REVIEW ARTICLES

Association of Breast Cancer with Epstein-Bar Virus and Cytomegalovirus Infection: Histological Types and Risk Factors

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Abstract

Cancer is one of the most important global health problems and it is the most common diagnosed cancer in women in developing and developed countries. Around two-thirds of new cases are in developed

countries. Breast cancer is also the most common cancer in females in developing countries with the age standardized incidence rate around 20 per 100,000. The factors that contribute to the international variation in incidence rates are largely due to the differences in reproductive and hormonal factors and the availability of early detection services, Incidence rates in some countries, including the United States, United Kingdom, France, and Australia, sharply decreased from the beginning of the millennium, partly due to lower use of combined postmenopausal hormone therapy. In all countries of the Arab world, breast cancer now occupies the number one position of all female malignancies. Cases tend to be young and almost half of patients are below 50, with a median age of 49-52 years as compared to 63 in industrialized nations. In recent years the higher increase in incidence of cancer worldwide is likely to be in the Eastern Mediterranean Region, where breast cancer is reported as the commonest type of female malignancy in almost all national cancer registries. Breast cancer ranks the first among cancers in Iraqi population and forms 16.28/100000. Additionally, breast cancer account for 34% of the reported cancer cases for the year 2018. The incidence of breast cancer in Iraqi women increased in the last two decades and forms one of the major threats to female health.

Keywords: Breast cancer, Cytomegalovirus, Epstein-Barr virus, Eastern Mediterranean Region, Risk factor, Breast feeding, Parity, Menarche.

I. Anatomy and physiology of the Breast

Breasts develop as down growths from the epidermis along the milk line which runs obliquely from the axilla toward the groin on each side. The nipple and its simple system of ducts are present at birth, but full development does not occur until puberty, and then usually only in females. Continued estrogen secretion after onset of puberty leads to progressive enlargement and complexity of the breast [1], due initially to an increase in adipose tissue, and then the ductular system of the nipple becomes more complex, with branches extending into the adipose tissue [2].

Inside the breasts are located the mammary glands, modified sweat glands responsible for the production and secretion of milk, which are composed of 12-20 distinct lobes, with its own separate

opening at the nipple. Each lobe form of a branching ducts which penetrating deeply into the breast fibroadipose tissue. The branching duct system ends in a cluster of blind-ending terminal ductules, each cluster and its feeding duct comprising a mammary lobule. The terminal ducts and lobules are embedded in a loose fibrous support tissue, which is rich in capillaries and also contains a few lymphocytes, macrophages and mast cells [2,3]. The ducts are lined by cuboidal epithelium (luminal side) with an outer discontinuous layer of myoepithelial cells (basal surface). This polarity of cellular organization allows transport through the mammary epithelium in a single direction: secretion into the lumen. Contractile myoepithelial cells have the ability to generate a flow of milk through the ducts to the nipple [4].

Breast's full functional activity is only reached under the influence of pituitary (prolactin) and ovarian hormones (estrogen and progesterone), which are secreted in high concentrations during pregnancy and throughout breastfeeding. During the follicular phase of the menstrual cycle, cell proliferation is low and does not increase with the pre-ovulatory peak of estrogen. Following ovulation, progesterone stimulates up to three times the proliferation of the epithelial cells in the terminal ductules that become enlarged and begin to show evidence of early secretary activity. If fertilization does not occur, progesterone levels fall dramatically at the end of the menstrual cycle and the structure of the breast lobule reverts to normal along with some cell death. However, if fertilization occurs, increasing amounts of progesterone stimulate the continued proliferation and secretary activity in the terminal ductules of the lobule, in order to produce milk. When breastfeeding ceases, the breast returns to its normal state by gradual involution together with massive apoptosis leading to the loss of alveolar structures [2,5,6].

Throughout a woman's lifetime the breast goes through a 450 cycles of growth and involution in response to hormones produced during the menstrual cycle and pregnancy [4]. As women age the amount of fibrocollagenous tissue in the breast increases, replacing some of the adipose tissue, and the mammary lobules become enclosed in dense collagen [2]. Knowledge of normal histological appearances is essential to recognize abnormal structures, and to

understand how the altered biochemical and physiological processes result in disease.

II. Epidemiology

Breast cancer is the most common form of malignancy affecting women worldwide [7,8] accounting for 23% of all cancers in women [9]. It is estimated that more than one million women are diagnosed with breast cancer every year worldwide [10]. Overall, one in ten women will develop breast cancer in their lifetime [11]. It is a leading killer in women. Its mortality is second to mortality from cancer of the lung and bronchus [11]. Despite significant developments seen in diagnostic as well as improvement in the early recognition and intensive treatment, every fourth women suffering from breast cancer dies because of progression of the illness [12]. Nowadays , breast cancer ranks as the fifth cause of death from cancer overall [13].

Around two-thirds of new cases are in developed countries. Breast cancer is also the most common cancer in females in developing countries with the age standardized incidence rate around 20 per 100,000 [9]. The factors that contribute to the international variation in incidence rates are largely due to the differences in reproductive and hormonal factors and the availability of early detection services, Incidence rates in some countries, including the United States, United Kingdom, France, and Australia, sharply decreased from the beginning of the millennium, partly due to lower use of combined postmenopausal hormone therapy [14].

In all countries of the Arab world, breast cancer now occupies the number one position of all female malignancies. Cases tend to be young and almost half of patients are below 50, with a median age of 49-52 years as compared to 63 in industrialized nations [15,16] . There is also a high rate of advanced or metastatic stage reaching 60 to 80% of cases, and high Mastectomy rates [10,15]. In recent years the higher increase in incidence of cancer worldwide is likely to be in the Eastern Mediterranean Region (EMR), where breast cancer is reported as the commonest type of female malignancy in almost all national cancer registries [17].

