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PROGRAMA DE PÓS-GRADUAÇÃO GRADUAÇÃO EM MEDICINA E CIÊNCIAS DA SAÚDE
DOUTORADO EM MEDICINA E CIÊNCIAS DA SAÚDE

ALESSANDRA BORBA ANTON DE SOUZA

ACESSO AO TESTE GENÉTICO GERMINATIVO PARA CÂNCER HEREDITÁRIO EM MULHERES COM CÂNCER DE MAMA:

ANÁLISE DO ESTUDO AMAZONAIII

Porto Alegre
2023

PÓS-GRADUAÇÃO - *STRICTO SENSU*

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do Rio Grande do Sul

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Aprovado em:

BANCA EXAMINADORA:

Dedicatória

Para Catarina, que me permitiu viver a minha maior transformação e ilumina a minha vida.

AGRADECIMENTOS

Ao longo desse trabalho amadureci. São pelo menos 7 anos lendo sobre a temática de câncer de mama hereditário. Durante o tempo de 4 anos do doutorado, teve pandemia COVID19, mudanças de locais de trabalho, perdas, gestação e nascimento. E construção de um artigo. Me permito compreender e aceitar que cada vez me surgem mais dúvidas e menos certezas. Essa persistência e paciência com os estudos, no meu próprio ritmo, foram parcialmente inspiradas pelos mestres que encontrei na minha trajetória na medicina, e parcialmente semeadas em mim pela minha família.

Eu contei com a sorte de ter como professores, mastologistas e oncologistas, pessoas admiráveis que me inspiraram desde sempre na minha trajetória: Dr Antonio Frasson, Dr Felipe Zerwes, Dra Betina Vollbrecht, Dra Janaína Viegas, Dr Carlos Barrios, Dr Marcio Debiase, Dr Gustavo Werutsky. Outros tantos mestres que me deparei e me ajudaram como: Dr João Steibel, Dra Marta Hentschke, Dr Tomas Reinert, entre tantos.

Ao longo da curiosidade e estudos sobre câncer de mama hereditário tive a honra de ser orientada no mestrado pela Dra Patricia Prolla e no doutorado pelo Dr André Fay. Duas pessoas que também me ensinaram muito e inspiraram.

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RESUMO

Importância: Estima-se que 10% das mulheres com câncer de mama (CM) têm uma variante patogênica (VP) em algum gene de alto ou moderado risco associado ao CM. A identificação dessas VPs possibilita: mudanças no tratamento cirúrgico e radioterápico, decisão para o uso de terapias direcionadas, seleção de exames de imagem no seguimento individualizados, estratégias para redução de risco de novos canceres e identificação e manejo de familiares em risco. O acesso ao teste genético germinativo (GGT – *germline genetic test*), o qual identifica os indivíduos com CM hereditário, evoluiu na última década com maior oferta e menos custo nos testes genéticos, assim como um aumento nos indivíduos identificados como portadores dessas VPs. Com base nos benefícios citados, as recomendações atuais para a realização de GGT variam desde a identificação de indivíduos de alto risco para CM hereditário até a recomendação de testar todas as mulheres com CM. Apesar de todos esses avanços e recomendações, o número de mulheres com CM testadas continua baixo em todo o mundo, incluindo países de baixa e média renda (LMIC – *low-and-middle-income country*). A frequência de testes realizados e as estratégias de melhorias ao acesso ao GGT são desconhecidos no Brasil. **Objetivo**: Analisar a frequência de realização do GGT em mulheres com CM e identificar as barreiras para a realização do GGT em LMIC.

Metodologia: Análise transversal do estudo de coorte prospectivo, multicêntrico, brasileiro em mulheres com câncer de mama, AMAZONA III. Foram coletados dados relacionados ao acesso e frequência do GGT na coorte e um grupo de alto risco para CM hereditário foi identificado. Variáveis das pacientes e dos centros de tratamentos foram analisadas para identificar possíveis barreiras a realização do GGT através de análise de regressão multivariada de Poisson associando as varáveis com a realização do GGT. Um valor de $p< 0,05$ foi considerado significativo.

