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REVIEW



Nutrition and Breast Cancer Research in Arab Countries: Gaps, Opportunities, and Recommendations

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ABSTRACT

According to the WHO, Arab countries have the highest relative increase in Breast Cancer (BC) rates worldwide. Current shifts in dietary patterns in these countries are postulated as important modifiable risk factors of the disease. The objectives of this review were to examine the gaps and opportunities in the extent, range and nature of nutrition-related BC research in Arab countries. Studies ($n = 286$) were identified through searching 14 electronic databases. Among the gaps identified were limited international collaborations, preponderance of laboratory-based research at the expense of population-based research, focus on single supplement/nutrient/food research, limited use of dietary assessment tools, and studying nutrition in isolation of other environmental factors. Despite these gaps, several opportunities appeared. The distribution of papers among Arab countries suggested that collaboration between high and middle income countries could create a positive synergy between research expertise and wealth. In addition, the steady increase in the number of articles published during the last two decades reflected a promising momentum in nutrition and BC research in the Arab world. These gaps and opportunities constituted context-specific evidence to orient nutrition and BC research in Arab countries which could ultimately lead to development of effective interventions for prevention of BC in these countries.

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1. Introduction

Despite major advances in early detection and treatment of Breast Cancer (BC), the disease continues to be the most common cancer among women, representing 25% of all cancers. In 2018, 626,679 women lost their lives from BC (1). Globally, the incidence of BC is 46.3 per 100,000 females, with a large variation across countries and ethnicities, ranging from 25 per 100,000 in South-Central Asia to 113 per 100,000 in Belgium (2).

The Arab region includes 22 countries from the Middle East and North Africa, whose populations share many cultural and ethnic backgrounds. Among Arab countries, the incidence of BC is 45.3 per 100,000 females with the highest incidence rate in Lebanon (106 per 100,000), followed by Algeria and

Syria (57 and 21 per 100,000, respectively) (1). According to the World Health Organization (WHO), BC rates across Arab countries are expected to double between 2012 and 2030, which is the highest relative increase of any region in the world (3). Of particular concern in these countries are the more advanced stage of the disease upon diagnosis and the earlier age of onset (4).

In light of the growing burden of BC, the importance to identify modifiable lifestyle risk factors for disease prevention is widely acknowledged as a priority. BC is a highly preventable disease since only 5–10% of all cases is due to genetic predisposition whereas the rest is associated with environmental and lifestyle risk factors (5,6) including unhealthy diet; physical inactivity; and obesity from an unhealthy diet

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and inactivity; smoking, exogenous female hormone use, ionizing radiation, and alcohol in excess (7). Among these factors, obesity and the shift in dietary patterns are perceived as important modifiable risk factors of BC, whereby diet and obesity were reported to account for about 30–35% and 10–20% of all BC cases, respectively (8,9). The recent scientific literature has witnessed a plethora of studies investigating the association of diet and BC, whether as single nutrients or as dietary patterns. Results of several meta-analyses suggested a negative association between a high intake of soy foods (10), marine *n*–3 polyunsaturated fatty acids (11), green tea (12), vitamin D and calcium (13) fiber (14) folate (15), and BC risk. On the other hand, a positive association was reported between processed meat consumption (16), and saturated fat intake and risk of the disease (17). A recent systematic review and meta-analysis of the association of dietary patterns with BC risk showed that adherence to a prudent diet characterized by high intake of fruit, vegetables, legumes, poultry, fish, whole grains, and low fat dairy, was associated with 11% lower risk of BC. Alternatively, the western/unhealthy dietary pattern (high in sugar, trans fats, and refined carbohydrates) and the alcohol drinker dietary pattern had negative effects on BC as they were associated with a 9% and 21% higher risk of BC, respectively (18).

With rapid urbanization and economic growth, many Arab countries have been undergoing nutrition transition characterized by shifts in dietary habits toward a more westernized diet high in energy and fat-rich foods, concomitant with an erosion of traditional dietary patterns (rich in fruits, vegetables, and complex carbohydrates) (19). In fact, the results of the WHO Stepwise surveys in six Arab countries (Egypt, Jordan, Iraq, Kuwait, Saudi Arabia, and Syria) revealed a high prevalence of low intake of fresh fruit and vegetables (below five servings/day), ranging from 79% in Egypt to 95.7% in Syria (20). A few studies in Lebanon revealed that the traditional Lebanese diet is slowly being replaced by a western type of diet with the latter showing strong associations with noncommunicable diseases (21–24). The changes in dietary habits observed in many Arab countries were also accompanied by a marked sedentary lifestyle and increased stress (25). As such, the shifts toward western style diets coupled to physical inactivity and stress may interact synergistically with each other leading to further enhanced risk of BC.

The increasing burden of BC in Arab countries, especially among younger women, coupled to the high prevalence of unhealthy lifestyle and dietary trends led

many Arab countries to rally for solutions to halt the escalating burden of the disease at various political, scientific, and social fronts. A common denominator for all proposed solutions is the development of policies, strategies, and public health programs to promote a healthy lifestyle with an emphasis on balanced diet and nutrition. For such interventions to be effective, they ought to be grounded in context-specific and culturally adaptable evidence base. However, most of the current knowledge for the role of diet in the etiology of BC stems from research conducted in high income countries, and hence their results have limited applicability to Arab countries given their distinct BC profiles, the specificities of their dietary habits and practices, and preponderance of middle and low income countries (26). In fact, a recent review of diet and BC in Arab countries highlighted the scarcity of research in these countries as a major impediment to the development and implementation of successful public health interventions (27). It is important to note, though, that the last couple of decades have witnessed an increasing interest in nutrition research in Arab countries, whereby the number of published papers addressing nutrition and noncommunicable diseases was five times higher between the years 2014 and 2015 than in 2006 and 2007 (26). Such a promising momentum for research, however, should be coupled with systematic assessment of existing evidence in order to decrease research redundancy and optimize use of resources (28).

In health research, scoping reviews have emerged as a useful tool in the increasing arsenal of evidence-based approaches, especially in areas with complex multifactorial concepts, whereby an array of study designs are employed. Among the reasons cited for conducting scoping reviews are to identify and analyze knowledge gaps, inform a practice, program, and policy; and provide recommendations for future research priorities (28). The main objectives of this scoping review were to: (1) examine the extent, range and nature of nutrition related BC research in Arab countries and (2) identify research gaps and opportunities in the existing literature.

2. Methods

The methodological framework for synthesis of research which was proposed by Arksey et al. (and later revised by Levac et al.) was used in this study (29,30). The framework consisted of five steps: (1) identifying the research question, (2) search strategy, (3) selection of relevant studies, (4) data charting, and

finally (5) collating, summarizing, and reporting results (29).

2.1. Identifying Research Questions

The research questions for this review were kept broad to ensure a breadth of coverage of the topic under review. The specific questions that guided this review were:

- What empirical research has been published addressing nutrition and BC in Arab countries?
- What are the gaps and opportunities in nutrition and BC research in Arab countries?

