Original Article

The Study of Socioeconomic and Clinic Risk Factors of Breast Cancer in Algerian Women Population

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Abstract

Purpose: Breast cancer is the most frequent cancers type and represents the first cause of cancer death for woman. This study was conducted aiming at evaluating some risk factors in patients with breast carcinoma in El Oued (Algeria) region.

Materials and Methods: Our study is based on 300 voluntary individuals divided into 150 healthy women reserved as a control and 150 female cancer patients with average age of 44.15 ± 0.91 years old; their origin covers the whole El Oued (Algeria) region and they were selected from the oncology service of the hospital of BEN AMOR DJILANI El Oued (Algeria). Risk of certain socio-clinical factors has been estimated by the determination of the value of Odds Ratio (OR).

Results: Our study reports show a strong association between socioeconomic behavior such as passive smoking, social problems, sunshine exposed. ($2.27 < OR > 4.69$; $p<0.05$), and clinical factors such as chronic diseases and contraceptive pull ($1.97 < OR >12.56$; $p<0.001$) with breast cancer, but in this study we show that the phone in bras and fast food are the most dangerous risk factor, ($OR = 31.06$, $OR =19.05$; $p<0.001$) respectively, for breast cancer. Yet spices and breastfeeding more than 8 months ($OR = 0.444$, $OR =0.27$; $p<0.05$) are important protective factors against this disease.

Conclusion: Social behavior and lifestyle is a contributing factor in breast cancer attainment in the region of El Oued (Algeria), which requires high sensitivity to modify these behavior for limited progression of the disease in this region.

1. Introduction

Cancer is a group of diseases characterized by rapid and uncontrolled growth of cells resulting in abnormal cell assembly. These cells undergo transformations to obtain a continuous replication which can cross towards other organs and tissues leading to a malignancy [1]. There are more than 100 types of cancers affecting the human eye. Breast cancer, prostate cancer, cancer of the colon and rectum, lung cancer and bronchial cancer are the most common types of cancer [2]. Also breast cancer is the most commonly diagnosed type in women [3], considered the leading cause of death in many countries [4]. There is no specific cause of breast cancer, but several scientific studies have shown that certain behaviors specific to a person were more often observed in women with cancer than in other healthy women [5]. Several factors are considered causative factors of breast cancer, as genetic susceptibility [6]. The environment is also an important factor, 5-10% of all cases of cancer [7], caused by exposure to environmental pollution (such as pesticides and heavy

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metals), and lifestyle plays an important role in the etiology of this disease, including diet, late age of first pregnancy, duration of breastfeeding, menopause, use of contraception [8]. One of the ways to detect breast cancer is breast self-examination [9]. There are several imaging techniques available to evaluate the breast. The most widely used and studied modality for breast cancer screening is mammography [10]. Ultrasound is generally used as an adjunct to mammography for women with dense breasts. Magnetic Resonance Imaging (MRI) is currently being used to screen high-risk patients in combination with mammography [11]. This article is about an evaluation of a relation between some social and clinic factors with breast carcinoma in women of El Oued (Algeria) region.

2. Materials and Methods

2.1. Subject of Study

Ethical approval was requested and approved by the ethics committee of the department of cellular and molecular biology, faculty of natural sciences and life, University of El Oued. Our study was based on 300 voluntary individuals divided into healthy women reserved as a control and female cancer patients with average age of 44.15 ± 0.91 years old. All of the volunteers (control and patients) in this study live in the El Oued area located in the southeast of Algeria. Therefore, their social and demographic information including age, age of marriage, number of children, weight, social case, job, educational level, and blood group were collected by completing the questionnaires from their medical records or through a direct discussion with patients.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria for breast cancer: clinical diagnosis shows breast cancer suffering for three months confirmed by specialist doctors, also patients receiving chemotherapy but no other type of chronic disease treatment for 30 days. Regarding the control group, the participants are healthy people not suffering from chronic or acute diseases and consume no drug for 30 days. Exclusion criteria were to eliminate all other types of cancer and cases of metastasis of breast cancer.