Resultados: De um total de 2.974 mulheres da coorte, 1.476 (49%) foram classificadas como grupo de alto risco para CM hereditário e 289 dessas 1.476 (19.58%) foram classificadas como não sendo de alto risco pelo seu próprio centro de tratamento. O aconselhamento genético foi recomendado para 521 (17% da coorte e 35,2% do grupo de alto risco) e 282 (9% da coorte e 19% do grupo de alto risco) realizaram o GGT. Entre as pacientes classificadas de alto risco, 97% das tratadas pelo sistema de saúde público e 56% das mulheres tratadas pelo sistema de saúde privado não realizaram o GGT. Idade, escolaridade, renda mensal, assim como a presença de profissional para realização de aconselhamento genético e ser tratada num centro acadêmico foram associadas a taxa de realização do GGT ($p<0,05$). Entre as 282 mulheres testadas, 50 (17%) tinham VP no GGT.

Conclusão: Nesta grande coorte de mulheres brasileiras com CM, menos de 10% realizaram o GGT. Mesmo no sistema de saúde privado, onde o teste é disponível, menos de 50% das pacientes de alto risco foram testadas. As disparidades e barreiras identificadas enfatizam a necessidade de investimento em educação e podem auxiliar nas estratégias para melhorar o acesso ao aconselhamento e realização do GGT em LMIC.

Palavras-Chave: Câncer de mama, Síndrome Hereditária de Câncer de Mama e Ovário, Teste genético.

ABSTRACT

Importance: It is estimated that 10% of women with breast cancer (BC) have a pathogenic variant (VP) in some BC-associated genes. The identification of these PVs associated with hereditary BC allows for changes in local treatment, use of targeted therapies, individualized follow-up imaging tests, reduced risk of new cancers, and identification and management of family members at risk. Access to germline genetic testing (GGT) has evolved over the last decade with greater availability and lower cost of genetic testing, as well as an increase in individuals identified as having PV. Based on the cited benefits, current recommendations for performing GGT range from identifying individuals at high risk for hereditary BC to recommending testing all women with BC. Despite all these advances and recommendations, the number of women with hereditary BC remains low worldwide, including in low- and middle-income countries (LMIC). The frequency of tests performed and the strategies for improving access are unknown in Brazil.

Objective: To analyze the frequency of GGT performance in women with BC and to identify the barriers to GGT uptake in an LMIC.

Methodology: Cross-sectional analysis in the prospective, multicenter, Brazilian cohort study of women with BC, AMAZONA III. GGT access and frequency data were collected, and a high-risk group for hereditary CM was identified. Patient and treatment center variables were attended to identify potential barriers to performing the GGT through multivariate Poisson regression analysis associating variables with performing the GGT. A value of $p< 0.05$ was considered significant.

Results: Of 2974 women in the cohort, 1476 (49%) were classified as a high-risk group for hereditary BC, and 289 of these 1476 (19.58%) were classified as not high-risk by their treatment center. Genetic counseling was recommended for 521 (17%) of the cohort and only 282 (9%) underwent the GGT. Among patients classified as high risk, 97% of those treated by the public health system and 56% of the women treated by the private health system did not undergo the GGT. Age, schooling, monthly income, as well as the presence of a professional to provide genetic counseling and being treated at an academic center were associated with the GGT performance rate ($p<0.05$). Among the 282 women tested, 50 (17%) had VP in the GGT.

Conclusion: In this robust cohort of women with BC, less than 10% underwent the GGT. Even in the private health system, where the test is available, less than 50% of high-risk patients have been tested. The disparities and barriers identified emphasize the need for investment in education and can help with strategies to improve access to counseling and the performance of the GGT in LMIC.

Keywords: Breast Cancer, Hereditary Breast and Ovarian Cancer Syndrome, Genetic Testing.

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1 INTRODUÇÃO

1.1 CÂNCER DE MAMA NO MUNDO

O câncer de mama (CM) foi a neoplasia mais diagnosticada no mundo em 2020 e é a principal causa de morbidade e mortalidade relacionada a câncer entre as mulheres, com uma estimativa de mais de dois milhões de novos casos anualmente [1]. A incidência do CM vem crescendo mundialmente, particularmente nos países em desenvolvimento, tornando esse diagnóstico um tema de interesse de saúde pública. Esforços globais e medidas de saúde pública visando o controle da doença são necessários e devem incluir um conjunto de ações visando melhorias na prevenção primária, diagnóstico precoce, rastreamento e tratamento [2].

