Inés Gil Castelló

COULD NUTRITION HELP IN THE PRIMARY PREVENTION OF BREAST CANCER IN WOMEN? BIBLIOGRAPHIC RESEARCH ON THIS TOPIC

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Biochemistry and Molecular Biology

Directed by Josep Gómez Alvarez

Biochemistry and Biotechnology Department

UNIVERSITAT ROVIRA I VIRGILI

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1 ABSTRACT

Introduction: Breast cancer (BC) is the fifth leading cause of cancer mortality worldwide and, among women, this cancer accounts for 1 in 4 cases and 1 in 6 deaths from cancer. As the nutrition is a modifiable risk factor, it could have a significant impact on primary prevention in BC.

Materials and Methods: A bibliographical research was carried out using the PubMed search tool, including the terms ("breast cancer") AND ("diet" OR "alimentation" OR "nutrition") AND ("prevention" OR "risk" OR "association") in the title/abstract and with a date of publication in the last 5 years. Once selected, the articles were submitted to a quality assessment study, and their main results were synthetized and summarized including a critical point of view.

Results: In all, 19 studies were considered: 3 meta-analysis, 3 systematic reviews and 13 meta-analysis and systematic reviews. A higher intake of ultra-processed foods (UPFs), or foods with high glycaemic index (GI) or dietary inflammatory index (DII) would seem to be associated with a higher risk of BC. The menopausal status also seems to affect the risk of BC in some cases such as in the consumption of trans fatty acids (TFA) and UPFs in which the risk is higher in postmenopausal women. Other foods, such as mushrooms seem to be inversely associated with BC risk and one study suggested an inverse association between BC and the consumption of olive oil. Some nutrients also appear to be inversely associated with BC risk, including calcium, vitamin D and carotenoids. Finally, the evidence in some cases is still conflicting in other dietary elements (e.g., dairy products, acrylamide, or cadmium).

Conclusion: Dietary choices may influence health and minimize the risk of suffering cancer. In general, following healthy eating habits seems to significantly reduce the risk of developing BC.

Key words: breast cancer (BC); nutrition; primary prevention; diet.

Abbreviations: BC: breast cancer; UPFs: Ultra-processed foods GI: glycaemic index; DII: dietary inflammatory index; TFA: trans fatty acids.

2 INTRODUCCTION

Cancer is an uncontrolled growth and spread of abnormal cells that results from a change in a single cell. The process by which a normal cell transforms into a cancer cell is called carcinogenesis or oncogenesis and is a multifactorial process stimulated by genetic predisposition and environmental factors (Łukasiewicz *et al.*, 2021).

It can occur in any cell, tissue, and organ, and eventually leads to pathological alterations resulting in a great number of cancers. The main mechanisms that allow cancer cells to progress are the unlimited ability to divide, apoptosis evasion, the ability to metastasize, improved angiogenesis, resistance to anti-growth signals and induction of growth signals (Hanahan and Weinberg, 2000).

2.1 BREAST CANCER EPIDEMIOLOGY

Cancer is one of the leading causes of mortality in the world today. The number of deaths related to it is increasing alarmingly every year. In addition, although not all cancers result in death, the quality of life of cancer patients decreases whereas the costs they require increase (Łukasiewicz *et al.*, 2021).

Among all the cancers, breast cancer (BC) is the fifth leading cause of cancer mortality worldwide. In 2020, it had an incidence of 2.3 million new cases, being the main cause of global cancer incidence. Among women, this cancer accounts for 1 in 4 cases and 1 in 6 deaths from cancer (Sung *et al.*, 2021). By 2030, the number of newly diagnosed cases worldwide is expected to reach 2.7 million a year, while the number of deaths will reach 0.87 million (Łukasiewicz *et al.*, 2021).

Currently, as can be seen in Figure 1, BC has a higher incidence in developed countries such as Australia/New Zealand and Western Europe than in underdeveloped countries. However, deaths due to this cancer are more prevalent in countries in transition (mortality rates exceed 17%) such as Melanesia or West Africa (Sung *et al.*, 2021).

On the one hand, high incidence rates show a higher prevalence of hormonal and reproductive risk factors such as late menopausal age or the use of oral contraceptives,

as well as risk factors related to lifestyle such as obesity or alcohol intake. In addition, these rates can also be explained by a better record of cancer cases in developed countries than in countries in transition. On the other hand, high mortality rates in underdeveloped countries may be due to the fact that most women who develop BC in high-income countries have more accessibility to screening programs or to different procedures such as preventative behaviours that enable to implement the treatment as soon as possible and, as a result, to increase their chances of living (Sung *et al.*, 2021).

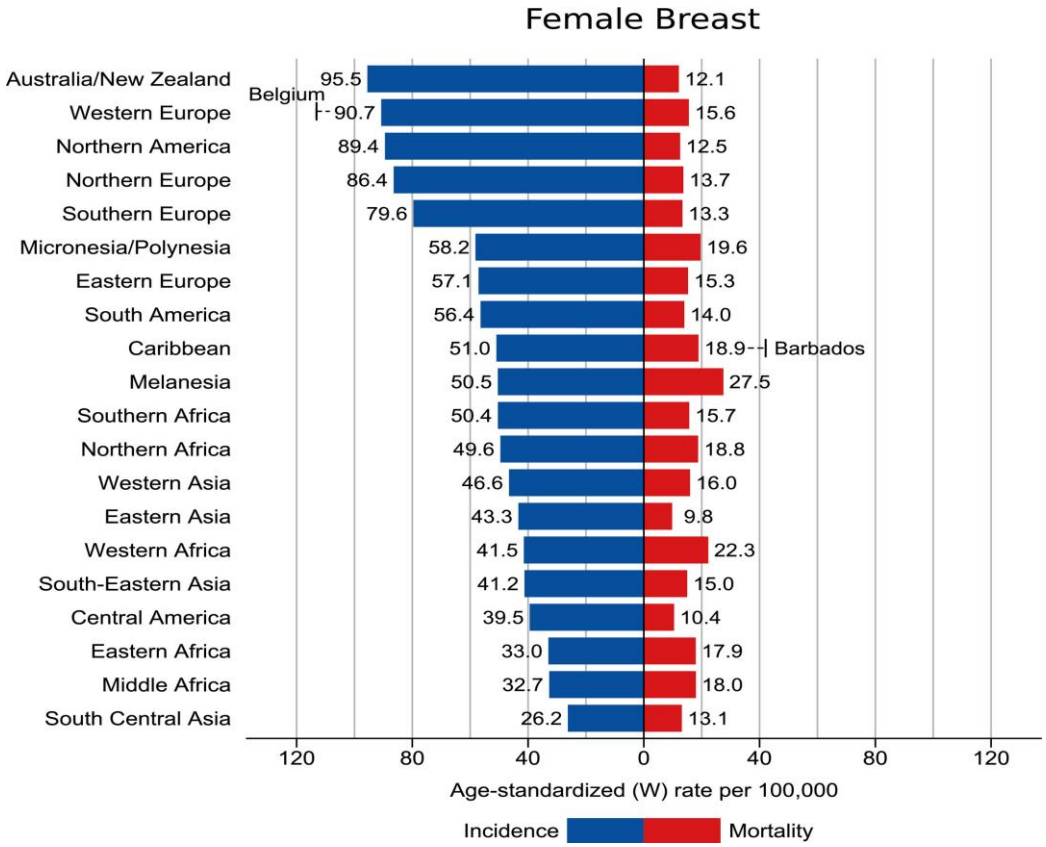

Figure 1: Mortality and Incidence of Female Breast Cancer in different regions in 2020. The highest national age-standardized rates for incidence and mortality are superimposed and rates are shown in descending order of the world (W) age-standardized incidence rate. Source: Global Cancer Observatory, no date.

In Spain, according to the Spanish Society of Medical Oncology (SEOM), the BC is the most common and it is estimated that 1 in 8 Spanish women will have this cancer at some point in their lives. Although mortality has decreased in recent years thanks to screening programs and improved treatments, this cancer continues to be the leading cause of death in Spanish women. In addition, the stage at which this cancer is diagnosed influences survival, with a more than 98% chance of surviving if detected in stage I and a 24% chance of being detected in stage IV (*Cancer de mama - SEOM: Sociedad Española de Oncología Médica © 2019*, no date).

2.2 BREAST CANCER

2.2.1 Breast anatomy

Since breast cancer can start in different parts of the breast, knowing the normal anatomy of the breast can be useful. As it can see in Figure 2, the breast is made up of the glands that produce breast milk (lobules), small channels that come out of the lobules and carry milk to the nipple (ducts), connective tissue and fatty that surround the lobes and ducts and help keep them in place and blood and lymphatic vessels (*What Is Breast Cancer? | American Cancer Society*, no date).

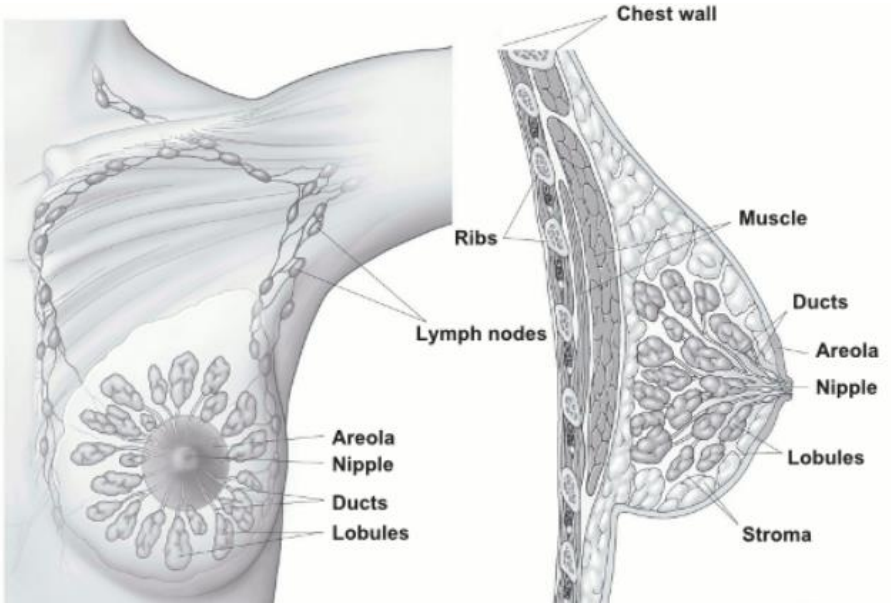

Figure 2: Normal anatomy of the breast. Breast is formed by lobules that convert into ducts. Those ducts converge in turn into bigger ducts that carry milk outside body through the nipple. These structures are surrounded by fatty and connective tissue (stroma). Source: What Is Breast Cancer? | American Cancer Society, no date.

2.2.2 Classification

As breast cancer can appear in different areas of the breast, various types of this cancer exist. The breast cells that are affected determine the type of cancer, and it can be broadly divided into carcinomas and sarcomas, depending on the origin of the cell involved. However, in some cases, a single breast tumour can be a combination of different cells so, for this reason these two categories are not always enough (Feng *et al.*, 2018).

In general terms, sarcomas are a very rare form of BC, <1% of primary BC, and they arise from the stromal components of the breast, which include blood vessel cells and myofibroblasts. In contrast, carcinomas are the most common BC, and they are originated from the epithelial component of the breast, in which there are involve the cells that connect the lobules and the terminal ducts responsible for milk production (Feng *et al.*, 2018).

Among the huge group of carcinomas, there can be find different types of BC according to their invasiveness in relation to the primary tumour sites (Feng *et al.*, 2018).. Typically, three main groups of BC can be find following this criteria:

- Non-invasive (or in situ) breast cancer: Inside this group, the Ductal Carcinoma in situ (CDIS) or intraductal carcinoma is found. It is one of the most typical and it is a non-invasive or pre-invasive BC developed within the pre-exiting normal ducts. (Feng *et al.*, 2018).
- Invasive or infiltrating breast cancer: These cancers grow into the surrounding breast stromal tissue due to invasion and expansion of cancer cells outside of the normal breast ducts and lobules. They have the possibility to spread to other locations of the body, such us lymph nodes or other organs, and consequently form metastasis. Depending on the tissue and cell types involved, invasive breast cancers are divided in Invasive Ductal Carcinoma (IDC) and Invasive Lobular Carcinoma (ILC) and account approximately 90-95% of all BC cases. (Feng *et al.*, 2018).
- Metastatic, or stage IV or advanced breast cancer: It happens when BC has spread to other organs in the body. Metastases from BC can be in the lymph nodes in the armpit and/or in distant sites such as the liver, brain, lung, and bone. (Feng *et al.*, 2018).