2.2. Search Strategy

The search strategy was developed by a multidisciplinary team consisting of nutrition epidemiologists; two biologists specialized in BC, a clinical nutritionist/statistician, a laboratory researcher in the field of BC, and a librarian. To review all available literature on the topic, 14 electronic databases were searched including four health science and medicine related databases: EMBASE, Global Health, MEDLINE OVID interface (1946 to present), PubMed; six multidisciplinary databases: Academic Search Ultimate, Directory of Open Access Journals, Google Scholar, ProQuest Central, Scopus, Web of Science; and four Arab world related databases: Al Manhal, Arab World Research Source, E-Marefa, Iraqi Academic Scientific Journals.

In addition to using controlled vocabulary (e.g., MeSH in PubMed and MEDLINE, Emtree thesaurus in Embase), keywords suggested by the subject specialists were included with different permutations in the abstract/title/keyword fields (whenever applicable) to cover the three concepts related to the research question: (1) nutrition, (2) BC, and (3) Arab countries. The search was conducted between November 14 and 23, 2018, by combining the variations of the three concepts listed below using the Boolean operator “AND”

Concept 1: eating OR nutrient* OR nutrit* OR diet* OR food OR hunger OR malnutriti* OR malnourish* OR undernutri* OR undernourish* OR weight OR obesity OR obese OR overweight OR underweight OR “body mass index” OR BMI OR “energy intake” OR “herb* supplement*” OR “herb* extract*” OR “caloric restriction” OR “caloric intake” OR “plant extract*” OR “plant supplement*”

Concept 2:

“breast cancer” OR “breast carcinogenesis” OR “breast carcinoma” OR “breast neoplasm*” OR “breast tum*r” OR “mammary carcinogenesis” OR “mammary carcinoma” OR “mammary neoplasm*” OR “mammary tum*r” OR “mammary cancer” OR “lobular carcinoma”

Concept 3:

“Abu Dhabi” OR Ajman OR Alger* OR Alger* OR arab OR arabic OR arabs OR arabia OR Bahrain* OR Bahrein* OR Comores OR Comoros OR Comorian* OR Djibouti* OR Dubai OR “East* Mediterranean” OR Egypt* OR Emirat* OR EMRO OR Fujaira* OR Gaza* OR Gulf OR Irak* OR Iraq* OR Jordan* OR Kuwait* OR Koweit* OR Kuweit* OR KSA OR Lebanese OR Lebanon OR Liban* OR Levant OR Libya* OR Libye* OR Mauritania* OR Mauritanie* OR Morocc* OR Maroc* OR MENA OR “Middle East*” OR “Near East” OR “North* Africa” OR Oman* OR Palestin* OR Qatar* OR “Ras al-Khaima*” OR Saudi* OR Saoudi* OR Sharja* OR Somalia* OR Somalie* OR Sudan* OR Syria* OR Syrie* OR Tunis* OR UAE OR “United Arab Emirates” OR “Um* al-Qaiwain” OR “Oum al-Qaiwain” OR “Um* al-Quwain” OR “Oum al-Quwain” OR “West Bank” OR Yemen*

To locate gray literature, Google Scholar was searched for the keywords breast or mammary with the individual country/region names in the title field, and documents related to diet were selected.

2.3. Selection of Relevant Studies

A comprehensive search strategy was adopted that targeted mainly published journal articles, books and book chapters, whereas thesis, dissertations, conference proceedings, abstracts, and posters were excluded. Only materials published post-2000 written in English, French, and Arabic were considered. Abstracts, editorials, announcements, and news (listed in the databases as journal articles) were excluded during screening.

For documents to be included in this review, the following inclusion criteria ought to be met:

1. The document had to be a journal article, book, or book chapter.
2. The affiliation of the first, last or the corresponding author was with an institution in any of Arab country.
3. The articles focused on BC.
4. The articles addressed nutrition or nutrition-related topics, such as energy, macro-/

micronutrients, food, diets, dietary habits, BMI and metabolic correlated of dietary intake.

Numerous meetings of the research team were held through the screening process to discuss issues related to selection of studies. Selection of relevant articles was divided into two steps and was carried out by two reviewers (Hibeh Shatila, Zaynab Fatfat) who independently reviewed the documents and assessed their eligibility. The first step focused on screening the title and abstract of the identified articles. The second step consisted of the full text screening. After each step percent agreements were identified. Disagreements regarding inclusion and exclusion of certain documents were resolved through discussion by the two reviewers together with a third reviewer (Farah Naja) from the research team.

Following the comprehensive database search, a total of 1,857 publications were identified and exported into the EndNote software. Of these, 894 duplicates and 42 irrelevant items (abstracts, editorials, announcements, and news) were removed. The remaining 921 unique records were screened on title–abstract–keywords and 612 publications were excluded for not meeting the inclusion criteria. A detailed full-text screening was conducted for the remaining 309 documents resulting in the further exclusion of 23 items (17 were irrelevant, four were abstracts and proceedings, two did not have accessible texts). The screening process, therefore, resulted in 286 items which were included in the final analysis. [Figure 1](#) illustrates the selection process.

2.4. Data Charting

The data extraction tool was developed and piloted to record information to answer the research questions of this review. For this purpose, the research team adapted a previously published data extraction form, used in scoping reviews addressing research in nutrition and disease (26, 31). The extraction form/tool in this study had three main sections. The first section included general questions about the documents such as document type, study design, funding source, and affiliation of the authors. The second section focused on the biological aspect of the research and had questions related to the classification of BC (histological, immuno-pathological, and molecular classifications), staging of the BC, types of cell lines and animal models used. The third section of this form included questions related to nutrition, more specifically types of nutrition exposures, dietary assessment methods, and

use of food composition data bases. The developed tool was pilot tested by reviewing and extracting data from 10 articles in order to ensure that the coding framework is consistently applied. For a few questions, the listed options were modified and the data extraction framework updated accordingly. Questions arising when piloting the framework were discussed by the team and disagreements were resolved through team consultations.

2.5. Collating, Summarizing, and Reporting the Results

Data were entered into the Statistical Package for the Social Sciences (SPSS) software version 24.0 for Windows (32). Following data entry, data cleaning and cross checking of the data entry were done. Descriptive characteristics statistics of the documents in the review were presented as proportions, n (%).

3. Results

[Table 1](#) has the characteristics of the 286 documents in this review. All documents were articles published in scientific journals. While the majority of the articles were published in English (97.9%), only 1.7% of the articles were in Arabic and 0.3% were in French. Regarding study design, more than half of the articles were laboratory-based (52.1%) followed by case-control (21.0%) and cross-sectional (20.3%) designs. Only 2.1% were cohort studies and none had a clinical trial/intervention. Nearly half of the studies (47.6%) used in vitro models, 2.4% included animal models and the rest (48.3%) were carried out with human subjects. Of the latter, a considerable proportion (30.4%) was focused on awareness and knowledge and did not include any biochemical/clinical marker.