O CM é uma doença hetereogênea caracterizada por inúmeras alterações somáticas genéticas e inúmeras instabilidades genômicas, tornando sua apresentação e tratamento uma tarefa complexa [3]. Devido essa complexidade, uma equipe multidisciplinar desde o diagnóstico até o tratamento é necessária para se ter os melhores desfechos. O prognóstico das mulheres com CM melhorou significativamente nos últimos anos, principalmente nos países com melhores acessos a diagnóstico precoce e tratamento personalizado. Os países de alta renda (HIC – *high-income countries*) apresentam taxas de incidência mais elevadas para CM quando comparados com países de média e baixa renda (LMIC – *low-and-middle income countries),* enquanto os LMIC apresentam as taxas mais altas de mortalidade [4]. Na maioria dos HIC 5 anos de sobrevida global ultrapassam os 90%, enquanto em alguns países africanos essa taxa fica em torno de 66%, chegando a 12% na Uganda[2] .

1.2 O CÂNCER DE MAMA NO BRASIL

Os LMIC enfrentam alta mortalidade relacionada ao câncer. Estima-se que 60% das mortes relacionadas ao CM no mundo ocorram em países economicamente em desenvolvimento, como o Brasil. Os desafios são expressivos, sendo mais comum o CM em estágios mais avançado ao diagnóstico e acesso inadequado ao tratamento ideal [4,5]. Na América Latina vários países geraram programas de ações para melhorias na prevenção e controle do

CM, mas ainda seguem pendentes base de dados para avaliações de resultados que consigam analisar a eficácia e impacto dessas implementações. Embora reduções significativas na mortalidade por CM tenham sido alcançadas em HICs, o mesmo não pode ser dito na América Latina (LATAM – *Latin American*)[6].

Na LATAM, se estima cerca de 200.000 novos casos de CM e mais de 52.000 mortes anualmente. Uma grande proporção dos casos são diagnosticados em estágios mais avançados ou metastáticos, quando o sucesso do tratamento do câncer é mais limitado[7]. Outro desafio da LATAM é a alta prevalência de mulheres jovens com CM, o que pode ser parcialmente explicado pela pirâmide etária desses países, aonde as mulheres jovens compreendem 30% da população[8].

O Brasil tem quase 215 milhões de habitantes em uma grande área territorial e é considerado como um país de renda média alta (MIC – Middle Income Country), segundo o Grupo Banco Mundial. No Brasil, estima-se 74.000 novos casos de CM por ano em 2023 [9,10]. Existem algumas diferenças relevantes entre as regiões do país, incluindo heterogeneidade socioeconômica e variabilidade na qualidade dos serviços de saúde, e também faltam registros nacionais de câncer completos[11,12].

1.3 O CÂNCER DE MAMA HEREDITÁRIO E O TESTE GENÉTICO

A origem do CM é multifatorial e a grande maioria dos casos são considerados esporádicos. Estima-se que cerca de 5 a 10% dos casos de CM sejam associados a fatores hereditários, sendo a maioria atribuídos a variantes patogênicas ou provavelmente patogênicas (VP) nos genes *BRCA1* e *BRCA2* (*BRCA1/2*). Os cânceres hereditários são caracterizados por VP em genes de alta ou moderada penetrância associadas com uma maior probabilidade de desenvolver câncer, transmissão vertical através do pai ou da mãe e, também, apresentam associação com outros tipos de câncer[13,14] .

O diagnóstico de uma VP em um gene de alta e moderada penetrância associado ao CM resulta em condutas diferenciadas de manejo para o paciente e familiares em risco. Existem diretrizes para manejo de CM hereditário incluindo aconselhamento pré e pós teste genético,

critérios para realização do teste genético com identificação das pacientes de alto risco e as condutas clínicas de acordo com cada gene alterado relacionado ao CM[15–19].

Para identificar o CM hereditário, o teste genético germinativo (GGT- *germline genetic testing*) é uma ferramenta crucial. Diversas organizações recomendam diretrizes para a realização do GGT para indivíduos com risco de CM hereditário[19–22] . Os critérios para testagem do *National Comprehensive Cancer Network Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic* (NCCN) são atualizados, de fácil acesso *on-line* e por isso um dos mais utilizados na prática clinica e em estudos[17] .

