



Update on the Major Aspects Related to Breast Cancer

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ABSTRACT

This article is about a partnership of researchers with the Academic League of Oncology of Pará - LAOPA, its objective is to provide a brief exploration, on scientific articles and publications between the years 2010 and 2017, of the general aspects of cancer from a contemporary perspective. The justification lies in the need to deal with cancer-related issues, in this case breast cancer, seeking recognition about possible novelties on the subject, since even with all the subsidies for effective treatment, it still remains a disease with increasing annually. In the conclusion, it is observed that revisiting this theme becomes fundamental not only for academics and professionals, but also for the community in general, in order to serve as a tool for awareness, and actions taken.

Key Words: Breast Cancer, Breast Cancer, Public Health.

1. INTRODUCTION

Breast cancer is the type of cancer that affects women the world over in developing and developed countries¹ and is considered a major public health problem.²

Like other malignant neoplasms, it is due to uncontrollable proliferation of atypical or abnormal cells, which derive from hereditary or acquired genetic alterations due to exposure to environmental and / or physiological risk factors. Thus, genetic alterations cause changes in cell growth and programmed cell death, which leads to tumor formation. Because it forms such a heterogeneous group, breast cancer has different behaviors in relation to genetics, morphology, clinical presentation and therapeutic response.²

Despite being considered a relatively good prognosis cancer, if it has an early diagnosis and treatment, mortality rates are still high in Brazil, mainly due to the late diagnosis that already shows advanced cancer.¹

The increase in the number of cases alerts to the severity and magnitude of the problem. Breast cancer forms a great set of challenges to health policies and, therefore, requires implementation of programs and actions aimed at the promotion, prevention, treatment and control of the disease.³

2. EPIDEMIOLOGY

The incidence of breast cancer is increasing worldwide as a result of increased life expectancy, increased urbanization, and the adoption of Western living habits.⁴ It is the second most common cancer in the world and the most common in women with an estimated 1.67 million new cases diagnosed in 2012 (25% of all cancers in women). It is the fifth leading cause of death for all cancers⁵ and in 2012 was responsible for about 520,000 deaths among women in the world.¹

For Brazil, in 2014, more than 57 thousand new cases of female breast cancer were expected, an estimated risk of 56.09 cases per 100,000 women. Without considering non-melanoma skin cancer, breast cancer is the most frequent in women in the Southeast, South, Center-West and Northeast. In the North Region it is the second most incident tumor, with 21.29 cases in every 100 thousand milheres.¹

More than 80% of breast cancers originate from the ductal epithelium. Survival is increasing in developed countries, currently 85% in 5 years, and in developing countries by 50-60% in 5 years.¹

3. RISK AND PREVENTION FACTORS

3.1 Risk factors

The main known risk factors for breast cancer are related to age, genetic and endocrine factors.²

Age is the most important risk factor, since the risk of breast cancer increases with age, about 70-80% of tumors diagnosed after the fifth decade of life⁶ and mortality also increases as the disease progresses of age.²

Endocrine factors are mainly related to the estrogenic, endogenous or exogenous stimulus, with an

increased risk the longer the exposure time to this hormone. Thus, women with a history of early menarche (first menstruation before 12 years), late menopause (after 50 years), first pregnancy after 30 years and nulliparity are at greater risk. The evidence linking the use of oral contraceptives with breast cancer is still conflicting and controversial.^{2,3}

Family history and the early age at diagnosis (less than 50 years) may indicate genetic predisposition associated with the mutation of certain genes (such as BRCA1, BRCA2 and p53), but hereditary breast cancer corresponds to 5 to 10% of all cases.⁷ Family history is very important when you have one or more first-degree relatives (mother or sister) who had breast cancer before the age of 50.³ The risk is two to three times higher for to develop this neoplasm in cases of genetic predisposition.^{1,4}

Other risk factors include exposure to ionizing radiation at age 40, irregular alcohol intake (even in moderate amounts - 30g / day), obesity (especially after menopause), and sedentary lifestyle. Smoking is not considered a risk factor for breast cancer.² Breastfeeding, healthy eating with optimal weight maintenance, and physical exercise are associated with a lower risk of breast cancer.¹

According to the 2004 Breast Cancer Consensus Document, there are very high-risk groups for developing breast cancer^r:

- Women with a family history of at least one first-degree relative (mother, sister or daughter) have a diagnosis of breast cancer under the age of 50;
- Women with a family history of at least one first-degree relative diagnosed with bilateral breast cancer or ovarian cancer in any age group;
- Women with histopathological diagnosis of proliferative mammary lesion with atypia or lobular neoplasm *in situ*;
- Women with a family history of male breast cancer.

