p < 0.05$) than the control group. QoL (FACT-B): improvements in physical well-being ($p < 0.05$) and BC-specific items ($p < 0.05$).	Assessment based upon women who completed the trial (12 weeks); 18 in the intervention group and 10 from the control group.
Demark-Wahnefried, 2015	USA	The ENERGY trial: single-blinded randomised phase 3 trial. Participants: women diagnosed within the previous 5 years on cancer stage I–III, aged > 21 years and BMI 25–45. Intensive intervention ($n = 344$) or less intensive intervention (control arm) ($n = 348$).	Intervention: group-based, semi-structured weight loss program + telephone counselling and tailored newsletters, according to ACS guidelines. 4 months: 1 h group session/week + 1 session/week for 2 months and 1 session/week during 6–12 months + personalised guidance in between the sessions. + mailed newsletter on a quarterly basis from 6–24 months (individually tailored). Control group received two contacts: at baseline and at 6 months.	Primary outcome: quality of life (QoL).	SF-36: refined Impact of Cancer Scale (IOCV2); BCPT Symptom Scales; CES-D.	Assessment at 12 and 24-month. Non-significant changes for SF36 vitality subscale score (p -values 0.509 and 0.185). Improvement ($p = 0.051$) of SF-36 physical function at 12 months and no significant change at 24 months ($p = 0.185$). Greater positive impact of cancer ($p = 0.046$) at 12 months. Depressive symptoms (CES-D) increased at 24 months ($p = 0.03$).	The SF36 only included specific scales for vitality and physical functioning; the IOCV2 measures impact of cancer on QoL, the BCPT Symptom Scales measures side effects of medical interventions; the CES-D measures depressive symptoms. Unexpected findings related to depressive symptoms.

Table 2. Cont.

Author, Year	Country	Population (Clinical Features, Sample Size, Age, Follow-Up)	Intervention Description	Outcome (Primary, Secondary)	QoL Assessment	Results: Effect Parameter (CI or p-Value)	Observations
Kwiatkowski, 2017	France	PACThe trial. Patients enrolled within 9 months after chemotherapy or radiotherapy completion. 251 participants randomised: 117 intervention, 115 control group.	2-week intervention in hydrothermal centres including APANE (adapted physical activity and nutritional education). Energy intake: 1200 kcal/day. Diet program based on Four-Group Point Method. Control group: individual standard recommendations at home.	Primary outcome: long-term (6-month to 5-years) quality of life.	SF36 (global score).	Effect-sizes (difference between means of the two groups divided by the common standard deviation) for the SF36 score at different time periods: 6 months 0.63 (0.37, 0.89); 1 year 0.29 (0.03, 0.55); 2 years 0.27 (−0.01, 0.56). Effect-size over the whole follow-up period 0.33 (0.23, 0.43), $p < 0.01$.	Secondary endpoints: anxiety/depression (HAD), sleep (adapted from Leeds sleep questionnaire), physical/sedentary activity scores.
Zick, 2017	USA	Pilot study, 30 breast cancer patients stage 0–IIIa (15 intervention, 15 control group)	FRD: rich in fruits, vegetables, whole grains, and omega-3 fatty acid-rich foods. 3-months, phone counselling. Control: 8 sessions general health topics excluding diet).	Primary outcome: fatigue. Secondary: sleep quality.	BFI, PSQI	Adjusted means (difference between baseline and 3-months). BFI decreased by 2.4 in the FRD group vs. controls ($p = 0.01$). PSQI score decreased by 2.5 t in FRD group and increased by 0.9 in the control group ($p = 0.03$).	Intention-to-treat (ITT) analysis. Dietary assessment: at baseline and 3 months by means of day food records and 24-h recalls.
Chlebowski, 2020	USA	WHI-DM trial. 3374 breast cancer survivors (1299 intervention, 2075 controls) median follow-up 19.6-year.	Low-fat dietary pattern: the goals were to reduce fat intake to 20% of energy and increase vegetable, fruit, and grain intake. Intervention period: 8.5-years.	Overall mortality, breast cancer specific mortality.	-	Mortality: HR 0.85 (0.74–0.96), $p = 0.01$. Breast cancer mortality: HR 0.79 (0.64–0.97), $p = 0.02$.	Intention-to-treat, secondary analysis (the primary outcome was recurrence). Lack of breast cancer therapy information.
Ruiz-Vozmediano, 2020	Spain	72 women stage IIA–IIB with treatment completed within previous 12 months. Randomised to intervention ($n = 36$) and control group ($n = 36$). completion of treatment 12 mo earlier. Follow-up: 6 month after intervention.	Intervention (6-month): diet: three 5-h workshops on healthy eating patterns and information on risk factors and prevention; exercise: 7-week period, 60-min class, 3/week, and mindfulness program (4-week, 2/week, 90 min. Control group: usual care.	Primary outcome: quality of life (QoL). Secondary outcome: change in weight.	EORTC QLQ-C30, 5 functional domains: physical, role, cognitive, emotional, and social.	Comparison of means (intervention vs. control at 6-month: significant improvements in physical functioning ($p = 0.027$), role functioning ($p = 0.028$), dyspnoea symptoms ($p = 0.066$). No significant changes in global health and fatigue.	only 15 patients completed at least 75% of program sessions.
Colorectal cancer (CRC)							
Bourke, 2011	UK	Pilot trial; 18 colon cancer survivors, mean age 69 years, Dukes stage A–C, recruited months post-surgery; 9 intervention, 9 controls.	Intervention: 12-week program of home-based exercise sessions and dietary advice ($n = 9$); controls: standard care.	Exercise and dietary behaviours, fatigue and quality of life (QoL).	FACT-F (fatigue) and FACT-C (CRC-specific QoL).	Intervention vs. control: improved fatigue (FACT-F score) $p = 0.005$ and no change in QoL (FACT-C score) $p = 0.80$.	

Table 2. Cont.

Author, Year	Country	Population (Clinical Features, Sample Size, Age, Follow-Up)	Intervention Description	Outcome (Primary, Secondary)	QoL Assessment	Results: Effect Parameter (CI or <i>p</i> -Value)	Observations
Bonelli, 2013	Italy	Double-blind, phase III, placebo-controlled trial. 411 post-polypectomy (within 6 months from enrolment), 200 intervention, 211 placebo group. Median follow-up 4 years.	Active compound (200 µg selenium, 30 mg zinc, 2 mg vitamin A, 180 mg vitamin C, 30 mg vitamin E) vs. placebo; daily, 5 years.	Primary: recurrent adenomas or incident colorectal cancer. Secondary: advanced adenoma.	-	Recurrent adenomas (intervention vs. placebo): HR = 0.61 (0.41–0.92); for small tubular adenomas HR = 0.61 (0.37–0.99); advanced adenomas HR = 0.50 (0.24–1.01).	Intention-to-treat analysis in 330 (out of 411) participants with follow-up colonoscopy (164 intervention and 166 placebo group).
Hu, 2020	China	223 colorectal cancer survivors (82 women), mean age 65 years. 4 groups: Group A (Diet + PA), Group B (Diet only), Group C (PA only), Group D (control group).	Intervention: 'Moving Bright, Eating Smart'. Reduce red/processed meat to <5 servings/week (<2 servings of processed meat) and to limit refined grains to 2 servings/day. Overall 12-month, with decreasing frequency on contacts along the year. Control: usual care.	Quality of life (QoL); assessment at 6, 12, 18, and 24 months.	SF-12 (health-related QoL), SF-6D utility index, FACT-C (CRC-health related QoL), FACT-G (excluding disease-specific items), HADS (anxiety and depression).	Mean difference between groups, dietary intervention vs. not receiving diet intervention: At 12-month, SF-6D utility index scores 0.042 (0.003–0.081) and FACT-G total score 3.09 (0.13–6.04). At 24-month, SF-12 PCS scores (2.57 (0.69–4.45) and the FACT-G total scores 3.14 (0.23–6.04). Overall, reduction in HADS-depression 0.71 (1.28–0.14).	Intention-to-treat principle. Results on physical activity intervention available, but no results on combined intervention.
Prostate cancer							
Parsons, 2020	US	Men's Eating and Living (MEAL) study, 478 men, 50–80 years, with biopsy-proven prostate adenocarcinoma early-stage (cT2a or less and PSA < 10 ng/mL). Intervention (<i>n</i> = 237), controls (<i>n</i> = 241).	MEAL intervention: counselling behavioural intervention by telephone promoting consumption of 7 or more vegetable servings daily; duration 24 months. Control group: written information about diet and prostate cancer.	Primary: time to progression (by biopsy and PSA changes). Secondary: health related quality of life (QoL).	Several functional and health prostate cancer-related QoL scores.	No significant difference in time to progression (intervention vs. control: adjusted HR 0.97 (0.76–1.25), <i>p</i> = 0.84).	Results on QoL not reported.
Koutoukidis, 2019	UK	DEUS pilot trial: parallel, randomised, controlled pilot trial; 54 survivors stage I–IVA endometrial cancer; allocation to either intervention (<i>n</i> = 26) or usual care (<i>n</i> = 28).	Intervention: the 'Shape-Up' following cancer treatment; 8 weeks, group-based weekly 1.5 h sessions on healthy eating and physical activity based on Social Cognitive Theory and Control Theory. Control group: usual care.	Diet, physical activity, body composition, and health-related quality of life (QoL)	EORTC Core 30 and Endometrial Cancer Module (QLQ-EN24)	Change (mean) from baseline to 8 weeks: EORTC QLQ-C30, 5.0 (−3.4–13.3), <i>p</i> = 0.24; at 24 weeks 8.9 (0.9–16.8), <i>p</i> = 0.029.	Intention-to-treat analysis in participants with complete data at 24 weeks (24 intervention, 25 controls)

Abbreviations: BMI, body mass index; PACThe, programme of Accompanying women after breast Cancer treatment completion in Thermal resorts; WHI-DM, Women's Health Initiative—Dietary Modification; LEACH, Leadership and Coaching for Health program; USA, Lifestyle Intervention in Adjuvant Treatment of Early Breast Cancer Study; HADS, Hospital Anxiety and Depression scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SF36, Short Form Health Survey; Physical component scale (PCS) and Mental Component Scale (MCS); FACT-B, Function After Cancer Therapy-Breast; FACT-C, Function After Cancer Therapy-Colorectal; FACT-G, Function After Cancer Therapy-excluding the colorectal cancer-specific items; BCPT, Breast Cancer Prevention Trial; BFI, Brief fatigue inventory; PSQ, Pittsburgh sleep quality index; PTGI, post-traumatic growth inventory; PA, physical activity; mo, months; FRD, fatigue reduction diet; APANE, adapted physical activity and nutritional education.

Quality of life, as measured by the FACT-B (specific scale for breast cancer), showed significant improvements in the intervention group for survivors that followed a 6-month individualised exercise and a hypocaloric healthy eating programme [63]. Similarly, a shorter intervention that combined moderate physical activity and nutrition advice with the goal to decrease dietary fat by 200 kcal weekly, improved quality of life (measured by the FACT-B total score) among triple-negative BC survivors [62]. In addition, mean change in EORTC QLQ-C30 physical condition score was significantly greater for women in the telephone-based weight loss intervention (versus the mail-based arm) among postmenopausal BC survivors in the LISA study [60]. Actually, the LISA study had disease-free survival and overall survival as primary outcomes, but the results were not reported due to lack of financial support to reach the sample size initially planned. In a large study, the ENERGY trial (344 participants in intervention arm, 328 in the control arm) reported a weak or null associations after a 24-months intervention assessing specific items of the SF-36 with a nutritional weight loss programme among breast cancer survivors with overweight or obesity (BMI > 25) [61].

A unique 2-week intervention in hydrothermal centres that included physical activity and nutritional education with calorie restriction (1200 kcal/day) reported improvements on breast cancer patients' quality of life according to the SF-36 global score at several times of follow-up, with the highest difference between group arms at 6 months [64]. In a randomised pilot trial investigating the effect of a 3-month 'fatigue reduction diet' (defined as a diet rich in fruit, vegetables, whole grains, and foods rich in omega-3 fatty acids) revealed an improvement in fatigue and sleep quality in 15 breast cancer survivors compared to the 15 participants from the control group. In contrast, in a RCT with 72 cases (36 in each study group) there was no significant change in global health and fatigue with a 6-month intervention including dietary counselling and physical activity sessions, although only half of the participants in the intervention group completed at least 75% of the programme sessions [65].

Finally, the Women's Health Initiative (WHI) Dietary Modification (DM) clinical trial, with a long dietary intervention (8.5 years) and extended follow-up (median 19.6 years), reported that the adoption of a low-fat dietary pattern (characterised by increased vegetable, fruit and grain intake) reduced significantly the risk of overall (15%) and breast cancer-specific mortality (21%) among postmenopausal women [66].

3.3.2. Randomised Controlled Trials on Other Cancers

The Leadership and Coaching for Health (LEACH) program, a 12-month intervention based on counselling for balanced dietary habits, physical activity and distress management, improved anxiety according to the Hospital Anxiety and Depression Scale (HADS), social functioning and appetite loss scores from baseline to 3 months in survivors of several tumour sites (breast, stomach, colon, lung) with favourable prognosis (non-metastatic cases with treatment completed within the last two years). In addition, from baseline to 12 months, the intervention group showed a significantly greater decrease in the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) fatigue score [67].

Three RCT were conducted on CRC survivors, including a small (18 participants, 9 per arm) randomised pilot study [58]. An improvement on fatigue score after a 12-week program of home-based exercise and dietary advice in the intervention versus control group was reported, but no change in cancer-specific quality of life according to the FACT-C (Function After Cancer Therapy-Colorectal) was observed. A recent study in China reported that participants receiving a 12-month dietary intervention (aimed to reduce red/processed meat to less than 5 servings/week [with processed meat less than 2] and limiting refined grains to 2 servings/day) experienced a significant improvement in generic and CRC-specific QoL, and reduced levels of depression at 12 and 24 month of follow-up [68]. On the other hand, the double-blind, phase III, randomised, placebo-controlled trial providing daily antioxidant supplementation (active compound of 200 µg selenium,

30 mg zinc, 2 mg vitamin A, 180 mg vitamin C, 30 mg vitamin E) for 5 years reported a significant 39% reduction of recurrence risk in the intervention compared to the placebo group in CRC patients post-polypectomy [69].

Regarding prostate cancer survivors, there were no significant differences in time to progression for participants of the MEAL (Men's Eating and Living) study that received a telephone-counselling intervention addressed to increase vegetables consumption over a 24-month period compared to the control group, which received written information on diet and prostate cancer [70].

Finally, in a randomised pilot study in endometrial cancer survivors, an 8-week intervention based on healthy eating and physical activity sessions was associated with a significant improvement in global quality of life (as measured by the EORTC QLQ-C30) in the intervention arm at 24 weeks compared to the control group [59].

4. Discussion

This systematic review summarises the evidence of the impact of diet, as measured by dietary patterns and nutritional interventions, on cancer prognosis, based upon thirty-five prospective cohort studies and fourteen randomised controlled trials. As expected, the vast majority of the articles focused on breast and colorectal cancer survivors.

A better overall diet (i.e., with a high diet quality index) may improve survival after breast cancer diagnosis. The evidence is rather limited to draw conclusions about breast cancer specific-mortality and recurrence. A meta-analysis of four prospective cohort studies including over 9200 breast cancer survivors estimated that women in the highest versus the lowest category of diet quality index had a significant 23% lower mortality. Moreover, for a 10-point increase in the score, which is equivalent to moving from one quartile to the next, there was a significant 9% reduction in mortality. Although the point estimates were similar for breast cancer-specific survival, the association with a better diet quality turned out to be non-significant.

We identified evidence of an increased risk of overall mortality for breast cancer survivors following more pro-inflammatory diets [29]. However, the effect of the inflammatory potential of diet on breast cancer progression needs to be confirmed in larger studies. In fact, these findings are in good agreement with previous studies showing an association between better post-diagnosis diet quality and lower levels of chronic inflammation, as measured by C-reactive protein, independent of body mass index or physical activity [71].

A wide variety of dietary patterns have been assessed for their prognostic value in colorectal cancer survivors. A potential protective effect for overall mortality was identified with Mediterranean dietary pattern, although the results need to be confirmed in other large cohorts and trials [43]. In contrast, the DASH diet (a dietary pattern in principle intended to reduce hypertension) revealed no association with colorectal cancer survival, based on results from two large cohorts [41,42].

The 'processed meat' pattern and two other clusters, the first characterised by meat and dairy intake, and another one characterised by intake of total grains, sugar and soft drinks, were associated with worse overall prognosis (combined mortality, recurrence, or metastasis) [40]. Instead, other derived patterns, the 'Prudent' and the 'Western' dietary patterns showed no associations with mortality outcomes in a different study [41]. The finding of a potential role in disease progression for processed meat is in good agreement with previous evidence confirming its role as a cause of colorectal cancer [72].

A better post-diagnostic diet quality, assessed by the HEI, was associated with lower mortality among female breast and gynaecological cancers [31]. A potential mechanism explaining these findings could be mediated through inflammation since higher quality diets after diagnosis exhibited lower C-reactive protein levels in cancer patients [73] and diets corresponding to higher adherence to HEI score are considered diets with low inflammatory potential [71]. Moreover, a higher adherence to the WCRF/AICR guidelines showed a better overall survival among older female cancers [36].

There seems not be enough evidence to draw conclusions on the prognosis of cancers other than breast and colorectal cancer, but according to three studies in prostate cancer survivors, a ‘Western’ dietary pattern and a diet with higher inflammatory potential were associated with higher overall and cancer-specific mortality, respectively [49,50]. In contrast, the Mediterranean diet, which is attributed with an anti-inflammatory potential, was associated with lower overall mortality [48].

The randomised clinical trials included in this review evaluated the effect of a dietary intervention, often in combination with physical activity, on cancer prognosis. Despite most of the studies focused on quality of life as primary or secondary outcome, differences in study design and tools used for QoL assessment did not allow us to calculate an overall estimate for each specific cancer. Three studies on breast cancer survivors reported significant improvement in quality of life following interventions aimed at weight loss or energy reduction, combined with physical activity advice [60,62,63]. However, a large study in overweight or obese patients reported no effect on quality of life after a long 24-month nutritional weight loss program [61]. Inconsistent results were found between two small trials on breast cancer survivors investigating fatigue, which is one of the most researched aspects of quality of life among cancer survivors; one was a pilot study, randomised and controlled, that reported improvement on fatigue after a 3-month diet rich in fruit, vegetables, whole grains and foods rich in omega-3 fatty acids [57], and the other did not see changes in fatigue after a 6-month intervention based on dietary counselling and physical activity sessions [65]. Key differences in the design of the studies may partly explain inconsistencies in results when examining the same outcome in the same type of cancer.

As for other cancers, generally, interventions that combined dietary counselling and physical activity improved overall quality of life among survivors, although evidence was limited to draw precise conclusions or make recommendations.

Study Strengths and Limitations

Strengths of this systematic review are the inclusion of dietary patterns instead of individual foods, food groups or nutrients as well as the restricted inclusion of only prospective cohort studies and randomised controlled trials. Furthermore, probably because of strict application of the selection criteria, the studies included in the review had good validity, according to the high score achieved on a scale designed to assess the risk of bias. In addition, examining the diet as a whole provides a quick translation into real-life scenarios that can be used to derive recommendations for cancer survivors. Moreover, we assessed studies conducted in a wide variety of settings, and hence we were able to summarise and report associations between dietary patterns and different cancer prognostic outcomes separately, by specific dietary pattern, outcome and cancer type.

A limitation of this systematic review and meta-analysis was that eligible studies were predominantly observational, including, in some instances, several publications based on the same cohort. In general, most studies derived dietary intake from a single FFQ, although a few used data accumulated from multiple dietary assessments. Additionally, the small number of studies that investigated a common dietary pattern and outcome in a cohort of survivors of the same cancer type limited our ability to conduct meta-analyses to estimate the pooled effect across included studies for tumours other than breast cancer. Similarly, we were unable to perform a meta-analysis across randomised controlled trials, including three pilot studies, owing to heterogeneity between the instruments used for quality of life assessment, which was the most common outcome.

5. Conclusions and Final Remarks

An overview of the results reveals that the majority of dietary patterns characterised by a ‘high quality’ diet, often defined according to existing guidelines, as well as *a priori* patterns defined as nutritionally ‘healthy’, can be associated with improved survival in breast and colon cancer survivors. Despite the assumption that dietary patterns are intended to evaluate diet quality as a whole and are a holistic approach to nutrition, this is

to some extent, an expected result, which basically leaves us in the same situation already pointed out for nutritional recommendations [8]: we may end up with a tendency to use cancer prevention guidelines for cancer survivors. In this context, a promising approach could be the assessment of dietary patterns directly related to underlying mechanisms linking nutrition factors to cancer progression [10]. Dietary patterns based on biological processes assume that mechanisms underlying the associations between a dietary pattern and cancer are likely due to the individual or synergistic effects of the various dietary components of this pattern. Indeed, accumulating evidence suggests that diet can modulate these mechanisms. Several interrelated biological processes have been proposed, including antioxidant capacity, hyperinsulinemic potential, metabolic or hormonal disruption, and inflammation and immune function [74–77].

Most randomised trials included in this review evaluated quality of life as primary or secondary outcome related to prognosis. Overall, we may conclude that most dietary interventions tend to improve quality of life and some specific quality of life components among breast cancer survivors. It must be kept in mind, however, that in many instances the effect of diet cannot be assessed independently, as most interventions combined diet and physical activity. However, differences in study design and tools used for quality of life assessment did not allow us to calculate an overall estimate for each specific cancer. Therefore, one of the key issues arising from this review is the recommendation that future trials evaluating quality of life always include one of the questionnaires widely validated and accepted by most researchers, regardless of the specific aspects and dimensions of quality of life of interest in this particular investigation. On the other hand, there is still need of large, prospective, randomised intervention trials to generate data demonstrating improvements in cancer-specific outcomes (recurrence, disease-free survival) as a result of these dietary (and other lifestyle) interventions. It has long been recognised that such kind of trials are resource- and time-intensive [78]. Since evaluating the impact of lifestyle interventions on survival and cancer-related events requires long follow-up of participants, usually accompanied by a high economic burden, a potential alternative is the assessment of short- and medium-term outcomes of changes in prognostic-related markers. This needs, additionally, further research addressed to assess biomarkers with potential prognostic value (epigenetic, metabolic, and molecular) susceptible to modification by diet and other lifestyle factors.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Risk of bias assessment according to the Newcastle-Ottawa Scale (NOS) for cohort studies.

Study Reference		Selection (0–4)	Comparability (0–2)	Outcome (0–3)	Total Score (0–9)
Several cancers					
	Inoue-Choi, 2013 *	4	2	3	9
	Karavasiloglou, 2019	4	2	2	8
Breast cancer					
	Kim, 2011	4	2	2	8
	George, 2011	4	1	2	7
	Vrieling, 2013	4	1	2	7
	Inoue-Choi, 2013	4	2	3	9
	Izano, 2013	4	2	2	8
	George, 2014	4	2	2	8
	McCullough, 2016	4	2	2	8
	Jang, 2018	3	1	1	5
	Sun, 2018	4	2	3	9
	Zheng, 2018	4	2	3	9
	Karavasiloglou, 2019	4	2	2	8
	Wang, 2020	4	2	3	9
	Wang, 2021	4	2	2	8
Colorectal cancer					
	Inoue-Choi, 2013	4	2	3	9
	Zhu, 2013	4	2	2	8
	Pelser, 2014	4	2	2	8
	Fung, 2014	4	2	3	9
	Romaguera, 2015	4	2	1	7
	Jacobs, 2016	4	2	2	8
	Yuan, 2017	4	2	2	8
	Ratjen, 2017	4	2	2	8
	Sharma, 2018	4	2	2	8
	Zheng, 2020	4	2	2	8
	Tabung, 2020	4	2	2	8
Prostate cancer					
	Kenfied, 2014	4	2	2	8
	Yang M (1), 2015	4	2	3	9
	Zucchetto, 2016	4	1	2	7
Head and Neck cancer					
	Arthur, 2013	4	1	2	7
	Crowder, 2019	4	1	1	6
Ovarian cancer					
	Thomson, 2014	4	1	1	6
	Hansen, 2020	4	1	2	7
Bladder cancer					
	Westhoff, 2018	4	1	2	7
Multiple myeloma (MM)					
	Lee, 2020	4	1	3	8

Each item included the following subcategories: Selection (0–4 points): Representativeness of the exposed cohort, Selection of the non-exposed cohort, Ascertainment of exposure, Demonstration that outcome of interest was not present at start of study; Comparability (0–2 points): Comparability of cohorts on the basis of the design or analysis; Outcome (0–3): Assessment of outcome, Was follow-up long enough for outcomes to occur, Adequacy of follow-up of cohorts. * The paper by Inoue-Choi 2013 (Ref. [36]) is listed twice since it was considered as two different cohort studies (or two different analyses within the same cohort): one of them analyzed a group of survivors of a group of several cancers, the second one was restricted to breast cancer survivors. Since some items owing to selection and comparability were dealt with differently in each analysis they were considered as two independent studies.

Table A2. Summary of cohort study data used for meta-analysis calculation.

Study Reference, Cohort	Diet Quality Index	HR (95% CI)					10-Unit Increase
		Q1	Q2	Q3	Q4	Q5	
Kim, 2011 NHS	AHEI						
	Overall mortality	1.00	0.82 (0.61–1.10)	0.83 (0.62–1.12)	0.98 (0.73–1.32)	0.85 (0.63–1.17)	-
	BC-specific mortality	1.00	1.06 (0.68–1.66)	1.12 (0.72–1.74)	1.28 (0.83–1.98)	1.53 (0.98–2.39)	-
George, 2011 HEAL	HEI-2005						
	Mean	50.10	62.90	70.80	79.00	-	
	Overall mortality	1.00	0.39 (0.18–0.85)	0.85 (0.43–1.71)	0.40 (0.17–0.94)	-	0.80 (0.60–1.05)
	BC-specific mortality	1.00	0.65 (0.23–1.86)	0.70 (0.24–2.06)	0.12 (0.02–0.99)	-	0.53 (0.28–0.99)
George 2014 WHI	HEI-2005						
	Range (Midpoint)	34–63 (48.5)	63–71 (67)	71–77 (74)	77–91 (84)	-	
	Overall mortality	1.00	0.93 (0.71–1.22)	0.86 (0.65–1.14)	0.74 (0.55–0.99)	-	0.92 (0.85–1.01)
	BC-specific mortality	1.00	0.99 (0.66–1.50)	0.93 (0.61–1.43)	0.91 (0.60–1.40)	-	0.97 (0.86–1.10)
Wang 2020 SBCSS	HEI-2015						
	Range (Midpoint)	38.0–58.7 (48.35)	58.7–61.9 (60.3)	61.9–65.8 (63.85)	65.8–78.5 (72.15)	-	
	Overall mortality	1.00	1.08 (0.82–1.42)	1.01 (0.76–1.36)	0.79 (0.57–1.10)	-	0.91 (0.79–1.05)
	BC-specific mortality	1.00	1.10 (0.79–1.53)	0.91 (0.63–1.31)	0.86 (0.58–1.27)	-	0.93 (0.79–1.11)

NHS, Nurses' Health Study; HEAL, Health, Eating, Activity, and Lifestyle Study; WHI, Women's Health Initiative; SBCSS, Shanghai Breast Cancer Survival Study; AHEI, Alternative Healthy Eating Index; HEI, healthy eating index; BC, breast cancer; HR, hazard ratio; CI, confidence interval; Q1, first quartile or quintile; Q2, second quartile or quintile; Q3, third quartile or quintile; Q4, fourth quartile or quintile; Q5, fifth quintile.

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CHAPTER II

HYPOTHESES

CHAPTER II. HYPOTHESES

HYPOTHESIS 1:

INFLAMMATORY POTENTIAL OF DIET AND RISK OF BREAST CANCER

Given that inflammation is now recognized as a hallmark of cancer and that low-grade chronic inflammation is likely associated with the risk of breast cancer, possibly through obesity and physical activity, our hypothesis is that diets capable of modulating inflammatory biological processes, such as pro- or anti-inflammatory diets, may exert an impact on the risk of developing this disease.

HYPOTHESIS 2:

DIETARY PATTERNS RELATED TO UNDERLYING BIOLOGICAL MECHANISMS AND BREAST CANCER SURVIVAL

Elevated oestrogen levels are known to be associated with postmenopausal breast cancer risk and factors such as insulin resistance, hyperinsulinemia and chronic low-grade inflammation, associated with obesity and sedentary lifestyles, also contribute to breast cancer risk and disease progression. In addition, breast cancer survivors with type 2 diabetes often experience worse breast cancer prognoses, including an increased risk of recurrence, with mechanisms involving hyperinsulinemia and chronic inflammation playing potential roles. Based on that, we hypothesise that greater adherence to a low-risk type 2 diabetes diet (T2D), an anti-inflammatory diet, and a more anti-estrogenic diet may be associated with lower mortality in breast cancer survivors.

HYPOTHESIS 3:

MEDITERRANEAN DIET AND BREAST CANCER SURVIVAL

The Mediterranean dietary pattern has previously shown an association with a reduced risk of breast cancer within the EPIC study. While factors affecting cancer development may differ from those influencing survival and prognosis, we hypothesize that this dietary pattern may also underscore beneficial biological mechanisms (such as reducing insulin resistance and anti-inflammatory effects) that could potentially impact on better prognostic outcomes (lower mortality) among breast cancer survivors.

HYPOTHESIS 4:

INFLAMMATORY BIOMARKERS AND BREAST CANCER SURVIVAL

The role of inflammation prior to breast cancer diagnosis and its prognostic implications are still unclear. Moreover, some studies have focused mainly on acute phase protein CRP at different times with respect to diagnosis, yielding conflicting results. We hypothesise that elevated levels of inflammatory cytokines and adipokines measured before diagnosis could influence the «latent» inflammation that precedes cancer and have an impact on breast cancer prognosis.

CHAPTER III

OBJECTIVES

CHAPTER III. OBJECTIVES

- 1) To evaluate the link between inflammatory potential of diet and breast cancer risk:
 - To evaluate the association between the inflammatory potential of the diet, by means of the inflammatory score of the diet (ISD), and the risk of breast cancer.
 - To investigate this association considering menopausal status and hormone receptor status of the tumour.
- 2) To examine the association between dietary patterns related to biological mechanism and mortality among breast cancer survivors:
 - To assess the associations with both overall and breast cancer-specific mortality of three pre-diagnostic dietary patterns related to biological mechanisms: the Diabetes Risk Reduction Diet [DRRD], the Inflammatory Score of Diet [ISD], and the Estrogen-Related Dietary Pattern [ERDP].
 - To examine these associations while considering menopausal status, hormone receptor status, and tumour stage.
- 3) To assess the association between Mediterranean diet and mortality among breast cancer survivors:
 - To evaluate the association between adherence to the Mediterranean diet before diagnosis, by means of the adapted relative Mediterranean diet (arMED) score, and all-cause and breast cancer-specific mortality.
 - To investigate this association based on menopausal status, hormone receptor status, and tumour stage.

- 4) To investigate the association between inflammatory biomarkers and mortality among breast cancer survivors:
- To analyse the associations between pre-diagnostic inflammatory biomarkers (IL-6, IL-8, IL-10, IL-13, IL-17D, IL-1RA, IFN- γ , TNF- α , leptin, adiponectin, and CRP) and breast cancer survival.
 - To examine whether individual levels of these biomarkers or a composite score is able to predict overall and breast cancer-specific mortality in breast cancer survivors.
 - To explore these associations according to menopausal status, hormone receptor status, and tumour stage.