Estudos americanos demonstram inúmeras barreiras para a não realização do teste genético e menos de 50% dos casos de pacientes com risco para CM hereditário realizam o teste [23–25]. Algumas barreiras de acessibilidade ao teste descritas em estudos prévios são: o custo do teste genético e poucos profissionais habilitados para a realização de aconselhamento genético[26].

No Brasil, assim como outros LMIC, o Sistema público de Saúde não contempla a realização de teste genético para câncer e em torno de 75% da população brasileira depende desse sistema de saúde[27]. No Brasil, existem poucas publicações analisando os dados epidemiológicos das pacientes com CM, especialmente aquelas em risco para câncer hereditário. O estudo AMAZONA III é um estudo de coorte multicêntrico, prospectivo com novos casos de CM invasor em 23 centros, sendo o maior estudo epidemiológico do Brasil com dados demográficos, clínicos-patológicos, terapêuticos e de sobrevida relacionado ao CM.

2 REVISÃO DE LITERATURA

2.1 O QUE SABEMOS

O CM é o câncer mais diagnosticado entre as mulheres, globalmente, e esforços de saúde pública são necessários sobre esse tema. O CM hereditário é raro e essencial de ser identificado, pois a detecção de VP nessa pequena proporção de pacientes tem impacto nas decisões de rastreamento, redução de risco e tratamento cirúrgico, radioterápico e medicamentoso[15,17].

A identificação de predisposição ao câncer hereditário permite os indivíduos e seus familiares em risco à um manejo diferenciado, resultando em redução do risco de incidência e mortalidade associado ao câncer, através de rastreamento e tratamento personalizados. As VP nos genes associados ao CM também estão associadas a outros cânceres, os quais necessitam de orientação específicas para rastreamento e medidas redutoras de risco específicas [17].

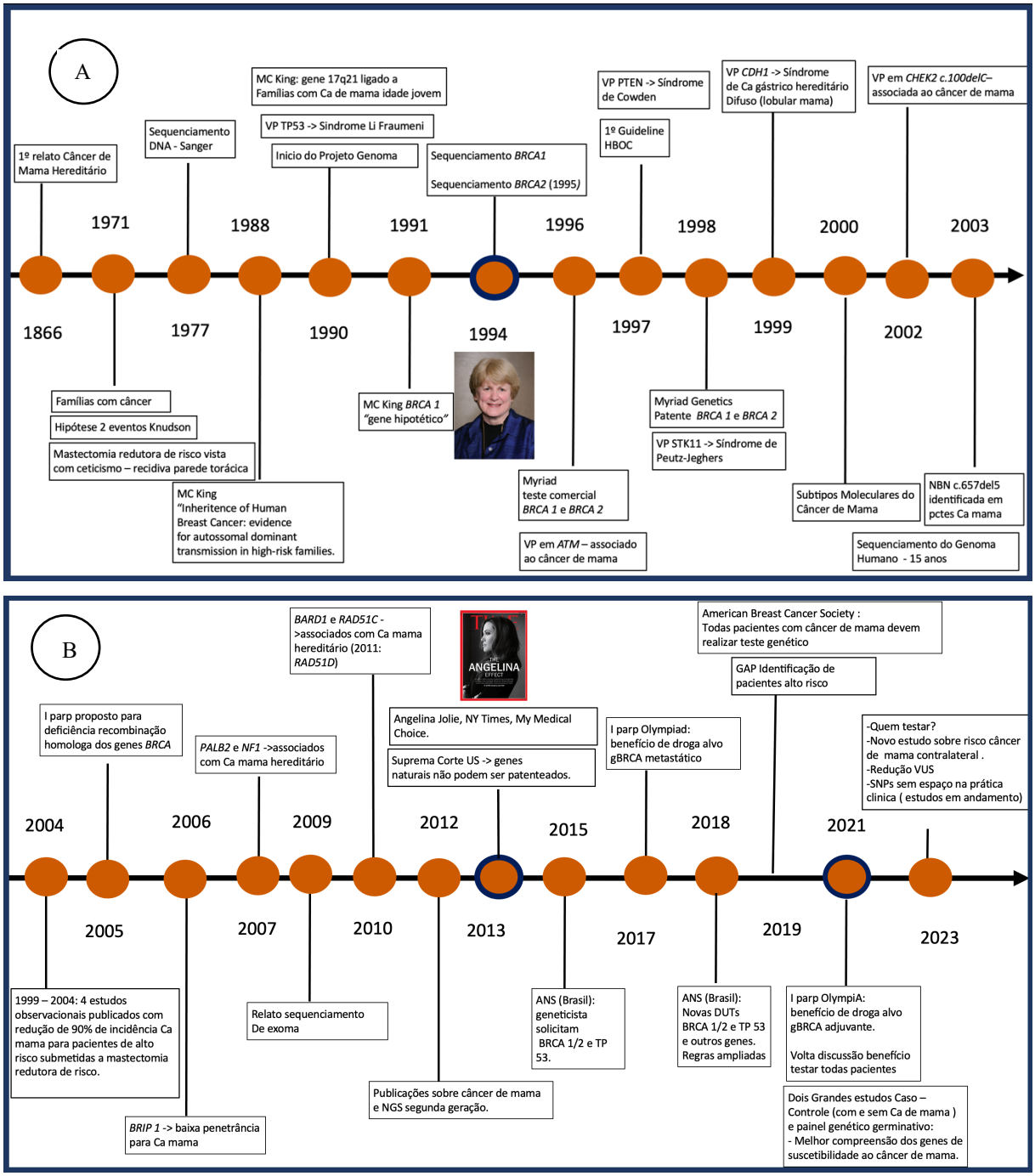
As VP nos genes *BRCA1*/*2* estão associados a um risco aumentado de CM e ovário em mulheres. Em menor grau, se associam com risco aumentado de câncer pancreático, CM masculino, câncer de próstata de início precoce e melanoma. Em geral, o risco de desenvolver CM é de aproximadamente 45% a 65% até os 70 anos de idade. O risco de desenvolver câncer de ovário, trompa de Falópio ou peritoneal é em torno de 39% em *BRCA1* e entre 10% a 17% em *BRCA2*. As VP nos genes *BRCA1*/*2* são responsáveis pela maioria dos casos de CM hereditário, sendo identificadas em 3%-4% de todas as mulheres com CM [28,29].

