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Thesis presented to the Institute of Biosciences of the University of São Paulo, as a requirement to obtain the Doctoral degree in Biological Sciences, in the field of Biology (Genetics).

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São Paulo
2024

Abstract

Breast cancer (BC) is a complex disease that results from the synergic interaction of genetic and environmental factors. While most cases are sporadic and emerge from an accumulation of genetic mutations in somatic cells throughout life, it is estimated that 5 to 10% of cases have a strong germline genetic component that increases the likelihood of developing BC. Some well-established BC predisposing genes, such as *BRCA1* and *BRCA2*, are frequently investigated in high-risk patients (e.g., multiple affected relatives or with early onset diagnosis). However, a substantial proportion of hereditary BC cases remain without a determined genetic etiology.

To address this knowledge gap and uncover novel BC predisposing genes, we conducted a study based on family-based exome sequencing (ES) analysis in a discovery cohort integrated with an independent validation phase in a group composed of women with BC from different nationalities. Candidate variant prioritization was based on quality, populational frequencies, prediction of impact in protein function, and segregation analysis among the affected women within the families.

In the discovery phase, we identified by ES analysis 38 candidate genes harboring 38 unique likely deleterious variants. This evaluated cohort comprised eight Brazilian families with 29 women with a BC history, all negative for pathogenic or likely pathogenic variants in known predisposing genes. Among the candidate genes, *SMARCA4, RAD54L2, and SHQ1* stand out because of their biological functions. *SMARCA4* emerged as the most promising candidate, since it is a known gene for rhabdoid and ovary cancer predisposition, and participates in processes such as cell growth and DNA damage repair. In an independent validation phase, the *SMARCA4* was screened for deleterious variants in NGS data from three different cohorts: a) Brazilian women with BC diagnosis (n = 291); (b) unrelated Polish women with familial BC (n = 510); and (c) Canadian women with BC diagnosis aged 40 or younger (n = 815). Following, we performed an association study using a case-control approach on the UK Biobank database of females with and without BC (14,130 cases and 162,980 controls), uncovering an association between rare loss-

of-function (LoF) *SMARCA4* variants and BC risk (odds ratio = 4.94, 95% CI = 0.05-1.28, P = 0.006).

The independent validation phase cohorts were assessed in collaboration with Dr. Dirce Maria Carraro, a researcher at the A.C. Camargo Cancer Center, and during a six-month internship at the Women's College Hospital, an institution fully associated with the University of Toronto. This internship was supervised by Dr. Mohammad Reza Akbari and in collaboration with Dr. Steven Narod, both professors at the University of Toronto.

This is the first proposed association between LoF *SMARCA4* variants and predisposition to BC, as a moderate penetrance susceptibility gene. We suggest that these findings support the investigation of *SMARCA4* as a novel BC predisposition gene, both in a basic research setting as well as in genetic testing offered to high-risk patients. Therefore, our results hold significant potential to enhance the understanding in the field and also to improve informed clinical management and genetic counseling in the future.

Resumo

O câncer de mama (CM) é uma doença complexa que resulta da interação sinérgica de fatores genéticos e ambientais. Embora a maioria dos casos sejam esporádicos e decorram do acúmulo de mutações genéticas em células somáticas ao longo da vida, estima-se que 5 a 10% dos casos tenham um forte componente genético em linhagem germinativa que aumenta a probabilidade de desenvolver CM. Alguns genes de predisposição ao CM bem estabelecidos, como *BRCA1* e *BRCA2*, são frequentemente investigados em pacientes de alto risco (por exemplo, múltiplos parentes afetados ou com diagnóstico precoce). No entanto, uma proporção substancial de casos de CM hereditário permanece sem uma etiologia genética determinada.

Para abordar esta lacuna de conhecimento e descobrir novos genes de predisposição ao CM, conduzimos um estudo baseado na análise de sequenciamento de exoma (SE) de famílias em uma coorte de descoberta integrada a uma fase de validação independente em um grupo composto por mulheres com CM de diferentes nacionalidades. A priorização das variantes candidatas baseou-se na qualidade, frequências populacionais, previsão do impacto na função proteica e análise de segregação entre as mulheres afetadas nas famílias.

