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Vitamin D Level in Breast Cancer Patients before and after Adjuvant Therapy

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MANY factors have been claimed to increase breast cancer risk; as age at menarche and menopause, hormonal exposures,previous benign breast lesions, family history of breast cancer, exposure to ionizing radiation, smoking and alcohol.Researches claimed vitamin D deficiency as acause of multiple diseases, including cancer.Perhaps its deficiency upregulatesthe hormonal and genetic predisposition of the patients and there is a need for investigating more factors for breast cancer etiology and therapy.Sources of vitamin D are sunlight exposure or diet and dietary supplements.The aim of this studyisto demonstrate vitamin D level in breast cancer patients at diagnosis,and weather this level changeswith chemotherapy and radiotherapy.This case control prospective study was carried out on 35 premenopausal patients diagnosed as breast cancer patientsand 20 healthy women in whom serumhydroxy vitamin D (25OHD) levels were analyzed at the beginning of study,and after chemotherapy and radiotherapy.The data revealed that mean serum vitamin D concentration in healthy control group was (22.35 ± 5.92ng/ml), whichis considered insufficient. Patients at diagnosis were vitamin D deficient with mean level(16.62±1.92ng/ml); then after receiving adjuvant therapy in the form of chemotherapy and radiotherapy, vitamin D mean level was (11.11± 2.52ng/ml); i.e.the mean level decrease by about 33%. It could be concluded that breast cancer patients had lower vitamin D levels than the age matched control women. Vitamin Dlevel in breast cancer patients decreased more after chemotherapy and radiotherapy.

Introduction

Breast cancer isestimated as one of the most commonly diagnosed cancers worldwide with percentageof11.9%. It is the most common cause of cancer deathamong women and the most frequently diagnosed cancer in 140 out of 184 countries worldwide (*Ferlay* et al., 2012) including Egypt; where there were an estimated 49.5 cases of breast cancer per 100,000 adults in 2012, and an estimated 18,660 cases in total (UN, 2013), withyearly rise of percentage. In the cancer research field, many researchers connect vitamin D with risk reduction in various epithelial cancers.Vitamin D controlscalcium homeostasis with wide range of immunogenic and antiproliferative activities in the body (*Khan* et al., 2011). Oncologists found decreased incidence of breast, colon, and prostate cancers with higher sun exposure, higher intake or higher serum levels of vitamin D (*Garland* et al., 2009).There are few dietary sources of vitamin D, butadequate amounts of vitamin D can be synthesized in the skin using the energy of ultraviolet (UV) radiation in sunlight,which maintains adequate vitamin D stores (*Lefkowitz, and Garland, 1994)*.Ultraviolet B rays (290-315 nm) through the skin, converts 7-dehydrocholesterol to pre-vitamin D3, which is converted to vitamin D3 and released into the circulation where the majority is quickly hydroxylated in the liver by cytochrome P-450-dependent enzyme. The 25-hydroxyvitamin D3 is the major circulating D3 derivative that is used to measure serum vitamin D status. In the renal proximal convoluted tubule, 25-hydroxyvitamin D is hydroxylated to biologically active metabolite, 1, 25-dihydroxyvitamin D (Calcitriol) (Henry, 2011).Calcitriol exerts its actions by binding to a nuclear receptor protein, the vitamin D receptor (VDR) (Racz and Barsony 1999). VDR is active in all tissues including breast and in cancer cells (*Tagliabue* et al., 2015). Vitamin D binds to and activates the nuclear VDR which regulates as much as 3% to 5% of the human genome (*Oh* et al., 2007). Interestingly, it was found that people with higher vitamin D levels have shown reduced incidence of breast cancer (*Garland* et al., 2009 *and Boeke* et al., 2015).Among Egyptian women,vitamin D deficiency was