Outros genes de alta e moderada penetrância associados com suscetibilidade aumentada ao desenvolvimento do CM incluem: *PTEN, TP53, STK11, CDH1, PALB2, ATM e CHEK2.* O risco de desenvolver CM ao longo da vida associado a uma VP em *PALB2* é de aproximadamente 35% a 60%. Nos genes *ATM* e *CHEK2* esse risco é de 25% a 30%, embora modificadores genéticos e não genéticos possam modificar essa probabilidade. O conhecimento de oncogenética e dos genes suscetibilidade ao CM estão em constante evolução[30,31] .

Dois recentes grandes estudos de caso-controle envolvendo 113.000 e 64.791 mulheres demostraram informações câncer-específica associada a predisposição hereditária. No estudo

com 64.791 mulheres dos EUA, VP nos genes conhecidos associados a CM foram identificadas em 5,03% dos casos de mulheres com CM e em 1,63% dos casos de mulheres controle (sem câncer de mama). A detecção de VP nos genes *BARD1, RAD51C e RAD51D* foram associadas com risco aumentado de CM com receptor de estrogênio (RE) negativo e CM triplo negativo, enquanto VP nos genes *ATM, CDH1 e CHEK2* foram associadas com risco aumentado de CM com RE positivo. O estudo com 113.000 mulheres, majoritariamente da Europa e da Asia, também associou VP no gene *MSH6* com risco aumentando de desenvolver CM. A distribuição de VP entre mulheres com CM foi diferente da distribuição de VP detectadas entre mulheres controles. Entre os casos de CM, a maioria das VP foi em *BRCA1/2* e *PALB2*. Nas mulheres controles, a maioria das VP foi em *CHEK2* e *ATM*. Essa diferença pode ser associada a penetrância diferente desses genes. As VP em *BRCA1/2* e *PALB2* estão associadas a um alto risco de CM (OR: 5,0 - 10,6), já as VP nos genes *CHEK2* e *ATM* estão associadas a um risco moderado (OR: 2,1 - 2,5)[32,33].

