

Estrogens, insulin status and interrelated lifestyle factors on females with breast carcinomas

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SUMMARY Background: lifestyle is a significant vital part of malignancy care, as well as metabolic health disorders, which could be a high-risk factor for breast cancer. The objective of this scientific work is to study at the time of diagnosis the changes in insulin, estrogens (Estradiol E2 and Estriol E3) concentrations and some other related lifestyle aspects as a risk factor of breast cancer.

Materials and Methods: A total of 160 Sudanese women were subjected for study and then divided into two groups, 80 females were breast cancer patients against 80 other healthy women of matching the age and Body Mass Index (BMI) was acted as reference subjects. Smoking, medical prescriptions, physical activity BMI and nourishment behaviour were considered and studied as an individual lifestyle factor.

Results: Upon comparison between premenopausal breast carcinoma subjects versus matching healthy volunteers, the insulin levels showed no significant difference as the (p-value was 0.08). While the estradiol (E2) concentration recorded a significant elevation with (p-value=0.001) and both E2 levels were within the reference values, the estriol (E3) values registered a significant drop of a p=<0.001. Concerning the postmenopausal patient's comparison against the controls, although the insulin levels of both groups were exceeding the normal international range, correspondingly showed no significant variations between the same studied groups as p-value=0.2. Estradiol (E2) concentration of the patients showed a significant raise up comparing to the control groups with a p-value equivalent to 0.001, while estriol (E3) levels decreased in both postmenopausal groups cases patients and controls.

Conclusion: In conclusion, high E2 levels found to be related to breast CAs of both premenopausal as well as postmenopausal females, while the low level of E3 was associated with only premenopausal breast CAs women. Poor metabolic healthiness could be a strong risk factor of having breast CAs irrespective to the Body Mass Index (BMI). Nutrition, maintaining a healthy weight, and physical activity may reduce the risk of breast cancer.

Key words: breast cancer, insulin, estrogen, menopausal, nutrition

Abbreviations:

E2: Estradiol; E3: Estriol; RIA: Radioimmunoassay; ELISA: Enzyme-Linked Immunosorbent Assay; BMI: Body Mass Index

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INTRODUCTION

Breast CAs is one of the most frequently diagnosed malignancies among female society and the major top cause of female deaths. It is a heterogeneous disease that contributes to hormonal changes. Nevertheless, the predictive role of hormonal fluctuations in recently detected breast carcinomas cases is still indistinguishable [1]. The risk of having breast CAs may be highest in the presence of insulin through modifications in estrogen concentrations. Long-lasting excess secretion of insulin is accompanying with high estrogen secretion from the ovaries, low levels in sex hormone-binding globulin as well as high levels of free E2 [2]. Estrogens are essential substances due to their physiological roles in sexual development. Estrogens are secreted in ovaries of the women during reproductive age and fat tissue in postmenopausal female, due to the absence of the hormone changeability levels during normal menstruation. The estradiol (E2) level of postmenopausal women is expressively lower than of premenopausal ones [3]. The decrease in insulin sensitivity with menopause suggests that estrogen protects against insulin resistance in women. Furthermore, loss of estrogen role has been revealed to cause insulin resistance [4].

While some studies reported a strong relationship between poor prognosis and high estradiol (E2) level at diagnosis of the postmenopausal female with breast carcinomas, others disagreed with them [5]. Estrogen deficiency, due to natural menopause, has been suggested to influence insulin resistance; estrogen acts directly on beta cells to make them resistant to apoptosis and increase insulin production. This mechanism is assisting the pancreatic cells to adapt to higher insulin levels associated with some conditions, like obesity. However, abnormal increases in estrogen can affect insulin resistance [6]. Positive correlation among endogenous estrogen (E2) and breast cancer progress have reported continuously. Estriol is one of the three principal estrogens produced by the body; it is the weakest estrogenic effects compared with estrone and estradiol. Studies suggest that estriol was administered topically; it does not increase

