Importance of predictive biomarkers related to Pharmacogenetics in breast cancer and prostate: a systematic review

Importância de biomarcadores preditivos relacionados à Farmacogenética no câncer de mama e próstata: uma revisão sistemática

Importancia de los biomarcadores predictivos relacionados con farmacogenética en cáncer de mama y próstata: una revisión sistemático

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Abstract
Pharmacogenetics allows to verify the genetic polymorphisms that influence the success of an oncological pharmacotherapy, therefore, the need for progression in the pharmacogenomic oncological field is evident. This study aims to describe the importance of predictive biomarkers related to pharmacogenetic breast and prostate cancer through a literature review. The search for original articles took place between February and November 2020 in databases such as Pubmed, Scielo, Medline and search directories such as Google Scholar. As for the inclusion criteria, the original articles in English, Portuguese and Spanish published between 2010 and 2020 were included. The search result found 102 articles on the subject, 36 excluded because they were review articles, 22 excluded after reading the abstract and 13 excluded because they did not align with the theme. 31 original articles were selected for which the authors prove the importance of validating independent studies on predictive values of biomarkers for breast and prostate cancer. The conclusion of the analyzed studies suggests that the use of biomarkers makes it possible to predict responses to clinical treatment, appropriate therapeutic conduct where they are associated with better treatment results.
Keywords: Carcinogenesis; Pharmacogenomics; Biomarker; Treatment.

Resumo
Antecedentes: Este estudo objetiva descrever a importância de biomarcadores preditivos relacionados à farmacogenética no câncer de mama e de próstata. Materiais e Métodos: A busca de artigos originais se deu entre fevereiro e novembro de 2020 em bases de dados como Pubmed, Scielo, Medline e diretórios de busca como Google Acadêmico. O critério de inclusão se deu através de artigos originais, de linguagem inglesa, portuguesa e espanhola publicados entre o ano de 2010 a 2020. Resultados: A busca encontrou 102 artigos, 36 excluídos por serem de revisão, 22 excluídos após leitura do resumo e 13 excluídos por não seguirem a temática. Foram selecionados 31 artigos originais pelos quais os autores comprovam a importância da validação de estudos independentes sobre valores preditivos de biomarcadores. Conclusão: A conclusão dos estudos analisados sugere que a utilização de biomarcadores possibilita a previsão de respostas ao tratamento clínico, conduta terapêutica adequada onde são associados a melhores resultados do tratamento.
Palavras-chave: Carcinogênese; Farmacogenômica; Biomarcador; Tratamento.

Resumen
Antecedentes: este estudio tiene como objetivo describir la importancia de los biomarcadores factores predictivos relacionados con la farmacogenética en el cáncer de mama y de próstata. Materiales y Métodos: La búsqueda de

artículos originales se realizó entre febrero y noviembre de 2020 en un datos como Pubmed, Scielo, Medline y directorios de búsqueda como Google Scholar. La el criterio de inclusión se dio a través de artículos originales, en inglés, portugués publicado entre 2010 y 2020. Resultados: La búsqueda encontró 102 artículos, 36 excluidos para ser revisados, 22 excluidos después de leer el resumen y 13 excluidos para no sigas el tema. Se seleccionaron 31 artículos originales para los cuales los autores demostrar la importancia de validar estudios independientes sobre valores predictivos de biomarcadores. Conclusión: La conclusión de los estudios analizados sugiere que el uso de los biomarcadores permiten predecir las respuestas al tratamiento clínico, la conducta terapéutica donde se asocian con mejores resultados del tratamiento.

Palabras clave: Carcinogénesis; Farmacogenómica; Biomarcador; Tratamiento.

1. Introduction

According to the National Cancer Institute (INCA), in 2020, 66,280 new cases of breast cancer and 65,840 new cases of prostate cancer are estimated in Brazil. These are the neoplasms with the highest incidence in men and women in the country, therefore, it is extremely important to optimize treatment, rationalizing and individualizing antineoplastic therapy with the aid of PGx tests identifying polymorphism in specific pharmacogenes (INCA, 2021).

Pharmacogenetics (PGx) is a genetic tool that emerged in the 1950s through several observations of inheritable enzyme deficiencies that caused toxicity to certain drugs. It is the science that provides the optimization of therapeutic management in terms of safety and effectiveness, based on the genetic characteristics of patients (Álvarez et al., 2019).

Pharmacogenetic tests allow to verify the genetic polymorphisms that influence the success of a pharmacotherapy. Through the administration of personalized treatments, we can increase the number of positive responses and reduce the rate of occurrence of adverse reactions and toxicity (Fricke et al., 2018). The preference for the application of PGx tests in the area of oncology is due to its aggressiveness, rapid proliferation of cancer cells and the severity of symptoms. In the clinical context, PGx has shown great importance in the treatment of prostate and breast cancer. Which are the most prevalent cancers among men and women in Brazil (Schilling et al., 2017).

