EARLY DETECTION OF BREAST CANCER IN WOMEN EXPOSED TO ENVIRONMENTAL ESTROGEN

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ABSTRACT

We aim in this research to evaluate the role of screening of women for exposure to environmental estrogens and to determine its predictive value for early detection of cancer breast.Recognition of the potential harmful effects related to cancer breast, may facilitate screening, and early detection of cancer breast.Fifty adult women with breast cancer who were referred to the radiology department were included as the study group. The cases were compared to control group of fifty women who were referred to the radiology department for routine screening for breast cancer and had no breast complaint or abnormalities detected.All women in both groups were subjected to a comprehensive structured questionnaire including the following: age, residency, marital status, parity, occupation, breast feeding, family history, age of menarche, age at menopause, hormone replacement therapy, contraceptive pills/injections, applications of cosmetics (body lotion, cream, make up, foundations, perfumes), wearing bras, implant, use of plastic wrappings, use of bottles/foams, dietary habits (fast/fresh food), chest irradiation, complaint of women (breast mass, pain, nipple discharge, skin discharge), history of exposure to other possible risk factors such as smoking, exposure to chest irradiation, radon, asbestos, pesticides and children toys. The collected data were organized, tabulated and statistically analyzed using statistical package for social science, version 16.Results were a significant relationship was found between incidence of breast cancer and exposure to cosmetics, smoking, physical inactivity, frequent fish consumption and low fruit intake.Exposure toxenoestrogens (e.g., insecticides, food preservatives) was a serious factor to breast cancer incidence.Some environmental factors showed rather insignificant relationship with exposure to radon or asbestos,

wearing bra, or plastic use to incidence of cancer breast.Conclusion wasBreast cancer has currently no available cure so perhaps the best strategy to combat breast cancer perhaps relies on early detection and prevention through avoiding the exposure to high risk factors.
Key Words: xenoestrogens (insecticides, food preservatives) - exposure to cosmetics, smoking - low fruit intake-plastics - pesticides .

INTRODUCTION

Risk is anything that affects the chance of getting a disease, such as cancer. Different cancers have different risk factors. Many risk factors were related to cancer breast such as female gender, older age, genetic risk factor and environmental factors (Key *et al*, 2001). Environmental risk factors that are related to cancer breast include oral contraceptive use, hormone therapy after menopause, and alcohol. Other environmental factors of controversial effect on breast cancer risk include dietary as amount of fat, intake of fruits, and intake of meat, antiperspirants and wearing bras (Johnson *et al*, 2003).

A great deal of research has been reported on possible environmental influences on breast cancer risk. Of special interest are compounds in the environment that have estrogen-like properties such as plastics, cosmetics, personal care products, pesticides such as dichlorodiphenyldichloroethylene (DDE) & poly-chlorinated biphenyls (PCBs). Most studies have found no link between cigarette smoking and breast cancer (Cui T *et al*, 2006). This issue understandably invokes a great deal of public concern. Several Egyptian researchers studied the effect of environmental variables related to breast masses among Egyptian women. The results warned from potential harmful effects of environmental materials such as air pollution, building material, and lead-containing cosmetics (Salama, 2008; Selim, 2013).

Till date, researches did not show a clear link between breast cancer risk and exposure to these substances (Desaulniers *et al*, 2001).

Early detection of cancer breast has utmost effect on management and prognosis of the condition. The American Cancer Society recommends clinical breast examination every 3 years for women in their 20s and 30s and every year for women above the age of 40 years (Saslow *et al*, 2007). The Society recommends yearly mammograms starting at age 40 yearsand that some women at high risk breast cancer be screened with ultrasonography or magnetic resonance imaging (MRI) in addition to mammograms (Smith et al., 2013; Kerlikowske *et al.*, 2010).

We aim in this research to evaluate the role of screening of women for exposure to environmental estrogens and to determine its predictive value for early detection of cancer breast.

MATERIAL AND METHODS

Fifty adult women with breast cancer who were referred to the radiology department were included and will be referred to as study group (gp 1). The cases were compared to fifty women who were referred to the radiology department for routine screening for breast cancer and had no breast complaint or abnormalities detected and will be referred to as control group (gp 2).

For inclusion of cases in either group as study (cancer breast), or control (no cancer breast) the following investigation were revised:

1. Detailed clinical examination with special emphasis on the breast with examination of the axilla & neck in addition to other systems.