the possibility of having hormone-dependent breast CAs [7]. Estriol (E3) much safer form of estrogen because it hasn't metabolized into other hormones, also estriol does not have the potential to damage DNA and initiate cancer like estradiol and estrone. By looking at this ratio of good estrogen (Estriol E3) to bad estrogen (Estradiol E2), the physician can evaluate breast cancer risk [8]. It is well predictable that estrogens level specially Estradiol (E2) in postmenopausal women may be susceptible by host physical appearance as BMI lifestyle as well as nutritional aspects, though, it is not identified yet whether these factors change estrogen metabolism [9]. Physical laziness overweight with obesity, are self-determining risk factors for breast cancer, while high BMI found to be related to a high risk of postmenopausal breast malignancies, showed an opposite correlation for pre-menopausal females [10]. The risk of having breast cancers is minimalizing with increasing dose of physical activity [11]. However, feeding of low energy foods such as legumes, fruit, and vegetables playing a significant role in weight management and then lowering the risk of having a series of diseases including breast CAs [12]. This study was aiming to evaluate the behavior of estradiol (E2) and estriol (E3) with insulin levels in pre and postmenopausal breast cancer females, in addition, to assess their relationship with lifestyle factors, such as physical activity, passive smoking, pills, BMI and dietary intake for the same cancer patients.

MATERIALS AND METHOD

Study population

Eighty Sudanese women recently diagnosed with breast cancer were compared with other matching healthy eighty as a reference subject. Their ages ranged from 25 to 85 years. Factors include diets, physical activity; drug prescriptions, menopause status, and passive smoking, were provided in the designed questionnaire. The questionnaire evaluated the frequency of necessary nutrient consumption; include milk products, vegetables, legumes, fruits, fish, chicken and red meat such as beef.

Sampling

Approximately 5 ml of venous blood was collected in plain vacutainers, and then sera were separated and kept frozen at -20°C ready for analyses.

Laboratory investigations

Insulin and Estriol (E3) levels were measured by the sensitive nuclear medicine *in vitro* radioimmunoassay (RIA) technology, while estradiol (E2) scored out using Enzyme-Linked Immunosorbent Assay (ELISA) reagents.

Statistical analysis

The program of choice for handling out the statistical work of this study was the Statistical Package for the Social Sciences (SPSS) 20th version. Found outcomes were stated as (mean ± sd). Hormones levels of the two studied groups (patients versus controls) were compared together using Student's t-test. p-values of <0.05 were the significant ratio.

Ethical consideration

This study was reviewed and approved by the National Health Research Ethics Committee, Federal Ministry of Health, Sudan. All participants in the study were informed, and verbal consent was taken.

RESULTS

The levels of insulin, estrogens (E2, E3) were studied associated with lifestyle aspects for breast carcinomas patients, and their characterisation were shown in (Table 1). Regarding the BMI, obesity was seen in postmenopausal breast cancer women rather than in premenopausal, while the percentage of normal weight subjects was 40% in both pre and postmenopausal women as clearly seen in (Figure 1).

Table 2 shows the hormonal levels in both study and control groups.

High insulin levels were seen in approximately 40% postmenopausal women for both patients and the control group with normal weight. 20% were seen in patients and control obese subjects, as shown in (Figure 2). Figure 3 shows the percentage of subject with overproduction of estradiol. It was observed that the control subjects are all having normal levels of E2 except for the obese postmenopausal women were around 15% were having elevated levels of E2. When looking at the study groups, E2 was found to be high in around 40% in normal-weight pre or post-menopause patients. Out of the overweight pre and postmenopausal patients, 25%-35% have high E2 levels compared to approximately 5%-20% for the obese pre and postmenopausal patients, for E3 serum levels see (Figure 4). Clearly recognized that E3 decreased in postmenopausal women for both patients and control groups, while decreased in premenopausal patients only upon comparison to their control group. Regarding the nutrient feeding, for premenopausal breast cancer patients, diet rich in nutrient is not taken regularly excepting for vegetables see (Figure 5), while in postmenopausal women, diet rich in nutrient is taken occasionally in both patients and the control subjects except in legumes and fruits where they are taken weekly in the control women, as well as the vegetables, are taken daily in both the patients and the control group as explain in (Figure 6). Regarding the effect of passive smoking and the impact of the contraceptive pills on the levels of the studied hormones, the number of breast cancer patients