Thus, it is essential to set goals that allow this therapeutic approach to be included as an important portion of pharmacotherapy, being present in hospital and outpatient settings. Increasingly relevant, scientific information is able to allow the personalization of therapy, where PGx, pharmacodynamics and pharmacokinetics, needs to be assimilated and used by pharmacists in order to promote an increase in the patient's quality of life, through greater efficiency and drug safety (Santos, 2017).

Therefore, the use of PGx tests allows cancer patients to experience an individualized treatment, with the correct, specific, safe drug, with the most appropriate and consequently more effective dosage and with a lower incidence of adverse effects during chemotherapy. It is also considered, the significant advance in the area of molecular oncology, or oncobiology, taking into account the adoption of PGx and pharmacogenomics, resulting in positive consequences in the enhancement and improvement of pharmacological treatment. The accessibility to these genetic tests is increasing, since the values are increasingly lower, making it possible to use them in clinical practice as a medullary tool in the fight against cancer (Santos et al., 2016).

Thus, the objective of the study was to describe the importance of pharmacogenetic tests in the treatment of breast and prostate cancer in clinical practice, through a systematic review, analyzing the main predictive biomarkers for these neoplasms.

2. Methodology

It was a study with an investigative approach constituted by a qualitative systematic review, carried out according to the checklist of the PRISMA protocol, with data collection from bibliographic searches in the period between February to November 2020.

The study took place through articles, mainly national and foreign, in addition to original articles, related to breast and prostate cancer and PGx. The sources were selected from the year of publication 2010 and addressing the topic of pharmacogenomics, precision medicine, breast and prostate cancer, predictive biomarkers and the importance of applying PGx tests in the therapy of cancer patients.

Articles in English, Portuguese and Spanish were selected from digital platforms: Medical Literature Analysis and Retrieval System Online (MEDLINE), PubMed, Scientific Electronic Library (SCIELO) and the Google Scholar directory, in addition to sites like INCA. Research carried out in the period between February and November 2020, searched through descriptors in English, Portuguese and Spanish such as: pharmacogenetics, breast cancer, pharmacogenomics, prostate cancer, personalized medicine, precision medicine, predictive biomarkers and molecular markers.

For the elaboration of this study, articles and research on technological development in health related to the pharmacogenetics of breast and prostate cancer were included, with publication date from 2010, in addition to original articles, field research and clinical studies.

Exclusion criteria were non-original articles, review articles, articles that address pharmacogenetics in other types of cancer, which are irrelevant, not aligned with the issue at hand and with a publication date prior to the year 2010.

The articles selected within the inclusion criteria were presented in order to describe the results. The main results were summarized in tables, generated in Microsoft Office Excel, for better visualization of the data.

3. Results

Prostate Cancer

The search strategy identified 61 articles. Of this total, 28 were excluded because they were duplicated and / or the study model was based on a literature review, leaving 33 original articles. When reading the abstracts, 6 articles were excluded because they did not address the topic in question, leaving 27 articles read in full. After reading and analyzing the articles in full, 12 were excluded because they did not fit the research theme and finally, 15 were selected (Figure 1).

The main information about the 15 studies used in our results can be found in Table 1.

Table 1. Main information about studies associated with predictive biomarkers in the pharmacogenetics of prostate cancer.

Author / Year	Study title	Objective of the study	Biomarker	Study outcome
Armstrong et al, 2017	MicroRNA-181a promotesdocetaxelresistance in prostate cancercells	Understanding the involvement of miRNAs in docetaxel resistance in CRPC	miR-181a	Significant expression of miR-181a in docetaxel-resistant CaP cells and by inhibiting them, they are resensitized
Markowsk et al, 2017	Clinical Utility of CLIA-Grade AR-V7 Testing in Patients With Metastatic Castration-Resistant Prostate Cancer	To investigate the clinical utility of the AR-V7 test in patients with (mCRPC).	AR-V7	The detection of AR-07 + and / or AR-V7– can guide the clinical treatment of mCRPC.
Antonarakis, et al, 2017	Clinical Significance of Androgen Receptor Splice Variant-7 mRNA Detection in Circulating Tumor Cells of Men With Metastatic Castration-Resistant Rostate Cancer Treated With First- and Second-Line Abiraterone and Enzalutamide	Expand studies on the effectiveness of AR-V7 as a marker for mCRPC treatment selection	AR-V7	Negative results in the detection of AR-V7, based on CTC, were confirmed in patients with mCRPC, impacting the treatment decision.