2. The results of any available breast investigations were revised

a. Digital Mammogram: images were taken both in cranio-caudal and mediolateral oblique views and displayed on high resolution dedicated workstations. Image analysis was according to the 'Breast Imaging Data and Reporting System' (BIRADS).

b. Ultrasound using Selenia dimensions with the following features: Breast tomosynthesis providing high quality images of breast tissue in three dimensions. This helps the clinician to see the features that might be obscured in 2D mammogram.

c. Magnetic resonance imaging (MRI) of the breast: MRI was performed on a 1.5 T magnet (MagnetomAvanto, Siemens Medical Solutions, Erlangen, Germany; Sonata, Siemens Medical Solutions, Erlangen, Germany) with a dedicated four-element two-channel coil. Examination included diffusion weighted echoplanar sequence, T2-weighted short time inversion recovery, and non-fat saturated T1-weighted spoiled gradient echo. Intravenous gadolinium injection were indicated in cases with heavily fibrocystic breast with suspected lesions. Contrast medium used was gadobenatedimeglumine (MultiHance; Bracco Imaging, Milan, Italy injected at a dose 0.1 mmol/kg (0.2 ml/kg); followed by a 20 ml saline flush.

3. Chest x-ray; 4. Ultrasound abdomen and pelvis; 5. Tumor markers; 6. Bone survey

All women in both groups were subjected to a comprehensive structured questionnaire including the following: age, residency, marital status, parity,

occupation, breast feeding, family history, age of menarche, age at menopause, hormone replacement therapy, contraceptive pills/injections, applications of cosmetics (body lotion, cream, make up, foundations, perfumes), wearing bras, implant, use of plastic wrappings, use of bottles/foams, dietary habits (fast/fresh food), chest irradiation, complaint of women (breast mass, pain, nipple discharge, skin discharge), history of exposure to other possible risk factors such as smoking, exposure to chest irradiation, radon, asbestos and pesticides.

Statistical analysis of data: The collected data were organized, tabulated and statistically analyzed using statistical package for social science, version 16 (SPSS, Inc, USA); running on IBM-compatible computer. Graphic presentation was done using Microsoft excel version 2010. Qualitative data were presented as mean and standard deviation (SD); minimum and maximum often calculated; while qualitative (categorical) variables were presented as relative frequency and percent distribution. For comparison between groups; student samples (t) test or Chi square (X2) were used. For risk estimate, odds ratios were calculated. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated by equations (see tables), considering MRI as a standard diagnostic reference method. P value ≤ 0.05 was considered significant for interpretation of results.

RESULTS

In the present study, age ranged from 45 to 63 years with a mean of 53.04±3.65; and there was non-significant difference between study and control group (52.66±4.34 vs 43.82±3.15 respectively). On the other hand,

weight ranged from 59 to 78 kg with a mean of 65.72±3.70 kg and there was statistical significant increase of weight in study group when compared to control group (67.98±3.34 vs 63.46±2.49 respectively). Similarly, there was significant increase of BMI in study group when compared to control group (25.68±1.31 vs 23.84±0.94 respectively).

As regard residence, 56% of cases were urban and 44% were rural and there was significant increase of rural cases in study group when compared to control group (56.0% vs 32.0% respectively). In addition, there was significant increase of unmarried cases (singles) in study group when compared to control group (30.0% vs 10.0% respectively). Finally, there was significant decrease of cases with higher education in study group when compared to control group (12.0% vs 54.0% respectively). However, there was no significant difference between cases and controls as regard to employment (80.0% vs 76.0% respectively).

Comparison between study and control groups in regards to exposure to environmental estrogen and other risk factors are included in (Table 1).

As regard to factors of exposure or possible risk factors; there was significant increase of cosmetics, smoking exposure, physical inactivity, frequent fish consumption and decrease of frequent fruit intake in study group when compared to Control group (88.0%, 68.0%, 62.0%, 23.0%, 22.0% vs 70.0%, 14.0%, 42.0%, 8.0%, 74.0% in the same order). On the other hand, no significant difference was found between study and control groups as regard to hormone replacement therapy, hormonal contraceptive,, wearing bra or type of diet.