Breast cancer ranks the first among cancers in Iraqi population and forms 16.28/100000. Additionally, breast cancer account for 34% of the reported cancer cases for the year 2018 [18]. The incidence of

breast cancer in Iraqi women increased in the last two decades and forms one of the major threats to female health [19]. The age standardized incidence rate of breast cancer is 18.4/100000 for Iran, 22.4 for Saudi Arabia, 23.0 for Syria, 28.3 for Turkey, 31.1 for Iraq, 47.0 for Jordan, and 47.7 for Kuwait [20]. Al-Hashimi and Wang conducted incidence trends from 2000 to 2009 and included 23,792 cases reported that breast cancer in Iraqi women increased from 26.6 per 100000 in 2000 to 31.5 /100000 in 2009 [21], while it increased to 32/100000 in 2018 [18]. The incidence rate of breast cancer in Iraqi women is Iraqi National Programs for early detection of breast cancer were developed in order to decrease morbidity and mortality of breast cancer [22]. Age at which breast cancer diagnosed is with important implications since cancer in younger age group is more aggressive [23,24].

III. Histological Types of Breast Cancer

3.1. In Situ Breast Carcinoma

Although the initiating steps and precise pathways of breast tumorigenesis remain poorly defined, it appears that nearly all invasive breast cancers arise from in situ carcinomas [25,26].

3.1.1 Ductal Carcinoma in Situ (DCIS):

Called intraductal carcinoma [26], accounts for approximately 20% of mammographically detected breast cancers [25]. Morphologically, DCIS resembles and often coincides with ductal and related (tubular, cribriform, mucinous) types of invasive breast cancer [27]. It can recur or progress to invasive breast cancer, but the ability to predict the outcome of patients with DCIS remains limited [25].

The pathological classification of ductal carcinoma in situ is based on the nuclear grade of the tumor cells (low, intermediate, or high), the architectural pattern of tumor growth (solid, papillary, micropapillary, cribriform, clinging, or cystic hypersecretory), and the presence or absence of comedonecrosis [25,26,28]. DCIS has no metastatic potential. Clinically, however, from 1% to 2% of patients with a diagnosis of pure DCIS subsequently develop metastases either because of occult invasion or the progression of unsuspected residual disease to Invasive breast cancer [25].

3.1.2 Lobular carcinoma in situ:

The clinical significance of lobular carcinoma in situ has been debated since it was first described in 1941[29]. It is now considered a high-risk marker for the development of infiltrating breast carcinoma and not a premalignant lesion. Moreover, lobular carcinoma in situ is thought to be an incidental finding at breast pathology [30]. Intracytoplasmic vacuoles, pagetoid ductal involvement and loss of cohesion are characters of lobular carcinoma in situ; however, in ductal carcinoma in situ these three characters are absent. In contrast, microacini, absent in lobular carcinoma in situ, are present in ductal carcinoma in situ. In reality, the distinction is not always clear [29].

From the point of view of the differential diagnosis with DCIS, the two important immunohistochemical features of LCIS are the lack of reactivity for E-cadherin and ß-catenin [31]. The term "indeterminate in situ lesions" or "mixed type lesions" is used to describe certain breast carcinomas in situ, in which the cytological or architectural properties and distribution deviated from the typical patterns, render it difficult, if not impossible, to determine whether the proliferation was lobular or ductal, based only on morphological criteria [32,33].

3.2. Invasive breast carcinoma

Invasive ductal (IDC) and lobular carcinomas (ILC) are the most common histological types of invasive breast cancer [34].

3.2.1. Invasive ductal carcinoma not otherwise specified (IDC-NOS)

This is the most common type, accounting for 75% of breast cancer cases. Microscopically, the tumor can grow in diffuse sheets, well-defined nests, cords, or as individual cells. Tubular/glandular differentiation may be well developed, hardly detectable, or altogether absent. The tumor cells vary in size and shape, but by definition they are larger and more pleomorphic than those of the classic form of invasive lobular carcinomas. There are more numerous figures of mitosis and more prominent nucleoli and nuclei. Areas of necrosis, foci of squamous metaplasia, apocrine metaplasia, or clear cell changes may be seen. The amount of stroma ranges from none to abundant, and its appearance from densely fibrotic to cellular (desmoplastic), with or without elastosis and calcifications [31].

3.2.1.1. Mucinous carcinoma:

This type usually occurs in women after menopause and also named as colloid, gelatinous or mucoid carcinoma. Mucinous carcinoma is a rare histological type of breast cancer characterized by abundant production of extracellular and/or intracellular mucin [35]. Pure mucinous carcinomas (defined as tumors with more than 90% of mucinous component) account for up to 2% of all breast carcinomas, preferentially affect older women, and are usually associated with a good clinical outcome [36]..Such tumors are characterized by uniform neoplastic cells arranged in clusters floating in a large amount of mucin, nuclear atypia and mitotic figures are uncommon [35].

3.2.1.2. Medullary carcinoma:

It represents a rare breast cancer subtype [37], accounts for 1.1–7% of all mammary carcinomas [38], and tends to affect patients of younger age [39]. Despite their aggressive morphology, with nuclear atypia and high mitotic indices [37].

3.2.1.3. Tubular carcinoma:

It is an uncommon histologic subtype, accounting for 1% to 4% of invasive breast cancer [40]. It has been shown to have a favorable prognosis as manifested by a low incidence of metastases and recurrences and an excellent overall survival [41].

3.2.1.4. Inflammatory carcinoma (IC):

Inflammatory breast carcinoma is a rare, aggressive tumor associated with poor outcome owing to early metastases [42]. The diagnosis depends on clinical (erythema, edema and breast heat without any pain) and/or histological findings (any subtype of breast carcinoma with tumor emboli in the dermal lymphatics or/and tumor emboli in the vessels) [43]. Recent studies have demonstrated that E-cadherin is always over-expressed in inflammatory breast cancer specimen and cell lines [44].

