RISK FACTORS RELATED TO BREAST CANCER DEVELOPMENT

Fatores de risco relacionados ao desenvolvimento do câncer de mama

Daniel Rodrigues de Bastos[1] ⓘ

ABSTRACT

Breast cancer is a disease that affects women worldwide, and therefore is a health problem of global concern. Despite scientific and technological advances in basic researches and in clinical studies, breast cancer still presents numerous obstacles that need to be overcome in order to ensure better survival for patients affected by this disease. Science's work is not only to predict the best methods of treatment, but also to prevent the onset of symptoms and, consequently, of the tumor. Recent articles discuss numerous factors which may contribute to tumor initiation and progression. They take into consideration social habits, such as smoking, alcohol drinking, diets that contribute to hyperlipidemia or increased availability of antagonist molecules that act on the cell in order to create a favorable microenvironment to tumorigenesis. In addition to that, factors related to family history and hereditary predisposition are important, even though they explain a minimal portion of cases. Thus, the purpose of this article is to address modifiable and non-modifiable risk factors, related to breast cancer progression.

KEYWORDS: breast cancer; risk factors; neoplasms.

RESUMO

O câncer de mama é uma doença que acomete mulheres em todo o mundo, sendo por isso um problema de saúde de preocupação global. Apesar dos avanços científicos e tecnológicos nas pesquisas básicas e nos estudos clínicos, o câncer de mama ainda apresenta inúmeras barreiras que necessitam ser transpostas, a fim de garantir melhor sobrevida às pacientes acometidas por essa doença. A atuação da ciência consiste não apenas em prever as melhores formas de tratamento, mas também de como evitar o aparecimento dos sintomas e, por consequência, do tumor. Artigos recentes discutem inúmeros fatores que podem contribuir para a iniciação e progressão tumoral. São considerados os hábitos sociais, como o ato de fumar, ingestão de bebidas alcoólicas, dietas que contribuam para a hiperlipidemia ou aumento da disponibilidade de moléculas antagonistas que agem sobre a célula de modo a construir um microambiente favorável à tumorigênese. Além disso, fatores ligados ao histórico familiar e predisposição hereditária são importantes, apesar de explicar uma parcela mínima dos casos. Com isso, o presente artigo tem por objetivo abordar sobre fatores de risco modificáveis e não modificáveis, relacionados com a progressão do câncer de mama.

PALAVRAS-CHAVE: câncer de mama; fatores de risco; câncer.

INTRODUCTION

Breast cancer is a disease of worldwide interest that affects women on a global scale and a small part of the male population[1-3]. Statistics of the project Globocan/IARC (International Agency for Research on Cancer) of 2018 highlight that breast cancer ranked the second most common type of cancer worldwide (2,089 million), only behind lung cancer (2,094 million), and it is eligible as the fifth leading cause of death, considering both genders, rising to first place of most incident type and at the top of mortality when only women are counted[4,5].

According to Atlas of Cancer Mortality (2018), 15,593 breast cancer deaths were registered in Brazil during 2015, being 187 men and 15,403 women[6]. In Brazil, breast cancer is responsible for 29.5% of all new cases each year. Its incidence in 2018 is estimated at 59,700, with an approximate risk of 56.33 per 100,000 women. In the state of São Paulo, statistics estimated 16.340 new cases of breast cancer in 2018. In the metropolis of São Paulo, the prediction was 5,900 new cases of breast cancer per 100,000 inhabitants, and the risk was approximately 90,41[6].

It is known by the scientific community that certain aspects directly or indirectly affect the progression of breast cancer, the so-called risk factors[7,8].

This article aims to address, briefly, the main risk factors which have been discussed in world literature.

RISK FACTORS

Risk factors for breast cancer incidence include the ones classified as modifiable and non modifiable[7,8]. Modifiable factors are those in which a direct or indirect action becomes possible to minimize the risk of development of the disease, such as obesity, sedentarism, alcohol and 0tobacco consumption, in addition to the use of hormone replacement therapy and, more recently, the administration of hormones with the objective of gender transitioning has been discussed[9]. On the other hand, non-modifiable factors — like family history and hereditary aspects — are the ones on which no action can be taken in order to have a significant impact over the individual[7].