Desde a descoberta de genes de câncer hereditário na década de 1990, o número de genes associados a CM e seus relativos riscos, assim como os tipos de teste genético oferecidos paras as pacientes evoluíram e seguem em constante evolução (figura 1). Inicialmente, o teste sequencial de um único gene através da metodologia SANGER foi o teste genético mais utilizado. Após 2013, com o término do patenteamento sobre genes nos EUA, a concorrência dos laboratórios de análises genéticas e a melhora da tecnologia dos GGT ocasionaram uma redução nos preços dos testes e um aumento do uso de tecnologia de nova geração (NGS – *Next Generation Sequence*). Atualmente, um painel de genes associados a CM hereditário, que possível através da NGS, é o tipo de GGT mais utilizado em estudos e na prática clínica [24,34–36]. A possibilidade de testar mais rápido e um número maior de genes permitiu resultados de estudos com grande número de mulheres testadas com e sem câncer, assim como com indivíduos com e sem critérios de realização do teste segundo algumas diretrizes [32,33].



Nota: A e B compreendem uma linha do tempo relacionada com a evolução do conhecimento sobre câncer de mama hereditário. Imagem adaptada de duas publicações[37,38]. Um resumo da evolução de inclusão nos estudos clínicos: década de 90 eram incluídas famílias com história familiar positiva sem teste genético. A partir de 2000 observa-se um predomínio de pacientes com história familiar positiva ou história clínica de câncer associada a câncer hereditário e VP, principalmente em BRCA. A partir de 2014, diversos estudos com VP em gene alto/moderado risco, testes predominantes de painel genético e, também, VP se torna alvo terapêutico e critério de inclusão em estudos.

FIGURA 1: Linha do tempo relacionada a evolução do conhecimento sobre câncer de mama hereditário.

O Brasil é o país mais populoso da LATAM e apresenta características étnicas únicas devido a grande miscigenação da nossa população[39]. No Brasil, a maioria dos estudos de CM hereditário analisou os genes *BRCA1/2* em centros únicos, bem como o gene *TP53*, devido a alta frequência populacional nas regiões Sul e Sudeste da variante R337h desse gene (c.1010G>A, p.Arg337His)[40,41]. Mais recentemente foram publicados estudos de laboratórios de teste genético ou de centros que realizam painel genético confirmando os genes *BRCA1/2* como os mais frequentes em mulheres com CM e VP detectada[42–44]. Um desses estudo baseado em um único laboratório de testagem analisou 1.663 mulheres brasileiras com CM e VP e comparou com casos controles (pacientes testados pelo mesmo laboratório sem câncer). Esse estudo demonstrou um total de 335 (20,1%) participantes com VP, sendo 167 (10,0%) nos genes *BRCA1/2* e 122 (7,3%) em genes não-*BRCA* acionáveis para CM. Os genes com VP detectados foram: *BRCA1* (27,4%), *BRCA2* (20,3%), *TP53* (10,5%), monoalélico *MUTYH* (9,9%), *ATM* (8,8%), *CHEK2* (6,2%) e *PALB2* (5,1%). A variante brasileira R337h no gene *TP53* R337H (c.1010G>A, p.Arg337His) foi detectada em 1,6% de pacientes com CM e 0,1% nas pacientes controle, sendo fortemente associada ao risco de desenvolver CM, OR = 17,4 (95% CI: 9,4–32,1;p < 0,0001). Esse dado reforça a importância de estudos regionais e que no Brasil, atenção especial deve ser dada ao gene *TP53*[45]. Os estudos em outros países da LATAM e outros LMICs são similares aos estudos brasileiros: coortes de centros únicos ou de laboratórios de testagem analisando os genes mais frequentes com VP em mulheres com CM[46–48].

2.2 LACUNAS NO CONHECIMENTO

Até 2021, os resultados dos testes germinativos foram usados para discussão sobre cirurgias de redução de risco, decisões de vigilância e aconselhamento familiar conforme referenciado no capítulo anterior. Dados recentes indicam que as informações sobre VP em *BRCA1/2* também podem influenciar o tratamento sistêmico para o CM. Em 2021 um estudo randomizado, fase III, duplo-cego, com 1.836 pacientes de alto risco com CM inicial HER2 negativo e portadoras de VP nos genes *BRCA1/2*, demonstrou sobrevida livre de doença a distância significativamente melhor com uso de olaparibe vs placebo (HR 0,57; 99,5% CI 0,39 , 0,83; p< 0,0001). Em 2022 a atualização desse estudo confirmou também benefício de

sobrevida global significativa. Esse estudo foi considerado *practice-changing* e aumentou o racional para a recomendação de testar todas as pacientes, além da importância da discussão sobre o acesso e a frequência dos GGT[49–52].