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identified in middle-aged, postmenopausal and geriatric women(Botros et al., 2015). According to De Lyra et al. (2006) suboptimal vitamin D levels might lead to cancer development through impairment of cell proliferation, differentiation, apoptosis, and angiogenesis. Vitamin D can alter the defenses of the body(*Platz* et al., 2000), and can limit the development of multiple diseases, including cancer (*Feskanich* et al., 2004). VDR has been implicated in cell cycle arrest, apoptosis, and promotion of differentiation. It inhibits cell proliferation via p21 and p27, which act on G0/G1 cell cycle arrest with regulation of apoptosis via the p53 pathway. VDR is able to detect DNA damage and facilitate DNA repair, preventing mutations and promoting appropriate development (Thorne and Campbell, 2011). VDR facilitates normal development by promoting differentiation and preventing progression to malignancy (*Althuis* et al., 2004). There is a close relation between calcitriol and estrogen receptor (ER) signaling, in ER-positive breast cancer cell lines, calcitriol reduced ER expression by direct transcriptional repression of the ERαgene (*Stoica* et al., 1999 *and Swami* et al., 2000).Calcitriol downregulates aromatase gene expression, so decrease conversion of androgen to estrogen (*Krishnan* et al., 2010). Of note, the effects of vitamin D compounds on breast cancer cells also occur via ER-independent pathways (*Hussain* et al., 2003).Effects of calcitriol on angiogenesis may be mediated by prostaglandins, which are important proangiogenic factors (*Krishnan and Feldman,* 2011). Vitamin D can potentiate the effects of certain therapies such as platinum analogs, taxanes, and DNA-intercalating agents (Ma et al., 2008).

Patients and Methods

This prospective case-control study included 35 premenopausal women as patients group with (operable early stage non metastatic breast cancer) and 20 healthy womenas control group. The study was conducted atAin Shams University Hospital from February 2016 to December 2016. The study protocol was approved by the Scientific Research Committee and consent was obtained from each patient prior to inclusion in the study. All patients were in the middle age and still menstruating at diagnosis. Demographic, personal and clinical data were collected upon recruitment. Gynecological examination and investigations were done to evaluate uterus, ovaries and pelvis in all patients and during follow up. Patients with chronic medical conditions or with metastatic disease were not included in the study.Patients included in the study hadhistopathologic type ofinvasive intraductal carcinoma which constitutes about 90% of all pathological types of breast cancer. Surgery came first in the protocol of treatment of all patients. Factors affecting surgical decisions include tumor size, location and ability to achieve a free safety margin with good cosmetic outcome. None of the patients had received neo-adjuvant chemotherapy or radiotherapy which started prior to surgery as all patients were with no metastasis. All the patients received adjuvant chemotherapy and radiotherapy following surgery.The Protocols of chemotherapy were1- FEC/Tin (82.8%). FEC regimen were given to patients at a dose of; cyclophosphamide (500mg/m2, day 1), Epirubicin (100mg/ m^2, day 1) and fluorouracil (500mg/m2, days 1), intravenously and the cycle was repeated every 3 weeks.

Day 1: 5-fluorouracil 500mg/m^2 IV, Day 1: Epirubicin 100mg/m^2 IV

Day 1: Cyclophosphamide 500mg/m^2 IV. Repeat cycle every 3 weeks for 3 cycles, then followed by:Day 1: Docetaxel 100mg/m^2 IV. Repeat cycle every 3 weeks days for 3 cycles.

2- CMF in (17.2%) of cases for six cycles. CMF regimen received cyclophosphamide (500 mg/m^2, day 1,8), methotrexate (40mg/m^2, day 1,8) and fluorouracil (500mg/m^2, day 1,8),intravenously (i.v.).Days 1,8: Cyclophosphamide 500 mg/m^2

Days 1 and 8: Methotrexate 40mg/m^2 IV, Days 1 and 8:5-fluorouracil 500mg/m^2 IV.Repeat cycle every 4weeks for 6 cycles.

[F=Fluorouracil,E=Epirubicin,C=Cyclophosphamide, M= Methotrexate, T= Docetaxel].Radiation therapy to all the patientswereat a dose of 50 Gy divided to 20-25 sessions of radiationin the radiotherapy unit. Radiation was delivered by the Linear accelerator which delivers high energy photon beam. Radiotherapy was delivered to the chest wall with daily fractions of 2 Gy on 5 consecutive days a week. Median total doses of 50 Gy given in fractions over a period of ~5 weeks were applied to the chest wall including the surgical scar as well as internal mammary nodes. The chest wall and internal mammary lymph nodes were irradiated through two tangential fields, supraclavicular and axillary nodes were treated with an anterior field to a total dose of 50 Gy. Blood samples were obtained from healthy

women in the control group and from patients firstbefore chemo-radiotherapy. The second blood samples were obtained from the patients after completing their chemotherapy and radiotherapy. The blood was immediately transferred into tube and centrifuged. The serum samples were then maintained at −20°C until further analysis. All the samples were run in the same assay. Serum 25-hydroxyvitamin D3 (25-OHD) levels were measured by an ELISA kit using DRG ELISA kit (EIA-5396)-USA. Results are expressed as ng25-OHD per 1 ml serum. Vitamin D levels were classified according to the Endocrine Society guidelines for 2011, to sufficient defined as ≥30 ng/ml (75nmol/L), insufficient defined as 20–29 ng/mL (50–72 nmol/L), and deficient defined as <20 ng/mL (<50 nmol/L).