2.3. Statistical Analysis

Values were expressed as percent per population or as the mean ± Standard Deviation (SD). Relative risks and Odds ratios were calculated by Cochran's and Mantel Haenszel statistics using SPSS 16. Odds ratios >1 and $P<0.05$ indicate a significant risk factor. OR<1 and $P<0.05$ indicate a significant protective factor.

3. Results

3.1. Description of the Study Population

The general data of socioeconomic characteristics of the two groups of subjects include age, age of marriage, number of children, weight, social case, job, educational level, and blood group. These indicators do not have any statistically significant differences (as shown in Table 1), at $P > 0.05$.

Table 1. Socioeconomic description of control and breast cancer patients

		Control	Patients
Age (ys)		42.82±1.20	45.48± 1.37
Age of marriage (ys)		20.532±0.575	21.957±0.720
Number of children		5.087±0.387	4.630±0.427
Body Weight (kg)		73.40±1.67	72.48±2.07
Social case	Married%	88	86
	Single%	6	10
	Divorced%	4	2
	Widow%	2	2
Job	Worker%	16	16
	Housewife %	84	84
Educational level	Illiterate%	12	14
	Primary%	14	36
	Junior high%	30	30
	High School%	32	14
	Higher education%	12	6
Blood group	A%	20.40	34
	B%	30	15.90
	O%	48.97	47.72
	AB%	0	2.27

3.2. Study of Socioeconomic and Clinic Factors

Odds Ratio (OR) values for socioeconomic factors (Table 2) and clinic-pathological factors (Table 3) show that passive smoke, chronic diseases, contraceptive pill and radiation exposure are shown to be significant risk factors for breast cancer (OR = 4.29; p = 0.001, OR=1.976; p=0.0001, OR = 4.15; p = 0.001 and OR = 5.42; p = 0.0001), respectively. Social problems (OR = 4.69, p = 0.0001) and sunshine exposure (OR = 2.27, p

= 0.035) are also highly significant predictors of breast cancer. In addition, taking contraceptive pill after the age of 30, menopause before 45, family history factor and first born after 30 are all predictive factors (OR ranging from 5.52 to 12.56, p <0.05). Also, fast food and phone in bras are considered to be very important risk factors in the study population, with the highest OR value (OR = 19.05; p = 0.0001 and OR = 31.06; p = 0.0001). In contrast, spices and breastfeeding more than 8 months are protective factors for breast cancer in the study population (OR ranging from 0.279 to 0.444, p <0.036). In addition, our results indicate that tap water, cosmetics, detergents, puberty after 14 years old, PMS irregular and paracetamol are not considered as predictors of breast cancer in our population since the OR values obtained are not significant.

	Control %	Patient %	OR	CI$_{95\%}$	P
Positive	1.29	16.88			
Negative	53.24	28.57			
Detergent			1.397	0.626-3.119	0.270
Positive	28	32			
Negative	22	18			
Sedentarily			3.092*	1.009-9.478	0.037
Positive	5.05	13.13			
Negative	44.44	37.37			
Tight Bras			0.625	0.247-1.584	0.224
Positive	14.14	10.10			
Negative	35.35	40.40			
Cosmetics			0.545	0.239-1.242	0.107
Positive	30	15			
Negative	20	35			

Table 2. Comparison of the Socioeconomic features of breast cancer patients and control group (N=300)