Apesar dos diversos benefícios relacionados ao reconhecimento para um manejo diferenciado dos indivíduos com CM hereditário e do alto número de mulheres diagnosticadas com CM anualmente, um número limitado dos indivíduos com CM e VP nos genes acionáveis relacionados a CM são identificados no mundo todo. O GGT é menos ofertado e realizado do que as recomendações atuais sobre CM hereditário, e essa baixa realização é ainda maior em minorias raciais e países em desenvolvimento [53–55].

O debate sobre ofertar GGT em mulheres com CM para todas mulheres ou para aquelas com critérios baseados no NCCN envolvem principalmente dois estudos em pacientes com CM. Esses estudos observaram uma proporção em torno de 50% de portadoras de VP não sendo identificada com base nos critérios para realização do GGT do NCCN. No entanto, a maioria dos genes analisados nos painéis desses estudos não apresentam relevância clinica para o manejo do CM. Esses estudos, os quais foram a base inicial para a oferta do GGT para todas mulheres com CM, também não avaliaram o aumento do número de testes necessários para essa demanda e a quantidade de locais e profissionais habilitados para essa oferta.[56,57].

As recomendações e debates atuais sobre se todas as mulheres com CM precisam realizar GGT ou como selecionar com maior efetividade quais pacientes devem testar ainda estão em evolução e análise. Uma importante publicação avaliou, numa coorte de mulheres com CM, a sensibilidade e especificidade dos critérios NCCN para teste genético e, também, de um outro critério: CM com idade < ou = a 65 anos. Esse estudo concluiu que a expansão dos critérios para incluir todas as mulheres diagnosticadas com idade < ou = a 65 anos, melhora a sensibilidade dos critérios de seleção, sem exigir o teste de todas mulheres com CM, tendo sensibilidade de 90% para os 9 genes acionáveis de predisposição hereditária ao CM e sensibilidade de 98% para *BRCA*1/2. Esse estudo não fez uma análise custo efetiva desse critério. Esse estudo teve um excelente controle dos dados clínicos e patológicos através de aconselhadores genéticos sobre a presença dos critérios NCCN nas mulheres com CM. Um dos achados mais relevantes com base nesses dados foi que seguindo os critérios NCCN, 30% das pacientes com VP nos genes acionáveis de predisposição ao CM hereditário não seriam identificadas. Além disso, foi identificado que sensibilidade dos critérios NCCN foi de 70% para 9 genes acionáveis de predisposição e 87% para *BRCA*1/2, com especificidade de 53% [58].

No Brasil, como esperado, o debate ainda é anterior aos critérios de testagem, pois vivemos uma realidade diferente. As pacientes do Sistema Único de Saúde (SUS) não tem acesso ao teste genético e, em 2021, em torno de 75% da população brasileira depende apenas do SUS [27]. No sistema complementar existe um acesso parcial aos testes, baseados nas recomendações da Agência Nacional de Saúde Suplementar (ANS)[59] .

A dificuldade de realização e acesso ao GGT é ainda mais evidente em LMICs, onde o GGT geralmente não está disponível pelo sistema de saúde público ou é proibitivamente caro (em torno de 250 dólares) para a maioria da população[60],[53].

A escassez de recursos e a ausência de banco de dados nacionais sobre CM, incluindo CM hereditário torna a frequência da realização da testagem genética no Brasil, assim como outros LMICs, um dado não conhecido.

3 OBJETIVOS

3.1 GERAL

Analisar o acesso ao teste genético germinativo para câncer hereditário e identificar as barreiras para a realização do teste em mulheres com câncer de mama no Brasil

3.2 ESPECÍFICOS

Descrever o percentual de mulheres que realizaram o teste genético germinativo para câncer de mama hereditário na coorte.

Identificar o número de mulheres com indicação para realização de teste genético, de acordo com os critérios do NCCN.

Identificar os fatores demográficos, clínico-patológicos das mulheres com câncer de mama, assim como fatores dos centros de tratamentos, associados a realização do teste genético.

4 HIPÓTESE

A realização de teste genético entre as mulheres com câncer de mama no estudo de coorte AMAZONA III é baixa, especialmente, entre as mulheres tratadas pelo serviço de saúde público.