Table (1): Comparison between study and control groups as regard to factors of exposure to environmental estrogen or risk factors

Variables		Study		Control		Total		t-Test	P value
		n	%	n	%	n	%		
Hormone replacement therapy		10	20	6	12	16	16	1.19	0.27 (NS)
Contraceptives		13	26	16	32	29	29	0.43	0.5 (NS)
Cosmetics		44	88	35	70	79	79	4.88	0.027*
Silicon implant		2	4.	1	2	3	3	0.34	0.6 (NS)
Smoking exposure		34	68	7	14	41	41	30.13	<0.001*
Physical inactivity		31	62	21	42	52	52	4.01	0.045*
Frequent fish consumption		16	32.	4	8	20	20	11.21	0.004*
Frequent fruit intake		11	22.	37	74	48	48	27.08	<0.001*
Exposure to radon or asbestos		10	20	7	14	17	17	0.63	0.4 (NS)
Bra		31	62.	34	68	65	65	0.39	0.5 (NS)
Diet	Takeaway	26	52.	17	34	43	43	3.31	0.06 (NS)
	Home-made	24	48.	33	66	57	57		
Plastics	covers	3	6.	2	4	5	5.0	0.46	0.8 (NS)
	plastic bottles	30	60	33	66	63	63		
	Foam dishes	17	34	15	30	32	32		

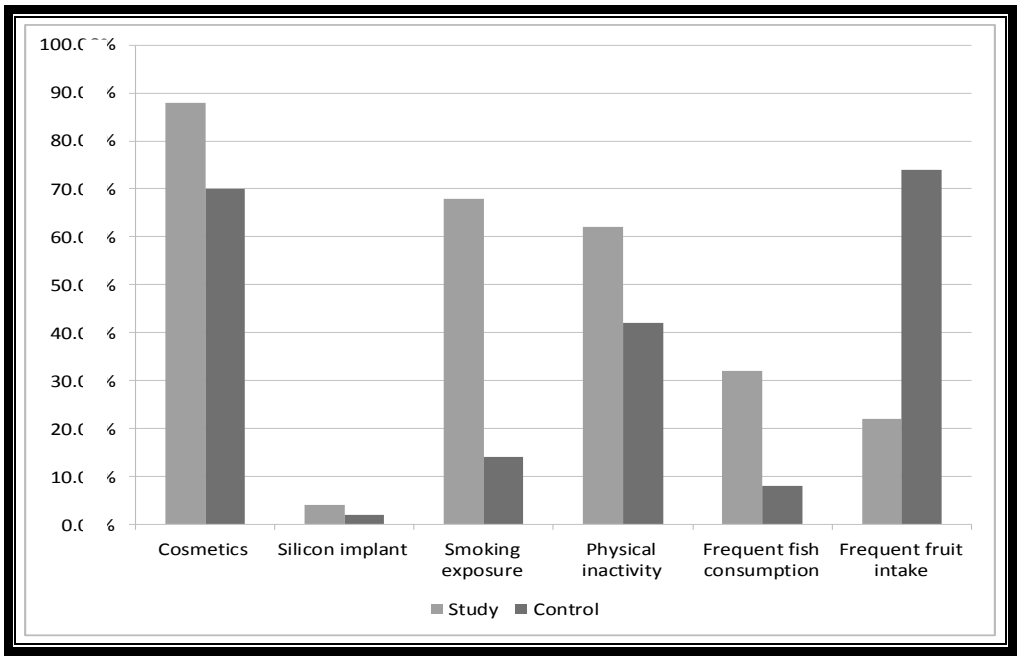

Figure (1): Comparison between study and control groups as regard to significant factors of exposure to environmental estrogen or risk factors

Searching for possible risk factors for development of breast cancer in exposed group; we can identify employment, smoking and cosmetics as the most important risk factors in this group.

DISCUSSION

Among environmental contaminants, halogenated and non-halogenated polycyclic aromatic hydrocarbons (HAHs/PAHs), such as polychlorinated dibenzo-p-dioxins and biphenyls and benzo[a] pyrene, have been recognized as significant and widespread contaminants (Pliskova *et al.* 2005). Aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor which mediates the adverse effects of dioxins and polycyclic aromatic hydrocarbons

(PAHs) in biological organisms (Van derHeiden *et al*. 2009). The cumulative exposure to estrogens is another important determinant in the risk of breast cancer. Long-term estrogen-exposed cells, in comparison with control cells, showed higher levels of AHR mRNA and protein and a 6-fold higher initial level of benzo(a)pyrene-DNA adducts, marked differences in the expression of numerous genes, and a higher rate of estrogen dependent tumor growth as xenografts (Jiang *et al*., 2010, Burrai *et al*., 2010).

