WHIOCE PUBLISHING PTE. LTD. Cancer+

REVIEW ARTICLE

Hereditary Breast Cancer

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Abstract: Breast cancer occurs when breast cells grow out of control because they escape the fine controls that regulate cell multiplication, resulting in cell proliferation unresponsive to regulation. Most cases of breast cancer have no identifiable cause, but approximately 5% to 10% are caused by inherited genetic mutations. Although other genes are known to cause hereditary breast cancer, most studies evaluating clinical management strategies have focused on women with mutations in the BRCA1 or BRCA2 (Breast Cancer) genes. People with these mutations have a significantly increased lifetime risk of cancer compared to the general population.

Keywords: Breast cancer, Hereditary mutations, BRCA1 gene

1 Introduction

Cancer is currently one of the leading causes of death worldwide. It accounted for 7.6 million deaths (approximately 13% of all deaths) worldwide in 2008. The number of cancer deaths is expected to continue to rise and to exceed 13.1 million by 2030[1,2].

Breast cancer is considered a public health problem in many developed and developing countries, due to its frequency, the amount of resources it consumes and the social alarm it generates. In general terms, a global increase in the incidence of breast cancer has been observed, the causes of which are largely unknown[2].

In industrialized countries, breast cancer represents the main cause of oncological death. In the female population, an increase has been observed in the diagnosis of this pathology in the initial clinical stages (I and II), which represent approximately 85% of all cases diagnosed. This reality is very different in Venezuela, where the highest percentage of breast cancer diagnoses are made in more advanced clinical stages (III and IV), currently constituting the first cause of mortality in women, after cervical cancer[1-3].

Cancer is the pathological tissue growth caused by a continuous proliferation of abnormal cells, which produces a disease due to the possibility of elaborating substances with harmful biological activity, due to their capacity for local expansion or due to their potential for invasion and destruction of adjacent tissues or at a distance (metastasis). Breast cancer occurs when breast cells grow uncontrollably, because they

Received: November 20, 2019
Accepted: February 24, 2020
Published Online: March 18, 2020

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CITATION
Fernández A, Reigosa A, 2020, Hereditary Breast Cancer. *Cancer+,* 2(1):21-29.
DOI: 10.18063/cp.v2i1.341

escape the exquisite controls that regulate cell multiplication, causing cell proliferation without response to regulation[4].

Breast cancer is a heterogeneous disease composed of a growing number of recognized biological subtypes, with substantial variability in disease progression within each category. It is generally accepted that the varied clinical course of patients with histologically identical tumors is the result of molecular differences. Currently, there are four molecular classes of breast cancer: a) luminal A, b) luminal B, c) HER2 and d) triple negative (TN) with basal and non-basal phenotype[5,6].

Breast cancer exhibits a wide range of morphologic phenotypes and specific histologic types that have particularly clinical and prognostic characteristics. Infiltrating ductal carcinoma of the breast is the most frequent histologic type. Approximately 80% is considered poor prognostic due to the cellular complexity evidenced by molecular findings. It is characterized by a proliferation of malignant epithelial cells of the mammary ducts, which exceed the basal membrane and whose forms of presentation, clinical evolution and response to the systemic treatment employed are extraordinarily variable and heterogeneous, which represents a permanent challenge for the medical oncologist[4,7].

Most cases of breast cancer have no identifiable cause, but approximately 5%–10% are caused by inherited genetic mutations. Although other genes are known to cause hereditary breast cancer, most studies evaluating clinical management strategies have focused on women with mutations in the BRCA1 or BRCA2 (Breast Cancer) genes. BRCA1 mutation carriers have an average lifetime risk of 60% for developing breast cancer and BRCA2 mutation carriers have a 50% risk[8,9].

Remember that genes are a set of instructions (DNA sequences) that tell every cell in the body what to do. Genes, for example, determine eye color, blood type and the number of fingers and toes. Each gene has 2 possible copies called alleles, one of them coming from the father and the other from the mother. A mutation is any change in the nucleotide sequence of the deoxyribonucleic acid (DNA) corresponding to a given gene[10,11].