Modifiable factors

Hyperlipidemia and physical activity

The practice of physical activity has been suggested as an important factor to improve life quality in patients with breast cancer, including the protector effect this activity has on reducing the risk of tumor development in the mammary region[8,10]. Lahart et al. conducted a meta-analysis, in which twenty-two prospective cohort studies were chosen to be part of the analysis, with a total of 123,574 participants. The researchers concluded that physical activity is of great importance in reducing mortality among patients affected by the disease, even if the onset of activities occurred after cancer diagnosis[11].

In a recent review, Buss and Dachs gathered works by other authors and presented a proposal regarding the action of hyperlipidemia over breast cancer progression[12]. In fewer words, cholesterol metabolism leads to the production of a metabolite called 27-hydroxicholesterol (27HC) that is able of activating Estrogen Receptors (ER) in mammary cells, inducing their proliferation, or even their acting on the epithelial-mesenchymal transition (EMT), with the activation of Liver X Receptor (LXR). The pathways through which LXR leads to EMT are not clear yet. In addition, cholesterol appears as the protagonist in macrophage recruitment, which in turn, is involved in chronic inflammation and, therefore, in tumorigenesis. The signaling of PI3K/AKT pathway, frequently dysregulated in human cancers, is one of the molecular targets of cholesterol that is directly involved in increasing cellular proliferation. Finally, androgen signaling pathways still lacking study are raised in this review[12].

The physical activity role is suggested as an important factor to decrease the overall levels of cholesterol, fact that implies minimization of the factors discussed above. Furthermore, physical activity is able to improve the immune system, so that defense cells are more effective in recognizing and eliminating the tumoral cell, also contributing to the decrease of insulin 1 growth factor (IGF-1) and to the improvement of IGF 3 binding protein (IGFBP-3). Even though physical exercises act by decreasing the level of body lipids, the high-cholesterol diet is also responsible for the increase and maintenance of lipids bioavailability and, therefore, it is capable of contributing to the risk of development of the disease[12,13].

Diet

The prevention related to eating habits, considering not only mammary tumors, is something that still meets resistance, either from the patient, or from researches that need to go further in the complexity of the subject. Strategies have been adopted to contribute to the reduction of incidence of breast cancer and other comorbidities, emphasizing vegetable sources and fiber intake[8,14].

Adequate intake of fiber and green vegetables, fruits, vegetables, lean proteins and whole grains has been associated with reduced serum levels of estradiol and estrogen and increased sex hormone binding globulin (SHBG)[15]. Estrogen levels are related to susceptibility to breast cancer development[8,16]. On the other hand, meat consumption in general, both red and processed, was related to a higher risk of breast cancer[17].

One of the points discussed about the increase in the incidence of breast cancer cases includes obesity, caused by unbalanced dieting. In the Eastern Mediterranean region, a clear body weight gain in the population was directly related to the number of new cases of cancer in the mammary tissue[18].

Aryl hydrocarbon receptor (AhR) has been identified with strong relation to BRCA1 methylation in triple-negative tumor samples. AhR agonists are found in foods and have been shown

as contributors, increasing the risk of development of the mammary disease, as well as the dietary AhR antagonists provided a preventive effect against breast cancer[19].

Obesity

Obesity is defined as an excessive fat accumulation in tissues, and can be diagnosed when the body mass index (BMI) is ≥30 kg/m^2 [20]. It is a public health problem that affects more than 600 million people worldwide. Developed countries show the highest rates of adults affected by obesity. While the impact of BMI on diabetes and on heart disease is well known, the relation to breast cancer and other human cancers remain a current topic[21,22]. Obesity is an important risk factor to breast cancer development and there is a substantial association with postmenopausal women, as well as worse prognosis for women at all ages[21]. About 9% of cases of women with postmenopausal breast tumors are believed to be affected due to overweight of the patients[8].

Breasts are composed of three special structures: adipose tissue, mammary glands and fibrous tissue. The adipose tissue is subdivided into yellow and brown, being the former able to produce a wide range of metabolites, hormones and cytokines, called adipocytokines[20]. The adipose tissue may also undergo aromatization, leading to the increase of estrogen levels, upregulation of pro-inflammatory cytokines, insulin resistance, hyperactivation of IGF, adipocytes-adipokines derivatives, hypercholesterolemia, and excessive oxidative stress, thus contributing to the development of breast pathology[23,24].

Positive correlations between triple-negative breast cancer and high BMI have been reported, reflecting the importance of obesity control to improve the prognosis of these patients[23].

