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Correlation Between Over Expression of HER-2 neu and Certain Risk Factors in Breast Cancer

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ABSTRACT

Background: Many risk factors have been identified either genetic factors which include family history of breast cancer, obesity and high fat diet or hormonal factors which include female sex, long interval between menarche and menopause and older ladies at first full-term pregnancy. A total of 328 women were selected retrospectively this group the tissue samples of breast cancer had been analyzed using immunohistochemical techniques for HER-2/neu over expression and its correlation to other prognostic factors. **Objective:** To evaluate the correlation between the HER-2/neu over expression and others prognostic factors in breast cancer which include family history of breast cancer, menarche , older ladies at first full-term ,body mass index, abortion and use of oral contraceptives. **Results:** Premenopausal women having age at first full pregnancy at 23 years, HER-2/neu + cases were 32 (41%) and HER-2/neu- cases were 45 (59%). The figures for postmenopausal and all women were 53 (42%) +, 72 (58%) – and 43 (37%) +, 72 (63%) – cases. HER-2/neu expression in relation to body mass index > 29 kg/m² showed premenopausal 7 (37%) + cases, 12 (63%) - cases, postmenopausal 8 (38%) + cases, 13 (62%) – cases . All women HER-2/neu + cases 15 (37%), HER-2/neu- cases 25 (63%). HER-2/neu expression in relation to history of abortion was found to be 21 (39%) + cases, 33 (61%) - cases in premenopausal women and 18 (44%) + cases, 23 (56%) - cases among postmenopausal women, while among all women 39 (41%) + cases, 56 (59%) - cases. HER-2/neu expression in relation to history of breast cancer in a first degree relatives was found 3 (25%) + cases, 9(75%) - cases in premenopausal and 4 (22%) + cases, 14 (78%) - cases among postmenopausal, while among all women 7 (23%) + cases, 23 (77%) – cases. HER-2/neu expression in relation to history of use of oral contraceptives (ever) was found 3 (37%) + cases, 5 (63%) - cases in premenopausal women and 3 (27%) + cases, 8 (73%) - in postmenopausal, whereas among all women it was 6 (31%) + cases, 13 (69%) – cases. HER-2/neu expression in relation to age at menarche 12 years was found 39 (51%) + cases, 38 (49%) - cases in premenopausal women and 36 (56%) + cases, 28 (44%) - cases in postmenopausal, whereas among all women it was 75 (53%) + cases, 66 (47%) – cases. **Conclusion:**Breast cancer had been analyzed using immunohistochemical techniques for HER-2/neu over expression and its correlation to other prognostic factors was found.

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INTRODUCTION

The cancers have types; the most common one is a carcinoma which constitutes about 85% of cancer. According to data from UK at 2001 the breast cancer is most common (29% of all cancers) (Souhami R, et al, 2001).

The American cancer society estimates that about 30% of Americans will get cancer at some point during their lives and about 40% of those in whom cancer is diagnosed will be alive five year later. Currently in the United States, one death in five is from cancer.

Breast cancer is the most frequently diagnosed cancer among women in the United States and is the second leading cause of cancer deaths among women today (American Cancer Society).

In the Sudan breast cancer accounts for 34.5% of all female cancer. The alarmingly high frequency of women presenting with advanced breast cancer to the Radiation Isotope Center Khartoum (RICK record) (Hidytalla , 1988).

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Several well-established factors have been associated with an increased risk of breast cancer (Underwood JCE, 1996). These include family history, early menarche, advanced age, and a personal history of breast cancer (in situ or invasive).

The tumor tissue will be stained by a specific solution. A pathologist will examine the tissue checking for high lighted area where high levels of over-expression are present. Depending on the level of staining, the tumor tissue sample may be classified as HER-2 positive or HER2 negative sample. It is estimated that 200,000 HER2 diagnostic tests are performed each year. Women are encouraged to be tested for HER2 over-expression at the time of breast cancer diagnosis since results of the test may help determine treatment modalities and to predict prognosis.

MATERIALS AND METHODS

This is a descriptive study to evaluate the tumor marker HER-2/neu expression in malignant breast palpable lumps. 328 females, all originating from the **Sudanese**, were eligible for analysis. An age-stratified random sample of 100 women was used as a control group.

The following variables were analyzed for all patients and controls:

Age at menarche (more than 12 years old), age at first full birth (more than 23 years old), abortions and miscarriages, use of oral contraceptives for more than 2 months, family history of breast cancer in a first degree relative, obesity on the day of the interview (more than BMI > 29 kg/m²)

Sample collection:

428 sections, taken from patients with breast palpable lumps. For histopathology and immunohistochemistry biopsies collected from patients.

Sample processing:

For histopathology:

Biopsies will be collected from tissues, and stained in hematoxylin & eosin.