BRCA1 and BRCA2 belong to the group of tumor suppressor genes whose key function is the maintenance of DNA integrity. Each of these genes encodes proteins bearing the same name (BRCA1 and BRCA2 respectively), which are involved in the repair of double-stranded DNA breaks. They are also members of a complex network of proteins associated with multiple functions, such as transcription regulation, chromatin remodeling, cell cycle control, regulation of centrosomes, induction of apoptosis, ubiquitination and protein degradation, among others[10,11].

If a woman inherits a BRCA1 or BRCA2 mutation, the breasts and ovaries will be the organs most susceptible to developing cancer. The reason for the specificity of these tissues that tend to malign is unknown, although it is related to the action of steroid hormones and their receptors in these tissues[8,12].

2 Genetic predisposition to breast cancer

Inherited and acquired mutations play a fundamental role in the development of cancer. While many cancers result from acquired genetic alterations in somatic cells, some cancer patients have inherited mutations that play an important etiological role in their disease. More than 50 different types of cancer demonstrate familial contribution suggesting an inherited predisposition, including breast, ovarian, colon, and prostate tumors[9,13].

Breast cancer is considered a multifactorial disorder caused by both genetic and non-genetic factors[9,13]. Currently, several genes associated with breast cancer are known. Some of them correspond to rare genetic syndromes that within their manifestations present this pathology, such as: Cowden Syndrome, Li-Fraumeni Syndrome, Ataxia Telangiectasia, Bloom Syndrome, Peutz-Jraumeni Syndrome and Werner Syndrome. All of them have very low population frequencies and a low contribution to the number of hereditary breast cancer cases[12,13].

In general terms, the genes that have been

identified to date and whose mutations are associated with hereditary breast cancer are: BRCA1, BRCA2, HRAS1, PTEN, Tp53, CHk2 and ATM. They are all part of the cellular machinery that maintain genomic integrity and repair DNA[8,9].

2.1 Biological basis of hereditary breast cancer

Cancer arises from mutations in several genes in a single cell, which allow the normal control of growth and proliferation to be circumvented, until the development of a clinically evident tumor. Many of these tumors are the result of mutations that essentially affect genes of two types: a) oncosuppressor genes and b) proto-oncogenes[10,11].

Oncosuppressor genes cause cancer as a consequence of a mutation experienced by the normal form, also called a tumor suppressor gene or anti-oncogene. The normal form of the gene encodes, an anti-oncogene protein, acts by arresting proliferation or inducing apoptosis, for example, the p53 gene[10,11].

On the other hand, the proto-oncogene encodes, a normal protein, generally related to cell proliferation or apoptosis, which acts only when it receives specific regulatory signals. In contrast, the mutated form, or oncogene, expresses an abnormal protein (oncoprotein) that remains active independently of regulatory signals[10,11].

Mutations are usually acquired, due to exposure to internal or external carcinogens or failures during cell division, but in a minority of cases, mutations are inherited. These mutations, called germline, are found in sperm or egg cells and are transmitted through the zygote to each and every cell of the new individual. Thus, hereditary cancer occurs because all the somatic cells of the organism have one of the two copies of the gene altered. The probability of losing the other copy in this individual is high, because only the other allele in any somatic cell must be mutated. The increased risk caused by the inherited mutations far outweighs the risks from other factors[8,13,14].

Although these genes are transmitted with an autosomal dominant inheritance pattern, that is, an individual carrying a mutation has a 50% risk of passing it on to the next generation, regardless of sex, and it has been shown that they do not have complete penetrance, that is, a carrier individual does not have a 100% chance of developing the disease, since the cellular behavior of the mutation is like that of recessive genes. Therefore, the loss of the normal copy of the gene is required to express the malignant phenotype[12].

2.2 Epidemiological data

The prevalence of BRCA1 and BRCA2 mutations varies according to country and ethnic group. Among different ethnic groups, the highest frequency is found in individuals with Ashkenazi Jewish ancestry of European origin. Other populations with a high presence of mutations include those from countries such as Iceland, Canada (especially French-Canadians), Poland and the Netherlands. This prevalence is due to the presence of founder mutations, which are one or more specific mutations in these populations that have been inherited from a common ancestor and have been amplified through the generations, with the geographic isolation of the population contributing to this[9,13].