Alcohol Consumption

Alcohol consumption is associated with the development of a wide range of diseases, including cancer of the colon, rectum, female breast, oral cavity, larynx, pharynx, liver, and esophagus[8,25].

There are multiple cellular mechanisms, promoted by alcohol consumption whose consequence is enhancement in tumoral aggressiveness:

- alcohol metabolism, which produces acetaldehyde, a toxic and carcinogenic substance with affinity to DNA and proteins;
- production of reactive oxygen species, which may favor tumorigenesis based on the oxidation process (oxidative stress);
- reduced absorption performance of important nutrients and vitamins;
- increased serum estrogen levels;
- reduced immune system performance[8,26,27].

Additionally, there may be alterations on the menstrual cycle promoted by the versatile role of alcohol[28].

Exposure to alcohol can help in the promotion of carcinogenesis; even with the existing malignancy, consuming alcohol can contribute to enhance the progression and aggressiveness of existing tumors by promoting cell mobility, EMT and angiogenesis[25,27]. Furthermore, cancer stem-like cells (CSC) are directly influenced by alcohol consumption and may increase their population, which may result in different behaviors of the tumor mass, leading to different therapeutic responses[25,27].

Zakhari and Hoek discuss high and moderate consumption of alcohol, highlighting the importance of the analysis of molecular signatures that can better assess the causal relationships with breast cancer and suggesting different roles based on the levels of consumption[29].

Tobacco Consumption

The use of tobacco is related to the development of numerous pathologies, including lung cancer that represents the leading cause of cancer death worldwide, including both the male and the female population[30]. Regarding breast cancer, studies have demonstrated that not only active smoking, but also passive smoking, can predispose the individual to the risk of developing the disease[8,31].

Among the thousands of chemical products found in tobacco, 69 different compounds are classified as carcinogenic, specifically, the 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Nicotine-derived nitrosamine ketone), considered the most aggressive nitrosamine among the ones present in tobacco[31]. NNK is found in cigars, cigarettes, electronic cigarettes, tobacco and in the smoke from these products, causing nitrosamines to affect not only the consumer, but also non-smokers or passive smokers exposed to environmental tobacco pollution[31]. On the other hand, environmental exposure to tobacco was criticized, and a meta-analysis published by Lee and Hamling assessed 47 studies. A weak association between non-smoking women and breast cancer development and stratified results were observed, having higher association in Asian than in European countries[32].

Gaudet et al., aiming at defusing the controversy between tobacco smoking and breast cancer risk, performed a meta-analysis in which the data of 73,388 women were analyzed. The work showed that active smoking is significantly associated to the risk of breast cancer development in women that began tobacco consumption before their first childbirth. Moreover, the authors discuss the role that tobacco may play on tumor initiation[33].

Hormone replacement therapy (HRT)

Hormone replacement therapy (HRT) is a procedure to relieve the climacteric symptoms of menopause and its applicability has decreased after studies linking it to the increased risk of developing breast cancer[34]. The use of HRT was associated to lobular breast cancer, positive ER and low level, concerning its immunohistochemical characteristics[34,35].

Wang et al. analyzed prospective cohort studies and case control studies evaluating HRT users. Among the observed variables and

in order to identify the dose relationship, the time of use and the abandonment of HRT use were considered. The authors concluded that HRT application was associated with he risk of breast cancer[35].

Non-Modifiable Factor

Family history

Brewer et al. conducted a study aiming at analyzing the relation between family history and the risk of developing breast cancer. A score was assigned to this relation and a significant connection was found to those who reported a family history of female breast cancer[36]. Haber et al. observed a significant association not only in relation to first-degree relatives with breast cancer and women with breast cancer, but they could also verify the significant risk that first-degree relatives with any other kind of cancer could exert on women with breast cancer[37].

Early menarche and late menopause

Menarche is the first menstrual bleeding of a woman, while menopause is the period in which ovaries stop producing reproductive hormones. This period between menarche and the menopause is a hypothesis of risk of breast cancer, consequence of mitotic activity of mammary cells, driven by estrogen and progesterone exposure, during the luteal phase of the menstrual cycle[38].