	Control %	Patient %	OR	CI$_{95\%}$	P
Smoke Passive			4.292*	1.839-10.017	0.001
Positive	13.26	30.61			
Negative	35.71	20.40			
Fast Food			19.056*	2.395-151.598	0.000
Positive	01	14			
Negative	49	36			
Sunshine Exposed			2.279*	1.017-5.108	0.035
Positive	17	27			
Negative	33	23			
Chemicals Exposed			0.506	0.157-1.635	0.194
Positive	09	05			
Negative	41	45			
Sport			1.536	0.503-4.693	0.318
Negative	42.42	43.43			
Positive	8.08	6.06			
Canned Foods			0.900	0.331-2.450	0.520
Positive	10.30	9.27			
Negative	40.20	40.20			
Social Problems			4.696*	1.931-11.418	0.000
Positive	10	27			
Negative	40	23			
Industrial Area			5.930	0.667-52.726	0.085
Positive	1.04	4.16			
Negative	51.04	43.75			
Spices			0.444*	0.199-0.989	0.036
Positive	31	21			
Negative	19	29			
Tap Water			2.070	0.641-6.686	0.172
Positive	5.10	9.18			
Negative	45.91	39.79			
Obesity			1.833	0.611-5.502	0.207
Positive	06	10			
Negative	44	40			
Phone in Bras			31.069*	3.932-245.472	0.000

Table 3. Comparison of the Clinico-pathological features of breast cancer patients and control group (N=300)

	Control %	Patient %	OR	CI$_{95\%}$	P
Breastfeeding			0.521	0.046-5.942	0.523
Negative	2.24	1.12			
Positive	49.43	47.19			
Breastfeeding more than 8 Ms			0.279*	1.078-11.915	0.027
Positive	43.42	39.47			
Negative	3.94	13.15			
Contraceptive Pill			4.156*	1.801-9.587	0.001
Positive	18.08	32.97			
Negative	34.04	14.89			
Contraceptive Pill After 30 y			10.907*	3.446-34.525	0.000
Positive	4.16	37.5			
Negative	31.25	27.02			
Puberty after 14			0.843	0.322-2.208	0.459
Positive	10.63	9.57			
Negative	38.29	41.48			
PMS Irregular			0.299	0.057-1.559	0.128
Positive	6.06	2.02			
Negative	43.43	48.48			
Menopause before 45			6.864*	2.178-21.636	0.000
Positive	3.84	30.76			
Negative	30.76	34.61			
First birth after 30			12.564*	1.541-102.417	0.003
Positive	1.14	10.34			
Negative	49.42	39.08			
Childbearing Less than 1 year			1.904	1.579-2.296	0.530
Positive	0	1.26			
Negative	46.83	51.89			
Radiation Exposure			5.429*	2.302-12.799	0.000
Positive	16.12	37.63			
Negative	32.25	13.97			
Using Paracetamol			2.158	0.916-5.087	0.059
Positive	12.24	21.42			
Negative	36.73	29.59			
Family History			5.527*	1.523-20.053	0.004
Positive	2.70	22.97			

Negative	31.08	43.24			
Chronic Diseases			1.979*	1.593-2.450	0.000
Positive	0	17.85			
Negative	40.24	41.46			

OR>1 and P<0.05 indicate a risk factor
OR<1 and P<0.05 indicate a protective factor