3.2.1.5. Paget Disease:

It is accompanied in nearly all instances by an underlying breast carcinoma of in situ ductal type, with or without associated stromal invasion. Specifically, it is characterized by a red, oozing, crusted lesion which is often unresponsive to topical steroid and antibiotics [45]. Microscopically, large clear cells with atypical nuclei are seen within the epidermis, usually concentrated along the basal layer but

also permeating the Malpighian layer. The cells can be isolated or in clusters, and sometimes they form small glandular structures [31].

3.2.2. Invasive lobular carcinoma (ILC): (Classic Type)

Also known as infiltrating lobular carcinoma is a type of breast cancer that starts in a lobule and spreads to surrounding breast tissue. ILC comprises approximately 10-15% of breast cancers and appears to have a distinct biology [46]. Data from a recent epidemiologic study indicate that for unknown causes the incidence of this type of breast cancer is increasing, especially among postmenopausal women [47]. Replacement hormonal therapy may be implicated as the underlying cause [48].

Microscopically, classical ILC is characterized by the presence of small and relatively uniform tumor cells growing singly, in Indian file, and in a concentric (pagetoid) fashion around lobules involved by in situ lobular neoplasia [31], less well appreciated is a group of variant forms of ILC, which includes solid, alveolar, mixed, apocrine, signet-ring, histiocytoid, and tubulolobular variants [49,50]. Lobular carcinomas are more likely to be ER and PR positive and to have normal p53 status and low to absent HER-2 [46], with loss of expression of E-cadherin and β-catenin [51] as Inactivation of E-cadherin by mutation, loss of heterozygosity, or methylation is considered a characteristic of ILC [52].

ILC has a tendency to spread diffusely or between the collagen fibers of the breast and produces little desmoplastic response with a substantially increased propensity for multifocal and multicentric distribution and for bilaterality [53]. Metastatic IDC commonly involves the lung, bones and liver, whereas ILC can spread on the surfaces of the leptomeninges and peritoneum; permeate through the walls of the gastrointestinal tract organs, uterus, and ovaries; and diffusely infiltrate through the retroperitoneal soft tissues [48,54,55].

Now, it seems reasonable to conclude that at least four groups of women are at increased risk for lobular breast cancer: women with lobular breast cancer and a family history of breast cancer, women with a known CDH1 mutation, women from families with diffuse gastric cancer in whom no CDH1 mutation has yet been identified; and women with a germline BRCA2 mutation [56].

3.2.2.1. Mixed Ductal and Lobular Breast Carcinomas

Biphasic carcinomas which are composed in part of a component with definite features of invasive ductal carcinoma and in part of a component with definite features of invasive lobular carcinoma do occur, but they are very rare. These tumors, of course, should be distinguished from the cases in which two separate neoplasms of different microscopic appearances are present in the same breast [31].

IV. Prognosis

Despite the huge number of discovered prognostic and predictive factors for breast cancer, the American Society of Clinical Oncology has concluded that most of them are not satisfactory yet to be recommended for general clinical use. The factors that are currently used include: staging (size of the tumor), lymph node involvement and distant metastasis, grading, ER, progesterone receptor (PR) and human epidermal receptor-2 neu (HER2/neu) expression [57-59]. Patients with breast cancer grouped according to disease extent and these groups referred to as tumor staging.

The first clinical staging system was the Columbia Clinical Classification, which was developed in the 1940-50's. In 2002, a new system was introduced adopted by the International Union against Cancer and the American Joint Committee on Cancer. This system is the one currently in use and is based on the principle of the tumor size (T), nodes involvement (N) and metastases (M) known as TNM [60]. These factors are only prognostic for breast cancer death regardless of other tumor characteristics but do not predict response to therapy. Lymph node involvement is another important independent prognostic factor. Women with lymph node involvement and increasing number of affected lymph nodes are associated with poorer prognosis [61]. Finally, metastasis is a third factor of clinical importance. In general, women with distant metastasis have a median overall survival time of only 2 years [62].

Tumor grade is the classification of the differentiation of the tumor into three groups: low, high and moderate. High grade cancers may be faster growing and more likely to spread. Grading was first introduced by Greenough in 1925 and modified by Bloom and Richardson in 1957, using three criteria; glandular formation, cell size and shape and proliferation. Currently the most commonly used

grading system is the Nottingham histological grade [63]. Grade is moderately reproducible [64] but is nevertheless a prognostic factor used after adjustment for tumor size and lymph node involvement.

The most important predictive markers is the expression of two members of the steroid hormone receptor group, ER and PR. Expression of ER and PR is associated with better survival and higher response rate to hormonal therapy. Women expressing both receptors have 80% better response, women expressing only ER have 30% and women who do not express either of the two receptors do not respond to estrogen receptor modulators [65].

The last few years a huge effort has been given to discover expression profiles that could eventually prove useful to predict the likelihood of breast cancer recurrence and response to treatment. The following four gene expression assays Oncotype DX (evaluates the likelihood of breast cancer recurrence and assesses the benefit of adjuvant chemotherapy), Mamma Print test (to predict the likelihood of breast cancer recurrence within five to 10 years), Rotterdam Signature (predict risk of breast cancer recurrence), and the Breast Cancer Gene Expression Ratio (to help predict recurrence of breast cancer) are under investigation and for the first two expression profiles trials are underway to confirm their clinical value [66].