For immunohistochemistry:

Sections were cut at 3-5 μ m thicknesses, mounted onto silanized slides, and left to dry overnight at 37°C. Sections were then deparaffinized and rehydrated. Antigen retrieval was achieved by heat retrieval using a bench autoclave. Briefly, slides were placed in Coplin jars containing enough 0.01 M sodium citrate solution (pH 6.0) to cover the sections, then autoclaved at 121°C for 10 minutes for Her-2 (waterpath 95°C for 30 min). Slides were incubated with Peroxidase blocking reagent for 10 min followed by protein blocking reagent for 10 min, then rinsed in PBS. Slides were incubated with 100-200 μ l of primary antibodies for 30 minutes at room temperature in a moisture chamber, then rinsed in PBS. The dilution of the primary antibodies against Her-2/neu (Dako, Carpinteria, Ca, USA) 1:50. After washing, binding of antibodies was detected by incubation for 10 minutes with biotinylated goat anti-mouse antibody ready to use (LSAB2) from Dako; the slides were then rinsed with PBS. Sections were then incubated with streptavidin-horse radish peroxidase for 10 minutes. Finally, the sections were washed in 4 times in 4 minute changes of PBS, followed by adding 3, 3-diaminobenzidine tetra hydrochloride (Biogenex) as a chromogen to produce the characteristic brown stain.

For each run of staining, a positive and negative control slide were also prepared. The positive control slides were prepared from breast carcinoma known to be positive for the antigen under study. The negative control slides were prepared from the same tissue block, but incubated with PBS instead of the primary antibody.

Her-2/neu was scored on a 0 to 3 scale according to the criteria set by Dako. The staining was scored as: negative (0) when no membrane staining was observed, or when membranous staining was observed in less than 10% of the tumor cells; weak positive (1+) if weak focal membrane staining was seen in more than 10% of the tumor cells; intermediate (2+) if weak to moderate, complete membrane staining was seen in more than 10% of the tumor cells; and strongly positive (3+) if intense membrane staining with weak to moderate cytoplasmic reactivity was seen in more than 10% of the tumor cells. In the final analysis, however, scores 0 and 1 were considered negative; score 2 was considered weakly positive; and score 3 was considered strongly positive. Only score 3 cases were considered as Her-2 overexpressing cases.

Result:

Pre-menopausal women having age at first full pregnancy at 23 years, HER-2/neu + cases were 32 (41%) and HER-2/neu- cases were 45 (59%) odd ratio 1.30, (Chi-square 0.234). The figures for postmenopausal and all women were 53 (42%) +, 72 (58%) - and 43 (37%) +, 72 (63%) - cases with odd ratios 1.24 and 1.03 respectively.

HER-2/neu expression in relation to body mass index $> 29 \text{ kg/m}^2$ showed premenopausal 7 (37%) + cases, 12 (63%) - cases odd ratio 1.17, postmenopausal 8 (38%) + cases, 13 (62%) - cases odd ratio 0.92. All women HER-2/neu + cases 15 (37%), HER-2/neu- cases 25 (63%), odd ratio 1.05.

HER-2/neu expression in relation to history of abortion or miscarriage (ever) was found to be 21 (39%) + cases, 33 (61%) - cases in premenopausal women and 18 (44%) + cases, 23 (56%) - cases among postmenopausal women, while among all women 39 (41%) + cases, 56 (59%) - cases. The odd ratios were 1.27, 1.43 and 1.32 respectively.

HER-2/neu expression in relation to history of breast cancer in a first degree relatives was found 3 (25%) + cases, 9(75%) - cases in premenopausal and 4 (22%) + cases, 14 (78%) - cases among postmenopausal, while among all women 7 (23%) + cases, 23 (77%) - cases. The odd ratios were 0.84, 1.11 and 0.95 respectively.

HER-2/neu expression in relation to history of use of oral contraceptives (ever) was found 3 (37%) + cases, 5 (63%) - cases in premenopausal women and 3 (27%) + cases, 8 (73%) - in postmenopausal, whereas among all women it was 6 (31%) + cases, 13 (69%) - cases. The odd ratios were 0.80, 0.86 and 0.83 respectively.

HER-2/neu expression in relation to age at menarche 12 years was found 39 (51%) + cases, 38 (49%) - cases in premenopausal women and 36 (56%) + cases, 28 (44%) - cases in postmenopausal, whereas among all women it was 75 (53%) + cases, 66 (47%) - cases. The odd ratios were 1.61, 1.10 and 1.38 respectively.

Discussion:

This study confirmed correlation between the HER2/neu expression and certain risk factors which include family history of breast cancer, menarche , older ladies at first full-term ,body mass index, abortion and use of oral contraceptives.

Their findings will provide us with greater insight into breast cancer aetiology and will help us identify any association that would help discriminate subgroups of women at higher risk.

Conclusion and Recommendation:

Their findings will provide us with greater insight into breast cancer aetiology and will help us identify any association that would help discriminate subgroups of women at higher risk and HER-2/neu over expression.

Further innovative studies with larger sample sizes are needed to examine how the status of this potentially modifiable breast cancer risks factors.

Lastly, we recommend further studies in this field with wider scope.

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