CHAPTER IV

MATERIAL AND METHODS AND RESULTS



Inflammatory potential of the diet and risk of breast cancer in the European Investigation into Cancer and Nutrition (EPIC) study

Carlota Castro-Espin¹ · Antonio Agudo¹ · Catalina Bonet¹ · Verena Katzke² · Renée Turzanski-Fortner² · Krasimira Aleksandrova^{3,4} · Matthias B. Schulze^{5,4} · Anne Tjønneland⁶ · Christina C. Dahm⁷ · José-Ramón Quirós⁸ · María-José Sánchez^{9,10,11,12} · Pilar Amiano^{13,11} · María-Dolores Chirlaque^{14,15,11} · Eva Ardanaz^{16,17,11} · Giovanna Masala¹⁸ · Sabina Sieri¹⁹ · Rosario Tumino²⁰ · Carlotta Sacerdote²¹ · Salvatore Panico²² · Anne M. May²³ · Stina Bodén²⁴ · Inger T. Gram²⁵ · Guri Skeie^{25,26} · Nasser Laouali²⁷ · Sanam Shah²⁷ · Gianluca Severi^{27,28} · Dagfinn Aune²⁹ · Melissa A. Merritt^{29,30} · Manon Cairat³¹ · Elisabete Weiderpass³² · Elio Riboli²⁹ · Laure Dossus³¹ · Paula Jakšzyn^{1,33}

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Abstract

The role of chronic inflammation on breast cancer (BC) risk remains unclear beyond as an underlying mechanism of obesity and physical activity. We aimed to evaluate the association between the inflammatory potential of the diet and risk of BC overall, according to menopausal status and tumour subtypes. Within the European Prospective Investigation into Cancer and Nutrition cohort, 318,686 women were followed for 14 years, among whom 13,246 incident BC cases were identified. The inflammatory potential of the diet was characterized by an inflammatory score of the diet (ISD). Multivariable Cox regression models were used to assess the potential effect of the ISD on BC risk by means of hazard ratios (HR) and 95% confidence intervals (CI). ISD was positively associated with BC risk. Each increase of one standard deviation (1-Sd) of the score increased by 4% the risk of BC (HR = 1.04; 95% CI 1.01–1.07). Women in the highest quintile of the ISD (indicating a most pro-inflammatory diet) had a 12% increase in risk compared with those in the lowest quintile (HR = 1.12; 95% CI 1.04–1.21) with a significant trend. The association was strongest among premenopausal women, with an 8% increased risk for 1-Sd increase in the score (HR = 1.08; 95% CI 1.01–1.14). The pattern of the association was quite homogeneous by BC subtypes based on hormone receptor status. There were no significant interactions between ISD and body mass index, physical activity, or alcohol consumption. Women consuming more pro-inflammatory diets as measured by ISD are at increased risk for BC, especially premenopausal women.

Keywords Prospective study · Breast cancer · Inflammatory potential of the diet · Chronic inflammation

Abbreviations

BC	Breast cancer
BMI	Body mass index
CI	Confidence interval
DII	Dietary inflammatory index

EPIC	European prospective investigation into cancer and nutrition
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
IARC	International agency for research on cancer
ICD-O	International classification of diseases for oncology
ISD	Inflammatory score of the diet
LR	Likelihood ratio
PR	Progesterone receptor
SD/Sd	Standard deviation

Disclaimer: Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

✉ Antonio Agudo
a.agudo@iconcologia.net

Extended author information available on the last page of the article

Introduction

Inflammation is now widely accepted as one of the hallmarks of carcinogenesis, and chronic inflammation has been found to be associated with several cancers [1]. Regarding breast cancer (BC), the underlying mechanisms of inflammation are largely unknown. Inflammatory BC is a rare and aggressive disease, accounting for about 2–4% of all BC cases. It is defined by its clinical characteristics and, despite its name it does not show the histologic features of the inflammatory process [2]. The impact of chronic inflammation on BC risk is often assumed to have an indirect role, as one of the underlying pathways which may partially explain the causal association with obesity and physical activity [3, 4]. No dietary components other than alcohol have been found to be associated with BC risk with a convincing degree of evidence [4]. However, those for which a potential effect has been suggested (fats, foods containing carotenoids, non-starchy vegetables, fruit, and fibre) may be associated with inflammatory processes [5].

The relationship between the inflammatory potential of the diet and breast cancer has been evaluated through the Dietary Inflammatory Index (DII) in recent systematic reviews and meta-analyses [6–8]. Overall, evidence suggests that BC risk increases slightly with increasing DII scores, but this association is mainly driven by case–control studies, while summary estimates from cohort studies are either non-significant or marginally significant. Among the six prospective studies published so far [9–15] there are limitations that make it difficult to obtain a clear picture of the evidence. Some have a limited number of cases [12, 14], some focus on postmenopausal women [10, 11, 13] while others do not report the menopausal status of women [9, 12], and only two took into account different types of tumour according to the hormone receptor status [11, 15].

We aimed to assess the association between the inflammatory potential of the diet and risk of breast cancer in a prospective study in a European population. The large sample size of our study allowed us to assess differences of the association according to the menopausal status and hormone receptors status. Moreover, we considered the potential modifying effect of other lifestyle factors related to chronic inflammation.

Methods

Study population

The European Investigation into Cancer and Nutrition (EPIC) is a large prospective cohort study including over half a million participants recruited from ten European

countries between 1992 and 2000. The study design, recruitment, follow-up procedures, and data collection have been described elsewhere [16]. In this work we had data available for the 351,284 women from nine out of the ten EPIC countries (Denmark, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). After excluding participants with prevalent cancers at recruitment, without data of follow-up or diagnosis, lacking dietary information or with implausible diet, a population of 318,686 women were included in this study (see details in the supplementary materials, Figure S1). All participants provided informed consent. The ethical committees from the International Agency for Research on Cancer (IARC) and from the participating centres approved the study.

Follow-up and ascertainment of breast cancer

In most countries, incident cancer cases and vital status were identified through a record linkage to regional or national registries. In France and Germany an active follow-up used a combination of cancer and pathology registries, health insurance records, and contacts with participants or their next-of-kin. BC cases were defined as tumours coded as C50.0–50.9 in the International Classification of Diseases for Oncology (ICD-O-2). Only primary malignant (invasive) tumours were considered; non-epithelial tumours or carcinoma in situ were excluded. Finally, 13,246 incident BC cases diagnosed during an average follow-up of 14 years were included in our analysis. Information on tumour receptor status was gathered on the basis of pathology reports. Information on oestrogen receptor (ER) and progesterone receptor (PR) status was available for 70% and 60% of cases respectively, whereas only 27% of cases had information on the human epidermal growth factor receptor 2 (HER2) status. Further information about geographical distribution and main features of cases is shown in Table S1.

Dietary and lifestyle data collection

Anthropometric data, blood samples and a lifestyle questionnaire including information on medical and reproductive history, sociodemographic characteristics, educational level attained, history of smoking habits, and physical activity were collected at recruitment. The participant's usual diet over the previous year was measured by country-specific food-frequency questionnaires or diet-history questionnaires. Energy, macro- and micronutrients, and other dietary components were calculated using country-specific food composition databases, which had been standardized across countries [17]. Furthermore, standardized 24-h dietary recalls were obtained from representative samples (5–12%) of each cohort to correct for systematic differences between the dietary questionnaires [18]. Sex- and country-specific

calibration models were applied to obtain individual predicted values of dietary intakes. The 24-h recall measurements were regressed on dietary intake from the questionnaire, including in the model total energy intake, age at recruitment, centre, education, smoking status, BMI, and physical activity. These models may be used to obtain predicted values (calibrated intake) of specific dietary items for all participants. A more detailed description of the procedure is shown in the supplementary material.

The inflammatory score of the diet (ISD)

To characterize the inflammatory potential of the diet we used an Inflammatory Score of the Diet (ISD) [19]. The ISD is initially based upon the DII. The DII is calculated using the intake of 45 dietary components (food, nutrients, or bio-active compounds) to which a weight has been assigned that reflects their degree of association with well-known inflammatory markers [20].

For the present study, a set of 27 food items (including macro- and micronutrients, other dietary components, and foods) available in the EPIC databases were used to calculate the ISD. Although we also had data on alcohol consumption, we decided to use a version of the ISD excluding alcohol, despite the anti-inflammatory weight of ethanol in the original DII [20]. A detailed description of the procedure is shown in the supplemental material (Table S2). Briefly, in order to calculate the individual ISD for each subject, the calibrated intake of each food item was standardized with the use of the mean and standard deviation (Sd) of our study population, and then converted to percentiles scores to avoid the right skewness of data and centred on 0 by doubling each percentile score and subtracting 1. These centred percentiles were multiplied by its corresponding inflammatory weight to obtain a specific ISD for each food item, which were summed to produce the overall ISD for each participant.

Owing to the way the ISD is calculated, its value indicates a more pro-inflammatory diet when is positive, while negative values correspond to a more anti-inflammatory diet. However, the weights to compute the score do not have units; they are only an indicator of the inflammatory potential of a singular dietary component. The value of the ISD for an individual must be interpreted as a relative index that allows the categorization of diets on a continuum scale from maximally anti-inflammatory to maximally pro-inflammatory.

Statistical analysis

We used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% CIs for the association between BC risk and the inflammatory potential of the diet as measured by the ISD, with attained age as the underlying time scale. Cohort entry time was defined as age at recruitment,

and exit time was considered age at diagnosis (cases), death, end of follow-up or last known contact, whichever occurred first. Proportional hazards assumptions were assessed by Schoenfeld residuals and were not significantly violated. All models were stratified by centre and age at recruitment (10-years categories) and adjusted for total energy intake.

A selection of potential confounders was done a priori, based on recognized risk factors of breast cancer available in our dataset. The multivariable model included the following covariates: educational level (none and primary school, technical/professional school, secondary school, university or higher and not specified), alcohol consumption (no consumption, < 5, 5–10, 10–20, 20–40, or > 40 g/day), physical activity (inactive, moderately inactive, moderately active, active and not specified), body mass index (BMI; < 25.0 and ≥ 25.0 kg/m²), waist circumference (< 88 and ≥ 88 cm), menopausal status (pre-, peri- and postmenopausal), age at menopause (non-menopausal, < 45, 45–50, 50–5y or ≥ 55 years), number of live births (1, 2, 3, 4 or more), age at first birth (nulliparous, < 20, 20–30, and ≥ 30 years), age at menarche (< 12, 12, 13 or ≥ 13 years), breastfeeding (no, yes, or unknown), ever use of hormonal treatment (no, yes, or unknown), and ever use of oral contraceptives (no, yes, or unknown). An interaction term between menopausal status and BMI was also introduced to take into account the differential effect of excess body weight in BC risk before or after menopause. The ISD was both analysed as a categorical variable by quintiles using the lowest quintile as the reference category, and as a continuous variable using the standard deviation as unit of the ISD (i.e. the HR represents the increase in risk for 1-Sd increase of the ISD). Trend tests across quintiles of the ISD were calculated by entering the categorical variable into the model as a continuous term. The nonlinearity of the effect of the ISD on BC risk was assessed by adding a quadratic term to the model with the ISD as continuous variable and comparing the likelihood of the models with and without the quadratic term by means of the likelihood ratio (LR) test. The nonsignificant *P*-value was interpreted as an indication of a linear effect of the ISD on BC risk.

Separate analyses according to menopausal status were carried out. The menopausal status at recruitment was primarily based upon menstrual cycles over the past 12 months. Women were categorized as postmenopausal (no menstrual cycles), perimenopausal (1–9 menstrual cycles) or premenopausal (≥ 10 menstrual cycles). When data on menstrual status was lacking (about 1% of women) age cut-offs were applied as follows: premenopausal, < 42 years; perimenopausal, 42–55 years; postmenopausal, ≥ 55 years). Women with bi- or unilateral oophorectomy and/or hysterectomy (surgical menopause) were also classified as postmenopausal. To assess whether the association between BC risk and

ISD was different in pre-, peri- or postmenopausal women we used the likelihood ratio (LR) test of the interaction between ISD and menopausal status. The LR test of corresponding interactions with ISD was also used to evaluate the effect modification by BMI, waist circumference, physical activity, and alcohol consumption. The homogeneity of the risks of ISD by tumour receptor status was assessed by means of the Wald test.

We performed sensitivity analyses by excluding participants diagnosed during the first 2 years of follow-up to assess potential reverse causality caused by modification of dietary and lifestyle habits due to pre-existing subclinical conditions. Furthermore, the main Cox models (overall and by menopausal status) were repeated with additional adjustment for smoking to evaluate its potential confounding effect in the association of interest.

Results

The ISD, representing the inflammatory potential of the diet in our population (318,686 women) had a mean of 0.65 (Sd 1.59) and median of 0.80, ranging from -5.45 (the maximum anti-inflammatory value) to 5.49 (the maximum pro-inflammatory value). The distribution of the baseline characteristics of the whole population and BC cases, together with the main parameters of the ISD are reported in Table 1; the ISD is described according to sociodemographic and lifestyle variables using the median, 25th and 75th percentiles, and age-, country- and energy-adjusted means (with 95% CIs) estimated by means of linear regression. Higher values of the ISD were observed in women between age 40–50 years, among highest alcohol consumers, women with 2 or ≥ 4 live births, women whose first birth was before age 20, having breastfed, and among those who used neither menopausal hormone treatment nor oral contraceptives. Decreasing trends of the ISD were observed with higher educational attainment, higher level of physical activity, lower BMI and lower waist circumference, younger age at menarche, and older age at menopause.

The association of the inflammatory potential of the diet with BC risk is presented in Table 2. The multivariable model showed positive association between higher values of the ISD and BC risk both with ISD as continuous ($HR_{1-Sd\ increase} = 1.04$; 95% CI 1.01–1.07) or categorical variable ($HR_{Q5vsQ1} = 1.12$; 95% CI 1.04–1.21) with a significant trend. A significant increase of BC risk with higher values of ISD was also evident in premenopausal and perimenopausal women (8% and 7% increased risk for 1-Sd increase of ISD respectively), while the association among postmenopausal women was not significant. However, the interaction between menopausal status and ISD was not significant (P value 0.09). No heterogeneity was observed

in the association between ISD and BC risk according to different combinations of hormone receptor status. Despite some differences in the point estimates, the Wald test was consistently not significant.

Since body fatness, physical activity and alcohol consumption are well-established factors associated with BC and may contribute to low-grade chronic inflammation, we explored the association of the inflammatory potential of the diet with BC risk for different levels of these factors overall and separately in pre- and postmenopausal women (Table 3). For the sake of simplicity in the interpretation of results, perimenopausal women were excluded from this analysis. Overall, positive associations were observed for all categories, but significant associations (with ISD as continuous variable) were observed only among women with normal weight ($HR = 1.05$; 95% CI 1.01–1.09) and among inactive or moderately inactive women ($HR = 1.06$; 95% CI 1.02–1.10), and in nearly all categories of alcohol consumption. The same pattern with even higher estimates were observed among premenopausal women, with $HR = 1.07$ (95% CI 1.00–1.15) for women with normal weight, $HR = 1.12$ (95% CI 1.03–1.22) for inactive or moderately inactive women, and $HR = 1.11$ (95% CI 1.01–1.22) for non-to-low alcohol consumers (< 5 g/day). The picture was relatively similar for postmenopausal women though the point estimates were always weaker. It should be noted that the categories of women with normal weight and with moderate physical activity or inactive are those with the higher number of cases, so the significance may simply reflect a greater power. All the interactions were non-significant; therefore, from a statistical point of view there was no evidence of modification of the effect of ISD on BC risk by BMI, physical activity, or alcohol consumption, either overall or according to menopausal status.

Finally, the sensitivity analysis showed that the main associations observed were not substantially altered after excluding participants diagnosed during the first 2 years of follow-up in order to assess the possible reverse causality produced by any pre-diagnosis diet modification (Table 4). On the other hand, although tobacco smoking is not yet accepted as a cause of BC, a weak but significant association was observed in EPIC [21]. Therefore, we added tobacco smoking (status, time since quitting and intensity) to the multivariable model, but the pattern of associations remained largely unchanged.

Discussion

In this large cohort study, we observed a positive association between more pro-inflammatory diets and an increased risk of breast cancer, more pronounced in premenopausal women. Overall, women with the highest pro-inflammatory

Table 1 Main characteristics, number of events, and Inflammatory Score of the Diet (ISD) in the EPIC population (women)

	N	%	BC cases	ISD		P value
				Median (P ₂₅ , P ₇₅)	Mean (95% CI) ^a	
Age at recruitment (years)						<0.001
<40	38,464	12.1	664	−0.42 (−1.90–1.23)	0.54 (0.52–0.55)	
40 to <50	104,598	32.8	3871	0.95 (−0.19–1.94)	0.79 (0.78–0.80)	
50 to <60	120,903	37.9	6204	0.88 (−0.16–1.85)	0.58 (0.57–0.59)	
≥60	54,721	17.2	2507	0.89 (−0.13–1.88)	0.67 (0.66–0.68)	
Educational level						<0.001
None/primary	84,650	26.6	3276	1.56 (0.50–2.46)	1.07 (1.06–1.08)	
Technical	71,124	22.3	3027	1.05 (−0.12–2.04)	0.76 (0.75–0.77)	
Secondary	76,461	24.0	3195	0.70 (−0.31–1.56)	0.45 (0.44–0.46)	
Longer (including University)	73,408	23.0	3139	−0.03 (−1.19–0.99)	0.23 (0.22–0.24)	
Unknown	13,043	4.1	609	0.22 (−0.83–1.19)	1.08 (1.06–1.10)	
Alcohol consumption (g/day)						<0.001
Non-consumers	47,157	14.8	1695	1.28 (0.25–2.18)	0.78 (0.77–0.79)	
<5	127,083	39.9	4854	0.90 (−0.30–1.90)	0.62 (0.61–0.62)	
5 to <10	52,151	16.4	2176	0.54 (−0.65–1.60)	0.57 (0.56–0.58)	
10 to <20	52,462	16.5	2395	0.52 (−0.68–1.60)	0.62 (0.61–0.63)	
20 to <40	30,790	9.7	1621	0.67 (−0.39–1.65)	0.77 (0.76–0.79)	
≥40	9043	2.8	505	0.72 (−0.31–1.70)	1.01 (0.98–1.03)	
BMI (kg/m ²)						<0.001
<18.5 (underweight)	6583	2.1	205	0.61 (−0.74–1.62)	0.69 (0.66–0.72)	
18.5 to <25 (normal weight)	184,406	57.9	7600	0.61 (−0.56–1.61)	0.60 (0.60–0.61)	
25 to <30 (overweight)	91,071	28.6	3936	1.08 (−0.07–2.11)	0.71 (0.70–0.72)	
>30 (obesity)	36,626	11.5	1505	1.20 (0.04–2.23)	0.82 (0.81–0.83)	
Waist circumference (cm)						<0.001
<88	176,585	55.4	7302	0.50 (−0.81–1.65)	0.64 (0.63–0.64)	
≥88	48,275	15.1	2110	1.05 (−0.10–2.08)	0.81 (0.80–0.82)	
Unknown	93,826	29.4	3834	1.13 (0.25–1.98)	0.63 (0.62–0.64)	
Height (cm)						<0.001
Quartile1 (<158)	82,930	26.0	3122	0.95 (−0.12–1.92)	0.74 (0.73–0.75)	
Quartile2 (158–162.5)	76,802	24.1	3182	0.77 (−0.36–1.80)	0.68 (0.67–0.69)	
Quartile3 (>162.5–167)	82,297	25.8	3620	0.79 (−0.37–1.83)	0.64 (0.63–0.65)	
Quartile4 (>167)	76,657	24.1	3322	0.69 (−0.61–1.78)	0.57 (0.56–0.58)	
Physical activity						<0.001
Inactive	64,957	20.4	2666	1.18 (0.07–2.14)	0.99 (0.98–1.00)	
Moderately inactive	109,295	34.3	4708	0.68 (−0.48–1.70)	0.59 (0.58–0.60)	
Moderately active	88,520	27.8	3600	0.83 (−0.29–1.80)	0.59 (0.59–0.60)	
Active	50,163	15.7	2076	0.41 (−0.80–1.55)	0.42 (0.41–0.43)	
Unknown	5751	1.8	196	1.93 (1.00–2.70)	1.42 (1.39–1.45)	
Age at menarche (years)						<0.001
<12	46,724	14.7	1914	0.64 (−0.57–1.71)	0.59 (0.58–0.60)	
12	65,654	20.6	2766	0.73 (−0.43–1.75)	0.62 (0.61–0.62)	
13	79,957	25.1	3353	0.74 (−0.43–1.79)	0.64 (0.63–0.64)	
>13	115,619	36.3	4830	0.89 (−0.26–1.90)	0.70 (0.69–0.70)	
Unknown	10,732	3.4	383	1.53 (0.65–2.24)	1.00 (0.97–1.02)	
Menopausal status						0.01
Premenopause	110,678	34.7	3297	0.53 (−0.92–1.68)	0.67 (0.66–0.68)	
Perimenopause	62,796	19.7	2990	1.01 (−0.02–1.95)	0.66 (0.65–0.67)	
Postmenopause	136,381	42.8	6597	0.91 (−0.14–1.90)	0.66 (0.65–0.66)	

Table 1 (continued)

	N	%	BC cases	ISD		P value
				Median (P ₂₅ , P ₇₅)	Mean (95% CI) ^a	
Surgical menopause	8831	2.8	362	0.68 (− 0.37–1.65)	0.61 (0.59–0.64)	
Age at menopause (years)						<0.001
<45	16,821	5.3	628	1.01 (− 0.16–2.06)	0.68 (0.67–0.70)	
45 to 50	36,096	11.3	1594	1.00 (− 0.09–1.99)	0.68 (0.67–0.69)	
50 to 55	47,893	15.0	2288	0.92 (− 0.13–1.90)	0.61 (0.60–0.62)	
≥55	8947	2.8	528	0.78 (− 0.21–1.80)	0.52 (0.49–0.54)	
Unknown	35,455	11.1	1921	0.75 (− 0.21–1.71)	0.68 (0.67–0.69)	
Number of live births						<0.001
0	46,826	14.7	1777	0.16 (− 1.37–1.43)	0.53 (0.52–0.54)	
1	47,019	14.8	2089	0.89 (− 0.24–1.89)	0.66 (0.65–0.68)	
2	121,629	38.2	5453	0.86 (− 0.24–1.86)	0.67 (0.66–0.67)	
3	57,390	18.0	2307	0.87 (− 0.23–1.87)	0.66 (0.65–0.67)	
4 or more	24,338	7.6	864	0.83 (− 0.29–1.86)	0.67 (0.65–0.68)	
Unknown	21,484	6.7	756	1.18 (0.17–2.05)	0.87 (0.85–0.89)	
Age at first birth (years)						<0.001
Nulliparous	46,826	14.7	1777	0.17 (− 1.36–1.45)	0.52 (0.51–0.53)	
1st birth <20	20,522	6.4	796	1.45 (0.26–2.43)	0.93 (0.91–0.94)	
1st birth 20–30	201,401	63.2	8415	0.85 (− 0.22–1.85)	0.67 (0.66–0.67)	
1st birth >30	35,147	11.0	1698	0.67 (− 0.53–1.69)	0.57 (0.56–0.58)	
Unknown	14,790	4.6	560	1.17 (0.19–2.01)	0.86 (0.84–0.88)	
Breastfeeding						<0.001
No	80,126	25.1	3334	0.47 (− 0.82–1.54)	0.62 (0.62–0.63)	
Yes	203,432	63.8	8648	0.85 (− 0.29–1.87)	0.64 (0.63–0.64)	
Unknown	35,128	11.0	1264	1.28 (0.29–2.11)	0.88 (0.86–0.89)	
Ever use of hormonal treatment						<0.001
No	216,794	68.0	7889	0.78 (− 0.45–1.81)	0.66 (0.65–0.66)	
Yes	80,282	25.2	4482	0.76 (− 0.25–1.76)	0.63 (0.62–0.64)	
Unknown	21,610	6.8	875	1.36 (0.13–2.28)	0.80 (0.78–0.82)	
Ever use of contraceptive pill						<0.001
No	120,803	37.9	5203	0.98 (− 0.10–1.97)	0.66 (0.66–0.67)	
Yes	189,455	59.4	7776	0.64 (− 0.57–1.70)	0.64 (0.63–0.64)	
Unknown	8428	2.6	267	1.63 (0.85–2.26)	1.07 (1.04–1.10)	

^aMeans (95% CI) adjusted by age, country, and energy intake, obtained from linear regression models

diets (fifth quintile of the ISD) had a significant increased risk of 12% compared with those with the most anti-inflammatory diets (first quintile). Each increase in 1 Sd of the index had a significant increased risk of 4%; rising to 8% among premenopausal women. This finding is particularly relevant for BC prevention since diet together with physical activity and weight control are key modifiable lifestyle factors, and BC is the most common cancer in women, with over 2 million new cases in 2018, and the leading cause of cancer death worldwide [22]. It is also worth noting that so far, no single dietary component apart from alcohol has been found to be a cause of BC with convincing degree of evidence [4]. On the contrary, looking at the totality of diet, as it is done by means of dietary patterns, it is likely to reflect

an interactive, synergistic, and combined effect of dietary components [23]. Moreover, examination of diet as a whole can be more readily translated into dietary guidelines. In our population, a more anti-inflammatory diet is defined by a high consumption of legumes, vegetables, fruits (all kinds), and to a lesser extent, fruit and vegetable juices, coffee, and tea, as reflected by strong inverse correlation of these food group with ISD (Table S3). On the contrary, a more pro-inflammatory diet is characterized by high consumption of meat and meat products (including red and processed meat), foods rich in fats and oils, and sugar and confectionery.

To our knowledge the association between the inflammatory potential of the diet and BC risk has been assessed in six prospective studies. Our results are in line with those from

Table 2 Adjusted hazard ratios (HR) and 95% confidence intervals (CI) of breast cancer by quintiles of the ISD

	Cases	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	<i>P</i> -trend	ISD continuous
Breast cancer (Global)								
Basic model ^a	13,246	Referent	1.01 (0.95–1.07)	1.04 (0.98–1.11)	1.05 (0.99–1.13)	1.09 (1.01–1.17)	0.012	1.03 (1.00–1.06)
Multivariable model ^b		Referent	1.01 (0.95–1.07)	1.05 (0.98–1.11)	1.06 (0.99–1.14)	1.12 (1.04–1.21)	0.002	1.04 (1.01–1.07)
Menopausal status^c								
Premenopausal BC	3297	Referent	1.05 (0.93–1.19)	1.10 (0.97–1.25)	1.08 (0.94–1.25)	1.17 (0.99–1.38)	0.086	1.08 (1.01–1.14)
Perimenopausal BC	2990	Referent	1.00 (0.87–1.14)	1.01 (0.88–1.15)	1.09 (0.94–1.26)	1.23 (1.04–1.45)	0.008	1.07 (1.00–1.13)
Postmenopausal BC ^d	6959	Referent	0.99 (0.91–1.07)	1.04 (0.95–1.13)	1.04 (0.95–1.14)	1.06 (0.96–1.17)	0.149	1.02 (0.98–1.06)
<i>P</i> value for interaction ^e								0.091
BC by Hormone. receptors status^b								
ER(+)	7508	Referent	1.02 (0.94–1.10)	1.06 (0.98–1.15)	1.06 (0.97–1.16)	1.14 (1.03–1.26)	0.012	1.04 (1.01–1.08)
ER(–)	1668	Referent	0.93 (0.79–1.10)	1.03 (0.87–1.22)	1.05 (0.87–1.26)	1.14 (0.93–1.41)	0.106	1.06 (0.98–1.15)
<i>P</i> -Wald test ^f								0.597
PR(+)	5080	Referent	1.00 (0.91–1.10)	1.02 (0.92–1.12)	1.06 (0.95–1.18)	1.15 (1.02–1.31)	0.024	1.05 (1.00–1.10)
PR(–)	2604	Referent	1.00 (0.87–1.14)	1.09 (0.95–1.25)	1.05 (0.90–1.22)	1.16 (0.98–1.39)	0.09	1.06 (0.99–1.13)
<i>P</i> -Wald test ^f								0.556
ER(+)/PR(+)	4830	Referent	1.02 (0.92–1.12)	1.02 (0.92–1.13)	1.06 (0.95–1.19)	1.17 (1.03–1.33)	0.023	1.05 (1.00–1.10)
ER(–)/PR(–)	1261	Referent	0.91 (0.75–1.09)	0.97 (0.80–1.17)	0.95 (0.77–1.18)	1.10 (0.86–1.40)	0.45	1.05 (0.95–1.15)
<i>P</i> -Wald test ^f								0.762
HER2(+)	861	Referent	1.16 (0.92–1.47)	1.25 (0.97–1.60)	1.10 (0.84–1.45)	1.07 (0.78–1.46)	0.872	1.00 (0.89–1.12)
HER2(–)	2670	Referent	0.99 (0.87–1.12)	0.98 (0.86–1.13)	1.00 (0.86–1.16)	1.22 (1.02–1.46)	0.1	1.05 (0.99–1.13)
<i>P</i> -Wald test ^f								0.391
Triple negative	320	Referent	0.96 (0.66–1.41)	1.06 (0.71–1.58)	1.07 (0.70–1.65)	1.12 (0.67–1.87)	0.565	1.13 (0.93–1.36)
Non-triple negative	2917	Referent	1.02 (0.90–1.16)	1.05 (0.92–1.20)	1.03 (0.89–1.19)	1.18 (1.00–1.40)	0.126	1.03 (0.97–1.10)
<i>P</i> -Wald test ^f								0.386

^aStratified by age and centre, and adjusted for energy intake^bMultivariable model: basic model further adjusted by educational level, alcohol consumption, BMI, physical activity, menopausal status, age at menopause, age at menarche, number of live births, age at first birth, breastfeeding, ever use of hormonal treatment, ever use of contraceptive pill, waist circumference, height and interaction between BMI and menopause^cMultivariable model: basic model further adjusted by educational level, alcohol consumption, BMI, physical activity, age at menopause (only in postmenopausal model), age at menarche, number of live births, age at first birth, breastfeeding, ever use of hormonal treatment (only in postmenopausal model), ever use of contraceptive pill, waist circumference and height^dThis category includes women with natural menopause and surgical menopause^e*P* value for interaction is based upon the likelihood ratio (LR) test^f*P* value for the Wald test assessing the homogeneity of the relative risks

the Swedish Women's Lifestyle Health [9], in which there was significant increase of 4% of risk for each increase of one unit of the DII, as well as in the Iowa Women's Health study [13], with a marginally significant increased risk of BC of 11% for women in the highest tertile of the DII. The latter reported a significant interaction with BMI; the only significant increase in risk was observed among obese women. No association between DII and BC risk in postmenopausal women was found in the Women's Health Initiative [10], but an extended follow-up of the same study [11] reported a significant increased risk for women in the highest quintile of the DII limited to cases ER + PR + HER2+. The authors stated that it is no clear why a diet with high inflammatory

potential would be associated with this specific subtype of BC. No association were found in small cohorts in France [12] and Spain [14]; but owing to the small sample size (158 and 100 BC cases respectively) both studies had little statistical power. The French study [12] reported a significant interaction with alcohol intake: DII was associated with increased BC risk in low-moderate drinkers but had a protective effect among heavier drinkers. According to authors the latter is unlikely to be causal. In this study the DII included alcohol intake and it is unclear how this may have affected the results. Finally, no association between DII and BC risk was observed in the Sister Study cohort [15] but in subgroup