Hereditary predisposition

In addition to the factors described above, numerous germ-line mutations are related to hereditary predisposition to breast cancer, among them are noteworthy the mutations in genes p53, BRCA1 and BRCA2 (breast cancer susceptibility 1 and 2), responsible for conferring high risk. Other genes that can undergo mutations are CHEK2 (Checkpoint Kinase 2), PTEN (Phosphatase and tensin homolog), PALB2 (Partner and localizer of BRCA2), RAD51C (S. cerevisiae, homolog of C), CDH1 (cadherin 1) PPM1D (Protein phosphatase, Mg2+/Mn2+ dependent 1D) and genes that determine Lynch syndrome that pose moderate to high risk[39–41]. Furthermore, more than 90 other common low penetrance variants are mentioned[42].

Breast cancers of hereditary origin are different from the ones of somatic origin not only concerning the mutations involved but also regarding the pathological characteristics, being more aggressive and with a worse prognosis, besides affecting younger women[41].

Mutations on genes BRCA1 and BRCA2 constitute major susceptibility genes for the development of ovarian and breast cancer[43]. However, only 10% of the predisposed families present some mutation in the coding regions of these genes[43]. Thereby, efforts have been performed trying to identify mutations in non-coding regions, and in relation to the action of associated epigenetic factors — as well as the activity of non-coding RNAs, like the microRNAs (miRNAs) — involved in the process of gene silencing and in the role of long non-coding RNA (lncRNAs), both in BRCA1 and BRCA2, as well as in a variety of other related genes[43-46].

CONCLUSION

Breast cancer is a multifactorial disease. Scientific advances in understanding tumor appearance and behavior have provided effective tools for prevention, treatment, and aftercare.

Nevertheless, epidemiological and *in vivo* studies are still necessary to better understand the mechanism of intra- and extracellular action modulated by exposure to the risk factors described in this study and, consequently, to resolve the contradictions found in the meta-analyses and reviews referred to herein.

REFERENCES

1. Ghoncheh M, Mahdavifar N, Darvishi E, Salehiniya H. Epidemiology, Incidence and Mortality of Breast Cancer in Asia. Asian Pacific J Cancer Prev [Internet]. 2016 [accessed on December 19, 2018];17(Supl. 3):47-52. Available on: http://koreascience.or.kr/journal/view.jsp?kj=POCPA9&py=2016&vnc=v17nsup3&sp=47 https://doi.org/10.7314/APJCP.2016.17.S3.47

2. American Cancer Society. Cancer Facts and Figures 2018. United States: American Cancer Society; 2018.

3. Medimegh I, Omrane I, Privat M, Uhrhummer N, Ayari H, Belaiba F, et al. MicroRNAs expression in triple negative vs non triple negative breast cancer in Tunisia: Interaction with clinical outcome. PLoS One [Internet]. 2014 [accessed on December 22, 2018];9(11): e111877. Available on: http://www.ncbi.nlm.nih.gov/pubmed/25369070 https://doi.org/10.1371/journal.pone.0111877

4. Global Cancer Observatory. All Cancers. Globocan. 2018.

5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492

6. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2018. Brazil: Ministério da Saúde/Instituto Nacional de Câncer José Alencar Gomes da Silva; 2018.

7. Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis [Internet]. 2018 [accessed on December 22, 2018];5(2):77-106. Available on: http://www.ncbi.nlm.nih.gov/pubmed/30258937 https://doi.org/10.1016/j.gendis.2018.05.001

8. Guerrero VG, Baez AF, González CGC, González CGM. Monitoring modifiable risk factors for breast cancer: an obligation for health professionals. Rev Panam Salud Publica [Internet]. 2017 [accessed on December 22, 2018];41:e80. Available on: http://www.ncbi.nlm.nih.gov/pubmed/28614486

9. Nikolić D, Granić M, Ivanović N, Zdravković D, Nikolić A, Stanimirović V, et al. Breast cancer and its impact in male transsexuals. Breast Cancer Res Treat [Internet]. 2018 [accessed on December 22, 2018];171(3):565-9. Available on: http://link.springer.com/10.1007/s10549-018-4875-y https://doi.org/10.1007/s10549-018-4875-y

10. Schmidt T, Van Mackelenbergh M, Wesch D, Mundhenke C. Physical activity influences the immune system of breast cancer patients. J Cancer Res Ther [Internet]. 2017 [accessed on December 22, 2018];13(3):392-8. Available on: http://www.ncbi.nlm.nih.gov/pubmed/28862198 https://doi.org/10.4103/0973-1482.150356