While all of the studies addressed female BC, none tackled BC among male. Most of the studies considered menopausal status in addressing nutrition and BC. The authors of the articles were mainly collaborating with other authors within the same institutions (88.1%), followed by within country (42.3%), collaborations with European authors (16.0%), regional collaborations (14.7%), collaborations with authors from USA (5.6%) and authors (5.2%) from other countries such as Pakistan, Malaysia, Australia, South Africa, Canada, Taiwan, China, Korea, and India. When funding source was reported, the majority of studies (81.5%) were funded by government institutions, with only 16.7% funded by the private/industry sector. Of human studies that ought to have ethical approval

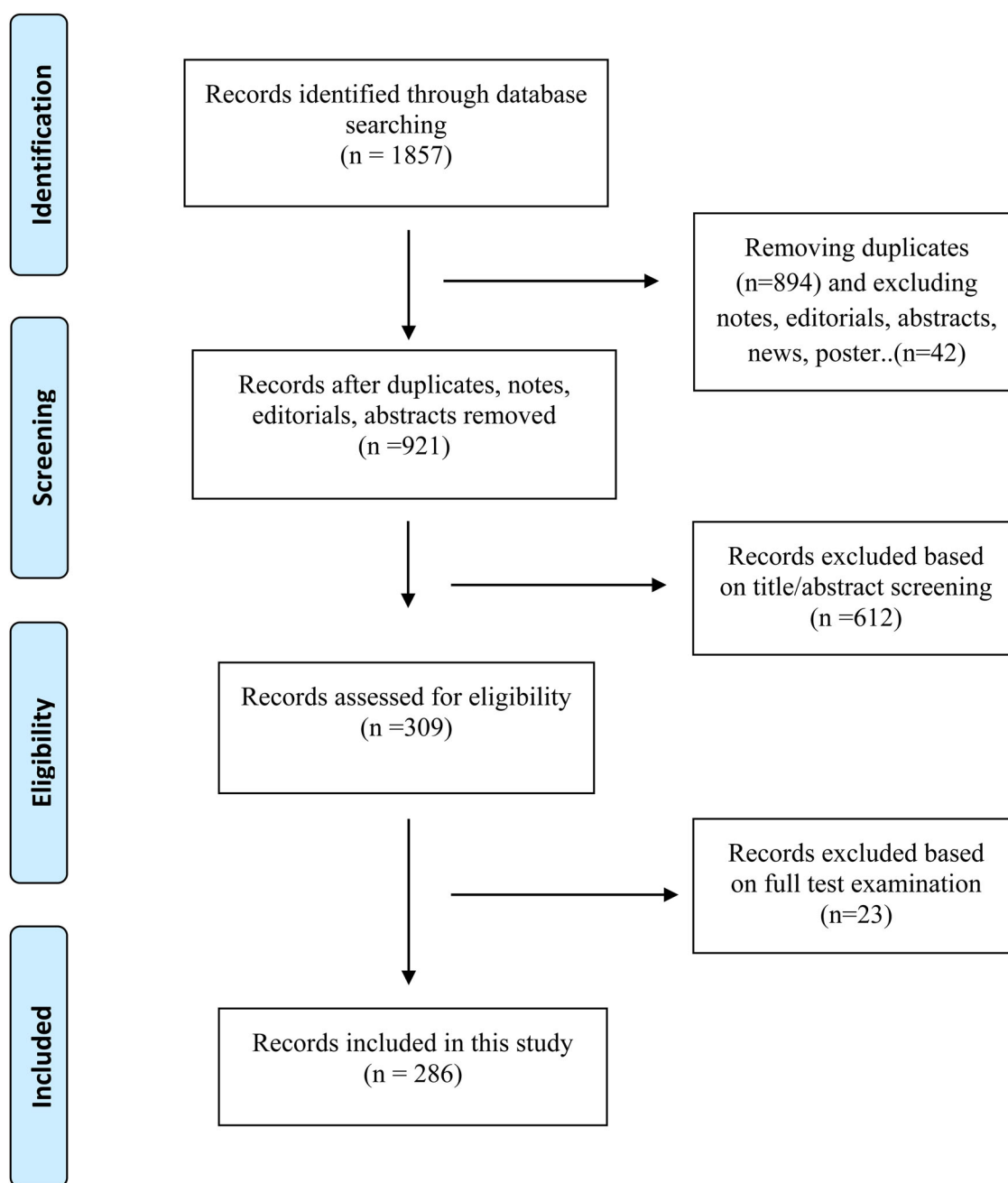


Figure 1. Flowchart describing the selection of records/documents to be included in this study. *Records/documents included review journal articles, books, and book chapters.

($n = 120$), only 56.7% indicated that such an approval was obtained while 43.3% had no mention of IRB approval. The proportions were comparable for the reporting of IACUC approval among animal studies. Most of the articles had BC (61.9%) as their only focus; however, articles that address BC as well as other cancers in relation to nutrition constituted 38.1% (Table 1).

Table 2 has the biological aspects of BC research on human subjects and includes a clinical component ($n = 96$). Only 12.5% of the articles considered

histological classifications, 26.0% included immuno-pathological classification-Estrogen receptor (ER), 24.0% had immuno-pathological classification-Progesterone receptor and lastly 17.7% immuno-pathological classification-Human epidermal growth factor receptor 2 (HER2). None of the studies considered any type of molecular classification. Of the 96 articles on human subjects with a clinical component, only 36.5% considered BC stage. Almost half of the 286 articles used cell lines 141 (49.3%), the most frequent cell line was the MCF-7 in 103 (73.0%).

Table 1. Characterization of research studies addressing nutrition and breast cancer among Arab countries (2000–2018) ($n = 286$).

