# An Evaluation of Some Risk Factors and ABO Blood Groups in Breast Cancer Patients

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**Abstract**

The study involved 120 women, who were distributed into two groups of breast tumor patients (30 malignant and 30 benign) and a group of controls (60 women). The patients were referred to the Center for Early Detection of Breast Tumor at Al-Alwayia Hospital for Gynecology and Obstetrics (Baghdad) during the period June-December 2011. They were investigated for the frequency of ABO blood group phenotypes, menopausal status, oral contraceptive use, body mass index and family history of breast cancer or other cancers. The results demonstrated that 60.0% of malignant cases clustered after the age 50 years, while it was 20.0% in benign cases. Fifty percent of malignant breast tumor patients reached menopause, while in benign cases, the corresponding frequency was much lower (20.0%). It was also observed that 60.0% of malignant patients used oral contraceptives, while such frequency was lower in benign patients (20.0%). Overweight and obese cases were observed with a frequency of 43.3 and 26.7%, respectively in malignant patients, and the corresponding frequencies in benign patients were 36.7 and 33.3%, respectively. Positive family history of malignant breast cancer accounted for 43.3% in malignant cases, while in benign cases; it was less frequent (20.0%). The distribution of ABO blood group phenotypes demonstrated a significant difference ($P \leq 0.05$) between malignant patients and controls, but not between benign patients and controls. Such significant difference was mainly contributed by an increased frequency of B phenotype (36.7 *vs.* 16.7%) and a decreased frequency of O phenotype (26.7 *vs.* 55.0%) in malignant patients.

**Keywords**: Breast tumor, Risk factors, ABO blood groups.

# تقييم بعض عوامل الخطورة ومجاميع الدم في مريضات سرطان الثدي

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**الخلاصة:**

شملت الدراسة 120 امرأة توزعت على مجموعتين من مريضات ورم الثدي (30 خبيث و30 حميد) ومجموعة سيطرة (60 امرأة). كانت المريضات مراجعات لمركز الكشف المبكر لأورام الثدي في مستشفى العلوية للنسائية والتوليد في بغداد وللفترة حزيران–كانون الأول 2011. درست المريضات لتوزيع مجاميع الدم والحالة اليأسية واستعمال موانع الحمل الفموية ودليل كتلة الجسم والتاريخ العائلي لسرطان الثدي أو سرطانات أخرى. أوضحت

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النتائج بأن 60% من مريضات ورم الثدي الخبيث كانت بعد العمر 50 سنة، في حين كانت النسبة في مريضات ورم الثدي الحميد هي 20%. وكانت نسبة مريضات ورم الثدي الخبيث والتي وصلت لسن اليأس هي 50%، في حين كانت هذه النسبة أقل في مريضات ورم الثدي الحميد (20%). وفضلا عن ذلك فأن 60% من مريضات ورم الثدي الخبيث استخدمت موانع الحمل الفموية، وكانت هذه النسبة أقل في مريضات ورم الثدي الحميد (20%). وكانت نسبة مريضات ورم الثدي الخبيث التي تمتلك زيادة في الوزن والبدينات هي 43.3 و26.7%، على التوالي، في حين كانت النسب المناظرة في مريضات ورم الثدي الحميد هي 36.7 و33.3%، على التوالي. وأظهرت 43.3% من مريضات ورم الثدي الخبيث تاريخ عائلي موجب لسرطان الثدي، في حين كانت هذه النسبة أقل في مريضات ورم الثدي الحميد (20%). كما أوضحت النتائج وجود فروقا معنوية في توزيع مجاميع الدم مابين مريضات ورم الثدي الخبيث ونساء السيطرة، ولكن لم يظهر مثل هذا الفرق مابين مريضات ورم الثدي الحميد ونساء السيطرة. وتعود هذه الفروق المعنوية لزيادة تكرار مجموعة الدم B (36.7 مقابل 16.7%) وقلة تكرار مجموعة الدم O (26.7 مقابل 55.0%) في مريضات ورم الثدي الخبيث.

