










ORIGINAL ARTICLE

Relationship of the CA-15.3 marker, positivity of hormone receptors and histological diagnosis in breast cancer

Relación del marcador CA15.3, positividad de receptores hormonales y diagnóstico histológico en cáncer de mama

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ABSTRACT

Introduction: breast cancer is a health problem, its metabolic alterations and tumor markers can become a prognostic tool.

Objective: to determine the influence of the modifications and association of tumor marker 15.3, the degree of positivity of estrogen receptors, progesterin receptors, HER-2 receptors and histological diagnosis on the clinical characteristics, response to treatment and evolution of patients with breast cancer.

Methods: an analytical, retrospective and cross-sectional observational study was carried out in 45 patients with breast cancer treated at the Third Congress Oncology Center in Pinar del Río, Cuba, in the year 2022.

Results: we found a predominance of patients between 50-59 years old, with overweight and different degrees of obesity, with 60 % of both groups, according to BMI, white skin color, absence of family pathological antecedents, with university education level, with ductal histological diagnosis, tumors between 0.1 - 2.0 cm tumor, time of evolution between one and five years and left breast involvement.

Conclusions: in this study we determined the influence that the modifications and association of the tumor marker 15.3, the degree of positivity of estrogen receptors, progesterin receptors, HER-2 receptors and histological diagnosis have on the clinical characteristics, the response to treatment and the evolution of patients with breast cancer.

Keywords: Breast Cancer; Ca15.3 Marker; Hormone Receptors; Histological Diagnosis.

RESUMEN

Introducción: el cáncer de mama constituye un problema de salud, cuyas alteraciones metabólicas y los marcadores tumorales pueden constituir una herramienta para el pronóstico.

Objetivo: determinar la influencia que tienen las modificaciones y la asociación del marcador tumoral 15.3, del grado de positividad de los receptores estrogénicos, receptores progestágenos, los receptores HER-2 y del diagnóstico histológico en las características clínicas, la respuesta al tratamiento y la evolución de las pacientes con cáncer de mama.

Métodos: se realizó un estudio observacional analítico, retrospectivo y transversal en 45 pacientes con cáncer de mama atendidas en el Centro Oncológico Tercer Congreso en la provincia Pinar del Río de Cuba, en el año 2022.

Resultados: se encontró predominio de pacientes entre 50-59 años, con sobrepeso y diferentes grados de obesidad, con un 60 % de ambos grupos, según el IMC, el color de la piel blanca, la ausencia de antecedentes patológicos familiares, con nivel educacional universitario, con diagnóstico histológico ductal, tumores entre tumor 0.1 - 2.0 cm, tiempo de evolución entre uno y cinco años y afectación de la mama izquierda.

Conclusiones: en este estudio se determinó la influencia que tienen las modificaciones y la asociación del marcador tumoral 15.3, del grado de positividad de los receptores estrogénicos, receptores progestágenos, los receptores HER-2 y del diagnóstico histológico en las características clínicas, la respuesta al tratamiento y la evolución de las pacientes con cáncer de mama.

Palabras clave: Cáncer de Mama; Marcador Ca15.3; Receptores Hormonales; Diagnóstico Histológico.

INTRODUCTION

Breast cancer has been known since antiquity; its oldest description comes from Egypt in the Ebers papyrus.^(1,2) For centuries, doctors have described cases, expanding their clinical description and proposing treatment and prevention alternatives that have improved the evolution of patients, their quality of life and life expectancy.