	<i>n</i> (%)
<i>Document type</i>	
Journal	286 (100)
Book chapter	0 (0)
<i>Language of publication</i>	
English	280 (97.9)
Arabic	5 (1.7)
French	1 (0.3)
<i>Study design</i>	
Laboratory-based (animal-based/pathological/in vivo studies)	149 (52.1)
Case control	60 (21.0)
Cross-sectional	58 (20.3)
Review	12 (4.2)
Cohort	6 (2.1)
Systematic review/Meta-analysis	1 (0.3)
Clinical trials	0 (0.0)
<i>Basic, translational, and clinical research</i>	
In vitro	136 (47.6)
Animal model	7 (2.4)
Both (in vitro/in vivo)	5 (1.7)
<i>Human subjects n = 138</i>	
With clinical markers/samples	96 (69.6)
Without clinical markers ^b	42 (30.4)
<i>Sex of study population</i>	
BC among females	132 (46.1)
BC among males	0 (0)
N/A	154 (53.8)
<i>Study population</i>	
Premenopausal women	8 (2.8)
Postmenopausal women	8 (2.8)
Both (pre and postmenopausal women)	102 (35.7)
N/A	168 (54.2)
<i>Institutional collaborations</i>	
Within same institute	252 (88.1)
Within same country	121 (42.3)
Regional	42 (14.7)
USA	16 (5.6)
Europe	46 (16.0)
Other (Pakistan, Malaysia, Australia, South Africa, Canada, Taiwan, China, Korea, and India)	15 (5.2)
<i>Funding sources</i>	
Not reported	178 (62.2)
Governmental	88 (30.8)
Private/industry	18 (6.3)
NGO	1 (0.3)
More than one	1 (0.3)
<i>IRB approved among human research n = 120</i>	
Yes	68 (56.7)
Not specified	52 (43.3)
<i>IACUC approval for animal studies n = 12</i>	
Yes	7 (58.3)
No	5 (41.7)
<i>Only breast cancer in the study n = 286</i>	
Yes	177 (61.9)
No	109 (38.1)
<i>Type of other cancers n = 109^a</i>	
Liver	45 (41.3)
Lung	29 (26.6)
Cervix	19 (17.4)
Colon	14 (12.8)
Prostate	14 (12.8)
Brain	12 (11.0)
Cancer in general	20 (18.3)
Other cancers ^c	40 (36.7)

^aMore than one apply therefore does not add up to 100.

^bKnowledge, awareness campaign, studies with human subjects but no clinical tests done.

^cRectal = 2, adencarcinoma = 2, malignant melanoma = 1, larynx = 9, skin = 6, leukemia = 5, pancreas = 2, Muscle = 1 ovarian = 7 gastric = 1, bladder = 2, kidney = 2, uterus = 2.

Cytotoxicity was the main type of In Vitro analysis preformed in 118 (83.7%). Only 12 (4.2%) used animal models in their studies.

The nutrition-related aspects of the studies are presented in Table 3. In studying the association of nutrition and BC, over half of the studies focused on food supplements (54.2%) mainly plant extract (94.8%), as the nutrition exposure, while 36.0% considered dietary intake, 36.7% addressed anthropometry and 10.5% used biomarkers of dietary intake. Among the dietary studies, 42.7% examined food items/groups, 24.3% considered either energy, macro-, or micronutrients (separately or in combination), whereas dietary patterns were investigated in 4.9%. Of all the studies reviewed, only 10.8% used a dietary assessment method; and a food frequency questionnaire (FFQs) was the most common dietary assessment tool in 48.4%. It is important to note that only 26.7% of these FFQs were validated in the populations studied. Dietary habits were the second most common assessment tool (45.2%). The use of dietary assessment tools was further illustrated in Figure 2. The majority of dietary assessments (90.3%) were interviewer-based. Among the studies that addressed energy, macro or micronutrients in association with BC, only 44.0% used a nutrition analysis software, of which 36.4% used locally adapted software. The effect of cancer treatment on nutritional status was examined in 1.7% of the studies. The main anthropometric measurements were weight (33.9%), BMI (32.9%), and height (32.2%), followed by waist circumference (5.2%) and waist to hip ratio (3.8%). This scoping review showed 53.0% of the articles considered the relationship between nutrition and BC in isolation from other lifestyle or environmental risk factors such as sleep, breastfeeding, tobacco, stress, and physical activity (Table 3).

Table 4 presents the distribution of articles addressing nutrition and BC among the 22 Arab countries. Examination of the number of articles published by country before adjustment for population size, showed that Egypt had the highest proportion (25.9%) followed by Kingdom of Saudi Arabia (KSA) (19.9%). Middle Income Countries (MIC) had the highest number of publications ($n = 110$, 38.5%) followed by Lower-Middle Income (LMIC) ($n = 99$, 34.6%) and High Income Countries (HIC) ($n = 77$, 26.9%). No publications originated from Low Income Countries (LIC). After adjusting for population size, Jordan, Qatar, KSA, Lebanon, and Sudan rank as the top 5 countries in number of publications per million (3.0, 1.9, 1.8, 1.8, and 1.5, respectively). In terms of

Table 2. Biological aspects of nutrition and breast cancer research studies addressing clinical human subjects ($n = 96$).

Histological classification		
Yes (considered HC)		12 (12.5)
N = 12		
Ductal carcinoma in situ (DCIS)		3 (25.0)
Invasive ductal carcinomas (IDC)		12 (100.0)
Invasive lobular carcinoma (ILC)		7 (58.3)
Lobular carcinoma in situ		1 (8.3)
No (did not consider HC)		84 (87.5)
<i>Immunopathological classification Estrogen receptor (ER)</i>		
Yes (considered ER)		25 (26.0)
N = 25		
Positive		2 (8.0)
Negative		0 (0.0)
Both		23 (92.0)
No (did not consider ER)		71 (74.0)
<i>Immunopathological classification progesterone receptor (PR)</i>		
Yes (considered PR)		23 (24.0)
N = 23		
Positive		1 (4.3)
Negative		0 (0.0)
Both		22 (95.7)
No (did not consider PR)		73 (76.0)
<i>Immunopathological classification human epidermal growth factor receptor 2 (HER2)</i>		
Yes (considered HER2)		17 (17.7)
N = 17		
Positive		1 (5.9)
Negative		0 (0.0)
Both		16 (94.1)
No (did not consider HER2)		79 (82.3)
<i>Molecular classification</i>		
Yes (considered MC)		0 (0.0)
Luminal A subtype		0 (0.0)
Luminal B		0 (0.0)
HER2-enriched subtype		0 (0.0)
Normal-like subtype		0 (0.0)
Basal subtype		0 (0.0)
No (did not consider MC)		96 (100.0)
<i>Considered stages of BC</i>		
Yes		35 (36.5)
N = 35		
Stage 0		0 (0.0)
Stage 1		2 (5.7)
Stage 2		0 (0.0)
Stage 3		0 (0.0)
Stage 4		1 (2.9)
Stage 5		0 (0.0)
More than one stage		32 (91.4)
No		61 (63.5)
<i>Cell line used n = 286</i>		
Yes		141 (49.3)
No		145 (50.7)
Type of cell line $n = 141$	Type of cancer	Number of studies
MCF-7	Breast	103(73.0)
MDA-MB-231	Breast	26(18.4)
T-47D	Breast	11(7.8)
MCF-10A	Breast (normal)	5(3.5)
BT-474	Breast	5(3.5)
Other cell lines ^a	Breast	18(12.8)
<i>In vitro: Type of cell line primary n = 141</i>		
Yes		3 (2.12)
No		138 (97.9)
<i>Type of in vitro analysis n = 141*</i>		
Cytotoxicity		118 (83.7)
Proliferation assays		47 (33.3)
Apoptotic studies		34 (24.1)
DNA damage – oxidative stress		23 (16.3)
Cell cycle analysis		15 (10.7)
Biochemical analysis		9 (6.4)
Molecular analysis		8 (5.7)
Invasion and migration assays		7 (5.0)
Microbiome		0 (0.0)
Others		1 (0.7)
<i>Animal model (in vivo)</i>		