Table 3 Adjusted hazard ratios (HR) and 95% confidence intervals (CI) of BC and ISD (continuous variable) among premenopausal and postmenopausal women and by subgroups of body mass index, physical activity and alcohol consumption

	All participants		Premenopausal ^a		Postmenopausal ^b	
	cases	HR (95% CI) ^c	cases	HR (95% CI) ^c	cases	HR (95% CI) ^c
BMI						
Underweight	205	1.16 (0.90–1.49)	58	1.51 (0.88–2.59)	81	0.96 (0.60–1.54)
Normal weight	7600	1.05 (1.01–1.09)	2242	1.07 (1.00–1.15)	3545	1.03 (0.98–1.09)
Overweight	3936	1.01 (0.96–1.06)	746	1.02 (0.90–1.16)	2372	1.00 (0.93–1.06)
Obesity	1505	1.06 (0.98–1.16)	251	1.17 (0.94–1.45)	961	1.04 (0.94–1.16)
Overweight + Obesity	5441	1.03 (0.98–1.07)	997	1.07 (0.96–1.19)	3333	1.02 (0.96–1.07)
<i>P</i> value for interaction ^d		0.257		0.133		0.740
<i>P</i> value for interaction ^e		0.303		0.345		0.554
<i>P</i> value for interaction ^f		0.772		0.743		0.470
Waist circumference						
< 88 cm	7302	1.03 (0.99–1.07)	2000	1.04 (0.97–1.12)	3917	1.02 (0.97–1.07)
≥ 88 cm	2110	1.01 (0.95–1.08)	325	1.20 (0.99–1.44)	1432	1.00 (0.92–1.09)
<i>P</i> value for interaction		0.158		0.250		0.218
Physical activity						
Inactive	2666	1.06 (0.99–1.13)	557	1.15 (0.98–1.34)	1685	1.04 (0.96–1.13)
Moderately inactive	4708	1.05 (1.00–1.11)	1095	1.10 (0.99–1.22)	2576	1.05 (0.98–1.12)
Moderately active	3600	1.02 (0.96–1.07)	1046	1.04 (0.93–1.16)	1560	0.98 (0.90–1.06)
Active	2076	1.04 (0.97–1.11)	528	1.02 (0.89–1.17)	1069	1.01 (0.93–1.11)
Inactive + Mod. inactive	7374	1.06 (1.02–1.10)	1652	1.12 (1.03–1.22)	4261	1.05 (1.00–1.10)
Active + Mod. active	5676	1.02 (0.98–1.07)	1574	1.03 (0.95–1.12)	2629	0.99 (0.93–1.05)
<i>P</i> value for interaction ^g		0.321		0.525		0.231
<i>P</i> value for interaction ^h		0.238		0.775		0.237
Alcohol consumption						
Non consumers	1695	1.02 (0.94–1.11)	399	1.09 (0.91–1.30)	924	0.99 (0.89–1.11)
Non-to-low consumers	6549	1.04 (1.00–1.08)	1682	1.11 (1.03–1.21)	3385	0.99 (0.94–1.05)
Consumers < 5 g/d	4854	1.04 (1.00–1.09)	1283	1.11 (1.01–1.22)	2461	0.99 (0.93–1.05)
Consumers ≥ 5 g/d	6697	1.05 (1.01–1.09)	1615	1.05 (0.97–1.13)	3574	1.06 (1.01–1.11)
<i>P</i> value for interaction ⁱ		0.992		0.637		0.556
<i>P</i> value for interaction ^j		0.944		0.819		0.482

^aMultivariable model: stratified by age and centre, and adjusted for energy intake, educational level, alcohol consumption, BMI, physical activity, age at menarche, number of live births, age at first birth, breastfeeding, ever use of contraceptive pill, waist circumference and height

^bIncludes women with natural and surgical menopause. Multivariable model stratified by age and centre, and adjusted for energy intake, educational level, alcohol consumption, BMI, physical activity, age at menarche, number of live births, age at menopause, age at first birth, breastfeeding, ever use of contraceptive pill, ever use of hormonal treatment, waist circumference and height

^cHazard ratio (HR) and 95% confidence intervals (CI) for increase in one standard deviation (1-Sd) of the ISD

^d*P*-value for interaction based upon the likelihood ratio (LR) test with BMI classified in 4 categories: underweight, normal weight, overweight and obesity

^e*P* value for interaction based upon the likelihood ratio (LR) test with BMI classified in 3 categories: normal weight, overweight and obesity, excluding underweight

^f*P* value for interaction based upon the likelihood ratio (LR) test with BMI classified in 2 categories: normal weight and overweight + obesity. Underweight were excluded from this test

^g*P* value for interaction based upon the likelihood ratio (LR) test with physical activity classified in 4 categories: inactive, moderately inactive, moderately active and active

^h*P* value for interaction based upon the likelihood ratio (LR) test with physical activity classified in 2 categories: inactive + moderately inactive and moderately active + active

ⁱ*P* value for interaction based upon the likelihood ratio (LR) test with alcohol consumption classified in 3 categories: non-consumers, consumers of < 5 g/d and consumers of ≥ 5 g/d

^j*P* value for interaction based upon the likelihood ratio (LR) test with alcohol consumption classified in 2 categories: non-consumers + consumers of < 5 g/d (non-to-low consumers) and consumers of ≥ 5 g/d

Table 4 Sensitivity analysis. Association between breast cancer and the Inflammatory Score of the Diet (ISD) excluding the first 2 years of follow-up and an additional adjustment for smoking habits

	Cases	Quintiles of the ISD, HR (95% CI) ^a					<i>P</i> -trend	ISD continuous HR (95%CI)
		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Excluding first 2 years follow-up ^b								
All breast cancer cases	11,794	Referent	0.99 (0.92–1.05)	1.03 (0.97–1.11)	1.06 (0.98–1.13)	1.11 (1.02–1.20)	0.003	1.04 (1.01–1.07)
Premenopausal breast cancers	2976	Referent	1.02 (0.90–1.15)	1.08 (0.94–1.24)	1.07 (0.93–1.25)	1.14 (0.96–1.35)	0.132	1.07 (1.01–1.14)
Premenopausal subgroups								
BMI: Normal weight	2015	Referent	1.01 (0.87–1.18)	1.05 (0.89–1.24)	1.09 (0.91–1.30)	1.13 (0.91–1.41)	0.2	1.08 (1.00–1.16)
PA: Inactive/ Mod. Inactive	1502	Referent	1.10 (0.92–1.33)	1.29 (1.06–1.58)	1.28 (1.03–1.59)	1.33 (1.04–1.71)	0.017	1.12 (1.03–1.21)
Alcohol: Non-to-low consumers	1512	Referent	0.95 (0.79–1.15)	1.07 (0.87–1.31)	1.09 (0.88–1.36)	1.27 (1.00–1.63)	0.025	1.11 (1.02–1.21)
Adjustment for smoking status ^c								
All breast cancer cases	13,246	Referent	1.00 (0.94–1.06)	1.04 (0.98–1.11)	1.05 (0.98–1.13)	1.10 (1.02–1.19)	0.009	1.03 (1.00–1.06)
Premenopausal breast cancers	3297	Referent	1.05 (0.93–1.18)	1.09 (0.96–1.24)	1.07 (0.93–1.24)	1.15 (0.97–1.36)	0.156	1.07 (1.01–1.13)
Premenopausal subgroups								
BMI: Normal weight	2242	Referent	1.05 (0.91–1.21)	1.04 (0.89–1.22)	1.08 (0.91–1.29)	1.13 (0.92–1.40)	0.286	1.07 (0.99–1.14)
PA: Inactive/ Mod. Inactive	1652	Referent	1.14 (0.95–1.36)	1.30 (1.08–1.58)	1.27 (1.03–1.57)	1.39 (1.09–1.77)	0.01	1.13 (1.04–1.22)
Alcohol: Non-to-low consumers	1682	Referent	0.99 (0.83–1.19)	1.10 (0.90–1.33)	1.09 (0.88–1.34)	1.29 (1.01–1.64)	0.031	1.11 (1.02–1.21)

^aMultivariable model stratified by age and centre, and adjusted for energy intake, educational level, alcohol consumption, BMI, physical activity, age at menarche, number of live births, age at menopause, age at first birth, breastfeeding, ever use of contraceptive pill, ever use of hormonal treatment, waist circumference and height and interaction between BMI and menopause (overall model). Premenopausal: Multivariable model without the adjustment of menopause, age at menopause and ever use of hormonal treatment

^bMultivariable model excluding participants with less than 2 years of follow-up

^cMultivariable model with additional adjustment for smoking status and intensity, with the following categories: never smoker; current, 1–15 cigarettes/d; current, 16–25 cigarettes/d; current, > 25 cigarettes/d; former, quit ≤ 10 y; former, quit 11–20 y; former, quit > 20 y; or other smokers, including occasional smokers, exclusive smokers of cigar and/or pipe, and smokers with unknown status and/or unknown amount smoked

BMI body mass index, PA physical activity

analyses a significant increase of the DII was associated with risk of triple-negative BC.

The above-mentioned studies assessed the inflammatory potential of the diet by means of the DII, whereas we used the ISD. The two indices are quite similar; actually, we used the set of weights (inflammatory scores) of the DII to calculate the ISD. The major difference with respect to the DII was that the intake of each food item was standardized using the mean and standard deviation of the EPIC population instead of those from a regional worldwide database [20]. Furthermore, the Pearson's correlation coefficient between the ISD and the DII in the EPIC population was 0.91 (*P* value < 0.001) [19]. Therefore, although using slightly different methods to calculate the ISD and DII could be seen as a limitation when comparing our findings to those from

previous studies, this does not pose a serious drawback to the comparability of the results.

In this work we used a version of the ISD excluding alcohol based on two main considerations. First, although ethanol has an anti-inflammatory weight in the original DII [20] it seems it is a dose-dependent effect. The negative relationship with inflammatory markers has been observed only among moderate alcohol consumers suggesting that the presence of other bioactive components in alcoholic beverages rather than ethanol itself may provide anti-inflammatory properties [24, 25]. Second, and even more relevant, is that alcohol is a well-established cause of breast cancer [3, 4]. If a negative association of an anti-inflammatory diet is found, recommendations for BC prevention based on our results would never include the consumption of alcohol. We used the same approach when we assessed the association of BC

with the adherence to a Mediterranean diet [26]. Anyway, it is also reassuring that a significant association between the ISD and BC risk was independent of the level of alcohol consumption (Table 3).

Hormones play an important role in BC risk and progression. There is a consistent link between postmenopausal concentrations of endogenous hormones (mainly oestradiol and testosterone) and increased BC risk. There seems to be a similar pattern in premenopausal women, but data are sparser [22]. On the other hand, adiposity and physical activity are both associated with chronic inflammation, which could partially explain the association of these factors with BC. While a state of low-grade chronic inflammation is induced by changes in the pathophysiology of adipokines of obese subjects [27], physical activity may reduce the macrophage production of inflammatory cytokines [28]. We have observed that the association of ISD with BC risk was particularly marked among premenopausal women and showed a consistent (and significant) association among inactive women and those with normal weight. Our results are compatible with the hypothesis that the potential effects of a pro- or anti-inflammatory diet are stronger, or at least more evident, among women for which hormonal pathways are less relevant and those without other strong determinants of systemic chronic inflammation.

A limitation of the present study is that the dietary exposure was derived from self-reported information relying on subjects' memory. Dietary assessment relying on the ability of individuals to recall a complex collection of data is known to contain measurement error. However, since diet was measured before disease occurrence, this error is non-differential with respect to disease. The effect of random (nondifferential) misclassification is to increase the similarity between exposed and nonexposed groups, so that any true association between dietary exposure and outcome is diluted or underestimated. On the other hand, dietary information was gathered only once at recruitment. Repeated dietary assessments, which allows for a more accurate measure of dietary changes during follow-up, has often been recommended as an effective method of decreasing the measurement error; however, this needs to be considered having in mind the disease's latent period (the interval from when a cancer starts until it is diagnosed). In fact, the collected diet should correspond to the etiological relevant time window, assumed to take place before the onset of the disease. Further exposure afterwards, including the latency period, does not contribute to aetiology of the disease. In spite of the lack of precise knowledge of the natural history of breast cancer, a latency period of 16.3 years has been estimated recently [29]. In our study the average follow-up was 14 years; thus, the lack of repeated assessment of diet during follow-up

does not appear to have induced any bias in the association between ISD and breast cancer risk.

Major strengths of this study are the prospective design and its large sample size, allowing sufficient statistical power for subgroup analyses. It is now widely accepted that the factors that modify the risk of BC are not the same when diagnosed before or after the menopause. On the other hand, the importance of distinguishing tumour subtypes according to hormone receptors when evaluation aetiology is now well established [30]. Therefore, the ability to assess within a common framework the associations between ISD and BC risk overall, as well as by menopausal status and tumour receptor status is an advantage.

In conclusion, our findings suggest that a more pro-inflammatory diet is associated with an increased risk of breast cancer, especially among premenopausal women. These results could help provide dietary recommendations, although they require further confirmation, for the prevention of breast cancer. In this line, it may be of interest to study new hypotheses regarding the possible effect of the inflammatory potential of the diet and the progression and prognosis of breast cancer.

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Declarations

Conflict of interest The authors have no conflict of interest to disclose.

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Authors and Affiliations

Carlota Castro-Espin¹ · Antonio Agudo¹ · Catalina Bonet¹ · Verena Katzke² · Renée Turzanski-Fortner² · Krasimira Aleksandrova^{3,4} · Matthias B. Schulze^{5,4} · Anne Tjønneland⁶ · Christina C. Dahm⁷ · José-Ramón Quirós⁸ · María-José Sánchez^{9,10,11,12} · Pilar Amiano^{13,11} · María-Dolores Chirlaque^{14,15,11} · Eva Ardanaz^{16,17,11} · Giovanna Masala¹⁸ · Sabina Sieri¹⁹ · Rosario Tumino²⁰ · Carlotta Sacerdote²¹ · Salvatore Panico²² · Anne M. May²³ · Stina Bodén²⁴ · Inger T. Gram²⁵ · Guri Skeie^{25,26} · Nasser Laouali²⁷ · Sanam Shah²⁷ · Gianluca Severi^{27,28} · Dagfinn Aune²⁹ · Melissa A. Merritt^{29,30} · Manon Cairat³¹ · Elisabete Weiderpass³² · Elio Riboli²⁹ · Laure Dossus³¹ · Paula Jakszyn^{1,33}

¹ Unit of Nutrition and Cancer, Catalan Institute of Oncology – ICO; and Nutrition and Cancer Group; Epidemiology, Public Health, Cancer Prevention and Palliative Care Program, Bellvitge Biomedical Research Institute – IDIBELL, L'Hospitalet de Llobregat, Av. Granvia 199-203, 08908, L'Hospitalet de Llobregat, Barcelona, Spain

² Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

³ Nutrition, Immunity and Metabolism Senior Scientist Group, Department of Nutrition and Gerontology, German Institute of Human Nutrition, Potsdam-Rehbruecke (DIfE), Nuthetal, Germany

⁴ Institute of Nutritional Science, University of Potsdam, Potsdam, Germany

⁵ Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam, Nuthetal, Germany

⁶ Danish Cancer Society Research Center, Diet, Genes and Environment, Copenhagen, Denmark

⁷ Department of Public Health, Aarhus University, 8000 Aarhus C, Denmark

⁸ Public Health Directorate, Asturias, Spain

⁹ Escuela Andaluza de Salud Pública (EASP), Granada, Spain

¹⁰ Instituto de Investigación Biosanitaria ibs, GRANADA, Granada, Spain

¹¹ Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

¹² Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain

¹³ Public Health Division of Gipuzkoa, BioDonostia Research Institute, Donostia-San Sebastian, Spain

¹⁴ Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain

¹⁵ Department of Health and Social Sciences, Universidad de Murcia, Murcia, Spain

¹⁶ Navarra Public Health Institute, Pamplona, Spain

¹⁷ IdiSNA, Navarra Institute for Health Research, Pamplona, Spain

¹⁸ Cancer Risk Factors and Life-Style Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network -ISPRO, Florence, Italy

¹⁹ Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy

²⁰ Cancer Registry and Histopathology Department, Provincial Health Authority, Ragusa, Italy

²¹ Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital Via Santena, Turin, Italy

²² Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Naples, Italy

²³ Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

²⁴ Department of Radiation Sciences, Oncology Unit, Umeå University, Umeå, Sweden

²⁵ Faculty of Health Sciences, Department of Community Medicine, University of Tromsø, The Arctic University of Norway, Tromsø, Norway

²⁶ Nutritional Epidemiology Group, School of Food Science and Nutrition, University of Leeds, Leeds, UK

²⁷ Inserm, Gustave Roussy, “Exposome and Heredity” Team, CESP, Paris-Saclay University, UVSQ, 94805 Villejuif, France

²⁸ Departement of Statistics, Computer Science and Applications “G. Parenti”, University of Florence, Florence, Italy

²⁹ Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK

³⁰ Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, USA

³¹ Nutrition and Metabolism Section, International Agency for Research on Cancer, Lyon, France

³² Director Office, International Agency for Research on Cancer, World Health Organization, Lyon, France

³³ Faculty of Health Science Blanquerna, Ramon Llull University, Barcelona, Spain

ARTICLE OPEN



Epidemiology

Dietary patterns related to biological mechanisms and survival after breast cancer diagnosis: results from a cohort study

Carlota Castro-Espin^{1,2,✉}, Catalina Bonet^{1,2}, Marta Crous-Bou^{1,2,3}, Verena Katzke⁴, Charlotte Le Cornet⁵, Franziska Jannasch⁵, Matthias B. Schulze^{5,6}, Anja Olsen^{7,8}, Anne Tjønneland^{7,8}, Christina C. Dahm⁹, Christian S. Antoniussen⁹, Maria Jose Sánchez^{10,11,12,13}, Pilar Amiano^{12,14,15}, Maria Dolores Chirlaque^{12,16}, Marcela Guevara^{12,17,18}, Claudia Agnoli¹⁹, Rosario Tumino²⁰, Carlotta Sacerdote²¹, Maria Santucci De Magistris²², Malin Sund^{23,24}, Stina Bodén²⁵, Torill Enget Jensen²⁶, Karina Standahl Olsen²⁶, Guri Skeie²⁶, Marc J. Gunter²⁷, Sabina Rinaldi²⁷, Esther M. Gonzalez-Gil²⁷, Elisabete Weiderpass²⁷, Sofia Christakoudi^{28,29}, Alicia K. Heath²⁸, Laure Dossus²⁷ and Antonio Agudo^{1,2}

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BACKGROUND: Inflammatory, insulin and oestrogenic pathways have been linked to breast cancer (BC). We aimed to examine the relationship between pre-diagnostic dietary patterns related to these mechanisms and BC survival.

METHODS: The diabetes risk reduction diet (DRRD), inflammatory score of diet (ISD) and oestrogen-related dietary pattern (ERDP) were calculated using dietary data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Cox proportional hazards models were used to assess associations between dietary patterns and overall mortality and competing risk models for associations with BC-specific mortality.

RESULTS: We included 13,270 BC cases with a mean follow-up after diagnosis of 8.6 years, representing 2340 total deaths, including 1475 BC deaths. Higher adherence to the DRRD score was associated with lower overall mortality (HR_{1-SD} 0.92; 95%CI 0.87–0.96). Greater adherence to pro-inflammatory diets was borderline associated with 6% higher mortality HR_{1-SD} 1.06; 95%CI 1.00–1.12. No significant association with the oestrogen-related dietary pattern was observed. None of the dietary patterns were associated with BC-specific mortality.

CONCLUSIONS: Greater adherence to an anti-diabetic and anti-inflammatory diet prior to diagnosis is associated with lower overall mortality among BC survivors. Long-term adherence to these dietary patterns could be a means to improve the prognosis of BC survivors.

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INTRODUCTION

Breast cancer (BC) accounts for one in four cancer cases and one in six cancer deaths among women worldwide [1]. Declines in breast cancer mortality rates have been reported in many high-

income countries, likely due to the combined effects of earlier detection by screening and improvements in treatment. As a result, 5-year survival after breast cancer diagnosis has increased steadily, reaching 90% in North American countries, Australia, New

¹Unit of Nutrition and Cancer, Catalan Institute of Oncology-ICO, L'Hospitalet de Llobregat, Barcelona, Spain. ²Nutrition and Cancer Group, Epidemiology, Public Health, Cancer Prevention and Palliative Care Program, Bellvitge Biomedical Research Institute-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain. ³Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA. ⁴German Cancer Research Center (DKFZ), Heidelberg, Germany. ⁵German Institute of Human Nutrition Potsdam-Rehbruecke, Dept. of Molecular Epidemiology, Arthur-Scheunert-Allee, Nuthetal, Germany. ⁶Institute of Nutritional Science, University of Potsdam, Nuthetal, Germany. ⁷Danish Cancer Society Research Center, Diet, Cancer and Health, Copenhagen, Denmark. ⁸Department of Public Health, University of Copenhagen, Copenhagen, Denmark. ⁹Department of Public Health, Aarhus University, Aarhus, Denmark. ¹⁰Escuela Andaluza de Salud Pública (EASP), Granada, Spain. ¹¹Instituto de Investigación Biomédica en Ciencias de la Salud, Granada, Spain. ¹²Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain. ¹³Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain. ¹⁴Ministry of Health of the Basque Government, Sub Directorate for Public Health and Addictions of Gipuzkoa, San Sebastian, Spain. ¹⁵Biodonostia Health Research Institute, Epidemiology of Chronic and Communicable Diseases Group, San Sebastián, Spain. ¹⁶Department of Epidemiology, Regional Health Council, IMB-Arrixaca, Murcia University, Murcia, Spain. ¹⁷Navarra Public Health Institute, Pamplona, Spain. ¹⁸Navarra Institute for Health Research (IdiSNA), Pamplona, Spain. ¹⁹Epidemiology and Prevention Unit, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy. ²⁰Hyblean Association for Epidemiological Research, AIRE ONLUS Ragusa, Ragusa, Italy. ²¹Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital, Turin, Italy. ²²A.O.U. Federico II, Naples, Italy. ²³Department of Surgical and Perioperative Sciences/ Surgery, Umeå University, Umeå, Sweden. ²⁴Department of Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. ²⁵Department of Clinical Sciences - Pediatrics, Umeå University, Umeå, Sweden. ²⁶Department of Community Medicine, UiT the Arctic University of Norway, Tromsø, Norway. ²⁷Nutrition and Metabolism Branch, International Agency for Research on Cancer (IARC-WHO), Lyon, France. ²⁸Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK. ²⁹Department of Inflammation Biology, School of Immunology and Microbial Sciences, King's College London, London, UK. ✉email: ccastro@idibell.cat

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Zealand, and in many European countries, although with large differences across countries and world regions [2]. Despite the relatively high survival rates, large differences are still observed across age and stage at diagnosis [2, 3]. Therefore, for the effective management of BC, there is a need to investigate modifiable factors that could impact long-term prognosis.

A comprehensive review of the literature concluded that the current evidence suggests that excess body fatness is a predictor of poor survival, while physical activity may be associated with better prognosis among BC survivors [4]. The same review reported that there is evidence of links between better survival after BC diagnosis and some foods or dietary components. However, the evidence is not strong enough to make specific recommendations. Most previous research looked at individual foods, food groups or individual nutrients. More recently, dietary patterns have been used to better capture the complexity of dietary intake in contrast to single foods or nutrients. Accordingly, several epidemiological studies have investigated the possible role of diet through dietary patterns in BC survivors [5].

Prospective observational studies have found that dietary patterns defined as “healthy” or based on dietary guidelines (e.g., the Healthy Eating Index) are associated with better survival among breast cancer survivors [6–8]. Although the current trend of recommending cancer survivors to follow cancer prevention guidelines seems prudent, having specific recommendations for breast cancer survivors could have an important impact on prognosis. In relation to this, a promising approach is the study of dietary patterns based on the underlying biological processes or mechanisms of the relationship between diet and breast cancer prognosis [9].

Breast cancer is strongly influenced by hormones, especially oestrogens, which are involved in the aetiology of this disease [10]. High levels of endogenous sex hormones, especially oestrogens, are associated with postmenopausal breast cancer risk and current research suggests that diet influences endogenous hormone levels [11]. In addition, insulin resistance and hyperinsulinaemia, as well as chronic low-grade inflammation, are associated with obesity, which is a strong predictor of mortality, and sedentary behaviours, which are both linked to breast cancer risk and prognosis [12, 13]. Moreover, breast cancer survivors with type 2 diabetes (T2D) seem to have poor breast cancer prognosis, including increased risk of recurrence [14], and some of the mechanisms that may influence the neoplastic process include hyperinsulinemia and chronic inflammation [15–17]. A few dietary patterns have recently emerged in nutritional research aimed at assessing the biological mechanisms underlying associations between diet and breast cancer [18–20].

Herein, we examined the associations between adherence to three previously developed dietary patterns—the diabetes risk reduction diet (DRRD), the inflammatory score of diet (ISD), and the oestrogen-related dietary pattern (ERDP)—and breast cancer-specific and all-cause mortality among breast cancer survivors identified in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. We hypothesised that greater adherence to a low-risk diet for T2D, an anti-inflammatory diet, and a more anti-oestrogenic diet, may be associated with better prognosis outcomes in breast cancer survivors.

METHODS

Study population and case ascertainment

We used data from EPIC, a collaborative cohort study of more than half a million middle-aged adults recruited between 1992 and 2000. The methods have been previously described in further detail [21]. Briefly, at recruitment participants completed questionnaires on diet, lifestyle, and medical history, anthropometric parameters were measured, and a blood sample was drawn. All participants provided informed consent and EPIC was approved by the Ethics Committee of the International Agency for

Research on Cancer (IARC), Lyon, France, as well as the local ethics committees of the study centres.

After excluding participants with prevalent tumours at recruitment, subjects without information on follow-up, lifestyle, and diet, as well as those with implausible diet (extreme values of ratio between energy intake and energy requirement), a total of 318,686 women from nine countries participated in this study (Denmark, France, Germany, Italy, The Netherlands, Norway, Spain, Sweden, and the United Kingdom).

Incident breast cancer cases and vital status were identified through population-based cancer registries in Denmark, Italy, the Netherlands, Spain, Sweden, and the United Kingdom. In France and Germany, a combination of follow-up methods was used including health insurance records, cancer pathology registries and active follow-up of study participants and their next of kin. Follow-up for cancer endpoints, vital status, and causes of death was available until 2015.

We used the International Classification of Diseases for Oncology (ICD-O-2) and breast cancer coded as C50-50.9 to define breast cancer cases. A total of 13,320 incident primary malignant breast cancer cases were identified; after excluding 7 cases with unknown vital status, 12 with inconsistent follow-up data, and 31 with non-epithelial morphology, a total of 13,270 breast cancer cases (of which 14 in situ) were included in the present analysis. During the follow-up 2,340 cases died, of which 1475 due to breast cancer. Specific causes of death of women included in this analysis are shown in Table S1. Available information on the tumour receptor status of breast cancer cases, obtained from pathology reports, is generally limited varying by country and receptor type (Table S2).

Dietary assessment and derivation of dietary patterns

Lifestyle data collected at recruitment included questions on education, occupation, history of previous illness, lifetime history of smoking habit and alcohol consumption, and physical activity level. Usual diet during the previous 12 months was assessed at recruitment using validated country/centre-specific dietary questionnaires, mainly food frequency questionnaires and, to a lesser extent, diet history questionnaires [21, 22]. The participants' nutrient intakes were calculated by multiplying the daily amount consumed of each food item by its nutrient content using country-specific food composition tables [23].

The three dietary patterns used have been previously described in detail [18, 24, 25]. The DRRD is an a priori defined dietary pattern and the ISD and ERDP are data-driven. The three indices include food groups, individual foods or nutrients and use two different scoring systems. Intakes of the dietary components used in the DRRD and ERDP were expressed as food or nutrient density per 2000 kcal (intake in g/day, divided by the subject's energy intake and multiplied by 2000 kcal). On the other hand, energy is one of the components in the ISD.

The DRRD, developed by Rhee et al. [24] and further adapted by Kang et al. [19], includes 9 dietary components (Table S3), scored between one and five according to the distribution in quintiles of the intake. This value is assigned in ascending order for components whose consumption is consistent with low risk of T2D (cereal fibre, coffee (caffeinated and decaffeinated), nuts, ratio of polyunsaturated-saturated fats, whole fruits), and in descending order for components associated with high T2D risk (glycemic index, trans-fat, sugar-sweetened beverages and fruit juices, and red and processed meat). Thus, the DRRD score ranges from 9 (lowest adherence) to 45 (highest adherence), with higher scores indicating lower risk of T2D.

The ISD was initially based on the Dietary Inflammatory Index (DII) [26]. A modified version of the original ISD that includes 27 dietary components and excludes alcohol is used in this study (Table S4) [20]. Detailed methods to calculate the ISD have been described elsewhere [25]. Briefly, each component of the ISD, mainly nutrients, is assigned an inflammatory weight based on its association with six known inflammatory biomarkers (interleukin-1b (IL-1b), IL-4, IL-6, IL-10, tumour necrosis factor alpha (TNFα) and C-reactive protein (CRP)) [26]. The intake of each component is standardised using the mean and standard deviation (SD) from the EPIC population. The z scores were converted to percentile scores and then centred on 0 (by doubling each percentile score and subtracting 1); these values were then multiplied by the respective inflammatory weight to obtain the food item-specific ISD, which were summed to produce the overall ISD for each participant. The value of the ISD for an individual is a relative index that allows the diets of individuals to be categorised on a continuum from maximally anti-inflammatory to maximally pro-inflammatory. Adherence to the ISD resulted in a score between -4.7 (lowest adherence) and 5.4 (highest adherence).

Similarly, the ERDP score is comprised of foods with assigned weights according to levels of unconjugated oestradiol and the ratio of 2- and 16-hydroxylated oestrogen metabolites [18]. To calculate the ERDP in the present study we used the weights as reported in reference [18] for a total of 11 food items included in the original pattern and available in the EPIC databases (Table S5). Positively weighted intakes were assigned to refined grains, tomatoes, cruciferous vegetables, cheese, fish/shellfish high in ω -3 fatty acids, processed meats (frankfurters/luncheon meats in the original ERDP) and negatively weighted intakes were assigned to nuts/seeds, other vegetables, fish/shellfish low in ω -3 fatty acids, yogurt, and coffee. Adherence to the ERDP score ranged from -1.8 (lowest adherence) and 1.2 (highest adherence).

Statistical analysis

We used Cox proportional hazards models to prospectively analyse the association between the exposures (dietary patterns) and overall mortality. Fine-Gray competing risks models [27], considering other causes of death as a competing event, were applied for breast cancer-specific mortality. Entry time was considered as the date of diagnosis of primary breast cancer, and exit time was the date of death or end of follow-up.