Fan et al, 2019	Neuroendocrine differentiation markers guide treatment sequence selection in metastatic castration-resistant prostate cancer	Assess the value of serum neuroendocrine markers in choosing the strategic sequence of mCRPC treatment	NED	The results concluded that in mCRPC high levels of NED indicate better clinical results directed in DP-AA than with AA-DP
Jung et al, 2011.	Bone Turnover Markers as Predictors of Mortality Risk in Prostate Cancer Patients with Bone Metastases Following Treatment with Zoledronic Acid	To evaluate the predictive capacity of serum bone markers for mortality risk in patients with PC with bone metastases	PINP e ICTP	The ability of markers as predictors of OS was proven, implying clinical advantages in the management of treatment
Antonarakis et al, 2014	AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer	Investigate the possible association between the detection of AR-V7 with resistance to enzalutamide and abiraterone	AR-V7	The association between the variant AR-V7 and resistance to enzalutamide and abiraterone is concluded.
Miyamoto et al, 2018	An RNA-based digital circulating tumor cell signature is predictive of drug response and early dissemination in prostate cancer	Digital signature of prostate CTC in non-invasive monitoring to guide treatment selection	AR-V7	The digital quantification of transcripts derived from CTCs is predictive of treatment in mCRPC and early spread in localized CaP
Zhao et al, 2017	Associations of Luminal and Basal Subtyping of Prostate Cancer With Prognosis and Response to Androgen Deprivation herapy	Investigate prostate cancer subtypes based on luminal and basal lineage and associate them with clinical results and treatment	NKX3.1, KRT18 and CD49f	The segregation of the three CaP subtypes demonstrated that patients with luminal B tumors respond better to postoperative ADT enabling the customization of ADT treatment
Moul et al, 2014	Impact of NADiAProsVue PSA slope on secondary treatment decisions after radical prostatectomy	Assessing a patient's ProsVue results affects medical decision-making related to secondary Cap treatment	NADiA PSA	The results showed that ProsVue significantly reduced the number of recommendations for post-PR treatments
Badani et al, 2013	Impact of a genomic classifier of metastatic risk on postoperative treatment recommendations for prostate cancer patients: a report from the DECIDE study group	To evaluate the influence of the Predipher genomic prediction model in the decision making of urologists for patients at risk of metastasis	GC	It was confirmed that the GC test makes it possible to change the treatment recommendation after PR, among other benefits to patients and the health system
Crawford et al, 2014	Cell cycle progression score and treatment decisions in prostate cancer: results from na ongoing registry	Evaluate the Prolaris test in providing risk of CaP progression and mortality while further assessing the impact on	CCP	With the results, there was an increase and reduction in the interventional treatment according to

		medical treatment recommendations		the specific risk shown in the test
Badani et al, 2014	Effect of a genomic classifier test on clinical practice decisions for patients with high-risk prostate cancer after surgery	Predict the risk of metastasis after PR and assist in urologist decision making in adjuvant treatment based on the genomic classification test	GC	The test found an increase in the clinician's ability to discriminate against those who are less likely to experience disease progression, resulting in the best treatment strategy
Shore et al, 2016	Impact of the CCP test on physician and patient treatment selection for localized prostate cancer	Molecular assay for progression and risk of mortality when combined with clinical-pathological parameters.	CCP	The result of the CCP test brought a significant change in the clinical treatment strategy
[Someya et al, 2018	Prediction of acute gastrointestinal andgenitourinary radiation toxicity in prostatecancerpatients using lymphocyte microRNA	Investigate new biomarkers that can predict acute radiation toxicity through microRNA expression	miR-410 and miR-221	The results proved to be assertive to predict acute gastrointestinal toxicity from radiation therapy
Michalopoulos et al, 2014	Influence of a genomic classifier on post-operative treatment decisions in high-risk prostate cancer patients: results from the PRO-ACT study	To evaluate the possible metastasis prediction after PR from the PRO-ACT multicentre study	GC	Test results significantly changed urologists' adjuvant treatment recommendations for post-PR patients with CaP and risk of metastasis

Legend: miR-181a: microRNA-181a; AR-V7: variant 7 of the androgen receptor splice; NED: serum neuroendocrine differentiation; PINP: the amino terminals of procollagen type I collagen peptides; ICTP: cross-linked type I collagen C-terminal telopeptides; KRT18: keratin 18; NKX3.1: Related NK3 transcription factor, locus 1 (Drosophila); CD49f: Integrin α6; NADiA: nucleic acid detection immunoassay; PSA: prostate specific antigen; CG: genomic classifier; CCP: cell cycle progression test; miR-410: microRNA 410; miR-221: microRNA221. Source: Authors.

Breast Cancer

The search strategy identified 41 articles. Of this total, 8 were excluded because they were duplicated and / or the study model was based on a literature review, leaving 33 original articles. When reading the abstracts, 16 articles were excluded because they did not address the topic in question, leaving 17 articles read in full. After reading and analyzing the articles in full, 1 was excluded for not adapting the research topic. Thus, 16 articles were selected (Figure 1).