(Continued)

Yes	12 (4.2)
No	274 (95.8)
<i>Type of in vivo n = 12</i>	
Mice	6 (50.0)
Rat	6 (50.0)
<i>Type of in vivo analysis n = 12</i>	
Histological analysis	7 (58.3)
Tumor regression	6 (50.0)
Survival analysis	2 (16.7)
Toxicity	2 (16.7)
Others	5 (41.7)

³Other cell lines: MCF-10- 2A, hTERT-HME1, ZR-75-1, CRL-23, EMT-6, Hs578T, MDA-MB-435, BT-474, 4T1, JIMT1, SKRBR3, HTB26, AMN-3, MAXF, 66Cl-4.

matching the number of publications in nutrition and BC to BC mortality, this review showed that KSA, Oman, Jordan, Bahrain and Libya had the highest numbers per 100 BC deaths (6.56, 4.48, 4.27, 2.98, and 2.23, respectively). The quality of the publications was assessed using the impact factor (IF) of the journals. Accordingly, Palestine ranks number one with an IF = 10.83, followed by Tunisia (IF = 2.9) and Lebanon with (IF = 2.04) (Table 4).

The examination of the temporal trend in research productivity in nutrition and BC among Arab countries showed a steady increase in the number of articles from year 2001 until year 2018 in Figure 3. This increase in research productivity was concomitant with the escalating mortality rates of BC in these countries. However, the higher number of articles through the years was not accompanied by an increase in the IF of the journals where these articles are featured (Figure 3).

4. Discussion

This scoping review is the first study that aimed to identify gaps and opportunities in nutrition and BC research in Arab countries that are undergoing nutrition transition and an expected rate of increase in BC higher than any region of the world. Synthesis of existing literature revealed a few gaps in research protocols, including collaboration among researchers, study designs, ethics approval, and funding. In addition, gaps particular to BC biology and nutrition were identified. These gaps were related to research methodology, rigor and potential impact. Based on the findings of this review, a few opportunities were suggested.

This review revealed a main gap related to reporting ethical approval of research protocols, whereby almost half of the studies did not report a statement asserting ethical approval (human or animal). Whether it is a journal requirement or not, reporting ethical approval is critical for the credibility of the conduct of the study. In fact, the lack of regulatory

oversight of research ethics in many Arab countries has been raised as a main concern (33). In this context, a qualitative study in Lebanese women showed that the fear of 'lack of ethics' is a major deterrent for participation in medical research (34). To bridge this gap, obtaining and reporting ethical approval in nutrition and BC research in Arab countries is paramount. Therefore, efforts are needed to establish and enhance research ethics committees and training in research institutions and to provide leadership to national research ethics systems (35).

With regards to funding sources, biomedical research is generally funded by three main sources: government, private industry investing for commercial gain, and medical research charities disbursing donors' funds. In this review, while none of the studies reported funding by medical research charities, very few studies were funded by the private sector, and the majority relied on governmental sources. It is, however, undisputable that the deep economic recession which took place in 2008 and which affected many countries worldwide, including Arab countries, has led governments to apply major cuts in public expenditures including medical research (36). It is therefore important to recommend seeking diverse funding sources for nutrition and BC research and not rely exclusively on the government, a challenge that occurred before the recession (37).

In this review, the majority of studies rely mainly on within institution or within country collaborations with a few studies reflecting collaborations with Europe or the United States of America (USA). This finding is not in line with the recurrent recommendations of the scientific community to adopt a global perspective calling for international and interdisciplinary collaborations (38–42). Specifically in the area of nutrition and cancer, global research initiatives could provide a greater diversity in exposure to many dietary factors and hence allow for detecting their associations with cancer (43). In that context, the International Breast Cancer and Nutrition project was launched in October 2010. Among the main objectives

Table 3. Nutrition in the studies addressing nutrition and breast cancer among Arab countries (2000–2018). ($n = 286$).

Nutrition and nutrition related exposure considered $n = 286^*$	
Dietary intake	103 (36.0)
Food supplements	155 (54.2)
Obesity/BMI/weight/body composition	105 (36.7)
Metabolic correlates of dietary intake (leptin/adipokines,serum level of vitamins and minerals ...)	30 (10.5)
Type of dietary intake studied $n = 103$	
Micro/Macronutrients/Energy	25 (24.3)
Food item/Food group	44 (42.7)
Alcohol	10 (9.7)
Beverages (tea, coffee, carbonated etc.)	8 (7.8)
Dietary patterns	5 (4.9)
Ethnic eating (Ramadan Fasting)	2 (1.9)
Others	9 (8.7)
Type of supplement $n = 155$	
Plant-based extract	147 (94.8)
Micronutrients (vitamin and minerals)	4 (2.6)
Other	4 (2.6)
<i>Any dietary assessment methods</i>	
Yes	31 (10.8)
No	255 (89.2)
How was dietary assessment conducted? $n = 31$	
Interview-based questionnaire	28 (90.3)
Self-completed questionnaire	3 (9.7)
Type of dietary assessment methods $n = 31$	
FFQ	15 (48.4)
Dietary habits	14 (45.2)
24 h recall	1 (3.2)
3-day diet record	1 (3.2)
Was the FFQ validated $n = 15$	
Yes	4 (26.7)
No	11 (73.3)
<i>Dietary intake studies of micro/macro/energy $n = 25$</i>	
Did not use nutrition analysis software	14 (56.0)
Used nutrition analysis software	11 (44.0)
Data base used for nutrition analysis $n = 11$	
Diet analysis software (NSL Diet Analyzer and WinDiet)	4 (36.4)
Saudi food tables	4 (36.4)
USDA	1 (9.1)
Food processor for windows	1 (9.1)
Mosby's Nutitric Nutrition Analysis software	1 (9.1)
Effect of cancer treatment on nutritional status	
Yes	5 (1.7)
No	281 (98.3)
<i>Anthropometric used in breast cancer research/measure of adiposity^a</i>	
Weight	97 (33.9)
BMI	94 (32.9)
Height	92 (32.2)
WC	15 (5.2)
Waist to hip ratio	11 (3.8)
%Body fat	4 (1.4)
Other	9 (3.1)
<i>Risk factors addressed</i>	
Family history of breast cancer	57 (20.3)
Social determinants	55 (19.2)
Age of menarche/age of menopause	48 (16.8)
Contraceptive use	40 (14.0)
Breast feeding	39 (13.6)
Tobacco	37 (12.9)
Parity	34 (11.9)
Physical activity/inactivity	33 (11.5)
Age first birth/age/last birth	28 (9.8)
Hormone therapy for post-menopausal women	20 (7.5)
Hyperlipidemia	17 (5.9)
Genetic	12 (4.2)
High blood glucose	9 (3.1)
Hypertension	8 (2.8)
Stress	7 (2.5)
Sleep	3 (1.0)
Studies with human subjects ($n = 138$) that did not address lifestyle factors ^b	73 (53.0)

^aMore than one apply therefore does not add up to 100.