Statistical Analysis

Data analysis was done using IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL). The descriptive measures were presented in frequency and percentages. Description of quantitative variables as mean±SD. Independent- t-test was used to compare two groups as regard quantitative variable. Paired-t-test was used to compare different variables before and after treatment. Pearson's correlation was used to test correlation between numerical variables. P-value of ≤0.05 was considered significant.

Results

The results aredemonstrated through Tables (1-6).The mean age of patients was (39.85 ± 5.30) years and for the control group was (36.95± 6.51) years. Age, marital status, residential area, had almost similar distribution among the patients and the control groups.All cases live in Cairo. About 68.5 % of the patients and 65% of the healthy control women had more than three children, so there was no significant difference as regards parity in both groups. After chemotherapy irregular menstruation was found in 85.7% in breast cancer patients. Regarding the occupational history, there was a significant difference as 45.7% of the cases were working in different occupations, while 75% of the control group was working.Therewas no significant difference between the BMI for the patients (31.40±3.42) and the BMI for the controls (30.25±2.37) withp value 0.204. There was no significant difference in both groups as regards history of lactation as 65.7% of patients were lactating before and 70% of control group had a history of lactation at some time before.The percentage of passive smoking exposure in the patients group was 91.42% which was highly significant different than the control which was 55%. The tumor histological grade was grade 2 in 57.14% of the patients. About 71.5 % of the patients were with positive estrogen receptors. The mean serum vitamin D level in the breast cancer patients was (16.62 ±1.92)ng/ml and in the control group was (22.35 ± 5.92)ng/ml and thep value calculated was <0.001. After chemo-radiotherapy, the mean level of vitamin D was (11.11± 2.52) ng/ml. Vitamin D deficiency was seen in 100% breast cancer patients while 45% of the control group were deficient in vitamin D, the p value was <0.001. None of the breast cancer patients had a sufficient vitamin D level, while 1 patient in the control group had sufficient serum level. In our study 100 % of the patients were vitamin D deficient,butinthe control group45% weredeficient and 50% were insufficient and 5% only was sufficient.

TABLE 1. Clinical Data and Laboratory Investigations at starting the study inthe patientsand the control groups.

Parameters	Patient group(n=35) Mean±SD	Control group(n=20) Mean±SD	P-values
Age (years)	39.85 ± 5.30	36.95± 6.51	NS
Parity	3.17 ± 1.05	2.90 ± 0.71	NS
BMI kg/m2	31.40 ± 3.42	30.25 ± 2.37	NS
Hbgm/dl	10.75 ± 0.65	11.42 ±1.85	NS
TLC count×10^3/ml	5.87 ± 1.73	5.16 ± 1.23	NS
Platelet count ×10^3/ml	211.22 ± 35.81	216.55 ± 36.85	NS

TABLE 2. Comparison between vitamin DMean±SD in theControl group and in thePatients before starting chemotherapy and radiotherapy

Parameter	Control group Mean±SD	Patients before tttMean±SD	*p-value*
Vitamin D (ng/ml)	22.35±5.92	16.62±1.92	<0.0001

TABLE 3. Comparison between vitamin D before and after chemo- radiotherapy in the *Patients*

Vit. D (ng/ml) before ttt	Vit. D (ng/ml) after ttt	*p- value*
16.62± 1.92	11.11±2.52	<0.001

TABLE 4. Comparison of vitamin D (mean± SD) before adjuvant treatment between the patients in the two protocols of chemotherapy, and a comparison of vitamin D after adjuvant treatment between the patients in the two protocolswhich shows non-significant differences as p-value >0.05

Parameter	Chemo-protocol	N	Mean±SD	*p-value*
Vit.D. before ttt	FEC/T	29	16.82 ± 1.89	>0.05
	CMF	6	15.66 ± 1.96	
Vit.D. after ttt	FEC/T	29	11.20± 2.44	>0.05
	CMF	6	10.66± 3.14	

TABLE 5. Correlation of vitamin D in allcases with Parity and age, which showssignificant inverse correlation betweenvitamin D with age and with parity.