Apart from these types of cancer, there are other types which are rare or less common. Among these, there is Paget disease of the breast that starts in the breast ducts, spreads to the skin of the nipple and then a dark circle around the nipple appeared due to the expansion of this to the areola; the papillary carcinoma, which usually has a better prognosis than other invasive breast cancer; the inflammatory breast cancers that are characterised by inflammation-like breast swelling, red or purple colour of the skin and

thickening or pitting of the breast skin, probably due to blockage of the lymphatic vessels of the skin by cancer cells; Phyllodes tumours which are develop in the stromal cells of the breast and only one-quarter of these cancers are malignant; the angiosarcoma of the breast that can involve the skin of the breast or the breast tissue; and finally, breast cancer in men and children and adolescents may also find (Feng *et al.*, 2018).

On the other hand, the molecular and cellular heterogeneity of BC requires the analysis of multiple genetic alterations in concert. Thanks to the advance of gene expression profiling techniques, nowadays, BC are usually divided into five molecular or intrinsic subtypes that differ in the expression patter of particular genes which are related to human epidermal growth factor 2 (*HER2*) expression, estrogen receptor (ER) expression (the luminal cluster), progesterone receptor (PR) expression, proliferation, and a singular group of genes called the basal cluster (Table 1) (Feng *et al.*, 2018).

Table 1: Intrinsic or molecular subtypes of breast cancer. The name of the subtype, the molecular signatures as well as its characteristics are described. Adapted from: Feng *et al*., 2018.

SUBTYPES	MOLECULAR SIGNATURES	CHARACTERISTICS
Luminal A	ER+, PR±, HER2-, Low Ki67	Around 70%, most common and best prognosis.
Luminal b	ER+, PR±, HER2±, High Ki67	10%–20%, lower survival than Luminal A.
HER2	ER-, PR-, HER2+	5%–15%
Triple Negative	ER-, PR-, HER2-	15%–20%, more common in black women, diagnosed at younger age and worst prognosis.
Normal-like	ER+, PR±, HER2-, Low Ki67	Rare, low proliferation gene cluster expression.

It is vital to be able to accurately distinguish between the different subtypes because everyone has different prognostic, therapeutic target, treatment implications and different responses and behaviours to therapy (Feng *et al.*, 2018).

2.2.3 Initiation and progression of Breast Cancer and Cancer stem cells

Normally, breast tumours emerge from ductal hyperproliferation, and subsequently develop into benign tumours or even metastatic carcinomas after continuous stimulation by a variety of carcinogenic factors. Tumour microenvironments, such as stromal or macrophage influences, play vital roles in BC initiation and progression, as the stroma can be exposed to carcinogens and induce neoplasia, and macrophages can create a mutagenic inflammatory microenvironment that may promote angiogenesis and allow cancer cells to evade immune defence. Moreover, the epigenetic modifications can also promote the carcinogenesis because differences in DNA methylation between tumour-associated and normal microenvironments exist.

Lately, cancer stem cells (CSCs) have been observed as a new subclass of malignant cells within tumours and they are associated with initiation, invasion, escape, metastasis, recurrence, and resistance of the tumour. In the case of breast cancer stem cells (bCSCs), although more studies are required to understand this kind of cells, they may be developed from stem cells or progenitor cells in normal tissues, have self-renewal abilities and be resistant to conventional therapies. This kind of cells are identified by expression of surface markers such as EpCAM CD44, CD49f, CD133, CD61 and the absence of surface markers such as CD2, CD3, CD10, CD16, CD18, CD24, CD31 and CD64. Moreover, bCSCSs also express a high level of ATP-binding cassette (ABC) transporter G family (ABCG2) or breast cancer resistance protein-1 and aldehyde dehydrogenase-1 (ALDH1). In the activity and maintenance of CSCs, different signalling pathways are involved. Among these pathways, the Wnt, Hedgehog and Notch paths are important in stem cell differentiation and self-renewal capacity, so disruptions of these could have been involved in the bCSC phenotype. There are also, other transcription factors such as Oct4, Sox2, and Nanog that are implicated in the maintenance, proliferation, and tumorigenesis of the bCSCs. Moreover, the resistance to the treatment might be improved due to the use of different CSC mechanisms like the alteration of the cell cycle kinetics or the ABCG2 and ALDH1 proteins that can contribute to a rapid efflux of cytotoxic drugs and metabolize chemotherapeutic drugs into non-toxic compounds, respectively (Barzaman *et al.*, 2020).

Two hypothetical theories of BC initiation and progression have been described (Figure 3) and although both are supported by a wealth of data, neither can fully explain the origin of human BC (Sun *et al.,* 2017). On the one hand, one of these theories is the cancer stem cell theory (Figure 3A). This proposes that all tumour subtypes are originated from the same stem cells or transit-amplifying cells (progenitor cells). Both genetic and epigenetic mutations acquired in stem or progenitor cells will give rise to different tumour phenotypes. On the other hand, the other theory is the stochastic theory (Figure 3B) and it says that every tumour subtype is initiated from a single cell type (stem cell, progenitor cell or differentiated cell). In this case, random mutations can progressively accumulate in any breast cell, and when the right mutations have accumulated, these cells are transformed into tumour cells (Sun *et al.*, 2017).

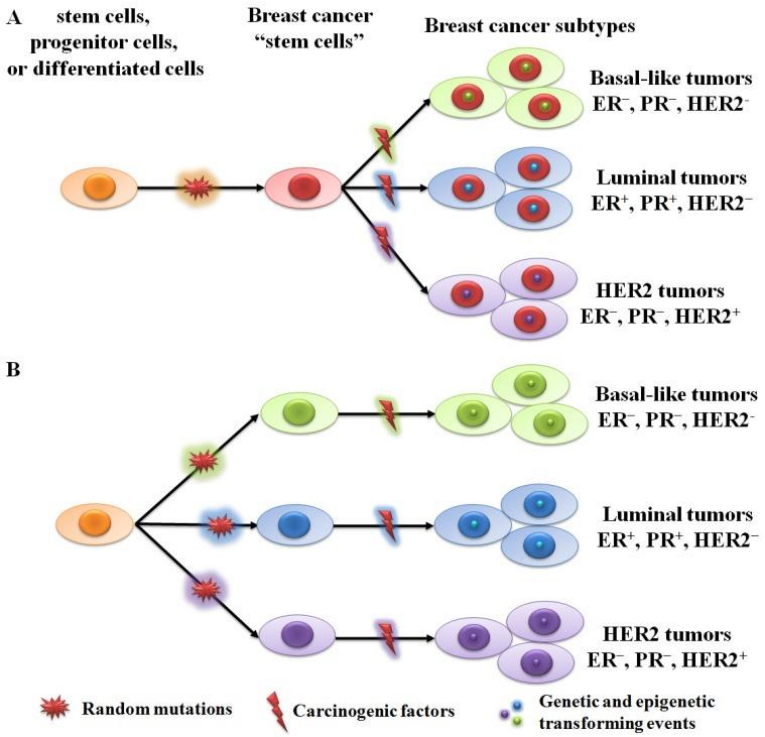

Figure 3. The hypothetical theories of breast cancer initiation and progression. (A) Every subtype of tumour is derived from the same progenitor or stem cell. The different phenotypes of tumour are determined by specific subtype transforming events. (B) From a single cell type (stem cell, differentiated cell, or progenitor cell) is initiated each tumour. Mutations can occur randomly and gradually accumulate in breast cells. This leads to their transformation into tumour cells when the number of accumulated mutations reach certain point. Source: (Akram *et al*., 2017)

2.2.4 Stages of breast cancer

According to Figure 4, BC is divided into 5 different stages, form stage 0 (non-invasive) to 4 (invasive kind of tumour). This division indicates the type and size of the tumour, if the

cancer cells are or not contained at the site of origin and helps to determine the most appropriate way to contain and eliminate the disease (Akram *et al.*, 2017).

In stages 0 and 1 cancer cells are confined to a very limited area of the breast. More specifically, in stage 0 only some abnormal cells are found and there is no evidence of invasion in the surrounding tissues. However, in stage 1 the cancer is evident and microscopic invasion could be possible. In stage 2 cancer is still growing but it is limited to the breast or has just extended to the near lymph nodes, specifically, in axillary or sentinel lymph nodes. About Stage 3, although no invasion to distant organs has happened yet, it has spread beyond the immediate region of the tumour and may have invasion of nearby lymph nodes and muscles. Finally, in stage 4 cancer has spread to other places of the body, such as the bone, brain, lungs, and liver, and it is characterised by advanced and metastatic stage (Akram *et al.*, 2017).

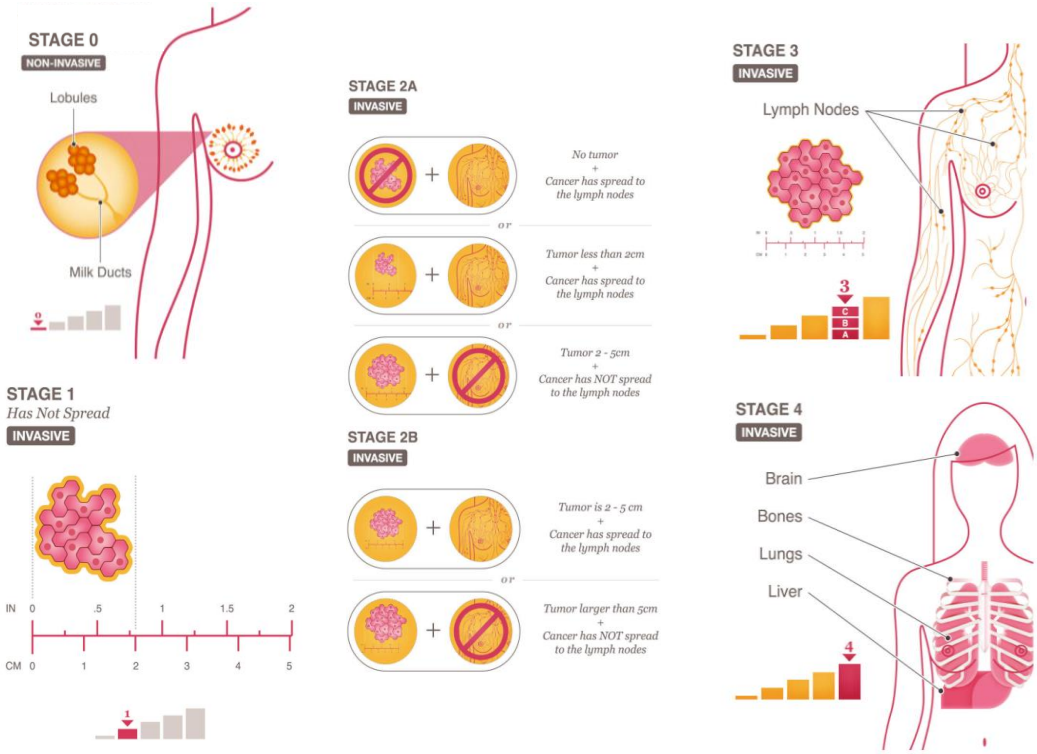

Figure 4: The different stages of breast cancer. In stage 0 the cancer only presents few cancer cells. In stage 1 the cancer is smaller than 2cm in diameter. BC in stage 2 can present different features and it is dived in two categories. On stage 3 cancer has spread to the breast skin or the chest wall and tumour can be any size. In this stage there are three categories. Finally, in stage 4 cancer has expanded to other parts of the body such as liver, lungs, bones, or brain. Adapted from: About Breast Cancer - National Breast Cancer Foundation, no date.

2.3 RISK FACTORS OF BREAST CANCER

There are a large number of risk factors associated with BC. These factors can be modifiable or non-modifiable. Regarding to modifiable factors, these are the ones that depend on our behaviour and therefore can be modified. However, non-modifiable factors do not depend on us. The risks factors associated with BC are listed in Table 2.