^bLifestyle factors considered: sleep breastfeeding, tobacco, stress, physical activity.

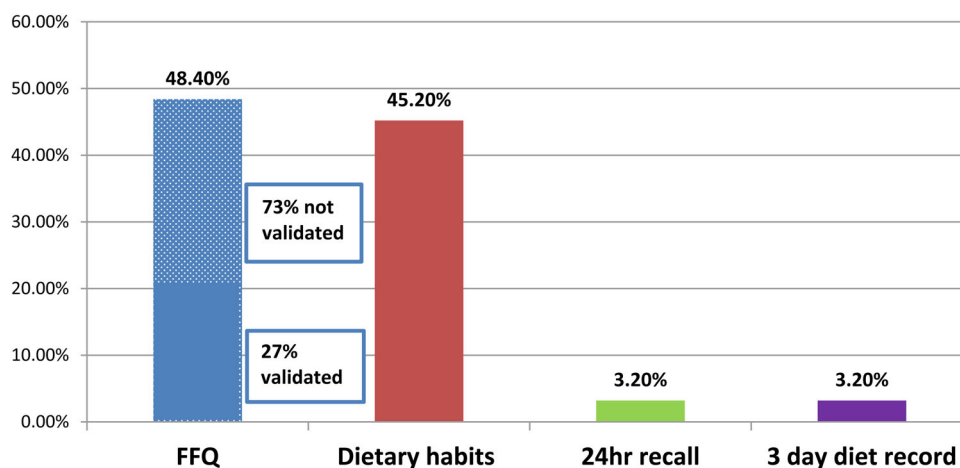


Figure 2. Types of dietary assessment methods used in nutrition and breast cancer research among Arab countries between years 2000 and 2018 ($n = 31$).

of this project is to create an international, multidisciplinary and integrated collaborative program to identify the impact of nutrition on BC onset. Through global collaborations, the IBCN provides a framework for research that takes into account culture and environment, including nutrition and lifestyle. This research initiative is based in the US and includes 10 countries, two of which are Arabic countries (Lebanon and Qatar) (44). Arab countries are encouraged to participate in global network initiatives, such as the IBCN, and to share knowledge with the international community.

Concerning research design, this review showed that over half of the studies on nutrition and BC among Arab countries were laboratory-based with only six cohorts but no clinical trials. Laboratory studies are, without a doubt, instrumental to advance the understanding of how BC starts, grows and metastasizes and to explain the differences between normal and cancer cells (45). However, unless such studies are coupled with epidemiological, translational and clinical practice research, including those involving human subjects, their impact remains limited and confined to the boundaries of their design. In fact, in the hierarchy of evidence, randomized controlled trials and other human and population-based research are ranked higher than laboratory studies and are prioritized for use in evidence-based medicine (45,46). The importance of population-based research is further underscored in studies where the exposure presents subtle differences between populations, such as diet and nutrition (47,48). While the results of diet related laboratory-based research could be extrapolated from one setting/country to another, those of population-based research are context-specific and hence ought to

be conducted and validated in the specific population to which conclusions are considered relevant (49,50). Therefore, further research involving human subjects in the study of nutrition and BC in Arab countries is warranted.

When considering the laboratory-based research in these studies, findings have shown that most were In Vitro studies using BC cell lines with only few in vivo studies. The majority of the In Vitro studies used the MCF-7 and MDA-MB-231 cell lines. Moreover, the in vitro experiments were limited to basic techniques such as proliferation and apoptosis studies, known to be useful for initial screening. However, more mechanistic studies and functional validation should be performed. Although cancer cell lines remain a critical resource in cancer research, results emanating from such studies should also be validated in clinical human samples. Moreover, almost all studies including human subjects were nonexperimental observational research with 41% case-control and cross-sectional studies. The majority of these studies were investigating risk factors of BC focusing mainly on the association between BC and obesity, BMI, leptin and other serum biomarkers. Importantly, these studies dealt with BC as one homogenous disease; few took into consideration the histological and immunological classification and none considered the molecular classification of BC, which was shown to impact the prognosis of the disease (51). Key challenges that might hinder advanced clinical research in these countries might include limited capacity, poor research infrastructure and minimal funding opportunities. Accordingly, more efforts should be done to leverage basic research and strengthen as well clinical research in the region. Indeed, investing in building

Table 4. Counts and impact factor (IF) of studies addressing nutrition in breast cancer research among Arab countries (2000–2018) classified by economic status as per the World Bank Gross Domestic Product data.

Country	Crude # of publications, <i>n</i> (%) ^a	BC mortality (number of death)	# of publications per 100 BC deaths ^b	# of publications/1,000,000 ^c	Number of articles with IF	IF mean ± SD including 0 IF
High income						
Bahrain	2 (0.7)	67	2.98	1.4	2 (100.0)	0.2 ± 0.0
KSA	57 (19.9)	899	6.56	1.8	48 (84.2)	1.75 ± 1.55
Kuwait	4 (1.4)	222	1.80	1.0	4 (100.0)	1.34 ± 1.00
Oman	6 (2.1)	134	4.48	1.4	5 (83.3)	1.80 ± 1.12
Qatar	5 (1.7)	50	10	1.9	5 (100.0)	1.9 ± 1.02
UAE	3 (1.0)	258	1.16	0.3	2 (66.7)	1.3 ± 1.33
Total number of publication HIC	77 (26.9)					
Upper-middle income						
Algeria	15 (5.2)	3367	0.45	0.4	14 (93.3)	1.4 ± 1.42
Iraq	36 (12.6)	1727	2.08	1.0	5 (13.9)	0.16 ± 0.76
Jordan	28 (9.8)	655	4.27	3.0	22 (78.6)	1.22 ± 1.06
Lebanon	11 (3.8)	920	1.20	1.8	11 (100.0)	2.04 ± 1.18
Libya	4 (1.4)	179	2.23	0.6	2 (50.0)	0.18 ± 0.20
Tunisia	16 (5.6)	766	2.09	1.4	14 (87.5)	2.90 ± 3.23
Total number of publication MIC	110 (38.5)					
Lower-middle income						
Djibouti	0 (0.0)	87	0	0	0	0
Egypt	74 (25.9)	9254	0.80	0.8	57 (77.0)	1.1 ± 1.12
Mauritania	0 (0.0)	191	0	0	0	0
Morocco	7 (2.4)	3518	0.20	0.2	6 (85.7)	1.31 ± 1.16
Palestine/Gaza/ West bank	6 (2.1)	314	1.91	1.2	3 (50.0)	10.83 ± 23.69
Sudan	6 (2.1)	2935	0.20	1.5	3 (50.0)	1.34 ± 1.56
Syria	3 (1.0)	1939	0.15	0.2	2 (66.7)	0.60 ± 0.78
Yemen	3 (1.0)	NA	N/A	0.1	3 (100)	1.30 ± 1.06
Total number of publication	99 (34.6)					
Low income						
Comoros	0 (0.0)	22	0	0	0	0
Somalia	0 (0.0)	1231	0	0	0	0
Total number of publication LIC	0 (0.0)					
Total	286			0.91	208	1.49 ± 3.74

^a*n* (%), refers to the number of papers and the percentage out of the total number of papers.