All survival models were stratified by country and menopausal status at diagnosis (women aged ≥ 55 years at diagnosis were considered postmenopausal regardless of the baseline information). Multivariable-adjustment for potential confounders included age at diagnosis (5-years categories), attained level of education (none, primary school, secondary school, technical/professional school, longer education, unknown), body mass index (underweight, normal-weight, overweight, obese), physical activity (inactive, moderately inactive, moderately active, active, unknown), alcohol consumption reported at recruitment (non-drinker, >0 -3, >3 -12, >12 -24, >24 g/day, unknown), smoking habits and intensity as cigarettes per day (cig/day) at recruitment (never, current 1-15 cig/day, current 16-25 cig/day, current >25 cig/day, former quit ≤ 10 years before recruitment, former quit 11-20 years before recruitment, former quit more than 20 years before recruitment, current smoker of cigars, pipes and occasional current smokers, current smokers with missing information on the intensity, unknown), ever use of hormone replacement therapy for menopause at diagnosis (yes, no, unknown), tumour stage (0/I, II, III, IV, non-metastatic but unknown specific stage, unknown), tumour grade (well-differentiated, moderately differentiated, poorly differentiated or undifferentiated, not determined), and tumour receptor status (positive, negative, unknown) for: oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).

The proportional hazards assumption was evaluated checking the graphs of the scaled Schoenfeld residuals. To further assess the association of mortality outcomes with dietary patterns on a continuous scale, restricted cubic spline models were used (Fig. S1), and non-linearity was tested using the Likelihood (LR) ratio test. Moreover, mutually adjusted models were performed for the three dietary patterns after testing for interaction between dietary patterns using pairwise interaction terms.

We fitted different models as follows: first, each dietary pattern was introduced independently as a categorical variable in quartiles, with the first quartile as the reference category. Tests for linear trend were performed using median value for each quartile of dietary patterns. Second, dietary patterns were used as continuous variables by 1-SD increase in the scores. On the other hand, mutually adjusted models were fitted by including the three dietary patterns as quartiles. The scores of the three dietary patterns were correlated; the Pearson correlation coefficients of DRRD with ISD and ERDP were -0.36 and -0.23, respectively, and the coefficient between ISD and ERDP was 0.12. Therefore, the residuals for each dietary pattern from a separate multiple regression model for each, including the other two patterns, were used as continuous variables to assess the association of mortality with a 1 SD increase in score.

Furthermore, we also dichotomised DRRD and ISD (below or equal to and above the median) and assessed the cross-classification of these patterns according to low-low, high-high, high-low DRRD and ISD categories, respectively, compared to the reference category (low-DRRD, high-ISD) in relation to overall mortality. We assumed that the mechanisms by which a low score of DRRD is associated with high risk of T2D is insulin resistance (IR). We used the label high-IR for women with DRRD below the median, and low-IR for those with DRRD score equal or above the median. Direct-adjusted survival curves by DRRD-ISD categories were derived from the multivariable Cox model with country and menopausal status as adjustment variables, followed by the rest of the covariates [28].

Subgroup analyses by menopausal status, body mass index (BMI), physical activity, stage of tumour, and hormone receptor status, were performed for DRRD, ISD and ERDP scores (mutually adjusted models). Heterogeneity across groups was determined using the LR test.

Sensitivity analyses were performed by additionally adjusting the survival models for time from recruitment to diagnosis, to check the assumption of stability of dietary assessment, and for the period of diagnosis to check potential influence of improvements in treatment and diagnosis over time. Stratified analyses were explored by categories of these two variables: time from diet measurement to diagnosis (<5 years, 5 to <8 years, 8 to <12 years, ≥ 12 years); period of diagnosis (before 2000, between 2000 to <2004 , between 2004 to <2008 , 2008 onwards). The cut-off points for both variables were based on the distribution of quartiles 1, 2 and 3 of breast cancer cases. Additionally, multivariable models further adjusted by these two variables (time from diet measurement to diagnosis as continuous; period of diagnosis as categorical) were performed. An additional adjustment was made for the presence of co-morbidities (separate variables: reported cardiovascular (CVD) problem and diabetes) given the outcome is overall survival. Other models excluding diabetic BC survivors to assess the effect of the low-insulin diet in women without pre-existing influence on this pathway were performed. We finally excluded breast cancer survivors with unknown tumour stage and unknown status of HER2 receptor, in separate models, to test whether treatment differences associated with these characteristics might modify the magnitude of the associations.

RESULTS

Our study included 13,270 incident breast cancer cases with a mean follow-up of 8.6 years from diagnosis (SD 4.9 years), of whom 2340 died and 1475 due to breast cancer. Breast cancer cases were predominantly 55-65 years old, non-smokers, moderate alcohol consumers, in the normal-weight range (mean BMI 24.9) and physically inactive. The majority were postmenopausal (77%) and had non-metastatic tumours (82%) (Table 1).

Results from the time-to-event analyses are shown in Table 2. Breast cancer survivors in the fourth quartile of the DRRD score had a 20% lower risk of overall mortality compared to the first quartile (reference), and a 7% decrease for each SD increase in the score. The ISD was borderline associated with an increased risk of overall mortality when assessed continuously: HR_{SD} 1.06; 95% CI 1.00, 1.12. Mutually adjusted models including the scores as residuals showed higher association for DRRD_{Q4vsQ1} HR 0.78 95% CI 0.68, 0.90; p -trend <0.001 and HR_{SD} 0.92 (0.87-0.96), remaining the same for ISD. The ERDP score, however, was not associated with survival outcomes. The assessment of associations of dietary patterns and overall mortality by means of restricted cubic splines (Fig. S1) showed no statistically significant deviation from linearity. For breast cancer-specific mortality, no associations were observed with any of the three dietary patterns, either independently or mutually adjusted (Table 2).

To further explore the observed association between DRRD and overall mortality, we performed models using different versions of the DRRD without a food item each time to see if there were any components driving the effect (Table S6). The HRs remained stable without pointing to any specific component leading the association.

Associations between DRRD and ISD and overall mortality (as continuous variables, adjusted for each other) were more apparent for postmenopausal, physically inactive women, with metastatic tumours, and in those with PR+, ER+ and HER2- (with DRRD), and ER- tumours (with ISD) (Table 3). Women presenting overweight or obesity, an important predictor of breast cancer prognosis, did not show a stronger effect on the association with dietary patterns. Instead, it was women of normal-weight who appeared to show a more evident effect (DRRD_{SD} = HR 0.91(0.85-0.97); ISD_{SD} = 1.10 (1.01-1.20), presumably because it was not masked by obesity. However, none of the interaction terms were statistically significant, suggesting that there is no strong evidence for differential effects of these dietary patterns on

Table 1. Baseline and tumour characteristics of breast cancer survivors in the EPIC cohort.

		All breast cancer survivors N = 13,270	
		n	%
Age at diagnosis (years)	<50	1342	10.1
	50–<55	2049	15.4
	55–<60	2671	20.1
	60–<65	2878	21.7
	65–<70	2332	17.6
	≥70	1998	15.1
Educational level	None/primary	3281	24.7
	Technical/professional	3035	22.9
	Secondary	3200	24.1
	Longer education	3143	23.7
	Unknown	611	4.6
Smoking status and intensity (cig/day or years)	Never	5940	44.8
	Current, 1–15 cig/day	1593	12.0
	Current, 16–25 cig/day	749	5.6
	Current, 26+ cig/day	134	1.0
	Former, quit ≤10 years	1063	8.0
	Former, quit 11–20 years	977	7.4
	Former, quit 20+ years	1099	8.3
	Miscellaneous ^a	1487	11.2
	Unknown	228	1.7
Alcohol consumption g/day	Non-drinker	1774	13.4
	>0–3	3820	28.8
	>3–12	4066	30.6
	>12–24	2069	15.6
	>24	1541	11.6
BMI (kg/m ²)	Underweight <18	206	1.6
	Normal-weight 18 to <25	7612	57.4
	Overweight 25 to <30	3943	29.7
	Obesity ≥30	1509	11.4
Physical activity	Inactive	2673	20.1
	Moderate inactive	4720	35.6
	Moderate active	3606	27.2
	Active	2076	15.6
	Unknown	195	1.5
Menopausal status at diagnosis	Premenopausal	3070	23.1
	Postmenopausal	10,200	76.9
Ever use of menopause hormone replacement treatment	No	7487	56.4
	Yes	5323	40.1
	Unknown	460	3.5
Grade of tumour	Well-differentiated	1298	9.8
	Moderately differentiated	2917	22.0
	Poorly diff/Undiff	2503	18.9
	Not determined	6552	49.4

Table 1. continued

		All breast cancer survivors N = 13,270	
		n	%
Stage of tumour	Stage 0/I	1954	14.7
	Stage II	1593	12.0
	Stage III	303	2.3
	Non-metastatic unk. stage	3984	30.0
	Stage IV	1777	13.4
	Unknown	3659	27.6
ER status	Negative	1678	12.6
	Positive	7500	56.5
	Unknown	4092	30.8
PR status	Negative	2612	19.7
	Positive	5072	38.2
	Unknown	5586	42.1
HER2 status	Negative	3587	27
	Positive	856	6.5
	Unknown	8827	66.5

BMI body mass index, cig cigarette, diff differentiated, Undiff undifferentiated, ER oestrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2.

^aCurrent smoker of cigars, pipes and occasional current smokers, current smokers with missing information on the intensity.

mortality in subgroups of breast cancer survivors according to potential determinants of prognosis or features of the tumour.

Since DRRD and ISD appeared to show independent effects on overall mortality, a dichotomised version of each score (above and below median) was computed to assess their combined effect (Fig. 1). Compared to women with high-IR and a pro-inflammatory diet (reference categories), higher adherence to a low-IR diet together with an anti-inflammatory diet was associated with a 17% lower risk of overall mortality (HR 0.83; 95% CI: 0.73–0.93). Intermediate diets (high-IR and anti-inflammatory diet, or low-IR and pro-inflammatory diet) showed better survival than the reference (high-IR and pro-inflammatory), but the associations did not reach statistical significance. There was no statistically significant interaction between the two dichotomised variables (DRRD and ISD scores). The adjusted survival curves for overall mortality by the four groups based on the combination of the two scores (DRRD and ISD) were consistent with the findings from the multivariable Cox model. The adjusted 5-year survival (and 95% CI) for women with high-IR and pro-inflammatory diet was 89% (88–90%) and 91% (90–92%) for those with low-IR and anti-inflammatory diet. The corresponding values for the 15-year survival were 69% (67–71%) and 73% (71–75%), respectively.

Sensitivity analyses were performed to assess the potential influence of two aspects: a possible modification of diet between the time of recruitment and diagnosis, and the period time of diagnosis (i.e., more recently diagnosed women may have received better treatments). Overall, the main results of DRRD and ISD scores, which were inversely and positively associated with all-cause mortality, respectively, remained stable (Table 4). On the other hand, analyses excluding BC survivors with diabetes or CVD reported at recruitment showed a slightly higher effect with DRRD (10% lower risk of overall mortality) compared to results including all survivors (8%). Further exclusions of breast cancer survivors with unknown tumour stage and unknown HER2 receptor status showed no attenuation of the previously observed

Table 2. Associations between dietary patterns and all-cause and breast cancer-specific mortality.

	HR (95% CI)				P-trend	HR (95% CI)
	Q1	Q2	Q3	Q4		
All-cause mortality						Continuous (1-SD increase)
DRRD	1 (ref)	0.96 (0.86–1.06)	0.89 (0.79–0.99)	0.80 (0.70–0.91)	<0.001	0.93 (0.89–0.97)
Multivariable model ^a						
Dietary patterns mutually adjusted ^b	1 (ref)	0.95 (0.85–1.06)	0.88 (0.78–0.99)	0.78 (0.68–0.90)	<0.001	0.92 (0.87–0.96)
ISD	1 (ref)	1.03 (0.91–1.17)	1.12 (0.98–1.27)	1.12 (0.96–1.30)	0.079	1.06 (1.00–1.12)
Dietary patterns mutually adjusted	1 (ref)	1.01 (0.89–1.15)	1.07 (0.94–1.22)	1.05 (0.90–1.22)	0.423	1.06 (1.00–1.12)
ERDP	1 (ref)	1.03 (0.91–1.16)	0.95 (0.83–1.08)	0.99 (0.86–1.15)	0.609	0.99 (0.94–1.05)
Multivariable model	1 (ref)	0.99 (0.88–1.12)	0.89 (0.78–1.01)	0.92 (0.79–1.06)	0.100	0.97 (0.92–1.03)
Dietary patterns mutually adjusted						
Breast cancer-specific mortality						
DRRD	1 (ref)	0.99 (0.87–1.14)	0.96 (0.83–1.11)	0.89 (0.76–1.05)	0.167	0.96 (0.91–1.02)
Multivariable model						
Dietary patterns mutually adjusted	1 (ref)	0.98 (0.86–1.13)	0.94 (0.81–1.10)	0.87 (0.73–1.04)	0.135	0.96 (0.90–1.01)
ISD	1 (ref)	1.03 (0.88–1.20)	1.10 (0.94–1.30)	1.12 (0.93–1.35)	0.161	1.02 (0.96–1.10)
Multivariable model						
Dietary patterns mutually adjusted	1 (ref)	1.01 (0.86–1.19)	1.08 (0.91–1.27)	1.09 (0.90–1.32)	0.302	1.02 (0.95–1.10)
ERDP	1 (ref)	0.94 (0.81–1.09)	0.90 (0.76–1.06)	0.90 (0.75–1.07)	0.192	0.96 (0.90–1.03)
Multivariable model						
Dietary patterns mutually adjusted	1 (ref)	0.92 (0.79–1.08)	0.86 (0.73–1.02)	0.86 (0.71–1.03)	0.070	0.95 (0.89–1.02)

All models were stratified by country and menopausal status at diagnosis and adjusted for age at diagnosis, attained level of education, physical activity, body mass index, alcohol consumption reported at recruitment, smoking habit and intensity as cigarettes per day at recruitment, ever use of hormone for menopause at diagnosis, cancer stage at diagnosis, cancer grade, and tumour receptor status: ER, PR, HER2. Ref: Reference, HR hazard ratio, CI confidence interval, DRRD diabetes risk reduction diet score, ISD inflammatory score of diet, ERDP oestrogen-related dietary pattern, Q quartile.

^aMultivariable model: Hazard ratios derived from a multivariable Cox regression model where exposure is a dietary pattern without including the other two patterns in the model.

^bDietary patterns mutually adjusted: hazard ratios derived from a multivariable Cox regression model where each dietary pattern is further adjusted for the other two dietary patterns.

association between DRRD and ISD and overall mortality. Finally, additional adjustment for the presence of co-morbidities in the multivariable models did not introduce any changes to the results (Table 4).

DISCUSSION

In this large, prospective cohort study of 13,270 breast cancer survivors followed for a mean of 8.6 years after diagnosis, we found that women with a higher adherence to a low-risk diet for T2D (higher DRRD score) before diagnosis had lower risk of all-cause mortality after BC diagnosis. In the opposite direction, a more pro-inflammatory diet (higher ISD) was positively associated, though borderline statistically significant, with risk of all-cause mortality. The ERDP, a dietary pattern capturing the oestrogenic potential of diet, showed no association with mortality among breast cancer survivors. None of the three dietary patterns were associated with breast cancer-specific mortality. To our knowledge, this is the first time that insulinemic, inflammatory and oestrogenic potential has been assessed through dietary patterns in relation to breast cancer survival.

In line with previous excellent research on the subject, the role of diet as a protective factor in cancer survival appears to be still limited. Obesity is a strong predictor of prognosis; in fact, in our study, the HR (95%) of mortality for obesity was 1.29 (1.14–1.47). One may think that part of the relationship between diet and mortality could be mediated by BMI. However, we have accounted for the effect of obesity by including BMI in all models. Furthermore, the potential confounding effect of BMI on the associations between the anti-diabetic and anti-inflammatory patterns and mortality seem to be small: when BMI is taken out from the model the HRs (95% CI for 1-SD) increase from 0.92 (0.87–0.96) to 0.91 (0.87–0.95) for the DRRD, and from 1.06 (1.00–1.12) to 1.07 (1.01–1.14) for the ISD.

These scores were chosen because they are related to underlying biological processes or mechanisms that have been found to be associated with breast cancer risk or progression. T2D is linked to insulin resistance, which has been shown to have a negative impact on breast cancer prognosis [14, 29]. Insulin levels increase insulin-like growth factor-1 (IGF-1) activity, important in tumour initiation and progression [30], and is associated with increased oestrogen bioavailability, which promotes breast carcinogenesis. Moreover, higher dietary glycemic index, one of the components of the DRRD (and also linked to IR), has been reported to be associated with increased overall mortality [31]. In addition, metformin, a widely used treatment for patients with T2D, has been associated with lower breast cancer-specific mortality through mechanisms that induce a reduction in glucose and insulin levels [32]. This suggests that it is biologically plausible to hypothesise that increased adherence to a diet associated with a lower risk of T2D [24] may be a potential strategy to improve breast cancer prognosis. A similar conclusion was reached in the analysis of two prospective cohorts in the US [15], where greater adherence to DRRD after breast cancer diagnosis was associated with lower all-cause and breast cancer-specific mortality in a smaller sample of long-term breast cancer survivors. On the other hand, a recent study [31] reported a suggestive increased risk of CVD mortality among women with higher dietary glycemic index and glycemic load after diagnosis. Furthermore, breast cancer survivors are at increased risk of CVD owing to side effects of adjuvant breast cancer treatment. However, the limited number of deaths by CVD in our data set (Table S1) precluded exploring in deep the association of the dietary patterns of interest with CVD-related mortality.

Another mechanism that is believed to contribute to BC progression is chronic low-grade inflammation [33]. The positive association found between ISD and overall mortality (6% higher risk per 1-SD increase) is in line with this biological plausibility.

Table 3. Associations between DRRD, ISD and ERDP mutually adjusted and overall mortality by subgroups of BC survivors.

	N cases (events)	HR (95%CI)		
		DRRD ^a	ISD ^a	ERDP ^a
All breast cancer survivors	13,270 (2340)	0.92 (0.87–0.96)	1.06 (1.00–1.12)	0.97 (0.92–1.03)
Menopausal status at diagnosis				
Premenopausal	3070 (527)	0.97 (0.87–1.07)	0.95 (0.83–1.08)	0.94 (0.83–1.06)
Postmenopausal	10,200 (1813)	0.91 (0.86–0.95)	1.09 (1.02–1.16)	0.99 (0.93–1.05)
P-value for heterogeneity ^b		0.951	0.074	0.693
BMI				
Normal-weight	7612 (1193)	0.91 (0.85–0.97)	1.10 (1.01–1.20)	1.04 (0.96–1.12)
Overweight- obesity	5452 (1113)	0.93 (0.87–1.00)	1.03 (0.95–1.12)	0.93 (0.86–1.01)
P-value for heterogeneity ^b		0.950	0.773	0.104
Physical activity level				
Inactive	7393 (1468)	0.90 (0.85–0.96)	1.07 (0.99– 1.16)	1.00 (0.93–1.07)
Active	5682 (837)	0.94 (0.87–1.01)	1.02 (0.92–1.12)	0.93 (0.85–1.02)
P-value for heterogeneity ^b		0.716	0.970	0.464
Stage of tumour				
Metastatic (stage IV)	1777 (585)	0.89 (0.81–0.99)	1.17 (1.04–1.33)	1.02 (0.91–1.14)
Non-metastatic	7834 (968)	0.95 (0.88–1.02)	1.02 (0.93–1.12)	0.99 (0.91–1.08)
P-value for heterogeneity ^b		0.261	0.795	0.089
Non-metastatic tumours				
Stage I ^c	1940 (108)	0.93 (0.74–1.18)	1.13 (0.85–1.50)	1.14 (0.87–1.50)
Stage II	1593 (250)	0.95 (0.81–1.12)	0.99 (0.82–1.20)	0.90 (0.76–1.07)
Stage III	303 (79)	1.17 (0.84–1.63)	0.82 (0.56–1.19)	0.93 (0.65–1.34)
P-value for heterogeneity ^b		0.269	0.716	0.131
Oestrogen receptor status				
ER(+)	7500 (1071)	0.91 (0.85–0.97)	1.04 (0.95–1.13)	1.01 (0.93–1.09)
ER(-)	1678 (426)	0.93 (0.84–1.05)	1.17 (1.01–1.34)	1.04 (0.91–1.19)
P-value for heterogeneity ^b		0.764	0.402	0.244
Progesterone receptor status				
PR(+)	5072 (620)	0.88 (0.80–0.96)	1.14 (1.02–1.29)	0.98 (0.88–1.09)
PR(-)	2612 (515)	0.92 (0.83–1.03)	1.08 (0.95–1.24)	1.07 (0.95–1.20)
P-value for heterogeneity ^b		0.819	0.169	0.980
HER2 status				
HER2(+)	856 (166)	1.07 (0.87–1.31)	0.99 (0.78–1.25)	1.09 (0.86–1.36)
HER2(-)	3587 (473)	0.88 (0.79–0.98)	1.12 (0.98– 1.28)	0.99 (0.87–1.12)
P-value for heterogeneity ^b		0.956	0.631	0.934

All models were stratified by country and menopausal status at diagnosis and adjusted for age at diagnosis, attained level of education, physical activity, body mass index, alcohol consumption reported at recruitment, smoking habit and intensity as cigarettes per day at recruitment, ever use of hormone for menopause at diagnosis, cancer stage at diagnosis, cancer grade, and tumour receptor status: ER, PR, HER2.

BMI body mass index, HER2 human epidermal receptor status 2, HR, Hazard Ratio; CI, Confidence Interval; DRRD, Diabetes risk reduction diet; ISD, Inflammatory score of diet; ERDP, Oestrogen-related dietary pattern.

^aUsing the scores as residuals of multiple regression model including DRRD, ISD and ERDP.

^bP-values for heterogeneity by introducing interaction terms in the multivariable models between the dietary pattern and the variable containing the subgroups using likelihood ratio tests.

^cIn situ BC cases are not included in these analyses since they are only 14 with 1 single event (death).

Dietary components that constitute to the ISD are associated with well-known inflammatory biomarkers, including IL-1, IL-6, TNF α and CRP [25, 26]. Previous studies have reported inverse associations between healthy dietary patterns and inflammatory cytokines, but positive with Western dietary patterns [34, 35]. To the best of our knowledge, only a few studies have prospectively investigated the association between inflammatory potential of diet and survival in breast cancer patients [36, 37]. In line with our results, one of these cohort studies found that DI was positively associated with higher overall mortality and recurrence among BC

survivors [36], while in the other study [37] the association was limited to cardiovascular mortality. However, these studies had a smaller number of survivors and assessed the inflammatory potential of diet using the DI, whereas we used the ISD; in the latter, intakes were standardised using the mean and SD of the EPIC population instead of a global regional database [26].

According to our results, it appears that dietary patterns related to mechanisms of insulin resistance and inflammation may have a more evident effect in postmenopausal, normal-weight, physically inactive women. This could be partially explained by the potential

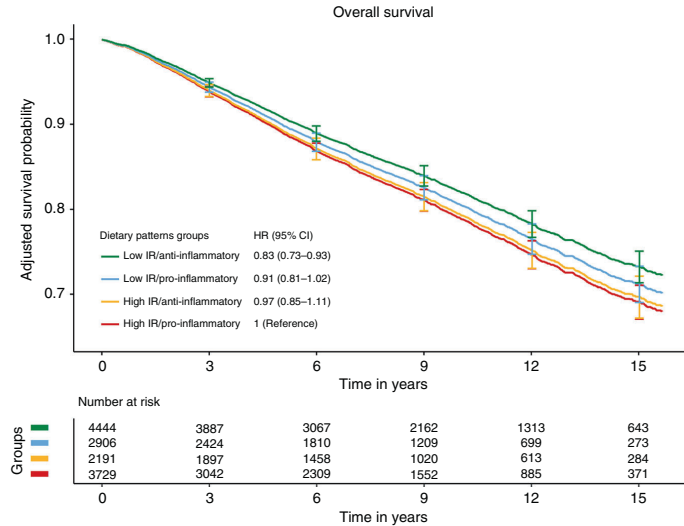


Fig. 1 Adjusted survival curves for the four groups of the cross-classification of DRRD and ISD in relation to overall mortality in breast cancer survivors. HR hazard ratio, CI confidence interval, DRRD diabetes risk reduction diet, ISD inflammatory score of diet, IR insulin resistance. Combined variable of DRRD and ISD (dichotomised above and below median) creating a 4-level variable (low IR-anti-inflammatory, low IR-pro-inflammatory, high IR-anti-inflammatory, high IR-pro-inflammatory). HRs and CI 95% from multivariable Cox models stratified by country and menopausal status at diagnosis and adjusted for age at diagnosis, attained level of education, physical activity, body mass index, alcohol consumption reported at recruitment, smoking habit and intensity as cigarettes per day at recruitment, ever use of hormone for menopause at diagnosis, cancer stage at diagnosis, cancer grade, and tumour receptor status: ER, PR, HER2.

effects of a low-insulin resistance diet and an anti-inflammatory diet becoming evident only among women for whom hormonal pathways are less relevant and without other strong determinants of these mechanisms such as obesity and physical activity. In addition, previous studies have consistently reported that inflammatory cytokines and higher insulin levels increased oestrogen synthesis by aromatase activation [32, 38, 39]. Consistent with our results, a recent study [40] concluded that a more anti-inflammatory diet after breast cancer diagnosis was associated with better overall survival among postmenopausal BC survivors.

On the other hand, breast cancer hormone receptor status is considered a predictor of prognosis, and diet might have differential effects on overall survival depending on this. In stratified analysis by hormone receptor status, associations between DRRD and ISD with overall mortality were observed among PR+ subtype tumours, although interactions were not statistically significant. Owing to the high proportion of missing data on hormone receptor status we had limited power to detect differences in overall mortality between these subtypes. Indeed, we found no association with the oestrogenic dietary pattern, which is an unexpected result; we have no explanation for it.

Given the potential inter-relationship between the pathways represented by the DRRD and ISD scores, it was worth exploring the combination of DRRD and ISD on mortality among breast cancer survivors. Survivors following a low-IR and anti-inflammatory diet had a 17% lower risk of all-cause mortality compared to those following a high-IR and pro-inflammatory diet. The combination of these two dietary patterns that previously showed an individual effect on mortality is of interest to explore new dietary strategies to improve survival after breast cancer. The adjusted mean intakes (Table S7) indicated that the foods most associated with a low-IR and anti-inflammatory diet, were vegetables, legumes, fruits, nuts and seeds, yogurt, non-white bread, fish and shellfish, fruit and vegetable juices, coffee, and tea.

On the contrary, higher means in the group of high-IR and a pro-inflammatory diet were seen for milk, cheese, fresh and processed meat, butter, the sugar and confectionery group, cakes, and alcoholic beverages.

Strengths of this study include its prospective design, the large number of breast cancer survivors and events (deaths), the long follow-up from the date of diagnosis, and detailed information on potential confounders. Furthermore, the availability of dietary components from which dietary patterns are derived from standardised dietary intake using means and standard deviations derived from EPIC captures the main food groups consumed by the European population.

One important limitation of our study is the lack of information on treatment, which is a strong determinant of prognosis and survival. To mitigate this issue, at least partially, we used the available information on tumour stage at diagnosis, grade of tumour differentiation and receptor status as a potential surrogate for treatment, since these characteristics often determine the therapeutic approach in these patients. In addition, we also considered the hypothesis that patients with an older diagnosis would have a worse prognosis than newly diagnosed patients due to advances in treatment. However, the effect estimates remained similar in sensitivity analyses for different time periods. Secondly, dietary intakes were measured only once at baseline, which may not be sufficient in determining the patient's usual intake over the years and after diagnosis. Despite this, sensitivity analyses concluded that the association for high adherence to DRRD and to a lesser extent to ISD was maintained across the different time periods from diet measurement to diagnosis. Finally, as in every observational study, residual confounding is possible, although we controlled for a wide range of predictors of diet and breast cancer mortality.

In conclusion, our findings from a large prospective cohort study suggest that anti-diabetic (or low insulin resistance) and anti-inflammatory diets prior to breast cancer diagnosis are

Table 4. Sensitivity analyses: mutually adjusted models with the three dietary patterns and overall mortality.

N (events)	N cases (events)	HR (95% CI) ^a		
		DRRD	ISD	ERDP
Multivariable model ^b	13,270 (2340)	0.92 (0.87–0.96)	1.06 (1.00–1.12)	0.97 (0.92–1.03)
Time from diet measurement to diagnosis				
<5 years	3842 (1086)	0.92 (0.86–0.98)	1.00 (0.92–1.1)	0.96 (0.89–1.04)
5 to <8 years	2712 (528)	0.92 (0.83–1.01)	1.05 (0.92–1.2)	0.96 (0.85–1.09)
8 to <12 years	3671 (489)	0.92 (0.83–1.02)	1.13 (0.99–1.28)	1.00 (0.89–1.14)
12 years or more	3045 (237)	0.85 (0.73–0.99)	1.14 (0.94–1.38)	1.06 (0.88–1.26)
Period of diagnosis (year)				
Before 2000	3491 (987)	0.92 (0.85–0.99)	1.02 (0.93–1.12)	0.98 (0.90–1.07)
2001–2003	3512 (680)	0.90 (0.83–0.98)	1.03 (0.93–1.15)	0.89 (0.80–0.99)
2004–2007	3470 (459)	0.93 (0.84–1.04)	1.07 (0.93–1.23)	1.04 (0.91–1.18)
2008 or later	2797 (214)	0.87 (0.75–1.02)	1.18 (0.97–1.44)	1.06 (0.88–1.29)
Excluding BC survivors				
With T2D or CVD	10,697 (1758)	0.90 (0.86–0.95)	1.06 (0.99–1.14)	1.02 (0.95–1.08)
With unknown stage of tumour	5627 (1023)	0.92 (0.86–0.99)	1.10 (1.00–1.20)	0.98 (0.90–1.06)
With unknown HER2 status	4443 (639)	0.89 (0.81–0.98)	1.10 (0.98–1.23)	1.00 (0.90–1.12)
Additional adjustments ^c				
By time from diet measurement to diagnosis (continuous)	13,270 (2340)	0.91 (0.87–0.96)	1.05 (0.99–1.12)	0.98 (0.92–1.03)
By period of diagnosis (categorical)	13,270 (2340)	0.92 (0.87–0.96)	1.05 (0.99–1.12)	0.98 (0.93–1.03)
By co-morbidities ^d	13,270 (2340)	0.91 (0.87–0.96)	1.06 (1.00–1.13)	0.97 (0.92–1.02)

^aAll models are mutually adjusted with DRRD, ISD and ERDP by adding the residuals of the two remaining scores from the multiple regression models.

^bModel from Table 2: stratified by country and menopausal status at diagnosis and adjusted for age at diagnosis, attained level of education, physical activity, body mass index, alcohol consumption reported at recruitment, smoking habit and intensity as cigarettes per day at recruitment, ever use of hormone for menopause at diagnosis, cancer stage at diagnosis, cancer grade, and tumour receptor status: ER, PR, HER2.

^cNew variables added in the multivariable model.

^dIncluding 2 co-morbidities: diabetes and a cardiovascular problem reported at recruitment.

associated with mortality among breast cancer survivors. This may be tempered by the fact that we did not see a clear association with improved breast cancer outcomes; moreover chronic inflammation and hyperinsulinemia maybe be related to a variety of causes of death. Nevertheless, although we do not fully understand the pathways and mechanisms, the long-term adherence to anti-diabetic and anti-inflammatory dietary patterns could be a means to improve the prognosis of breast cancer survivors, and hence could help provide dietary recommendations. Further studies using dietary patterns related to biological mechanisms, especially nutritional intervention studies, are warranted.

IARC DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organisation, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organisation.

DATA AVAILABILITY

EPIC data are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC Centres. The primary responsibility for accessing the data belongs to IARC and the EPIC centres. Access to materials from the EPIC study can be requested by contacting epic@iarc.fr.

