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Risk factors for breast cancer in Iraqi women

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ABSTRACT

Background: Breast cancer is now the most common cancer in Iraq, and since it is increasing in frequency, so determination of risk factors is essential in prevention and treatment.

Aim of study: Determination of breast cancer risk factors in Iraqi women. Patients and methods: Fifty Iraqi female patients with breast cancer were enrolled in this study. Breast cancer risk factors were determined and statistically analysed.

Results and discussion: History of benign lesions were observed in 8 (16)%, while previous history of mastitis were observed in 15 (30)%, and 40(80)% had systemic disorders. All the patients were following bad nutritional behaviours, and none of them were practicing physical activities. Twenty patients (40)% presented with thyroid disorders. Fourty patients (80)% have administered contraceptive pills many years ago.

Conclusion: This study indicates that the incidence and mortality rates of breast cancer is rising and it is under the effect of many factors, so prevention of these risk factors is essential in treatment and avoidance of recurrence.

Key words: breast cancer, cancer cell, malignant phenotype

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INTRODUCTION

Breast cancer is the most frequently diagnosed neoplastic disease in women around menopause often leading to a significant reduction of these women's ability to function normally in everyday life. The increased breast cancer incidence observed in epidemiological studies in a group of women implicates the necessity of conducting multidirectional studies in order to identify risk factors associated with this type of neoplasm.

All risk factors initiating the process can be divided into two groups. The first group would include inherent factors such as age, sex, and race, genetic makeup promoting familial occurrence of the neoplastic disease or the occurrence of benign proliferative lesions of the mammary gland. They all constitute independent parameters and do not undergo simple modification in the course of an individual's life. The second group includes extrinsic factors conditioned by lifestyle, diet or long-term medical intervention such as using oral hormonal contraceptives or hormonal replacement therapy and their influence on the neoplastic process may be modified to a certain degree. Identification of modifiable factors may contribute to development of prevention strategies decreasing breast cancer incidence [1].

Epidemiology and incidence

The incidence rate of breast cancer is estimated to reach 3.2 million by 2050. Lifetime risk of developing breast cancer in every woman in the United States is 12.4% or one in eight women.

In 2012, 1.67 million new cases of breast cancer were identified worldwide, accounting for 25% of all cancers.

In 2017, approximately 252, 710 new cases of invasive breast cancer and 6,341 cases of breast cancer in situ were diagnosed in the United States. Nearly 24% of all breast cancer cases occur in the Asia-Pacific region, with the highest rates seen in China, Japan, and Indonesia.

In 2012, it was estimated that 277,054 new cases of breast cancer were diagnosed in East Asia, 107,545 in Southeast Asia and 223,899 in south-central Asia.

In 1988–2006, Korea accounting for the highest prevalence of breast cancer in and Southeast Asia in 1988–2013

The incidence rate of breast cancer varies among different parts of the world, varying from 27 per 100,000 in Middle Africa and East Asia to 92 per 100,000 in Northern America. With increasing population age in developed countries, the incidence rate of breast cancer among older people is increasing.

In addition to Japan, the prevalence of breast cancer is increasing among Asian and American women. Because of the delay in seeking diagnosis and treatment for breast cancer among African women, survival rate is low among them [2-5].

The incidence (age-standardized rate per 100,000) of breast cancer in different regions of the world is as follows: more developed regions: 74.1, less developed regions: 31.3, Western Europe: 96.0, Northern America: 91.6, Northern Europe: 89.4, Australia/New Zealand: 85.8, South-Central Asia: 28.2 and Eastern Asia: 27.0 (Table 1).

Tab. 1. The incidence (age-standardized rate per 100,000) of breast cancer in different regions of the world

	Incidence
United states	74.1
Less developed regions	31.3
Western Europe	96
Northern America	91.6
Northern Europe	89.4
Australia/New Zealand	85.8
South-Central Asia	28.2
Eastern Asia	27

Pathophysiology of cancer

A new study by Harvard researchers indicates that "good" cells can become cancerous because of exposure to a "bad" environment within the body — similarly to the way a "good boy" may turn to crime when exposed to pressures of life in a crime-ridden neighbourhood [6-9].