Table 2: Breast cancer risk factors. Adapted from: Łukasiewicz *et al.,* 2021.

NON-MODIFIABLE FACTORS	MODIFIABLE FACTORS
Female sex	Hormonal replacement therapy
Older age	Diethylstilbesterol
Family history (of breast or ovarian cancer)	Physical activity
Genetic mutations	Overweight/obesity
Race/ethnicity	Alcohol intake
Pregnancy and breastfeeding	Smoking
Menstrual period and menopause	Insufficient vitamin supplementation
Density of breast tissue	Excessive exposure to artificial light
Previous history of breast cancer	Intake of processed food
Non-cancerous breast diseases	Exposure to chemicals
Previous radiation therapy	Other drugs

2.3.1 Non-Modificable factors

Some of the non-modifiable factors that have an impact in the possibility of suffering BC are female sex, age, and genetic mutations, among others (Table 2).

Female sex is one of the most important risk factors due to women exhibiting enhanced hormonal stimulation. As a result, breast cells are very vulnerable to hormones (specifically, estrogen and progesterone) as well as disruptions in their balance. Regarding age, the risk of developing BC increases with older age. Exposure to possible carcinogens and the accumulation of a large number of cell alternations over time causes

an increase in carcinogenesis. Another important factor is the family history of BC in which, around 13% to 19% of patients diagnosed with BC present a first-degree relative affected by the same disease. This association is driven by epigenetic changes as well as environmental factors that act as potential triggers. Moreover, the risk of suffering a renewed cancerous lesion within the breasts is associated with personal history of BC. Genetic mutations are also an essential risk factor that will determine an increased probability of having BC (Table 3). (Łukasiewicz *et al.*, 2021).

Table 3: Main genes associated with an increased risk of breast cancer occurrence. Main genes that associated with the appearance of BC, its penetrance, the chromosome where they are located, their main functions and the percentage of risk. It should be noted that these genes are also associated with other syndromes or disorders. Adapted from: Łukasiewicz *et al.,* 2021.

PENETRATION	GENE	CHROMOSOME LOCATION	MAJOR FUNCTIONS	BREAST CANCER RISK
HIGH	*BRCA1*	17q21.31	DNA repair Cell cycle control	45-87%
	BRCA2	13q13.1	DNA repair Cell cycle control	50-85%
	TP53	17p13.1	DNA repair Cell cycle control Induction of apoptosis Induction of senescence Maintenance of cellular metabolism	20–40% (even up to 85%)
	CDH1	16q22.1	Regulation of cellular adhesions Control of the epithelial cells (proliferation and motility)	63–83%
	PTEN	10q23.31	Cell cycle control	50–85%
	STK11	19p13.3	Cell cycle control Maintenance of energy homeostasis	32–54%
MODERATE	*ATM*	11q22.3	DNA repair Cell cycle control	20–60%
	PALB2	16p12.2	DNA repair	33–58%
	BRIP1	17q23.2	Involvement in the *BRCA1* activity	ND
	CHEK2	22q12.1	Cell cycle control	20–25%

Lastly, density of breast tissue can also be a factor to take into consideration. Generally, an increased risk of BC correlates with a higher density of breast tissue. Regarding ethnicity, although the incidence of BC is higher in white, non-Hispanic women, the mortality rate is much higher in black women. However, the mechanisms associated with this phenomenon have not yet been understood. (Łukasiewicz *et al.*, 2021).

2.3.2 Modificable factors

Some of the modifiable factors that have an impact in the possibility of suffering BC are the intake of chosen drugs, physical activity, body mass index, alcohol intake, smoking habits, or unhealthy nutrition, among others (Table 2).

Regarding to chosen drugs, the intake of diethylstilboestrol during pregnancy is associated with an increased risk of BC in both mothers and offspring. Several studies also indicate an increased risk of BC in females who use hormonal replacement therapy (HRT) especially longer than 5 or 7 years. Numerous research indicated that the intake of antidepressants, the prolonged intake of antibiotics and the use of tetracyclines might be associated with a greater risk of BC. On the other hand, regular physical activity is considered a protective factor against the incidence of BC. In contrast, smoking habits and alcohol intake are associated with major probability of BC. In active and passive smoking an induction of pro-carcinogenic events is produced as carcinogens found in tobacco are transported to the breast tissue, which leads to an increase of mutations within oncogenes and suppressor genes (*p53* in particular). In the case of alcohol, a great number of evidence confirm that excessive alcohol consumption is a factor that is related to the risk of BC. This is due to the increased levels of estrogens and a hormonal imbalance that will affect the risk of carcinogenesis within the female organs caused by alcohol intake, among others. Finally, dietary choices and being overweight or obese are also associated with different risks of BC incidence and recurrence as increasing body fat might affect the levels of circulating hormones and increase the inflammatory state and affects which facilitate pro-carcinogenic events (Łukasiewicz *et al.*, 2021).

2.4 NUTRITION AND BREAST CANCER

The connection between human disease and diet it has a long history in epidemiology. However, the mechanisms by which dietary factors might increase or decrease disease risk are still unclear. The modern notion about this connexion says that the individual dietary components can change the epigenetic status of genes and these epigenetic alterations and their concomitant changes in gene expression could be the molecular pathway by which diet alters disease risk (Sapienza and Issa, 2016).

There are many studies focused on the role of different types of food in BC risk but the evidence in the literature sometimes reports divergent results and no consistent or no statistically strong associations. Nonetheless, as the diet is a modifiable risk factor, it could have a significant impact on primary prevention of BC because a reduced of these factors have a positive different effects in the development of BC (Cicco *et al.,* 2019).

According to the recommendation of The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) based on the latest evidence (i) being physically active, (ii) keeping a healthy body weight, (iii) following a diet rich in soy and fibre, and (iv) restricting fat intake (particularly saturated fatty acids) can reduce the risk of BC. In addition, lifestyle changes, including diet and exercise, can promote long-term overall health by decreasing BC comorbidities (e.g., obesity, hypertension, hyperlipidemia, and diabetes mellitus) (*Breast cancer - WCRF International, no date)*. That is why, if all of these taken into account, a potential role for nutrition as primary prevention of BC could be used to reduce the incidence of this type of cancer.

3 OBJECTIVES

Since nutrition is one of the most important modifiable factors of human lifestyle, and diet's choices can affect both health and cancer risk, the main objective of this assignment is to determine which kind of foods, nutrients or dietary patterns could help in the primary prevention of breast cancer in women as well as which ones could contribute to the development of this type of cancer.

In addition, as the literature published have not assembled useful evidence to develop health guidelines and policies to promote healthy eating styles to prevent breast cancer, another objective is to provide a summary of the evidence produced between 2017 and 2022 about this topic and a judicious and critical analysis about the quality of the current literature.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

To accomplish the objectives mentioned above, a general review involving a critical examination of the literature was carried out (Figure 5). To this end, the first step was to analyse the disponible literature, then the synthesis of previously published second-level research, and finally, a critical review of all available evidence.

Figure 5: Scheme of the process performed to accomplish the objectives. Three main steps were carried out to collect all the information available and to analyse it to perform a great review in relation with nutrition and prevention of BC.

4.2 SEARCHING THE LITERATURE

In the first instance, PubMed search tool was used to analyse the scientific literature. As an any relationship between risk, prevention, or association of BC with any type of diet, alimentation or nutrition were wanted to study, in the query box was added: ("breast cancer") AND ("diet" OR "alimentation" OR "nutrition") AND ("prevention" OR "risk" OR "association"). After that, the results were refined using a filter by date of publication, including all papers published in the last 5 years to be aware of the most recent and updated information. The filters of species and sex were also applied to focus only on female humans, due to BC having a much higher incidence in women. Between the different types of articles, meta-analysis and systematic reviews were included. Finally,

the field of only in “title or abstract” was also applied because many of the articles did not focus on this topic.

From this point forward, the search concentrated on meta-analysis and systematic review on the risk of BC in the female population. Particularly, the studies that examined the presence and intake of foods in the diet were included. However, some studies had to be excluded. The characteristics of these studies were:

- Studies written in languages other than English.
- Studies involving BC recurrence.
- General and descriptive reports, comments and updates with no dietary association measures reported.
- Studies that discussed prevention but not prior to diagnosis.
- Studies on populations or groups at higher risk.

4.3 DATA EXTRACTION

Firstly, the extraction of the general characteristics of each eligible systematic review or meta-analysis was done. In case of the articles that dealt with more types of cancer, only the information about BC was collected. Among the general characteristics, the reference of the article, the search range applied, the type of epidemiological design, the association/s that were examined and the total size of the samples in all the studies included in a review as well as the places where they were developed were extracted. Secondly, the main findings of each study, including how exposure was measured, the overall results, and the summarize of the meta-analytic estimates were extracted. Finally, the limitations of the study and the authors' conclusions and recommendations were provided for a better understanding of the results.

4.4 STUDY QUALITY ASSESSMENT

For a critical assessment of the internal validity of the reviews and meta-analyses considered, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (Page *et al.*, 2021), developed in 2020, was used. A checklist was compiled for each study included in the overall assignment (see Table A1).

5 RESULTS

The literature search identified 5,609 results in PubMed (Figure 6). Then, 4,484 of the former studies were removed after applying publication, language, sex, and species filters. Another 1,024 studies were excluded after focus the research in only the types of articles that were required. After discarding articles that did not have the key words in the abstract and title, 77 studies were rejected. In the end, 24 studies were included, and 5 of them were deleted after reading the full text because they did not contain the information required. Finally, a total of 19 studies were tabulated for the purposes of the umbrella review: 3 meta-analysis, 3 systematic reviews and 13 meta-analysis and systematic reviews. The quality of these studies varied considerably was around 23.47 points.

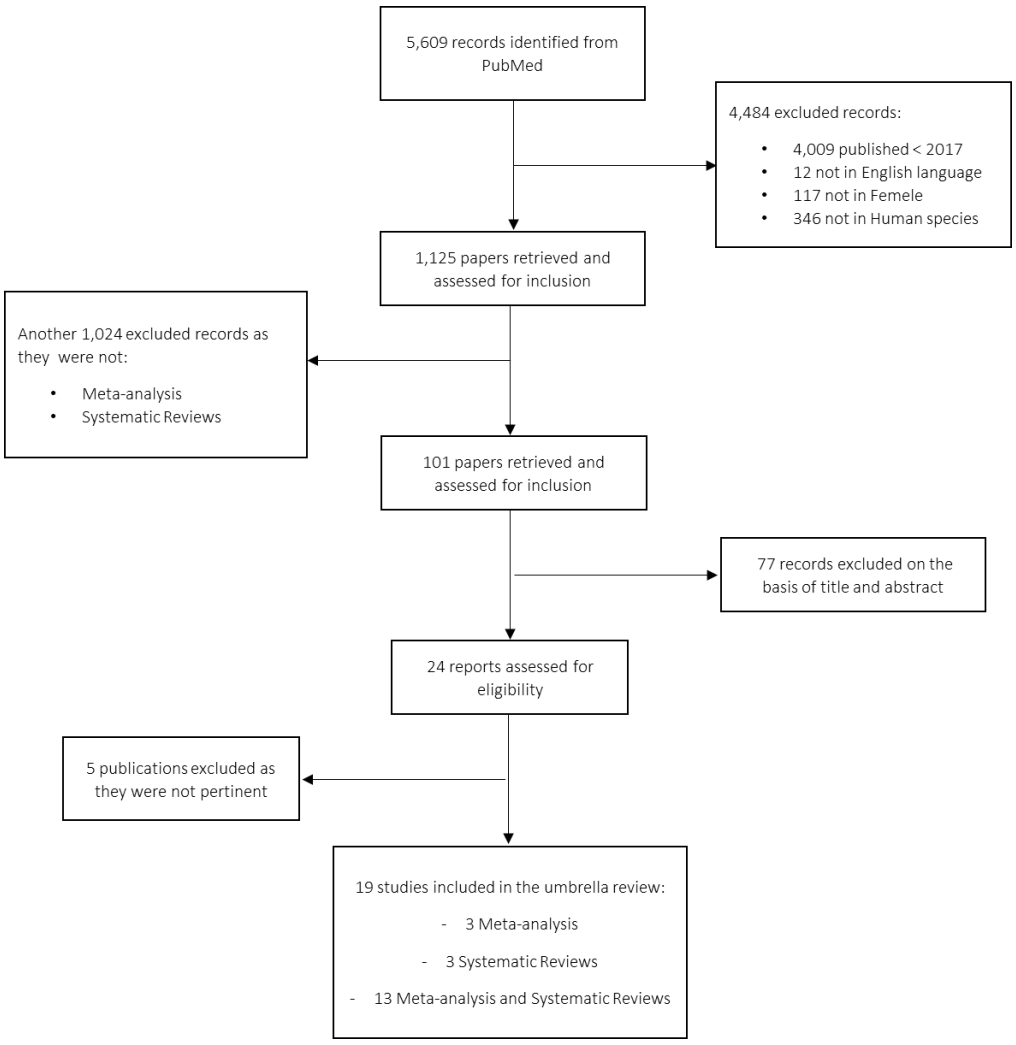

Figure 6: The research strategy used to identify the articles for the umbrella review.