3.2 Health Promotion and Prevention

Primary prevention of breast cancer is a very promising research and intervention scenario.¹

For the prevention and control of breast cancer, intersectorial actions capable of promoting greater access to information and creating opportunities to increase, for example, body weight control and encourage the regular practice of physical exercise are of great importance.²

In particular, it is necessary to increase the access of the population to the correct and clear information, as well as culturally appropriate. This need should be at the initiative of the health services at all levels of care, especially in basic care.²

Primary prevention is based on the control of modifiable risk factors for breast cancer. Scientific evidence shows a relative risk reduction of about 4.3% every 12 months of breastfeeding² and^d that around 30% of breast cancers are avoidable, adopting healthy habits of life.¹

Prophylactic mastectomy has been researched as a form of prevention for women at high risk for breast cancer. However, evidence of decreased incidence and mortality after bilateral mastectomy is very limited. Evidence exists that are insufficient to prove increased survival in women who perform prophylactic contralateral mastectomy with a personal history of breast cancer.²

Although it contributes to risk reduction, prevention strategies can not eliminate most breast cancers, especially when the diagnosis of the disease is advanced. Thus, early detection to improve prognosis and survival continues to be a great way to control breast cancer.⁴

Among the early detection strategies are: recognition of early signs and symptoms of the disease and results of clinical breast exploration.⁴ Screening with the Mammography Examination is the public health strategy that has been adopted in scenarios where the incidence and mortality from breast cancer are high. Countries that adopted effective screening programs had the tendency to reduce mortality due to this neoplasm. Results of randomized clinical trials have shown that, when mammography is offered to women aged 50-69 years, every two years, with coverage greater than or equal to 70% of the target population, mortality can be reduced by 15% to 23% .⁸

4. Diagnosis

The diagnosis of breast cancer is based on the clinical observations through the Clinical Breast Examination and the imaging examinations.

In this context, the Clinical Examination of Mamas in the diagnostic investigation is the procedure that aims to perform the differential diagnosis between suspicious changes of Cancer and those related to benign conditions. This consists of static inspection, dynamic inspection, palpation and expression of the breasts, together with the palpation of the lymph node chains, mainly axillary and supraclavicular. It also has the function of complementing the breast health alert policy as a method of early diagnosis.²

Imaging tests are indicated for screening and diagnosis. In the screening, they aim at the early detection of breast cancer, allowing a less invasive treatment, as well as the improvement in the quality of life and reduction in morbimortality rates. For diagnostic purposes, the imaging tests are used to confirm or not the suspicion of cancer from the signs referred by the patient or detected in the clinical evaluation. In these cases, the main tests used are Mammography, Ultrasonography and Magnetic Resonance.^{2,9}

The use of imaging tests has enabled the detection of non-palpable lesions in the breast, however, frequently, it does not allow differentiation between benign and malignant lesions due to the significant overlap of findings between them. Therefore, biopsy is indicated for many non-palpable lesions identified by imaging methods, especially mammography screening.¹⁰

If there are suspicious lesions in the ultrasound and mammographic examinations, the confirmation of the diagnosis, which may be cytological, by fine needle aspiration (FNA) or histological examination, should be sought when the material is obtained by puncture using a needle (PAG) or conventional surgical biopsy. The FNAB is an outpatient procedure, accessible, easy to perform and rarely presents complications, which allows the cytological diagnosis of the lesions. This does not require the use of anesthesia⁹

Core biopsy or PAG is also an outpatient procedure, carried out under local anesthesia, which provides material for histopathological diagnosis, allowing the dosage of hormonal receptors. In palpable lesions with negative imaging (mammography and ultrasonography), the investigation should be continued with FNAB, PAG or surgical biopsy.

In non-palpable lesions, surgical biopsy should be preceded by marking (MPC pre-surgical marking), which can be guided by X-rays (free hand, biplanar or stereotaxic) or by ultrasonography. Surgical biopsy is also indicated in cases of scar radial histopathology, *atypical* hyperplasia, carcinoma *in situ*, *microinvasive* carcinoma and inappropriate material, when the biopsy is performed on material obtained by PAG or mamot^{omy}.