In their paper in today's edition of the journal nature, they report that normal blood stem cells "are dependent upon their environment. They get their cues from the surrounding 'neighborhood' of bone cells". "It is the environment in which the cells develop, can make the system go askew" [10-13].

Oxidative stress is the emerging risk factor not only in breast cancer but also proved to be contributory factor in almost all types of cancers. Oxidative stress can be broadly defined as an imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage [14-18].

Oxygen species are high and overcome the antioxidant defence mechanisms of the human body, oxidative damage can occur to lipids, proteins, or directly to DNA. Reactive Oxygen Species are produced by both enzymatic and non-enzymatic systems within eukaryotic cells and play important roles in cellular physiology and pathophysiology. Although physiological concentrations are crucial for ensuring cell survival, ROS overproduction is detrimental to cells, and considered as key-factors for the development of several diseases, such as neurodegenerative diseases, cardiovascular disorders, and cancer [19].

Cancer cells are usually submitted to higher ROS levels that further stimulate malignant phenotype through stimulus to sustained proliferation, death evasion, angiogenesis, invasiveness, and metastasis. Breast cancer cells have been shown to be susceptible to oxidative damage and have high levels of oxidative stress, including protein damage, DNA damage, and lipid peroxidation [10].

Factor conditioning breast cancer occurrence

Intrinsic factors:

Patient's age: It is the first basic factor in this group. Breast cancer is most frequently found in women around menopause. It is significantly less frequently found in women below 45 years of age.

Race: Is a very important intrinsic factor elevating the risk of breast cancer occurrence.

Familial susceptibility: Intensive studies have been conducted in recent decades, which led to identification of genes whose function disorder is associated with an increased risk of occurrence of malignant breast or ovarian cancer. The most important are genes BRCA1 and BRCA2. The occurrence of changes in the coding sequence may lead to the development of hereditary syndromes called HBC-SS (Hereditary Breast Cancer Site Specific) or HBOC (Hereditary Breast Ovarian Cancer syndrome), which manifest themselves in the form of breast and/or ovarian cancer. They constitute about 10% of all newly diagnosed neoplasms of these organs.

Identification of mutations in BRCA1 or BRCA2 genes is associated with an increased risk of occurrence of breast and/or ovarian cancer in 65% or 45% of mutation carriers, respectively, depending on the mutation type . The hereditary syndromes caused by BRCA1 or BRCA2 gene mutations are associated with several clinical symptoms [2].

Hormonal changes: As it was pointed out, early menarche is associated with a higher risk of occurrence of breast cancer due to a longer period of exposure to estrogens activity. Each delay of menarche by 2 years reduces the risk of occurrence of breast cancer by 10%.

Benign lesions: Proliferative lesions of benign character occurring in can significantly increase the risk of occurrence of malignant lesions. Based on the epidemiologic data, in the group of women diagnosed with benign proliferative lesions of the mammary glands with cellular atypia and familial aggregation of breast neoplasms in first- and second-degree relatives there was an 11-fold increase in the breast cancer risk compared to women without cellular atypia and family history of cancer [3].

Systemic disorders: The prevalence of metabolic syndrome (obesity, glucose intolerance, low serum High-Density Lipoprotein cholesterol (HDL), high serum triglycerides, and hypertension) is high and increasing in parallel with an increasing breast cancer incidence worldwide.

High energy intake, physical inactivity, high Body Mass Index (BMI), hyperinsulinemia with insulin resistance, and weight gain were associated with increased breast and endometrial cancer risk which are increased by hyperglycemia and hypertension in overweight and obese women.

Thyroid disorders: The interactions between thyroid gland and breast tissue are based on the common property of the mammary and thyroid epithelial cell to concentrate iodine by a membrane active transport mechanism, As well as on the presence of TSH receptors in fatty tissue, which is abundant in mammary gland. Additionally, some endocrine stimuli identified in thyroid products that exert a simultaneous action on the breast and the various thyroid antibodies, which could also interact with receptors on breast tumours, have been postulated to be responsible for the coincidence of mammary and thyroid gland disorder [4].

Mastitis: Approximately 20% of all cancers are associated with chronic inflammation and infection.