V. Invasion and Metastasis

One of the most lethal aspects of breast tumors is their ability to invade the surrounding normal mammary tissue and re-locate to other sites in the body distal to the primary tumor, whereby tumor growth begins anew (metastasis). While the process by which cancer cells lose adherence to the primary tumor and develop migratory and invasive capacities has been well-described at the cellular level, the progression of invasion is still poorly understood at the molecular level [67,68]. Cancer cells from a primary tumor enter lymphatic and blood vessels, circulate through the bloodstream, and settle down to grow within normal tissues elsewhere in the body. Malignant tumors mostly metastatised to other sites if not treated. In contrast, some tumors are with very low potential for metastasis such basal cell carcinoma and glioma. When tumor cells metastasize, the new tumor is known as a secondary or metastatic tumor, and often displays properties of the original (primary) tumor. Metastasis can occur long after the apparent elimination of the primary tumor. In breast cancer,

metastases have been known to occur decades after the primary treatment [68]. Cancer cells can exist in three separate states in a secondary site, solitary cells in quiescence, active pre-angiogenic micro metastases, in which proliferation is balanced with apoptosis and no net increase in tumor size occurs, and vascularize metastases, either small and clinically undetectable, or large and detectable by current technology [69].

The spread of cancer cells may occur via the blood or the lymphatic system or through both routes. Some tumors metastised to particular organs [70]. Successful formation of metastases requires angiogenesis at the primary tumor, down regulation of cohesive molecules, increased motility of tumor cells, invasion into neo-vessels, tumor cell embolism, arrest and attachment in capillary beds of distant organs, extravasations and proliferation in the organ parenchyma and re-establishment of angiogenesis when the tumor reaches > 1-2 mm in size [67].

VI. Risk Factors of Breast Cancer

A wide variety of factors have been incremented in the aetiology of breast cancer. Some of these factors have been causatively related to the disease and are called “established” risk factors; other has a suspected association with breast cancer and is called “speculated” risk factors. While the rest are still have little or no scientific support and are called unsupported risk factors [71].

6.1 Gender

Simply being female is the most important risk factor for breast cancer. Although men can do develop breast cancer, the disease is 100 times more likely to occur in women than in men. Women are at higher risk of breast cancer because they have much more breast tissue than men do. In addition, the female hormone estrogen promotes the development of breast cancer [72].

6.2 Age

The incidence of breast cancer increases with age, doubling about every 10 years until menopause, when the trend of increase slows dramatically [73]. The peak of breast cancer incidence around menopause might be due to the physiological hormonal changes [74]. Breast cancer is uncommon in younger women. Several studies have shown that women who develop breast cancer in their 20s and 30s have a poorer prognosis and worse survival with more biologically

aggressive cancers and higher rates of proliferation and lymphovascular invasion than older patients with cancers of the same stage [75].

In developed countries about 0.3%, 4% and 19% of breast cancer cases are younger than 30, in their 30s and in their 40s respectively [76]. Patients under 30 year age form about 5% while about 75% of cases occurred in women older than 40 years of age [77]. In Iraq there has been a sharp increase in the incidence of this tumor in younger age groups. Recent study in Iraq indicated a shift of breast cancer development toward younger age group [78]. Age distribution indicated that 52.7% of breast cancer cases were in women with age of < 30 years and odd ratio confirmed a significant association between age and breast cancer development. Women with age of 21 to 30 years show the higher frequency of breast cancer as compared to other age groups.

6.3 Benign Breast Disease

A history of benign breast disease has been shown to confer a 2 to 3 fold increase in risk for the subsequent occurrence of breast cancer. Moreover, only 5% of breast cancer patients reported earlier benign breast disease [79]. The various types of benign breast disease are not all associated with the same degree of risk; some types have little or no effect on the risk. While others may represent early stages in the progression to breast cancer. Women with severe atypical epithelial hyperplasia have 4 to 5 times higher risk of developing breast cancer than women who do not have any proliferate changes in their breast. Women with this change and a family history of breast cancer (first degree relative) have nine folds increase in risk [73, 80,81].

Women whose earlier breast biopsies detected proliferative breast disease without atypical or usual hyperplasia have a slightly higher risk of breast cancer (1.5 to 2 times greater than other women). Furthermore, fibrocystic changes without proliferative breast disease do not affect breast cancer risk [82,83].

Several studies have also assessed the relation between palpable breast cyst and breast cancer, studies that have followed up groups of women with cysts diagnosed mainly or exclusively by aspiration have all suggested that patient with palpable breast cysts are at an increased

risk of breast cancer, which range from 1.7 to 7.5 times that expected [84].

6.4 Previous Breast Cancer

A woman who has previously had breast cancer has a three to four times increased risk of developing a new cancer in the other breast. Such a new or second cancer arises from a completely different location and should not be confused with a cancer that has recurred or metastasized from another site [80]. The likelihood of a new cancer increases by 0.5% to 0.7% each year after the original diagnosis. After 20 years, a woman has a 20% to 15% chance of developing a new breast cancer [71].

6.5 Family History/Genetic Factors

The most important risk factor for breast cancer, besides advanced age, is a family history of breast cancer [85]. Development of breast cancer increased in women with family history of breast cancer and the risk increased in those with history in the first degree family relatives. The risk is even higher if more than one first-degree relative had breast cancer, or if the relative developed breast cancer at an early age, or in both breasts [86-88]. Approximately 5% to 10% of breast cancer cases result from inherited mutations in breast cancer susceptibility genes, such as BRCA 1 and BRCA 2 [89,90].

The absolute risk of breast cancer mutation carriers has not been estimated precisely, but seems to be at least 50% by age 50 years with little increase in risk after the menopause [91]. The inheritable type of breast cancer is characterized by an early age onset, bilaterality, an autosomal dominant mode of inheritance and associated with other cancer. Susceptibility to breast cancer is inherited as an autosomal dominant trait, whereas the allele generally behaves as a recessive allele in somatic cells. On average, half of the off spring of a parent with BRCA 1 or BRCA 2 mutation will inherit the same mutation and the females will be at high risk of breast cancer [92].

There is increasing evidence that BRCA1 and BRCA2 are classic tumor suppressor genes and not oncogenes creating a protein that repairs DNA and prevents carcinogenesis. Every cell in mutation carriers has been demonstrated to lack one functional allele (i.e. the tumor-suppressor function of that gene is lost); a situation that favors cancer development [93-95].