11. Lahart IM, Metsios GS, Nevill AM, Carmichael AR. Physical activity, risk of death and recurrence in breast cancer survivors: A systematic review and meta-analysis of epidemiological studies. Acta Oncologica [Internet]. 2015 [accessed on December 22, 2018];54(5):635-54. Available on: http://www.tandfonline.com/doi/full/10.3109/0284186X.2014.998275 https://doi.org/10.3109/0284186X.2014.998275

12. Buss LA, Dachs GU. The Role of Exercise and Hyperlipidaemia in Breast Cancer Progression. Exerc Immunol Rev [Internet]. 2018 [accessed on February 16, 2019];24:10-25. Available on: http://www.ncbi.nlm.nih.gov/pubmed/29461968

13. Adraskela K, Veisaki E, Koutsilieris M, Philippou A. Physical Exercise Positively Influences Breast Cancer Evolution. Clin Breast Cancer [Internet]. 2017 [accessed on February 16, 2019];17(6):408-17. Available on: http://www.ncbi.nlm.nih.gov/pubmed/28606800 https://doi.org/10.1016/j.clbc.2017.05.003

14. LoConte NK, Gershenwald JE, Thomson CA, Crane TE, Harmon GE, Rechis R. Lifestyle Modifications and Policy Implications for Primary and Secondary Cancer Prevention: Diet, Exercise, Sun Safety, and Alcohol Reduction. Am Soc Clin Oncol Educ B [Internet]. 2018 [accessed on December 22, 2018];38:88-100. Available on: http://www.ncbi.nlm.nih.gov/pubmed/30231343 https://doi.org/10.1200/EDBK_200093

15. Dandamudi A, Tommie J, Nommsen-Rivers L, Couch S. Dietary Patterns and Breast Cancer Risk: A Systematic Review. Anticancer Res [Internet]. 2018 [accessed on December 24, 2018];38(6):3209-22. Available on: http://www.ncbi.nlm.nih.gov/pubmed/29848668 https://doi.org/10.21873/anticanres.12586

16. Ortega JAF. Cáncer de mama y dieta: revisión. Univ Salud [Internet]. 2010 [accessed on December 24, 2018];12(1):120-34. Available on: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0124-71072010000100014

17. Wu J, Zeng R, Huang J, Li X, Zhang J, Ho JCM, et al. Dietary protein sources and incidence of breast cancer: A dose-response meta-analysis of prospective studies. Nutrients [Internet]. 2016 [accessed on December 24, 2018];8(11). Available on: http://www.ncbi.nlm.nih.gov/pubmed/27869663 https://doi.org/10.3390/nu8110730

18. Taha Z, Eltom SE. The Role of Diet and Lifestyle in Women with Breast Cancer: An Update Review of Related Research in the Middle East. Biores Open Access [Internet]. 2018 [accessed on December 24, 2018];7(1):73-80. Available on: http://www.ncbi.nlm.nih.gov/pubmed/29862141 https://doi.org/10.1089/biores.2018.0004

19. Donovan MG, Selmin OI, Romagnolo DF. Aryl Hydrocarbon Receptor Diet and Breast Cancer Risk. Yale J Biol Med [Internet]. 2018 [accessed on December 24, 2018];91(2):105-27. Available on: http://www.ncbi.nlm.nih.gov/pubmed/29962921

20. Li J, Han X. Adipocytokines and breast cancer. Curr Problems Cancer [Internet]. 2018 [accessed on December 26, 2018];42(2):208-14. Available on: https://www.sciencedirect.com/science/article/pii/S0147027217301216?via%3Dihub https://doi.org/10.1016/j.currproblcancer.2018.01.004

21. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. CA Cancer J Clin [Internet]. 2017 [accessed on December 24, 2018];67(5):378-97. Available on: http://www.ncbi.nlm.nih.gov/pubmed/28763097 https://doi.org/10.3322/caac.21405

22. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and Cancer Risk: Emerging biological mechanisms and perspectives. Metabolism [Internet]. 2018 [accessed on December 26, 2018];92:121-35. Available on: http://www.ncbi.nlm.nih.gov/pubmed/30445141 https://doi.org/10.1016/j.metabol.2018.11.001

23. Engin A. Obesity-associated breast cancer: Analysis of risk factors. In: Engin A, Engin A (eds.). Obesity and lipotoxicity. Advances in Experimental Medicine and Biology [Internet]. Springer; 2017 [accessed on December 24, 2018]. p. 571-606. Available on: http://link.springer.com/10.1007/978-3-319-48382-5_25 https://doi.org/10.1007/978-3-319-48382-5_25