Inflammation at different sites is a strong risk factor for many cancers; examples include the link between bronchitis and lung cancer; gastritis and gastric cancer pancreatitis and pancreatic cancer, inflammatory bowel disease and colon cancer, others. Several studies have reported an association between repeated inflammations at a young age, especially among lactating women, and cancer. The overall risk of breast cancer was elevated in women with a history of mastitis [5].

Psychological stress: Potential mechanisms linking psychological stress and breast cancer etiology. Chronic cortisol exposure predisposes to various medical conditions including cancer.

Psychological stress induces sympathetic nervous system activation leading to release of epinephrine and norepinephrine from adrenal medulla.

Glucocorticoids interfere with P53 and thus cell cycle surveillance. Stress signaling impairs DNA repair capabilities and causes direct DNA damage, increasing the chance of mutation and cancer.

Physical activity: There is evidence from prospective studies of a protective association between physical activity (generally leisure time physical activity – PA) and postmenopausal breast cancer. Additionally, there seems to be a dose-response association. A few possible interrelated mechanisms have been implicated: the positive impact of PA in decreasing body fatness, the effects on endogenous hormone metabolism, improved insulin and glucose profiles, and the possible positive impact on the immune system. A modest but significant effect on reducing circulating sex hormones has also been highlighted [6].

Extrinsic factors:

Diet: Human diet has the potential to contain both anti- and pro-carcinogenic chemicals. After Doll and Peto's publication in1981, which estimated that diet could be involved in up to 70% of all cancers in the USA, it became imperative to investigate diet.

One of basic groups of extrinsic factors modifying the risk of breast cancer occurrence includes dietary habits, which may lead to obesity occurring especially frequently in populations of developed countries. Processed products containing a range of chemical substances, used to enhance flavour or preserve food, may be a factor promoting the neoplastic transformation process in mammary gland cells. This correlation, especially when observed in women in the postmenopausal period, is associated with an increased risk of breast cancer [7].

Contraceptive pills: Use of oral contraceptive pills at any age and for any duration can increase the risk of breast cancer 2.27-fold more among those taking pills compared to non- consumers. The increased proliferation with Ethinyl Estradiol at equivalent blood level ingredients provides an opportunity for mutated cells to continue to grow which is the basis for cancer. On the other hand, the

toxicity at high levels of EE links its impact to mutations that could potentially cause apoptosis.

Environmental exposure: Environmental exposures as ionizing radiation, smoke in combination with genetic pre-disposition, age at exposure, and hormonal milieu have a cumulative effect on breast cancer risk [8].

METHODOLOGY

Patient selection

This retrospective study was conducted on 50 female patients in the breast clinic in (Al-Yermouk teaching Hospitals) with nonmetastatic breast cancer from Jan. 2017 to Jan. 2019; follow up lasts for24 months. The same procedures done for all patients.

Data collected by questionnaire including socio-demographic factors (age, and marital status, socioeconomic status), reproductive factors (menstrual history, parity, age at first pregnancy, menopausal status, breast-feeding), Body Mass Index (BMI), reported ages at menarche and menopause, and pill usage).

Extensive questionnaire also included questions pertaining to:

- Education and work
- Nationality,
- Social network and support
- Feelings and thoughts,
- Leisure time physical activity (including sleeping habits)
- Tobacco use
- Alcohol consumption
- Health status (including weight change, past/current diseases, dietary change, use of medications,
- Family history of diseases
- Psychological well-being

Parameters and measures

Specific parameters were depended to categorize the patients:

- Age: categorical variable: <20 years, 20 years - 29 years, 30 years - 39 years, 40 years - 49 years, 50 years - 59 years and 60 years old.
- BMI: underweight (BMI < 18.5), normal weight (18.5 ≤ BMI ≤ 24.9), overweight (25 ≤ BMI ≤ 29.9) and obese
- (BMI ≥ 30). Determined based on adult weight in kg and height in meters (BMI=kg/m^2).
- Hormone replacement therapy (HRT): 'ever use' and 'never use'
- Age at menarche: less than 11 years, 12 years - 13 years, and 14 years - 16 years.
- Age at first full term pregnancy (FFTP): 0 (for nulliparous), < 25 and 30$^+$
- Parity: nulliparous, parous
- Menopausal Status: Pre/perimenopausal, postmenopausal.
- Education: less than college and some college or more
- Family History (FH): yes or no family history of at least one 1st degree female relative (sister, mother, daughter) with breast cancer.
- Smoking history: Binary variable ('ever smoked' and 'never smoked'). Ever smoked includes both current and past smokers.
- Physical activity: not active, moderately active, and very active.