The BRCA1 is a large gene, encoding a messenger RNA (mRNA) of 1865 amino acids. It is expressed during cellular proliferation and its function is necessary for cell proliferation and tissue differentiation. Recent research has suggested that BRCA 1 protein may also have more specific roles in controlling the rate of cellular proliferation, ensuring the fidelity of DNA duplication, maintaining genome integrity and/or preventing the replication of damaged DNA [96].

At the present time over 250 different disease causing mutations, scattered throughout the genes, have been discovered [97]. It has been estimated that between 1 in 2000 and 1 in 500 in the general population carry high risk mutations in BRCA 1, Mutations in BRCA1 account for breast cancer in about 50% of families with three or more cases of early onset breast cancer [98]. The lifetime risk of breast cancer in women with BRCA 1 mutations was estimated to be 87%. Recent studies of women who develop breast cancer at a very young age indicate that 13% of those who are diagnosed with breast cancer under the age of 30 years, and 7% of women who are diagnosed with breast cancer under the age of 35 years, have gremlin BRCA 1 alterations [99].

The cumulative risk of developing a second breast cancer was estimated to be 60-80% of affected mutation carriers who live to the age of 70 years [100]. The BRCA 2 is almost twice as large as BRCA 1 and so even more complex to screen fully for mutations. It encodes a protein of 3418 amino acids [101]. Over 100 mutations have been described in BRCA 2 [102]. Women with BRCA 2 mutations appear to have a breast cancer risk similar to that of women with BRCA 1 mutations (about 70% by age 70 years) [100]. Many studies were done in many Arab and Asian countries and all of them concluded that BRCA1 and BRCA2 mutations are likely to contribute to the pathogenesis of familial breast cancer [92,103,104].

Another gene associated with breast cancer is the human P53 gene. This gene is known to be a tumor suppressor gene that can be inactivated by point mutations. The risk of breast cancer is increased in women of families suffering from Li-Fraumeni syndrome, which is an autosomal dominant cancer syndrome [105]. The onset of breast cancer is often at a very early age (20-30 years) [106]. Rarely, people suffering from cowden disease, which is a rare autosomal dominant

syndrome, are more liable to develop breast cancer due to the presence of PTEN gene [107,108].

The risk breast cancer in women with cowden disease is 30-50% by age 50 years [109]. It is often bilateral and typically is diagnosed at a younger than average age [110]. In our recent study in Iraq, P53 mean serum level was significantly higher in women with breast cancer as compared to control [111]. Another gene, encoded by sequences on chromosome 2, named BARD 1 (BRCA 1-associated RING-domain 1) has recently been identified [112]. The role of BARD1 in the development of both sporadic and familial breast and ovarian cancer is currently under investigation. Many other cancer related genes, such as myc, erb B2, cyclin D1, M dhi and Tsg 101, have been shown to be involved in the tumorigenesis of breast cancer [113].

6.6 Reproductive Factors

Several studies have suggested that reproductive factors influence breast cancer risk through their effect on cell proliferation and DNA damage, as well as promotion of cancer growth [114,115]. Women who reach menarche at a relatively early age (12 or younger) and these who reach menopause at a relatively late age (55 or older) are more likely than other women to develop breast cancer [111] . Those relationships are believed to be mediated through the effect of estrogen, and the risk of breast cancer is associated with the period of exposure of breast tissue to the hormone [71,116,117]. Estrogen action is mediated by a nuclear receptor, the estrogen receptor [118]. Two studies performed in Iraq reported increased mean serum levels of estrogen and progesterone receptors in women with breast cancer [78,119].

The increase in breast cancer risk, associated with a five-year increase in age at menopause, is about 17%. Similarly, the decrease in breast cancer risk associated with a two-year delay in menarche is about 10% [71]. Women who have a natural menopause after the age of 55 are twice as likely to develop breast cancer as women who experience the menopause before the age of 45. Furthermore, women who undergo bilateral oophorectomy before the age of 35 have only 40% of the risk breast cancer of women who have a natural menopause [73].

Another important reproductive factor is age at first full term pregnancy [111]. Nulliparity and late age at first full term birth both increase the life time incidence of breast cancer [120]. The risk of breast cancer in women who have their first full term baby after age of 30 is about twice that of women who have their first child before the age of 21 year [73]. Several studies have been done in different developed countries, as in Northern Italy, a case control study was conducted at 2000 by Vecchia [121]. This study confirms that age at first full term birth is the major determinant of subsequent breast cancer risk while the age at subsequent birth has independent effect. Similar results have been reported from different studies conducted in developed and developing countries. In a case control study carried out in Spain, it was found that breast cancer risk decreased with increasing number of full term pregnancies and also it indicates that parity is an independent risk factor associated to breast cancer [122]. Pregnancy may reduce breast cancer risk by bringing about persistent changes in the mammary gland that make the breast less susceptible to carcinogenic factors[123].

Recent study in Kirkuk, Iraq, indicated that serum mean value of prolactin, progesterone receptor, estrogen receptor, glucose, HbA1C and calcium were significantly higher in women with breast cancer than in controls [119]. However, circulating estrogen, progesterone, IGF-1, parathyroid hormone, and vitamin D mean values were significantly higher in controls as compared to that in women with breast cancer [124]. In addition, another study performed in Erbil, Iraq, indicated nulliparity and non married women are risk factors for development of breast cancer [111]. However, they found that increased parity and pregnancy are with protective effect against development of breast cancer.

6.7 Obesity and Physical Inactivity

Breast cancer risk increased in obese postmenopausal women [125]. Fat cells liberate some estrogen and obese postmenopausal women, therefore, tend to have higher blood estrogen levels than lean women do. Obesity does not seem to be a risk factor for breast cancer in premenopausal women [71,126]. However, most studies indicated that overweight is a risk factor for breast cancer development in postmenopausal women. Some studies have found that timing of weight gain and body fat distribution could be more significant

factors of an increased risk. Obesity and central fat distribution are believed to act through endocrine intermediates such as hyper insulinaemia and steroid hormones. Since obesity is one of the few breast cancer risk factors that can be modified. The influence of weight loss, particularly in women at high risk, deserves to be further investigated [127].