## Introduction

Breast cancer is the most frequent malignant disease and the leading cause of death due to cancer among women in the world, and In Iraq, it is the commonest type of female malignancy, accounting for approximately one-third of the registered female cancers [1]. The disease is associated with several risk factors, and epidemiological studies have suggested that menopause, oral contraceptive use, body mass index (BMI) and family history of breast cancer or other cancers may have different relations to the disease [2]. Other risk factors may include some immunogenetic markers; for instance ABO blood groups [3].

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* [4]. Numerous reports have documented a relation between susceptibility to cancer and blood groups. High incidence of blood group A in various cancers, including neurologic tumors, salivary gland, colon, uterus, ovary, pancreas, kidney, bladder and cervix, and consistent relation to O blood group in skin and melanoma has been reported [5]. 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 [6]. 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 once they are diagnosed with breast cancer. 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 [3].

Based on these findings, the present investigation was planned to shed light on the frequency of ABO blood group phenotypes and alleles in a sample of Iraqi breast cancer female patients. Furthermore, menopausal status, oral contraceptive use, BMI and family history of breast cancer or other cancers were also evaluated.

## Subjects, Materials and Methods

**Subjects**: The study involved 120 women, who were distributed into two groups of patients and a group of controls. The patients were women who had a breast tumor, and according to the type of tumor, they were distributed as malignant and benign groups, each with 30 patients. Malignant tumor group included patients whose age was ranged between 30 and 65 years (mean ± standard error: 49.8 ± 1.7 year), while such range in the benign tumor group was 21-60 years (39.5 ± 1.9 year). The patients were referred to the Center for Early Detection of Breast Tumor at Al-Alwayia Hospital for Gynecology and Obstetrics (Baghdad) during the period June-December 2011. The diagnosis was made by the consultant medical staff, which was based on a Triple Assessment Technique (i.e. physical breast examination, ultrasonography, with or without mammography and fine needle aspiration cytology). With respect to controls, 60 women were enrolled in the study, and they were a hospital staff and they had no history of breast

cancer in their families (mother, aunt and grandmother). Their age range was 18-64 year (35.6±1.8 year), and they were ethnically matched with breast tumor patients (Iraqi Arabs).

**Demographic data**: Demographical and risk factor data were collected using a short structured questionnaire, including information on age at presentation, menopausal status, weight, height and family history of breast cancer (mother, aunt and grandmother).

**Laboratory methods**: ABO blood group phenotypes (A, B, AB, and O) were determined by employing the conventional slide agglutination method, which is based on agglutination reactions between blood group specific anti-sera (Biotest, Germany) and blood group antigens on the cell surface of erythrocytes.

**Statistical methods**: Data were presented as percentage frequencies, and significant differences between these frequencies were assessed by Pearson Chi-square test. In addition, odds ratio, etiological fraction (EF) and preventive fraction (PF) were also estimated. In both cases, the computer packages PEPI version 4 and S2 ABO estimator were used. The BMI was calculated by dividing weight (kilogram) by squared height (meter) and presented as $Kg/m^2$ [7].

**Results and Discussion**

**Age Groups of Patients**: Distributing patients into age groups revealed that 33.3% of malignant tumor patients were at the age group ≥ 60 years, 26.7% at 50-59 years, 23.3% at 40-49 years, 13.3% at 30-39 years and 3.3% at 20-29 years. The corresponding frequencies for benign tumor patients (3.3, 16.7, 26.7, 33.3 and 20.0%, respectively), and they were significantly ($P \leq 0.01$) different Table -1.