Antidepressant medication: 'never used', and 'ever used. A detailed case history and clinical examination of all the patients was done. Ultrasonic examination, MRI, And mammography were done to all patients so for age ≤ 30 years, only 2 cases were observed, while for age ≥ 30 years, 48 cases were observed (Table 2).

Tab. 2. Distribution of patients according to their reproductive variables

Parameters	Variables	No. of patients
Age	< 30	2(1.3)%
	>30	48(96)%
Marital status	Marital status: Married	34(68)%
	Single	3(6)
	Divorced	4(8)%
	Widow	9(18)%
BMI	BMI > 30	29(58)%
	25-29	11(22)%
	20-24	9(18)%
	<20	1(2)%
No. of children	05-Oct	25(50)%
	01-Apr	14(28)%

	no children	9(18)%
Family history	positive	31(62)%
	negative	13(26)%
	not sure	6(12)%
Age of menarche	Nov-13	35(70)%
	14-16	15(30)%
	Lactating	9(18)%

- Married cases were 34 compared to 4 cases were divorced, 3 cases were single, and 9 were widow.
- About 29 cases were observed with the BMI>30, 11 cases were observed with the BMI 25–29, 9 cases with BMI 20–24, and only 1 cases with BMI <20.
- Women with more number of children like >10 was observed in 2 cases, 23 cases had 5–10 children, 14 cases had 1–4 children, and 11 cases had no children.
- Breast feeding was observed in 24 cases, whereas 26 women were not breasting feeding.
- Patients with family history of breast cancer were 31 cases, whereas females with no family history showed 13 cases, and not sure was 6 cases.
- Menopausal status: for age ≤ 45 years were 5 women, for 46 years–50 years were 34, and for women > 50 years showed 11 cases.
- About 12 patients were smokers for more than 15 years–20 years, 38 are non-smokers.

History of benign lesions were observed in 8 (16)%, while previous history of mastitis were observed in15 (30)%, and 40 (80) % had systemic disorders. All the patients were following bad nutritional behaviors, and none of them were practicing physical activities. Twenty patients (40)% presented with thyroid disorders. Fourty patients (80)% have administered contraceptive pills many years ago (Table 3).

Tab. 3. Distribution of patients according to their Fisk factors

No. of patients	Risk factors
48 (96)%	Age >30
15(30)%	Mastitis
8(16)%	Benign lesions
40(80)%	Systemic disorders
40(80)%	CCP
20(40)%	Thyroid disorder
29(58)%	BMI >30
12(8)%	Smoking
31(62)%	+family history
48(96)%	Bad Nutritional habits &
	No Physical activity
9(18)%	Non lactating
5(10)%	Retracted nipple

Laboratory investigations

All patients were submitted to clinical thyroid evaluation; Blood samples were drawn for free T3, T4, TSH, Thyroglobulin antibody (TgAb).

Five millilitres of fasting blood sample (10-12 h) was collected under aseptic conditions, and triglycerides (TGs), Total Cholesterol (TC), High-Density Lipoprotein (HDL), very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) were analyzed.

Blood tests are conducted to detect diabetes are:

- A1C Test HB
- We evaluated fasting C-peptide level

Low C-peptide level is a biomarker for characterizing patients with Type 1 diabetes.

The biomarkers of inflammation were analyzed for IL-1β, IL-6, and IL-8.

The leukocyte counts were assessed at the time of the baseline examinations as totals (White Blood Cells – WBC) and differentials (i.e., neutrophils, lymphocytes and mixed cells, including monocytes, eosinophil, and basophils).

The participants' food diary was recorded (e.g., the specific ingredients in mixed dishes, the type of fats used in cooking, etc.).