The main information about the 16 studies used in our results can be found in Table 2.

Table 2. Main information about the studies associated with predictive Biomarkers in the pharmacogenetics of breast cancer.

Author / Year	Study title	Objective of the study	Biomarkers	Study outcome
Kurozumi et al, 2015.	ER, PgR, Ki67, p27 (Kip1) and histological grade as predictors of complete pathological response in patients with HER2-positive breast cancer receiving neoadjuvant chemotherapy using taxanes followed by fluorouracil, epirubicin and concomitant cyclophosphamide with trastuzumab	Determine whether pCR was related to histological grade (HG) and to several biological factors, including p27 (Kip1). E Also assess the prognosis of the pCR and non-pCR groups, and the expected differences between those positive and negative for lymph node metastases after chemotherapy.	HG, ER, PgR, Ki67 and p27 (Kip1).	High HG, low ER, low PgR, high Ki67 and low p27 (Kip1) were identified as predictive factors for pCR in NAC with trastuzumab, while pCR and negative nodules were predictive of better survival.
Carrasco et al, 2011.	Antisense Inhibition of Survivin Expression as a CancerTherapeutic	Identification of survivin oligonucleotide (ASO) that downregulates survivin expression and also shows that inhibition of survivin expression by LY2181308 sensitized tumor cells to chemotherapy-induced apoptosis.	Survivina	Inhibition of survivin expression by LY2181308 sensitized tumor cells to chemotherapy-induced apoptosis.
Hao et al, 2020	Analysis of Circulating Tumor DNA to Predict Neoadjuvant Therapy Effectiveness and Breast Cancer Recurrence	Assess the benefits for the management of breast cancer in neoadjuvant therapy	Circulating tumor DNA (ctDNA)	Highlight the potential of ctDNA analysis at different points in time to assess tumor progression and treatment effectiveness, such as predicting breast cancer recurrence
Zhou et al, 2020.	CXCR4 Antagonist AMD3100 Reverses the Resistance to Tamoxifen in Breast Cancer via Inhibiting AKT Phosphorylation.	Explore the importance of the CXC type 4 chemokine receptor (CXCR4) in tamoxifen-treated breast cancer and tamoxifen resistance	CXCR4	The AMD3100 CXCR4 antagonist reversed tamoxifen resistance in breast cancer. The relationship between tamoxifen and AMD3100 increases the tumor suppressor effects and reduces the side effects caused by the dosage of the drug.
Zhou et al, 2020	High expression of TRAF4 predicts poor prognosis in tamoxifen-treated breast cancer and promotes tamoxifen resistance	Seek to explore the roles of TRAF4 in tamoxifen -treated breast cancer and tamoxifen resistance	TRAF4	TRAF4 is strongly related to a poor prognosis of breast cancer treated with tamoxifen. Involved in tamoxifen resistance
Vázquez et al, 2019	MicroRNA-143 is Associated With Pathological Complete Response and Regulates Multiple Signaling Proteins in Breast Cancer	Show that miR-143 can be a predictor of complete pathological response to neoadjuvant chemotherapy in breast cancer patients	MicroRNA-143	MiR-143 could be a potential predictor of response to neoadjuvant therapy, and also provide clues to the molecular functions of miR-143 in signaling networks related to carcinogenesis in breast cancer.

Ding et al, 2017	Predictive factors of pathologic complete response in HER2-positive and axillary lymph node positive breast cancer after neoadjuvant paclitaxel, carboplatin plus with trastuzumab	Investigate the proportion, as well as predictive factors of complete pathological response in HER2-positive breast cancer	Ki67	The preoperative PCH regimen was an effective neoadjuvant therapy in HER2 positive patients and positive axillary lymph nodes, and patients who coexisted with negative HR and a high Ki67 index could benefit more from this regimen.
Tan et al, 2014	Prognostic value of Ki67 expression in HR-negative breast cancer before and after neoadjuvant chemotherapy	To evaluate the benefit of the Ki67 assessment in HR-negative breast cancers after neoadjuvant chemotherapy (NAC)	Ki67	Ki67 expression in HR negative breast cancer may improve the assessment of pathological response after NAC, and the Ki67 score in residual tumor was an independent predictor for DFS in HR negative breast cancer patients
Haddad, 2010	Trastuzumab in breastcancer	Check data on the clinical use and efficacy of trastuzumab in the treatment of early and advanced breast cancer	Trastuzumab	Trastuzumab offered an improvement in HER-2 positive breast cancer therapy. It has wide acceptability and greatness in the treatment of breast cancer
Manica et al, 2017	Down regulation of ADAM33 as a Predictive Biomarker of Aggressive Breast Cancer	Produce monoclonal antibodies against the ADAM33 protein and investigate the role of the ADAM33 protein in breast cancer	ADAM33	Showing ADAM33, in combination with currently available biomarkers, may be a new molecular marker for better determining breast cancer prognosis.
Kim et al, 2014	Yes-associated protein (YAP) is differentially expressed in tumor and stroma according to the molecular Subtypeofbreastcancer	To clarify the expression profiles of Yes-associated protein (YAP) and phosphorylated YAP protein (pYAP) and to verify the clinical implication of YAP protein expression in human breast cancer	YAP e pYAP	There was a significant difference in the expression status of YAP and Pyap. We found that the nuclear and cytoplasmic expression of YAP may be a prognostic marker for breast cancer patients
Shokouh et al, 2015	Interrelationships Between Ki67, HER2/neu, p53, ER, and PR Status and Their Associations With Tumor Grade and Lymph Node Involvement in Breast Carcinoma Subtypes	To verify the interrelationships of these predictive and prognostic factors, as well as their effects on breast carcinoma subtypes	Ki67, HER2 / neu, p53, ER e status de PR	Tumors with a higher Ki67 index showed more HER2 / neu overexpression, larger size and more lymph node involvement compared to other types and can be considered aggressive. Young patients with breast carcinoma, Ki67 rates with overexpression of HER2 / neu and p53 mutations are higher and have a more aggressive behavior.
Bownes, 2019	On-treatment biomarkers can improve prediction of response to neoadjuvant chemotherapy in breast	Study changes in gene expression that affect the treatment of breast cancer	AAGAB	The study resulted in the discovery of a new biomarker, showed