**Table 1-** Breast tumor (malignant and benign) patients distributed by age groups.

| Age Groups (Years) | Breast Tumor | | | |
|---|---|---|---|---|
| | Malignant (No. = 30) | | Benign (No. = 30) | |
| | No. | % | No. | % |
| ≥ 60 | 10 | 33.3 | 1 | 3.3 |
| 50-59 | 8 | 26.7 | 5 | 16.7 |
| 40-49 | 7 | 23.3 | 8 | 26.7 |
| 30-39 | 4 | 13.3 | 10 | 33.3 |
| 20-29 | 1 | 3.3 | 6 | 20.0 |

Pearson Chi-square = 14.27; D.F. = 4; $P \leq 0.01$

These results demonstrated that 60.0% of malignant cases clustered after the age 50 years, while the corresponding frequency in benign cases was 20.0%, and instead, the 60.0% of benign cases were observed at the age range 30-49 years. It is also worth to mention that one patient had malignant breast tumor at the age 25 years, while 20.0% of benign cases were observed at the age range 20-29 years. Such findings should be interpreted with caution, because of sample size in both types of tumors, but it can be justified because the cases were randomly selected. Furthermore, it has been established in most of regional regions that breast cancer is recorded at the approximation of the age 50 years. In a recent study from Yemen, it has been reported that 70.0% of the registered breast cancer at age 50 years or less. Approximated frequencies has also been reported in Sudan (74%), Iran (60%) and Libya (71%), but such frequencies are higher than observed frequencies in some Western countries such as England (19%) and Australia (24%) [8,9[. Therefore, age can be considered as an important risk factor, and the breast cancer risk increases as the age advances.

**Menopausal Status:** Fifty percent of malignant breast tumor patients reached menopause, while in benign cases, the corresponding frequency was much lower (20.0%). Such difference augmented the view that menopause could be considered as a risk factor for malignant breast tumor with an odds ratio of 4.0. The difference was also significant ($P \leq 0.01$), as shown in table -2.

**Table 2-** Breast tumor (malignant and benign) patients distributed by menopause status.

| Menopausal Status | Breast Tumor | | | |
|---|---|---|---|---|
| | Malignant (No. = 30) | | Benign (No. = 30) | |
| | No. | % | No. | % |
| Postmenopausal | 15 | 50.0 | 6 | 20.0 |
| Premenopausal | 15 | 50.0 | 24 | 80.0 |

**Pearson Chi-square = 5.93; D.F. = 1; P ≤ 0.01 (Odds ratio = 4.0)**

These findings are in agreement with several studies in which it has been presented that women who experienced menopause at a late age are at a higher risk of breast cancer than those who cease menstruating earlier, with risk increasing by about 3% for each year older at menopause. The magnitude of this effect is similar whether menopause occurred naturally or as a result of bilateral oophorectomy [10]. However, other investigators were unable to confirm that, and they justified their inconsistent observation by the fact of other effecting factors; for instance, lifestyle and race [11].

**Oral Contraceptive Use:** It was observed that 60.0% of malignant patients used oral contraceptives, while such frequency was lower in benign patients (20.0%), and such differences attended a significant level at P ≤ 0.001. The odds ratio of such factor (oral contraceptives use) and its contribution to malignancy in the current sample was 6.0 Table -3.

**Table 3-** Breast tumor (malignant and benign) patients distributed by oral contraceptive use.

| Oral Contraceptive Use | Breast Tumor Patients | | | |
|---|---|---|---|---|
| | Malignant (No.= 30) | | Benign (No.= 30) | |
| | No. | % | No. | % |
| Yes | 18 | 60.0 | 6 | 20.0 |
| No | 12 | 40.0 | 24 | 80.0 |