Early studies of gene expression supported the idea that hereditary breast cancers, especially those linked to BRCA1 mutations, were different in many ways from nonhereditary cancers. They have different clinical and histopathological features from sporadic breast cancer, including:

a) Diagnosed at a younger age.

b) Frequency of bilateral involvement (both breasts).

c) Due to aneuploidy (a change in chromosome number), high histological grade, and high proliferation index, the prognosis is poor and the aggressiveness is high[15,16].

In addition, breast cancer associated with BRCA1 mutations is more frequent of TN type with basal phenotype, compared to those with BRCA2 alteration or sporadic ones. As mentioned above, the basal phenotype is one of the molecular subgroups and is characterized by negativity for hormone receptors (estrogen and progesterone) and HER2 (triple negative), in addition to expressing basal/myoepithelial

markers, such as cytokeratins 5/6, 14 and 17, as well as P-cadherin, CD10, p63, EGFR, actin, and calponin[15,16].

Tumors associated with BRCA2 mutations are more diverse, although with a preponderance of hormone receptor expression. These types of tumors have not been studied in depth from the point of view of gene expression, but immunohistochemical analysis does not appear to include them in the basal epithelial phenotype, and they have not been associated with an adverse prognosis[13,15,16].

The risk of developing breast cancer in women who have a mother or sister with this pathology is two to three times higher than in the rest of the population. In those cases in which both the mother and sister were affected, the risk increases up to 6.5 times that of the population with no first-degree family history[13,17].

Since it is a germline mutation that causes the predisposition to cancer, i.e., present in any nucleated cell of the organism, very few somatic mutations are needed in the breast ductal cells for the development of the neoplasm to take place. It can be inherited from either the mother or the father, with the mutation being present from birth in carriers[8,9].

2.3 The BRCA1 gene and the function of its protein

BRCA1 is a human tumor suppressor gene, which regulates the cell cycle and prevents uncontrolled proliferation. The BRCA1 protein, a product of this gene, is part of the DNA damage detection and repair system. BRCA1 is located on the long arm of chromosome 17. In female carriers of mutations in the gene, the cumulative risk up to the age of 70 is estimated to be between 50% and 95% for breast cancer and between 22% and 66% for ovarian cancer. Male carriers of the BRCA1 mutation have an approximate 1% risk of developing breast cancer[8,18].

The first evidence of the existence of this gene was obtained by Mary-Claire King (American geneticist) at the University of California in 1990. Four years later, in 1994, after an international race for looking for it, the gene was cloned by the University of Utah, Environmental Health Sciences, National Academy of Sciences, USA and Myriad Genetics[8,9].

BRCA1 is expressed in different epithelia of the body during development, and its expression is increased during pregnancy and decreases after delivery. BRCA1 has been shown to be estrogen-induced. Inhibition of BRCA1 causes increased proliferation of both normal and cancerous breast epithelial cells. In hereditary and in some sporadic breast cancers, decreased expression of the normal BRCA1 protein has been detected[17,18]. Accordingly, expression of the normal gene, but not of the mutated forms, inhibits the growth of breast and ovarian tumor cells. Deletion of the last ten amino acids of the BRCA1 protein is sufficient to abolish its ability to inhibit tumor growth[18].

Approximately half of the breast and ovarian tumors of mutation carriers have loss of the normal copy of the gene, leaving only the form containing the inherited mutation, indicating the nature of BRCA1 as a suppressor gene and its specific effect on the genesis of these types of cancers[18,19].

2.4 Types of BRCA1 mutations

They usually consist of small insertions or deletions in the DNA sequence corresponding to the BRCA1 gene, which cause a change in the reading frame, leading to the appearance of a premature stop codon, the consequence of which is the truncation of the BRCA1 protein. To date, hundreds of different mutations in BRCA1 and BRCA2 have been described and are listed in the Breast Cancer Information Core (BIC) database (http://research.nhgri.nih.gov/bic/) (16,18). Typically, a mutated BRCA1 gene produces a protein that does not function properly because it is abnormally short. Defective BRCA1 proteins are not able to help correct mutations that occur in other genes. These defects accumulate and can allow cells to grow and divide uncontrollably[18,20].