The degree of obesity, age at onset of obesity, weight gain (peri to post menopausal) and possibly body fat distribution are the major determinants of post menopausal estrogen levels which might be the key risk factors for post menopausal breast cancer [128]. Physical activity has been thought to be associated with a reduction in breast cancer risk. In a review article conducted by Gammon [129], covered 16 published studies on recreational physical activity. Ten were case-control studies, and a risk reduction was found in 8 of them which ranged from 26% to 60%. The other six were cohort studies, where the results observed ranging from 50% reduction in risk to a 20% increase in risk.

There is some evidence that exercise delays age at menarche associated with an earlier age at menopause, with a reduction in life time estrogen exposure and this may be the causal link observed. A recent scientific workshop concluded that available evidence supports a small inverse (protective) association between physical activity and breast cancer. The protective effects may be greater among lean women, women who have carried children to term, and premenopausal women. The underlying mechanism of this potential protection are not well understood, although it has been hypothesized that the benefit may be due to the effects of physical activity on hormones, energy balance, and the immune system [130].

6.8 Exposure to High Doses of Radiation

Women who were exposed to high doses of radiation, especially association has been observed both among atomic bomb survivors and among women who received high-dose radiation for medical purposes. Doubling of the risk together with a dose response relationship was observed in some studies [131,132]. The risk has been found to be increased among medical diagnostic X-ray workers, especially in those who have been worked more than 25 years and those who are exposed before the age of 30 years [133,134].The low dose radiation exposures involved in modern X-ray (including chest

X-ray and mammograms) have not been associated with any measurable increase in breast cancer risk [71].

6.9 Alcohol Consumption

Alcohol is the dietary factor most consistently associated with an increased breast cancer risk. A meta-analysis of more than 50 epidemiologic investigations suggested that the equivalent of two drinks a day may increase breast cancer risk by approximately 25%. This increased risk is dose-dependant, and exists regardless of the type of alcoholic beverage consumed. [135]. A recent pooled analysis of cohort studies also concluded that alcohol consumption is associated with a linear increase in breast cancer incidence, and that reducing alcohol intake may be a useful strategy for reducing breast cancer risk for regular consumers of alcohol [136].

A case-control study conducted by Levi [137] in Switzerland concluded that alcohol is a correlate of breast cancer risk in the European population and alcohol could explain 25% of breast cancer cases of this population. The same association was consistent for wine, beer and spirits.

6.10 Breast-feeding

Breast-feeding may modestly reduce the risk of developing breast cancer and may play as protective factor [111]. Many studies, reported that women who breast-fed had a decreased risk of developing breast cancer (ranging from 10%-64%) compared to women who never breast-fed [138,139]. The others reported that breast-feeding had no influence on the risk of developing breast cancer [140]. Additionally, women age at first birth and number of children influence breast-feeding and thus these may be risk factors for breast cancer. Finally, it is also possible that breast-feeding has different effects on the risk of developing premenopausal breast cancer compared to postmenopausal breast cancer [141]. Compared with parous women who never breast fed, women who had breastfed for 25 months or more had a lower relative risk. If women who do not breastfed or who breastfed for less than 3 months were to do so for 4 to 12 months , breast cancer among parous premenopausal women could be reduce by 11% , if all women with children lactated for 24 months or longer , the incidence might be reduced by nearly 25[142]. Women who were breastfed as infants , even if only for a short time , showed an approximate 25% lower risk of developing premenopausal

or postmenopausal breast cancer ,compared to women who were bottle-fed as an infant, Lactation provides a hypo estrogenic effect with less stimulation of the endometrial lining . This event may offer a protective effect from endometrial cancer [143]

6.11 Diet

There are conflicting results concerning the relationship between dietary fat and breast cancer. Many U.S. studies have found no association between the two; however, international findings suggest that breast cancer rates are minimal in countries where the standard diet is low in fat [144]. Food pattern consumption is associated with breast cancer risk [145]. The effect of diet on the risk of breast cancer is probably exerted via its influence on hormone metabolism. Epidemiological evidence indicates that the nutrition determines the levels of circulating estrogen, and may affect the risk of breast cancer [146].

The ideal condition to determine the risk of breast cancer associated with a dietary exposure is to compare an intervention group with a control group which is restricted from related exposures (null contamination). In the Women's Health Initiative Dietary Modification trial, a randomized, controlled, primary prevention trial with over forty-eight thousand participants, Rohan and colleagues [147] showed that a benign proliferative breast disease not influence by modest reduction in increase in vegetable, grain and fruit intake with low consumption of fat.

6.12 Smoking of Tobacco

There is some evidence that a small increase in breast cancer risk may be associated with cigarette smoking. . Also smoker women may carry a poor prognosis. In a case-control study conducted in Switzerland, between 1992 and 1993, active and passive exposure to tobacco smoke found to increase the risk of breast cancer [148]. In a cohort study conducted in USA, current smoking was significantly related to fatal breast cancer risk. This association was also increased with the increasing number of cigarettes smoked per day and with total number of years of smoking. [149]. On the other hand, many studies showed no association between tobacco smoking and breast cancer risk. In a well designed case-control study conducted in USA, showed no association between breast cancer risk and tobacco

smoking, nor were any apparent relationship, with more detailed exposure measures [150].

6.13 Duration of Pregnancy and Risk of Breast Cancer

Women who have had a pregnancy interruption might be at increased risk of breast cancer, compared with women have delivered at term, in incomplete pregnancy, the breast is exposed only to the high estrogen levels of early pregnancy and thus may be responsible for the increased risk seen in these women. However, some other studies have found no association between abortions and increased risk of breast cancer [151].