4. Discussion

In this study, we investigated the association between some risk factors and breast cancer. Our study shows that the passive smoking is associated with the risk of having breast cancer in women of our region, especially if the exposure is long or begins before the first pregnancy, suggesting that the effect of smoking may vary over the course of life and the onset of exposure [12]. In 2005, a pooled analysis of 20 studies that measured both active and passive tobacco exposure was conducted. This study was able to show an increased risk of breast cancer in women who were exposed directly or indirectly to cigarette smoke compared with women who had never been exposed to [13]. In our study, the results show that eating fast food, overweight and inactive women was significantly associated with breast cancer risk; other study proved that there is a strong relationship between these three risk factors [14]. Obesity and overweight have been linked to various health disorders, including breast cancer [15]. Also known to activate NF-B are several cytokines produced by adipocytes, such as leptin, Tumor Necrosis Factor (TNF), and Interleukin-1 (IL-1) [16]. Also, the most accomplished studies about the effect of physical activity on the breast cancer risk demonstrate that inactive women have a higher risk of the breast cancer compared to physically active women [17]. On the other hand, our study showed that psychological stress is a risk factor for breast cancer in Algerian women. The study of Mei-Ling and Tso-Ying (2015) showed that anxiety, depression, and stress might tentatively be related to breast cancer incidence [18]. Psychosocial factors such as personality traits and depression may alter immune and endocrine function, with possible effects on cancer incidence [19]. Catecholamine, glucocorticoids and other stress hormones are subsequently released from the adrenal gland, stress hormones can also activate oncogenic viruses and alter several aspects of immune function [20]. Our study shows that sun radiation (UV) exposure is a risk factor associated with breast cancer. Ultraviolet A (UVA) photons trigger oxidative reactions by excitation of endogenous photosensitizers, such as porphyrins, NADPH oxidase, and riboflavin. 8-Oxo-7,8-dihydroguanine (8-oxoGua) is the main UVA-mediated DNA oxidation product formed by the oxidation of OH radical, 1-electron oxidants, and singlet oxygen that mainly reacts with guanine [21]. Our result showed that putting cellphones in bra is a risk factor for breast cancer in women; chronic exposure to radiofrequency electromagnetic radiation of cellphone leads to that is associated with increased oxidative stress because the soft fat breast tissue readily absorbs such radiation [22]. In addition, a study conducted at the University of California reported that women, regularly kept their cellphones in their bra adjacent to their breast during the day, which was estimated to be about 10 hours every day for several years, each presented with tumors in the same regions of their breasts, next to where their phones were kept [23]. Furthermore, our study shows that first birth after the age of 30 years old is a risk factor. These results are in agreement with the studies of McPherson et al. (2000), who showed the risk of breast cancer in women who have their first child after the age of 30 years old is about twice that of women who have their first child before the age of 20 years old [24]. Importantly; our study showed an association for menopause and risk of having breast cancer. The results found were similar to those observed in Howell et al.'s (2014) studies [25]. The increased risk may be due to longer lifetime exposure to reproductive hormones and has been more strongly related to breast cancer than other subtypes [26]. In our study it was observed that the radiation is associated with breast cancer, where Key et al., (2001) explain that the breast is among the tissues that are most sensitive to the effects of radiation [27]. In our study, consumption of contraceptives pills specifically after the age 30 years old is associated with increased risk of breast cancer. Contraceptive use among women with cancer was very important compared to women in control groups. According to the study of Soroush et al. (2016), the risk of breast cancer is increased by about 52% in women who commonly use contraceptives pills [28]. In our study, we found higher risk of breast cancer in association with the family history. Women and men with a family history of breast cancer, especially in an immediate family (parent,

child, or sibling), are at increased risk for the disease [29]. Genetic linkage studies in multiple-breast cancer families have identified the Mutations in BRCA1 and BRCA2 genes that are tumor suppressor genes. Our results showed that the patients with concomitant diseases associated with developing breast cancer. The presence of one or more chronic diseases may make receipt of cancer screening even more complex. Some chronic illnesses, such as diabetes, serve as independent risk factors cancers [30] and may be associated with cancer mortality [31]. In our study population, breastfeeding for more than 8 months is a protective factor for breast cancer, According to Stuebe (2009), breastfeed is associated with an increased incidence of premenopausal breast cancer, ovarian cancer [32]. In general, the longer the duration of breastfeeding, the more women are protected against breast cancer [33]. Lactation produces endogenous hormonal changes, in particular a reduction of estrogens that play a regulatory role or stimulation of cancerous proliferation [34]. Lactation increases prolactin production, which is believed to decrease cumulative estrogen exposure in women. Therefore, lactation would suppress the onset and development of breast cancer [35]. Our results showed that the spices are protective factors of breast cancer. According to Jie *et al.* (2016), spices have been widely used as food flavorings and folk medicines for thousands of years. Numerous studies have documented the antioxidant, anti-inflammatory and immune modulatory effects of spices, which might be related to prevention and treatment of several cancers, including breast cancers [36].