It is classified as a multifactorial and heterogeneous disease that originates from a genetic anomaly, an "error" in the genetic material, of which only 5-10 % of cases are the product of an anomaly inherited from the mother or father and 85-90 % of breast cancer cases have their origin in genetic anomalies linked to the ageing process and the "natural wear and tear" of life.^(3,4)

It is the most prevalent neoplasm and with the highest mortality rate in women, approximately 1.38 million new cases are reported each year and half a million deaths in the world derived from this pathology occur in a ratio of 100 to one between male and female sexes.⁽⁴⁾

The highest incidence rates are found in Western Europe, where 370 000 cases are diagnosed each year, representing 27,4 % of all cancer patients; Spain has the highest rates (30 % of women), while rates are lowest in East Asia.⁽⁵⁾

Among women in the United States and Canada, 24 % of new cases and 14 % of cancer deaths are due to breast cancer and although developed countries such as the United States have seen a drastic reduction in mortality by 30 % due to increased early detection through the use of mammography screening and the establishment of standardized detection systems, while developing countries such as Mexico show a steady upward trend (estimated incidence of 38,4 per 100,000 women and mortality). 4 per 100,000 women and standardized mortality of 16,8 deaths per 100,000 women), a result of the limited availability of screening instruments and cancer registration methods.⁽⁴⁾ In women in Latin America and the Caribbean, breast cancer accounts for 27 % of new cases and 16 % of cancer deaths.⁽⁴⁾

The World Health Organization (WHO) considers breast cancer to be a major problem in developed countries and increasingly in underdeveloped countries, as this disease represents the leading cause of cancer deaths in the world. It is estimated that one in every nine to twelve women with risk factors will suffer from the disease in her lifetime.⁽⁵⁾

According to data from the Pan American Health Organization (PAHO), in the Americas and the Caribbean, breast cancer accounts for 29 % of all cancer cases and is the second leading cause of death from malignant tumors, surpassed only by lung cancer; but by 2030, PAHO estimates more than 596 000 new cases and more than 142 100 deaths in the region. In Latin America: Cuba and Uruguay have one of the highest incidence rates.⁽⁵⁾

Cuba is among the countries with the highest breast cancer mortality rate in the Americas and is one of the countries with the highest number of years of life lost due to breast cancer. The Health Statistical Yearbook 2021 reports that malignant breast tumors are the second leading cause of death in women.^(6,7)

The goal of the WHO's Global Breast Cancer Initiative is to reduce global breast cancer mortality by 2,5 % per year, which would prevent 2,5 million deaths worldwide between 2020 and 2040. The three pillars to achieve this goal are: health promotion for early detection; timely diagnosis; and comprehensive management of breast cancer.⁽⁵⁾

In the opinion of the authors, screening methods are a fundamental part in reducing mortality in this pathology, allowing early diagnosis in early stages, achieving control of the disease and avoiding late diagnosis with complications, pillars that must be systematically maintained and strengthened every 19 October in the framework of the celebration of World Breast Cancer Day.⁽⁵⁾

Molecular markers are used to identify new cases among individuals at high risk of developing breast cancer, to aid in early diagnosis, to determine prognosis, to predict response and possible resistance to specific therapies, surveillance after the first surgery and to monitor therapy in patients with advanced disease.

Breast cancer is undoubtedly a global health problem today, due to its great social and economic impact, which affects women at an early age and has a huge impact on their lives, due to the complications of the disease and the therapeutic approach. For this reason, it is important to study the characteristics of the tumor, using tumor markers, and given that there have been few previous studies in the province on the influence of the association of tumor markers in the care and follow-up of these patients, we studied the possible influence of changes in the tumor marker CA 15.3, the degree of positivity of estrogen receptors, progesterone receptors, HER-2 receptors and histological diagnosis on the clinical characteristics, response to treatment and evolution of patients with breast cancer treated at the "Tercer Congreso" Oncology Centre, in Pinar del Río, Cuba. Objective to determine the influence of the modifications and association of

the tumor marker CA 15.3, the degree of positivity of estrogen receptors, progesterone receptors, HER-2 receptors and histological diagnosis on the clinical characteristics, response to treatment and evolution of patients with breast cancer.

METHODS

In this study, the variables of age, skin color, educational level, body mass index, personal and family pathological history, histological diagnosis, affected breast, histological grade, time of evolution, tumor size in cm, affected nodes, estrogen/progesterone receptors, treatment, CA15.3 marker, HER-2 marker and relapses were analyzed.