CODE AVAILABILITY

All statistical analyses were performed using R 4.1.2 statistical software. Code can be made available upon reasonable request.

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AUTHOR CONTRIBUTIONS

AA, CB, MCB and CCE were involved in the conception and design of this study. All co-authors are from EPIC centres and contributed to the data collection. AA and CB designed the data analysis. CCE did the statistical analyses and drafted the first version of the manuscript. CCE and AA interpreted the data. CCE and AA obtained the funding and supervised the work. CB, MCB, VK, CLC, FJ, MBS, AO, AT, CCD, CSA, MJS, PA, MDC, MG, CA, RT, CS, MSDM, MS, SB, TEJ, KSO, GS, MJG, SR, EMGG, EW, SC, AKH, and LD critically revised the manuscript. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study complies with the Declaration of Helsinki. EPIC was approved by the Ethics Committee of the International Agency for Research on Cancer (IARC), Lyon, France, as well as the local ethics committees of the study centres. All participants provided written informed consent for data collection and storage, as well as individual follow up.

CONSENT FOR PUBLICATION

Not applicable.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Carlota Castro-Espin.

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RESEARCH ARTICLE

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Association of Mediterranean diet with survival after breast cancer diagnosis in women from nine European countries: results from the EPIC cohort study

Carlota Castro-Espin^{1,2*} , Catalina Bonet^{1,2}, Marta Crous-Bou^{1,2,3}, Núria Nadal-Zaragoza^{1,2}, Anne Tjønneland^{4,5}, Lene Mellemkjær⁴, Mariem Hajji-Louati⁶, Thérèse Truong⁶, Verena Katzke⁷, Charlotte Le Cornet⁷, Matthias B. Schulze^{8,9}, Franziska Jannasch⁸, Giovanna Masala¹⁰, Sabina Sieri¹¹, Salvatore Panico¹², Chiara Di Girolamo¹³, Guri Skeie¹⁴, Kristin Benjaminsen Borch¹⁴, Karina Standahl Olsen¹⁴, Maria-Jose Sánchez^{15,16,17,18}, Pilar Amiano^{17,19,20}, María-Dolores Chirlaque^{21,22}, Marcela Guevara^{17,23,24}, Malin Sund^{25,26}, Stina Bodén²⁷, Marc J. Gunter^{28,29}, Esther M. Gonzalez-Gil²⁸, Elisabete Weiderpass²⁸, Inmaculada Aguilera-Buenosvinos^{24,28,30}, Kostas K. Tsilidis^{29,31}, Alicia K. Heath²⁹, Dagfinn Aune^{29,32,33}, Laure Dossus²⁸ and Antonio Agudo^{1,2}

Abstract

Background The Mediterranean diet has been associated with lower risk of breast cancer (BC) but evidence from prospective studies on the role of Mediterranean diet on BC survival remains sparse and conflicting. We aimed to investigate whether adherence to Mediterranean diet prior to diagnosis is associated with overall and BC-specific mortality.

Methods A total of 13,270 incident breast cancer cases were identified from an initial sample of 318,686 women in 9 countries from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Adherence to Mediterranean diet was estimated through the adapted relative Mediterranean diet (arMED), a 16-point score that includes 8 key components of the Mediterranean diet and excludes alcohol. The degree of adherence to arMED was classified as low (score 0–5), medium (score 6–8), and high (score 9–16). Multivariable Cox proportional hazards models were used to analyze the association between the arMED score and overall mortality, and Fine-Gray competing risks models were applied for BC-specific mortality.

Results After a mean follow-up of 8.6 years from diagnosis, 2340 women died, including 1475 from breast cancer. Among all BC survivors, low compared to medium adherence to arMED score was associated with a 13% higher risk of all-cause mortality (HR 1.13; 95%CI 1.01–1.26). High compared to medium adherence to arMED showed a non-statistically significant association (HR 0.94; 95% CI 0.84–1.05). With no statistically significant departures from linearity, on a continuous scale, a 3-unit increase in the arMED score was associated with an 8% reduced risk of overall mortality

*Correspondence:

Carlota Castro-Espin
carlota.castroespin@gmail.com; ccespin_ext@iconcologia.net
 Full list of author information is available at the end of the article



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(HR_{3-unit} 0.92, 95% CI: 0.87–0.97). This result sustained when restricted to postmenopausal women and was stronger among metastatic BC cases (HR_{3-unit} 0.81, 95% CI: 0.72–0.91).

Conclusions Consuming a Mediterranean diet before BC diagnosis may improve long-term prognosis, particularly after menopause and in cases of metastatic breast cancer. Well-designed dietary interventions are needed to confirm these findings and define specific dietary recommendations.

Keywords Mediterranean diet, Breast cancer, Cancer survivors, Dietary patterns, Prospective studies

Background

Breast cancer (BC) is the most commonly diagnosed cancer and the fifth most common cause of cancer death worldwide, accounting for approximately one in four cancer cases and one in six cancer deaths in 2020 [1, 2]. The survival rate for BC varies depending on the stage of the cancer at the time of diagnosis, age of the patient, and type of BC diagnosed. Despite differences in survival across world regions, with lower rates in transitioning countries than in transitioned countries, early detection and advances in treatment are leading to an increase in the number of BC survivors [3].

Recent reviews show persuasive evidence that body fatness and physical activity may predict important outcomes for patients with breast cancer [4, 5]. However, evidence concerning diet is rather limited or inconclusive, and BC survivors are advised to follow cancer prevention guidelines once their treatment is completed [6, 7].

Adherence to the Mediterranean diet (MD) has been associated with lower risk of breast cancer [8]. Accordingly, most recommendations of the World Cancer Research Fund (WCRF) for cancer survivors are compatible with the MD pattern [4]. However, few studies have explored the role of this dietary pattern in relation to BC survival [9–12]. These studies were conducted in the USA and used slightly different versions of the MD pattern, different dietary assessment methods and collection times, and overall the results were inconclusive.

Our objective was to assess the association between adherence to a MD pattern, by means of the adapted relative Mediterranean diet (arMED) score [8], using dietary data collected prior to diagnosis, and all-cause and BC-specific mortality in women diagnosed with BC from nine European countries.

Methods

Study population

We used data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a prospective, multicenter European cohort with more than half a million women and men recruited between 1992 and 2000. Full details of the study design and data collection

have been described elsewhere [13, 14]. Participants completed questionnaires on diet, lifestyle, and medical history at the time of recruitment and anthropometric measurements were also obtained. All participants provided written informed consent and the study was approved by the ethical review committees of the International Agency for Research on Cancer (IARC-Lyon, France) and all local centers.

Dietary assessment

The dietary assessment was conducted using a combination of methods, including detailed dietary questionnaires, and food frequency questionnaires (FFQs). At recruitment, participants completed a validated country- or center-specific dietary questionnaire that included questions on the frequency and portion sizes of foods and drinks consumed in the previous year and was designed to capture the geographical specificity of the diet [13].

Derivation of the arMED score

To measure adherence to the MD, we used the arMED score [8], a variant of the original MD scale defined by Trichopoulou et al. [15]. The arMED score was based on tertiles of energy-adjusted intake of eight foods/food groups to reflect consumption in relation to the individual's total daily energy intake. Unlike the original score [15], the arMED includes olive oil instead of monounsaturated fats, and alcohol was excluded from the list of components due to its causal association with BC carcinogenesis. For five items presumed to fit the MD, a score of 0 to 2 was assigned to tertiles of intake: fruits (including nuts and seeds), vegetables (excluding potatoes), legumes, fish, and cereals. The scoring was inverted for the components presumed to not fit MD: meat (red meat and processed meat) and dairy products. The score was slightly modified for olive oil due to the relatively high proportion of non-consumers in some countries; a score of 0 was assigned to non-consumers, 1 to participants below the median (calculated among consumers), and 2 to participants at or above the median. Thus, the arMED score ranged from 0 to 16, with higher scores indicating greater adherence to MD.

Ascertainment of breast cancer cases

The International Classification of Diseases for Oncology (ICD-O-2) codes C50.0–50.9 were used to define BC cases. Women with prevalent tumors at recruitment, no follow-up data, no information on lifestyle and diet, or implausible diets were excluded; furthermore, BC cases ($N=50$) with unknown vital status, inconsistent follow-up data, or with non-epithelial morphology were also excluded. Out of 318,686 women from nine countries (Denmark, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the UK), a total of 13,270 incident primary malignant breast cancers (including 14 in situ) were diagnosed during the follow-up and were included in the present analysis.

Statistical analyses

The baseline characteristics of the participants were described as mean (SD) for continuous variables and frequencies for categorical variables. Cox proportional hazard models were used to prospectively analyze associations between the arMED score and overall mortality. Fine-Gray competing risks models were performed to evaluate the association with BC-specific mortality, with other causes of death considered competing events. Entry time was defined as the date of diagnosis of primary breast cancer, and exit time was defined as the date of death or end of follow-up. The arMED score was assessed as a categorical variable according to low (score 0–5), medium (score 6–8), and high (score 9–16) adherence, using the medium category as the reference, as well as per 3-unit increase in the score. Restricted cubic spline models with five knots were fitted, and non-linearity was tested using the likelihood (LR) ratio test.

All models were stratified by country, menopausal status at diagnosis (women aged ≥ 55 years at diagnosis were considered postmenopausal regardless of the baseline information) and stage of the tumor (non-metastatic, metastatic, unknown) and adjusted for: age at diagnosis (5-years categories), education level (no formal education, primary school, secondary school, technical or professional training, university, and not specified), body mass index (BMI) (kg/m^2 , continuous), physical activity (inactive, moderately inactive, moderately active, active, unknown), alcohol consumption (non-drinker, 0 to <3 g/day, 3 to <12 g/day, 12 to <24 g/day, ≥ 24 g/day, unknown), smoking status and intensity (never smokers, current smokers 1–15, 16–25, and >25 cigarettes/day, former quit ≤ 10 , 11–20, and >20 years before recruitment, current smoker of cigars, pipes and occasional current smokers, current smokers with unknown intensity, and not specified), ever use of hormone replacement therapy for menopause at diagnosis (yes, no, unknown),

grade of tumor (well differentiated, moderately differentiated, poorly differentiated or undifferentiated, not determined), and tumor receptor status (positive, negative, unknown) for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). BMI was modeled as a restricted cubic spline to account for its non-linear association with mortality [5, 16].

Separate models for pre- and postmenopausal cases were performed and heterogeneity was tested by comparing models with and without the cross-product terms using the Likelihood ratio (LR) test. The proportional hazards assumptions were tested by using the Schoenfeld goodness-of-fit test.

Stratified analyses were performed for overall mortality according to potential modifiers of the association with arMED: BMI, physical activity, smoking status, tumor stage, and hormone receptor status (ER, PR, HER2, and triple negative), and adherence to dietary patterns related to underlying biological mechanisms of BC previously associated with BC survival [17]: low/high adherence to the Diabetes Risk Reduction Diet [DRRD] [18] and Inflammatory Score of Diet [ISD] [19].

In sensitivity analyses, we examined whether further adjustment for the time interval between recruitment (time at which dietary information was collected) and BC diagnosis modified our main results, as well as for the period of diagnosis, to account for the potential influence of improvements in treatment and diagnosis over time. Comorbidities, including cardiovascular disease and presence of diabetes at baseline, and a combined variable with mechanistic dietary patterns (DRRD-ISD) were also used to further adjust separate models and test the robustness of the results.

Direct adjusted cumulative incidence function (CIF) curves for the three levels of adherence to the arMED score and overall mortality were derived from the multi-variable Cox proportional hazards model [20].

All analyses were performed using R version 4.2.2. We used a significance level of 0.05, but also considered the confidence intervals and point estimate magnitudes. Data analysis was conducted from October 1, 2022, to January 13, 2023.

Results

Our population included 13,270 incident cases of breast cancer. During a mean follow-up of 8.6 years from the date of diagnosis, 2340 women died, including 1475 specifically from breast cancer. Baseline characteristics of the women in relation to three levels of adherence to the arMED score are summarized in Table 1. Women with low arMED were older, with lower educational level, more likely to be current smokers, more likely to have a higher

Table 1 Baseline characteristics of the 13,270 breast cancer (BC) cases in the EPIC cohort according to the adherence to Mediterranean diet as measured by the adapted relative Mediterranean diet (arMED) score

	All BC cases (N = 13,270)	Adherence measured by the arMED score		
		Low (N = 3427)	Medium (N = 5162)	High (N = 4681)
Age at diagnosis, mean (SD)	61 (8.8)	63 (8.8)	61 (8.5)	60 (8.9)
Educational level				
None/primary	3281 (24.7)	998 (29.1)	1049 (20.3)	1234 (26.4)
Technical/professional	3035 (22.9)	1148 (33.5)	1242 (24.1)	645 (13.8)
Secondary	3200 (24.1)	622 (18.1)	1317 (25.5)	1261 (26.9)
Longer education	3143 (23.7)	588 (17.2)	1294 (25.1)	1261 (26.9)
Smoking status				
Never	5940 (44.8)	1465 (42.7)	2276 (44.1)	2199 (47)
Former	3139 (23.7)	806 (23.5)	1233 (23.9)	1100 (23.5)
Current	2476 (18.7)	895 (26.1)	936 (18.1)	645 (13.8)
Miscellaneous	1487 (11.2)	236 (6.9)	605 (11.7)	646 (13.8)
Alcohol consumption				
Non drinker	1774 (13.4)	422 (12.3)	598 (11.6)	754 (16.1)
> 0–3 g/day	3820 (28.8)	990 (28.9)	1455 (28.2)	1375 (29.4)
> 3–12 g/day	4066 (30.6)	1035 (30.2)	1641 (31.8)	1390 (29.7)
> 12–24 g/day	2069 (15.6)	523 (15.3)	801 (15.5)	745 (15.9)
> 24 g/day	1541 (11.6)	457 (13.3)	667 (12.9)	417 (8.9)
Body mass index (BMI)				
Normal weight	7612 (57.4)	1834 (53.5)	3058 (59.2)	2720 (58.1)
Overweight	3943 (29.7)	1105 (32.2)	1473 (28.5)	1365 (29.2)
Obesity	1509 (11.4)	440 (12.8)	556 (10.8)	513 (11)
Underweight	206 (1.6)	48 (1.4)	75 (1.5)	83 (1.8)
Physical activity				
Inactive	2673 (20.1)	583 (17)	891 (17.3)	1199 (25.6)
Moderately inactive	4720 (35.6)	1200 (35)	1820 (35.3)	1700 (36.3)
Moderately active	3606 (27.2)	867 (25.3)	1555 (30.1)	1184 (25.3)
Active	2076 (15.6)	709 (20.7)	809 (15.7)	558 (11.9)
Menopausal status at diagnosis				
Premenopausal	3070 (23.1)	613 (17.9)	1152 (22.3)	1305 (27.9)
Postmenopausal	10,200 (76.9)	2814 (82.1)	4010 (77.7)	3376 (72.1)
Ever use of hormones for menopause				
No	7487 (56.4)	1785 (52.1)	2805 (54.3)	2897 (61.9)
Yes	5323 (40.1)	1434 (41.8)	2166 (42)	1723 (36.8)
Unknown	460 (3.5)	208 (6.1)	191 (3.7)	61 (1.3)
Grade of tumor differentiation				
Well differentiated	1298 (9.8)	269 (7.8)	547 (10.6)	482 (10.3)
Moderately differentiated	2917 (22)	603 (17.6)	1176 (22.8)	1138 (24.3)
Undifferentiated or poorly diff	2503 (18.9)	462 (13.5)	982 (19)	1059 (22.6)
Not determined	6552 (49.4)	2093 (61.1)	2457 (47.6)	2002 (42.8)
Stage of tumor				
Stage 0/I	1954 (14.7)	573 (16.7)	798 (15.5)	583 (12.5)
Stage II	1593 (12)	506 (14.8)	624 (12.1)	463 (9.9)
Stage III	303 (2.3)	98 (2.9)	119 (2.3)	86 (1.8)
Non-metastatic, unknown stage	3984 (30)	773 (22.6)	1622 (31.4)	1589 (33.9)
Stage IV (metastatic)	1777 (13.4)	350 (10.2)	699 (13.5)	728 (15.6)
Unknown	3659 (27.6)	1127 (32.9)	1300 (25.2)	1232 (26.3)

Table 1 (continued)

	All BC cases (N = 13,270)	Adherence measured by the arMED score		
		Low (N = 3427)	Medium (N = 5162)	High (N = 4681)
ER status				
Negative	1678 (12.6)	391 (11.4)	646 (12.5)	641 (13.7)
Positive	7500 (56.5)	1739 (50.7)	2968 (57.5)	2793 (59.7)
Unknown	4092 (30.8)	1297 (37.8)	1548 (30)	1247 (26.6)
PR status				
Negative	2612 (19.7)	571 (16.7)	1029 (19.9)	1012 (21.6)
Positive	5072 (38.2)	1129 (32.9)	1983 (38.4)	1960 (41.9)
Unknown	5586 (42.1)	1727 (50.4)	2150 (41.7)	1709 (36.5)
HER2 status				
Negative	3587 (27)	931 (27.2)	1377 (26.7)	1279 (27.3)
Positive	856 (6.5)	202 (5.9)	312 (6)	342 (7.3)
Unknown	8827 (66.5)	2294 (66.9)	3473 (67.3)	3060 (65.4)

Except for values where the mean and SD are specified, all values are presented as the total number (N) and %

Cut-off points of arMED categories: low adherence, 0–5; medium adherence, 6–8; high adherence, 9–16

Unknown categories of educational level (N = 611), smoking habit and intensity (N = 228), and physical activity (N = 195) are not shown in this table

BMI, and were mostly postmenopausal. Women with low adherence to the arMED were also less likely to have well-differentiated tumors, more likely to be diagnosed at an earlier stage, and with a higher proportion of ER-positive and PR-positive tumors. Mediterranean countries in the cohort had the highest arMED scores (Spain, Italy, mean 10), and lowest for Sweden and the Netherlands (mean 5) (Additional file 1: Table S1). The adjusted HRs for overall and BC-specific mortality according to levels of adherence to the arMED score are summarized in Table 2. Among all BC survivors, low compared to medium adherence to arMED was associated with a 13% higher risk of all-cause mortality (HR 1.13, 95% CI: 1.01–1.26). Compared to medium adherence, the association for high adherence was not statistically significant (HR 0.94; 95% CI 0.84–1.05). Despite this, an assessment of the association of arMED and overall and BC-specific mortality using restricted cubic splines (Additional file 1: Fig. S1) showed no statistically significant departures from linearity ($p=0.8$). Therefore, on a continuous scale, a 3-unit increase in the arMED score was associated with an 8% (HR_{3-unit} 0.92, 95% CI: 0.87–0.97) reduced risk of overall mortality. In postmenopausal BC survivors, the arMED score showed an 8% (HR_{3-unit} 0.92, 95% CI: 0.86–0.98) lower risk of overall mortality per 3-unit increase, whereas there was no statistically significant association in premenopausal BC survivors (HR_{3-unit} 0.94, 95% CI: 0.84–1.06). Heterogeneity between the association of arMED and overall mortality according to menopausal status did not reach statistical significance ($p=0.437$). Multivariable models for BC-specific mortality showed no evidence of association with the arMED score, in all

BC survivors and in neither premenopausal nor postmenopausal BC survivors. Stratified analyses by Mediterranean and non-Mediterranean countries (Additional file 1: Table S2) showed overall inverse associations by increasing the arMED score and overall mortality with stronger associations among Mediterranean (HR_{3-unit} 0.81, 95% 0.69–0.95) countries and no longer statistically significant among non-Mediterranean countries.

Results for arMED and overall mortality were unchanged with further adjustment for time between dietary data collection and BC diagnosis, period of diagnosis, or presence of comorbidities at baseline (Table 3). However, adjustment for adherence to DRRD-ISD dietary patterns attenuated the association. We also examined the association between arMED and non-BC-related deaths, including deaths from CVD and cancers other than BC (Additional file 1: Table S3). The arMED score was not associated with CVD mortality, whereas a statistically significant inverse association was observed for total non-BC-related mortality ($p<0.01$) and cancer mortality (excluding BC) ($p<0.01$). Figure 1 shows subgroup analyses for arMED per 3-unit increase in relation to overall mortality. Although there were clear associations in some subgroups but not others, there were no statistically significant interactions for the association between arMED score and overall mortality with BMI, physical activity, adherence to the DRRD-ISD dietary patterns, smoking status, or hormone receptor status, including triple negative tumors.

The only statistically significant interaction was observed with tumor stage at diagnosis (non-metastatic versus metastatic tumors) ($p<0.01$): a protective

Table 2 Multivariable hazard ratios (HR) and 95% confidence interval (95%CI) of overall and breast cancer-specific mortality according to the adherence to the Mediterranean diet measured by the arMED score

	Categories of adherence of the arMED score ^a			arMED score, continuous
	Low	Medium	High	3-units increase
Overall mortality				
All BC survivors ^b	1.13 (1.01–1.26)	1.00 reference	0.94 (0.84–1.05)	0.92 (0.87–0.97)
N (deaths)	3427 (736)	5162 (871)	4681 (733)	13,270 (2340)
Premenopausal BC survivors ^{c,d}	1.21 (0.94–1.56)	1.00 reference	1.11 (0.89–1.38)	0.94 (0.84–1.06)
N (deaths)	613 (131)	1152 (183)	1305 (213)	3070 (527)
Postmenopausal BC survivors ^{c,e}	1.10 (0.98–1.24)	1.00 reference	0.89 (0.78–1.01)	0.92 (0.86–0.98)
N (deaths)	2814 (605)	4010 (688)	3376 (520)	10,200 (1813)
P value heterogeneity [*]				0.437
BC-specific mortality				
All BC survivors ^b	1.12 (0.98–1.29)	1.00 reference	0.99 (0.86–1.13)	0.97 (0.90–1.04)
N (deaths)	3427 (441)	5162 (541)	4681 (493)	13,270 (1475)
Premenopausal BC survivors ^{c,d}	1.23 (0.92–1.63)	1.00 reference	1.16 (0.91–1.48)	0.97 (0.85–1.11)
N (deaths)	613 (103)	1152 (145)	1305 (180)	3070 (428)
Postmenopausal BC survivors ^{c,e}	1.10 (0.94–1.28)	1.00 reference	0.93 (0.78–1.09)	0.97 (0.89–1.05)
N (deaths)	2814 (338)	4010 (396)	3376 (313)	10,200 (1047)
P value heterogeneity [*]				0.992

Abbreviations: arMED Adapted relative Mediterranean diet, N Number of breast cancer cases

^a Categories of arMED: low adherence, 0–5; medium adherence, 6–8; high adherence, 9–16^b Model stratified by country, stage (metastatic, non-metastatic, unknown) and menopausal status at diagnosis and adjusted for age at diagnosis, attained level of education, physical activity, body mass index (modeled as restricted cubic spline), alcohol consumption reported at recruitment, smoking habit and intensity at recruitment, ever use of hormones for menopause at diagnosis, grade of differentiation, and tumor receptor status (ER, PR, HER2)^c Same model as above without stratification for menopausal status at diagnosis^d Model premenopause: variable age into 2 categories, < 50 and ≥ 50, and not adjusted for every use of hormone therapy replacement for menopause^e Model postmenopause: variable age into 2 categories, < 65 and ≥ 65^{*} P value for heterogeneity between pre- and postmenopausal subgroups for the association of arMED and mortality outcomes**Table 3** Sensitivity analysis: association between overall mortality and adherence to the arMED score by additional adjustments for time from baseline to diagnosis, period of diagnosis, presence of comorbidities, and other dietary patterns (N = 13,270, events/deaths = 2340)

	Categories of adherence of the arMED score ^a			arMED score, continuous
	Low (N = 3427)	Medium (N = 5162)	High (N = 4681)	3-units increase
Reference model ^b	1.13 (1.01–1.25)	1.00 Reference	0.94 (0.84–1.05)	0.92 (0.87–0.97)
Model further adjusted for:				
Time from baseline to diagnosis ^c	1.13 (1.02–1.26)	1.00 Reference	0.94 (0.84–1.04)	0.92 (0.87–0.97)
Period of diagnosis ^d	1.13 (1.01–1.25)	1.00 Reference	0.94 (0.84–1.05)	0.92 (0.87–0.97)
Comorbidities ^e	1.13 (1.02–1.26)	1.00 Reference	0.93 (0.84–1.04)	0.92 (0.86–0.97)
Mechanistic dietary patterns (DRRD-ISD) ^f	1.10 (0.99–1.23)	1.00 Reference	0.98 (0.87–1.09)	0.95 (0.89–1.01)

Abbreviations: arMED Adapted relative Mediterranean diet, N Number of breast cancer cases

^a Categories of arMED: low adherence, 0–5; medium adherence, 6–8; high adherence, 9–16^b Model stratified by country, stage (metastatic, non-metastatic, unknown) and menopausal status at diagnosis and adjusted for age at diagnosis, attained level of education, physical activity, body mass index (modeled as restricted cubic spline), alcohol consumption reported at recruitment, smoking habit and intensity at recruitment, ever use of hormones for menopause at diagnosis, grade of differentiation, and tumor receptor status (ER, PR, HER2)^c Categories of time from baseline to diagnosis are < 5 years, 5 to < 8 years, 8 to < 12 years, and equal or more than 12 years^d Categories for period of diagnosis are before 2000, between 2000 and < 2004, between 2004 and < 2008, 2008 onwards^e Comorbidities include the presence of diabetes (categories yes, no, unknown) and the presence of cardiovascular problem reported at recruitment (categories yes, no, unknown)^f Adjusted for a 4-level variable that combines two dietary patterns in high-low adherence categories: Diabetes Reduced Risk Diet (DRRD) and Inflammatory Score of Diet (ISD)

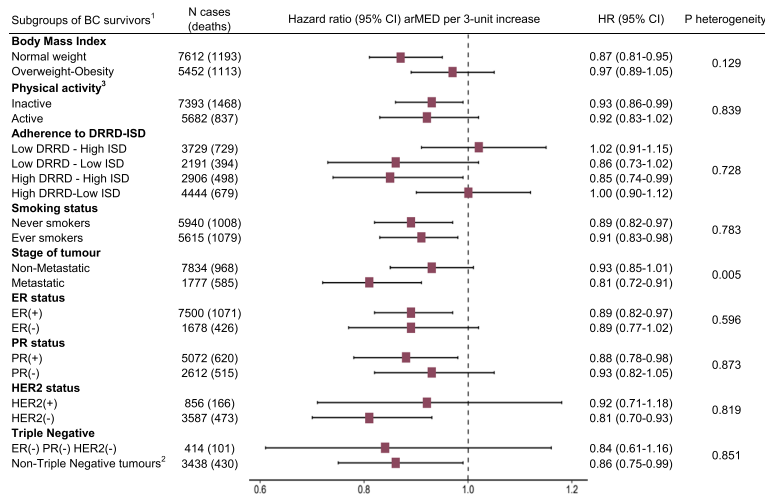


Fig. 1 Associations between arMED score and overall survival among subgroups of breast cancer survivors. Abbreviations: BC, breast cancer; BMI, body mass index; HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; DRRD, Diabetes Risk Reduction Diet; ISD, Inflammatory Score of the Diet; N, number of breast cancer cases. ¹Each model has excluded of their stratification/adjustment the specific variable that represents the subgroup in each case. Models stratified by country, stage (metastatic, non-metastatic, unknown) and menopausal status at diagnosis and adjusted for age at diagnosis, attained level of education, physical activity, body mass index (modeled as restricted cubic spline with five internal knots placed at equally spaced percentiles), alcohol consumption reported at recruitment, smoking habit and intensity as cigarettes per day at recruitment, ever use of hormones for menopause at diagnosis, grade of differentiation, and tumor receptor status: ER, PR, HER2. ²Only BC survivors with known status of the receptor (positive or negative) have been considered. ³Categories of physical activity. Inactive: includes moderately inactive and inactive. Active: includes moderately active and active

association of arMED was observed in metastatic BC survivors for overall mortality (HR_{3-unit} 0.81, 95% CI: 0.72–0.91): The same was observed for BC-specific mortality, with HR_{3-unit} 0.86 (95% CI: 0.76–0.98), with *p*-value heterogeneity < 0.01 (Additional file 1: Table S4). The direct adjusted CIF curves for overall mortality derived from the Cox model are presented in Fig. 2. The 15-year cumulative mortality estimates were 32% (30–34%), 29% (27–31%), and 27% (26–29%) for low, medium, and high adherence to the arMED score, respectively.

Discussion

In this prospective cohort study including 13,270 BC survivors, low adherence to a MD pattern before BC diagnosis was positively associated with all-cause mortality (13% higher risk compared to medium adherence). The results also showed an 8% lower overall mortality in all BC survivors for each 3-unit increase in the arMED score, which was sustained when restricted to postmenopausal women. Although no significant heterogeneity was observed by menopausal status, the smaller number of premenopausal cases may have limited our statistical power to detect significant associations. Additionally, while a statistically significant lower risk of all-cause mortality was observed with the arMED score modeled

continuously, the association did not reach statistical significance when comparing high versus medium adherence. Moreover, there were no clear associations for BC-specific mortality. In addition, high adherence to MD appears to be particularly beneficial against overall mortality in Mediterranean countries, whereas in non-Mediterranean countries, the impact of increased adherence to MD seems more relevant when moving from low to medium levels of adherence.

Two recent systematic reviews have evaluated the relationship of several dietary patterns with BC survival [21, 22]. Only three studies included in these reviews evaluated the role of a MD pattern on prognostic outcomes in BC survivors [9–11]. Our study found a statistically significant inverse association between adherence to MD and all-cause mortality which conflicts with the null results in these studies. This discrepancy could be owing to a number of differences, including the study population, the score used to measure adherence to MD, the time when diet was measured with respect to BC diagnosis, and the different method of dietary assessment. For instance, the three studies [9–11], conducted in the USA, did not consider olive oil, but used a ratio of monounsaturated to saturated fats instead, and all of them included alcohol consumption. One study was restricted

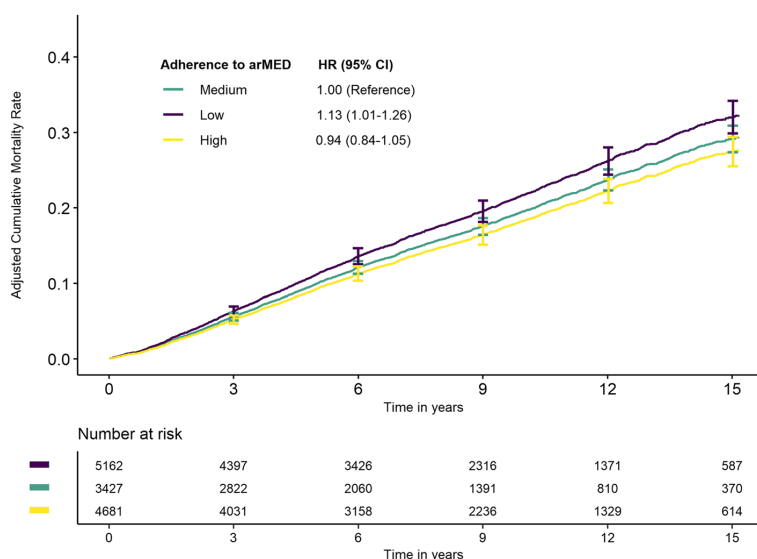


Fig. 2 Direct adjusted cumulative incidence function curves for overall mortality by categories of adherence to arMED score. HR hazard ratio, CI confidence interval, arMED adapted relative Mediterranean diet. Categories of arMED: low adherence, 0–5; medium adherence, 6–8; high adherence, 9–16. HRs and CI 95% from multivariable Cox model stratified by country, stage (metastatic, non-metastatic, unknown) and menopausal status at diagnosis and adjusted for age at diagnosis, attained level of education, physical activity, body mass index (modeled as restricted cubic spline), alcohol consumption reported at recruitment, smoking habit and intensity at recruitment, ever use of hormones for menopause at diagnosis, grade of differentiation, and tumor receptor status (ER, PR, HER2)

to postmenopausal women with stage I–III BC [9], and another [10] was a retrospective cohort with a small sample size ($N=110$) of self-reported BC survivors whose dietary information was based on a single 24-h dietary recall. Finally, whereas our study assessed diet before diagnosis, other studies did it either close to the time of diagnosis [11] or after diagnosis [9].