2.5 The BRCA2 gene

The BRCA2 protein is a protein encoded in humans by the BRCA2 gene (located on the long arm of chromosome 13). Like BRCA1, BRCA2 belongs to the family of tumor suppressor genes

and is involved in the repair of double-stranded DNA misfolding[8,9].

Certain variations in the BRCA2 gene can cause an increased risk of breast cancer. Hundreds of mutations have been identified in this gene, many of which cause an increased risk of cancer. These mutations are usually insertions or deletions of a small number of DNA base pairs in the gene. As a result of these mutations, the encoded BRCA2 protein is abnormal and does not function properly[9,21].

Alterations in this gene could be responsible for 25%–30% of breast cancer cases. Women carrying the BRCA2 mutation have a risk of approximately 50%–85% for developing breast cancer and 15%–20% for ovarian cancer. Male carriers of the BRCA2 mutation have an approximate 7% risk of developing breast cancer[9,18].

3 Recommendations for women carrying BRCA1 and/or BRCA2 mutations

Family history is the essential tool to identify and refer patients at risk of hereditary breast cancer. The identification of families in which a hereditary pattern of cancer is demonstrated is important to provide them with follow-up schemes for timely detection. It should be taken as part of the routine care of the patient, both by the first contact physician and by the oncologist; covering a minimum of first and second degree relatives (mother, sister, cousins)[20,21].

The recognition of a familial susceptibility to cancer leads to the use of molecular tools in order to identify carriers before the onset of the disease and thus reduce unnecessary follow-up in those patients who are not carriers[22].

Molecular diagnostics identifies individuals, both healthy and already affected, who may benefit from medical options specific to their inherited high risk, usually consisting of monitoring and early detection, prophylactic surgery or chemoprophylaxis[8,17-19].

a) Early detection. This includes breast self-palpation starting at 18 years of age and the initiation of annual mammograms, as well as transvaginal ultrasounds and determination of the CA-125 tumor marker every 6 or 12 months, for the early detection of breast and ovarian cancer, respectively. These practices should be initiated at 25 years of age or at least 10 years before the diagnosis of the first case of breast cancer in the family[8,23].

b) Prophylactic surgery. Bilateral prophylactic mastectomy reduces the risk of breast cancer by 90%, although it does not totally eliminate the possibility of malignization of residual tissue. It should be considered in women whose mammograms are difficult to interpret (fibrocystic breasts or very dense breasts in young women), with high-risk premalignant lesions or in those whose first-degree relatives (mother, sister, daughter) have had breast or ovarian cancer. However, this measure has considerable physical and psychological effects[8,24].

c) Chemoprevention. This is a controversial area in general and especially in hereditary breast cancer. The use of tamoxifen administered for 5 years appears to be effective in reducing risk (about 40%) in women with a family or personal history. However, there are doubts about the degree of risk that requires the use of this drug and at what age its administration should begin. However, some recent studies suggest its lifelong administration[8,24-26].

It should be considered that the finding of the mutation allows improving the estimation of personal risk and making consequent clinical decisions. Such estimates are always approximate, as factors such as a woman's genetic, environmental and reproductive history can modify each individual's susceptibility, producing differences in expression and penetrance (type and probability of cancer, respectively) between carriers, even within the same family[23].

4 Diagnosis of BRCA1 and BRCA2 gene mutations

The tests used to detect alterations in these genes should be accompanied by genetic counseling before and after they are performed. Genetic counseling consists of educating individuals at risk or affected by cancer about the role of genes in the transmission of the disease, advising an individual about the possible presence of

hereditary cancer in him/her and his/her family, explaining both the positive and negative implications of molecular testing, making recommendations on management plans and providing support to help the individual resolve psychosocial problems that may arise during the process[24-26].

The genetic counseling process should be carried out by a multidisciplinary team including an oncologist, psychologist or psychiatrist and a medical geneticist[17,21].

With advances in molecular biology and the advent of genetic testing in oncology practice, several techniques have been developed that allow the identification of the main mutations found in the BRCA genes, most of them based on polymerase chain reaction (PCR) and DNA sequencing[12,17,21].

However, these tests are expensive and therefore their usability and large-scale application is limited. The limited availability is compounded in many countries by the scarcity of centers trained and qualified to perform these genetic tests, which has led to the use of other techniques, such as immunohistochemistry (IHC)[6,27].