	cancer			potential in the precision of breast cancer treatment
Asiaf et al, 2018	MicroRNAs in Breast Cancer: Diagnostic and Therapeutic Potential	Discuss the role of miRNAs as oncogenes and tumor suppressors in the development and metastasis of breast cancer	MicroRNA	MiRNAs have a prognostic, diagnostic or predictive potential in breast cancer, as well as possible challenges in translating such observations into the clinic
Klopp-Schulze et al, 2020	Integrated Data Analysis of Six Clinical Studies Points Toward Model-Informed Precision Dosing of Tamoxifen	Dissect various levels of variability and identify predictive factors for exposure to endoxifene and (ii) evaluate different dosages of tamoxifen strategies for its potential to increase the number of patients reaching target concentrations of endoxifene	CYP3A e CYP2D6	MIPD has proved to be the most promising strategy for reaching target concentrations of endoxifene
Sumoza-Toledo et al, 2016	Evaluation of the TRPM2 channel as a biomarker in breast cancer using public databases analysis	Investigate the prognostic value of the TRPM2 channel in breast cancer	TRPM2	TRPM2 is a promising biomarker for the aggressiveness of breast cancer and a potential target for the development of new therapies

Legend: HG: histological grade; ER: estrogen receptor; PgR: progesterone receptor; Ki67: proliferating protein; p27: The cyclin 1B-dependent kinase inhibitor; CXCR4: type 4 chemokine receptor; TRAF4: factor 4 associated with the TNF receptor; ADAM33: Protein Containing Disintegrin Domain and Metalloproteinase; YAP and pYAP: protein associated with Yes and the phosphorylated YAP protein; HER2 / neu: human epidermal growth factor 2 receptor; p53: tumor protein; AAGAB: alpha-binding protein and gamma-adaptin; CYP3A and CYP2D6: cytochrome P450 and CYP2D6 enzyme; TRPM2: cationic channel of the potential transient receptor, subfamily M, member 2. Source: Authors.

Figure 1 - Flowchart of bibliographic research and selection of articles.
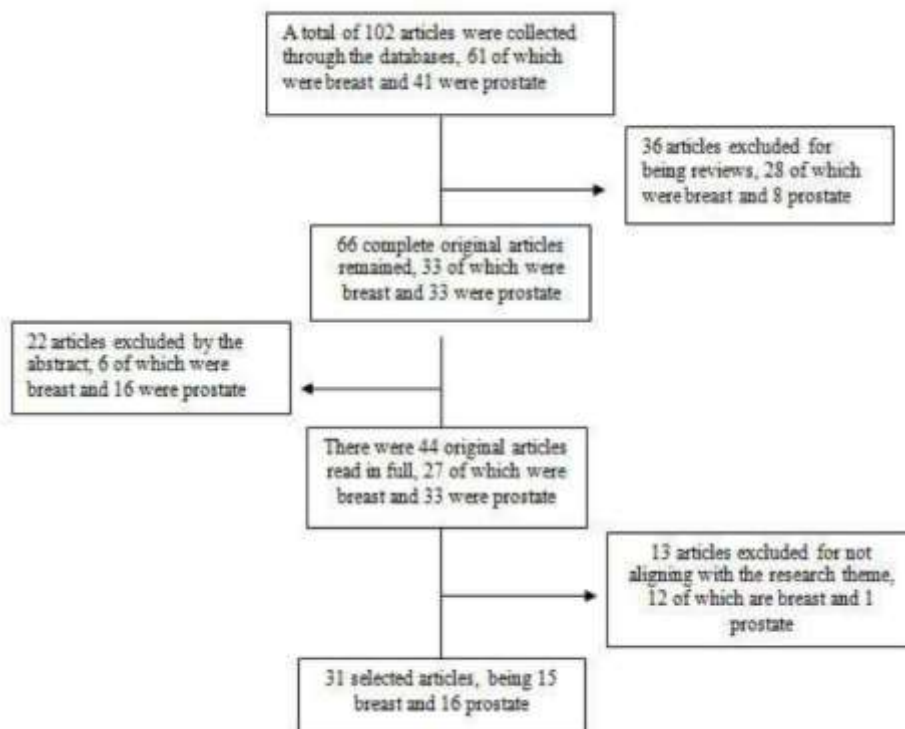
Source: Authors.