Table 4 provides data on the general characteristics of the identified studies; Table 5 shows the exposure measures and the main results of the studies and in Table 6 the conclusions and recommendations are shown.

5.1 DIETARRY PATTERNS

The overall assignment finally includes 5 studies (1 meta-analysis (Shridhar *et al.*, 2018) and 4 meta-analysis and systematic reviews (Godos *et al.,* 2017; Schwingshackl *et al.,* 2017; Hou *et al.,* 2019; Dianatinasab *et al.,* 2020) in the association between dietary patterns and risk of BC. Among the different diets examined in these studies, the following are found: a healthy diet, the Mediterranean Diet (MedD), vegetarian diets and the Western Diet (WD).

A diet is defined as "healthy" when includes high fibre and limited amounts of saturated fats, animal proteins and refined sugar. Specifically, the MedD also includes moderated consumption of red wine and the use of extra virgin olive oil as a condiment. On the contrary, the WD includes large amounts of refined sugars, protein, saturated fat, and alcohol. Among the vegetarian diets, the pure-vegetarian diet (characterised by eating meat less than once per month), semi-vegetarian diet (characterised by low consumption of meat, more than once per month but less than once per week) and pesco-vegetarian diet (consumption of fish more than once per month) were evaluated in one study (Godos *et al.*, 2017) and lacto-vegetarian diet (characterised by no consumption of animal products except diary) and lacto-ovo-vegetarian diet (characterised by no consumption of animal products except diary and eggs) in another one (Shridhar *et al.*, 2018).

The dietary patterns typified as a healthy diet and MedD have been associated with a protective role against the development of BC. A study that contains nineteen cohort studies (Hou *et al.*, 2019) shows a statistically significant lower risk of BC associated with a healthy diet. Moreover, a study focused on MedD (Schwingshackl *et al.,* 2017) which included seven cohort studies, nine case-control studies, and one randomized controlled trial (RCT) found that in the cohort studies were a small decreased in BC risk (6 %) in association with MedD.

Regarding to WD, there is a study that evaluated the effect of this diet and MedD in the risk of IDC and ILC subtypes (Dianatinasab *et al.*, 2020). In this case, this study included six case-control studies and four cohort studies. The observation of a statistically significant inverse association between MedD and the risk of IDC was found in case-control studies (pooled RR: 0.47 95% C.I. 0.39-0.55) but no in cohort studies (pooled RR: 0.98 95% C.I. 0.92-1.05) and a highly protective effect was observed between MedD and the risk of ILC (pooled RR: 0.76 95% C.I. 0.64-0.87). However, a direct association between the WD and the risk of IDC (pooled RR: 1.36 95% C.I. 1.18-1.53) and a weakly association between WD and ILC (pooled RR: 1.45 95% C.I. 1.04-1.86) was found.

On the other hand, there are two studies that focus on vegetarian diets (Godos *et al.*, 2017; Shridhar *et al.*, 2018). In one of these (Godos *et al.*, 2017), the analysis showed no significant association of a vegetarian diet and a lower risk of cancer compared to a non-vegetarian diet. And in the other one (Shridhar *et al.*, 2018), that focused on Indian women, found that BC risk was lower in lacto-ovo-vegetarians compared to non-vegetarians and lacto-vegetarians maybe because of egg consumption patterns.

5.2 FOODS

In the case of the foods, a total of different studies about milk, dairy products, ultra-processed food (UPFs), mushroom and olive oil consumption and BC risk were considered.

Two meta-analyses (Chen, Li and Li, 2019; Wu *et al.*, 2021) examined the association between the consumption of milk and dairy products such as hard cheese, cottage/ricotta cheese, yogurt and ice cream. One included eight case-control studies and the other one twenty-one cohort studies. Both studies reported no clear evidence between milk and dairy products and the risk of BC. However, modest inverse associations were observed for yogurt and cottage/ricotta cheese consumption when they were modelled as categorical variables (Wu *et al.*, 2021).

One systematic review (Chen *et al.*, 2020) about a prospective cohort study was focus on the association between UPFs consumption and risk of BC among others. In this case, a positive association between UPFs consumption and risk of BC in postmenopausal

women was observed and when UPF consumption was considered as a continuous variable, also a direct association on overall BC risk was observed.

A meta-analysis and systematic review composed by seven case-control studies and three cohort studies (Ba *et al.*, 2021) studied the intake of mushroom and a significant association between a higher consumption of this food and lower risk of BC (RR pooled 0.65, 95% CI 0.52, 0.81) was showed.

Finally, it was found in another systematic review and meta-analysis (Sealy, Hankinson and Houghton, 2021) a link between olive oil intake and the risk of suffering BC. The study suggests an inverse association between the consumption of this oil and BC, although the relation was not significant in prospective or case-control analyses.

5.3 NUTRIENTS

Among the nutrients, the studies that the final assignment include are focus on calcium, vitamin D, cadmium, trans-fatty acids (TFA), acrylamide, carotenoids, glycaemic index (GI) or glycaemic load (GL) and Dietary Inflammatory Index (DII).

Regarding the studies that focus on vitamin D and calcium intake, there are two: each one related to one of these nutrients (Hossain *et al.*, 2019; Wu *et al.*, 2021). On the one hand, the meta-analysis and systematic review that focus on vitamin D (Hossain *et al.*, 2019) contained nineteen case control studies and three prospective cohort studies and showed a net direct association between 5-hydroxy-cholecalciferol (25(OH)D) deficiency (RR pooled: 1.91, 95% CI 0.81 (1.51–2.41) and BC occurrence and a weaker inverse association for total vitamin D intake from foods and supplements (RR pooled: 0.99, 95% CI 0.97–1.00) and BC risk. On the other hand, the study about calcium intake (Wu *et al.*, 2021) did not show strong associations with BC risk. Moreover, there was other meta-analysis and systematic review with twenty cohort studies that focus on cadmium intake by measuring urine levels (excretion of cadmium) and the dietary consumption (Filippini *et al.*, 2020). In this case, an imprecise and marginal positive relation between dietary cadmium intake and BC was observed. However, no association was found neither in urine levels nor in postmenopausal women.

One study (Michels *et al.*, 2021) analysed the trans-fatty acid (TFA) and its subtypes (e.g., TFA from ruminant, fish, vegetables, industrial, monounsaturated…) intake and the risk of BC. It was compounded by thirteen case-control studies and four cohort studies. The total TFA intake or three TFA subgroups were not significant to cancer risk, although the total TFA intake was rather questionable as menopause could be a modifier because only in postmenopausal women was a significantly increased risk observed for higher serum TFA.

Carotenoids, specifically β-carotene, were examined in one systematic review which contained eight cohort studies, thirteen case-control studies, and seven reviews (Peraita-Costa, Carrillo Garcia and Morales-Suárez-Varela, 2022) that found that carotene consumption had a significant protective effect against BC.

The dietary intake of acrylamide and risk of BC was analysed by a systematic review and dose-response meta-analysis with sixteen cohort studies and two case-control (Adani *et al.*, 2020). A null or inverse relationship between exposure and risk of BC was proved, especially among never smokers and postmenopausal women.

Finally, two different specific index were found in three different articles. Two of them were about Dietary Inflammatory Index (DII) (Jayedi, Emadi and Shab-Bidar, 2018; Chen *et al.*, 2021a) and the other one was about glycaemic index (GI) or glycaemic load (GL) (Long *et al.*, 2022).

As some specific dietary components may act as moderators of chronic inflammation, the DII is an interesting tool because provides a summary measure of diet-associated inflammation. In one study (Chen *et al.*, 2021a), the DII was composed by seven pro-inflammatory dietary components: vitamin B12, carbohydrates, cholesterol, total fat, protein, saturated fat, and trans-fat. In the other one (Jayedi, Emadi and Shab-Bidar, 2018), by forty-five dietary components: nine that have pro-inflammatory properties (energy, cholesterol, carbohydrates, total fat, TFA, saturated fat, iron, vitamin B12 and protein) and another thirty-six that have demonstrated anti-inflammatory characteristics. In the first case, eight case-control studies and six cohort studies were included and in the second case, four perspective cohort studies and three case-control studies were added. In summary, it was observed in both studies that women in postmenopausal and

premenopausal states showed a higher risk of BC in the most pro-inflammatory diet category than those in the most anti-inflammatory category and an increase of 1 unit in DII was associated with BC risk.

In the case of the meta-analysis and systematic review about dietary GI/GL and BC risk (Long *et al.*, 2022) it was positively associated dietary GI with BC risk for higher vs. lower intake categories (RR summary: 1.05, 95% CI 1.01-1.09). However, a null association was observed when a comparation of the highest vs. lowest categories of dietary GL was done. The analysis based on menopausal status and GI showed that the association was marginally positive for postmenopausal BC (RR summary: 1.06, 95% CI 1.00-1.13), whereas it was not positive for premenopausal BC (RR summary: 1.06, 95% CI 0.95-1.17). In the case of GL, no relation was observed between this diet and postmenopausal BC.

5.4 QUALITY DIETARY PATTERNS

The quality of the dietary patterns was also studied in one systematic review (Du *et al.*, 2018). The study was centred in the relation between twelve different diet quality scores (two versions of the DII, four versions of the MedD score, the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension (DASH) score, and three versions of low-carbohydrate diet scores that differentiate between different sources of protein and fat) and the risk of ER-breast cancer. In this case, of the four studies on MedD scores, three exhibited a significant inverse association with ER-postmenopausal BC, while no solid association was observed with the other diet quality scores. In this case, while most of the diet quality scores share similarly dietary components, most of the non-MedD scores were represented by only one study each, and the associations with ER-postmenopausal BC were mixed.

The results show that more research is required in the association of dietary patters, types of foods and specific nutrients with BC, including the risks of the different subtypes of this cancer, besides, literature still does not offer clear evidence of a link between BC risk and a healthy diet or specific foods or nutrients. Moreover, the components of a one special diet sometimes are insufficient between different studies and only a very small number of studies are available to study one special diet or one specific component.

Table 4. Characteristics of the studies included in the general review.

Reference	Continent, Region or Country, n. of Studies	Search Range Applied	Total n. of Studies Included in the Review	Total Sample Size of all Studies Included in the Review	Type of Study	Study Design	Association/s Examined
(Schwingshackl *et al.*, 2017)	-	until August 2017	Among 83 studies, 33 studies talk about BC	-	Systematic review and meta-analysis	1 RCT, 7 cohorts, 9 case control and 16 observational	The effects of MedD and cancer risk
(Chen, Li and Li, 2019)	2 studies in the US, 1 in Europe, French, Netherlands, Norwegian, Finland and Japan	up to June 2009	8 studies	-	Meta-analysis	8 case-control studies	Intake of milk and its products (yoghurt) and risk of BC
(Filippini *et al.*, 2020)	5 studies in US, 4 in Europe and 1 in Japan	up to April 2020	10 studies	344,180 subjects	Systematic review and dose-response meta-analysis	10 cohort studies	Cadmium exposure and BC risk
(Godos *et al.*, 2017)	3 studies in UK, 1 in Netherlands and another one in USA and Canada	up to March 2016	Among the 9 studies, 3 were focus on BC and 2 in BC and prostate cancer or in BC, prostate, and colorectal cancers	In BC cases more than 35,000 subjects	Meta-analysis and systematic review	Cohort studies	Association between vegetarian diets and BC among others
(Chen *et al.*, 2020)	The study that focusses on the cancer was in France	up to October 2019	Among the 22 studies that were selected, one was about cancer in general, prostate, colorectal and BC.	104,980 subjects	Systematic review	Prospective cohort study	The association between UPFs consumption and risk of cancers

Table 4. Cont.