An analytical, retrospective and cross-sectional observational study was carried out on 45 patients with breast cancer treated at the Oncology Centre of the "Third Congress" who met the inclusion criteria by having a histological diagnosis of breast cancer and measurements of the selected tumor markers (estrogen-progesterone receptors, HER-2 and CA 15.3) in their medical records.

Universe: Total of 60 patients admitted to the Oncology Centre of the "Third Congress" with a diagnosis of cancer, who had CA15.3, PR, ER and HER-2 tumor markers performed and underwent treatment in the period.

Sample: 45 patients with breast cancer who met the inclusion criteria (n=45) were included on a non-probabilistic, purposive basis.

Nutritional classification was performed according to the Body Mass Index (BMI) according to international references of the World Health Organization (WHO) for the adult population.⁽⁸⁾

The laboratory techniques used for the determination of the biochemical variables studied were performed in the clinical laboratory of the Hospital Tercer Congreso, complying with quality control, the samples were processed by a certified laboratory technique, the examination was performed only with a blood sample from the patient and did not require any preparation.

The collected blood was sent to the laboratory, processed and analyzed, where the values of the tumor marker CA 15.3 were determined from the serum in the automated ELISA system and using Roche monoclonal antibodies and the Roche COBAS C 311 automatic analyzer for biochemical tests. The reference value for this test is 30 U/mL.

With the information obtained, a database was created with Microsoft® Excel 2010 software and processed with SPSS version 22 running on Windows XP. For the statistical analysis of this information, the Wilcoxon test for quantitative variables was applied after checking the normality of the variables using the Shapiro-Wilk test. In all cases, a significant association was considered when the p-value was ≤ 0.05 . In addition, bivariate correlation between quantitative variables was analyzed using Spearman's test.

Ethical regulations were strictly adhered to, which included informed consent of the patients, compliance with confidentiality of the information provided, and the principles: autonomy, justice, beneficence, and non-maleficence, with no profit motive. The study was governed by the ethical principles guiding medical research involving human subjects as set out in the Declaration of Helsinki in 2008 and updated in 2013.

RESULTS

The age range of 50-59 years (37,77 %), overweight and different degrees of obesity predominated, with 60 % of both groups, according to BMI, white skin color, no family history of pathology and a university education. (table 1)

Skin color influences the occurrence of breast cancer, as white-skinned women are slightly more likely to develop this type of cancer than African-American women, although African-American women are more likely to present a greater malignancy and die from this cause at an earlier age. The higher proportion of white patients corresponds to the predominance of white skin color in our population.

Table 1. Clinical characteristics of patients with breast cancer treated at the Third Congress Oncology Centre.

Aspects	Rank	No	%
Age (years)	30-39	2	4,44
	40-49	10	22,22
	50-59	17	37,77
	60-69	11	24,44
	70-79	4	8,88
	80-89	1	2,22
IMC	Undernourished	1	2,22
	Normal weight	17	37,77
	Overweight	19	42,22
	Obesity I	5	11,11
	Obesity II	2	4,44
	Obesity III	1	2,22
Skin color	B	38	84,44
	N	7	15,55
Family pathological history of cancer	No	39	86,7
	yes	4	13,3
Educational level	Secondary	10	22,22
	Pre-university	16	36,36
	University	19	42,22

Source: Medical records.

It can be seen that there is a prevalence of ductal histological diagnosis (60,00 %), with a time of evolution between one and five years (71,11 %), a tumor size of 0.1-2.0cm in 91,11 % of the patients, where the left breast was the most affected (53,33 %), Grade I (57,77 %), and 36 patients did not have ganglionoma. 53,33 %), Grade I (57,77 %), and 36 patients had no nodes (80,0 %). It was rare that both breasts were affected synchronously (less than 1 %) and corresponded to infiltrating ductal carcinoma by histology. (table 2)

Table 2. Tumor characteristics in breast cancer patients seen at the Third Congress Cancer Centre.