**Pearson Chi-square = 10.00; D.F. = 1; P ≤ 0.001 (Odds ratio = 6.0)**

These findings suggest that using oral contraceptives may increase the risk of breast cancer but not benign breast tumor. Data available from other studies also suggest that women who currently use oral contraceptives or who have used them in the previous 10 years have an increased risk of breast cancer, and in a pooled analysis of 54 studies, the relative risk of breast cancer among women who were currently using oral contraceptives, as compared with those who had never used them, was 1.24 [12], while in the present study the odds ratio was much higher (6.0); therefore using oral contraceptives by Iraqi women has to be evaluated further in order to determine its risk of breast cancer, especially in women who use oral contraceptives late in their reproductive life, because it has been suggested that such time of using oral contraceptives will result in an increased relative risk of breast cancer at a time when the background risk is becoming appreciable. Thus, the later use of oral contraceptives may justify the larger number of resulting excess cases of breast cancer [13]. Furthermore, the use of combined oral contraceptives has been augmented to be associated with a larger excess of localized cancers than those that have spread beyond the breast [14].

**Body Mass Index**: Overweight and obese cases were observed with a frequency of 43.3 and 26.7%, respectively in malignant patients, and the corresponding frequencies in benign patients were 36.7 and 33.3%, respectively. However, overweight in control women accounted for only 20.0%. Such difference was significant at a P of ≤ 0.05 Table -4.

**Table 4-** Breast tumor (malignant and benign) patients and controls distributed by body mass index.

| Groups | Number | Body Mass Index ($Kg/m^2$) | | | | | |
|---|---|---|---|---|---|---|---|
| | | < 25 (Normal) | | 25-29.9 (Overweight) | | 30-40 (Obese) | |
| | | No. | % | No. | % | No. | % |
| Malignant | 30 | 9 | 30.0 | 13 | 43.3 | 8 | 26.7 |
| Benign | 30 | 9 | 30.0 | 11 | 36.7 | 10 | 33.3 |
| Controls | 10 | 8 | 80.0 | 2 | 20.0 | 0 | 0.0 |

**Pearson Chi-square = 10.13; D.F. = 4; P ≤ 0.05**

These findings revealed that breast tumor, whether malignant or benign, was associated with overweight and obesity, which collectively represented 70% of cases in both types of tumor. The strong association between BMI and breast cancer risk in case-control studies compared with prospective cohort studies may be explained by the larger age-related weight increases among women who eventually develop breast cancer than those in women who remain cancer free. Weight gain during adult life is also consistently associated with increased risk of postmenopausal breast cancer. Some studies have shown a stronger association between BMI and postmenopausal breast-cancer risk in women who have never used hormone replacement therapy [15]. This finding is consistent with the hypothesis that the effect of increased adiposity on breast cancer risk may be mediated by increased endogenous estrogen production, especially in women with low estrogen concentrations (i.e. postmenopausal women who are not receiving hormone replacement therapy) [16]. Most studies on breast cancer and obesity have been done in developed countries, but of the few studies that have been done in less developed countries; the majority has produced similar findings. A meta-analysis of case-control studies done in countries with high (Wales and USA), moderate (Greece, former Yugoslavia and Brazil), or low (Japan and Taiwan) risk of postmenopausal breast cancer showed that the increase in risk associated with increasing BMI is mainly observed in countries with low or moderate risk. However, in contrast to countries with high risk of breast cancer, the risk increase in developing countries does not level off at a BMI of 28 $kg/m^2$, but continues to increase exponentially [17].

**Family History**: Positive family history of malignant breast cancer accounted for 43.3% in malignant cases, while in benign cases; it was less frequent (20.0%). The adjusted odds ratio was 3.06 and it was significant ($P \leq 0.05$) Table -5. These assessments were extended to include family history of all types of cancers. In malignant cases, positive family history frequency was increased to 63.3%, and in benign cases, it was also less frequent (26.7). Accordingly, the odds ratio was also increased (odds ratio = 4.75), and associated with a higher level of significance ($P \leq 0.01$) Table -6.