^bBreast cancer mortality data extracted from the WHO International Agency for research on cancer http://gco.iarc.fr/today/online-analysis-multi-bars?v=2018&mode=cancer&mode_population=countries&population=900&populations=788&key=crude_rate&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=10&group_cancer=0&include_nmssc=0&include_nmsc_other=1&type_multiple=%257B%2522inc%2522%253Afalse%252C%2522mort%2522%253Atrue%252C%2522prev%2522%253Afalse%257D&orientation=horizontal&type_sort=0&type_nb_items=%257B%2522top%2522%253Atrue%252C%2522bottom%2522%253Afalse%257D&population_group_globocan_id=#collapse-group-0-3.

^cPublication per 1000,000 (source <http://www.who.int/nmh/countries/en/>, http://www.unicef.org/infobycountry/oPt_statistics.html#113).

research capacity, advocating for better research funding while improving regional and international collaborations would help in advancing research.

Of note, this review did not focus on nutrition and male BC in Arab countries. Although not as prevalent as it is in women, the incidence of male BC has steadily increased over the past three decades in many countries including Arab countries (1, 51). The low incidence of the disease has resulted in limited knowledge of its etiology, biological behavior, and treatment, despite the fact that the etiologic and prognostic factors are different for males than females (52). The recent data on the burden of male BC underscores the need for screening, detection, trials and treatment/prevention guidelines specific to male BC (53), therefore suggesting that research addressing

nutrition and BC, including that conducted in Arab countries, ought also to extend to the male in addition to female genders.

Nutrition constitutes a unique type of exposure and includes a few indicators such as dietary intake, food supplements, anthropometry as well as biomarkers. Among these indicators, dietary intake, both in terms of quantity and quality, is considered a key element to study the association between nutrition and diseases (54,55). The results of this review showed that the majority of studies addressed food supplements, while the rest tackled dietary intake and body composition. Among food supplements, plant-based extracts (such as *Thymus vulgaris*, *Juniperus communis*, and *Glaucium flavum* root.) were the most common. Though important in advancing knowledge in the

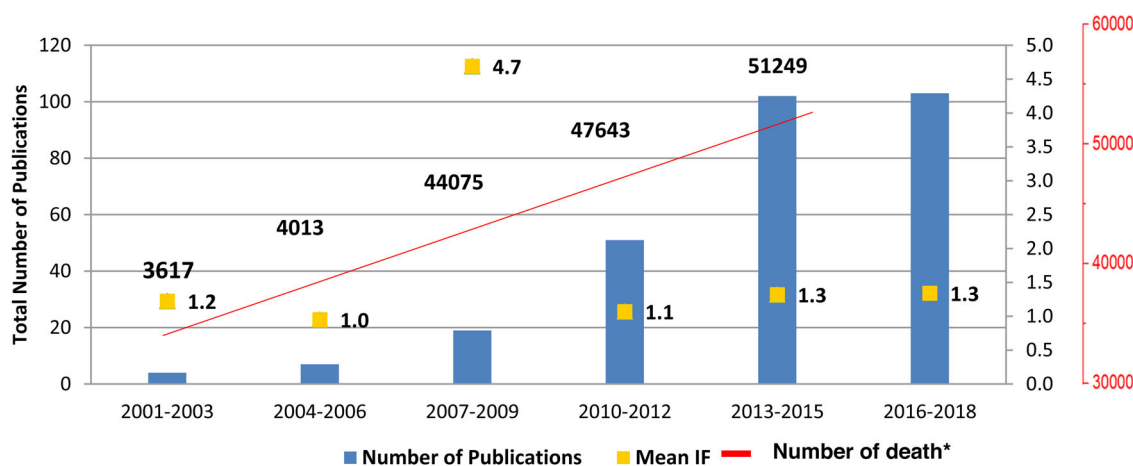


Figure 3. Time trend in the numbers of papers addressing nutrition and breast cancer research among Arab countries (2001–2018). *Number of deaths in all Arab country in each year (from 2000 till 2017) using Global Health Data Exchange which provides data based on estimates from the Institute for Health Metrics and Evaluation (IHME). <http://ghdx.healthdata.org/gbd-results-tool>.

etiology of BC, examining plant extracts rarely informs public health interventions and rather holds implications for the pharmaceutical industry (49, 56). This field of research cross cuts boundaries with the complementary and alternative medicine and hence ought to be interpreted with caution since, in many instances, the safety and toxicity of these plant extracts are not fully examined (57). The findings of this review showed that dietary intake was mainly addressed in the form of single foods and food groups, with very few studies investigating dietary patterns. While studies of single nutrient/food/food group has greatly advanced the understanding of the dietary risk factors for BC, this approach has several conceptual limitations. A main limitation relates to the fact that foods are usually consumed as part of a whole diet and in various characteristic combinations that deliver a variety of nutrients at the same time which can have either synergistic or interactive metabolic actions (58). Furthermore, messages stemming from single nutrient/food/food group research have limited public health implications given the difficulties to interpret or translate into diets by the public as well as by health care professionals (59). In the case of BC in particular, a disease with complex and multifactorial etiology, the effect of nutrition is unlikely to be mediated by a single food and nutrient (58). In fact, supplementation with a single nutrient has led to disappointing outcomes, as in the case of beta carotene supplementation and lung cancer in the PHS, CARET and ATBC trials. In these trials, supplementation with high doses of D-carotene did not reduce the risk of lung cancer and probably increased the risk in certain groups such as the heavy smokers and asbestos

exposed workers (60). Consequently, it is recommended that research on nutrition and BC in Arab countries consider the overall dietary pattern, rather than any single nutrient, in examining dietary intake exposure.

Within the context of nutrition exposure, this scoping review showed that majority of studies did not use any form of dietary assessment tools. In addition, among studies that included dietary assessment, FFQs and general questions about dietary habits were the most commonly used. Of The FFQs, very few were validated in the context where they were used. Together these findings raise concerns about the relevance of nutrition and dietary recommendations stemming from this research to the prevention of BC in Arab countries. While acknowledging the difficulties in measuring dietary intake, dietary assessment tools, including FFQs, 24 h, recalls and dietary records, among others, are important to describe the quantity and quality of individual's dietary intake, without which examining the association between dietary intake and BC becomes rather challenging and in many instances irrelevant (61). Furthermore, these tools should be tested for their validity and reliability. Using tools that are not validated could lead to a misrepresentation of the dietary intake and hence would mask potential associations between diet and disease including BC (62). Therefore, enhancing dietary assessment in nutrition and BC research in Arab countries is an elemental step toward a better understanding of their association within the local context. Also linked to dietary assessment, this review showed that the use of food composition databases was rare and even when used these databases were not local

Table 5. The gaps and their corresponding recommendations to enhance research on nutrition and breast cancer (BC) among Arab countries.