Parameter	Pearson	Parity	Age
Vit.D.before ttt	Correlation	**r**=-.300-*	**r**=-.350-**
	p	.026	.009
	N	55	55

TABLE 6. Correlation of age in the patients with vitamin D(after chemoradiation) and with tumor grade,age shows asignificant inverse correlation with vitamin D and a significant inverse correlation with grade

Parameter	Pearson	Vitamin D after	Grade
	Correlation	**r** = -.604	**r** = -.595
Age	*p*	.000	.000
	N	35	35

Discussion

A variety of single nucleotide polymorphisms in genes are thought to interact with hormonal, nutritional, and radiological exposures to increase the risk of breast cancer. Vitamin D exerts its antiproliferative effect by binding to vitamin D receptor (VDR) found in various tissues and cells of the body. Several human genes contain vitamin D response elements (specific DNA sequences) that encode for proteins important in regulation of cell proliferation, differentiation, apoptosis, and angiogenesis (De lyra et al., 2006 and Lowe et al., 2005). When the serum vitamin D levels reduced, these activities are impaired and as a result enhanced a cellular growth and neoangiogensis, with cancer development (Giovannucci, 2005). Biological and epidemiological data have revealed the protective functions of vitamin D against

different cancers, especially breast cancer (Garland et al., 2006, Holick, 2006,and Ness et al.,2015). The most recent Endocrine Society guidelines recommend the use of the 25-OH vitamin D test for screening and diagnosis of vitamin D deficiency (Holick et al., 2011). From the data in our study there is no significant difference in the age of the participants in both groups, there isirregularity in menstruation in the patients in which about 85.7% of them have irregular menstruations which is due to the effect of chemoradiation on ovaries,but in control group about 15 % have menstrual irregularity.The percentage of employment in the patients (45.7%) is significantly lower than in the controls (75%), perhaps the house wife women do nothave enough UVR as they stay most of the time indoors. The percentage of the married participants andmultiparityin both groups arealmost the same. Tumor characteristics in the patients as regards stage of breast cancer wereearly stage with no metastasis, the grade of tumor showed the highest percentage was grade 2 equals 57.14%.The grade of tumor showeda significantinverse correlation with age, younger patients showeda higher tumor grade as grade 3. The histological type of breast cancer in our study was invasiveintraductal carcinoma, as this pathological type is the most prevalenthistological type in breast cancer. Positive Estrogen receptors were among 71.4% of the patients;this is similar tothe study of Thapa et al.(2013).Both groups were subjected to passive smoking which reaches about 91.4% in the patients and about 55% inthe control group. Second handsmoke or passive smoking,and impaired vitamin D3 activation by cigarette smoke represents a novel mechanism by which cigarette smoke induces its pro-inflammatory effects, so the epidemiology of breast cancer seems to depend on these two factors,Furthermore, according to many studies,smoking increases significantly the likelihood of having vitamin D deficiency(Kassi etal., 2015). Another study reported thatvitamin D is decreased among active and passive smokers, and this lower plasma vitamin D in smokers was associated with higher risk of tobacco-related cancers(Afzal et al.,2013). Also air pollution could influence the amount of UVB reaching the earth's atmosphere, which in turn, influences the amount of UVB ground-level. One of the most recent WHO reports for the ambient air pollution database showed the PM_{10} and $PM_{2.5}\mu g/m^3$ [which is a measure of fine particulate matter of 10/2.5 microns or less that has been associated with health risks] in Cairo and the Delta region to be PM_{10} 135 and $140\mu g/m^3$, respectively, and $PM_{2.5}$ 73 and $76\mu g/m^3$, respectively. They are considered to be among the areas with the highest ambient air pollution as designated by the most recent WHO map for ambient air pollution in 1600 countries (WHO,2014). As statedby Hosseinpanahet al.(2010), the level of air pollution is inversely proportionate to the amount of UVB reaching the earth. This is another explanation for the decrease of vitamin D level in the patients and thecontrols. About 65.7 % of patients had history oflactating their children, and 70% of control group had history of lactating their children, which showed no significant difference.Females, especially those pregnant or lactating, are at a higher risk of vitamin D deficiency or insufficiency, as highlighted by several studies in the Middle East (Al Refai et al., 2014). This result supposes that lactation reduces serum vitamin D level and this can be one of the causesfor development of breast cancer.Low levels of vitamin D are the normal finding rather than the exception in Egypt. The prevalence of vitamin D deficiency in healthy asymptomatic people is reported to be in the range of 54-77% in Egypt and this is more common in the urban population (Botros et al., 2015). We foundthat themean serum levels of vitamin D in the breast cancer patients (16.62±1.92 ng/ml) were significantly lower than in the control women (22.35±5.92ng/ml). Hence, the association between breast cancer risk and serum levels of vitamin D parallels other studies from the developed world. Studies from United States reported 50-74% vitamin D deficiency in newly diagnosed premenopausal breast cancer patients (Khan and Fabian, 2010).In the healthy control group vitamin D levels lie within the range (12-30 ng/ml). Only 5% in the control group were vitamin D sufficient, 55% insufficient and 40% were deficient in vitamin D with the mean value (22.35±5.92ng/ml).This agrees with the results of a study in which only 24% of women were categorized as sufficient (≥30 ng/mL) (Goodwin et al., 2009).Accumulating data on the vitamin D status of Egyptian women over the last two decades clarified that there was vitamin D deficiency among healthy premenopausal womenwith mean level of (21.8 ± 4.1ng/ml) in the research of Ragab et al.(2013). In the study ofFawzi et al.(2012) the mean vitamin D level was (22.8±12.75 ng/ml) in middle aged university student females.These levels are consistent with