According to WHO reports, breast lesions are the most common cause of death in women worldwide. In particular, breast cancer is strongly related to age, with only 5 % of all breast cancers occurring in women under 40 years old. One of the reasons for the high occurrence of breast cancer is that there is currently no cure available. The best strategy to combat oncological diseases perhaps relies on early detection and prevention (Chow *et al*., 2012). However, the method of detecting early breast cancer is still not clear (Lei *et al*., 2014).

In this study the incidence of exposure of the study group to some possible risk factors for cancer breast was significantly higher in this study compared to the control group. These possible risk factors included cosmetics, smoking exposure, reduced physical inactivity, frequent fish consumption and infrequent fruit-vegetable intake. Similar findings were obtained by a study by Selim on 2013 on Egyptian women with breast swellings; the results indicated significant increase of smoking exposure in cases with breast swellings in comparison to control group.

On the other hand, no significant difference was found between study and control groups as regard to hormone replacement therapy, hormonal contraceptive, wearing bra, type of diet or plastic use. These results are comparable to previous studies, where there are significant proofs to indicate that xenoestrogens (e.g., insecticides, food preservatives) are serious factors in breast cancer incidence by inducing epigenetic changes on breast epithelial cells (Hsu *et al.,* 2009). Citizens of polluted environments could be exposed to estrogen-like substances by many different sources, even by groundwater (Kuch *et al.,* 2010). The aryl hydrocarbon receptor (AHR) mediates the effects of many dioxin like compounds, xenoestrogens and endocrine disruptors and contributes to the loss of normal ovarian function in polluted environments (Valdez *et al*., 2009). In fact one of the main causes of AHR overexpression in MCF breast cancer cells is the loss of ER alpha functions. This phenomenon is likely to be based on the mutually antagonistic relationship between ER and AHR (Wong *et al.,* 2009). This event suggests AHR as a potential drug target for the treatment of ER negative breast cancer patients (Zhang *et al.,* 2009).

In the present work, there was significant increase of smoking and frequent fish eating in study groups when compared to control group.Cadmium from industrial effluents pollutes sea and river water and hence may accumulate in fish population.The positive association between dietary exposure to cadmium from intake of fish and breast cancer risk has been hypothesized (Romieu I., 2011). Some heavy metals such as cadmium can function as endocrine disruptors by mimicking the action of estrogens.

Since estrogen itself plays an important role in the development and progression of the disease, the ability of Cadmium to bind to and activate the estrogen receptors suggests that these compounds may also contribute to the development of breast cancer (Ikeda *et al.,* 2006).Johnson *et al.* (2003) also reported that cadmium increased uterine weight and promoted hyperplasia of mammary glands in female rats. In addition, cadmium may play a role in the development of ER-positive (ER+) breast cancer. A positive association between urinary cadmium and serum testosterone among postmenopausal Japanese women has also been reported (Nagata *et al.,* 2005).

This hypothesized role of cadmium in the etiology of breast cancer, an estrogen-dependent disease, has focused attention on its estrogenic activity (Julin et al., 2012; Sawada *et al.,* 2012). However, other studies could not provide support for the hypothesis that dietary exposure to cadmium increases the risk of breast cancer (Van Maele-Fabry *et al* 2016).Epidemiological evidence for positive association between intake of fish and breast cancer risk is thus less conclusive, but could be suggestive (Romieu, 2011).

In this work, there was significant increase of BMI, physical inactivity, low fruit and vegetable intake, low education in the study group with cancer breast when compared to the normal control group. These factors are likely associated with theincidence of breast cancer in the study group. These results are comparable with previous reports. It was reported thathigh BMI, low physical activity, low fruit-vegetable and increased fish intake were also significant factors for breast cancer.(Chow *et al.,* 2005; Montazeri et al. 2008; Peters *et al.,* 2009).

In addition, Fu and colleagues in 2015 reported that their data strongly strengthened the role of second-hand cigarette smoke exposure and low education as risk for breast cancer (Fu *et al.* 2015).A study in 2017 by Strumylaite and colleagues on 585 cancer breast cases and 1170 controls concluded that lifetime exposure to passive smoking is associated with the risk of breast cancer with the strongest association in postmenopausal Caucasian women. Using lard instead of vegetable oil for cooking was a significant risk factor. Therefore, the increased incidence of BC in Shantou, and in China too, was likely due to endogenous cultural factors (cooking with lard) plus externally-introduced risk factors (passive cigarette smoke exposure, sedate life style). They added, their much stronger association with passive exposure to cigarette smoke (OR = 4.82, 95%CI = 2.63–8.85) compared to other investigations is meaningful. This strong association is because the overwhelming majority of females in China never smoked. However, Shantou males smoked frequently (about 50% males are smokers) and without interference, e.g. at work and at home. Therefore, passive exposure for our studied females can be exceedingly higher than that in Western countries.