RESULTS AND DISCUSSION

Data of 50 female patients diagnosed with breast cancer was collected. patients enrolled in the study was during the period between Jan.2019 and 2020 ,with ages ranged from 30 and less to 60 and above years old (mean ± SD: 52.75 years ± 12.2 years) and a median follow-up was 36 months.

The plurality of tumors was located in the upper outer quadrant (85%), The other 10% was located in the lower lateral, and 5%for the remaining quadrants.

Overweight or obesity is associated with poorer prognosis, and may influence disease-free survival, reduce quality of life, and increase risk for comorbid conditions [9].

Many inflammation-associated diseases, including cancers, increase in women after menopause and with obesity. In contrast to anti-inflammatory actions of 17β-estradiol, we find estrone, which dominates after menopause, is pro-inflammatory. In human mammary adipocytes, cytokine expression increases with obesity, menopause, and cancer

A new study by Harvard researchers indicates that “good” cells can become cancerous because of exposure to a “bad” environment within the body similarly to the way a “good boy” may turn to crime when exposed to pressures of life in a crime-ridden neighbourhood [10].

In their paper in today’s edition of the journal Nature, they report that normal blood stem cells “are dependent upon their environment. They get their cues from the surrounding ‘neighborhood’ of bone cells”. “It is the environment in which the cells develop, can make the system go askew” [11].

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Oxygen species are high and overcome the antioxidant defence mechanisms of the human body, oxidative damage can occur to lipids, proteins, or directly to DNA. Reactive Oxygen Species are produced by both enzymatic and non-enzymatic systems within eukaryotic cells and play important roles in cellular physiology and pathophysiology. Although physiological concentrations are crucial for ensuring cell survival, ROS overproduction is detrimental to cells, and considered as key-factors for the development of several diseases, such as neurodegenerative diseases, cardiovascular disorders, and cancer. Cancer cells are usually submitted to higher ROS levels that further stimulate malignant phenotype through stimulus to sustained proliferation, death evasion, angiogenesis, invasiveness, and metastasis. Breast cancer cells have been shown to be susceptible to oxidative damage and have high levels of oxidative stress, including protein damage, DNA damage, and lipid peroxidation [12].

It was demonstrated in the study of Ban et al., who analyzed data included in SEER (Surveillance, Epidemiology, and End Results) database, the frequency of occurrence of breast cancer in Caucasian women is about 127.4 in 100 000 individuals. The indicators of mortality and 5-year survival are 12.3% and 90.4%, respectively. In the case of Blacks, the frequency of occurrence of the neoplasm is about 121.4 in 100 000 individuals and the indicators of mortality and 5-year survival are 18.2% and 78.6%, respectively [13].

The first basic criterion is early age of breast and/or ovarian cancer occurrence, usually in relatively young people below 45 years of age. The second criterion is the identification of familial breast and/or ovarian cancer cases in first- and second-degree relatives on a pedigree. The hereditary syndromes caused by BRCA1 or BRCA2 gene mutations are associated with several clinical symptoms.

However, they all assume the necessity of performing genetic testing to evaluate the presence of BRCA1 and/or BRCA2 mutations in patients diagnosed with breast cancer by the age of 35. Examination should also be performed in all patients diagnosed with breast cancer by the age of 40 whose tumour was characterized by lack of estrogen, progesterone and HER2 receptor overexpression (triple negative patients). Genetic consultation is also recommended to patients with bilateral breast cancer and family history of breast and/or ovarian cancer. To understand the role of genes that might play. We have to know these details:

- If your grandmother or cousin develops breast cancer (i.e. a second-degree relative or a third-degree relative), her own risk is hardly affected.
- If her mother or sister (a first-degree relative) develops the disease, that doubles her risk. But if only one of your close relatives has had breast cancer, that doesn't necessarily mean that she have a genetic predisposition caused by a mutated gene. Gene tests usually don't provide any useful information.
- If, for example, several close relatives have breast cancer that may indeed suggest that their cancer was caused by a genetic mutation passed on in the family.

Recently the American and European Diabetes and Oncology associations published a consensus report on

diabetes and cancer. They agreed that most observational evidence suggests a strong link between diabetes and breast, colorectal, endometrial, liver and pancreatic cancers, and that the likely pathogenesis of the link is due to hyperinsulinaemia, hyperglycemia, inflammation and also diabetes therapies.