Na fase de descoberta, identificamos pela análise SE 38 genes candidatos contendo 38 variantes únicas prováveis deletérias. Esta coorte avaliada compreendeu oito famílias brasileiras com 29 mulheres com histórico de CM, todas negativas para variantes patogênicas ou provavelmente patogênicas em genes de predisposição conhecidos. Dentre os genes candidatos, *SMARCA4*, *RAD54L2* e *SHQ1* se destacam por suas funções biológicas. *SMARCA4* emergiu como o candidato mais promissor, uma vez que é um gene conhecido para predisposição de tumores rabdóides e câncer de ovário, e participa de processos como crescimento celular e reparo de danos no DNA. Em uma fase de validação independente, variantes deletérias em *SMARCA4* foram investigadas em dados NGS de três coortes diferentes: a) mulheres brasileiras com diagnóstico de CM (n = 291); (b) mulheres polonesas não aparentadas com CM familiar (n = 510); e (c) mulheres canadenses com diagnóstico de CM com 40 anos ou menos (n = 815).

Posteriormente, realizamos um estudo de associação usando uma abordagem de caso-controle no banco de dados UK Biobank, com dados genômicos de mulheres com e sem câncer de mama (14.130 casos e 162.980 controles). Nós descobrindo uma associação entre variantes raras de perda de função em *SMARCA4* e risco de CM (odds ratio = 4.94, IC 95% = 0.05-1.28, P = 0.006).

As coortes da fase de validação independente foram avaliadas em colaboração com a Dra. Dirce Maria Carraro, pesquisadora do A.C. Camargo Cancer Center, e durante um estágio de seis meses no *Women's College Hospital*, instituição associada à Universidade de Toronto. Este estágio foi supervisionado pelo Dr. Mohammad Reza Akbari e em colaboração com o Dr. Steven Narod, ambos professores da Universidade de Toronto.

Esta é a primeira associação proposta entre variantes de perda de função em *SMARCA4* e predisposição ao CM, como um gene de predisposição de penetrância moderada. Sugerimos que estes resultados apoiem a investigação de *SMARCA4* como um novo gene de predisposição para CM, tanto num ambiente de investigação básica como em testes genéticos oferecidos a pacientes de alto risco. Portanto, nossos resultados têm um potencial significativo para melhorar a compreensão na área e também para melhorar o manejo clínico informado e o aconselhamento genético no futuro.

Introduction

Cancer, a genomic disease

Cancer is the term for multiple diseases characterized by uncontrolled cell proliferation and the accumulation of mutations, shaping the multigenic basis of cancer. A cancer cell can originate from any histological cell type in the body. Therefore, more than a hundred subtypes of cancers exist and have different prognoses, progression, and responses to treatment (BYRNE *et al.*, 2023; DAGOGO-JACK; SHAW, 2018). Cancer can be primarily defined as a genomic disease caused by the multistep accumulation of alterations in driver genes underlying the oncogenesis. These alterations mostly originate in somatic cells, potentially giving rise to sporadic cancer; however, part of these genetic variants is germline, related to hereditary cancer (TAKESHIMA; USHIJIMA, 2019).

The oncogenesis process is triggered mainly by deleterious alteration in the sequence or expression of proto-oncogenes and tumor suppressor genes. Proto-oncogenes are genes that positively regulate cell proliferation, differentiation and several other functions in response to external and internal signals, leading to the orderly mitotic division of cells. Tumor suppressor genes encode proteins responsible for several critical cellular functions, including cell cycle control, apoptosis, cell differentiation, surveillance of genomic integrity, and DNA repair (KONTOMANOLIS *et al.*, 2020).

Genetic and epigenetic alterations that result in the activation of proto-oncogenes in oncogenes or the inactivation of tumor suppressor genes lead to oncogenesis by the acquisition of permissive characteristics for tumor progression. Hanahan and Weinberg termed these key characteristics cancer hallmarks (HANAHAN; WEINBERG, 2000). Based on this model, the hallmarks of cancer cells include the ability to continuously divide, evade tumor suppressors and the immune system, achieve replicative immortality, invade and spread to other parts of the body, promote angiogenesis, resist cell death, cause inflammation that supports tumor growth, disrupt normal cellular metabolism, and promote genetic instability and mutations. Further suggested emerging hallmarks and facilitating traits encompass activating phenotypic adaptability, non-mutational epigenetic reconfiguration, polymorphic microbiomes, and senescent cells (HANAHAN, 2022).

Breast cancer epidemiology and genetic etiology

Breast cancer (BC) has a high worldwide prevalence, with approximately 2.29 million new cases diagnosed and 666,100 deaths, representing 12.4% of all cancer cases in both sexes and 23.8% of the total in women in 2022, year of the last estimates published by the World Health Organization (FERLAY *et al*., 2024). In the USA and the European Union, the women lifetime risk of developing BC is 12.9% and 9.1%, respectively (ECIS, 2023; Siegel et al., 2023). In Brazil, an estimated 73,610 new BC cases per year are expected for the triennium of 2023-2025, with an incidence rate of 66.54 cases per 100,000 women (INCA, 2024).