**Table 5-** Breast tumor (malignant and benign) patients distributed by family history of breast cancer.

| Family History | Breast Tumor | | | |
|---|---|---|---|---|
| | Malignant (No. = 30) | | Benign (No. = 30) | |
| | No. | % | No. | % |
| Positive | 13 | 43.3 | 6 | 20.0 |
| Negative | 17 | 56.7 | 24 | 80.0 |

Pearson Chi-square = 3.84; D.F. = 1; $P \leq 0.05$ (Odds ratio = 3.06)

**Table 6-** Breast tumor (malignant and benign) patients distributed by family history of different types of cancers.

| Family History | Breast Tumor | | | |
|---|---|---|---|---|
| | Malignant (No. = 30) | | Benign (No. = 30) | |
| | No. | % | No. | % |
| Positive | 19 | 63.3 | 8 | 26.7 |
| Negative | 11 | 26.7 | 22 | 73.3 |

Pearson Chi-square = 8.14; D.F. = 1; $P \leq 0.01$ (Odds ratio = 4.75)

Studying family history of breast cancer can highlight the genetic predisposition to develop the disease, and in this regard, the results clearly established an odds ratio of 3.06 or 4.76 for women who have breast cancer or other cancers in their families in comparison with benign cases. Familial aggregation can be attributed both to shared genes and to shared physical environments and lifestyles. and it has been demonstrated that the risk of developing breast cancer is twice as high in women who have an affected first-degree relative than women in the general population [18]. The majority of the genetic risk is due to low-risk or moderate-risk susceptibility alleles, each of which confers only a very small increased risk in isolation but which in combination may have quite a significant effect [19]. Such profile was

evaluated in the present study in the ground of ABO blood group polymorphism.

**ABO Blood Groups**: The distribution of ABO blood group phenotypes demonstrated a significant difference ($P \leq 0.05$) between malignant patients and controls, but not between benign patients and controls. Such significant difference was mainly contributed by an increased frequency of B phenotype (36.7 *vs*. 16.7%) and a decreased frequency of O phenotype (26.7 *vs*. 55.0%) in malignant patients Table -7.

As B blood group phenotype can have two genotypes ($I^*{}^BI^*{}^B$ and $I^*{}^BI^*{}^O$); therefore to seek a better understanding of $I^*{}^B$ allele and its association with malignant breast tumor, the gene frequency of ABO blood group alleles were estimated from the observed phenotypes Table -8, and from gene frequencies, the number of ABO blood group alleles was estimated Table -9. Such estimation confirmed that the estimated percentage frequency of $I^*{}^B$ alleles was significantly increased (29.2 *vs*. 11.4%) in malignant patients, while $I^*{}^O$ allele was significantly decreased (50.5 *vs*. 73.3%) at a $P \leq 0.01$

**Table 7-** Observed numbers and percentage frequencies of ABO blood group phenotypes in breast tumor (malignant and benign) patients and controls.

| ABO Blood Group Phenotypes | Breast Tumor | | | | Controls (No.= 60) | |
|---|---|---|---|---|---|---|
| | Malignant (No.= 30) | | Benign (No.= 30) | | | |
| | No. | % | No. | % | No. | % |
| A | 7 | 23.3 | 6 | 20.0 | 14 | 23.3 |
| B | 11 | 36.7 | 9 | 30.0 | 10 | 16.7 |
| AB | 4 | 13.3 | 3 | 10.0 | 3 | 5.0 |
| O | 8 | 26.7 | 12 | 40.0 | 33 | 55.0 |

**Malignant *vs*. Controls (Pearson Chi-square = 8.739; D.F. = 3; $P \leq 0.05$)**
**Benign *vs*. Controls (Pearson Chi-square = 3.434; D.F. = 3; $P > 0.05$)**

**Table 8-** Gene frequency of ABO blood group alleles in breast tumor (malignant and benign) patients and controls.

| ABO Blood Group Alleles | Breast Tumor | | Controls (No.= 60) |
|---|---|---|---|
| | Malignant (No.= 30) | Benign (No.= 30) | |
| $I^*{}^A$ | 0.203 | 0.162 | 0.153 |
| $I^*{}^B$ | 0.291 | 0.223 | 0.114 |
| $I^*{}^O$ | 0.506 | 0.615 | 0.733 |
| Total | 1.000 | 1.000 | 1.000 |