the results of vitamin D levels in normal premenopausal females in the present study. Foumani and Khodaie, (2016), in their study, provided an evidence that vitamin D deficiency has been very prevalent in patients with breast tumorsmore than matched control population, and that the risk of breast cancer has increased with low vitamin D levels. According to our results, there was no correlation between vitamin D levels before and after chemoradiotherapy with + ve estrogen receptors.According to a study by Kim et al. (2011), triple negative hormones breast cancer patients have the highest percentage of vitamin D deficiency. According to Lowe et al. (2005) women with serum levels of vitamin D more than 50 ng/ml had a 50% lower risk of breast cancer compared to those with serum values less than 30 ng/ml in various studies from the developing world.In the present study, vitamin D is significantly inversely correlated with age (r = -. 300 and p= .026), and with parity (r=-.350 and p= .009), which means that the increase in age and increase in parity is associated with the decrease of vitamin D level. Also there is a significant inverse correlation between age of patient and grade of tumor, increasing age is associated with lower grade (r=-.595 and p=.000). Increasing age is associated with a decrease of vitamin D level after chemoradiation with (r=-.604 and p=.000).Several studies suggest that high vitamin D intake, with or without calcium, may protect against premenopausal breast cancer. Low calcium or vitamin D intake has been associated with larger and higher grade breast tumors(Abbas et al., 2007,Braverman, 2007, Lin et al., 2007).According to the presentstudy, after chemoradiation, vitamin D mean level further decreasesuntil reaching (11.11±2.52 ng/ml) which is consistent with astudy of Kim et al.(2014)who found a decreased level of vitamin D after chemotherapy in breast cancer patients. We explain that the reduction in vitamin D level may be due toa decreasein intake of vitamin D in food or supplements or due to diarrhea affecting patients during chemotherapy that leads to deficient vitamin D absorption, and also keeping indoors away from UVR due to severe illness from chemotherapy and due to radiation sickness. Egyptian women are under four major risk factors for reduction in vitamin D level which are:poor diet not enriched with vitamin D, repeated pregnancy and lactation without adequate ante- and post-natal health care, passive smoking , andlack of exposure to sun UVR due to air pollution and being indoors. These factors increase the incidence of breast cancer in Egypt.

Conclusion

We concluded that vitamin D deficiency is common among Egyptian women and in cancer breast patients is the common finding which further decreases after chemo-radiation. Vitamin D deficiency may be correlated to increasing breast cancer incidence in Egypt.