Tumor characteristics		Number	%
Histological Diagnosis	Ductal	27	60,00
	Lobular	15	33,33
	Tubular	3	6,66
Time of Evolution	1-5	32	71,11
	6-10	10	22,22
	11-15	2	4,44
	16 y más	1	2,22
Tumor Size (cm)	0.1-2.0	41	91,11
	2.1-4.0	3	6,66
	4.1-6.0	1	2,22
Affected Breast	MD	21	46,66
	MI	24	53,33
Histological Grade	Grade I	26	57,77
	Grade II A	12	26,66
	Grade II B	2	4,44
	Grade III A	4	8,88
	Grade III B	0	0
	Grade VI	1	2,22
Presence of nodes	Yes	9	20,00
	No	36	80,00

Sources: Medical records

According to the characteristics of the tumor and estrogen/progesterone receptors, there is a predominance of moderate in the histological diagnosis, with 28,88 %, as well as the time of evolution 37,77 %, the size of the tumor 48,88 %, equal proportion in both breasts (26,66), as well as grades I and II (22,22 %) and without the presence of lymph nodes (45,0 %). (table 3)

Table 3. Histological Diagnosis and Time of Evolution according to Estrogen/Progesterone Receptor positivity in patients with breast cancer treated at the "Third Congress" Oncology Centre.

characteristics	tumor	Estrogen/Progesterone Receptor					
		Mild	%	Moderate	%	Intense	%
Histological Diagnosis	Ductal	9	20,45	13	28,88*	5	11,11
	Lobular	5	11,11	10	22,22	0	0
	Tubular	2	4,44	0	0	1	2,22
Time of Evolution (years)	1-5	10	22,22	17	37,77*	5	11,11
	6 - 10	4	8,88	4	8,88	1	2,22
	11 - 15	2	4,44	0	0	0	0
	16 y más	0	0	1	2,22	0	0
Tumour Size (cm)	0,1 - 2,0	16	35,55*	22	48,88*	3	6,66
	2,1 - 4,0	0	0	1	2,22	2	4,44
	4,1 - 6,0	0	0	0	0	1	2,22
Breast Affected	MD	6	13,33	12	26,66	3	6,66
	MI	9	20,45	12	26,66	3	6,66
Histological Grades	Grade I	14	31,11	10	22,22	3	6,66
	Grade II	2	4,44	10	22,22	1	2,22
	Grade III	0	0	2	4,44	2	4,44
	Grade IV	0	0	1	2,22	0	0
Presence of nodes	yes	2	4,44	5	11,11	2	4,44
	No	14	31,11*	18	45,0*	4	8,88

Source: Medical Records (*Significance. $p < 0.05$)**Table 4.** Relationship between estrogen and progesterone receptors with HER-2 and levels of the tumor marker CA 15.3.

Receptors E/P	HER-2		Total	CA 15.3		Total
	-	+		Normal	Increased	
Mild	16	0	16	15	1	16
Moderate	21	2	23*	20*	3	23
Intense	4	2	6	6	0	6
Total	41	4	45	41	4	45

Source: Medical records (*Significance. $p < 0.05$)

According to the relationship between estrogen/progesterone receptors and HER-2 is moderate with 21 patients, 46,66 % and the CA 15.3 marker was also moderate with 20 patients, 44,44 %.