4 Discussion

Prostate cancer

The tumor marker most used in the diagnosis and prognosis of prostate cancer is the prostate specific antigen (PSA), however, its contribution is limited because this marker is specific for the prostate and not only for malignancy, therefore, in cases of pathologies such as benign prostatic hyperplasia and prostatitis serum PSA levels may also be elevated (Almeida et al., 2007; Saxby et al., 2020). Therefore, validating new biomarkers that optimize the evaluation of the response to CaP treatment would benefit patients with individualized therapies. In this review we seek to explore relevant studies that focus on promising biomarkers in the clinical management of men diagnosed with PCa.

Patients with castration-resistant prostate cancer (CRPC) are directed to two main antiandrogen drugs (enzalutamide and abiraterone). This medication class meant an advance in the treatment of this neoplasia, in relation to the treatment with androgen deprivation therapy (TPA), improving the quality of life and the overall survival of these men. However, 20-40% of patients treated with these drugs do not benefit from their effects because they acquire primary resistance and almost all have secondary resistance. One study shows the association between resistance to enzalutamide and abiraterone, the detection in CTCs of messenger RNA variant 7 of the androgen receptor splice (AR-V7) and PSA results (Antonarakis et al., 2014). The authors show that 31 patients received treatment with enzalutamide and 31 with abiraterone and PSA measurements were obtained every 1 and 2 months. Thus, 39% and 19% of patients respectively had AR-V7 expressed as CTCs in blood samples, in addition, AR-V7 negative patients had lower PSA response rates and longer PSA progression-free survival and overall survival, the which means that this androgen receptor isoform encoded by the splice variant 7 may represent a predictive biomarker for treatment with antiandrogen drugs, since the expression of AR-V7 in these patients with CRPC does not indicate any form of resistance to taxane chemotherapy . In addition, a study conducted in Canada and the United States has shown that the use of the AR-V7 test can impact decision-making when choosing therapy. Patients with positive AR-V7 were those who had the greatest changes in therapeutic management, which led to clinical improvement due to the use of taxanes (Markowshi et al., 2017).

Another molecular group that is linked to drug resistance in the treatment of CaP are miRNAs. Small RNAs of approximately 22 nucleotides, which at the post-transcriptional level negatively regulate gene expression and when deregulated can serve as oncogenes or tumor suppressing agents. These RNAs can be detected in the serum and serve as predictive biomarkers in resistance to chemotherapy drugs such as docetaxel (Shi et al., 2010). In a study whose objective was to characterize the role of miR-181a in docetaxel-resistant prostate cancer, it measured the expression of miR-181a in C4-2B and DU145 parental and docetaxel-resistant cells in TaxR (DU). It was concluded that the expression of miR-181a is elevated in TaxR cells (8.6 times) and DU145-DTXR (7.4 times) compared to parental C4-2B and DU145 cells, respectively. Overexpression of miRNA-181a significantly improved cell survival in the presence of docetaxel (ie, resisted this treatment) compared to the miR mimicking control in parental C4-2B cells. However, docetaxel-resistant TaxR cells were resensitized by miR-181 to that same drug. The same study also demonstrated cross-resistance to cabazitaxel and resensitization of miR-181a TaxRcomknockdown cells. Thus, these findings are significantly relevant and may contribute to a more appropriate choice of therapy for the patient that presents data that prove resistance to docetaxel (Armstrong et al., 2017).