Tab. 1. Characteristics of the study population (Mean ± SD)

Factors	Patients	Control
BMI (premenopausal) Kg/m ²	21.7 ± 4.5	21.7 ± 4.5
BMI (postmenopausal) Kg/m ²	23.7 ± 5.6	23.7 ± 5.6
Age (premenopausal) years	38 ± 5.6	38 ± 5.6
Age (postmenopausal) years	60 ± 9.5	60 ± 9.5
Pills users (Numbers)	4	10
Physical activity (Numbers)	0	30 (Premenopausal only)
Passive Smoking (Numbers)	5	4

exposed to smoking or using pills was very low (4, 5 patients). Therefore, their data were not included in the results of this study due to statistical insufficiency.

DISCUSSION

Insulin and two estrogens types (E2, E3) behaviour were studied in correlation to lifestyle factors on breast cancer female subjects to clear out which of them could be a risk factor for such severe alike disease. Partial hyperinsulinemia used to be a trend on postmenopausal women since their body is no longer respond to average concentration of insulin mentioned by Ma H, Bernstein et al., this finding agrees with high insulin levels registered by this study in both postmenopausal cases in addition to controls and explains the insignificant deferent of insulin levels between patients and controls subjects [13]. The significant-high E2 levels recorded by this study for the postmenopausal cancers women are in agreement with Hankinson SE et al., who reported that the postmenopausal women of high estradiol (E2) levels might have an increased risk of breast cancer [14].

After menopause, most women face a dramatic increase in central obesity, insulin resistance, and dyslipidemia, all factors

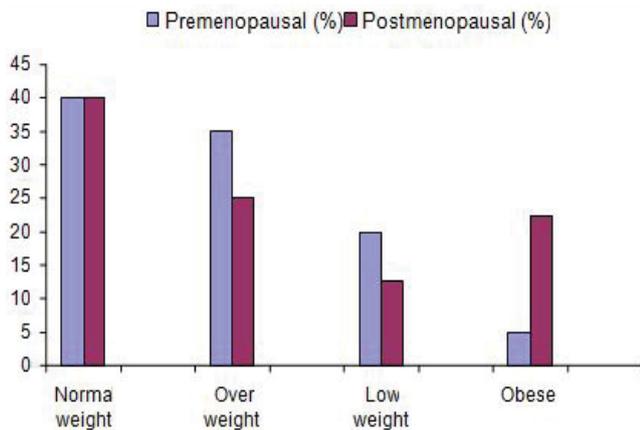


Fig. 1. Distribution of breast cancer women with body mass index.

Tab. 2. Hormones levels expressed as Mean ± SEM in pre-menopause and post-menopause women

Hormones	Pre-menopause			Post-menopause		
	Patients group (n=40)	Reference group (n=40)	p-value	Patients group (n=40)	Reference group (n=40)	p-value
Insulin (Normal value=4-16 mIU/L)	16.6 ± 0.25	12.6 ± 0.24	0.08	17.6 ± 0.22	20.2 ± 0.38	0.2
Estradiol (E2) (Normal value= 50-300 pg/L)	219 ± 4.3	71.4 ± 3.1	<0.001	602 ± 12.5	37.6 ± 2.2	<0.001
Estriol (E3) (Normal value=0-5 nmol/L)	0.5 ± 0.01	2.3 ± 0.03	<0.001	0.8 ± 0.02	0.5 ± 0.01	0.8