The link between chronic inflammation and several steps of tumour genesis (such as cell transformation, promotion, proliferation, survival, angiogenesis, invasion and metastasis) is also widely accepted.

Many cytokines released by inflammatory cells have a pro-tumour action. One such example is TNF-α and its role along with the interleukins (e.g., IL-1) in many steps of the carcinogenesis [14].

There is now considerable evidence that the chemo preventive properties of plant-based food are related to their ability to block the progression of latent micro tumours, as well as by modifying the tumour's microenvironment (stroma) and creating physiologic conditions that are hostile to tumour growth.

So the effects of phytochemicals on tumour cells are:

- Direct inhibitory actions on tumor cells:
  Reduction of damage to DNA: Free radicals, environmental or diet-associated chemicals and some metabolites all have the capacity to severely damage cell DNA, which might ultimately lead to cancer. Several chemo preventive phytochemicals elicit their anticancer effects by modulating the enzymatic systems responsible for neutralizing these carcinogens, either by reducing their carcinogenic potential or by increasing their excretion.
- Cytotoxicity against tumour cells:
  Several phytochemicals also inhibit tumour growth by directly inducing cancer cell death by apoptosis. For example, isothiocyanate from cruciferous vegetables, curcumin from turmeric, grapes have all been shown to possess strong pro-apoptotic activity against cells isolated from a variety of tumours.

- Effects on tumour microenvironment:
  Antiangiogenic properties: Angiogenesis is the process by which tumour cells stimulate formation of new blood vessel networks that sustain the development of cancer by providing oxygen and nutrients to tumour cells. Many laboratories have shown that several phytochemicals possess strong anti- antigenic activity and that this effect likely plays an important role in their chemo preventive properties.

  Anti-inflammatory effects: It is becoming increasingly clear that inflammatory stimuli participate in the progression of several cancers, including those of the colorectal, breast, and lung. The close relationship between inflammation and cancer is suggested by the identification of a number of inflammatory conditions that predispose patients to cancer.

There is now considerable evidence that Western diets rich in refined starches, sugar, hydrogenated un-saturated and Trans fatty acids and poor in fruit, vegetables, fiber, can promote inflammation.

Inflammatory and immune cells from those consuming typical Western diets contain a high proportion of the pro inflammatory ω-6 Polyunsaturated Fatty Acid (PUFA) arachidonic acid and low proportion of anti-inflammatory ω-3, PUFAs eicosapentenoic acid and docosahexenoic acid which results in generation of several diseases, including cardiovascular disease, diabetes and certain types of cancer [15].

CONCLUSION

This study indicates that the incidence and mortality rates of breast cancer is rising and it is under the effect of many factors, so prevention of these risk factors is essential in treatment and avoidance of recurrence.

Breast cancer develops through a multistep process. In the last decade, the tumor microenvironment and breast CSCs (cancer stem cells) have been identified as contributors to breast tumor genesis, and is also influenced by genetic and environmental factors. Targeted prevention strategies against these risk factors should be taken ahead of time.

Although the incidence rate of breast cancer is high in developed countries, the fact which we can't ignore is that almost half of the breast cancer cases and over half of deaths occur in developing countries.

Nowadays, with the reduction in the cost of DNA sequencing, individual genome sequencing may be affordable by middle-class populations, and this could be a new method in preventing breast cancer as well as other hereditary diseases. If a woman have a family history of breast cancer, it is wise to do a screen especially on hereditary cancer susceptibility genes such as BRCA1 or BRCA2. The risk of breast cancer could then be evaluated based on the screening results and prevention advice could be offered personally. Additionally, risk factors should be taken more seriously either in normal or high-risk women. Environmental factors such as the exogenous estrogen intake, alcohol abuse and bad dietary habits could be avoided to minimize breast cancer risk. Though some risk facts such as aging and reproductive factors are inevitable, measures should be taken ahead of time to reduce the risk.

In the modern world, many people spend countless hours sitting at tables. However, physically active women have a 25% lower risk of breast cancer on average than women who are less active. Regular physical exercise may be a convenient and inexpensive way to prevent breast cancer in women from both developed and developing countries.

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