Despite this, and in line with our results, a recent study observed statistically significant inverse associations with overall mortality for higher adherence to the Alternative Mediterranean Diet (aMED), a version of the MD adapted to the US population [12]. However, the Breast Cancer Family Registry is based on families with multiple cases of BC and the findings may not be generalizable to women without a family history of BC.

In our study, 63% of deaths were related specifically to BC, and BC used to be the most common cause of death following a BC diagnosis [23]. However, evidence now suggests that cardiovascular disease (CVD) accounts for a substantial number of non-BC-related deaths in the 10 years following diagnosis [23, 24]. Although MD is well-known to be protective against CVD [25], in our study, most deaths by causes other than BC were related to other cancers (13%) and only 150 (6%) were from CVD (Additional file 1: Table S3). Our findings showed

statistically significant inverse associations between arMED score and overall non-BC mortality, including cancer mortality (excluding BC), but a non-significant association with CVD-related mortality. This warrants further investigation in future studies with a greater number of deaths related to these causes. On the other hand, Cox models additionally adjusted for the presence of comorbidities, including CVD or diabetes at the time of recruitment, showed no apparent differences with respect to the main results (Table 2), suggesting that the effect of the MD on mortality could occur beyond its protective role on these diseases.

Consistent with our results, the Nurses' Health Study found a statistically significant reduced risk of all-cause mortality with higher adherence to MD restricted to BC survivors with low physical activity [9]. Our subgroup analyses also showed a statistically significant inverse association between adherence to MD and all-cause mortality in BC survivors who were inactive, and additionally in those with normal weight. Similarly, a recent study reported a statistically significant inverse association for adherence to MD with overall mortality in BC cases of normal BMI range [12]. A plausible interpretation for this might be that the impact of diet is more evident in BC survivors without the presence of other strong

prognostic determinants such as obesity and physical activity, where perhaps the mechanisms underlying these conditions may blur the modest effect of diet. However, no heterogeneity was found, hence no firm conclusions can be drawn.

With respect to hormone receptors, BC survivors with ER/PR-positive and HER2-negative tumors showed lower overall mortality with increasing arMED score, although there was no statistically significant interaction between groups ($p > 0.05$). Metastatic BC survivors seemed to benefit more from adherence to the MD when assessed by the arMED score than non-metastatic BC survivors, with a statistically significant reduced risk of overall mortality and BC-specific mortality, however, we do not have a clear interpretation for these results.

The positive effect on health attributed to the MD [26] is thought to be due to several mechanisms, including weight control, antioxidant potential, improvement of glycemic profile, and anti-inflammatory properties [27, 28]. Some of these mechanisms are also involved in the prognosis of breast cancer [29]. However, to our knowledge, the impact of the MD pattern on these mechanisms in relation to BC prognosis has rarely been investigated [30]. We have recently reported that two dietary patterns related to lower insulin resistance and the inflammatory potential of the diet (the DRRD and the ISD, respectively) were associated with overall mortality among BC survivors [17]. To investigate the independent effect of the arMED score we adjusted a model with a variable combining high and low adherence to the DRRD and ISD scores. We found that the observed association of the arMED with mortality was attenuated, probably reflecting that, at least partially, the observed effect of MD may be explained by mechanisms of inflammation and insulin resistance or hyperinsulinemia.

Strengths and limitations

This study has several strengths. The prospective study design and long follow-up time allowed us to identify large numbers of deaths among a large sample of BC survivors. One specific advantage of this study is the inclusion of populations from Mediterranean and non-Mediterranean countries, which allowed us to have a broad representation of degrees of adherence to the MD pattern, with enough participants (and events) in different categories of the arMED.

One important limitation is the lack of information on treatment, a strong determinant of prognosis and survival. We used the available information on tumor stage at diagnosis, grade of tumor differentiation, and hormone receptor status as potential surrogates for treatment, since these characteristics are strong determinants of the therapeutic strategy, at least in most settings where the

EPIC cohorts were recruited. Although we investigated differences by hormone receptor status for BC mortality outcomes, estimates were imprecise probably due to the missingness among these variables in our analysis. In addition, our results are based on a single dietary assessment, which may not reflect possible changes in dietary habits. To address to what extent the diet collected at baseline remains constant until diagnosis we performed sensitivity analyses adjusting for the time from diet measurement to diagnosis, and the results were unchanged. Similarly, we considered the possibility that survivors with an older diagnosis would be less likely to benefit from the early detection and advances in treatments, resulting in a worse prognosis, as compared to those with a more recent diagnosis. We performed sensitivity analyses adjusting for different periods of diagnosis and the observed results remained stable.

Conclusions

Our research suggests that adherence to a Mediterranean diet before BC diagnosis may improve long-term prognosis, especially in postmenopausal women. Furthermore, we found that the protective effect of MD appears to be stronger in women diagnosed with metastatic BC tumors. The link between postdiagnosis dietary patterns and BC outcomes remains unclear and BC survivors are still advised to follow general guidelines for cancer prevention once their treatment is completed. Further research, including large, well-designed dietary interventions will help provide more specific dietary recommendations for breast cancer survivors. In the meantime, research on the underlying biological mechanisms of various dietary patterns may provide relevant insights on the role of nutrition in breast cancer prognosis.

Abbreviations

arMED	Adapted relative Mediterranean diet
BC	Breast cancer
BMI	Body mass index
CI	Confidence interval
DRRD	Diabetes Risk Reduction Diet
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
ISD	Inflammatory score of the diet
MD	Mediterranean diet
PR	Progesterone receptor
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-023-02934-3>.

Additional file 1. Association of Mediterranean diet with survival after breast cancer diagnosis in women from nine European countries: results

from the EPIC cohort study. **Table S1.** Summary of the arMED score in women from different EPIC countries. **Table S2.** Multivariable hazard ratios and 95% confidence interval of risk of overall mortality according to adherence to the Mediterranean diet across Mediterranean and non-Mediterranean countries in the EPIC study. **Table S3.** Multivariable hazard ratios and 95% confidence interval for the adherence to the Mediterranean diet measured by the arMED score and other causes of death in all BC survivors. **Table S4.** Associations between the arMED score and BC-specific survival among breast cancer cases with non-metastatic and metastatic tumours. **Figure S1.** Assessment of linear associations between arMED score and overall and BC-specific mortality using restricted cubic spline models.

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IARC disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer / World Health Organization.

Authors' contributions

CCE and AA designed the study. AA supervised the statistical analyses. CCE performed the statistical analyses. CCE and AA drafted the manuscript. CB, MCB, NNZ, AT, LM, MHL, TT, VK, CLC, MBS, FJ, GM, SS, SP, CDG, GS, KBB, KSO, MJS, PA, MDC, MG, MS, SB, MJG, EMGG, EW, IAB, KKT, AKH, DA, and LD contributed to the acquisition and interpretation of data and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

EPIC data are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the

EPIC centers. The primary responsibility for accessing the data belongs to IARC and the EPIC centers. For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at https://login.research4life.org/tacsgr0epic_iarc_fr/access/index.php.

Declarations

Ethics approval and consent to participate

This study complies with the Declaration of Helsinki. EPIC was approved by the Ethics Committee of the International Agency for Research on Cancer (IARC) (ref IEC 14–02), Lyon, France, as well as the local ethics committees of the study centers. All participants provided written informed consent for data collection and storage, as well as individual follow-up.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests to disclose.

Author details

¹Unit of Nutrition and Cancer, Catalan Institute of Oncology-ICO, L'Hospitalet de Llobregat, Barcelona, Spain. ²Nutrition and Cancer Group, Epidemiology, Public Health, Cancer Prevention and Palliative Care Program, Bellvitge Biomedical Research Institute-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain. ³Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA. ⁴The Danish Cancer Society Research Center, Copenhagen, Denmark. ⁵Department of Public Health, The University of Copenhagen, Copenhagen, Denmark. ⁶Université Paris-Saclay, UVSQ, Inserm "Exposome, Heredity, Cancer and Health" Team, CESP U1018, Gustave Roussy, Villejuif, France. ⁷German Cancer Research Center (DKFZ), Heidelberg, Germany. ⁸Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany. ⁹Institute of Nutritional Science, University of Potsdam, Nuthetal, Germany. ¹⁰Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy. ¹¹Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano Via Venezian, 1. 20133, Milan, Italy. ¹²Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Naples, Italy. ¹³Centre for Biostatistics, Epidemiology, and Public Health (C-BEPH), Department of Clinical and Biological Sciences, University of Turin, Regione Gonzole 10, Orbassano (TO), Italy. ¹⁴Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway. ¹⁵Escuela Andaluza de Salud Pública (EASP), Granada 18011, Spain. ¹⁶Instituto de Investigación Biosanitaria ibs.GRANADA, Granada 18012, Spain. ¹⁷Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBER-ESP), Madrid 28029, Spain. ¹⁸Department of Preventive Medicine and Public Health, University of Granada, Granada 18071, Spain. ¹⁹Ministry of Health of the Basque Government, Sub Directorate for Public Health and Addictions of Gipuzkoa, San Sebastian, Spain. ²⁰Biodonostia Health Research Institute, Epidemiology of Chronic and Communicable Diseases Group, San Sebastian, Spain. ²¹Department of Epidemiology, Regional Health Council, IMIB-Arrixaca, Murcia University, Murcia, Spain. ²²CIBER in Epidemiology and Public Health (CIBERESP), Madrid, Spain. ²³Instituto de Salud Pública y Laboral de Navarra, Pamplona 31003, Spain. ²⁴Navarra Institute for Health Research (IdiSNA), Pamplona 31008, Spain. ²⁵Department of Surgical and Perioperative Sciences/ Surgery, Umeå University, Umeå, Sweden. ²⁶Department of Surgery, University of Helsinki & Helsinki University Hospital, Helsinki, Finland. ²⁷Department of Clinical Sciences/Pediatrics, Umeå University, Umeå, Sweden. ²⁸International Agency for Research on Cancer, World Health Organization, Lyon, France. ²⁹Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK. ³⁰Department of Preventive Medicine and Public Health, University of Navarra, Pamplona, Spain. ³¹Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece. ³²Department of Nutrition, Oslo New University College, Oslo, Norway. ³³Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital Ullevål, Oslo, Norway.

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Prognostic role of pre-diagnostic circulating inflammatory biomarkers in breast cancer survival: Evidence from the EPIC cohort study

Carlota Castro-Espin^{1,2}, Manon Cairat³, Anne-Sophie Navionis⁴, Christina C. Dahm⁵, Christian S. Antoniuussen⁵, Anne Tjønneland^{6,7}, Lene Mellemkjær⁶, Francesca Mancini³, Mariem Hajji³, Gianluca Severi³, Charlotte le Cornet⁸, Rudolf Kaaks⁸, Matthias B. Schulze⁹, Giovanna Masala¹⁰, Claudia Agnoli¹¹, Carlotta Sacerdote¹², Marta Crous-Bou^{1,2,13}, Maria-Jose Sánchez^{14,15,16,17}, Pilar Amiano^{16,18,19}, María-Dolores Chirlaque^{16,20}, Marcela Guevara^{16,21,22}, Karl Smith-Byrne²³, Alicia K. Heath²⁴, Sofia Christakoudi^{24,25}, Marc J Gunter²⁴, Sabina Rinaldi⁴, Antonio Agudo^{1,2}, Laure Dossus⁴

¹ Unit of Nutrition and Cancer, Catalan Institute of Oncology-ICO, L'Hospitalet de Llobregat, Barcelona, Spain

² Nutrition and Cancer Group, Epidemiology, Public Health, Cancer Prevention and Palliative Care Program, Bellvitge Biomedical Research Institute-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

³ Université Paris-Saclay, UVSQ, Inserm "Exposome, heredity, cancer and health" team, CESP U1018, Gustave Roussy, Villejuif, France

⁴ Nutrition and Metabolism Branch, International Agency for Research on Cancer, World Health Organization, Lyon, France

⁵ Department of Public Health, Aarhus University, Bartholins Alle 2, DK-8000 Aarhus C, Denmark

⁶ Danish Cancer Society Research Center

⁷ Department of Public Health, University of Copenhagen

⁸ Department of Cancer Epidemiology, German Cancer research Center (DKFZ), Heidelberg, Germany

⁹ German Institute of Human Nutrition, Dept. of Molecular Epidemiology, Arthur-Scheunert-Allee 114-116, 14558 Nuthetal, Germany

¹⁰ Clinical Epidemiology Unit, Institute for cancer research, prevention and clinical network (ISPRO), Villa delle Rose Via Cosimo il Vecchio, 2- 50139 Florence, Italy

¹¹ Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian, 1 - 20133 Milan (Italy)

¹² Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital Via Santena, Turin, Italy

¹³ Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, 02115, USA

¹⁴ Escuela Andaluza de Salud Pública (EASP), 18011 Granada, Spain

¹⁵ Instituto de Investigación Biosanitaria ibs.GRANADA, 18012 Granada, Spain

¹⁶ Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), 28029 Madrid, Spain

¹⁷ Department of Preventive Medicine and Public Health, University of Granada, 18071 Granada, Spain

¹⁸ Ministry of Health of the Basque Government, Sub Directorate for Public Health and Addictions of Gipuzkoa, San Sebastian, Spain

¹⁹ BioGipuzkoa Health Research Institute, Epidemiology of Chronic and Communicable Diseases Group, San Sebastián, Spain

²⁰ Department of Epidemiology, Regional Health Council, IMIB-Arrixaca, Murcia University, Murcia, Spain

²¹ Instituto de Salud Pública y Laboral de Navarra, 31003 Pamplona, Spain

²² Navarra Institute for Health Research (IdiSNA), 31008 Pamplona, Spain

²³ Cancer Epidemiology Unit, University of Oxford, Oxford, UK

²⁴ Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom

²⁵ Department of Inflammation Biology, School of Immunology & Microbial Sciences, King's College London, United Kingdom

Corresponding author: Carlota Castro-Espin

Address for correspondence:

Unit of Nutrition and Cancer, Cancer Epidemiology Research Program

Catalan Institute of Oncology (ICO)

Av. Granvia de L'Hospitalet 199-203, 08908 L'Hospitalet de Llobregat, Spain

Phone: +34 609196736

Email: carlota.castroespin@gmail.com

2nd email: ccastro@idibell.cat

ORCID: <https://orcid.org/0000-0001-9050-7590>

Abstract

Background

Breast cancer (BC) is a major global concern, with high incidence and mortality rates worldwide. Inflammation, closely linked to cancer, plays a role in promoting tumor growth, metastasis, angiogenesis, and immune suppression, which contribute to poorer prognosis. Nevertheless, the impact of inflammation preceding BC diagnosis and its prognostic implications demand further exploration and a deeper understanding.

Methods

We evaluated the relationship between pre-diagnostic plasma inflammatory biomarkers (interleukin (IL)-6, IL-8, IL-10, IL-13, IL-17D, IL-1RA, tumour necrosis factor alpha (TNF- α), Interferon-gamma (IFN- γ), C-reactive protein (CRP), leptin, and adiponectin) and all-cause and BC-specific mortality in 1538 women with a BC diagnosis from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Cox proportional hazards models were conducted with adjustment for tumour characteristics and potential confounders related to lifestyle, including body mass index.

Results

During an average 7-year follow-up after diagnosis, a total of 229 BC cases died, including 163 due to BC. Circulating markers of inflammation were measured approximately 8 years before BC diagnosis. Overall, higher IL-6 levels were associated with higher risk of all-cause mortality (HR_{1SD} 1.25, 95%CI 1.07-1.47). Among postmenopausal cases ($N=1172$), IL-6 levels were positively associated with all-cause (HR_{1SD} 1.41, 95%CI 1.18-1.69, $P_{heterogeneity(pre/post)} = 0.008$) and BC-specific mortality (HR_{1SD} 1.31, 95%CI 1.03-1.66, $P_{heterogeneity(pre/post)} = 0.007$) while IL-10 and TNF α were positively associated with all-cause mortality only (HR_{1SD} 1.19, 95%CI 1.02-1.40 and HR_{1SD} 1.28, 95%CI 1.06-1.56, respectively). No statistically significant associations were observed among premenopausal BC cases ($N=366$). A higher inflammatory score, derived from the combination of IL-6, IL-8, IL-10, IL-17D, IL-1RA, IFN- γ , TNF- α , and CRP, was associated with higher risk of all-cause mortality (HR_{1SD} 1.19, 95%CI 1.01-1.40), and this was even more pronounced in postmenopausal women (HR_{1SD} 1.30, 95%CI 1.07-1.58).

Conclusions

Elevated IL-6 levels prior to BC diagnosis may be an important prognostic marker for long-term survival in BC survivors. Greater inflammatory status, based on a higher inflammatory score, and specifically higher levels of IL-6, IL-10 and TNF α seem to be especially relevant among postmenopausal women, as predictor of increased all-cause mortality. In addition, IL-6 might also influence BC-specific mortality after menopause, underlining its importance in assessing prognosis.

Introduction

Breast cancer (BC) remains a global health concern, standing as the most frequently diagnosed cancer and ranking as the fifth leading cause of cancer-related deaths worldwide (1). Cancer-associated inflammation plays a significant role in the progression of proliferation and metastasis, stimulating angiogenesis, suppressing antitumor immunity, and ultimately leading to a poor prognosis (2). The role of inflammation preceding BC diagnosis and its prognostic implications is less clear.

To investigate the relationship between inflammatory status and BC prognosis, numerous studies have predominantly relied on measurements of C-reactive protein (CRP) measured in samples collected at different time points with respect to diagnosis (3–6). These studies have yielded conflicting results, underlining the need to better understand this relationship, not only with CRP, but also with other inflammatory mediators. By exploring biomarkers prior to diagnosis, the influence of preceding or "latent" inflammation can be better captured and can provide insight into its impact on BC survival. This would help increase our ability to predict BC outcomes, which may help develop targeted interventions that can improve treatment strategies and ultimately impact survival rates.

In this study, we evaluated the associations between inflammatory biomarkers and survival in women diagnosed with BC. To achieve this, we selected a panel of cytokines, including interleukin (IL)-6, IL-8, IL-10, IL-13, IL-17D, IL-1RA, tumour necrosis factor alpha (TNF- α), Interferon-gamma (IFN- γ), and adipokines leptin and adiponectin, as well as the acute-phase protein CRP, all measured before BC diagnosis as part of the European Prospective Investigation into Cancer and Nutrition (EPIC). Our aim was to determine whether circulating levels of these inflammatory biomarkers individually, or combined in a composite score, could predict overall and BC-specific mortality in BC survivors.

Methods

Study design and participants

EPIC is a cohort study that recruited more than half a million of participants from 10 countries, between 1992 and 2000. The study design and methods of the EPIC study have been described in detail elsewhere (7). For the analyses of the current study, data were available from eight EPIC countries: France, Italy, Spain, United Kingdom, The Netherlands, Germany, Sweden, and Denmark.

Blood samples were obtained following a standard protocol in France, Germany, Italy, the Netherlands, Spain, and the UK. Serum, plasma, erythrocytes, and buffy coat aliquots were stored in liquid nitrogen (-196°C) in a centralized biobank at the International Agency for

Research on Cancer (IARC). In Denmark, blood fractions were stored locally in the vapour phase of liquid nitrogen containers at -150°C , and in Sweden, they were stored locally in standard freezers at -80°C (8).

All participants provided written informed consent for data collection and storage, as well as individual follow-up. The EPIC study was approved by the Ethics Committee of the IARC, Lyon, France, as well as the local ethics committee of each study centre.

Breast cancer cases and outcome assessment

Incident BC cases and vital status were assessed during follow-up based on population cancer registries or national cancer registries and national mortality registries in Denmark, Italy, the Netherlands, Spain, Sweden, and the UK. Cancer cases in France and Germany were identified through cancer and pathology registries, health insurance records, and proactive follow-up by contacting participants or their next-of-kin. BC cases were defined as malignant tumors coded C50.0–50.9 in the International Classification of Diseases for Oncology.

After exclusions of women with prevalent cancers (except non-malignant skin cancer) at blood collection and with no follow-up data or no lifestyle information, we included 327,927 women, among which 13,671 developed invasive breast cancers. Exclusions were made if BC cases did not have a blood sample available, had follow-up period shorter than 2 years, or had no information on hormone receptor status (oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)). After these exclusions, 1595 BC cases were selected for measurement of biomarkers. A total of 57 cases had incomplete information on tumour characteristics or vital status. The final population included 1538 breast cancer cases (**Figure S1**).

Inflammatory biomarker assessment

A selection of cytokines (IL-6, IL-8, IL-10, IL-13, IL-17D, IL-1RA, TNF- α , IFN- γ), adipokines (leptin and adiponectin) and CRP were measured on plasma samples in the laboratories of the Nutrition and Metabolism Branch at IARC, by Meso Scale Discovery (a commercially available and highly sensitive immunoassay platform) (8). No measurements below the lower limit of quantification (LOQ) were observed for leptin, CRP, IL1-RA, IL-8, and IFN- γ . Measurements below the LOQ represented less than 3% for adiponectin and IL-17D, less than 8% for IL-6, and less than 22% for IL-10 and TNF α , and around 80% for IL-13 (**Table 1**). In cases where biomarker measurements fell below the LOQ, the value was replaced with half the LOQ. Given that a substantial part of IL-13 was below this threshold, a dichotomous variable was used (above vs below the LOQ).

Covariates

At recruitment, dietary, lifestyle, reproductive, medical, and anthropometric data were collected using questionnaires. Menopausal status at diagnosis was determined by combining the baseline information with the data collected during a second follow-up assessment. Women whose age at diagnosis was 55 years or older were classified as postmenopausal, regardless of the information collected during the initial recruitment phase. Regarding the use of hormonal replacement therapy, at diagnosis, if women were initially identified as non-users at recruitment but reported ever using hormonal replacement treatment in a subsequent follow-up questionnaire before diagnosis, or if they started using hormones for menopause prior to or during age at diagnosis, they were categorized as "ever users" at the time of diagnosis.

Additionally, we utilized the inflammatory score of diet (ISD) (9), a measure of the inflammatory potential of diet, to investigate the associations between the inflammatory markers and mortality outcomes within these groups. The ISD ranked individuals based on their consumption of either more pro- or anti-inflammatory diets. Previous studies in EPIC study has shown a positive association between pro-inflammatory diets with risk of BC and, more modestly, risk of overall mortality among BC patients (10,11).

Statistical analyses

Log-transformed biomarker concentrations were used in all analyses. To comprehensively assess the association between inflammatory biomarkers and BC survival, we created two composite inflammatory scores. The first score combined all the inflammatory biomarkers (without IL-13), while the second score was constructed without including the adipokines (leptin and adiponectin). The inflammatory scores were derived from log-transformed biomarker concentrations standardized using the mean and SD of our population (z-score) of 1538 BC cases; the z-scores of adiponectin were multiplied by -1 to account for its anti-inflammatory effect. These z-scores were summed to generate an overall inflammatory score for each BC case.

Baseline characteristics of BC cases were described using frequency and percentages or mean and standard deviation (SD). Geometric means were used to describe biomarker concentrations among BC cases (**Table 1**). Partial Spearman's correlations, adjusted for age at the time of blood collection and laboratory batch, were calculated among the biomarkers, and also with ISD and BMI.

We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for each SD increase in individual inflammatory biomarkers and composite inflammatory scores. IL-13 was treated as a categorical variable based on values above and below LOQ. The outcomes assessed were all-cause mortality and BC-specific mortality. For BC-specific mortality, Fine and Gray subdistribution hazard models were

employed, accounting for other causes of death as competing events (12). Entry time was defined as the date of diagnosis, and exit time was determined by death, emigration, or end of follow-up.

All survival models were stratified by country, menopausal status at diagnosis and stage of tumour (metastatic, non-metastatic, unknown), and adjusted for age at diagnosis, laboratory batch, fasting status, education level, physical activity, body mass index (BMI), alcohol consumption, smoking status and intensity, ever use of hormones for menopause at diagnosis, cancer grade, and tumour receptor status (ER, PR, HER2). Cancer grade and hormone receptor status, while strong prognosis factors, have no true confounding effect due to the timing of biomarker measurements, which occurred prior to diagnosis. Considering this, we conducted separate analyses in which these variables were excluded from our models. Model assumptions were evaluated with graphs and tests based on the scaled Schoenfeld residuals. Additionally, separate survival analyses were performed according to menopausal status at diagnosis. Further subgroup analyses were performed for the main associations (IL-6, IL-10, TNF α , and inflammatory scores) according to lifestyle factors, including BMI, physical activity, and anti-inflammatory vs. pro-inflammatory diets. Tumour characteristics, including stage and hormone receptor status, were also considered in these subgroup analyses. To assess between-group heterogeneity, Likelihood ratio (LR) tests were used by adding an interaction term in the model between biomarker exposure and the group-defining variable.

Several sensitivity analyses were performed to assess the robustness of the results. First, we derived the inflammatory scores without IL-6 to test to what extent this biomarker drove the observed association with the score and analyzed its relationship with all-cause mortality as well as according to menopausal status. Second, models were further adjusted by time from blood collection to diagnosis dichotomized below and above 9 years (median time). Third, we performed the analyses excluding BC cases with a relatively short period from blood collection to diagnosis (6 years, value close to the 25th percentile). The decision to exclude these cases was made to reduce the likelihood of including cases where cancer may have already existed at the time of blood collection but had not been diagnosed yet. We also examined main results excluding cases with a short survival time after diagnosis (less than 1 and 2 years) to rule out the potential influence of other factors that could be significant in determining prognosis, beyond the biomarkers studied. Finally, we restricted our analyses to non-users of exogenous hormones at blood collection as the use of hormone replacement therapy (HRT) or oral contraceptives may influence inflammatory biomarker levels, apart from breast cancer risk itself, which could confound the associations we intended to examine.

All statistical analyses were performed using R 4.2.2 statistical software. All tests were 2-sided, and *P* values less than .05 were considered statistically significant.

Results

Baseline characteristics

The characteristics of BC cases in the EPIC study are summarized in **Table 2**. After a median follow-up of 7 years from diagnosis, there were 229 deaths, including 163 BC-specific deaths. On average, circulating markers of inflammation were measured 8.7 (Interquartile range: 6.2-10.7) years before BC diagnosis. The average age at BC diagnosis was 61 years, with approximately 75% of cases occurring after menopause. At blood collection, approximately half of the women had a normal BMI, were physically inactive, non-smokers, and consumed alcohol moderately. Early stages (I, II) comprised the 50.1% of cases, with a small proportion (6%) of cases at stage III and 11.6% with metastatic tumours. Most participants had moderately or poorly differentiated tumours, and ER-positive, PR-positive and HER2-negative represented 80.5%, 68.1% and 78.3%, respectively, of all BC cases. A total of 158 cases were classified as triple negative cases (7.3%).

Correlations between inflammatory biomarkers

Overall, age- and batch-adjusted Spearman correlations showed positive correlations between biomarkers, except adiponectin (**Figure 1**). The highest positive correlation coefficients were observed between IL-6 and CRP ($r=0.46$), IL-17D and IL1-RA ($r=0.42$), CRP and leptin-to-adiponectin ratio (L:A ratio) ($r=0.40$), CRP and leptin ($r=0.39$), and TNF α and L:A ratio ($r=0.38$). Adiponectin showed the strongest inverse correlation coefficients, especially with TNF α , CRP, leptin, and IL-6 (r ranged between -0.12 and -0.29). BMI showed positive correlations especially with Leptin ($r=0.68$) and L:A ratio ($r=0.66$), CRP ($r=0.43$), and IL-1RA ($r=0.37$) and inflammatory diets according to ISD showed moderate-positive correlations with IL-17D ($r=0.07$), IFN- γ ($r=0.09$), L:A ratio ($r=0.13$), leptin ($r=0.14$), CRP ($r=0.14$), IL-6 ($r=0.16$).

Associations between inflammatory biomarkers and BC survival, overall and by menopausal status at diagnostic

HRs and 95% CIs for 1-SD increase in individual inflammatory biomarkers and inflammatory scores for overall and BC-specific mortality are listed in **Figure 2**. Elevated levels of IL-6 before diagnosis were associated with increased overall mortality (HR 1.25, 95%CI 1.07-1.47). Overall mortality was also associated with the composite inflammatory score without adipokines (HR 1.19, 95%CI 1.01-1.40). No statistically significant association was observed for BC-specific mortality among all BC cases. In separate analyses by menopausal status at diagnosis (**Figure 3**), among postmenopausal women, IL-6 was associated with overall mortality (HR 1.41, 95%CI 1.18-1.69; $P_{\text{Het pre/post}}=0.008$) and BC-specific mortality (HR 1.31,

95%CI 1.03-1.66; $P_{\text{Het pre/post}}=0.007$), while IL-10 and TNF- α were positively associated with a statistically significant 19-28% increased risk, respectively, with overall mortality only.

Associations between inflammatory biomarkers and BC survival by tumour characteristics, BC subtypes and lifestyle factors

Subgroup analyses for the main associations with the two outcomes of interest according to tumour characteristics are presented in **Table S1**. Among cases with non-metastatic tumors (stages I-III), IL-10 showed a positive association with overall mortality (HR_{1-SD} 1.32, 95% CI 1.09-1.59). This association was even stronger when restricted to early stages I-II (HR_{1-SD} 1.42, 95% CI 1.16-1.72). Moreover, elevated levels of IL-10 were found to be associated with a higher risk of overall mortality in cases with ER+PR+ tumors (HR_{1-SD} 1.35, 95% CI 1.10-1.65). Similarly, IL-10 was positively associated with BC-specific mortality among early stages I-II and ER+PR+ cases. Furthermore, TNF- α was associated with higher overall mortality among cases with HER2- tumors. All these results showed statistically significant heterogeneity between subgroups ($P_{\text{Heterogeneity}} < 0.05$).

We investigated the association between inflammatory biomarkers and mortality separately in women who developed triple negative breast cancer (TNBC) compared to other types of breast cancer (**Table S1**). When women who developed TNBC were excluded from the analyses, stronger associations between IL-6, IL-10, TNF- α , and inflammatory scores were observed with overall mortality. However, heterogeneity was not statistically significant comparing both groups (TNBC vs non-TNBC).

Furthermore, there were no statistically significant differences ($P_{\text{Heterogeneity}} > 0.05$) in the associations across subgroups of lifestyle factors, including BMI categories (<25 vs. ≥ 25), physical activity levels (inactive vs. active), and inflammatory diets (ISD Antiinflammatory vs. ISD proinflammatory) (**Table S2**).