Several risk factors have been associated with predisposition to BC: reproductive and menstrual history, obesity, alcoholism, exposure to ionizing radiation, physical inactivity, presence of atypical hyperplasia of the breast, prolonged use of hormonal therapy during menopause, breast tissue density, familial history of BC, ethnicity, and germline mutations in cancer predisposing genes (SUN *et al.*, 2017).

It has been observed that some important risk factors are associated with hormonal states in different age groups, such as nulliparity and menstrual history (DALY et al., 2024). This observation is consistent with population surveys, which show that around 70% of the diagnosed breast tumors are hormone receptor-positive. This means the breast tumor cells express estrogen and/or progesterone receptors at a higher level than normal breast cells (POMPEI; FERNANDES, 2020). Positive modulation of cell division in breast and other organs is associated with the level of these hormones, which is directly related to the oncogenesis of BC. This association may be even more relevant in women with high hormonal levels, often present in the pre-menopause phase or as a result of prolonged hormone replacement during or after menopause (LOIZZI *et al.*, 2023).

Due to hormonal modulation acting differently between sexes and the more significant proportion of tissues frequently altered in BC (e.g., mammary glands), women present a greater cumulative vital risk than men: only 1% of total cases occur in males, approximately <1 in every 100,000 men are diagnosed with BC (GUCALP *et al.*, 2019). In addition to the female sex, advanced age is the main risk factor for BC, with a median age of diagnosis of 62 years (SIEGEL *et al.*, 2023). It is related to the window time for the accumulation of a critical mass of genetic alterations in proto-oncogenes and tumor suppressors. The exposure to

endogenous and environmental factors throughout the lifespan generates these genetic alterations, which will contribute to transforming normal cells into tumor cells (Sung et al., 2021).

Despite identifying several risk factors, it is still impossible to determine the exact risk inherent to each individual. This highlights the relevance of researching genetic and environmental factors in an integrated manner to better understand susceptibility to BC.

Hereditary breast cancer: Genetic architecture and clinical features

With the advance of next-generation sequencing (NGS) techniques, it was possible to increase the identification of germline variants that confer susceptibility to BC, as well as to deepen the study of expression profiles in tumor tissue of genes responsible for the initiation and evolution of different molecular subtypes (NOLAN; LINDEMAN; VISVADER, 2023; WILCOX *et al.*, 2023).

According to the National Comprehensive Cancer Network (NCCN) (DALY *et al.,* 2024), hereditary BC (HBC) could be described as the presence and segregation to offspring through the mother and/or father of pathogenic or likely pathogenic (pathogenic/likely pathogenic) variants that increase the risk for BC throughout lifetime, exhibiting in general an autosomal dominant inheritance pattern. The HBC cases have a higher likelihood of exhibiting certain clinical features, such as two or more diagnoses of BC on the same side of the family, early age of onset (pre-menopause), bilaterality, and association of BC with other related neoplasms (e.g., ovarian cancer or early-onset prostate cancer). The NCCN guideline also describes familial BC as sharing some but not all features of hereditary cases. However, they generally do not exhibit the autosomal dominant inheritance patterns or early age of onset consistent with hereditary BC cases. Familial BC may be associated with clustering of sporadic cancer cases by chance among families (phenocopy), deleterious germline variants in low penetrance genes, a shared environment among relatives, or a combination of these factors.

The definition of hereditary or familial BC is not consensus in the literature. However, in the context of this thesis, we opted to use the term HBC to refer to cases compatible with an autosomal dominant inheritance pattern and presenting complementary clinical features, such as at least two other diagnoses of BC on the

same side of the family, bilaterality and early age of onset. We applied this terminology even if the germline causal variant in predisposing genes is unknown.

It is estimated that 5 to 10% of all BC cases have an underlying strong genetic component. Currently, more than 30 established and candidate genes are associated with BC predisposition (DORLING *et al.*, 2021; WILCOX *et al.*, 2023), many of them playing a role in restricted pathways and promoting different levels of cancer risk (NIELSEN; VAN OVEREEM HANSEN; SØRENSEN, 2016). Notwithstanding, only 4 to 5% of all female BC cases were found to be caused by pathogenic variants in high-penetrance (odds ratio [OR] ≥ 5) BC susceptibility genes, such as *BRCA1* and *BRCA2* (*BRCA1/2*) (DORLING *et al.*, 2021).