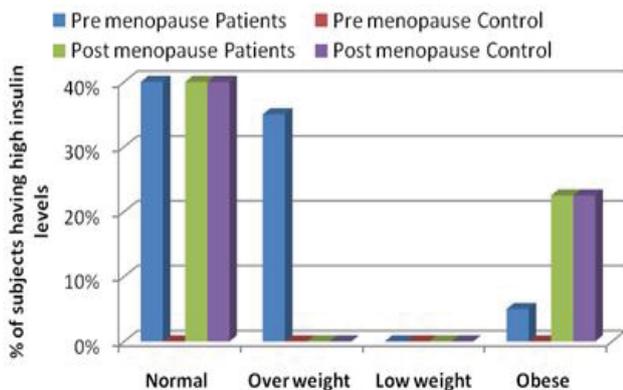


Fig. 2. Percentage of the higher level of insulin in study and control groups against BMI

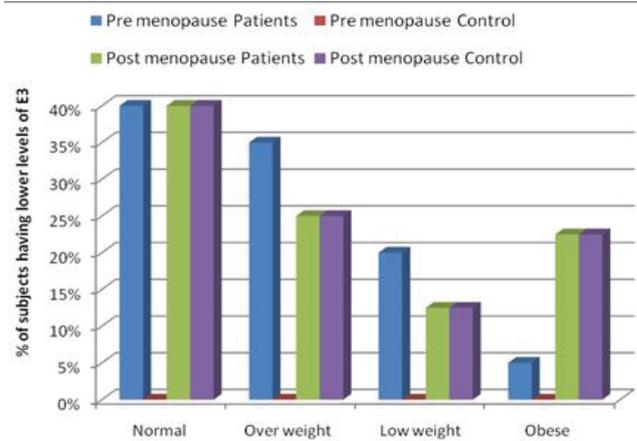


Fig. 4. Percentage of the higher level of estradiol in study and control groups against BMI

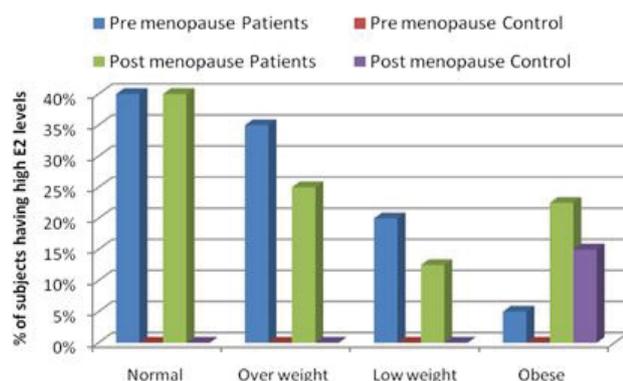


Fig. 3. Percentage of the higher level of estradiol in study and control groups against BMI