Sensitivity analyses

When the inflammatory scores without IL-6 were analysed, the estimates, overall, were attenuated and no longer statistically significant, except among postmenopausal BC (**Table S3**). Additionally, when models were further adjusted for the time from blood collection to diagnosis, in categories below and above the median (9 years), the main findings remained consistent (**Table S4**). Excluding cases with a short time interval between blood collection and diagnosis (<6 years) yielded overall sustained results, although a new association emerged between IL-10 and overall mortality among all cases (**Table S5**). Another sensitivity analysis excluding BC cases with a survival time of less than 1 or 2 years after diagnosis, showed similar associations for overall mortality, including IL-6 among all cases, and IL-6, IL-10, TNF- α , and inflammatory scores among postmenopausal cases (**Table S6**). To account for the

potential influence of external hormonal factors, an analysis was performed exclusively among non-users of contraceptive pills or hormone replacement therapy. The results showed stable findings, particularly in relation to IL-6 and the inflammatory score without adipokines (**Table S7**). Finally, models excluding cancer grade and hormone receptor status variables showed consistency in the results, particularly regarding the association between IL-6 and all-cause mortality (**Table S8**).

Discussion

In this prospective cohort study, we observed that elevated pre-diagnosis levels of IL-6 were significantly associated with a 25% higher risk of overall mortality among BC patients, after adjusting for lifestyle factors, including BMI, and tumour characteristics. Additionally, a composite score integrating eight cytokines as a measure of generalized inflammatory state, showed a higher risk of overall mortality (19% for each 1-SD increase in the score). Among postmenopausal cases, positive associations were observed between IL-6, TNF- α , IL-10, inflammatory scores and all-cause mortality, and between IL-6 and BC-specific mortality.

Consistent with our results, previous studies has reported an association between elevated levels of IL-6 and poor prognosis in BC patients (13–15). In particular, research suggest that higher IL-6 concentrations are often found in advanced stages of breast carcinoma, and patients with elevated IL-6 levels tend to have a poorer response to chemotherapy and hormone therapy (13), indicating worse treatment tolerance. Other studies have also described an association between IL-6 and poor survival in patients with metastatic disease, also influenced by chemotherapy resistance (16–19). Interestingly, in our study, the positive associations with IL-6 and poor survival were also observed in nonmetastatic BC (stage I-III) without significant differences across stages. While a clinical trial with early-stage BC cases reported that high IL-6 expression was associated with improved BC-specific survival (20), this finding was not consistently reported by other studies included in a meta-analysis (15).

The role of IL-10 and TNF- α in BC prognosis has been limitedly investigated in epidemiological studies. Previous reviews, primarily comprising cell line studies, have suggested that TNF- α promotes invasive and malignant behaviour in BC cells, contributing to tumour growth, progression, and metastasis (14,21). Furthermore, TNF- α concentrations can increase in response to chemotherapy and radiotherapy, leading to therapeutic resistance and potentially promoting BC recurrence (21). With respect to IL-10, our study showed positive associations with poor prognosis, including overall and BC-specific mortality, among non-metastatic cases, and in ER+PR+ and HER2- tumours. This finding partly contradicts previous evidence, where higher levels of IL-10 correlated with metastatic BC (22,23). Although there is limited literature

available on this specific relationship, one possible hypothesis is that elevated levels of IL-10 in non-metastatic tumors may contribute to the subsequent transition to metastatic disease, ultimately resulting in poorer survival outcomes.

In previous epidemiological studies, the prognostic value of inflammation for BC survival has often been examined by assessing circulating levels of CRP. However, these studies have assessed CRP at different time points (i.e., at diagnosis or after diagnosis) relative to BC diagnosis, which may have contributed to the conflicting results observed among them (3–6,24). With respect to pre-diagnosis measurements, one study, based on a small sample size, reported an association between CRP levels and improved overall mortality (25). Conversely, a larger cohort study observed that higher CRP levels were associated with increased all-cause mortality, though they did account for BMI in their analyses (26). In our study, we found that the association between CRP and overall survival was positive and significant only when not accounting for BMI (data not shown), suggesting that BMI influenced this relationship. Moreover, despite that IL-6 is involved in CRP production (27), its association with BC survival seemed to be independent of BMI. This suggests that IL-6 may have more direct impact on tumour behaviour or interact with other factors relevant to BC progression, which are not solely influenced by BMI.

Many tumours are triggered by inflammatory responses, that result in the formation of an inflammatory microenvironment around the tumour promoting favourable conditions for tumour growth, invasion, metastasis, and resistance to chemotherapeutic drugs (14,28,29). However, the precise mechanisms through which chronic inflammation affects BC prognosis remain unclear. It is known that chronic inflammation is related with several prognostic factors such as body fatness, physical activity, and cardiovascular comorbidity. Moreover, elevated levels of IL-6 and TNF- α have been linked to systemic insulin resistance (30), which can potentially contribute to a worse prognosis in BC patients (31,32).

In our study, we observed that elevated levels of IL-6 were associated with poorer overall survival in cases with a BMI under 25, those physically inactive, and those consuming anti-inflammatory diets before BC diagnosis. Conversely, IL-10, TNF- α , and the inflammatory score based on cytokines showed statistically significant associations with overall mortality, among cases with a baseline BMI above 25. Although these associations showed no significant heterogeneity across groups, it is worth considering that the impact of these inflammatory markers on BC prognosis may vary depending on individual lifestyle factors.

Strength and limitations

Our study benefits from several strengths, primarily the use of a large European prospective cohort study. This enabled us to investigate the associations between pre-diagnostic inflammatory biomarkers and BC prognosis in a large number of BC cases and events (deaths). We were also able to analyze these associations according to menopausal status and status of hormone receptors, including triple negative tumors. In addition, we could account for several potential confounders in our models, including lifestyle factors, such as BMI, physical activity, reproductive factors, and tumor characteristics. The data also allowed us to evaluate the robustness of the associations performing models further adjusted by time from blood collection to diagnosis and, separately, excluding those cases with less than 1 to 2 years of survival after diagnosis. The main results remained stable and TNF- α appeared now positively associated with poor survival among all BC cases.

Our study also has a number of limitations. One is the lack of information on treatment, which is a strong determinant influencing prognosis and survival. To address this, we relied on the information on tumor stage, grade of tumor differentiation, and hormone receptor status, as a potential surrogates for treatment. These factors often determine the therapeutic approach in cancer patients. Second, the measurement of inflammatory biomarkers was performed only once, which makes the interpretation of our results more complex as many additional conditions can occur over time that impact long-term prognosis. Moreover, although most inflammatory markers have shown good reproducibility over time (33), relying on a single measurement may not fully capture potential variations in levels throughout the disease progression or in response to other factors. Third, measurements for IL-13 had a large number of values below LOQ and we had to dichotomize this biomarker into values higher or lower than the LOQ. Finally, we acknowledge that multiple subgroup analyses were performed in this study, emphasizing the importance of replicating these results in other studies before deriving firm conclusions.

Conclusions

This study suggests that IL-6 measured before diagnosis may play an important role in long-term prognosis among BC patients, even after adjustment for age at diagnosis, stage of tumor, and BMI. Among postmenopausal BC patients, pre-diagnostic IL-6, IL-10, TNF- α and the composite inflammatory scores are related with poor overall survival, and IL-6 also with BC-specific survival. These associations require further investigation, including follow-up measurements with a broader panel of inflammatory components. To gain a better understanding of the significance of IL-6 in relation to BC survival, and the role of IL-6, IL-10, and TNF- α among postmenopausal BC survivors, further research and analyses are necessary.

Data availability

For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at

https://login.research4life.org/tacsqr0epic_iarc_fr/access/index.php.

Author contributions

CCE and LD designed the study. CCE performed the statistical analyses. LD supervised the statistical analyses and design of the draft. LD, SR, AA, and MC supervised the main results. CCE drafted the manuscript. MC, ASN, CCD, CSA, AT, LM, FM, MH, GS, CC, RK, MBS, GM, CA, CS, MCB, MJS, PA, MDC, MG, KSB, AKH, SC, MG, SR, AA, LD contributed to the acquisition and interpretation of data and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare that they have no competing interests to disclose.

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IARC Disclaimer

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Tables and Figures

Table 1. Summary statistics of the included inflammatory biomarkers in the analyses.

Table 2. Descriptive statistics of the breast cancer survivors (N=1538) with available inflammatory biomarkers in the EPIC study.

Figure 1. Spearman correlations of log-transformed inflammatory biomarkers adjusted for laboratory batch and age at blood collection.

Figure 2. Associations between inflammatory biomarkers (per 1 SD increment) and all-cause and breast cancer-specific mortality among breast cancer cases with available inflammatory biomarkers in EPIC.

Figure 3. Associations between inflammatory biomarkers (per 1 SD increment) and all-cause and breast cancer-specific mortality according to menopausal status at diagnosis.

Table 1. Summary statistics of the included inflammatory biomarkers in the analyses (n=1538 breast cancer cases).

Biomarkers	units	n <LOQ*	Geometric mean (95% CI)	Missing values
IL-6	pg/mL	111	0.43 (0.42-0.45)	4
IL-8	pg/mL	0	2.70 (2.61-2.79)	4
IL-10	pg/mL	326	0.13 (0.13-0.14)	4
IL-13	pg/mL	1234	0.28 (0.28-0.29)	5
IL-17D	pg/mL	41	6.67 (6.47-6.87)	5
IL1-RA	pg/mL	0	159.46 (155.16-163.88)	5
IFN- γ	pg/mL	0	2.98 (2.88-3.09)	4
TNF- α	pg/mL	382	1.06 (1.03-1.08)	4
CRP	μ g/mL	0	1.12 (1.05-1.19)	1
Leptin	ng/mL	0	9.05 (8.65-9.47)	1
Adiponectin	μ g/mL	2	10.52 (10.25-10.79)	0

Table 2. Descriptive statistics of the breast cancer survivors (N=1538) with available inflammatory biomarkers in the EPIC study.

	N/mean	%/SD
Sociodemographic, lifestyle and reproductive factors		
Age at diagnosis (years)	61.4	8.3
Time from blood collection to diagnosis (years)	8.7	2.8
Level of school (N unknowns = 29)		
None/Primary	550	35.8
Technical/Professional	379	24.6
Secondary	259	16.8
Longer education	321	20.9
BMI		
Normal weight	762	49.5
Overweight	524	34.1
Obesity	236	15.3
Underweight	16	1.0
Physical activity (N unknowns = 8)		
Inactive	343	22.3
Moderately Inactive	566	36.8
Moderately Active	344	22.4
Active	277	18.0
Smoking status (N unknowns = 14)		
Never	870	56.6
Former	340	22.1
Current	314	20.4
Alcohol consumption (g/day)		
Non drinker	218	14.2
>0-3	416	27.0
>3-12	434	28.2
>12-24	269	17.5
>24	201	13.1
Menopausal status at diagnosis		
Premenopausal	366	23.8
Postmenopausal	1172	76.2
Use of contraceptive pill/hormones menopause at blood collection		
No	1058	68.8
Yes	480	31.2
Ever use of hormones for menopause at diagnosis (N unknowns = 23)		
No	589	50.3
Yes	560	47.3
Tumour characteristics		
Stage of tumour		
Stage I	399	25.9
Stage II	372	24.2
Stage III	93	6.0

Non-Metastatic unknown stage	347	22.6
Stage IV	178	11.6
Unknown	149	9.7
Grade of tumour		
Well differentiated	170	11.1
Moderately differentiated	535	34.8
Poorly differentiated/Undifferentiated	353	23.0
Not determined	480	31.2
Estrogen Receptor Status		
Negative	300	19.5
Positive	1238	80.5
Progesterone Receptor Status		
Negative	490	31.9
Positive	1048	68.1
HER2 status		
Negative	1205	78.3
Positive	333	21.7
Triple Negative subtype		
ER-PR-HER2-	112	7.3

Figure 1. Spearman correlations of log-transformed inflammatory biomarkers adjusted for laboratory batch and age at blood collection.

*Asterisks indicate non-statistically significant correlations ($p>0.05$).

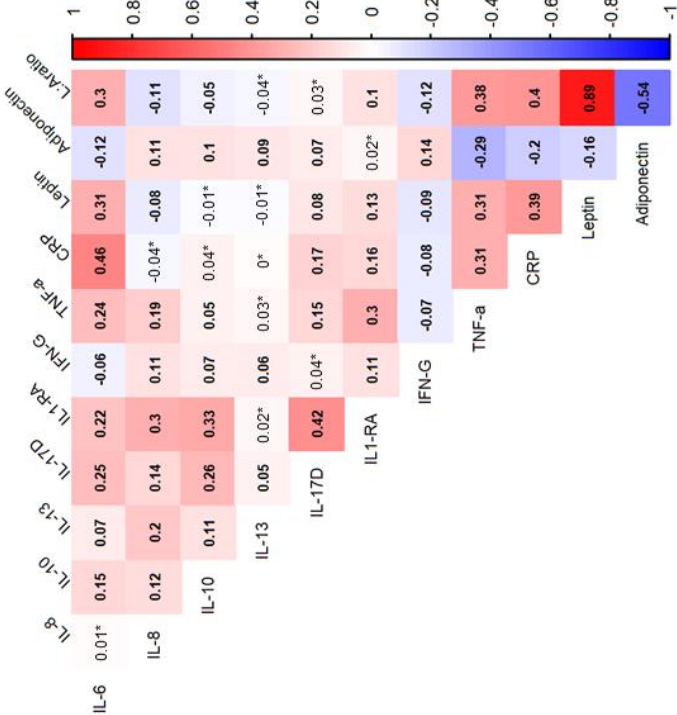
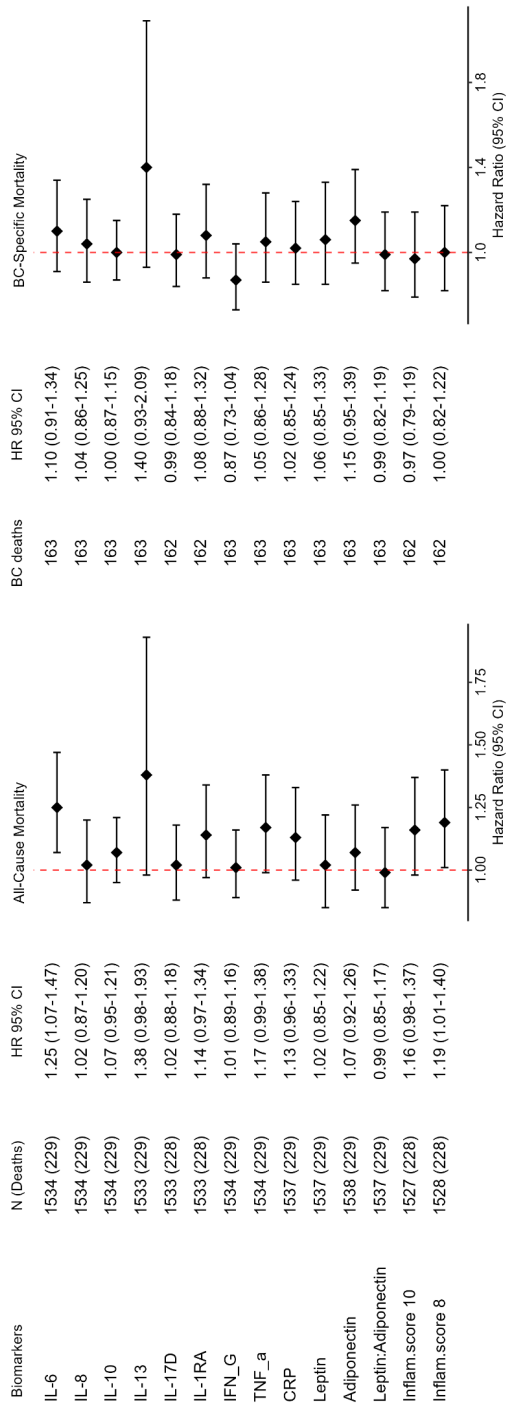


Figure 2. Associations between inflammatory biomarkers (per 1 SD increment) and all-cause and breast cancer-specific mortality among breast cancer cases with available inflammatory biomarkers in EPIC.

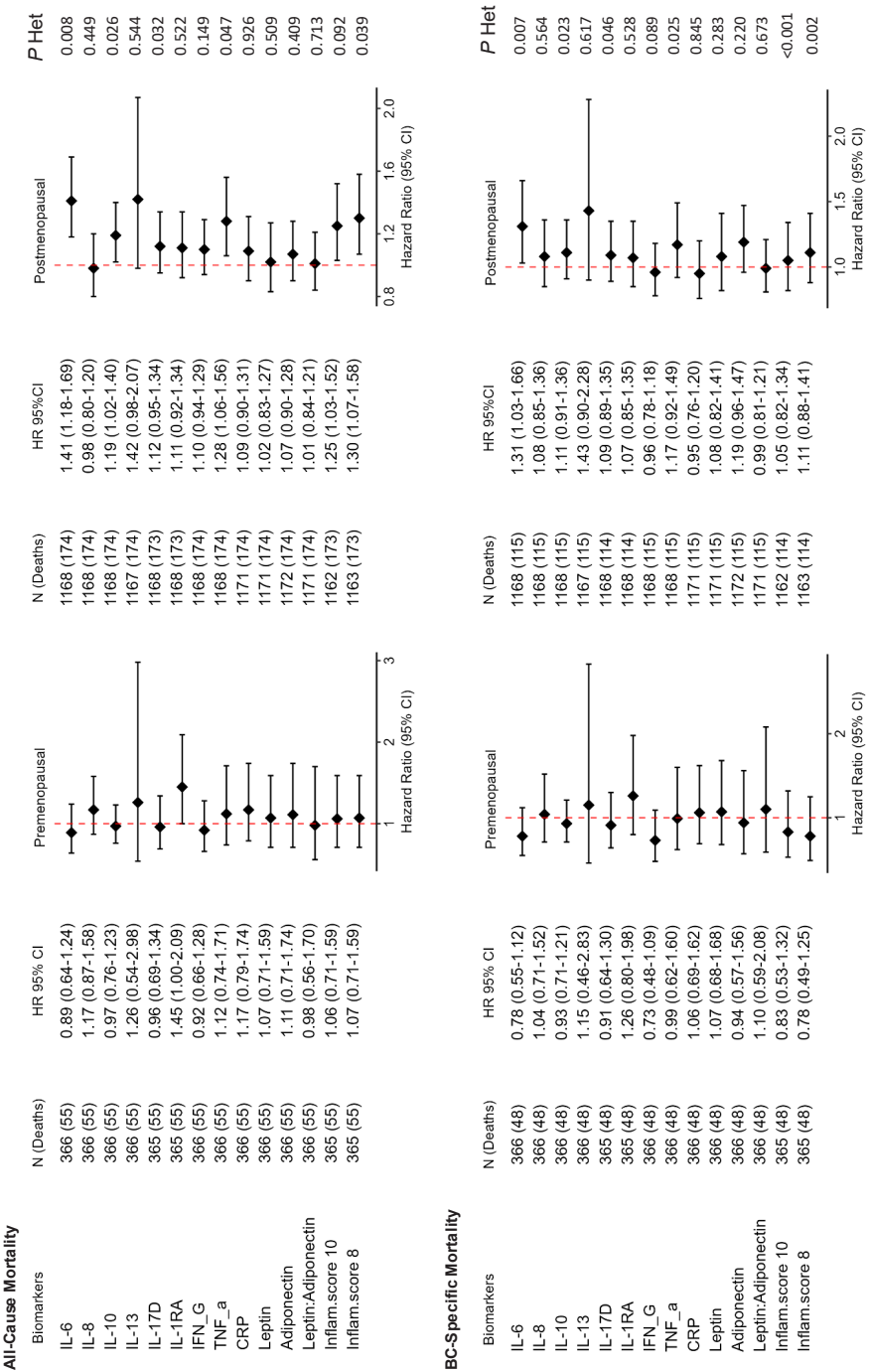


All individual biomarkers and scores have been assessed on a continuous scale, per 1 standard deviation (1-SD) increase (unless for IL-13, dichotomized based on values above and below the LOQ).

Models are stratified by country, menopausal status at diagnosis and stage of tumor (metastatic, non-metastatic, unknown), and adjusted for age at diagnosis, laboratory batch, fasting status at blood collection, education level, physical activity, body mass index, alcohol consumption, smoking status and intensity, ever use of hormones for menopause at diagnosis, cancer grade, and tumor receptor status (ER, PR, HER2).

The Inflammatory scores (Inflamm.score) are derived from log-transformed biomarker concentrations standardized using the mean and standard deviation of our population (z-score) of 1538 BC cases; the z-scores for adiponectin were multiplied by -1 to account for its anti-inflammatory effect. These z-scores are summed to generate an overall inflammatory score for each individual. The Inflammatory score-10 is composed of the following biomarkers: IL6, IL8, IL10, IL17D, IL-17A, IFN-γ, TNFα, CRP, Leptin, and Adiponectin; The Inflammatory score-8 includes the same components as the Inflammatory score-10, except for the adipokines Leptin and Adiponectin.

Figure 3. Associations between inflammatory biomarkers (per 1SD increment) and all-cause and breast cancer-specific mortality according to menopausal status.



All individual biomarkers and scores have been assessed on a continuous scale, per 1 standard deviation (1-SD) increase (unless for L1-13, dichotomized based on values above and below the LOQ).

Models are stratified by country, menopausal status at diagnosis and stage of tumor (metastatic, non-metastatic, unknown), and adjusted for age at diagnosis, laboratory batch, fasting status at blood collection, education level, physical activity, body mass index, alcohol consumption, smoking status and intensity, ever use of hormones for menopause at diagnosis, cancer grade, and tumor receptor status (ER, PR, HER2).

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ANNEXES

ANNEXES

ANNEX 1: DESCRIPTION OF THE EPIC STUDY

The European Prospective Investigation into Cancer and Nutrition (EPIC) study is a large prospective multicentre European cohort that recruited 519,978 participants, in 23 centres located in 10 European countries, between 1992 and 2000.



Figure 6. Map of the EPIC centres.

The main aim of EPIC is to prospectively investigate the aetiology of cancers at various sites, as well as other chronic disease, in relation to diet and lifestyle, from a plural perspective including the contrast in cancer rates and dietary habits between centres and countries. The EPIC study aims to increase the overall statistical power of identifying diet-disease relationships through combination of study populations with different types of diets and lifestyles and different incidence of cancer. The large size of the study allows to explore interactions between nutritional, genetic, hormonal and lifestyle factors.

Participants aged from 35 to 70 years, were overall general adult population but there were some exceptions: the French cohort was comprised by members of the health insurance for teachers; the Italian and Spanish cohorts included local blood donor associations; Utrecht and Florence included women invited for a local population-based breast cancer screening programme; In Oxford, half of the cohort were non-meat eaters, including vegans, lacto-ovo vegetarians and fish eaters.

Participants completed questionnaires on diet, lifestyle, and medical history at the time of recruitment. At baseline, anthropometric measurements and blood samples were also collected. The cohort participants were followed over time for the occurrence of cancer and other diseases, as well as for overall mortality, to allow incidence and mortality comparisons by exposure variables. All participants provided informed consent and EPIC was approved by the Ethics Committee of the International Agency for Research on Cancer (IARC), Lyon, France, as well as the local ethics committees of the study centres.

Dietary intake assessments

Different validated instruments have been used to assess dietary intake. Considering the local context, three dietary assessments methods were adopted: 1) Extensive self-administrated quantitative dietary questionnaires, structured by individual average portions or meals. In two centres, Spain and Ragusa, it was performed a face-to-face dietary interview using a computerised dietary program, and in France the dietary questionnaire

was self-reported. 2) Semi-quantitative food-frequency questionnaires with the same standard portions assigned to all subjects were used in Denmark, Norway, Naples, and Umea. 3) Combined dietary methods, semi-quantitative food-frequency questionnaire and 7-day record in the UK, and a short non-quantitative food-frequency questionnaire with a 14-day record on lunches and dinners in Malmö.

To calibrate dietary intakes across all sub-cohorts, additional dietary intake data was collected through 24-hour dietary recalls in representative sub-samples of 5-12% of participants in each sub-cohort. The calibration was done to improve the comparability of the dietary data across EPIC centres and to minimize measurement error (112).

Apart from diet, data on lifestyle and health factors were collected. The questionnaire included questions on education and socio-economic status, occupations, history of previous illness, history of tobacco smoking, alcohol consumption, physical activity, menstrual and reproductive history, use or exogenous hormones for contraception and menopause. Anthropometric measurements included weight, height, and waist and hip circumference from most EPIC centres. Blood samples were taken from plasma, serum, red cells and buffy coat fractions were separated and aliquoted for long-term storage, mostly in liquid nitrogen.

Follow-up and ascertainment of breast cancer

Incident cancer cases and vital status were identified through a record linkage to regional or national registries. France and Germany were an exception, where an active follow-up used a combination of cancer and pathology registries, health insurance records, and contacts with participants or their next-of-kin. Breast cancer cases were defined as tumours coded as C50.0-50.9 in the International Classification of Diseases for Oncology (ICD-O-2). In our studies, only primary malignant (invasive) tumours were considered; non-epithelial tumours or carcinoma in situ were excluded.

ANNEX 2: DESCRIPTION OF THE DIETARY PATTERNS USED IN THE THESIS AND ITS DERIVATION

Inflammatory score of diet (ISD)

The ISD measure the inflammatory potential of diet. The ISD takes the dietary inflammatory index (DII) as starting point (69), which comprises 45 dietary components, mainly nutrients. These components have been assigned an inflammatory weight derived of a literature review process according to the pro- or anti-inflammatory effect of food. We used the weights reported in Shivappa, et al., 2014 (69) based on the association of each component with six inflammatory biomarkers: IL-1 β , IL-4, IL-6, IL-10, TNF- α , and CRP.

The daily intake of each component included in the list of the ISD was calibrated, through 24-dietary recalls from the subsample of subjects, to improve comparability across EPIC centres and minimize measurement error. Sex- and country-specific calibration models were applied to obtain individual predicted values of intakes. Intakes from the 24-dietary recall were regressed on dietary intake from questionnaires, including total energy intake, age at recruitment, centre, education, smoking status, BMI, and physical activity in the model. These models were used to calculate predicted values (calibrated intake) of each food item. Then, a bootstrap sampling procedure was used to compute the mean and standard deviation of the predicted intakes for each food component. A total of 400 repetitions were used to ensure the stability of the estimates.

To calculate the individual ISD for each participant, the calibrated intakes of each dietary component were standardized using the mean and standard deviation of the EPIC population. Then, these z-scores were converted to percentiles scores to correct the right skewness of data, and then centred on 0 by doubling each percentile score and subtracting 1. The centred percentiles were then multiplied by the corresponding inflammatory weight obtaining a specific ISD for each component. Finally, these ISD are summed to produce an overall relative index for each participant.

The main difference between ISD and DII is that to calculate the subject's ISD, the individual intake of each food item was standardized using the mean and standard deviation of our study population, while the DII used the mean and standard deviation from a global regional database as the reference population (Shivappa et al. 2014). Finally, it is also worth noting that apart from those shown in the table we did not take into account two food items available in our dietary data that were included among the components of the original DII. First, total fat was not computed to calculate the ISD because the three components of dietary fat (saturated, monounsaturated, and polyunsaturated fat) are also included; hence, an inflammatory weight for total fat would overestimate the inflammatory potential of the diet. Second, we decided to calculate an ISD excluding alcohol. The negative relationship with inflammatory markers has been observed only among moderate alcohol consumers suggesting that the presence of other bioactive components in alcoholic beverages rather than ethanol itself may provide anti-inflammatory properties. On the other hand, alcohol is a well-established cause of breast cancer; if a protective effect of an anti-inflammatory diet is found, the recommendations for breast cancer prevention based on our results would never include the consumption of alcohol.

Table 1. Food items included in the Inflammatory Score of the Diet (ISD), and mean and standard deviation of daily intakes in the EPIC population.

Food parameters¹	Inflammatory effect score²	Daily mean intake	Standard deviation
Energy (kcal)	0.180	2063.7	430.5
Macronutrients			
Carbohydrate (g)	0.097	221.6	48.5
Protein (g)	0.021	81.8	18.4
Fibre (g)	-0.663	21.0	5.32
Fats (components)			
Saturated fat (g)	0.373	32.5	10.1
MUFA (g)	-0.009	30.9	9.37
PUFA (g)	-0.337	13.1	4.19
Cholesterol (mg)	0.110	308.2	106.6
Vitamins			
Vitamin A (RE) ³	-0.401	749.4	484.9
β-carotene (μg)	-0.584	2945.0	1526.0
Thiamin (mg)	-0.098	1.29	0.373
Riboflavin (mg)	-0.068	1.71	0.43
Vitamin B6 (mg)	-0.365	1.76	0.44
Folic acid (μg)	-0.190	273.7	64.8
Vitamin B12 (μg)	0.106	5.93	2.58
Vitamin C (mg)	-0.424	113.5	39.7
Vitamin D (μg)	-0.446	3.86	2.06
Vitamin E (mg)	-0.419	11.5	3.85
Minerals			
Fe (mg)	0.032	12.5	3.03
Mg (mg)	-0.484	351.0	72.0
Flavonoids			
Flavan-3-ol (mg)	-0.415	148.2	168.7
Flavones (mg)	-0.616	12.6	5.60
Flavonols (mg)	-0.467	44.1	32.8
Flavanones (mg)	-0.250	40.7	32.2
Anthocyanidins (mg)	-0.131	44.0	37.2
Isoflavonoids (mg)	-0.593	2.40	8.07

Table 1. Food items included in the Inflammatory Score of the Diet (ISD), and mean and standard deviation of daily intakes in the EPIC population. *Continuation.*

Food parameters ¹	Inflammatory effect score ²	Daily mean intake	Standard deviation
Foods			
Onion (g)	-0.301	10.6	8.55

⁽¹⁾ The following food parameters were also included in the original DII (*Shivappa et al. (69)(114)(114)*): caffeine, eugenol, ginger, fat (total), n-3 fatty acids, n-6 fatty acids, trans fat, garlic, ethanol, niacin, pepper, rosemary, saffron, selenium, turmeric, green/black tea, thyme/oregano, Zn.

⁽²⁾ Inflammatory effect score: reported as 'overall inflammatory effect score' (Table 2, *Shivappa et al. (69)*)

⁽³⁾ Retinol Equivalents: retinol + 1/6 β -carotene + 1/12 α -carotene.

Diabetes Risk Reduction Diet (DRRD) score

The DRRD score has been associated with a 40% lower risk of type 2 diabetes (independent of BMI). This is an a priori defined dietary pattern that include food groups and individual foods. The DRRD, developed by Rhee et al. (114) and further adapted by Kang et al. (115), includes 9 dietary components. Diet components are scored from one to five according to quintiles of intake. For components associated with a low risk of type 2 diabetes (cereal fibre, coffee (caffeinated and decaffeinated), nuts, ratio of polyunsaturated-saturated fats, whole fruits) the score assigned is from 1 to 5 from lower to higher adherence, and in descending order the components associated with high type 2 diabetes (glycemic index, trans-fat, sugar-sweetened beverages and fruit juices, and red and processed meat). The DRRD score was calculated as the sum of these quintile values with a final range from 9 (lowest adherence) to 45 (highest adherence), with higher scores indicating lower risk of T2D.

Intakes of the dietary components of the DRRD were expressed as food or nutrient density per 2000 kcal (intake in g/day, divided by the subject's energy intake and multiplied by 2000 kcal).

Table 2. Food items included in the Diabetes Risk Reduction Diet (DRRD) and mean intake and standard deviation values from women in EPIC study.