Deleterious variants in high-penetrance predisposing genes usually cause well-defined syndromes, with distinct relative risks associated with each potentially affected organ (IMYANITOV *et al.*, 2023). Among the high-penetrance genes predisposing to BC, *BRCA1*/*2* have the highest frequency of mutations in different populations, presenting a combined frequency of 0.5% among African Americans in the USA and 0.25% among the European non-Finnish population (ABUL-HUSN *et al.*, 2020; MAXWELL *et al.*, 2016). However, specific population groups, such as Ashkenazi Jews, may present higher mutation frequencies in these genes, with 2.5% carrying one of the three founder mutations (BEST *et al.*, 2019)

Established breast cancer susceptibility genes

BRCA1/*2* are tumor suppressor genes that play a central role in the maintenance of genome stability. When one of the alleles of either gene harbors a pathogenic/likely pathogenic germline variant, there is an increased lifetime risk to the development of the hereditary breast and ovarian cancer (HBOC) syndrome, with an autosomal dominant mode of inheritance (NEWMAN *et al.*, 1988; WOOSTER *et al.*, 1995). Women carrying germline pathogenic variants in *BRCA1* or *BRCA2* have a cumulative vital risk of developing BC of 57-65% and 45-55%, and cancer of ovary of 39-44% and 11-18%, respectively, for mutations in each of the two genes (NIELSEN; VAN OVEREEM HANSEN; SØRENSEN, 2016).

Recent studies investigated the mutational burden in known predisposing genes in the Brazilian population (ALEMAR *et al.*, 2017; BANDEIRA *et al.*, 2020; CIPRIANO *et al.*, 2019; DE OLIVEIRA, Jarbas Maciel *et al.*, 2022; FERNANDES *et al.*, 2016;

GUINDALINI *et al.*, 2022; SILVA *et al.*, 2014; TORREZAN *et al.*, 2018). However, the relatively small number of evaluated women does not represent all the genetic landscape of the Brazilian population, with approximately 200 million inhabitants in a recognized ethnically admixed population. In these studies, conducted with non-uniform selection criteria, the frequencies of pathogenic/likely pathogenic variants in *BRCA1/2* ranged from 9.8% to 22.5%. Studies with North American, European, and Asian populations conducted in patients with high-risk breast and/or ovarian cancer described *BRCA1/2* mutation frequencies between 6.1 and 17.3%, depending on the selection criteria of patients (COUCH *et al.*, 2015; DORLING *et al.*, 2021; LI, Jun Yan *et al.*, 2019; TUNG *et al.*, 2016; WILCOX *et al.*, 2023).

Beyond *BRCA1/2*, an additional portion of HBC cases is caused by pathogenic/likely pathogenic variants in genes with moderate penetrance (2≤ OR <5) that encode protein acting mainly in homologous recombination DNA repair, as well as in other pathways responsible for maintaining genome integrity (NIELSEN; VAN OVEREEM HANSEN; SØRENSEN, 2016). Diagnostic tests are primarily based on sequencing the coding region of high- and moderate-penetrance genes such as *ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, MAP3K1, NBN, PALB2, PTEN, RAD50, RAD51C*, and *TP53*. However, deleterious variants in these genes can explain only a portion of the HBC cases. Additionally, genome-wide studies continue to propose putative low penetrance genes (1< OR <2) associated with BC, which may contribute to an increased risk of BC under an oligogenic/polygenic model (LU *et al.*, 2019; ZHANG *et al.*, 2020).

Investigating novel breast cancer predisposing genes

Therefore, despite the theoretical framework about the genetic etiology and risk factors that predispose the oncogenesis of BC, there is still a relevant gap in the knowledge of the full spectrum of germline variants associated with HBC. Expanding the genetic architecture of BC susceptibility and assessing the risk attributed to potentially deleterious variants is extremely important.

For such investigation, two experimental designs are frequently employed using germline DNA samples: (a) a family-based approach based on exome sequencing (ES) or genome sequencing (GS) analyses of BC-affected members in the same family, searching for rare deleterious variants co-segregating with the phenotype; (b)

case-control studies, based on linkage or ES/GS performed in large cohorts of unrelated BC females irrespective of the family BC history, aiming to identify variants enriched in cancer cases compared to unaffected controls (ROTUNNO *et al.*, 2020). This approach can uncover a high degree of locus heterogeneity, being more powerful when ethnically homogeneous populations are studied, and with very large cohort sizes (DORLING *et al.*, 2021; WILCOX *et al.*, 2023; ZHANG *et al.*, 2020).