Another promising proposal for the treatment of patients with CaP is the neuroendocrine biomarkers. Neuroendocrine differentiation (NED) is equivalent to the association of unfavorable prognosis and serum levels of chromogranin A (CgA) and neuron specific enolase (NSE), neuropeptides stored in neuroendocrine cells (Genitsch et al., 2017). Study aimed to assess the value of the markers (NED) to help select the best treatment sequence for abiraterone acetate (AA) and docetaxel-prednisone (DP) in men with mCRPC, showed through blood samples from 88 patients, the levels ofCgA and NSE measured before first line treatment. Patients with a high level of baseline NED markers proved to be more beneficial in receiving a sequence of DP-

AA treatment instead of AA-DP. This group of men had an overall median survival of 21.7 months with DP-AA treatment and 19.9 months with AA-DP treatment, respectively. In addition, the same study found that a patient with mCRPC with elevated serum NED levels, has a response to chemotherapy with PD, decreased levels of NED. According to the authors, this fact is related to patients with high baseline NED levels that respond better to the DP-AA sequence instead of the AA-DP (Fan et al., 2019).

Almost 100% of patients with mCRPC have bone metastasis. These terminally ill men suffer from severe progressive pain, among other consequences of this distension. Bone metabolism occurs through the synthesis of new bone mediated by osteoblasts and bone resorption mediated by osteoclasts. This process is regulated by the balance between the two phenomena, however, in patients with mCRPC this homeostasis is not regulated and ends up being compromised by emphasizing the activity of osteoblasts and, therefore, favoring bone formation (Lara et al., 2014). A prospective multicenter study with the objective of evaluating the predictive capacity of serum bone markers in patients with mCRPC and the risk of mortality was developed between 2002 and 2005 with 52 patients. In the result, it was observed that 34 patients died and 18 were alive at the time of the last evaluation, where the concentrations of bone markers, mainly ICTP and PINP, were higher in the group of deceased compared to survivors ($p < 0.05$) and that the combination of these markers is able to predict mortality in the next 24 months in the analysis performed where AUC values > 0.7 were presented, with sensitivities / specificities between 70% and 80%. Therefore, patients with advanced mCRPC can especially benefit from ICTP and PINP markers as predictors of survival both to be aware of their health status and for the physician to rethink the best additional therapeutic management (Jung et al., 2011).

Breast cancer

Breast cancer is a prevalent malignancy in the female population, as it is a complex disease, several factors interfere with the prognosis and the outcome of a specific therapeutic regimen. Each type of breast cancer has a different behavior, precisely because these neoplastic cells express hormone receptors (estrogen and / or progesterone) and HER2 protein, causing the cancer to vary its way of tumor progression (Manica et al., 2017). The present study was therefore conducted by analyzing the status of different predictive factors in breast carcinoma subtypes, elucidating the correlations of these factors, in order to identify significant relationships between the types of breast cancer. It is necessary to identify predictive biomarkers that assist in individualized therapy in view of the heterogeneities of breast neoplasms.

Studies have observed the relationship of dasurvivin, a member of the apoptosis protein inhibitor family, as an attractive target for treatment against various carcinogens. Survivin expression is constantly related to poor prognosis in a wide variety of cancer patients. To express the expression of survivin, ASOs (survivin oligonucleotide) were employed, which negatively regulates the expression of survivin in human cancer cells, in an attempt to create another therapeutic drug, showing that the function or inhibition of survivin by the oligonucleotide LY2181308 boosted apoptosis in cancer cells and inhibiting the growth of xenograft tumors in nude mice. Furthermore, LY2181308 has been shown to sensitize tumors to chemotherapeutic agents such as gemcitabine, paclitaxel and docetaxel. Due to its differential expression in normal tissues and its function in apoptosis, survivin is a promising target for cancer therapy (Carrasco et al., 2011).

Another promising study is miRNAs, which act as oncogenes and tumor suppressors in the development and metastasis of breast cancer. It is possible that the various roles that miRNAs play have the potential to provide valuable information in a clinical setting, demonstrating the potential to act as both screening tools for stratifying high-risk patients, while informing the decision-making process of treatment (Asia et al., 2018). The miR-143 marker was investigated through data from studies with patients with locally advanced triple negative breast cancer, discriminating the complete pathological response and the polymerase-free chain reaction, receiving neoadjuvant treatment based on fluorouracil-cisplatin / paclitaxel. MiR-143 has been

shown to be a potential predictor of response to neoadjuvant therapy in triple negative breast cancer (García-Vázquez et al., 2019).

In another analysis, it highlights the tumor's circulating DNA (ctDNA), which is found in the bloodstream and refers to the DNA that comes from cancer cells and tumors. CtDNA are small pieces of DNA, usually comprising less than 200 nucleotide blocks in length. The study carried out by means of high-level sequencing of a personalized panel in blood samples, three somatically mutated genes were detected, PIK3CA, TP53 and KMT2C. This study was the first to explore the link between prognosis and ctDNA after neoadjuvant therapy in Chinese breast cancer patients. The incidence of KMT2C mutations was high in patients with breast cancer, especially among patients with triple-negative breast cancer (TNBC). Kaplan-Meier survival and multivariate analyzes show that KMT2C ctDNA could be a predictor of breast cancer recurrence, while the association between KMT2C and efficiency of neoadjuvant therapy was negligible. The study highlights the ability of ctDNA analysis at different times to assess tumor progression and treatment effectiveness, such as predicting breast cancer recurrence (Hao et al., 2020).