Reference	Continent, Region or Country, n. of Studies	Search Range Applied	Total n. of Studies Included in the Review	Total Sample Size of all Studies Included in the Review	Type of Study	Study Design	Association/s Examined
(Hossain *et al.*, 2019)	14 studies USA, 1 Canada, 4 Europe, and 3 studies in Asia	from January 2000 to March 2018	22 studies	229,597 subjects	Systematic review and meta-analysis	19 case-control and 3 prospective cohort studies.	Evidence linking serum 25(OH)D (both in serum and diet) with BC occurrence.
(Ba *et al.*, 2021)	2 studies from European countries, 6 in Asian countries and another one that included many cases of cancer in US	up to October 2021	Among 17 publications, 9 focused only on BC and another one in BC and other cancers	112,991 subjects in the study that include not only BC and in the studies that focused on BC a total of 322,948 subjects	Meta-analysis and systematic review	7 case-control and 3 cohort studies.	Consumption of mushroom and the risk of cancer
(Wu *et al.*, 2021)	14 studies in USA, 2 in Sweden and 1 in Canada, Japan, Australia, Netherlands and Italy	-	21 studies	1,141,849 women	Meta-analysis	21 cohort studies	Specific milk products and calcium intakes and risk of BC in general and for subtypes defined by ER status
(Sealy, Hankinson and Houghton, 2021)	8 studies in European countries and the other 2 in Kuwait and Turkey	up to June 2020	10 studies	81,436 participants	Systematic review and meta-analysis	8 case-control and 2 prospective studies	Olive oil intake and BC risk
(Chen *et al.*, 2021)	6 studies in European countries, 3 studies in USA, 2 in Asian countries and Iran and 1 in Argentina	up to January 2021	14 studies	312,885 participants	Systematic review and meta-analysis	8 case-control and 6 cohort studies	The DII and the risk of BC

Table 4. Cont.

Reference	Continent, Region or Country, n. of Studies	Search Range Applied	Total n. of Studies Included in the Review	Total Sample Size of all Studies Included in the Review	Type of Study	Study Design	Association/s Examined
(Hou *et al.*, 2019)	6 from Europe, 8 from North America, and the other 5 cohorts were not grouped together	up to June 2018	Among 32 articles, 19 were focus on BC risk	-	Meta-analysis and systematic review	19 cohort studies	Healthy dietary patterns and the risk and survival of BC
(Shridhar *et al.*, 2018)	Neighbouring states of Punjab and Haryana in North India	between 2013 and 2015	-	754 participants, 354 controls and 400 cases of BC	Meta-analysis	Multi-centre case-control study	Indian dietary patterns and BC risk
(Du *et al.*, 2018)	4 from Europe and 3 from the US	up to April 2017	7 studies	27,238 postmenopausal women	A Systematic Review	6 prospective cohort studies and 1 case-control study	Diet quality and the risk of ER-BC
(Michels *et al.*, 2021)	1 from Canada, 7 from European countries, 8 from USA and 1 from China	from 1995 to 2017	Among 46 articles, 17 were about BC risk	18,193 cases of BC among 361,109 subjects	A Systematic Review and meta-analysis	13 case-control studies and 4 prospective cohort	TFAs intake with any cancer risk
(Dianatinasab *et al.*, 2020)	5 in Uruguay and 2 Sweden and France and the other one in China	up to February 2020	10 studies (7 about IDC and 3 about ILC)	In case-control 2,136 controls and 1,642 cases of IDC and 35 of ILC and in cohort studies 106,555 participants and 3,085 IDC and 619 ILC cases	A Systematic Review and Meta-analysis	6 case-control and 4 cohort studies	WD/MedD dietary patterns and the risk of IDC and/or ILC of breast.

Table 4. Cont.

Reference	Continent, Region or Country, n. of Studies	Search Range Applied	Total n. of Studies Included in the Review	Total Sample Size of all Studies Included in the Review	Type of Study	Study Design	Association/s Examined
(Adani *et al.*, 2020)	The studies that focus on BC, 2 in US, 1 in Japan and 7 in Europe	up to February 2020	Among the 18 studies, 10 were about BC	In the case of BC 18,100 cases of BC among 360,157 population	A systematic review and dose-response meta-analysis	16 cohort studies and 2 case-control studies	Estimated dietary intake of acrylamide and risk of female breast, endometrial, and ovarian cancers
(Jayedi, Emadi and Shab-Bidar, 2018)	4 in European countries, 2 in USA and 1 in China	From 2014 to November 2017	Among 31 studies, 7 were about breast cancer	In the case of BC, 18,781 cases of BC among 219,286 population	A systematic review and dose-response meta-analysis	4 prospective cohort studies and 3 case-control studies	DII and risk of cancer
(Peraita-Costa, Carrillo Garcia and Morales-Suárez-Varela, 2022)	-	from 2014 to 2020	28 studies	-	A Systematic review	8 cohort studies, 13 case-control studies and 7 reviews	β-carotenoids and BC
(Long *et al.*, 2022)	7 studies in Nort America, 6 in Europe and 1 in Asia	up to March 2021	Among 55 articles, 28 where about BC risk (15 about GL and 14 about GI)	-	Meta-analysis and Systematic Review	All were prospective cohort studies	Between dietary GI/GL and cancer risk.

Table 5. Results of the studies included in the general review.

Reference	Menopausal Status	Exposure Measure	Overall Results of Review	Statistical Method	Summary Estimates and Related 95% CI	P-value
(Schwingshackl *et al.,* 2017)	-	The components of MedD such as alcohol, cereals, fish, dairy, fruit, legumes, meat, nuts, olive oil, vegetables, and whole grains	It was observed an inverse association between adherence to a MedD and cancer mortality and risk of several cancer types, specifically a small decrease in BC risk (6%) was found	The combined RRs, HRs or ORs of the highest compared to the lowest MedD adherence category, based on a random-effects model	Summary of RR in BC: - RCT: 0.43 (0.21-0.88) - Observational: 0.92 (0.89-0.96) - Cohort: 0.94 (0.90-0.99) - Case-control: 0.89 (0.85-0.94)	-
(Chen, Li and Li, 2019)	-	Milk (low-fat/skim milk and whole milk) or yogurt intakes	No consistent evidence between milk and dairy products and BC risk	Random-effects models of OR was used to compare the highest with the lowest category in the milk and milk products	Summary OR: - Low-fat/skim milk: 0.853 (0.702–1.037) -Whole milk: 0.951 (0.800-1.132) -Yogurt: 0.900 (0.684-1.183)	- Low-fat/skim milk: 0.110 -Whole milk: 0.572 -Yogurt: 0.4499
(Filippini *et al.,* 2020)	Pre- and post-menopausal	Cadmium exposure using urine levels and dietary intake	A marginal and imprecise positive relationship between dietary cadmium intake and BC, and no association in urinary cadmium excretion. Analysis in postmenopausal women showed no association in none of the cases	Random effects meta-analytical model of RRs from each study by comparing the highest versus the lowest exposure category	RR in: - Urine cadmium levels: 1.01 (0.70–1.47) - Cadmium dietary intake: 1.04 (0.90–1.21)	-
(Godos *et al.,* 2017)	-	Non-vegetarian, Pure vegetarian, Semi-vegetarian and Pesco-vegetarian diets	All analyses showed no significant association of a vegetarian diet and a lower risk of any cancer, compared to a non-vegetarian diet	Random-effects models to calculate RRs of cancer between diets	RR for vegetarian versus non-vegetarian diet: - On BC: 0.99 (0.88-1.05)	-

Table 5. Cont.

Reference	Menopausal Status	Exposure Measure	Overall Results of Review	Statistical Method	Summary Estimates and Related 95% CI	P-value
(Chen *et al.,* 2020)	Premenopausal and postmenopausal	UPFs consumption	Positive association between UPFs consumption and risk of cancer in general and postmenopausal BC but no significant association for general and premenopausal BC. However, when UPF consumption was considered as a continuous variable, a direct association on overall BC risk was observed	-	HR in overall cancer: 1.23 (1.08 - 1.40) HR in BC risk: 1.38 (1.05 - 1.81)	-
(Hossain *et al.,* 2019)	4 studies included only premenopausal and 6 only postmenopausal	Vitamin D exposure: - Serum 25(OH)D (per 10 ng/mL or deficient vs. not) - Dietary vitamin D (per 100 IU/d) - Supplemental vitamin D (yes vs. no) - Total vitamin D intake (per 100 IU/d)	Net direct association between 25(OH)D deficiency and BC occurrence, a weaker inverse association for BC and total vitamin D intake from foods and supplements and a similar association for supplemental vitamin D. However, no net association between BC and serum 25(OH)D or between BC and dietary vitamin D	RRs (Risk Ratios) were pooled using random effect models	RR pooled: - 25(OH)D deficiency: 1.91 (1.51–2.41) - Total Vitamin D: 0.99 (0.97–1.00) - Supplemental Vitamin D: 0.97 (0.95-1.00)	- 25(OH)D deficiency: <0.001. - Total vitamin D intake: 0.022, per 100 IU/d - Supplemental vitamin D: 0.026
(Ba *et al.,* 2021)	-	Mushroom consumption	Higher mushroom consumption is related with a lower risk of total cancer and with a lower risk of BC. Evidence of a significant non-linear dose-response association between intake of mushrooms and total cancer risk was also found	The ORs, RRs, or HRs reported were considered as the measures of the association between mushroom intake and the risk of cancer and a random-effects meta-analyses were conducted	RR pooled for the highest vs. lowest consumption groups: - Lower risk of cancer: 0.66 (0.55, 0.78) - Lower risk of BC: 0.65 (0.52, 0.81)	-

Table 5. Cont.

Reference	Menopausal Status	Exposure Measure	Overall Results of Review	Statistical Method	Summary Estimates and Related 95% CI	P-value
(Wu *et al.*, 2021)	-	Total milk, hard cheese, cottage/ricotta cheese, yogurt, ice cream, calcium intake	None or very weak inverse associations for the consumption of dairy products, dietary calcium, and total calcium were founded in the risk of overall and ER-positive BC	Study-specific HRs were estimated and then combined using random-effects models. The Wald test was used to prove a linear trend across categories of intake for each participant	HR pooled: -Dietary calcium intake associated with BC: 0.98 (0.97-0.99)	Dairy products and risk of BC: >0.05
(Sealy, Hankinson and Houghton, 2021)	3 studies only in postmenopausal women	Olive oil intake	Suggestion of an inverse association between olive oil consumption and BC although it was not significant in prospective or case-control analyses	The use of random effect models to estimated summary OR and 95 % CI for the highest versus lowest olive oil intake category and the use of restricted cubic splines to evaluate the dose–response relationship between olive oil and BC risk	Summary OR: - Prospective studies: 0.48 (0.09-0.27) - Case-control studies: 0.79 (0.54-1.06)	-
(Chen *et al.*, 2021)	Premenopausal and postmenopausal	7 pro-inflammatory dietary components: vitamin B12, carbohydrates, cholesterol, total fat, protein, saturated fat, and trans-fat	Women in the most pro-inflammatory diet category showed a higher risk of breast cancer than those in the most anti-inflammatory category. This association was strong in both pre- and postmenopausal women	. Multivariable adjusted RRs were clustered to compare the most pro- and anti-inflammatory diets using a random-effects model. Since the incidence of BC was low, the ORs reported in the case-control studies were considered equal to the RRs	Most pro-inflammatory vs less pro-inflammatory diet RR in: - Women: 1.37 (1.17-2.99) - pre-menopausal women: 1.87 (1.17-2.99) - postmenopausal women: 1.23 (1.08-1.40)	- Women: <0.001 - pre-menopausal women: =0.001 - post-menopausal women: < 0.001

Table 5. Cont.