24. Blücher C, Stadler SC. Obesity and breast cancer: Current insights on the role of fatty acids and lipid metabolism in promoting breast cancer growth and progression. Front Endocrinol [Internet]. 2017 [accessed on December 26, 2018];8:293. Available on: http://www.ncbi.nlm.nih.gov/pubmed/29163362 https://doi.org/10.3389/fendo.2017.00293

25. Xu M, Luo J. Alcohol and cancer stem cells. Cancers [Internet]. 2017 [accessed on December 26, 2018];9(11). Available on: http://www.ncbi.nlm.nih.gov/pubmed/29156633 https://doi.org/10.3390/cancers9110158

26. Castro GD, Castro JA. Alcohol drinking and mammary cancer: Pathogenesis and potential dietary preventive alternatives. World J Clin Oncol [Internet]. 2014 [accessed on December 26, 2018];5(4):713-29. Available on: http://www.ncbi.nlm.nih.gov/pubmed/25300769 https://doi.org/10.5306/wjco.v5.i4.713

27. Wang Y, Xu M, Ke ZJ, Luo J. Cellular and molecular mechanisms underlying alcohol-induced aggressiveness of breast cancer. Pharmacol Res [Internet]. 2017 [accessed on December 26, 2018];115:299-308. Available on: http://www.ncbi.nlm.nih.gov/pubmed/27939360 https://doi.org/10.1016/j.phrs.2016.12.005

28. Kolak A, Kamićska M, Sygit K, Budny A, Surdyka D, Kukiełka-Budny B, et al. Primary and secondary prevention of breast cancer. Ann Agric Environ Med [Internet]. 2017 [accessed on December 26, 2018];24(4):549-53. Available on: http://www.journalssystem.com/aaem/Primary-and-secondary-prevention-of-breast-cancer,75943,0,2.html https://doi.org/10.26444/aaem/75943

29. Zakhari S, Hoek JB. Epidemiology of moderate alcohol consumption and breast cancer: Association or causation? Cancers [Internet]. 2018 [accessed on December 26, 2018];10(10). Available on: http://www.ncbi.nlm.nih.gov/pubmed/30249004 https://doi.org/10.3390/cancers10100349

30. Pinsky PF. Lung cancer screening with low-dose CT: a worldwide view. Transl Lung Cancer Res [Internet]. 2018 [accessed on December 26, 2018];7(3):234-42. Available on: http://www.ncbi.nlm.nih.gov/pubmed/30050762 https://doi.org/10.21037/tlcr.2018.05.12

31. Gankhuyag N, Lee KH, Cho JY. The Role of Nitrosamine (NNK) in Breast Cancer Carcinogenesis [Internet]. J Mammary Gland Biol Neoplasia. 2017 [accessed on December 26, 2018];22(3):159-70. Available on: http://www.ncbi.nlm.nih.gov/pubmed/28664511 https://doi.org/10.1007/s10911-017-9381-z

32. Lee PN, Hamling JS. Environmental tobacco smoke exposure and risk of breast cancer in nonsmoking women. An updated review and meta-analysis. Inhal Toxicol [Internet]. 2016 [accessed on December 26, 2018];28(10):431-54. Available on: http://www.ncbi.nlm.nih.gov/pubmed/27541291 https://doi.org/10.1080/08958378.2016.1210701

33. Gaudet MM, Gapstur SM, Sun J, Ryan Diver W, Hannan LM, Thun MJ. Active smoking and breast cancer risk: Original cohort data and meta-analysis. J Nat Cancer Institute [Internet]. 2013 [accessed on December 26, 2018];105(8):515-25. Available on: https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/djt023 https://doi.org/10.1093/jnci/djt023

34. Narod SA. Hormone replacement therapy and the risk of breast cancer. Nature Rev Clin Oncol [Internet]. 2011 [accessed on December 26, 2018];8:669-76. Available on: http://www.nature.com/articles/nrclinonc.2011.110

35. Wang K, Li F, Chen L, Lai Y-M, Zhang X, Li H-Y. Change in risk of breast cancer after receiving hormone replacement therapy by considering effect-modifiers: a systematic review and dose-response meta-analysis of prospective studies. Oncotarget [Internet]. 2017 [accessed on December 26, 2018];8(46):81109-24. Available on: http://www.ncbi.nlm.nih.gov/pubmed/29113371 https://doi.org/10.18632/oncotarget.20154