The increasing use of the monoclonal antibody trastuzumaboth against the extracellular site of the human epidermal growth factor receptor type 2 (HER2). Its use caused a decrease in the progression of breast cancer in patients who underwent chemotherapy treatment alone or in combination with trastuzumab. Therapy involving anti-HER-2 is an ideal modality, and blocking HER-2 by means of trastuzumab is effective in cases of initial or metastatic breast cancer (Haddad, 2010).

As verified in a study of TRPM2 expression (potential cationic channel of transient receptor), it was observed that the low expression of TRPM2 is used to predict bad results and a greater possibility of recurrence in relation to ER- and HER2 + breast carcinoma. Therefore, TRPM2 is a biomarker for new therapies (Sumoza-Toledo et al., 2016).

Attested by means of a study, in which 678 cases of breast cancer tissue were selected by means of immunohistochemical staining of hormone receptors and growth of human hypodermic, that the increase of the nuclear expression of YAP (regulatory protein of the transcription of genes of cell proliferation and suppression of apoptotic genes) is related to decreased overall survival rate in breast cancer and overexpression of cytoplasmic YAP in HER-2 type breast cancer in which it was associated with shorter disease-free survival rate . That through this, there is an important difference in the expression of YAP and pYAP according to the molecular subtypes and tumor components. Nuclear and cytoplasmic expression of YAP appears to be a prognostic marker for patients with breast cancer (Kim et al., 2014).

It was also shown that hormone receptor (HR) negativity and the high Ki67 protein index are two independent factors to predict a higher complete pathological response (pCR) in breast cancer positive for axillary / HER2-positive lymph nodes. In particular in patients with HR-negative / high Ki67 index, the pCR rate reached 70.0%, suggesting that this patient population may obtain more benefits from neoadjuvant therapy containing paclitaxel, carboplatin and trastuzumab (Ding et al., 2017). We attest to the similarity of pCR biomarkers with the Ki67 marker, associated with cell proliferation and labeling index (LI) at baseline may be predictive of survival rates in patients with breast cancer with HER2 overexpression similar to luminal (Kurozumi, et al., 2015).

It was examined that the absence or low expression of the ADAM33 protein contributes to the increased aggressiveness and metastases of breast cancer. The present study has shown, in an unprecedented way, that ADAM33, in combination with currently available biomarkers, can be a new molecular marker to better determine the prognosis of breast cancer. The importance of ADAM33 in TNBC-negative triple carcinoma and basal-type carcinoma (BLBC) is clear and may improve our knowledge of the most aggressive breast cancer subtypes. In addition, LumA and LumB breast carcinomas showed a strong signal for ADAM33. Conferring that the absence of eobitus metastases was related to the high expression of ADAM33. These results suggest that ADAM33 may be a significant marker of good disease prognosis because breast carcinomas LumA and LumB are less aggressive compared to tumor subclasses HER2 +, TNBC and BLBC (Manica et al., 2017).

The chemokine receptor (CXCR4) is a receptor coupled to transmembrane G protein seven and stimulating tumor growth, angiogenesis and metastasis in various types of cancer. It is a class of biomarker with predictive potential associated with promoting resistance to tamoxifen via the AKT (Protein kinase B) pathway. In addition, the AMD3100 CXCR4 antagonist reversed tamoxifen resistance in breast cancer by inhibiting AKT phosphorylation. As mentioned, the combination of endocrine therapy and other component inhibitors that mediate endocrine resistance is one of the suggested methods for breast cancer resistant to endocrine therapy. The combination of tamoxifen and AMD3100, a specific CXCR4 antagonist, can increase the tumor suppressor effects and reduce the potential side effects arising from the dosage of the drug (Zhou et al., 2020).

5. Conclusion

The results of this study demonstrate the biomarkers with substantial potential in the treatment of breast and prostate cancer. The management in which the results were presented, consider the use and assistance of biomarkers for chemotherapy / radiotherapy, in which they provide the prediction of responses to clinical treatment, and they are associated with better results. The clinical application of these predictive biomarkers can enable numerous advantages, among them, better adherence to treatment because it becomes a therapy based on the genetic individuality of a given patient. Consequently, with a more specific therapy, less toxicity and possible side effects are observed, which reduces expenses with medications and additional hospitalizations.

However, there are no universally accepted predictive markers of response to cancer treatment, and the few that have been investigated in the neoadjuvant context are most often predetermined markers are present. The accession of new biomarkers can expand the therapeutic regimen options currently available to doctors. Therefore, it is necessary to expand experiences to characterize the real value of using each biomarker in cancer therapy, since, currently, studies demonstrate positive results with safe, efficient and cost effective therapies with the help of pharmacogenetics.

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