5. Conclusion

Hence, in this study it was found that passive smoke, contraceptive pill, radiation exposure, social problems, sunshine exposure, contraceptive pill after 30 years old, menopause before 45years old, giving first birth after 30 years old, fast food, and phone in bras are shown to be majors risk factors for breast cancer, which indicates the importance of social behavior and the clinical factor of breast cancer involvement. In contrast, spices and breastfeeding more than8 months are protective factors for breast cancer in the study population. In addition, our results indicate that tap water, tight clothes, cosmetics, detergents, puberty after 14 years old, PMS

irregular and paracetamol are not considered as predictive factors of breast cancer in our population.

Acknowledgements

References

1- A.K. Mitra, V. Agrahari, A. Mandal, K. Cholkar, C. Natarajan, S. Shah, M. Joseph, H.M . Trinh, R. Vaishya, X. Yang, Y. Hao, V. Khurana, D. Pal, Novel delivery approaches for cancer therapeutics; USA, *J Control Release*, vol. 219, pp. 248–268, 2016. doi:10.1016/j.jconrel.2015.09.067.

2- P. Shiwani, N. Saraswathy, Enzymes as targets for cancer therapy, *Int. J. Pharm. Sci. Res*. Vol. 8(11), pp. 4525-32, 2017. Doi.10.13040/IJPSR.0975-8232.

3- M. Salakari, L. Pylkkänen, L. Sillanmäki, R. Nurminen, P. Rautava, M. Koskenvuo, S. Suominen, Social support and breast cancer: A comparatory study of breast cancer survivors, women with mental depression, women with hypertension and healthy female controls; Finland 2017, *The Breast*, vol. 35, pp. 85-90, 2017. doi.org/10.1016/j.breast.2017.06.017.

4- A.M. Salinas-Martínez, L.I. Flores-Cortés, J.M. Cardona-Chavarría, B. Hernández-Gutiérrez , A. Abundis, J. Vázquez-Lara, E.E. González-Guajardo, Prediabetes, Diabetes, and Risk of Breast Cancer: A Case-Control Study; Monterrey, N.L., Mexico; 2014, *Arch. Med. Res*., vol. 45, pp. 432-438, 2014.

5- S. Koçan, A. Gürsoy, Body Image of Women with Breast Cancer After Mastectomy: A Qualitative Research, *J. Breast Health*, vol. 12, pp. 145–150, 2016.

6- A. Nkondjock, P. Ghadirian, Risk Factors for Breast Cancer, *Med. Sci*., vol. 21(2), pp. 175-180, 2005. doi: 10.7202 / 010550ar.

7- K. Cheeseman, E. Rouleau, A. Vannier, A. Thomas, A. Briaux, C. Lefol, P. Walrafen, A. Bensimon, R. Lidereau, E. Conseiller, M.Ceppi, A diagnostic genetic test for the physical mapping of germline rearrangements in the susceptibility breast cancer genes BRCA1 and BRCA2, *Hum. Mutat*., vol. 33(6), pp. 998-1009, 2012.

8- T. Norat, C. Scoccianti, M.C. Boutron-Ruault, A. Anderson, F. Berrino, M. Cecchini, C. Espina, T. Key, M. Leitzmann, H. Powers, M. Wiseman, I. Romieu, European Code against Cancer 4th Edition: Diet and cancer, *J. Cancer Epidemiol.*, vol. 39(1), pp. S56-S66, 2015.

9- R. Zareh, P. Wrya, F. Bagher, A.A. Mahdieh , S. Hossein, Evaluating the frequency of breast cancer risk factors in women referred to mammography center for breast cancer screening: a report from south part of Iran, *J.Cancer Policy*, vol. 16, pp. 33-38, 2018. https://doi.org/10.1016/j.jcpo.2018.04.004.

10- V.S. Subbhuraam, Y.N. Eddie, U.A. Rajendra, F. Oliver, Breast imaging: A survey. *World J. Clin. Oncol.*, vol. 2(4), pp. 171–178, 2011.