In the family-based approach, performing ES on relatives with BC segregating in an autosomal dominant pattern increases the likelihood of identifying rare deleterious variants in high/moderate penetrance genes. The more distant the kinship of the affected subjects, the smaller the list of shared variants, which increases the probability of identifying variant(s) likely associated with the phenotype. On the other hand, the pitfall is the inclusion of phenocopies in this approach, since BC has a high prevalence in women (DALY *et al.,* 2024).

Rotunno and collaborators (2020) conducted a systematic literature review of 186 articles that utilized ES and/or GS to explore genetic susceptibility to different types of cancer. Among these studies, 86% of them primarily applied the family-based approach, while 15% evaluated cohorts of unrelated individuals with a history of BC, compared to unaffected controls. The authors showed that the majority of studies explored a limited number of cancer cases (2-10 cases in 53% of total studies), a restricted number of families (1-10 in 54% of total studies), and only a few cases per family (1 or 2 cases in 61% of total studies) (**Table 1**).

Table 1. Number and percentage of cancer cases and families evaluated by study. Adapted from Rotunno et al., 2020.

Cancer cases evaluated	**Articles (%)**	**High-risk families evaluated**	**Articles (%)**	**Mean cases sequenced per family**	**Articles (%)**
2–3	62 (33%)	1	73 (39%)	1	49 (26%)
4–10	38 (20%)	2–10	27 (15%)	2	66 (35%)
11–50	39 (21%)	11–50	40 (22%)	3	27 (15%)
51–100	19 (10%)	51–100	10 (5%)	4	10 (5%)
101–1,000	22 (12%)	101–1,000	6 (3%)	5	4 (2%)
>1,000	6 (3%)	>1,000	2 (1%)	6–7	3 (2%)
Total	186 (100%)	Total	160 (86%) *	Total	160 (86%) *

*The sum of percentages does not add up to 100% due to studies using multiple approaches.

Such numbers reflect the challenges of performing ES and/or GS on a large number of affected families and their relatives. The authors found that studies with more families and affected family members were more likely to uncover candidate genes.

Notably, data obtained from families in the Brazilian population are especially relevant, as they are still underrepresented in international genomic databases or studies that investigate families with multiple cases of BC (DE OLIVEIRA, Thais C.; SECOLIN; LOPES-CENDES, 2023; ROTUNNO *et al.*, 2020).

To broaden the landscape of genetic alterations that impact BC susceptibility, we aimed to uncover novel BC predisposing genes using a combination of family-based ES and validation of the candidate genes in large cohorts of BC patients. Thus, in the discovery phase of our present study, ES was performed in eight Brazilian HBC families with multiple affected females (29), who were previously tested using NGS panel and found negative for pathogenic/likely pathogenic variants in the main BC predisposing genes: *ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, MAP3K1, NBN, PALB2, PTEN, RAD50, RAD51C,* and *TP53*.

Subsequently, in the independent validation phase, the candidate genes that emerged from the previous step were screened for deleterious variants in NGS data from Brazilian, Canadian and Polish cohorts.

As the final step of the independent validation phase, we performed a case-control analysis using a UK Biobank database. The purpose was to investigate the association of deleterious variants in selected candidate genes obtained during the discovery phase with BC predisposition in large cohorts. In total, we assessed the sequence data from 14,130 cases (women with BC history) and 162,980 controls (women with no reported history of cancer). This combined approach was recently applied to pinpoint novel BC predisposing genes that present a monogenic mode of inheritance, such as *RECQL*, *ATRIP*, and *MAP3K1* (CYBULSKI *et al.*, 2015, 2023; WILCOX *et al.*, 2023).

The results obtained during this doctorate are presented in the following chapter as an original article. Another original article describing the latest doctorate findings is currently being written.

Conclusions

Our findings demonstrate for the first time the association between LoF *SMARCA4* variants and predisposition to BC, as a moderate penetrance susceptibility gene (OR < 5). Additionally, this study highlights the relevance of validating findings from homogeneous familial contexts in large population cohorts, especially for very rare genetic variants such as germline LoF variants in *SMARCA4*.

Therefore, the identification of *SMARCA4* as a novel BC predisposing gene holds significant potential to positively impact informed clinical management and genetic counseling. While this study represents the first to elucidate the role of *SMARCA4* in BC susceptibility, further functional investigations are needed to elucidate the impact of germline LoF and missense variants at both the protein and cellular levels. Subsequently, integrating this gene into genetic testing offered to high-risk BC patients could offer several benefits, including elucidation of molecular etiology, identification of family members at risk of hereditary cancer, and tailored BC screening options.

This study has special relevance because it was conducted using data obtained from families in the Brazilian and Latin American populations, which are still underrepresented in international genomic databases or in studies that investigate families with multiple cases of BC.

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