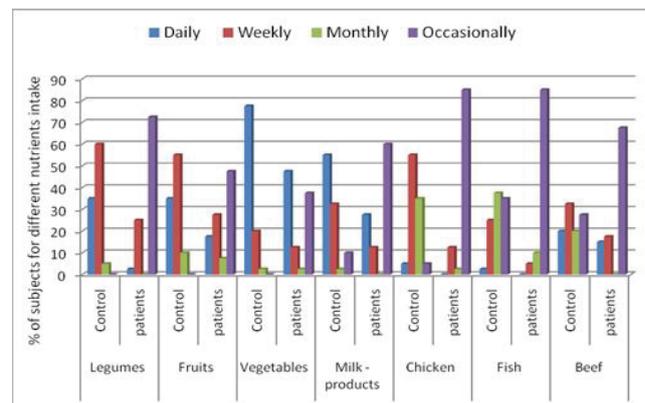


Fig. 5. Percentage of premenopausal women consuming different nutrient groups

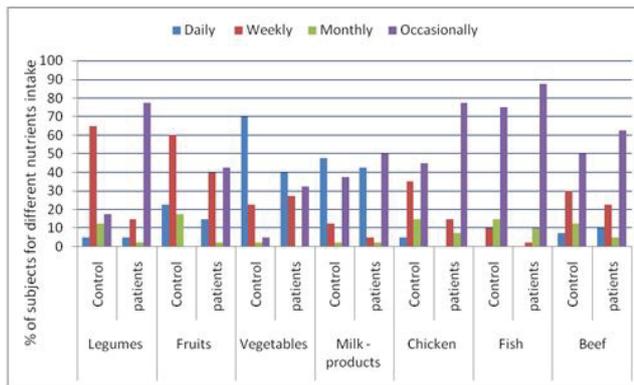


Fig. 6. Percentage of postmenopausal women consumption of different nutrient

associated with metabolism syndrome [15]. E2 may regulate insulin action directly via actions on insulin-sensitive tissues or indirectly by regulating factors like oxidative stress, which contribute to insulin resistance [16]. It seems clear that E2 exerts positive regulation on insulin action. However, this relationship is not submissive under conditions of high E2 levels, such as obesity. Obese postmenopausal women have more elevated serum E2 levels than slim postmenopausal women, as mentioned by R. Karim [17]. Clegg DJ, demonstrated the importance of Bodyweight factor as overweight individuals complain of excess fat tissue with high E2 concentrations which explains the high risk of breast cancer found in the studied obsessed postmenopausal group [18]. The relation of BMI and breast cancer risk has been verified by Msolly Awatef [19] and Cold S [20]. Their studies showed the BMI affects risk in a different way before and after menopause as it decreases premenopausal while increases postmenopausal due to higher levels of estrogen produced by excess aromatase activity in peripheral adipose tissues, this was also agreed with the finding in this study. So that maintaining a healthy weight is important for breast cancer survivors.

Many studies stated the positive effect of healthy nutrients for breast cancers patient. Significant High reductions in cancer risk and specific protective mechanisms against estrogen, when vitamin D and vegetables were consumed mentioned in previous studies [21-25], and explains these study findings in (Figures 5 and 6) of high consumption of rich nutrients by controls when compared to the patients for the two groups pre and postmenopausal. Dietary supplements and physical activity after diagnosis reduces cancer mortality, also to improve treatment outcomes, quality of life, and overall survival [26, 27]. The association between physical action and breast malignance risk is stronger for postmenopausal than premenopausal breast cancer cases was demonstrated by Monnikhof EM [28], which confirms our finding. However, lack of physical activity associated with high insulin levels in both postmenopausal controls and patients. Neilson HK also mentioned an inverse association between insulin sensitivity and physical activity levels to be independent of BMI [29].

Consumption of meat and its relation to bowel cancers

have been cross-examined by Missmer SA [30]. Boyd NF [31] reported more red meat consumption found to be of no significant association with breast cancers, while another study found higher meat intake associated with elevated breast cancer risk [30]. Epidemiological studies provide some limited evidence that suggests increased fish consumption may decrease the risk of breast carcinomas especially for premenopausal females [32, 33]. More red meat consumption in premature adulthood may be a risk factor for breast CAs, and then substituting red meat with a mixture of legumes, Chicken, and fish may decrease the risk of having breast cancers [34]. In one study, Dong JY reported the white meat intake association with lower breast density which a strong risk factor of breast CAs [35]. Many studies found no correlation between milk product intake and breast cancer risk [33-36]. These studies found the highest milk product consumption by healthy volunteers (controls) compared to the patients. These findings could list the milk product as a protective diet from breast cancers, which disagree with the data from the Nurses' Health Study II that found the consumption of high-fat dairy products increases the breast cancer risk on premenopausal women [37]. Concerning passive smoking and contraceptive pills affect our results for the only 5 and 4 patients respectively of this study showed the same finding of Folkerd EJ et al., and Hunter DJ who demonstrated no association between reflexive smoking and use of pills with breast cancer risk [38, 39].

LIMITATIONS OF STUDY

This research is an important contribution to the literature with some limitations. The type of pill and the dose rate don't consider in this study, and this may be some limitation concerning the pills study relationship as a risk factor of breast cancers. Study conducted in a small-scale study and does not representative of majority target population.

CONCLUSION

High estradiol (E2) levels may play a role of a tumor marker as well as an early detection sign for breast CAs on postmenopausal women, especially for those having excessive weight. Obesity is a major risk factor related to lifestyle among breast cancer in postmenopausal. Poor diet consumption may increase the risk of having breast cancers throughout the woman's life. Maintaining a healthy weight and physical activity may reduce breast cancer risk.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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