HER-2 negative was predominant in 41 patients, 91,12 %, with eight of the nine patients relapsing and all were treated with the four available treatment variants, i.e. surgery (C), chemotherapy (Q), radiotherapy (R) and hormone treatment (H). The eight relapsed and HER-2 negative patients had very low estrogen and progesterone receptor positivity, so they correspond to the triple negative group, which are considered to have the worst prognosis. (table 5)

Table 5. Relationship between HER-2 and relapses and treatments in patients with breast cancer treated at the Oncology Centre " Third Congress "

HER-2	Relapses				Treatment				
	Yes	No	Total	%	C	Q	R	H	Total
Positive	1	3	4	8,88	4	2	2	4	4
Negative	8	33	41	91,12 *	41	41	41	41	91,12 *
Total	9	36	45	100	45	43	43	45	100

Source: Medical Records (*Significance. $p < 0.05$)

The relationship between the tumor marker CA 15.3 and relapses shows that serum levels of the marker were normal ($< 30 \text{ U/mL}$) in 91,11 % and elevated in only four patients (8,89 %). The nine patients with relapses had levels of CA 15.3 considered normal and none of the four patients in whom it was found to be elevated had relapses, so we found no relationship between the marker and relapses in the study. (table 6)

Table 6. Relationship between the tumor marker CA 15.3 with relapses and with treatments.

CA 15.3	Relapses				Treatment			
	Yes	No	Total	%	C	Q	R	H
Normal	9	32	41*	91,11*	41	41	41	41
Elevated	0	4	4	8,89	4	2	2	4
Total	9	36	45	100	45	43	43	45

Source: Medical Records (*Significance. $p < 0.05$)

DISCUSSION

Familial breast cancer is considered to account for 5-10 % of all diagnosed cases, of which only 1 % is attributed to individuals with a history of first- and second-degree relatives (mother, sister, daughter) with the disease.⁽¹³⁾ Hereditary breast cancer suggests the existence of dominant high penetrance genes in which a genetic factor responsible has been identified: alteration of the Breast cancer tumor suppressor genes which are: BRCA I and BRCA II. One third of patients with a family history of breast cancer are carriers of the heritable mutation of these genes, or are associated with disorders in DNA repair. Hence, there is a five- to six-fold

increase in the likelihood of developing the disease, the higher the number of affected relatives and the younger the age of the relative at diagnosis.⁽⁹⁾

A history of benign breast disease, such as fibrocystic mastopathy, non-atypical proliferative lesions and atypical hyperplasia are histological precursor lesions, which have been shown to be associated with increased risk of subsequent development of breast cancer.

The results of this study were compared with others on the same subject, in a study by CitagezB et al⁽¹⁰⁾ with whom we agree.

The high prevalence of the disease in women between 35 and 60 years of age may be justified by the fact that there is high hormonal activity in these periods. The literature consulted attributes a causal relationship to the appearance of this disease according to age group, and in the case of the appearance in pre-menopausal women, it explains it by hereditary genetic reasons and hormonal imbalances, and in late post-menopausal women by environmental factors, such as dietary habits.

With regard to educational level, women with completed university studies, i.e. university level, were the most represented in the present study. The literature describes the close relationship between educational level, knowledge of proper breast self-examination (BSE) technique and early diagnosis of breast cancer. Ramirez et al.,⁽¹¹⁾ emphasize in their research that a high percentage of women do not know the BSE technique and that only a small percentage of these women perform it, without identifying whether they use an adequate technique.

In a study by González-Longoria,⁽¹²⁾ with which we partially agree, the mean tumor size was 3.88 ± 1.61 cm. More than half of the cases (56,8 %) had a moderately differentiated histological grade (grade II). Lymph node invasion was observed in the majority of patients (63,3 %). Histologically, invasive ductal carcinoma was found in almost all participants, accounting for 99,5 % of cases.

The histological type (found in 80,7 %) by Sepúlveda,⁽¹³⁾ was infiltrating ductal, which coincides with that reported in the world literature, which reports that it is the most frequent, where the cells lining the ducts through which milk circulates have become cancerous, but have not spread to the surrounding breast tissue.