Epidemiological studies of the relation between abortions that occur during the first trimester of pregnancy and risk of breast cancer have yielded conflicting results [152]. Hsieh and colleagues [153], shows a possible link between delivery during third trimester of pregnancy and breast cancer risk. They report a significantly increased risk of breast cancer among women aged 40 years and older who have a premature delivery, compared with women who delivered at term. Another study conducted by Ekbom and colleagues [154], they concluded that the risk of breast cancer increased two-fold in women whose babies were born before 33 weeks of gestation (OR=3.96), compared with women who delivered before 37 weeks (OR=1.17). About induced abortion as a risk of breast cancer many studies have been conducted. Daling et al. [155] concluded that women with history of induced abortion have a 20% increased risk of breast cancer than those who had not. The increase risk appeared to be confirmed to nulliparous women. He also concluded that there was no excess risk of breast cancer associated with induced abortion among parous women. Another study concluded that induced abortion among significant independent risk factors for breast cancer, regardless of parity or timing of abortion relative to the first full term pregnancy [156].

6.14 Hormones associated with breast cancer

Hormonal factors associated with breast cancer development in women include endogenous and exogenous oestrogens, progesterone and prolactin.

6.14.1 Exogenous Hormone Use

6.14.1.1 Oral Contraceptives

Most oral contraceptive formulations are a combination of ethinyl estradiol or mestranol and a progestin. Initial concern focused on the possibility that the hormones in an oral contraceptive would provide higher levels of estrogen and progestin during an oral contraceptive cycle than the woman would have produced during a normal ovulatory cycle [157].

The Collaborative Group on Hormonal Factors published a reanalysis of data from 54 epidemiological studies which specifically collected detailed information on oral contraceptive use [158]. The results showed that ever use of oral contraceptives was associated with a very small increase in risk (relative risk 1.07). The greatest risk was observed among current users, with the risk decreasing after stopping use. There was no increased risk in women who had discontinued use 10 or more years ago. Odd ratio and AUC not confirmed a positive association between oral contraceptive and breast cancer development in one of our study [111], while other study shows a positive association [119].

6.14. 1.2 Hormone Replacement Therapy

The increase in breast cancer risk associated with hormone replacement therapy depends on the duration of exposure and whether estrogen is used alone or in combination with progestin's. A reanalysis of data from 51 studies reported that current or recent use of hormone replacement therapy increases the relative risk of breast cancer by 2.3% for each year of use [159]. Long-term use for five years or more among current or recent users appears to be associated with a 30 – 50% increase in breast cancer risk [160].

Current evidence suggests that use of estrogen alone increases breast cancer risk more modestly than combination hormone use (estrogen plus progesterone). In these combined regimens, progestins may enhance the proliferative effects of estrogen [161].

Several large scale population-based epidemiologic studies have shown that adding a progestin to estrogen regimens increases breast cancer risk after five years of use from 10% (estrogen alone) to 30% (combined estrogen and progestin) [161]. Data from Women's Health Initiative Randomized Controlled Trial showed a 27% increase

in breast cancer risk in the estrogen plus progesterone treatment [162].

6.14. 2. Endogenous Hormone

6.14. 2.1. Estrogen

The steroid hormone group of estrogens induces responses in the reproductive tract, mammary tissue, and pituitary gland during the reproductive process, as well as playing roles in non-reproductive processes, such as bone formation and cardiovascular health [163]. The ovary is the main source of estrogen during most of the reproductive period, except during pregnancy, when the placenta is the main source. In premenopausal women, the serum levels of estrogens, mainly in the form of estradiol (E2), is 100 pg/ml during the follicular phase and approximately 600 pg/ml at the time of ovulation, but levels of estrogen, mainly estriol (E3) elevates to nearly 20,000 pg/ml during pregnancy. The level of estrogen falls to less than 20 pg/ml after menopuase, when estrone (E1) becomes the dominant forms. The growth and differentiation of ductal cells in breast tissue are stimulated by estrogens, which also plays an indirect role in the development of the mammary glands [164].

Estrogen normally binds to SHBG (Sex- hormone binding globulin) (approximately 37%). "Non-SHBG-bound hormone" (approximately 2% free estrogen) and estrogen bound to albumin (approximately 61%) are referred to as bioavailable [165] and affect target cells, including both normal and malignant breast cells. The serum concentration of bioavailable estradiol is thought to be more strongly associated with the risk of breast cancer than the total level of estradiol [165,166]. Estrogen bound to SHBG is also available to responsive tissues, where it reduces cell proliferation, so that a reduction in the binding capacity of SHBG results in more rapid proliferation in steroid-sensitive tissue such as breast cells [165]. In premenopausal women, the bibding capacity of SHBG is higher than that in postmenopausal women and an association between the levels of SHBG and ER has been detected in connection with postmenopausal, but not premenopausal breast cancer [167]. From conception until the 30th week of pregnancy, the level of SHBG is 6 to 10-fold higher in pregnant women than in those who are not pregnant [168].

A number of investigations on the difference in serum estrogen levels between pregnant compared and non-pregnant women and its association with the risk of breast cancer have been published. One review [169] concluded that the mean estrogen level in premenopausal women is 12% higher in those diagnosed with breast cancer, while another similar review on postmenopausal women arrive at a 15% higher value for those with breast cancer [170]. A meta-analysis on 9 prospective studies revealed that high levels of serum estrogen are associated with higher risk of postmenopausal breast cancer [171]. It has also been reported that the elevated level of estrogen during the first trimester of pregnancy is positively associated with the risk of developing breast cancer before 40 years of age, but that this association becomes negative at more advanced age [172]. Moreover, a European study observed that the estrogen levels in women diagnosed with breast cancer is higher than in control subjects three year prior to diagnosis [170]. The association between estrogen and breast cancer risk appears to be independent of family history [172]. Women with breast cancer show increased mean serum levels of ER in Iraqi community. [111,119].