Reference	Menopausal Status	Exposure Measure	Overall Results of Review	Statistical Method	Summary Estimates and Related 95% CI	P-value
(Hou *et al.*, 2019)	11 evaluated pre-menopausal and other 11 post-menopausal	Healthy dietary patterns characterized by high intake of vegetables, food with a low-fat content and fruit	Statistically significant lower risk of BC associated with healthy dietary patterns. The results of the subgroup analysis suggested that there was an inverse association between BC risk and healthy patterns derived from posterity, but no in the other stratified subgroups	Random-effects model	Healthy dietary patterns and BC risk: 0.93 (0.88, 0.98)	-
(Shridhar *et al.*, 2018)	-	Non-vegetarian diet and 2 common Northern Indian dietary patterns: lacto-vegetarianism and lacto-ovo-vegetarianism diets	BC risk was lower in lacto-ovo-vegetarians compared to both non-vegetarians and lacto-vegetarians	Multivariate unconditional logistic regression analysis that adjusts for a priori selected confounding factors and matching variables	OR in comparation of non-vegetarians: - Lacto-ovo-vegetarians: 0.6 (0.3-0.9) OR in comparation with lacto-vegetarians: - Lacto-ovo-vegetarians: 0.4 (0.3-0.7)	- If non-vegetarians are the reference: 0.033 - If lacto-vegetarians are the reference: <0.001
(Du *et al.*, 2018)	Post-menopausal	12 different diet quality scores: 2 versions of the DII, 4 of the MedD, the Healthy Eating Index, the Alternate Healthy Eating Index, the DASH score, and 3 of low-carbohydrate diet scores	Of the 4 studies on MedD scores, 3 exhibited a significant inverse association with ER - postmenopausal BC, while no solid association was observed with the other diet quality scores. While most of the diet quality scores in this review share similarly dietary components, most of the non-MedD were represented by only 1 study each, and the associations with ER - postmenopausal BC were mixed	Each study was adjusted for multiple covariates.	-	-

Table 5. Cont.

Reference	Menopausal Status	Exposure Measure	Overall Results of Review	Statistical Method	Summary Estimates and Related 95% CI	P-value
(Michels *et al.,* 2021)	Some focus on postmenopausal women	TFA and TFA subtypes (from ruminant, fish vegetables, industrial, monounsaturated…) intake	Meta-analyses of BC risk with total TFA intake or with 3 TFA subgroups were not significant, although in the first ones was rather questionable as in postmenopausal women was observed a significantly increased risk. In erythrocyte and adipose tissue TFA studies and trans-vaccenic acid, significant associations were found	Random-effects models	OR of the meta-analysis about total TFA: 1.12 (0.99–1.26)	-
(Dianatina sab *et al.,* 2020)	6 studies about pre- and post-menopausal women and 1 focused on postmenopausal women	WD and MedD	A statistically significant adverse association was observed between MedD and IDC in case–control studies but in cohort studies the association was nonsignificant. The analysis also suggested a significant and direct association between the WD and the risk of IDC. In the case of risk of ILC a highly protective effect in MedD and a weakly significant association in WD was observed	Multivariable adjusted RR and 95% CIs comparing the highest and lowest categories of WD and MedD patterns were pooled using the random-effects meta-analyses	RR pooled: - MedD in case-control studies: 0.47 (0.39-0.55) - MedD in cohort studies: 0.98 (0.92-1.05) - WD and risk of IDC: 1.36 (1.18-1.53) - MedD and risk of ILC: 0.76 (0.64-0.87) - WD and risk of ILC: 1.45 (1.04-1.86)	- MedD in case–control studies: <0.001 - MedD in cohort studies: = 0.003 - WD and the risk of IDC: =0.017 - MedD and the risk of ILC: < .001 - WD and risk of ILC: = 0.52

Table 5. Cont.

Reference	Menopausal Status	Exposure Measure	Overall Results of Review	Statistical Method	Summary Estimates and Related 95% CI	P-value
(Adani *et al.*, 2020)	6 recruited only pre- or post-menopausal women.	Dietary intake of acrylamide	For BC, a null or inverse relationship between exposure and risk has been proved, especially among never smokers and postmenopausal women	The global measure of association (RR, HR, OR) and corresponding 95% CIs for each cancer type comparing the lowest vs. the highest level of exposure in a random-effects model	RR in BC comparing the highest vs the lowest levels of acrylamide exposure: RR: O.96 (0.91-1.02)	-
(Jayedi, Emadi and Shab-Bidar, 2018)	5 studies focus on postmenopausal and 2 focus on premenopausal status	DII that includes 9 components that have pro-inflammatory properties (energy, cholesterol, carbohydrates, total fat, TFA, saturated fat, iron, vitamin B12 and protein) and another 36 that have anti-inflammatory characteristics	Dose-response meta-analysis showed an increase of 1 unit in DII was weakly associated with BC risk	Pooled RRs were calculated by using a random-effects model.	Pooled RR: 1.03 (1.00, 1.07)	= 0,03
(Peraita-Costa, Carrillo Garcia and Morales-Suárez-Varela, 2022)	-	caroneoids and β-carotenoids	Inverse association between carotene intake and breast cancer risk, highlighting the antioxidant role of carotenoids, among which β-carotene stands out	-	-	-

Table 5. Cont.

Reference	Menopausal Status	Exposure Measure	Overall Results of Review	Statistical Method	Summary Estimates and Related 95% CI	P-value
(Long *et al.,* 2022)	7 cohorts provide information about pre- and post-menopausal women, 3 only focus on post-menopausal	dietary GI/GL	It was positively associated dietary GI with BC risk for higher vs. lower intake categories. However, a null association was observed when this comparation was done of dietary GL. The analysis based on menopausal status and GI showed that the association was marginally positive for postmenopausal BC whereas it was not positive for premenopausal BC. In the case of GL, no relation was observed between this dietary and postmenopausal BC	A random-effects model was used to calculate the summary RR and 95% CI for the highest vs. lowest categories of dietary GI or CG. If a cohort reported associations stratified by participant character (e.g., menopausal status) rather than overall outcomes, a fixed-effects model was used to combine the risk estimates	GI and BC risk: 1.05 (1.01-1.09) GI in postmenopausal and BC risk: 1.06 (1.00-1.13) GI in premenopausal and BC risk: 1.06 (0.95-1.17)	GI and BC risk =0.008. GI in postmenopausal and BC risk: =0.044 GI in premenopausal and BC risk: =0.282

Table 6. Conclusions and limitations of studies included in the general review.

Reference	Limitations	Recommendations / Conclusions	Quality Assessment Tool	Quality Assessment
(Schwingshackl *et al.,* 2017)	The components of a MedD are inconsistent between different epidemiological studies and the results are limited by methodological shortcomings of some of the studies enrolled	It provided important additional evidence of a beneficial effect of high adherence to the MedD with respect to primary prevention of overall cancer risk and specific types of cancer. These observed beneficial effects are mainly due to an increased intake of fruits, vegetables, and whole grains. In addition, a small decrease in breast cancer risk (6%) is reported with the pooling of seven cohort studies. To further elucidate the relationship between MedD patterns and cancer types, future studies should adopt a precise definition of MedD	-	-

Table 6. Cont.

Reference	Limitations	Recommendations / Conclusions	Quality Assessment Tool	Quality Assessment
(Chen, Li and Li, 2019)	The moderate reliability of several methods used in epidemiologic studies and consequently the misclassification of intake; the correlation among nutrients in diet; the difference in the average intake in populations; the data analysis about the levels of vitamin D in milk products and whether the milk is derived from cow's receiving bovine growth hormone	The available epidemiologic evidence does not support a strong association between the milk/milk products and BC risk	-	-
(Filippini *et al.*, 2020)	The available data were too restricted to perform stratified analyses by age, smoking, and hormone receptor status	Little evidence of a positive association between cadmium and BC. Therefore, a possible association between cadmium exposure and BC cannot be completely ruled out	Risk of Bias in Non-randomized Studies of Exposures	-
(Godos *et al.*, 2017)	The number of studies was generally limited for all meta-analyses performed, differences in the background characteristics of the populations included in the cohort studies may weaken the results, most studies do not provide repeated measurements during follow-up periods and the study could not add more variation of vegetarian diets because of the limited data available	Fish-based and Plant-based dietary patterns constitute a healthy dietary choice in comparison to meat-based dietary patterns when cancer is considered as an outcome. Further studies are required to provide more evidence and to better investigate possible causal roles	-	-
(Chen *et al.*, 2020)	Most of the cohort studies recruited volunteers or university graduates as study subjects, who tended had lower UPFs consumption and to be more health-conscious than the general population. The median follow-up could be relatively inadequate. Epidemiological studies could not exclude reverse causality or residual confounders	The results of this study indicated a positive association between UPFs consumption and the risk of various health problems. Moreover, it suggested a decrease in the consumption of UPFs and an increase in the proportion of unprocessed or minimally processed foods. Large-scale prospective studies are required to verify the findings and to have a better understanding of the relative effects of different aspects on UPFs	The Newcastle-Ottawa Scale	High quality

Table 6. Cont.

Reference	Limitations	Recommendations / Conclusions	Quality Assessment Tool	Quality Assessment
(Hossain *et al.*, 2019)	The literature search was restricted to the PubMed and Cochrane databases; not search for cross-references or unpublished studies; some meta-analyses were low-powered given the limited number of data-points available; the evidence was mostly generated from observational studies which impedes the ability to confirm causality; the reported associations may be confounded by other micro - and macro-nutrients, and/or lifestyle factors known to affect the risk of BC; the issue of measurement error that is inherent in the dietary assessment of vitamin D; publication bias cannot be ruled out as an explanation for these study results	25(OH)D deficiency was directly related to BC, while total vitamin D and supplemental vitamin D intake had an inverse relationship with this outcome. Further randomised clinical trials are required to have more proved of observational studies	-	Relatively above-average quality set of studies
(Ba *et al.*, 2021)	Combining studies of different populations can lead to heterogeneity due to unequal characteristics of the study populations, a case-control design is subject to recall and selection bias, and finally, publication bias is unavoidable	A significant inverse association between lower cancer risk and higher mushroom consumption was found. Particularly, BC seemed to be the most affected, as a significant association with mushroom consumption was only observed in this type of cancers	Newcastle-Ottawa Quality Assessment Scale	-
(Wu *et al.*, 2021)	Dietary intake was inevitably measured with error, there could be misclassification of exposure and covariates, estimated intake during early life could not be measured, and the study population was predominantly about white women	It is unlikely that adult dairy consumption is associated with an increased risk of BC and that increased consumption of fermented dairy products could decrease the risk of the ER-negative subtype. Evaluation in more diverse populations and those with higher consumption of fermented dairy products may help to further elucidate any relationship	-	-

Table 6. Cont.

Reference	Limitations	Recommendations / Conclusions	Quality Assessment Tool	Quality Assessment
(Sealy, Hankinson and Houghton, 2021)	-	Olive oil may reduce the risk of BC; nevertheless, as the level of certainty is very low, further prospective studies and more detailed information on exposure assessment, such as type of olive oil and cooking method, are needed	-	-
(Chen *et al.*, 2021a)	Because of insufficient data, the association between DII and different BC subtypes based on hormone receptor expression and pathological features could not be analysed. Cohort and case-control studies might have caused bias. Substantial heterogeneity was found among the included studies	A very strong and independent association was observed between a pro-inflammatory diet and BC risk, irrespective of menopausal status. More studies are required to determine the relationship between a pro-inflammatory diet and different subtypes of BC	Newcastle-Ottawa Scale	-
(Hou *et al.*, 2019)	The findings are based directly on the covered studies, and these studies have their own strengths and limitations in terms of study design. The only comparison was between the highest and lowest categories of healthy dietary patterns without considering the middle categories. The differences in dietary assessment methods between the studies. The fact that the included studies only examined measurements of dietary patterns at a single point in time, and these do not consider changes in dietary habits over time. Finally, only studies published in English were included	The findings suggest that healthy dietary habits may be associated with a lower risk of BC and all-cause mortality among BC patients. It may be clinically important to promote healthy dietary patterns for BC prevention	Newcastle-Ottawa Scale	-

Table 6. Cont.