Knowing the degree of hormone receptor positivity in breast cancer helps doctors decide how to treat it. The presence of one or both of these hormone receptors means that hormone therapy drugs can be used to reduce estrogen levels or prevent estrogen from acting on breast cancer cells, as this therapy is useful for hormone receptor-positive breast cancers, but is not effective in hormone receptor-negative tumors (both ER and PR negative). Hormone receptor-positive cancers tend to grow more slowly than hormone receptor-negative cancers and women with hormone receptor-positive cancers tend to have a better short-term prognosis, but these cancers can sometimes return many years after treatment.⁽¹⁴⁾

We agree with the study by González-Longoria et al,⁽¹²⁾ where immunohistochemical (IHC) determination has been performed on estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor two (HER2) and Ki-67, which we did not determine in our research.

Most of the drugs developed in recent years are directed against specific molecular targets, so they are only effective in tumors where specific proteins are mutated. However, computer-assisted drug design opens the door to the possibility of personalized medicine, so that each patient receives treatment tailored to their own molecular profile. It even aims to design multi-target therapeutic candidates using master keys that selectively bind to different molecular targets and produce a desired clinical response. This involves the integration of genomics, transcriptomics, proteomics and metabolomics at a more complex level.⁽¹⁴⁾

CA15.3 is a polymorphic epithelial mucin-related antigen, a marker for breast cancer. Levels above 30 U/mL have been linked to lower overall survival, but are unrelated to tumor size, nodal status and age.^(4,15)

Their clinical use could be considered as a predictor of patient outcome and to determine adjuvant treatment for better outcome. Recent studies have shown that serial determination of CA15.3 during postoperative follow-up of breast cancer patients may be useful for early detection of preclinical recurrence or metastatic disease. Moreover, serum CA15.3 levels can be used to predict response to chemotherapy in patients with metastatic breast cancer.⁽¹⁵⁾

Two of the current clinical applications of the HER2 oncogene are the prognostic and predictive value of gene overexpression in breast cancer. A third application of the HER2 oncoprotein is its role as a therapeutic target for new treatments that are directed against the HER2 protein. There is currently a consensus that HER2 expression in breast carcinomas has an adverse prognostic value, although in general it is of lesser importance than the prognostic value conferred by classical indicators such as tumor size or the number of axillary nodes affected. Regarding the predictive value of HER2, all but one clinical study has shown that there is an association between HER2 expression and the efficacy of hormonal treatments.⁽¹²⁾

In a study by Santisteban,⁽¹⁵⁾ 66,6 % had normal CA15 values. Three before treatment, however, after chemotherapy serum values of this marker were elevated in 63,3 % of patients. In this study two of the patients with elevated CA15.3 did not receive chemotherapy treatment and all patients were treated with surgery, with elevated values found in only four patients (8,89 %).

Tumor marker levels increase before clinical or radiological findings of recurrence. In this study, patients were divided into two groups; the first group of patients who received medical treatment in case of negative conventional imaging findings but a significant increase in one or more components of the tumor marker panel including CA15.3 ("tumor marker-guided" treatment) and the second group of patients who were treated only after radiologically confirmed recurrence, conventional treatment. As a result of this study, "tumor marker-guided" treatment significantly prolonged overall and disease-free survival rates.⁽¹⁵⁾

CONCLUSIONS

In this study it can be affirmed that Ca 15.3 is a valuable tool in follow-up because it is elevated in the majority of patients who relapse. The fact that HER-2 negative and elevated CA15.3 was not associated with relapse in breast cancer patients is not considered to limit its usefulness in patient follow-up.

Conflict of interest

The authors declare no conflicts of interest related to the study.

Authors' contribution

MGP: Conceptualization, Research, Writing - original draft, Writing - proofreading and editing

NLF: Conceptualization, Writing - review and editing

IER: Data curation, Resources,

YCH: Data curation, Resources,

JCDC: Formal Analysis, Research, Project Management, Supervision, Writing - original draft, Writing - review and editing

YSA: Formal Analysis, Project Management, Supervision.

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Additional material

Additional material to this article can be consulted in its electronic version available at: www.revcmpinar.sld.cu/index.php/publicaciones/rt/suppFiles/6198

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