**Table 9-** Estimated numbers and percentage frequencies of ABO blood group alleles in breast tumor (malignant and benign) patients and controls.

| ABO Blood Group Phenotypes | Breast Tumor | | | | Controls | |
|---|---|---|---|---|---|---|
| | Malignant | | Benign | | | |
| | No. | % | No. | % | No. | % |
| $I^*{}^A$ | 12.2 | 20.3 | 9.7 | 16.2 | 18.4 | 15.3 |
| $I^*{}^B$ | 17.5 | 29.2 | 13.4 | 22.3 | 13.7 | 11.4 |
| $I^*{}^O$ | 30.3 | 50.5 | 36.9 | 61.5 | 87.9 | 73.3 |
| Total | 60.0 | 100.0 | 60.0 | 100.0 | 120.0 | 100.0 |

**Malignant *vs*. Controls (Pearson Chi-square = 11.458; D.F. = 2; $P \leq 0.01$)**
**Benign *vs*. Controls (Pearson Chi-square = 3.522; D.F. = 2; $P > 0.05$)**

To understand the association between B blood group phenotype and $I^*{}^B$ allele with malignant breast tumor in terms of a statistical evaluation, the odds ratio was assessed, together with etiological fraction (EF) for the increased frequency and preventive fraction (PF) for the decreased frequency. The B phenotype was associated with an odds ratio of 2.89, while such ratio was higher for $I^*{}^B$ allele (3.24). The EF values of such associations were 0.24 and 0.21, respectively. The PF values of the association between O phenotype and $I^*{}^O$ allele with

malignant breast tumor were 0.39 and 0.47, respectively. These associations were significant at a corrected significant level of 0.04-0.006 Table -10.

**Table 10-** Statistical evaluation of association between B blood group phenotype and $I^{*B}$ allele with malignant breast tumor.

| Comparison Type | Phenotype or Allele | Odds Ratio | EF | PF | P | Pc |
|---|---|---|---|---|---|---|
| Malignant Breast Tumor Patients *vs.* Controls | B | 2.89 | 0.24 | - | 0.034 | N.S. |
| | $I^{*B}$ | 3.24 | 0.21 | - | 0.003 | 0.009 |
| | O | 0.30 | - | 0.39 | 0.01 | 0.04 |
| | $I^{*O}$ | 0.36 | - | 0.47 | 0.002 | 0.006 |

**EF: etiological fraction; PF: preventive fraction; P: Fisher's exact probability; P: corrected P; N.S.: not significant.**

The present results of present study suggest that blood group B (phenotype or allele) may be considered as a significant immunogenetic prognostic marker for breast cancer, while blood group O (phenotype or allele) can be regarded as a protective factor. Previous studies have shown that women with A blood group are generally prone to develop neoplasms with poor prognosis and aggressive biological behavior and that these women represent a significant percentage among breast cancer patients, higher than the actual percentage of A blood group among the general feminine population. In contrast, women with O blood group may have some "protection" against the development of breast cancer; even when these women have breast cancer, prognosis is usually more favorable. An interesting observation of some investigators is that breast cancer patients with blood group B are at a higher risk of being re-affected by breast malignancy compared with women of other blood groups [5]. This may be partially due to the fact that women with blood group B have better prognosis. Blood group A has been further associated with ductal breast cancer in Greek patients, and has the worst prognosis [6]. However, much more recent results suggested no association between ABO blood group and breast cancer risk or survival in American women [3]. Therefore, the present findings of associations (positive or negative) between ABO blood groups and breast cancer share the interest of other investigators in this field, but further studies with larger number of patients are needed to clearly establish the role of ABO blood groups as a prognostic factor in breast cancer patients, especially if they are examined at the molecular level.

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