5. Carcinogenesis

Hereditary breast cancer accounts for approximately 12% of cases. Mutation in the BRCA1 and BRCA2 genes are responsible for the majority of cancers attributed to single mutations and about 3% of all breast cancers. Genetic alterations in BRCA1 also increase the risk of developing ovarian carcinoma, whereas mutations in BRCA2 are more associated with male breast cancer. Other known genes are less commonly implicated and together account for less than 10% of hereditary mammary carcinomas.¹¹

Li-Fraumeni syndrome (due to germline mutations in p53) and variant Li-Fraumeni syndromes (germline mutations in CHEK2) together account for about 8% of breast cancers caused by single genes. The tumor suppressor genes PTEN, LKBI / STK11 and ATM, are mutated in less than 1% of all breast cancers.¹¹

Traditionally, estrogen (ER) and progesterone (PR) receptors are known to be prominent elements in the progression and development of breast cancer, but they also play a significant role in the development of normal mammary glands.¹² Breast^t tumors of subtypes luminals are characterized by ER expression and represent a heterogeneous category in terms of gene expression, being composed of mutations mainly in ESR1, GATA3, FOXA1, XBP1 and cMYB. The most common mutations in the luminal A subtype are PIK3CA (45%), MAP3K1 and GATA3 (13% each), TP53 (12%), and CDH1 (9%). The most common mutations in luminal B-type tumors are TP53 and PIK3CA (29% each), GATA3 (13%), and TTN (12%).¹

The PI3K / AKT / mTOR pathway and its interference with the RAS / RAF / MEK / MAPK pathway play a crucial role in neoplastic cell growth, survival, differentiation, and proliferation. In addition, the PI3K / AKT / mTOR pathway participates in the control of the cellular complex related to energy generation, glucose metabolism, senescence and angiogenesis, and act on ER-positive cell transcription. The protein kinases involved in these pathways represent attractive and promising drug targets for the treatment of Breast Cancer.¹³

The HER2 positive subtype represents 20% to 25% of all breast cancers, and they exhibit overexpression of the HER2 protein. Within this group, about 50% of HER2-positive tumors clinically express the HER2 enriched mRNA subtype, while the remainder predominantly expresses the luminal mRNA subtype. HER2-enriched tumors show significantly greater expression of various receptor tyrosine kinases, including FGFR4, epidermal growth factor (EGFR), and HER2 (80%) itself. In the triple-negative subtype, the major mutations involve the TP53, p21 PTEN, CHK1, CHK2, PARP-1 and BRCA1.¹³ genes^{es}

Histological Types

a) Invasive Ductal Carcinoma: This is the most common type of breast cancer, accounting for about 80% of cases. Invasive ductal carcinoma begins in a milk duct, ruptures the wall of this duct, and grows in adipose tissue of the breast. Thereafter, it may undergo metastasis to other parts of the body through the lymphatic system and the bloodstream.

b) Invasive Lobular Carcinoma: It is the second most common type of invasive breast cancer, representing approximately 10% of the cases. Invasive lobular carcinoma is born in the mammary lobes (local milk production). It has the ability to invade other tissues and grow locally or spread through the veins and lymphatic vessels. This cancer has to be characterized by the presence and amount of hormone receptors (estrogen receptor and progesterone) on the surface of the cells, as well as the degree of Her-2 protein expression (there is rarely an increase in expression). This characterization is done by the technique called immunohistochemistry.

c) Inflammatory Breast Carcinoma: Inflammatory breast cancer is a rare (1 - 3%), yet more aggressive presentation of cancer. Some signs are: redness and swelling of the skin of the breast, local temperature increase, often without a palpable mass or nodule, nipple may be inverted, and often the axillary nodes in the armpit may increase in size. This cancer usually occurs in younger women. Inflammatory carcinoma also has to be characterized as to the presence and amount of hormonal (usually negative) receptors on the cell surface, as well as the degree of Her-2 protein expression.

d) Triple-negative breast carcinoma: they are cancers with negative estrogen and progesterone receptors and HER2 also negative, which tend to spread more rapidly than the other types. This type of cancer is more common in young and black women.

Other histological types also exist are carcinomas: medullary, mucinous, tubular, intraductal, papilliferous, apocrine, cribriform and secretory.