Food items ¹	Daily mean intake	Standard deviation	Q1	Q2	Q3	Q4	Q5
Cereal fiber, g/day	8,1	4,0	4,7	6,5	8,5	11,3	58,9
Coffee, ml/day	396,9	396,2	64,2	201,5	403,2	657,4	7249,2
Nuts, g/day	3,6	6,9	0,0	0,5	2,1	5,3	211,7
Whole fruits, g/day	243,3	173,2	106,4	172,8	247,0	355,2	2925,0
Polyunsaturated/saturated fat ratio	0,5	0,3	0,3	0,4	0,5	0,7	6,1
Glycemic index	60,2	17,6	45,7	53,5	61,5	72,8	199,5
Red and processed meat, g/day	67,1	40,9	32,5	54,7	74,2	98,7	563,9
Sugar-sweetened beverage/fruit juice intake, g/day	137,0	187,1	5,3	45,2	112,2	220,7	5133,9
Trans fat, g/day	1,8	1,5	0,6	1,1	1,6	2,7	19,9

⁽¹⁾Intakes of the dietary components expressed as food or nutrient density per 2000 kcal (intake in g/day, divided by the subject's energy intake and multiplied by 2000 kcal).

The ISD and DRRD scores are two dietary patterns that have shown an individual and combined impact on all-cause mortality and what these indices represent in terms of food intake is presented in **Table 3**.

Table 3. Adjusted mean intakes (g/day) of the main food groups in the EPIC questionnaires based on combined categories of ISD and DRRD scores

	Mean (95%CI) ¹		P value
	Low IR/ Anti-inflammatory diet	High IR/ Pro-inflammatory diet	
	(High DRRD - low ISD)	(Low DRRD - high ISD)	
Potatoes and other tubers	87.8 (82.4-93.2)	96.2 (91.0-101.5)	<0.001
Vegetables	246.2 (236-256.4)	141.1 (131.2-151)	<0.001
Leafy vegetables	33.2 (30.4-35.9)	18.9 (16.3-21.6)	<0.001
Fruiting vegetables	72.7 (68.4-77.1)	46.8 (42.5-51)	<0.001
Root vegetables	35.6 (32.7-38.5)	15.3 (12.5-18.1)	<0.001
Cabbages	33.5 (30.7-36.4)	21.6 (18.9-24.4)	<0.001
Onion, garlic	13.0 (12.0-13.9)	9.0 (8.1-10.0)	<0.001
Legumes	15.2 (13.5-16.9)	11.7 (10.1-13.4)	<0.001
Fruits	308.2 (294.0-322.3)	135.2 (121.4-148.9)	<0.001
Fruits	299.3 (285.2-313.5)	129.9 (116.2-143.7)	<0.001
Nuts and seeds	5.1 (4.3-5.8)	2.6 (1.8-3.4)	<0.001
Dairy products	304.9 (285.3-324.5)	312.5 (293.5-331.6)	0.172
Milk	153.6 (136.5-170.7)	173 (156.4-189.7)	<0.001
Yogurt	74.0 (66.3-81.7)	54.6 (47.1-62)	<0.001
Cheese	32.2 (29.5-34.9)	37.4 (34.8-40.1)	<0.001
Cereals and cereals products	215.5 (208.0-223.0)	193.9 (186.7-201.2)	<0.001
Pasta, rice, other grains	59.6 (55.4-63.8)	55.3 (51.2-59.5)	<0.001
Bread, crispbread, rusks	128.7 (123.4-134)	119.1 (113.9-124.3)	<0.001
Non-white bread	72.1 (67.6-76.6)	52.2 (47.8-56.6)	<0.001
Meat and meat products	75.2 (71-79.3)	103 (99-107)	<0.001
Fresh meat	28.4 (25.8-31.1)	45.7 (43.2-48.3)	<0.001
Processed meat	24.9 (23.0-26.8)	36.5 (34.7-38.4)	<0.001
Fish and shellfish	44.7 (41.9-47.5)	36.1 (33.4-38.8)	<0.001
Fish	35.2 (32.8-37.6)	27.7 (25.3-30)	<0.001
Eggs and egg products	17.6 (16.1-19.2)	18.3 (16.8-19.8)	0.146
Fat	24.8 (23.7-26)	28.3 (27.2-29.4)	<0.001
Vegetable Oils	9.7 (9.1-10.2)	7.3 (6.8-7.8)	<0.001
Butter	2.6 (1.8-3.3)	6.3 (5.6-7)	<0.001
Margarine	10.5 (9.5-11.5)	12.3 (11.3-13.3)	<0.001
Sugar and confectionery	29 (26.3-31.7)	41 (38.4-43.7)	<0.001
Cakes	30.9 (27.7-34.1)	45.9 (42.8-49)	<0.001
Non-alcoholic beverages	1226.4 (1174.1-1278.7)	1018 (967.2-1068.9)	<0.001
Fruit And Vegetable Juices	74.5 (66-82.9)	61.5 (53.2-69.7)	<0.001
Carbonated/Soft/Isotonic drinks	57.5 (43.6-71.5)	101.7 (88.2-115.3)	<0.001
Coffee, Tea And Herbal Teas	743.1 (708.2-778)	596.1 (562.3-630)	<0.001
Alcoholic beverages	165.3 (155.9-174.7)	177.4 (168.2-186.5)	<0.001

Abbreviations: IR, insulin resistance; DRRD, Diabetes risk reduction diet; ISD, Inflammatory score of diet.

⁽¹⁾To predict the mean intakes according to low-IR/Anti-inflammatory diets (equivalent to high-DRRD-low-ISD) and high-IR/Pro-inflammatory diets (low-DRRD-high-ISD), multiple regression models have been performed. The explanatory variables included in the models were energy, country, menopausal status at diagnosis, age at diagnosis, educational attainment, physical activity, BMI, alcohol consumption, smoking habit and intensity at recruitment, ever use of menopausal hormone at diagnosis, cancer stage at diagnosis, tumour grade and hormone receptor status (ER, PR, HER2). To dichotomise these dietary patterns the median as cut-off points were used.

The foods most represented by diets with lower risk of insulin resistance and anti-inflammatory capacity were vegetables, legumes, fruits, nuts and seeds, yogurt, non-white bread, fish and shellfish, fruit and vegetable juices, coffee, and tea. On the contrary, the group of foods that represent a higher risk for insulin resistance and pro-inflammatory diets includes milk, cheese, fresh and processed meat, butter, sugar and confectionery, cakes and alcoholic beverages.

Estrogen-related dietary pattern (ERDP)

The ERDP is a data-driven index based on the association with oestrogen metabolites hypothesized to be associated with risk of breast cancer (73). The rationale behind this is based on the evidence that 2-hydroxylation of the parent oestrogens is inversely associated, and 16-hydroxylation is positively associated with postmenopausal breast cancer. Therefore, increases in the ratio of 2- to 16-hydroxylated EMs is hypothesized to indicate a beneficial shift in oestrogen metabolism with respect to breast cancer risk. In addition to that, there is established evidence linking unconjugated oestradiol (E2) to postmenopausal breast cancer risk. To develop the ERDP RRR was used a dietary pattern associated with circulating E2 and 2/16 from serum samples of a subsample of Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO).

To calculate the ERDP with EPIC data, we used the weights as reported in reference (73) for a total of 11 food items included in the original pattern and available in the EPIC databases. Positively weighted intakes were assigned to refined grains, tomatoes, cruciferous vegetables, cheese, fish/shellfish high in ω -3 fatty acids, processed meats, and negatively weighted intakes were assigned to nuts/seeds, other vegetables, fish/shellfish low in ω -3 fatty acids, yogurt, and coffee. Adherence to the ERDP score ranged from -1.8 (lowest adherence) and 1.2 (highest adherence).

Table 4. Food items included in the estrogen-related dietary pattern (ERDP), and mean intake and standard deviation values from women in EPIC study.

Food items ¹	Weight ²	Daily mean intake	Standard deviation
Fish high in w-3 fatty acids	0.2	39.9	47.4
Cheese	0.16	37.5	29.3
Refined grains	0.12	138.7	83.2
Cruciferous vegetables	0.08	30.4	41.1
Processed meat	0.08	29.0	24.2
Tomatoes	0.09	25.3	35.1
Coffee	-0.1	396.9	396.2
Nuts and seeds	-0.11	3.6	6.9
Yogurt	-0.12	61.7	85.6
Other vegetables	-0.13	66.6	57.9
Fish low in w-3 fatty acids	-0.27	36.7	38.4

⁽¹⁾Intakes of the dietary components expressed as food or nutrient density per 2000 kcal (intake in g/day, divided by the subject's energy intake and multiplied by 2000 kcal).

⁽²⁾Model weights from final RRR (reduced rank regression) model used for ERDP scoring from Table 1 in the reference (24).

Adapted relative Mediterranean diet (arMED)

The arMED score is one of the indexes developed to measure adherence to the Mediterranean diet. First developed by Trichopoulou A, et al., (116), adherence to the traditional Mediterranean diet was assessed by a 10-point scale that included characteristics of this diet (higher scores indicated greater adherence) on which a value of 0 or 1 was assigned, depending on whether the intake of each food was below or at or above the median. We used an adapted version excluding alcoholic beverages to be a risk factor of breast cancer, and moreover, including olive oil instead of monounsaturated fats. In this adapted version the score consists of a 16-point scale that includes eight key components of the Mediterranean diet. A score from 0 to 2 was assigned to tertiles of intake of items that were presumed to be more or less

in accordance with the Mediterranean diet. Fruits (including nuts and seeds), vegetables (excluding potatoes), legumes, fish and cereals received scores from 0 to 2 according to lower or higher intake, respectively, and meat (red meat and processed meat) and dairy products, which were assumed not to fit the dietary pattern, received scores from 2 to 0 according to lower to higher intake, respectively. For olive oil, the score was adapted and a score of 0 was assigned to non-consumers, 1 to participants below the median (calculated among consumers), and 2 to participants at or above the median. The total arMED score ranged from 0 to 16 and higher scores indicated greater adherence to the Mediterranean diet.

CHAPTER V

DISCUSSION

CHAPTER V. DISCUSSION

Key findings

In the EPIC cohort, the data analysed provided elements indicating that consuming pro-inflammatory diets may exert a detrimental influence on both breast cancer risk and survival. Moreover, this study identified an association between the consumption of diets associated with a lower risk of type 2 diabetes and adherence to the Mediterranean diet before diagnosis and improved overall survival among breast cancer survivors. Beyond dietary factors, we explored the significance of pre-diagnostic circulating inflammatory biomarkers in predicting survival outcomes. Elevated levels of IL-6 emerged as a particularly robust predictor of poor survival reflected by both overall and breast cancer-specific mortality. Furthermore, our findings indicated that higher levels of IL-6, IL-10, and TNF α were associated with an increased risk of all-cause mortality among postmenopausal breast cancer survivors. A graphical representation of this key findings is shown in **Figure 7**.

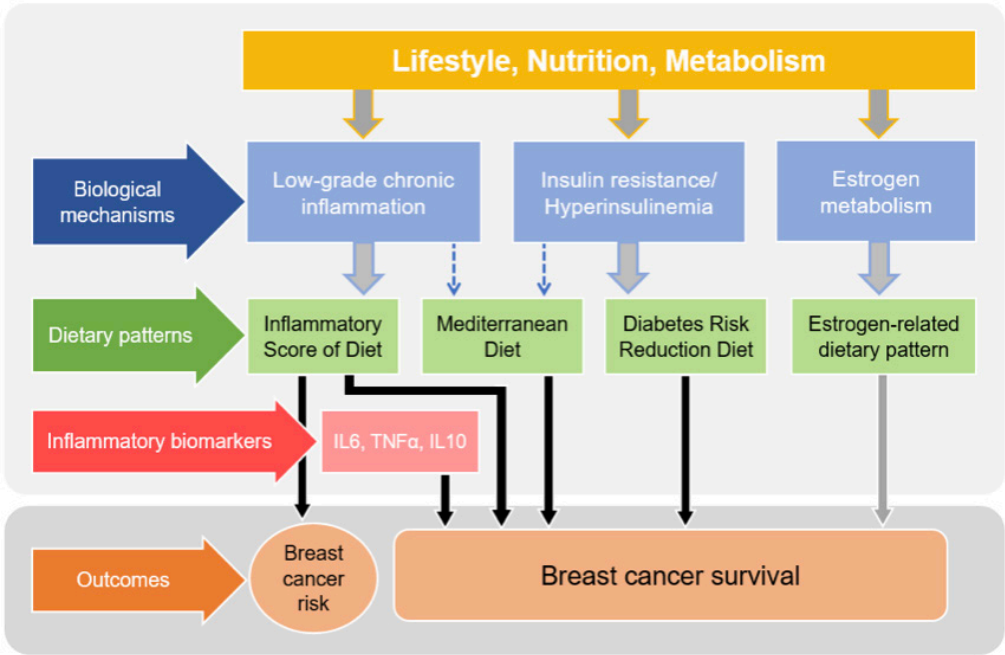


Figure 7. Diagram of the main aspects and associations that the thesis comprises.

This diagram represents the capacity of diet to regulate or modify biological mechanisms linked to breast carcinogenesis, as well as its potential to modify disease progression and prognosis. The vertical black arrows represent the statistically significant associations between dietary patterns or circulating biomarkers with breast cancer outcomes, while the gray arrow indicates no significant associations.

The approach of dietary patterns related to biological mechanisms

The approach of investigating dietary patterns, as employed in dietary pattern research, is relatively recent but holds immense promise. This methodology offers a valuable examination of the relationship and interaction of different dietary factors and their impact on cancer. Moreover, investigating diet as a whole can yield more robust effect estimates, facilitating the translation of results into dietary guidelines.

The dietary patterns examined in this thesis were selected for their association with biological markers or processes related to breast carcinogenesis. These associations likely result from the combined biological effects of various dietary components. Among the interrelated biological mechanisms influenced by specific dietary patterns, this thesis focuses on three key factors: low-grade chronic inflammation, hyperinsulinemia and insulin resistance, and abnormalities in sex hormones, particularly oestrogen metabolism. These comprehensive scores consider both an individual's dietary habits and the collective impact of various dietary factors on specific biological processes, rather than isolating specific nutrients or food items.

In alignment with our hypotheses, diet appears to significantly impact both the risk and prognosis of breast cancer through specific dietary patterns, with more evidence for pro-inflammatory diets, as well as low-risk diets for diabetes, and the Mediterranean diet with respect to improved survival. In contrast, no association was found between breast cancer prognosis and an oestrogen-related dietary pattern.

The role of pro-inflammatory diets on breast cancer risk

The results of our research on the influence of pro-inflammatory diets on breast cancer risk and survival agree with some studies in the existing literature. In general, studies have mainly focused on investigating the relationship between pro-inflammatory diets and breast cancer risk, although reaching conflicting results. In contrast, there is a limited body of research examining the connection between pro-inflammatory diets and breast cancer prognosis.

A common aspect in this field is the frequent use of the Dietary Inflammatory Index (DII) (69), including various versions of this score, to assess the inflammatory potential of the diet. A meta-analysis that included eleven cohort studies using the DII did not identify a statistically significant association with breast cancer risk (98). Conversely, a recently published French cohort study reported findings similar to ours, showing a positive association between the DII and breast cancer risk (99). Notably, this French

study adopted a methodology similar to ours to derive its DII: the intakes of each component were standardized using the mean and standard deviation of the study population, instead of relying on a worldwide database as a reference population used in the original version of the DII.

The ISD showed a stronger association with the risk of premenopausal breast cancer, although statistically speaking, our findings suggested that the inflammatory potential of diet on breast cancer may be independent of menopausal status. This last conclusion was also reached in a recent study (99). However, a number of previous studies found disparities in results regarding menopausal status: mostly prospective cohort studies supported the existing association among postmenopausal women (100,101). Further investigations are needed to clarify the evidence concerning the association between inflammatory potential of diet and risk of breast cancer based on menopausal status.

Mechanistic and traditional dietary patterns and breast cancer survival

In relation to the inflammatory potential of the diet previous studies have primarily relied on the DII and assessed diet post-diagnosis in breast cancer cases. In contrast, we used the ISD which was calculated from dietary information collected prior to diagnosis. Out of the three prospective studies examining this association (92,102,103), only one (102), has identified a significant relationship with overall mortality. Although our study initially found a borderline association between pro-inflammatory diets and overall mortality, this association strengthened when we restricted our analysis to post-menopausal cases, with confidence intervals becoming statistically significant. In this line, this study (102), not only identified positive associations for overall mortality but also specifically for breast cancer-related mortality. Moreover, it exclusively focused on post-menopausal breast cancer patients, even though dietary supplements were included in the DII (102).

Beyond the impact on the individual's nutritional status or tolerance to treatment, which will directly impact prognosis, diet can also influence prognosis by modulating the risk of developing chronic diseases or comorbidities that may arise during or after breast cancer diagnosis.

«Unhealthy» dietary patterns are associated with an increased risk of breast cancer, and individuals with comorbidities already have an increased risk of mortality. A common mechanism underpinning these relationships is low-grade chronic inflammation, which can manifest in various conditions beyond cancer, including stress, obesity, and sedentary lifestyles.

One of the key findings of our this thesis is the lower mortality related to consumption of diets associated with a lower risk of type 2 diabetes, assumed to act through reduction of insulin resistance. The findings associated with this dietary pattern align, and also are consistent when we combine low-insulin resistance and anti-inflammatory diets, based on higher and lower adherence to the DRRD and ISD respectively.

Although the Mediterranean dietary pattern is defined by a cultural way of eating believed to be healthy, share some dietary components in common with the DRRD score. In particular, the arMED and the DRRD scores include both cereals, fruits, nuts, and a detrimental weight from meat intake (including red and processed). One can hypothesize that the Mediterranean diet might exert an even more profound influence on biological mechanisms, given that it reflects a longstanding cultural dietary tradition.

The favourable impact of the Mediterranean Diet on health, as observed in previous studies (104), is believed to be due to several mechanisms, such as weight control, its antioxidant potential, its ability to improve glycaemic profiles, and its anti-inflammatory properties (105,106). However, research on the relationship between Mediterranean diet and these mechanisms in relation to breast cancer prognosis is limited. In our studies, we investigated the impact of arMED score independent to the effect of adherence to mechanistic patterns (DRRD, ISD), and our findings revealed that the initial association between arMED score and mortality was attenuated. This suggests that, to some extent, the beneficial effects of the Mediterranean Diet may be explained by mechanisms related to inflammation, insulin resistance or hyperinsulinemia.

There are other features concerning the relationship between Mediterranean Diet and mortality worth noting. First, despite the inverse association for a lower risk of all-cause mortality was observed with the

arMED score modelled continuously, when comparing high versus medium adherence, the association did not reach statistical significance. In other words, it seems that the detrimental effect of a lower adherence is more relevant than the beneficial effect of a higher adherence. On the other hand, metastatic breast cancer survivors seemed to benefit more from adherence to the Mediterranean Diet when assessed than non-metastatic survivors, with a statistically significant reduced risk of overall mortality and breast cancer specific mortality; however, we do not have a clear interpretation for these results.

Dietary patterns and breast cancer survival according to menopausal status and hormone receptor status

In our studies, the associations between dietary patterns and risk of all-cause mortality risk remained consistent among postmenopausal survivors, including pro-inflammatory diets, low-risk diets for diabetes, and the Mediterranean diet. However, it is important to note that there is no previous consistent evidence regarding the influence of diet on breast cancer outcomes stratified by menopausal status (41). Besides, a majority of studies have primarily focused on postmenopausal breast cancer survivors (46).

Other factors related to the type of tumour that might be influenced by dietary habits are hormone receptor status. In our case, we were unable to establish a clear association between dietary patterns and breast cancer risk or survival according to this stratification. Our analysis did not reveal any significant variation in the impact of the dietary patterns on breast cancer survival, and additionally, we found no substantial differences in the association between dietary patterns and breast cancer risk or survival among cases with different combinations of hormone receptors status in terms of ER, PR, and HER2. These findings align with previous studies, which emphasized the necessity for further experimental and epidemiological investigations to reach a consensus on the associations between diet and breast cancer subtypes (102).

Dietary patterns and inflammatory biomarkers

The potential role of chronic inflammation in breast cancer death is supported by evidence from studies on the association between inflammatory biomarkers and breast cancer mortality. In particular, elevated levels of IL-6, TNF α , and CRP have been associated with higher risk of breast cancer mortality (107,108). Moreover, previous epidemiological studies summarized in two systematic reviews (109,110), have reported inverse associations between healthy dietary patterns, including the Mediterranean Diet, and inflammatory cytokines, and, on the contrary, positive associations with «Western-like» patterns. One of the reviews included cross-sectional designs and a few intervention studies, but no prospective observational studies (109). Both reviews predominantly reported associations between dietary patterns and CRP levels. Among *a posteriori*-defined dietary patterns using PCA or factor analysis, overall dietary patterns that were positively associated with CRP levels were characterized by red meat, processed meat, and beer. Instead, negative loadings came from intake of fruit, vegetables, and whole-grain products. Evidence from *a priori* dietary patterns, which allows for a better comparison, found inverse associations with CRP but also other inflammatory biomarkers. In particular, most studies focused on Mediterranean diets concluded that these patterns may help lower low-grade chronic inflammation.

The growing body of research exploring dietary patterns in relation to inflammatory biomarkers indicates a promising avenue for understanding the interplay between diet and inflammation. A recent meta-analysis of RCTs provides data demonstrating that Mediterranean diet, among other dietary patterns, showed the most prominent reductions in inflammatory biomarkers such as IL-6 and CRP (111).

Strengths and limitations

The studies included in this thesis come with certain limitations that warrant consideration. Firstly, as the dietary patterns were derived from self-reported dietary questionnaires, despite the exclusion of participants

with extreme energy intakes, it is important to acknowledge the possibility of some degree of measurement error that could influence the accuracy of exposure classification. However, it is noteworthy that this error is nondifferential concerning the incidence of the disease and mortality, since dietary data was collected prior to the diagnosis of cancer.

Additionally, dietary information was captured only once at the time of recruitment. In this regard, although dietary habits may have changed after breast cancer diagnosis, our findings indicate that women who adhered to specific dietary patterns prior to their diagnosis may have greater chance of a favourable prognosis after breast cancer diagnosis compared to those who did not. Besides, while repeated dietary assessments offer the advantage of tracking dietary changes over time, we must take into account the latent period of the disease. When diet is assessed prior to the interval between the initiation of cancer and its diagnosis, it becomes more likely that the dietary information corresponds to the etiological time window we assumed to precede the onset of the disease. In this regard, we conducted sensitivity analyses for survival models across various time periods, ranging from the time of diet measurement to the time of diagnosis. We also incorporated this time from diet measurement to diagnosis as a continuous variable in the models. These analyses consistently indicated that overall adherence to dietary patterns likely remained relatively stable, and hence the estimates remained largely unchanged over these different time intervals.

Similarly, the measurement of inflammatory biomarkers was conducted only once, introducing some complexity into the interpretation of our results. Over time, numerous additional conditions may arise that can influence long-term prognosis. Relying on a single measurement may not fully capture potential fluctuations in biomarker levels throughout the progression of the disease or in response to various factors.

Another important limitation in our investigation of breast cancer prognosis outcomes within the EPIC study is the lack of information on the specific treatments received by breast cancer patients. Treatment is a strong determinant of prognosis and survival. We attempted to mitigate this limitation, at least in part, by including data on tumour stage at diagnosis,

degree of tumour differentiation, and hormone receptor status in all models. These factors often guide the therapeutic strategy selection in these individuals.

In addition, we explored the possibility that patients with older diagnoses might show a worse prognosis compared to more recently diagnosed patients, potentially due to advances in treatment over time. Nevertheless, our sensitivity analyses performed over different time periods consistently yielded similar effect estimates.

The investigations conducted within the framework of the EPIC study boast several strengths. These strengths stem from the prospective design and its large sample size, allowing sufficient statistical power, including the possibility to perform subgroup analyses. In the context of breast cancer research, the EPIC study recognizes the crucial importance of distinguishing between tumour subtypes based on hormone receptor status and considering menopausal status when analysing outcomes. Furthermore, the large number of breast cancer survivors and events (deaths) enabled the investigation of the hypotheses related to breast cancer survival.

Finally, to derive the dietary patterns, the EPIC study benefits from the availability of dietary components included in these scores which, in turn, capture the main food groups and dietary habits consumed by the European population. The inclusion of multiple countries allows for a broad representation, including different degrees of adherence to these dietary patterns, with enough participants in each category of adherence.

Clinical implications

While substantial progress has been achieved in recent years in treating breast cancer, it remains one of the most common cancers with high mortality in women worldwide.

Our findings may contribute to the development of personalized dietary recommendations for individuals at risk of breast cancer or those currently with a diagnosis of this disease. Understanding how specific dietary patterns impact biological mechanisms can help create customized nutritional

strategies to reduce the risk of developing breast cancer or enhance treatment (or post-treatment) outcomes. Moreover, identifying dietary patterns linked to reduced breast cancer risk can contribute to improved prevention strategies. Public health initiatives can promote these dietary changes to reduce the overall incidence of breast cancer, especially in high-risk populations. For individuals already diagnosed with breast cancer, insights into dietary patterns associated with better survival outcomes could be integrated into their treatment plans. Dietary modifications may complement traditional therapies, potentially improving treatment effectiveness and overall prognosis, especially from a preventive perspective before breast cancer diagnosis.

Healthcare professionals can use this knowledge to advise breast cancer patients about the importance of dietary choices and maintaining these dietary habits long-term (when possible, considering treatment symptoms). Empowering patients with information on how diet influences biological mechanisms and survival can encourage healthier eating habits.

Since the design of clinical trials is not always feasible and costly, dietary patterns can be derived based on the information collected through food frequency dietary questionnaires. Importantly, applying this approach to studies involving breast cancer survivors could provide valuable insights into the relatively unexplored area of dietary recommendations tailored specifically for this group.

Understanding the mechanisms by which inflammatory mediators promote breast cancer may provide insights on the potential effects of anti-inflammatory drugs in treating breast cancer, and eventually lead to novel therapeutic strategies to treat this disease.

Chemotherapy or radiation therapy, often combined with breast-conserving surgery or mastectomy, constitute standard treatments for all types of breast cancer. While these interventions provide improved survival rates, the challenge of tumour recurrence due to resistance to chemotherapy and radiotherapy persists as a significant clinical problem in the effective management of breast cancer. Understanding how dietary patterns may impact biological mechanisms associated with treatment resistance can

guide the development of strategies to mitigate or overcome this resistance, potentially leading to more effective therapies. Some markers of inflammation such as IL-6 or TNF α , are not only closely involved in breast cancer onset, progression, and metastasis, but they also participate in favouring therapy resistance (i.e., TNF α induces resistance to chemotherapy or radiotherapy through NF- κ B (108)).

Futures perspectives

After conducting extensive research into the role of diet in breast cancer risk and prognosis using data from a large prospective cohort study, the next phase involves examining various lifestyle factors, including diet, in relation to breast cancer prognosis, moving from the observational to the experimental setting. Within the same team, we are involved in a clinical trial including women diagnosed of non-metastatic breast cancer. Approximately half of these women (randomly selected) followed a one-year diet and exercise intervention, while the other half (the control group) followed the usual recommendations established at their centre. Comprehensive data, including clinical information, dietary habits, physical activity levels, and quality of life, as well as measurements of body composition, and blood samples were collected at the study's recruitment and after one year of follow-up. The main aim of this trial is to assess whether the intervention is able to reduce the risk of recurrence and the disease-free survival at 5 years. However, in the short-term (one year) we will assess whether women who followed the intervention have improved their diet, their level of physical activity and quality of life, and have controlled their weight.

Specifically, we anticipate that this intervention can modify various factors related to the intervention itself (such as diet and physical activity) as well as short-term outcomes (such as weight control and quality of life). Consequently, following the evaluation of pre-diagnostic dietary patterns related to underlying mechanisms linking nutritional factors and breast cancer in the EPIC study, the next step will be to assess whether a one-year diet and exercise intervention among breast cancer survivors can effectively alter these dietary patterns and, in turn, influence prognostic outcomes.

In addition to examining dietary patterns, our future research steps include broader aspects related to molecular epidemiology. Beyond inflammatory biomarkers, we intend to explore other markers associated with mechanisms affecting breast cancer prognosis potentially modifiable by lifestyle factors within the framework of the clinical trial.

In the context of the EPIC study, conducting a mediation analysis with biomarkers in the context of dietary patterns and breast cancer can provide valuable insights into the mechanistic pathways. This analysis not only leads to targeted interventions but also enriches our comprehension of this intricate relationship, potentially contributing to advancements in breast cancer prevention and treatment, which may ultimately lead to improved outcomes.

Furthermore, mediation will help to validate the observed associations with dietary patterns and quantify the extent to which the relationship between pre-diagnostic dietary patterns and breast cancer prognosis is mediated by changes in inflammation biomarker levels. With this, we aim to shed light on the intricate interplay between diet and cancer. If certain biomarkers are found to mediate the dietary-breast cancer relationship, tailored interventions can be designed to target these specific biological pathways. This can potentially lead to more effective preventive and therapeutic strategies.

CONCLUSIONS

CONCLUSIONS

In summary, our study underscores the significant impact of diet and inflammation on both breast cancer risk and survival. Pro-inflammatory diets are identified as potential risk factors, while specific dietary patterns, primarily those linked not only to inflammation but also to mechanisms of insulin resistance, hyperinsulinemia, and the traditional Mediterranean diet, present valuable opportunities for intervention and prognosis. Furthermore, the assessment of certain inflammatory biomarkers before diagnosis may serve as relevant predictors of prognosis.

These perspectives advocate for a comprehensive approach to breast cancer care, emphasizing the importance of addressing nutrition and inflammation as integrated components to further improve outcomes for breast cancer patients. In summary, the exploration of dietary patterns related to biological mechanisms offers a promising approach for understanding the intricate connections between diet and breast cancer, providing valuable insights for both research and public health guidelines.

The main conclusions are:

- 1) Consumption of more pro-inflammatory diets may represent a modest risk factor for breast cancer development; this effect seems to be limited to premenopausal women.
- 2) Consumption of more pro-inflammatory diets before breast cancer diagnosis may represent a factor for poor prognosis, especially among postmenopausal women.
- 3) Adherence to diets associated to a reduced risk of type 2 diabetes prior to a breast cancer diagnosis, primarily operating through mechanisms related to insulin resistance, may significantly contribute to improving overall survival for breast cancer patients. Specifically, when comparing the highest and lowest levels of adherence to these diets, the difference in overall survival is indeed substantial.

- 4) Higher adherence to the traditional Mediterranean diet before diagnosis, with exclusion of alcohol, may improve long-term prognosis, especially among postmenopausal breast cancer survivors. Overall, improving adherence from low to medium seems to be more beneficial than achieving a high adherence to the pattern. Moreover, the protective effect of Mediterranean diet appears to be stronger in women diagnosed with metastatic breast cancer tumours.
- 5) The associations between breast cancer prognosis and dietary patterns related to inflammation, insulin resistance, as well as the Mediterranean diet, seemed to not largely differ according to hormone receptor status.
- 6) High levels of IL-6 before a breast cancer diagnosis could serve as a significant prognostic marker for long-term survival in breast cancer survivors. A more pronounced state of inflammation, indicated by a higher inflammatory score and particularly elevated levels of IL-6, IL-10, and TNF α , appears to be particularly relevant among postmenopausal women, predicting a higher risk of all-cause mortality. Additionally, IL-6 may also impact breast cancer-specific mortality after menopause, underscoring its importance in evaluating a patient's prognosis.

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