IHC is a technique used to detect and quantify various markers (proteins) in the first instance in breast cancer. This technique measures protein overexpression using specific antibodies against the BRCA1 protein, located in the nucleus of the tumor cell. Coupling the technique with the use of tissue matrices (provides the possibility of studying the protein in a massive manner), the cost of the test is considerably reduced, making it more accessible to the population[27,28].

The criteria for indicating these tests varies according to the country and the population studied. There are no unanimous selection criteria, but all include indications of risk of inherited predisposition: number of breast and ovarian cancers in the family, early age of diagnosis, presence of bilateral or male breast cancer, among others[29,30].

In case there is no family history, it should be indicated to all those women who have triple negative breast cancer and who have been diagnosed at 40 years of age or earlier, also to all those women with ovarian cancer. If these conditions are not present, it should be performed in women who have a significant family history: two or more cases of breast cancer diagnosed at an early age (under 50 years of age) or ovarian cancer diagnosed at any age[31-33].

The Spanish Society of Medical Oncology considers other criteria, such as: a) one case of breast cancer in a woman under 50 years of age

Table 1. Sensitivity and specificity of potential biomarkers in the detection of bladder cancer

Marker	Sensitivity (%)	Specificity (%)	Reference
NMP22	49.5 − 92.1	66.0 − 87.3	[11-13]
TERT	84.8 − 95.0	84.0 − 100.0	[18,21-23]
HA	61.0 – 83.1	53.6 − 90.1	[47]
HAase	81.5	83.8	[47]
HA/HAase	88.1 − 94.0	63.0 − 84.4	[47]
Lewis X	79.8 − 84.0	80.0 − 86.4	[48]
Survivin	75.0	100.0	[49]
LOH	60 − 97.0	93.0	[43-45]
BLCA-4	89 − 96.4	95.0 − 100.0	[50]
UPK3A	83.0	83.0	[51]
CK20	78.0 − 87.0	56.0 − 80.0	[52]
AG-α3β1	>95	>95	[46]

NMP22, Nuclear matrix protein 22; TERT, Telomerase reverse transcriptase; HA, Hyaluronic acid; HAase, Hyaluronidase; LOH, Loss of heterozygosity; BLCA-4, Bladder cancer specific nuclear matrix protein 4; UPK3A, Human uroplakin 3A; CK20, Cytokeratin 20; AG-α3β1, Aberrantly glycosylated integrin α3β1

Table 2. Sensitivity and specificity of detection methods of bladder cancer.

Marker	Sensitivity (%)	Specificity (%)	Reference
Cytology	12.2 – 79.0	78.4 – 99.4	[12,18-20,42,57]
Quanticyt	42.1 – 69.0	67.9 – 87.0	[53]
ImmunoCyt	66.7 – 84.9	62.0 – 84.7	[54]
FISH	69.0 – 92.1	89.0 – 94.5	[41,42,57]
BTA STAT	50.0 – 70.0	67.0 – 78.0	[9,10,55]
TRAP	77.4 – 90.0	88.0 – 93.5	[56]

FISH, Fluorescence in situ hybridization; TRAP, Telomeric repeat amplification protocol

or bilateral, and one case of ovarian cancer in first or second degree relatives (cousin, grandmother, aunt), b) two cases of ovarian cancer in first or second degree relatives and c) one case of breast cancer in a man and at least one first or second degree relative with breast or ovarian cancer. It is also advisable in the general population or in patients without cancer but with proliferative breast lesions, such as usual or atypical ductal hyperplasia, intraductal papilloma, sclerosing adenosis and ductal or lobular carcinoma in situ. The management and interpretation of the genetic analysis are as follows[24,31-33].

a) Negative result. In the woman affected by cancer: the lack of detection of the mutation provides limited information and should be interpreted with great care, as the cause of the cancer has not yet been established. It is possible that the cancer is related to mutations not detected by the methods used, that it is caused by a different genetic predisposition, or that it is caused by non-genetic factors. Among unaffected relatives: confirm that the person has not inherited the family-specific mutation. In the case of both the cancer-affected and unaffected woman, the family should be aware that a negative result does not eliminate the possibility that a hereditary factor is present in the family[8,24,34].

b) Positive result. In the woman affected by cancer: this confirms the association of the cancer with a genetic origin and pre-establishes a specific mutation for that family. In the unaffected relatives: this confers an increased risk for cancers associated with BRCA1 or BRCA2 mutations in BRCA1 or BRCA2. In this case it is recommended to offer prophylactic treatment and appropriate follow-up[8,33-36].