11- S.P. Kimberly, C. Youngjee, W.S. Rosalyn, F.S. Heather, Screening for breast cancer, *Seminars in Oncology*, vol. 44, pp. 60–72, 2017. doi.org/10.1053/j.seminoncol.2017.02.004.

12- C.J. Shepperd, N. Newland, A. Eldridge, L. Haswell, F. Lowe, E. Papadopoulou, O. Camacho, C.J. Proctor, D. Graff, I. Meyer, Changes in levels of biomarkers of exposure and biological effect in a controlled study of smokers switched from conventional cigarettes to reduced-toxicant-prototype cigarettes, *Regul. Toxicol. Pharmacol.*, vol. 72(2), pp. 273-291, 2015.

13- KC. Johnson, Accumulating evidence on passive and active smoking and breast cancer risk, *Int. J. Cancer*, vol. 117, pp. 619-628, 2005.

14- B.A. Almutlaq, R.F. Almuazzi, A.A. Almuhayfir, A.M. Alfouzan, B.T. Alshammari, H.S. AlAnzi, H.A. Gadelkarim, Breast cancer in Saudi Arabia and its possible risk factors ; College of Medicine, University of Hail, Saudi Arabia, *J. Cancer Policy*, vol. 12, pp. 83–89, 2017. http://dx.doi.org/10.1016/j.jcpo.2017.03.004.

15- M.S. Alokail, N. Al-Daghri, A. Abdulkareem, Metabolic syndrome biomarkers and early breast cancer in Saudi women: evidence for the presence of a systemic stress response and/or a pre-existing metabolic syndrome-related neoplasia risk?, *BMC Cancer*, vol. 13, pp. 54, 2013. doi. org/10.1186/1471-2407-13-54.

16- A. Preetha, B.K. Ajaikumar, S. Chitra, B.H. Kuzhuvelil, T.T. Sheeja, S.L. Oiki, S. Bokyung, B.A. Bharat, Cancer is a Preventable Disease that Requires Major Lifestyle Changes, *Pharm. Res.*, vol. 25(9), pp. 2097–2116, 2008. DOI: 10.1007/s11095-008-9661-9.

17- C. Pizot, M. Boniol, P. Mullie, A. Koechlin, M. Boniol, *et al.*, Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies, *Eur. J. Cancer*, vol. 52, pp. 138-54, 2016.

18- Y. Mei-Ling, L. Tso-Ying, A Prospective Study of the Relationship between Psychological Factors and Breast Cancer, *Asia Pac. J. Oncol. Nurs.*, vol. 3, pp. 170-5, 2015. DOI: 10.4103/2347-5625.170223.

19- N. Naoki, Effect of Psychosocial Factors on Cancer Risk and Survival, *J. Epidemiol.*, vol. 24(1), pp. 1-6, 2014. DOI:10.2188/jea.JE20130124.

20- H.A. Michael, K.L. Susan, W.C. Steven, S.D. Firdaus, E.S. Sandra, G.M. Paige, Michael S, K.S. Anil, The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. *Nat. Rev. Cancer*, vol. 6(3), pp. 240-8, 2006. DOI: 10.1038/nrc1820.

21- B. Esra, M.S. Umit, S. Cansin, E. Serpil, K. Omer, Oxidative Stress and Antioxidant Defense, *World Allergy Organ J.*, vol. 5(1), pp. 9–19, 2012. doi: 10.1097/WOX.0b013e3182439613.

22- A.O. Oyewopo, S.K. Olaniyi, C.I. Oyewopo, A.T. Jimoh, Radiofrequency electromagnetic radiation from cell phone causes defective testicular function in male Wistar rats. *Andrologia*, vol. 49(10). Doi: 10.1111/and.12772.