Reference	Limitations	Recommendations / Conclusions	Quality Assessment Tool	Quality Assessment
(Shridhar *et al.,* 2018)	-	The results suggest that lacto-ovo vegetarian, but not lacto-vegetarian, dietary patterns may be associated with a lower risk of BC among North Indian women. Although this could be attributed to egg consumption patterns, the mechanisms of the observed association are unclear. The observed difference between lacto-vegetarian and lacto-vegetarian dietary patterns requires confirmation, and, if confirmed, further research is needed	-	-
(Du *et al.,* 2018)	The limited number of studies for each dietary score. The studies are observational so causal relationships cannot be directly established. There may also be some level of recall bias in the case-control study	There were mixed results for an association between a variety of diet quality scores and postmenopausal ER-BC. Nevertheless, results for versions of the MedD scores were more consistent in suggesting an inverse association	Scottish Intercollegiate Guidelines Network	Higher quality
(Michels *et al.,* 2021)	Questionnaires used to investigate TFA can be susceptible to recall bias and inaccuracy of measurements due to significant differences in TFA between products and over time. A more objective way to investigate intake is the assessment of biomarkers, measuring TFA concentration in blood or and in the adipose tissue. Finally, the lack of uniformity in the use of confounding variables as well as in the terminology used for various studies	Some potential adverse effects of high intakes of TFAs through an increased risk of cancer. Therefore, the review provides some support for the prohibition of industrial TFAs in food. Methods and study designs of higher methodological quality should be applied in the future studies of the association with fatty acid intake and cancer risk. Moreover, considering the possible differential effects of different TFA subtypes, for targeted prevention strategies, it is also interesting examine which TFA subtypes may be more carcinogenic and which populations are at higher risk	Newcastle-Ottawa scale	-

Table 6. Cont.

Reference	Limitations	Recommendations / Conclusions	Quality Assessment Tool	Quality Assessment
(Dianatinasab *et al.,* 2020)	Small number of studies, the number of the cases of ILC in cohort studies and in case-control studies may influence the reliability of results when a compaction of case-control and cohort studies is done	Evidence of an inverse general association between DM and the risk of CDI and LCI and straight associations between the pattern of WD and the risk of CDI and LCI. It is clinically important to promote healthy dietary patterns for the prevention of BC and to guide the nutritional care of patients with BC to improve the effects of treatment. More research is required to better understand the mechanisms involved in the association of dietary patterns and BC subtypes and how dietary patterns influence patients with common BC subtypes	Newcastle-Ottawa Scale	Medium to High quality
(Adani *et al.,* 2020)	-	While some results were based on a small number of studies, the results appear to support current efforts to control and minimise acrylamide intake as there is evidence of a small positive association with the risks of certain types of cancer. In contrast, there was limited evidence of an association between acrylamide intake and BC risk, except for an increased risk with ≥20 mg/day of acrylamide among premenopausal women	-	-
(Jayedi, Emadi and Shab-Bidar, 2018)	In the BC analyses, the associations were attenuated substantially in the subgroup of cohort studies and among studies with a fewer number of components used to calculate the DII because the increment in the number of components seems to strengthen the associations. However, the associations across different combinations of the DII could not appropriately be tested. Moreover, case-control studies are subject to recall bias, selection bias, and reverse causation bias	The meta-analysis suggested that an increased risk of cancers was associated with the higher inflammatory properties of the diet, as represented by DII. It may be useful to replicate research using more high-quality studies in different geographical regions with diverse dietary habits and different genetic susceptibilities	Newcastle-Ottawa Scale	-

Table 6. Cont.

Reference	Limitations	Recommendations / Conclusions	Quality Assessment Tool	Quality Assessment
(Peraita-Costa, Carrillo Garcia and Morales-Suárez-Varela, 2022)	-	The review identifies that β-carotene intake decreases the risk of BC, but this effect may differ depending on both the cancer hormone receptor status and the menopausal status. Carotenoid (β-carotene) consumption in adolescence has been shown to decrease the risk of BC in adulthood. Consumption of diets with a high level of antioxidants has been as sociated with a lower risk of BC, and vitamin and mineral supplementation might prevent or palliate the effects	Scottish Intercollegiate Guidelines Network	-
(Long *et al.*, 2022)	The lack of evidence of high-quality evidence, the limitation of the variety of foods listed in the FFQ which may restrict the detectable range of GI and GL, the factors that studies included in their analyses were different, and this may lead to residual confounding, information on long-term dietary behaviour was not available	High dietary GI increased the risk of cancer in general with low certainty of evidence. For specific cancers, such as BC, this trend is also followed especially for postmenopausal BC	Risk of Bias in Non-randomized Studies of Exposure	-

Abbreviations: *BC: Breast cancer; RTC: Random controlled trials; MedD: Mediterranean Diet; UPF: Ultra-processed food; 25(OH)D: 5-hydroxy-cholecalciferol; US: United Stated: USA: United State of America; ER: estrogen receptor; TFA: trans-fatty acids; ILC: Invasive Lobular Carcinoma ; ILD: Invasive Ductal Carcinoma; WD: Western Diet; GI: glycaemic index; GL: glycaemic load; OR: Odds Ratio; RR: Risk Ratio; HR: Hazard Ratio; CI: Confidence Interval; FFQ: Food frequency questionaries; DASH: Dietary Approaches to Stop Hypertension.*

6 DISCUSSION

Based on this bibliographic research, a higher intake of UPFs, or foods with high GI or high DII would seem to be associated with a higher risk of developing BC. Moreover, the menopausal status also seems to affect the risk of BC in some cases such as the consumption of TFA and UPFs in which the risk is higher in postmenopausal women. Other foods, such as mushrooms seem to be inversely associated with BC risk. One meta-analysis and systematic review suggested an inverse association between BC and the consumption of olive oil. Some nutrients also seem to be inversely associated with BC risk, including calcium, vitamin D and carotenoids. Finally, the evidence in some cases is still conflicting as concerns exposure to other dietary elements for example in the case of the dairy products, cadmium, or acrylamide.

6.1 DIETARRY PATTERNS

Focusing on the dietary patters it must be said that considering them as a whole rather than individual nutrients or food appears to have advantages in all aspects due to the fact that food is not consumed separately, and their health effects are additive or even synergistic (Cottet *et al.*, 2009). That is why, analyse a diet as a whole could facilitate the analysis of the effects related to BC prevention.

The findings indicate that most of the literature analysed attributed a protective role to the MedD (Schwingshackl *et al.,* 2017; Dianatinasab *et al.,* 2020). Research has shown that this type of diet is rich in antioxidants, which probably inhibit the synthesis and activity of growth factors that promote the development of cancer cells. Some authors have stated that adiposity control, calorie balance, and exercise are also important for the prevention of BC, as well as the diet composition and its quality (McTiernan *et al.*, 2004; Frank *et al.*, 2005; Pasanisi *et al.*, 2006; Campbell *et al.*, 2012). MedD also appears to have a beneficial influence against the risk of BC, independent of body weight and Body Mass Index (Murtaugh *et al.*, 2008; Wu *et al.*, 2009; Trichopoulou *et al.*, 2010). Traditional MedD literature has shown that dietary fibre has multiple protective effects, involving inhibition of intestinal reabsorption of estrogens and modulation of cholesterol levels and

glucose release, lowering the risk of BC (Rose *et al.,* 1991). The protective effect of fruits and vegetables appears to be related to their high content of valuable substances (minerals, vitamins, salicylates, glucosinolates, phytosterols, polyphenols, phytoestrogens, sulphides, phytoestrogens, lectins…), which have an antioxidant action, blocking the activation of many carcinogens, inhibiting spontaneous mutations, and protecting cellular structures and DNA against oxidative damage generated by metabolic processes (Rose *et al.*, 1991; Surh, 2003). Green leafy vegetables are rich in lutein, carotenoids folates, zeaxanthin, and vitamin A, which are antioxidants and have also the ability to regulate estrogen metabolism and inhibit tumour growth (Ribaya-Mercado and Blumberg, 2004; Masala *et al.*, 2012). Fruits appear to have anti-cancer potential because of their antioxidant properties, being especially true for red fruits. These fruits contain anthocyanins, ellagic acid and quercetin that inhibit angiogenesis, stimulate toxic elimination mechanisms, promote cell apoptosis mechanisms, and reduce inflammation (Surh, 2003). Although in the present analysis were not founded specific studies about the intake of fruits and vegetables with the risk of BC, a pooled analysis of eight large cohort studies and another comparative study of three cohorts unfortunately did not strongly associate the intake of fruit and vegetables with the risk of BC (Smith-Warner *et al.*, 2001). On the other hand, there is a controversial and specific "ingredient" of a MedD which is the ethanol, usually represented in the form of red wine. In some studies, alcoholic beverages consumption even in low or moderate amounts was associated with an increased risk of cancer, including BC (Allen *et al*., 2009). Moreover, a recent meta-analysis of studies on postmenopausal BC found that when the alcohol was included, the protective effect of the MedD in the risk of BC disappeared (Brandt *et al.,* 2017). Therefore, although red wine contains a variety of potentially protective ingredients, such as antioxidant polyphenols, its beneficial role with respect malignant disease is controversial.

The study included in the present work indicated that the Western diet, which involves a high intake of saturated fats, refined sugars, and alcohol, is strongly associated with an increased risk of ILC and IDC (Dianatinasab *et al.*, 2020). This type of diet influences inflammatory processes and induce an increase in adiposity and the production of hormones (testosterone and estrogen) and growth factors. Despite the fact that only one

study was included in this work, more studies that relate this diet with an increased risk of BC are found (Männistö *et al.*, 2005; Brennan *et al.*, 2010).

Evidence across different populations indicates an inverse association of BC risk with healthy dietary pattern consisting of vegetables, fruits, whole grains and legumes and a positive association with a dietary pattern consisting of red and processed meat, fried foods, and sugar. However, the evidence on vegetarian diets is less convincing as the associations found in the studies were uncleared. Vegetarian diets are rich in magnesium, fibre, antioxidants, phytochemicals, vitamin C and E, folic acid, Fe3+ and n-6 polyunsaturated fatty acids (PUFAs), whereas they are low in total fat, saturated fatty acid, cholesterol, sodium, zinc, Fe 2+, vitamins A, B12 and D and n-3 PUF(McEvoy *et al.,* 2012). Antioxidant vitamins, PUFAs and phenolic compounds may exert anti-inflammatory effects, as well as protective effects against DNA damage through the prevention of oxidation and the enhancement of biological pathways implicated in cancer initiation, including cell signalling, cell cycle regulation, angiogenesis, and inflammation (Grosso *et al.*, 2013; Fantini *et al.*, 2015). So, the basis for the hypothesis that a plant-based diet could protect against cancer is based in the benefits of a high fibre and antioxidant intake characterised by the content of vegetable, whole grains, and fruits. In this review it was not found significant differences between vegetarian diet and non-vegetarian diet with the risk of BC (Godos *et al.*, 2017), and in other study that lacto-ovo-vegetarian Indian women compared to non-vegetarians and lacto-vegetarians Indian women had a lower risk of BC (Shridhar *et al.*, 2018). This could be due for the consumption of eggs, however, the major dietary nutrients of the eggs (cholesterol, choline and protein intake relative to energy) are linked with and increased risk of BC (Keum *et al.*, 2015). Cholesterol is a precursor of steroid hormones, so it can impact in estrogen activity and contribute to cellular inflammation, which is crucial to BC progression (Ferretti *et al.*, 2006). Choline and high protein encourage tissue growth and tumour progression, although choline has also been found to be inversely associated with BC risk k (Keum *et al.*, 2015). Nevertheless, these biological mechanisms are not yet proved and other factors such as cooking pattern and genetic susceptibility could play complex roles in the association with BC risk. In addition, eggs also contain certain amino

acids, zeaxanthin, lutein, omega-3 and omega-6 fatty acids, which may be associated with reduced risk for BC as observed in some other studies (Si *et al*., 2014).

In summary, MedD could be used as a primary prevention measure for BC. However, in general, the studies selected did not provide solid results regarding specific dietary patterns and risk of BC. Due to the fact that a diet can contain several foods which could have opposite effects, the analysis of current dietary eating patterns could not provide evidence of any clear association. That is why further studies could probably be performed using machine learning techniques, as this type of analysis could test a priori undefined food groups, rather than prototypical dietary patters, in terms of their link with BC risk, or BC prevention.