5 Conclusions

The etiology of breast cancer is unknown, but hormonal, reproductive, environmental and hereditary risk factors have been implicated. Although most breast cancer are sporadic, advances in genetics have demonstrated a hereditary basis for a subset of these cancers. One of the main risk factors is the presence of breast cancer in first-degree relatives[10,11].

Several studies have estimated that between 5% and 10% of all breast tumors have a hereditary component directly related to germline mutations in autosomal dominant genes. Currently, BRCA1 and BRCA2 are the high penetrance genes that are associated with the highest proportion of hereditary breast and ovarian cancer cases[9,27].

The discovery of the BRCA1 and BRCA2 genes in 1994 and 1995 respectively, has led to the practice of cancer prevention and increasingly sophisticated genetic testing that allows the screening of women at high risk for hereditary breast cancer. The benefit of genetic testing in any population is due to its ability to reduce both the incidence and mortality of breast cancer. Currently, only mutations in the BRCA1/2 genes are criteria for indicating genetic testing[18-20,35].

Research over the past few years has led to a better understanding of the biology of breast cancer associated with BRCA mutations. It now seems clear that hereditary predisposition due to mutations in the BRCA1 and BRCA2 genes turn out to be, for many reasons, different diseases. There are quantitative differences in cancer risk associated with BRCA1 or BRCA2 mutations, particularly in ovarian cancer. Moreover, breast cancers arising in patients carrying a BRCA1 mutation have a propensity to manifest as a specific subtype of breast cancer. A propensity that is not evident in BRCA2 mutation-associated disease[36-40].

With no immediate clinical relevance, it is confirmed that in cancers arising in BRCA1 mutation carriers, the clinical behavior is more aggressive and adjuvant (postoperative) therapy decisions should be adjusted accordingly. Although there are no specific therapies directed against hereditary breast cancer, there are drugs currently in development that could be useful in treating these types of cancers. Until such treatments become available and are evaluated, hereditary breast cancer should be approached clinically in the same manner as non-hereditary cancer[15-17,37].

In summary, the predisposition associated with mutation in the BRCA1 gene turns out to be, in many respects, different from that associated with mutations in BRCA2, indicating that they may be different disorders[26-28,38].

The quantitative risks are not equal (especially in the case of ovarian cancer).

b) The phenotypes of breast cancer associated with BRCA1 or BRCA2 mutations are different.

c) The prognosis in each of the cases may be different.

Cases of breast cancer at high risk require specialized management:

a) One option is preventive breast surgery (total mastectomy).

b) Breast magnetic resonance imaging has proven to be a breakthrough for women who choose to undergo surveillance.

c) Non-surgical approaches have not proven to be effective.

Cases of ovarian cancer at high risk can pose a significant threat because[26,39]:

a) Ovarian cancer screening has uncertain efficacy.

b) Preventive ovarian surgery is advisable after 35 years of age.

Those responsible for the medical surveillance and treatment of women with mutations should ensure that all family members are aware of the risk.

Finally, it is important to point out that in relation to the frequency of mutations in BRCA genes in the breast cancer population in Venezuela, only the work of Lara *et al.*[41], who identified some mutations in 58 patients analyzed, has been published. However, there are no preliminary studies in the general population or in patients with proliferative breast lesions. For this reason and because breast cancer patients have a high survival rate when treated in the early stages of the disease, the ability to identify those women at high risk in our country is of great importance to public health.

Conflict of interest

No conflict of interest was reported by all authors.