23- D.J. Saddig, Is Long-Term Cell Phone Use Linked to Breast Cancer? A Review of the Evidence, Adv. *Breast Cancer Res.*, vol. 5, pp. 136-141, 2016. Doi.org/10.4236/abcr.2016. 54016.

24- M. McPherson, C.M. Steel, J.M. Dixon, ABC of Breast Diseases, Breast cancer epidemiology, risk factors, and genetics. *BMJ*, vol. 321, pp. 624-8, 2000.

25- A. Howell, S.A. Annie, B.C. Robert, W.D. Stephen, D.E. Gareth, M. Garcia-Closas, J.G. Andy, J.K. Timothy, M.S. John, N.H. Michelle, Risk determination and prevention of breast cancer, *Breast Cancer Res.*, vol. 16, pp. 446, 2014.

26- S.S. Julia, C.C. Laura, H.B. Andrew, M.T. Rulla, A.R. Bernard, EA. Heather, Reproductive risk factors in relation to molecular subtypes of breast cancer: results from the Nurses' Health Studies, *Int. J. Cancer*, vol. 138(10), pp. 2346–2356, 2016. doi: 10.1002/ijc.29968.

27- T.J. Key, P.K. Verkasalo, E. Banks, Epidemiology for breast cancer, *Lancet Oncology*, vol. 2(3), pp. 133-140, 2001.

28- A. Soroush, N. Farshchian, S. Komasi, N. Izadi, N. Amirifard, A. Shahmohammadi, The Role of Oral Contraceptive Pills on Increased Risk of Breast Cancer in Iranian Populations: A Meta-analysis, *J. Cancer Prev.*, vol. 21(4), pp. 294–301, 2016. doi: 10.15430/ JCP.2016. 21. 4.294.

29- R. Taheripanah, F. Balash, R. Anbiaee, M. Mahmoodi, S.A. Akbari, Breast Cancer and Ovulation Induction Treatments, *Clinical Breast Cancer*, 2018, pii: S1526-8209(17)30455-X. doi: 10.1016/j.clbc.2018.03.003.

30- K.B. Michels, C.G. Solomon, F.B. Hu, B.A. Rosner, S.E. Hankinson, G.A. Colditz, Type 2 diabetes and subsequent incidence of breast cancer in the nurses' health study, *Diabetes Care*, vol. 26, pp. 1752–1758, 2003. PubMed: 12766105- .

31- S.S. Coughlin, E.E. Calle, L.R. Teras, J. Petrelli, M.J. Thun, Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults, *Am. J. Epidemiol.*, vol. 159(12), pp. 1160–1167, 2004.

32- S. Alison, The Risks of Not Breastfeeding for Mothers and Infants, *Rev. Obstet. Gynecol.*, vol. 2(4), pp. 222–231, 2009.

33- J.M. Faupel-Badger, K.F. Arcaro, J.B. Jane, H.A. Eliassen, F. Hassiotou, C.B. Lebrilla, B.M. Karin, R.P. Julie, P. Schedin, A.M. Stuebe, J.W. Christine, M.E. Sherman, Postpartum Remodeling, Lactation, and Breast Cancer Risk: Summary of a National Cancer Institute–Sponsored Workshop, *J. Natl. Cancer Inst.*, vol. 105(3), pp. 166-174, 2013. doi.org/10.1093/jnci/djs505.

34- J. Cui, Y. Shen, R. Li, Estrogen synthesis and signaling pathways during ageing: from periphery to brain, *Trends Mol. Med.*, vol. 19(3), pp. 197–209, 2013. doi: 10.1016/j.molmed. 2012.12.007.

35- T.J. Key, M.C. Pike, The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer, *Eur. J. Cancer Clin. Oncol.*, vol. 24, pp. 29-43, 1988.

36- J. Zheng, Y. Zhou, Y. Li, X. Dong-Ping, L. Sha, L. Hua-Bin, Spices for Prevention and Treatment of Cancers, *Nutr. Rev.*, vol. 8, pp. 495, 2016. doi:10.3390/nu8080495.