6.2 FOODS

In this assignment, the relation between milk and dairy products could not be determined due to the associations not being clear (Chen, Li and Li, 2019; Wu *et al.*, 2021). On the one hand, these foods could have been associated with positive results likely because of the protective effect of calcium and vitamin D (Cui and Rohan, 2006; Gissel *et al.*, 2008; Chen *et al.*, 2010). Breast tissue has receptors for the biological active form of vitamin D, calcitriol 1,25(OH)2D, which seems to be involved in the control of more than 200 genes, including those that are responsible for cell proliferation, malignant cell differentiation, apoptosis, and angiogenesis. On the other hand, a higher risk of BC could also be found among these products, as a dairy product consumption could lead to an increased intake of estrogen hormone, which may increase the penetrance of BC related to breast cancer antigen (*BRCA*) mutations (Pasanisi *et al.*, 2011). Moreover, milk has the potential to raise blood levels of growth factors, which are significantly associated with a higher risk of BC (Norat *et al.*, 2007; Qin, He and Xu, 2009).

A significant association was demonstrated between the consumption of UPFs and a higher risk of postmenopausal and overall BC (Chen *et al.*, 2020). The UPFs intake is also often accompanied by high intakes of calories, sugar, fat and salt and low intakes of fibre and micronutrients as well as an increased of added sugar and changes in microbiota (Micha *et al.,* 2017). Moreover, cooking procedures, such as food additives and food

packaging as well as the heat treatments, to which these foods are subjected, can generate genotoxicity and carcinogenicity (Schnabel *et al.*, 2019). All of this leads to a poor dietary quality which make possible the development of noncommunicable diseases including cancers (Micha *et al.*, 2017)

Finally, it was found a lower risk of BC with a higher consumption of mushrooms (Ba *et al.*, 2021), and it was suggested that the olive oil could decrease the risk of BC (Sealy, Hankinson and Houghton, 2021). In the case of the mushrooms, their protective effect could derive from their antioxidant properties caused by mushroom-specific components (ergothionein and glutathione) and their bioactive components (such as β-glucans), which have been linked with anti-tumour and immunomodulatory properties (Hetland *et al.*, 2011; Patel and Goyal, 2012; Chen *et al.*, 2014; Friedman, 2016). On the other hand, the olive oil was proposed as a BC protector due to their possible chemoprotective proprieties because of its antioxidant activity of its polyphenolic (e.g., hydroxytyrosol, tyrosol) and secoiridoid derivatives (e.g. oleuropein, oleocanthal). However, concentrations of polyphenols in olive oil differ widely because of the agricultural factors, processing and extraction methods, and storage (Gorzynik-Debicka *et al.*, 2018). In this case, although it was suggested a protective effect, the study analysed did not found a significant association between olive oil and BC risk (Sealy, Hankinson and Houghton, 2021).

6.3 NUTRIENTS

The risk of BC in postmenopausal women could be increased with the consumption of TFA (Michels *et al.*, 2021). This could be due to the fact that it has been found that with the highest intakes of TFA an increase in the levels of inflammatory biomarkers (e.g., interleukin-6, C-reactive protein, and E-selectin) is produced (Mozaffarian *et al.*, 2004). This chronic inflammation and oxidative stress may induce cell proliferation and DNA/RNA/protein damage by oxidative free radicals (Coussens and Werb, 2002). DNA mutation could lead to decreased expression of tumour suppressor genes or increased expression of oncogenes, whereas damage at protein level can decrease the function of

the proteins and, therefore, uncontrolled growth of malignant cells is allowed (Slattery *et al.,* 2002).

A significant inverse association has been demonstrated between the consumption of carotenoids, specially β-carotenes, and the risk of BC (Peraita-Costa, Carrillo Garcia and Morales-Suárez-Varela, 2022). This association is because carotenoids have antioxidant properties and carotenes are able to bind and eliminate free radicals, repair DNA damage, inhibit cell proliferation, induce apoptosis and suppress angiogenesis (Cui *et al.*, 2007).

About the acrylamide and cadmium, in both cases the results were not cleared (Adani *et al.*, 2020; Filippini *et al.*, 2020). In the case of cadmium, although there is some biological plausibility of the association of a higher risk of BC related to some toxic properties of the heavy metal, such as reactive oxygen species production, estrogenicity, and DNA damage (Åkesson *et al.*, 2014), other studies reported cadmium properties compatible with a reduced risk of BC. These effects could be explained by the decrease in estradiol levels induced by this metal or the adverse effects of this on the cell viability and angiogenesis properties (Gaudet *et al.*, 2019; Amadou *et al.*, 2020). About the acrylamide, there are some evidence that it could alter the estrogens levels in premenopausal women (Hogervorst *et al.*, 2013; Nagata *et al.*, 2015), inducing cytotoxic and genotoxic effects through the induction of oxidative balance which leads to cell death or neoplastic transformation, altern protein function by the bind of cysteine residues in proteins and might also have endocrine disrupting properties (Valko *et al.,* 2004; Semla *et al.,* 2017). However, in both cases, none clear relationship between this compounds and the risk of BC have been found in the studies included on this work (Adani *et al.*, 2020; Filippini *et al.*, 2020).

There are two studies that indicate that a higher risk of BC is linked with higher DII score because it is representative of a more proinflammatory and less anti-inflammatory diet (Jayedi, Emadi and Shab-Bidar, 2018; Chen *et al.,* 2021). This could be due to clinical studies having indicated that a chronic inflammation caused by pro-inflammatory dietary components may elevate BC risk, as this inflammation is linked with BC (Coussens and Werb, 2002). Carbohydrates, cholesterol, and saturated fat have been considered as pro-inflammatory food components, while fibre and omega-3 fatty acids have been

considered as anti-inflammatory (Zheng *et al.*, 2013; Chen *et al.*, 2016). However, in some cases not all the studies report a positive association, and this could be because the association between diet and BC is mediated by different mechanisms other than inflammation (Chen *et al.,* 2021).

On the other hand, high GI foods, such as simple sugars, refined carbohydrates, and starches, promote a rapid increase in blood glucose, and thereby stimulating insulin production. High levels of insulin tiggers the production of insulin-like growth factor 1 (IGF-1) and testosterone, which are both recognized as risk factors for BC. Furthermore, chronic hyperinsulinemia with associated insulin resistance plays a role in the etiology of BC since it induces the production of IGF-1, which is capable of causing mutagenic changes (Papa and Belfiore, 1996). The study included in this work (Long *et al.*, 2022) demonstrated that a higher risk of BC is liked with a higher GI. However, in the case of GL this relation was no observed. These could be due to GL considering the GI and the amount of carbohydrate available at the same time, reflecting the quality and quantity of carbohydrate. So, the discrepancy between GI and GC results highlights the important role of the variety and quantity of carbohydrates in the diet, in which high-quality carbohydrates from fruits, vegetables and whole grains reduce the risk of BC, whereas refined sugar from sugary soft drinks has the contrarian effect.

Although in this review the PUFAs were not examinate, it was interesting to name them as well as the total and saturated fat. The n-3 PUFA and n-6 PUFA families compete for the same metabolic pathway, which is related with cell proliferation in breast tissue. The n-3 PUFA family reduces inflammation and controls triglyceride levels, which leads to reduction of the risk of BC via different mechanisms, such as modulating the expression and function of various receptors, transcription factors, and signalling molecules, altering the composition of the phospholipid cell membranes, and inhibiting arachidonic acid metabolism and pro-inflammatory molecule production (Murff *et al.*, 2011). However, n-6 PUFA contribute to carcinogenic processes with the production of pro-inflammatory eicosanoids, like the prostaglandin E2, which is implicated in angiogenic processes and in the suppression of cancer cell apoptosis (Murff *et al.*, 2011; Corso *et al.*, 2020). That is why, in some studies it could be found a contrary result between the effects of PUFAs and BC risk (Yang *et al.*, 2014; Mourouti *et al.*, 2015). Regarding a high consumption of

total or saturated fat, there are some evidences that relate this with a higher risk of BC, especially in postmenopausal women as well as with obesity and overweight in the case of saturated fat which are stablished risk factors of BC (Larsson and Wolk, 2008). Moreover, the synthesis of estrogen is increased with a diet rich in saturated fat, increasing cell proliferation and, consequently, also increasing the risk of BC (Key *et al.*, 2003). Other nutrients that are not contain in this review but could be related with lower risk of BC are the flavonoids which have been acknowledged to have a role in protecting against and preventing non-communicable diseases, and neoplasms, because of their potent antioxidant and DNA repairing activity (Neuhouser, 2004; Hui *et al.*, 2012)

6.4 QUALITY DIETARY PATTERNS

In this assignment, it was also included one systematic review about Quality Dietary Patterns and the risk of ER-BC (Du *et al.*, 2018). In this case, diet quality scores were constructed to measure specific dietary attributes (e.g., low carbohydrate diet scores) or to reflect healthy diet in general (e.g., Healthy Eating Index and Alternative Healthy Eating Index). Thus, their characteristics varied from those that emphasized fruits and vegetables while discouraging red and processed, to those that focused on particular nutrients.

It was found that the results from MedD scores suggested more consistent association with a reduced risk of ER-BC. It is due to a healthy diet can reduce the development of this type of through several mechanisms. The richness of dietary fibre, vitamins, and antioxidants may inhibit inflammatory responses, neutralize free radicals, and prevent DNA damage (Romaguera *et al.*, 2010; Verberne *et al.*, 2010). The favourable association may also be facilitated by weight control as increased adiposity has been identified as a risk factor of BC. Moreover, the MedD has been shown to improve insulin resistance and glycaemic control (Esposito *et al.*, 2010), which are more significantly associated with risk of BC. All of this is conscient with the other studies that were included in this work and inversely relate MedD to the risk of BC (Schwingshackl *et al.,* 2017; Dianatinasab *et al.,* 2020).

7 CONCLUSION

Overall, this assignment found moderate evidence that the consumption of foods containing carotenoids, higher intake of mushrooms, vitamin D or the adoption of diets with high content in calcium might reduce the risk of developing BC. However, a higher intake of UPFs, or of foods with high GI or high DII might increase the risk of developing BC, specially, in postmenopausal women. Regarding dairy products, cadmium, acrylamide, and olive oil the evidence is still conflicting as the results are confusing.

However, this work also reveals the weaknesses of the observational studies and reviews published in relation to diet, specific foods or nutrients and BC, as some studies did not provide solid results. The main weakness relates to measurement errors in dietary intake assessments, which bias the estimates of any such associations. Besides, meta-analyses and systematic reviews of case-control studies may also be influenced by interview and recalls bias, usually showing associations that are not validated in cohort studies.

All in all, one of the most modifiable aspects in people's lifestyle is nutrition. Dietary choices may influence health and minimize the risk of suffering cancer. In general, following healthy eating habits seems to significantly reduce the risk of BC.

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9 ANNEXES

ANNEX A: PRIMSA 2020-CHECKLIST

Table A1: Quality of studies included in the assignment

	PRISMA 2020-CHECKLIST																											
Reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total
(Schwingshackl et al., 2017)	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	24
(Chen et al., 2019)	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	23
(Filippini *et al.*, 2020)	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	23
(Godos *et al.*, 2017)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	25
(Chen *et al.*, 2020)	1	0	1	1	1	1	1	0	1	1	0	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	21
(Hossain *et al.*, 2019)	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	24
(Ba *et al.*, 2021)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	26
(Wu *et al.*, 2021)	0	0	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
(Sealy, Hankinson and Houghton, 2021)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	26
(Chen *et al.*, 2021)	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	25
(Hou *et al.*, 2019)	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	26

Table A1: Cont.

	PRISMA 2020-CHECKLIST																										
Reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total
(Shridhar *et al.*, 2018)	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	23
(Du *et al.*, 2018)	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	0	0	0	0	0	1	1	0	1	1	19
(Michels *et al.*, 2021)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	26
(Dianatinasab *et al.*, 2020)	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	26
(Adani *et al.*, 2020)	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	23
(Jayedi, Emadi and Shab-Bidar, 2018)	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	25
(Peraita-Costa, Carrillo Garcia and Morales-Suárez-Varela, 2022)	1	0	1	1	1	1	1	0	1	1	0	0	1	0	0	1	1	0	0	0	0	0	0	1	1	1	1	15
(Long *et al.*, 2022)	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	24