References

1. World Health Organization, 2012, Cancer. Fact Sheet. No. 297. Available from: http://www.who.int/mediacentre/factsheets/fs297/es/index.html. [Last accessed on 2012 March].
2. Jemal A, Bray F, Center MM, *et al.*, 2011, Global Cancer Statistics. *CA Cancer J Clin*, 61:69–90.
3. Ministry of People's Power for Health, Venezuela, 2010, Anuario de mortalidad 2010 [Mortality Yearbook 2010]. Available from: http://www.mpps.gob.ve/index.php?option=com_phoca download&view=category&id=11:anuarios-de- mortalidad. [Last accessed on 2013 January].
4. González L, Garavito A, Echeverri C, *et al.*, 2007, Cáncer de mama: HER2/neu, métodos diagnósticos y consideraciones clínicas [HER2/neu and Breast Cancer: Diagnosis and Clinical Issues]. *Rev Colomb Cancerol*, 11:40–57.
5. Reigosa A, Fernández A, Gutiérrez D, *et al.*, 2010, Expresión de p63 y citoqueratina 5/6 en los diferentes tipos moleculares del carcinoma de mama [p63 and Citokeratin 5/6 Expression in Different Molecular Subtypes of Breast Carcinoma]. *Rev Esp Patol*, 43:79–85.
6. Fernández A, Reigosa A, 2013, Clasificación molecular del cáncer de mama, obtenida a través de la técnica de hibridación in situ cromogénica (CISH) [Molecular Classification of Breast Cancer Patients Obtained through the Technique of Chromogenic in Situ Hybridization (CISH)]. *Invest Clin*, 54:406–6.
7. Rakha EA, Reis-Filho JS, Ellis IO, 2010, Combinatorial Expression of Biomarkers in Breast Cancer. Breast Cancer Res Treat, 120:293–308.
8. Narod SA, Rodríguez AA, 2011, Genetic Predisposition to Breast Cancer: BRCA1 and BRCA2 Genes. *Public Health Mex*, 53:420–9.
9. Apostolou P, Fostira F, 2013, Hereditary Breast Cancer: The Era of Novel Susceptibility Genes. *Biomed Res Int*, 2013:747318.
10. Lee EY, Muller WJ, 2010, Oncogenes and Tumor Suppressor Genes. *Cold Spring Harb Perspect Biol*, 2:1–18.
11. Perera RM, Bardeesy N, 2012, Oncogenes and Tumor Suppressor Genes in the Mammary Gland. *Cold Spring Harb Perspect Biol*, 4:34–66.
12. Silver DP, Livingston DM, 2012, Mechanisms of BRCA1 Tumor Suppression. *Cancer Discov*, 2:679–84.
13. Pal T, Vadaparampil ST, 2012, Genetic Risk Assessments in Individuals at High Risk for Hereditary Breast Cancer in the Breast Oncology Care Setting. *Cancer Control*, 19:255–66.
14. Meindl A, Ditsch N, Kast K, *et al.,* 2011, Hereditary Breast and Ovarian Cancer: New Genes, New Treatments, New concepts. *Dtsch Arztebl Int*, 108:323–30.
15. Bertucci F, Finetti P, Birnbaum D, 2012, Basal Breast Cancer: A Complex and Deadly Molecular Subtype. *Curr Mol Med*, 12:96–110.
16. Peshkin BN, Alabek ML, Isaacs C, 2010, BRCA1/2 Mutations and Triple Negative Breast Cancers. *Breast Dis*,

32:25–33.