5.1 Molecular subtypes

a) Luminal A: is characterized by the receptor phenotype, estrogen and progesterone, positive and HER2 negative. In addition, it is also characterized by the high expression of genes represented by luminal epithelial cells, such as cytokeratins 7, 8, 18 and 19. This phenotype is associated with better prognosis and responds to hormonal therapy (antiestrogens).

b) Luminal B: is characterized by the receptor phenotype, estrogen and progesterone, positive and HER2 positive. In addition, it is also characterized by low or moderate expression of genes expressed by luminal epithelial cells, such as cytokeratins 7, 8, 18 and 19. This phenotype is associated with a worse prognosis, being particularly related to the tumor recurrence, since it presents possible similarities with negative receptor tumors (subtypes with HER2 and basal overexpression).

c) Her-2 overexpression: it is characterized by the receptor, estrogen and progesterone, negative and HER2-positive phenotype. In addition, it is also characterized by the overexpression of one of the molecules of the epidermal growth factor receptor family, HER2. HER2 oncogene amplification and overexpression of its protein, is currently implicated as an important prognostic biomarker in breast carcinoma, since they have good responses to drugs that block the activity of HER2, such as the monoclonal antibody trastuzumab.

Other molecular subtypes are: hybrid luminal and basal-like.

6. Treatment

The treatment for breast cancer should be given by a multidisciplinary team aiming at the integral treatment of the patient. Therapeutic modalities are surgery and radiotherapy for locoregional treatment and chemotherapy and hormone therapy for systemic treatment.

the surgery:

Conservative: should always be followed by adjuvant radiotherapy and sentinel lymph node biopsy and / or axillary lymphadenectomy. The procedures that may be indicated are: 1. Quadrantectomy (may lead to aesthetic deformation); 2. Tumorectomy (difficult to remove oncologically satisfactory margins); 3. Segmentectomy or Segmental Resection (most used). Some contraindications for the indication of conservative surgery in carriers of operable breast carcinomas are: pregnancy of first and second trimesters; multicentric disease; history of anterior thoracic radiotherapy; personal history of collagen disease.

Non - conservative: The procedures that may be indicated are: 1. Skin preservative mastectomy (indicated for patients who are not candidates for conservative surgery and / or radiotherapy, who do not present cutaneous involvement, and those who, by their own choice, prefer to withdraw from the breast); 2. Therapeutic mammary adenectomy or subcutaneous mastectomy (indicated in patients with no indication of conservative surgery that necessarily meets the criteria: single or multiple tumors less than 2 cm, tumors more than 2.5 cm apart from the areola-papillary complex, intra- operative of the areolopapillary margin, by the service of pathological anatomy negative for neoplasia. Simple or total mastectomy (indicated in cases in which mastectomy and sentinel lymph node biopsy are indicated); 4. Radical mastectomy (indicated in invasive carcinomas more than 3 cm in diameter).

b) Radiotherapy: After conservative surgery, the entire breast of patients submitted to this type of surgery should be irradiated, regardless of histological type, age, use of chemotherapy and / or hormone therapy and even with surgical margins free of neoplastic involvement.

c) Neoadjuvant chemotherapy: aims to reduce tumor volume making tumors unresectable in resectable, and / or enabling conservative surgery in tumors initially candidates for radical mastectomy.

d) Adjuvant chemotherapy: Adjuvant chemotherapy should be recommended, in the absence of metastatic disease, in patients with positive lymph nodes and in those with negative lymph nodes when patients with tumors greater than 1 cm should be considered in patients less than 40 years of age (tumors ranging from 0.6 cm to 1.0 cm and with angiolymphatic invasion, or HER2-positive or 3-nuclear HER-2 + 3 + HER +, as well as high risk patients, which has been rapidly changing with the emergence of new "molecular targets".

e) Adjuvant hormone therapy: used in patients with hormone receptor positive, being the benefit observed in patients pre or postmenopausal, with or without the use of chemotherapy.

FINAL CONSIDERATIONS

In summary, after the presentation of relevant information regarding breast cancer, the Academic League of Oncology of Pará - LAOPA wishes to have achieved the noble objective of empowering the academic about the magnitude of this health problem that unfortunately has its outstanding growth statistics around the world. It is up to us, researchers and scholars in the area of health, dedication to women's health, applying the knowledge for appropriate diagnoses and treatments, as well as the responsibility of educating and guiding the population for effective health promotion and prevention, which are essential to lower incidence and better management of breast cancer.