36. Brewer HR, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. Family history and risk of breast cancer: an analysis accounting for family structure. Breast Cancer Res Treat [Internet]. 2017 [accessed on December 28, 2018];165:193-200. Available on: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5511313/pdf/10549_2017_Article_4325.pdf http://dx.doi.org/10.1007/s10549-017-4325-2

37. Haber G, Ahmed NU, Pekovic V. Family history of cancer and its association with breast cancer risk perception and repeat mammography. Am J Public Health [Internet]. 2012 [accessed on December 28, 2018];102(12):2322-9. Available on: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3519312/pdf/AJPH.2012.300786.pdf

38. Chang-Claude J, Andrieu N, Rookus M, Brohet R, Antoniou AC, Peock S, et al. Age at menarche and menopause and breast cancer risk in the International BRCA1/2 Carrier Cohort Study. Cancer Epidemiol Biomarkers Prev [Internet]. 2007 [accessed on December 28, 2018];16(4):740-6. Available on: http://cebp.aacrjournals.org/content/16/4/740.full-text.pdf http://dx.doi.org/10.1158/1055-9965.EPI-06-0829

39. Mavaddat N, Antoniou AC, Easton DF, Garcia-Closas M. Genetic susceptibility to breast cancer. Mol Oncol [Internet]. 2010 [accessed on January 8, 2019];4(3):174-91. Available on: http://www.ncbi.nlm.nih.gov/pubmed/20542480 https://doi.org/10.1016/j.molonc.2010.04.011

40. Rudolph A, Chang-Claude J, Schmidt MK. Gene-environment interaction and risk of breast cancer. Brit J Cancer [Internet]. 2016 [accessed on January 8, 2019];114(2):125-33. Available on: https://doi.org/10.1038/bjc.2015.439

41. Mahdavi M, Nassiri M, Kooshyar MM, Vakili-Azghandi M, Avan A, Sandry R, et al. Hereditary breast cancer; Genetic penetrance and current status with BRCA. J Cell Physiol [Internet]. 2019 [accessed on January 8, 2019];234(5):5741-50. Available on: http://www.ncbi.nlm.nih.gov/pubmed/30552672 https://doi.org/10.1002/jcp.27464

42. Michailidou K, Beesley J, Lindstrom S, Canisius S, Dennis J, Lush MJ, et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet [Internet]. 2015 [accessed on January 8, 2019];47(4):373-80. Available on: http://www.ncbi.nlm.nih.gov/pubmed/25751625 https://doi.org/10.1038/ng.3242

43. Santana dos Santos E, Lallemand F, Burke L, Stoppa-Lyonnet D, Brown M, Caputo S, et al. Non-Coding Variants in BRCA1 and BRCA2 Genes: Potential Impact on Breast and Ovarian Cancer Predisposition. Cancers (Basel) [Internet]. 2018 [accessed on January 8, 2019];10(11). Available on: http://www.ncbi.nlm.nih.gov/pubmed/30453575 https://doi.org/10.3390/cancers10110453

44. Davalos V, Martinez-Cardus A, Esteller M. The Epigenomic Revolution in Breast Cancer: From Single-Gene to Genome-Wide Next-Generation Approaches. Am J Pathol [Internet]. 2017 [accessed on January 8, 2019];187(10):2163-74. Available on: http://www.ncbi.nlm.nih.gov/pubmed/28734945 https://doi.org/10.1016/j.ajpath.2017.07.002

45. Karsli-Ceppioglu S, Dagdemir A, Judes G, Ngollo M, Penault-Llorca F, Pajon A, et al. Epigenetic mechanisms of breast cancer: An update of the current knowledge. Epigenomics [Internet]. 2014 [accessed on January 8, 2019];6(6):651-64. Available on: http://www.ncbi.nlm.nih.gov/pubmed/25531258 https://doi.org/10.2217/epi.14.59

46. Klinge C. Non-Coding RNAs in Breast Cancer: Intracellular and Intercellular Communication. Non-Coding RNA [Internet]. 2018 [accessed on January 8, 2019];4(4). Available on: http://www.ncbi.nlm.nih.gov/pubmed/30545127 https://doi.org/10.3390/ncrna4040040