17. Trainer AH, Thompson E, James PA, 2011, BRCA and Beyond: A Genome-first Approach to Familial Breast Cancer Risk Assessment. *Discov Med*, 12:433–43.
18. Van der Groep P, Van der Wall E, Van Diest PJ, 2011, Pathology of Hereditary Breast Cancer. *Cell Oncol (Dordr)*, 34:71–88.
19. Julian-Reynier C, 2011, Genetic Predisposition to Breast and Ovarian Cancer: Importance of Test Results. *Med Sci (Paris)*, 27:657–61.
20. Pruthi S, Gostout BS, Lindor NM, 2010, Identification and Management of Women with BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. *Mayo Clin Proc*, 85:1111–20.
21. Milne RL, Antoniou AC, 2011, Genetic Modifiers of Cancer Risk for BRCA1 and BRCA2 Mutation Carriers. *Ann Oncol*, 22:11–17.
22. Smith KL, Isaacs C, 2011, BRCA Mutation Testing in Determining Breast Cancer Therapy. *Cancer J*, 17:492–9.
23. Gibert O, 2006, Estudio molecular de los genes BRCA1 y BRCA2 en cáncer de mama hereditario [Molecular Study of BRCA1 and BRCA2 Genes in Hereditary Breast Cancer]. *Ed Cont Lab Clín*, 9:19–27.
24. Karami F, Mehdipour P, 2013, A Comprehensive Focus on Global Spectrum of BRCA1 and BRCA2 Mutations in Breast Cancer. *Biomed Res Int*, 2013:928562.
25. Birkbak NJ, Kochupurakkal B, Izarzugaza JM, *et al.*, 2013, Tumor Mutation Burden Forecasts Outcome in Ovarian Cancer with BRCA1 or BRCA2 Mutations. *PLoS One*, 8:80023.
26. Millot GA, Carvalho MA, Caputo SM, *et al.*, 2012, A Guide for Functional Analysis of BRCA1 Variants of Uncertain Significance. *Hum Mutat*, 33:1526–37.
27. Rademakers SE, Rijken PF, Peeters WJ, *et al.*, 2011, Parametric Mapping of Immunohistochemically Stained Tissue Sections; A Method to Quantify the Colocalization of Tumor Markers. *Cell Oncol*, 34:119–29.
28. Prasad K, Tiwari A, Ilanthodi S, *et al.*, 2011, Automation of Immunohistochemical Evaluation in Breast Cancer Using Image Analysis. *World J Clin Oncol*, 2:187–94.
29. Paradiso A, Formenti S, 2011, Hereditary Breast Cancer: Clinical Features and Risk Reduction Strategies. *Ann Oncol*, 22:31–6.
30. Mackay J, Szecsei CM, 2010, Genetic Counselling for Hereditary Predisposition to Ovarian and Breast Cancer. *Ann Oncol*, 21:334–8.
31. George SH, Shaw P, 2014, BRCA and Early Events in the Development of Serous Ovarian Cancer. *Front Oncol*, 23:4–5.
32. Li D, Bi FF, Cao JM, *et al.*, 2013, Effect of BRCA1 on Epidermal Growth Factor Receptor in Ovarian Cancer. *J Exp Clin Cancer Res*, 32:102.
33. Burco T, Cimponeriu D, Ion DA, *et al.*, 2013, Analysis of Several BRCA1 and BRCA2 Mutations in A Hospital-based Series of Unselected Breast Cancer Cases. *Chirurgia (Bucur)*, 108:468–72.
34. Mahdi KM, Nassiri MR, Nasiri K, 2013, Hereditary Genes and SNPs Associated with Breast Cancer. *Asian Pac J Cancer Prev*, 14:3403–9.
35. Berzina D, Nakazawa-Miklasevica M, Zestkova J, *et al.*, 2013, BRCA1/2 Mutation Screening in High-risk Breast/Ovarian Cancer Families and Sporadic Cancer Patient Surveilling for Hidden High-risk Families. *BMC Med Genet*, 14:61.
36. Kang HJ, Hong YB, Yi YW, *et al.*, 2013, Correlations Between BRCA1 Defect and Environmental Factors in the Risk of Breast Cancer. *J Toxicol Sci*, 38:355–61.
37. Guinan EM, Hussey J, McGarrigle SA, *et al.*, 2013, A Prospective Investigation of Predictive and Modifiable Risk Factors for Breast Cancer in Unaffected BRCA1 and BRCA2 Gene Carriers. *BMC Cancer*, 13:138.
38. Mazzola E, Cheng SC, Parmigiani G, 2013, The Penetrance of Ductal Carcinoma in Situ among BRCA1 and BRCA2 Mutation Carriers. *Breast Cancer Res Treat*, 137:315–8.
39. Meyer P, Landgraf K, Högel B, *et al.*, 2012, BRCA2 Mutations and Triple-negative Breast Cancer. *PLoS One*, 7:38361.
40. Larsen MJ, Thomassen M, Tan Q, *et al.*, 2014, RNA Profiling Reveals Familial Aggregation of Molecular Subtypes in Non-BRCA1/2 Breast Cancer Families. *BMC Med Genomics*, 7:9.
41. Lara K, Consigliere N, Pérez J, *et al.*, 2012, BRCA1 and BRCA2 Mutations in Breast Cancer Patients from Venezuela. *Biol Res*, 45:117–30.