Gaps	Recommendations
Reporting ethical approval of research protocol	Establish and enhance research ethical committees in research institutions and provide leadership to national research ethics systems
Relying primarily on governmental sources of funding	Engage the private industry and medical research charities in addition to the government in funding research on BC and nutrition
Collaborations are limited to within institution and within country	Adopt a global perspective for international and interdisciplinary collaborations
Study designs included mainly Laboratory studies	Diversify study designs to include population-based research such as cohorts and RCT
Lack of research tackling male BC	Address male in addition to female BC
Laboratory research are limited to basic techniques (proliferation and apoptosis)	Widen the scope of basic research to include mechanistic and functional validation studies
Scarcity of clinical research	Invest in capacity building and funding to advance clinical research
Regarding nutrition exposures, the focus was mainly on food supplement and single food/food group	Complement the single nutrient/food approach with that of a holistic examination of dietary pattern
Scarce use of dietary assessment tools and local food composition database	Develop and use context specific dietary assessment tools and food composition tables
Anthropometry was limited to the use of BMI mainly	Include body composition and fat distribution markers in addition to BMI
Nutrition and BC was studied in isolation from other environmental and lifestyle factors	Consider environmental, genetic and lifestyle factors and their interactions in the study of disease etiology

and rather included data bases from countries with distinct dietary consumption patterns (such as the US). According to the Food and Agriculture Organization, relevant, reliable and up-to-date food composition data are of fundamental importance not only in nutrition, dietetics and health, but also for other disciplines such as food science, biodiversity, plant breeding, food industry, trade, and food regulation (63). US-based food composition relies on foods grown in the US and therefore does not reveal the concentration of nutrients from food grown in an Arab country nor does the range in foods meet the range or type of foods eaten in Arab countries (64). Inadequate food composition data and their use may lead to erroneous research results and consequently incorrect public health recommendations for disease prevention and management. Hence, there exists an immediate need to accelerate the development of food composition data and tables relevant to the countries of the Arab region.

In addition to dietary intake as a marker of nutritional status, this study aimed at examining the use of anthropometric measurements in nutrition and BC research in Arab countries. The findings showed that BMI was the most commonly used anthropometric measure with fewer studies considering waist circumference, waist to hip ratio and percent body fat. BMI is in fact the most commonly investigated anthropometric risk factor of BC. Increased BMI has been convincingly associated with increased BC risk in postmenopausal women, specifically ER+ tumors, and with decreased premenopausal BC risk (65). Recently, however, body composition and fat distribution has been proposed as a modulator of BC risk (66–69). Furthermore, ethnicity is suggested to be an

important confounding factor for the association of these anthropometric measurements and BC risk (70,71). Therefore, it seems sensible to include body composition and fat distribution assessment, in addition to BMI, in nutrition and BC research in Arab countries.

The findings of this study showed that 53% of articles considered the relationship between nutrition and BC in isolation from other environmental and lifestyle exposures. BC is a multifactorial disease and its etiology depends on the interaction of environmental, genetic and lifestyle factors (72). In fact, existing evidence suggests that exposures, such physical activity, smoking, sleep, often interact and result in different health implications when examined in combination vs. a single exposure (56). The scientific community is increasingly moving toward adopting a paradigm, where lifestyle factors in their entirety are examined in association with many diseases, such the metabolic syndrome (24), diabetes (23), and obesity (21). Therefore, it is recommended to include other lifestyle factors in addition to diet, while examining the association between nutrition and BC in research conducted in Arab countries.

To recapitulate, a summary of the gaps in nutrition and BC research among Arab countries, as revealed in this study, as well as the corresponding recommendations is presented in Table 5. The suggested recommendations addressed general research governance (ethics review, public–private collaborations, global and international collaborations), type of research (study designs, clinical and mechanistic), research focus and tools (holistic approach to dietary intake, validation of tools, and inclusion of additional lifestyle factors) (Table 5).

Despite the aforementioned gaps, this review identified several opportunities in nutrition and BC research in Arab countries mainly related to collaboration among these countries and orienting/guiding future research. With regards to potential collaboration opportunities, this review showed that research productivity was not exclusive to HIC. In fact, a few MIC ranked higher than many HIC in terms of number of publications and the mean IF of research articles. These results indicate that wealth was not directly proportional to research productivity in these countries, neither in terms of quantity nor quality. Rather, MICs were more likely to conduct and publish research in the field of nutrition and BC. It could be argued that, over the past few decades, LMIC have experienced a progressive development of research expertise and infrastructure, leading to more established research networks and stronger nutrition and biology research centers in these countries. On the other hand, oil-producing Arab countries (HIC), have only recently increased their financial investment in research advancement (73). These findings suggested that the collaboration between HIC and MIC could create a positive synergy whereby the use of research expertise and wealth in these countries could be optimized to better address the rising burden of BC, especially in light of the similarities in dietary intake, and comparable nutritional challenges that these countries are facing (74).

The trend in research productivity since year 2001 until 2018 showed a steady increase in the number of publications in nutrition and BC in Arab countries. This trend reveals a promising momentum in both the researchers' interest to study the association between nutrition and BC, as well as funding opportunities for research in this area. This momentum, if appropriately oriented could serve to bridge important knowledge gaps in the study of diet and BC association.

5. Conclusions

This is the first scoping review to examine research on nutrition and BC in Arab countries. The findings revealed a promising trend in research productivity in these countries since year 2001, however, this trend was not paralleled by an improvement in the IF of journals in which research was featured. The findings of this review identified important gaps in the research currently undertaken in Arab countries, which if addressed, could potentially improve the quality as well as the impact of nutrition and BC

research in these countries. These gaps were related to study design, ethical approval, research protocols, collaborations and the types and methods of nutritional status exposure examined. This review identified collaboration among Arab countries and with international partners as a strategic opportunity to improve the quality of research in these Arab countries and to contribute to a better understanding of the association between diet and BC globally.

Author Contributions

Conceptualization, F.N., R.N., and R.T.; methodology and formal analysis, S.N., F.N., HS and Z.F.; resources, S.N., F.N. writing—original draft preparation, HS, F.N., writing—review and editing, F.N.,R.N. M.F., and R. T.; supervision, F.N., R.N., and R.T. project administration, F.N. funding acquisition, R.T. and M.F.

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The authors report no conflict of interests to declare

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