Recommendations

It is important for the oncologists to recognize, treat, and prevent vitamin D deficiency.The high percentage of vitamin D deficiency in the Egyptian women with its adverse impact on bone health leads to increasing the vulnerability to breast cancer. Further intolerance to various systemic cancer treatments leads us to recommend increasing dietary vitamin D and vitamin D supplementation with exposure to sunlight. Improving the quality of ambient air by decreasing air pollutionand prohibiting active andpassive smoking between women, especially in pregnant and lactating women as they are more vulnerable for vitamin D deficiency, will be among the modifiable risk factors for breast cancer.

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مستوى فيتامين د فى مريضات سرطان الثدي قبل وبعد العلاج المصاحب

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هناك الكثير من العوامل التى تزيد من خطر الإصابة بسرطان الثدي مثل زيادة الوزن ,العمر عند بدء وإنقطاع الطمث , العلاج بالهرمونات المختلفة, أمراض الثدى السابقة , التاريخ المرضى للعائلة , التعرض للإشعاعات المؤينة , التدخين و الكحول. وجد العلماء أن نقص فيتامين د يكون مصاحبا للعديد من الأمراض والأورام. تعتبر أشعة الشمس و الأغذية الغنية بفيتامين د, و المكملات الغذائية التى تحتوى على فيتامين د من أهم مصادر فيتامين د. ونظرا لعدم تعرض النساء المصريات لاشعة الشمس حيث ان بيئة العمل داخل المبانى دائما والملابس التى تغطى الجسم كاملا, لذلك فإن نسبة النقص فى فيتامين د فى النساء المصريات عالية. تم إجراء هذا البحث لمتابعة مستوى فيتامين د فى مريضات سرطان الثدي قبل بدء العلاج ومقارنته بالمستوى الطبيعى فى العينة الضابطة, ثم بعد العلاج الكيميائى والإشعاعى و بعد ستة أشهرأثناء العلاج الهرمونى.وقد أجريت هذه الدراسة على ٣٥ مريضة فى سن الإنجاب وتمثل المجموعة الأولى وللمقارنة بالاصحاءتم إختيار ٢٠سيدة فى نفس الفئة العمرية وتمثل العينة الضابطة. تم إختيار المريضات من قسم الأورام كلية الطب جامعة عين شمس وذلك بعد الحصول على موافقتهن.تم إجراء تسجيل تاريخ المرض وفحص إكلينيكى شامل قبل أخذ العينات لقياس مستوى فيتامين د وذلك بإستخدام تقنية "الإليزا". تم إخضاع النتائج للتحاليل الإحصائية المعتمدة لبيان معلومية النتائج. أظهرت النتائج أن هناك نقص معنوى فى مستوى فيتامين د فى مريضات سرطان الثدى(١٦,٦٢ ± ١,٩٢نانوجم/مل) عند بدء التشخيص مقارنة بالمجموعة الضابطة(٢٢,٣٥ ± ٥,٩٢نانوجم/مل). ثم حدث نقصان معنوى فمستوى فيتامين د(١١,١١ ± ٢,٥٢ نانوجم/مل) بعد العلاج الكيميائى والإشعاعى المصحابين بالمقارنة بالمستوى الأول. أظهرت النتائج وجود إرتباط معنوى سلبى بين مستوى فيتامين د وعمر السيدات حيث وجد مستوى فيتامين د أقل فى الأعمار الأكبر.أيضاوجود علاقة إرتباطية بين التدخين السلبى وحدوث سرطان الثدى و نقص مستوى فيتامين د.

وخلصت الدراسة إلى إمكانية تسبب نقص فيتامين د فى سرطان الثدى, حيث أنه يؤثر فى الكثير من العمليات الحيوية داخل الخلية والتى تعنى بالمحافظة على الحمض النووى والجينات المسئولة عن مهاجمة وقتل الخلايا السرطانية.وإمكانية تسبب التدخين السلبى فى حدوث سرطان الثدى. وأوصت الدراسة بعلاج جميع السيدات المصريات من نقص فيتامين د فى جميع المراحل العمرية مع الإهتمام بمرحلة الحمل والرضاعة حيث تزداد الحاجة أكثر للفيتامينات والحرص على زيادة الوعى الصحى والتعريف بأهمية فيتامين د والبعد عن المدخنين حتى لاتتعرض النساء لمخاطرالتدخين السلبى للوقاية من سرطان الثدى .