CONCLUSION

The best strategy to combat breast cancer perhaps relies on early detection and prevention through avoiding the exposure to high risk factors including cosmetics, smoking exposure, physical inactivity, frequent fish consumption and low fruit intake. Exposure to xenoestrogens (e.g., insecticides, food preservatives) is a serious factor to breast cancer

incidence.Some environmental factors showed insignificant relationship with exposure to radon or asbestos, wearing bra, or plastic use.

SUMMARY

Screening of women for exposure to environmental estrogens and other potential risk factors could be of value for early detection of cancer breast. Comprehensive structured questionnaire of fifty adult women with breast cancer compared to control group of fifty women suggested significant relationship between incidence of breast cancer and exposure to cosmetics, smoking, physical inactivity, frequent fish consumption and low fruit-vegetable intake.

RECOMMENDATION

The best strategy to combat breast cancer perhaps relies on early detection and prevention through avoiding the exposure to high risk factors. More awareness of the Egyptian governmental authorities is recommended to control air pollution, in door smoking in public areas, and review industrial materials for potential harmful effects. The increased awareness of healthcare providers about the potential harmful effects of some environmental variables, will promote screening and early detection of cancer breast.

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الاكتشاف المبكر لسرطان الثدي عند السيدات المعرضات للإستروجين البيئي

[٥]

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المستخلص

يهدف البحث إلى تقييم دور الفحص الفرزى للنساء المعرضات بيئياً لهرمون الاستروجين وتحديد قيمتها التنبؤية للكشف المبكر عن سرطان الثدي.يضم البحث خمسون من النساء البالغات المصابات بسرطان الثدي اللاتى أحلن إلى قسم الأشعة كمجموعة الدراسة. وتمت مقارنة الحالات بمجموعة موازية من خمسين امرأة أحلن إلى قسم الأشعة لفحص روتيني للكشف عن سرطان الثدي وليس لديهن شكوى أو أى أمور غير طبيعية فى الثدي. تعرضت جميع النساء في كل من المجموعتين إلى استبيان شامل بما في ذلك ما يلي: العمر، والإقامة، والحالة الاجتماعية، والانجاب، ونوع العمل، والرضاعة الطبيعية، والتاريخ العائلي، سن البلوغ، سن انقطاع الطمث، والعلاج بالهرمونات البديلة، وحبوب/ حقن منع الحمل، استعمال مستحضرات التجميل (غسول الجسم، كريم، المكياج، والمؤسسات، والعطور)، وارتداء حمالات الصدر، زرع، واستخدام الأغلفة البلاستيكية،

واستخدام زجاجات / الرغاوي، والعادات الغذائية (الغذاء السريع / المواد الأغذية الطازجة)، أشعة الصدر، الشكوى النسائية (كتلة بالثدي، ألم، إفرازات بالحلمة، إفرازات بالجلد)، وتاريخ التعرض لأى عوامل خطر محتملة أخرى مثل التدخين، والتعرض لأشعة الصدر، وغاز الرادون والأسبستوس، والمبيدات الحشرية ولعب الأطفال. تم تنظيم البيانات التي تم جمعها، وجدولتها وتحليلها إحصائيا باستخدام الحزمة الإحصائية للعلوم الاجتماعية.

من أهم النتائج تم العثور على علاقة هامة بين الإصابة بسرطان الثدي والتعرض لمستحضرات التجميل، والتعرض التدخين والخمول البدني والاستهلاك المعتاد للأسماك وقلة تناول الفاكهة. كان التعرض للزينواستروجينات (مثل، المبيدات الحشرية، المواد الحافظة) عاملا خطيرا لحدوث سرطان الثدي. وأظهرت بعض العوامل البيئية علاقة بسيطة لحالات لحدوث سرطان الثدي لدى التعرض لغاز الرادون أو الأسبستوس، وارتداء حمالة الصدر، أو استخدام البلاستيك.