References

- 1-Ministry of Health. National Institute of Cancer José Alencar Gomes da Silva. Coordination of Prevention and Surveillance[Internet]. Estimate 2014: incidence of cancer in Brazil. Rio de Janeiro: INCA; 2014[acesso em 2015 jun 9]. Available at: <<http://www.inca.gov.br/estimativa/2014/estimativa-24042014.pdf>>.
- 2-Ministry of Health. Secretariat of Health Care. Department of Basic Attention. Control of cancers of the cervix and breast. Brasília: Ministry of Health; 2013. 122 p. (Notebooks of Basic Attention n. 13);
- 3-Santos J, Gico VV, Reis LA, Marino TTA. Breast cancer overview - indicators for health policy in Brazil. Journal of Contemporary Nursing. 2014; 3 (1): 80-94.
- 4-World Health Organization. Breast cancer: prevention and control. 2015[acesso em 2015 jun 9]. Available at: <http://www.who.int/topics/cancer/breastcancer/en/>.
- 5-International Agency for Research on Cancer. World Health Organization[Internet]. GLOBOCAN 2012: estimated cancer incidence, and mortality and prevalence worldwide in 2012: cancer fact sheets. Lyon: IARC; 2013[acesso em 2015 jun 9]. Available at: <http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx#>.
- 6-Cancer Research UK. Breast cancer incidence statistics: breast cancer incidence by age (females). 2011[acesso em 2015 jun 9]. Available at <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-One>.
- 7-Adami H, Hunter D, Trichopoulos D, eds. Textbook of Cancer Epidemiology. 2. ed. New York: Oxford University Press, 2008. Apud Brasil. Ministry of Health. Secretariat of Health Care. Department of Basic Attention. Control of cancers of the cervix and breast. Brasília: Ministry of Health; 2013. 122 p. (Notebooks of Basic Attention n. 13).
- 8-US Preventive Services Task Force. Screening for breast cancer: an update for the U.S. : preventive services task force. Annals of International Medicine; 44 (15): 2118-2121. Apud Brasil. Ministry of Health. Secretariat of Health Care. Department of Basic Attention. Control of cancers of the cervix and breast. Brasília: Ministry of Health; 2013. 122 p. (Notebooks of Basic Attention n. 13).
- 9-Municipal Health Secretariat. Women's health program. Protocol of integral attention to women's health. Florianópolis: Ed. Copiart, 2010.

- 10-Ministry of Health. Breast cancer control: consensus document. Rio de Janeiro: Inca. 2004.
- 11-Kumar, V; Abbas, A K; Fausto, N. **Robbins & Cotran: Pathology-Pathological Foundations of Diseases**. 8ª Ed. Rio de Janeiro: Elsevier.
- 12-Mehta J, Ashtana S, Mandal CC, Saxena S. A molecular analysis provides novel insights into androgen receptor signaling in breast cancer. PLOS ONE. 2015; 10 (3): 1-27.
- 13-Toss A, Cristofanilli M. Molecular characterization and targeted therapeutic approaches in breast cancer. Breast Cancer Research. 2015[Acesso em 17 jun]; 17. Available at <<http://www.breast-cancer-research.com/content/pdf/s13058-015-0560-9.pdf>>.
- 14-Oliveira CF, Silva TS. Invasive breast carcinoma: from diagnosis to surgical treatment[internet]. Cap. 37. Available at: <http://www.fspog.com/fotos/editor2/cap_37.pdf>. Viewed on: 06/08/2015.
- 15-Lopes LAF, Linhares JJ, Ferraro O, Lopes RGC, Baracal FF. Prognostic value of histological grade (GH), nuclear grade (NG) and mitotic index (MI) for patients with stage II and III breast carcinomas with compromised axillary lymph nodes. Prognostic factors in patients with stage II and III breast cancer. 2006
- 16-Gobbi H. Classification of breast tumors: update based on the new classification of the World Health Organization 2012. J. Bras Patol Med Lab. v. 48; 6; P. 463-474. December 2012.
- 17-Breast Cancer. Staging. Treatment. Available at: <http://www.sbmastologia.com.br/downloads/estadiamento_e_tratamento.pdf> Displayed on: 06/08/2015
- 18-SBM - Brazilian Society of Mastology. Molecular subtypes of breast cancer. Available in: <<http://www.sbmastologia.com.br/cancer-de-mama/tipos-cancer-de-mama/subtipos-moleculares-do-cancer-de-mama-18.htm>> Displayed in: 08/06/2015
- 19-Team oncoguia. Types of Breast Cancer. Available at: <<http://www.oncoguia.org.br/conteudo/tipos-de-cancer-de-mama/1382/34/>>. Displayed on: 6/8/2015

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