6.14. 2.2 Progesterone

Progesterone is secreted by the ovary during most of the reproductive period, but primarily by the corpus luteum and placenta during pregnancy [173]. The main responsibilities of progesterone are to prepare the uterine muscles for implementation of the fertilized ovum and then support the pregnancy by inducing the proliferation and differentiation of uterine muscles to protect early embryonic development [174].

Whereas, Progesterone acts through its own receptor, and its levels may be important in breast carcinogenesis. Breast epithelial cell growth is related to progesterone levels [175]. The cell growth of the breast is greatest during the luteal phase of the menstrual cycle when levels of progesterone are highest, suggesting that progesterone may enhance breast cell growth [176]. Progesterone is expressed in the majority of breast carcinoma tissues and considered an important mediator of hormonal additive therapy in human breast tumors [177].

A possible association between the level of progesterone and risk of breast cancer remains unclear: certain reports have shown a negative association with premenopausal women [178], while no

association was found for postmenopausal women [179] or all cases of breast cancer [179,180]. However, estrogen and progesterone might interact to elevate the risk of breast cancer; the so-called (estrogen plus progesterone hypothesis) [178]. In Iraqi women with breast cancer, two studies demonstrated increased serum levels of PR as compared to controls [111,119].

6.14. 2.3 Prolactin

Prolactin was first determined as a hormone that plays an important role in the breast cancer initiation and development in rodents, and later partly in humans. In the culture there is evidence of a direct stimulatory role of prolactin on mammary epithelial cells and the breast cancer cells. Prolactin may play active roles in tumor development by stimulating angiogenesis and activating pathways involved in cellular adhesion and motility [181]. Serum prolactin concentrations in some breast cancer patients and women at risk of developing familial breast cancer may be increased [182]. Prolactin is generated by tumors and by a variety of normal tissues, placenta being the richest source of the extra pituitary prolactin and responsible for high levels in human amniotic fluid. The immune system, uterus, brain, dermal fibroblasts [182], human breast tissues and cells also produce prolactin. Prolactin levels decrease with each additional pregnancy [182,183] and concentrations are higher in nulliparous than porous women and among women using certain types of oral contraceptive [183].

VII. ABO Blood Group Polymorphism and Breast Cancer

Although the relation between ABO blood group and cancer was the subject of intensive research in the mid 1900's, there has been renewed interest after the recent publication of reports establishing associations between ABO blood groups and different types of malignancies [184,185]. Usually older studies reject the association, but recent studies confirm the association between ABO blood groups and specific subtypes of breast cancer like ductal or familial [186].

ABO blood group system as risk factor for breast cancer were studied [187]. Group A is more predominant in women with breast cancer and in these women the treatment response are not satisfactory and with high recurrence rate [186,188]. In contrast, women with blood group O are with resistance for the development of breast cancer and if they developed the cancer, their survival will be

more than the other women with different blood groups. The cause of these findings is not definite, but it seems that genetic products of this genetic position allele can have antigenic role [186,187].

ABO blood groups are erythrocyte-surface antigens coded for by a gene locus mapped at 9q34.2 region, and represented by three alleles (I*A, I*B and I*O). Alleles I*A and I*B are co-dominantly inherited, but both of them are dominant over the allele I*O [189].
Antigens of blood group has an important biologic role in the immunological system and effect on some tumors development like breast cancer [190]. The ABO antigen expressed on the surface of malignant cells appears to be different from the antigen expressed on normal tissue [191]. The different expression of antigens on the surface of cancer cells might alter motility, apoptosis and immune escape [192]. Thus cancer initiation and metastasis may be influenced by these mechanisms. The loss or presence of blood group antigens can increase cellular motility or facilitate the interaction between tumor cells and endothelial cells of distant organs [193].

The deficiency of B or A epitope has been reported in many cancer type and this is associated with accumulation of their precursor, which causes enhanced malignancy. Blood group carbohydrate antigens on the surface of cancer cells can be regarded as an end product of tumor progression that can be used as useful prognostic and diagnostic markers [194].Many studies documented the susceptibility to cancer development and blood groups [187]. With respect to breast cancers, some investigators suggested that blood groups may possess a predictive value independent of other known prognostic factors, and augmented further that a degree of the susceptibility to breast cancer, from a gene perspective, might be a result of a breast cancer-susceptibility locus linked to the ABO locus [190]. In this regard, it has been observed that blood group A women have a generalized tendency to worse outcomes and a more rapid progression with this cancer, and they have poorer outcomes. In contrast, blood group O has been shown to infer a slight degree of resistance against breast cancer, and a significantly lower risk of death [186]. Breast cancer was more predominant in women with blood group A in a study performed in Erbil, Iraq [111].

VIII. Viruses and Breast Cancer

A viral a etiology is one recently evocated theory behind the physiopathology of breast cancer [195-197]. Viruses may induce cancers through multiple mechanisms which related to the virus direct bor indirect oncogens or induction of immunosprresion [198-200]. Among the putative viruses observed in BC tissue, the presences of HCMV and EBV of the Herpesviridae family have been implicated as a cause of breast cancer. There was significance of EBV expression in breast tissue of young patients with breast cancer[201] and this finding confirmed by polymerase chain reaction (PCR)-based studies, positive correlation was shown [202], and the presence of EBV DNA was associated with more severe forms of breast cancer [203]. Human Cytomegalovirus had be shown to be involved in many cancers including malignant glioma, and prostate, skin, and colorectal cancers [204]. Increasing evidence in the last 10 years suggests that HCMV is associated with several human malignancies, and that HCMV gene products can modulate oncogenic properties of cells in vitro [205]. Since persistent of HCMV infection of breast epithelium could, in theory, promote malignant transformation of infected breast epithelium, that sought to determine the HCMV gene products in normal and neoplastic breast [206]. The risk factors for development of breast cancer is the high seroprevalence of CMV in Iraqi community [207-210].

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