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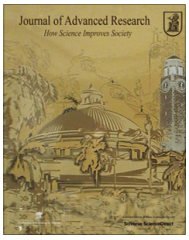

REVIEW

# Inflammatory breast cancer: New factors contribute to disease etiology: A review

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ABSTRACT

Inflammatory breast cancer (IBC) is a highly metastatic and fatal form of breast cancer. In fact, IBC is characterized by specific morphological, phenotypic, and biological properties that distinguish it from non-IBC. The aggressive behavior of IBC being more common among young women and the low survival rate alarmed researchers to explore the disease biology. Despite the basic and translational studies needed to understand IBC disease biology and identify specific biomarkers, studies are limited by few available IBC cell lines, experimental models, and paucity of patient samples. Above all, in the last decade, researchers were able to identify new factors that may play a crucial role in IBC progression. Among identified factors are cytokines, chemokines, growth factors, and proteases. In addition, viral infection was also suggested to participate in the etiology of IBC disease. In this review, we present novel factors suggested by different studies to contribute to the etiology of IBC and the proposed new therapeutic insights.



**Mona M. Mohamed** research interest is studying the interactions in breast cancer among inflammatory macrophages, their associated cytokines and proteolytic enzymes. She is also interesting in determining if a strongly suspected viral infection plays a prominent in the etiology of inflammatory breast cancer. Her ultimate goal is to understand mechanisms molecular mechanisms that may induce breast cancer progression and identifying novel targets for drug development.

**Diaa Al-Raawi** is assistant lecturer in Sana'a University, Yemen. After finishing her undergraduate studies at University of Sana'a and obtaining her Bachelor degree of Science in 2003, she worked as instructor in Sana'a University. She has been awarded a postgraduate fellowship at Cairo University and spent three years 2008–2011 as postgraduate student at Cancer Biology Laboratory, Faculty of Science, Cairo University – Egypt. Her thesis focused on examine the expression of hormone receptors, human epidermal growth factor receptor-2 (HER-2) and matrix metalloproteinases in an attempt to provide a more validated data on biological features of unique phenotype inflammatory breast cancer (IBC).

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**Salwa F. Sabet** research interest is studying the most prevalent diseases in Egypt as Cancer and Hepatitis C Virus. Regarding cancer, She is interested in studying genetic alterations associated with cancer disease, including epigenetic changes, polymorphism and their contribution in disease progression, which might help in cancer diagnosis and drug development. She is also interested in studying the expression and structure of different proteins of HCV4a in order to determine their active sites for drug development.

**Mohamed El-Shinawi** M.D., FACS is an Associate Professor of General Surgery – Ain Shams University, Egypt. He is the Lead Trainer of the Sequential Trauma Educational ProgrammS in collaboration with Maryland University, USA. He is the President of AMSRA and a member of a several prestigious associations and societies. He is pursuing a career in breast cancer surgery and research. He also pursues a career in trauma and emergency care and in the area of injury research. His Biography was included in Who's Who in Medicine and Healthcare. He is an investigator on four projects with different universities in the United States.

## Introduction

Inflammatory breast cancer (IBC) is the most lethal form of primary breast cancer (TNM classification T4) targeting young women. The term "inflammatory breast cancer" was first suggested in 1924 by Lee and Tannebanm as a type of cancer associated with inflammation of the breast [1]. In 1938, Taylor and Meltzer introduced two clinical varieties of IBC, namely primary IBC and secondary IBC [2], to differentiate between IBC and locally advanced breast cancer. The term "primary IBC" or "*de novo* IBC" is defined as the new development of IBC in a previously normal breast, whereas the term "secondary IBC" describes the inflammatory recurrence of non-IBC breast cancer [3]. IBC represents about 2.5% of newly diagnosed breast cancers in the United States [4], where incidence of IBC is higher among African–American compared to white women [5]. The frequency of IBC in North African countries such as Tunisia, Morocco, and Egypt represents about 10% to 15% of breast cancer [6,7]. Recent studies conducted by Schairer and colleagues compared percentage diagnosis of IBC at the National Cancer Institute, Egypt, and Institute Salah Azaiz (ISA), Tunisia, and they suggested that the increase in IBC cases in North Africa may be due to misdiagnosis of IBC with other types of locally advanced breast cancer [8]. In addition, the lack of breast cancer national registry programs in developing countries should also be taken into consideration.

There are two well recognized systems for case definition of IBC. The first is the French Poussée Évolutive (PEV) system devised in 1959 which defined IBC as a rapidly growing breast malignancy with PEV2 and PEV3 [9,10]. The second is the American Joint Committee on Cancer (AJCC) staging system that classifies IBC as T4d [11].

IBC diagnosis was shown to be associated with a worse survival rate than other types of breast cancer, which remains a therapeutic challenge despite the advances in treatment. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program found that the 3-year disease survival rate increased for IBC patients compared to non-IBC patients between 1975–1979 and 1988–1992. For IBC, survival rate increased from 32% to 42% for IBC patients and from 80% to 85% for non-IBC patients [12]. Improved survival rate of IBC patients may be due to the use of neoadjuvant chemotherapy and combination regimens in the treatment of IBC [13,14]. Clinically, IBC is defined by distinct features, including rapid onset within 6 months, erythema, edema of the breast, and a "peau d'orange" appearance to most areas of breast skin. Moreover, patients presented with positive metastatic lymph node involvement and up to one third of patients have distant metastasis at diagnosis [15]. Pathologically, the presence of dermal and stromal tumor emboli is considered a hallmark of IBC. The subsequent lymphatic obstruction by tumor emboli prevents proper drainage of the lymph fluid causing swelling of the breast tissue and produces the inflammatory nature of the disease [3,16].

## Biological markers associated with IBC

Molecular profiling studies suggested that the molecular subtypes of IBC are similar to those described in non-IBC. However, low frequency of luminal A and high expression of HER-2 are enriched among IBC patients as compared with non-IBC [17]. Other studies identified specific biological markers that may be associated with IBC poor prognosis, and disease aggressiveness. For instance, IBC is characterized by amplification/over-expression of growth factor receptor HER2 [17] and down regulation of hormone receptors ER/PR [18–20]. The absence of hormonal receptors expression was shown to be correlated with a high degree of malignancy and breast cancer shorter disease-free survival [21]. IBC patients with ER positive receptors have a better prognosis with a median survival of 4 years compared to 2 years median survival for patients with ER-negative IBC [4]. About 80% of IBC carcinoma tissue samples are characterized by loss of WNT1-inducible-signaling pathway *protein* 3 (WISP3) and also recognized as loss of inflammatory breast cancer gene [22]. WISP3, also known as CCN6, is a cysteine-rich protein found to inhibit invasive and angiogenic potential of IBC cells in tissue cultures and animal models [23]. In addition, IBC embolus is characterized by over-expression of a number of genes such as ras homolog family member C-guanosine triphosphatase (RhoC-GTPase) and E-cadherin [24]. The epithelial marker E-cadherin is a calcium dependent transmembrane glycoprotein that mediates epithelial cell–cell adhesion [25]. IBC cells are characterized by over-expression of E-cadherin, which is essential for adherence of cells together and formation of tumor emboli. Studies suggested that E-cadherin facilitates the dissemination of IBC within the lymphatic vessels by promoting cell–cell contact and maintaining the integrity of IBC tumor emboli within dermal lymphatics [24,26]. The role of E-cadherin in IBC is opposite to non-IBC. In non-IBC, loss of E-cadherin expression contributes to increased tumor proliferation and to the progression of metastasis and is associated with poor prognosis [27], while increased E-cadherin in IBC contributes to dis-