5 MÉTODOS

Para analisar o acesso ao teste genético germinativo relacionado ao câncer de mama hereditário em mulheres com câncer de mama foi realizado uma análise transversal dos dados relacionados ao teste genético no estudo de coorte AMAZONA III.

5.1 DESENHO DO ESTUDO

Análise Transversal de uma grande coorte prospectiva de mulheres com câncer de mama, Estudo AMAZONA III.

5.2 O ESTUDO AMAZONA III

O estudo AMAZONA III (GBECAM 0115/ identificador ClinicalTrials.gov: NCT02669373) é um estudo de coorte prospectivo, multicêntrico envolvendo aproximadamente 2.974 mulheres ≥18 anos com novo diagnóstico de CM invasivo. Vinte e três centros de diversas cidades do Brasil participaram do estudo entre janeiro de 2016 e março de 2018, incluindo pacientes atendidos nos sistemas de saúde público e privado. Um centro não incluiu nenhuma paciente.

Dados sociodemográficos, clínicos e patológicos foram coletados durante o estudo AMAZONA III, incluindo se havia história familiar de câncer. Os prontuários médicos dos pacientes estão sendo revisados anualmente, durante o período de seguimento de cinco anos após o diagnóstico, para coletar dados de acompanhamento sobre o tratamento, recorrência da doença, progressão da doença e desfecho de sobrevida. O conselho interno de revisão de cada instituição participante aprovou o protocolo do estudo, que foi conduzido de acordo com as diretrizes de boas práticas clínicas e as do Conselho Internacional de Harmonização (ICH) para pesquisa em seres humanos. Todos os participantes deram o seu consentimento informado (TCLE) assinado antes da inclusão.

5.3 COLETA DE DADOS GENÉTICOS

Durante as revisões de pacientes de 2019 e 2020, os investigadores coletaram dados sobre GGT, incluindo identificação de pacientes de alto risco, encaminhamentos para avaliação genética, realização de GGT, resultados de testes genéticos (variante de significado incerto, variante patogênica ou provavelmente patogênica ou negativo) e tipo de teste genético (painel ou teste de gene individual) (eFigura 1 no Suplemento do artigo incluído nos resultados e figura 2 em forma de fluxograma).

5.4 DEFINIÇÃO DE ALTO RISCO E VARIÁVEIS DO ATUAL ESTUDO

As mulheres que preenchiam os critérios para realização de teste genético relacionado ao CM hereditário de acordo com os critérios da National Comprehensive Cancer Network (NCCN) de 2019 foram definidos como tendo alto risco para CM hereditário. As seguintes variáveis foram analisadas nessa coorte: idade ≤ 45 anos no momento do diagnóstico, CM triplo negativo antes dos 60 anos de idade, CM bilateral, história pessoal de câncer de ovário, algum membro da família com câncer de ovário e paciente < 50 anos de idade no diagnóstico com uma história familiar ou história pessoal anterior de CM. Alguns dos mais de vinte critérios do NCCN para recomendação de GGT não puderam ser avaliados devido à indisponibilidade de informações no banco de dados AMAZONA III, incluindo histórico de outros tipos de câncer, como câncer de próstata ou pâncreas na família, ter descendência judaica Ashkenazi ou história familiar desconhecida.

5.5 CARACTERÍSTICAS DO CENTRO DE SAÚDE

Os 22 centros envolvidos no estudo informaram se o aconselhamento genético profissional estava disponível, se estava disponível no sistema público de saúde, se o centro de saúde estava localizado em um hospital de ensino e quais sistemas de saúde entre público, privado ou ambos eram aceitos para tratamento.

5.6 ANÁLISE ESTATÍSTICA

Todos os pacientes com dados disponíveis foram incluídos nesta análise. As variáveis quantitativas foram descritas como médias e desvios padrão. As variáveis categóricas foram expressas como percentagens de frequência e comparadas por teste t. As variáveis qualitativas foram descritas como frequências absolutas e relativas e comparadas por meio do teste qui-quadrado. Resíduos ajustados foram calculados sempre que necessário. Valores de $p < 0,05$ foram considerados estatisticamente significativos.

A análise de regressão de Poisson univariada e multivariada com variância robusta foi ajustada para avaliar as características associadas à taxa de GGT. As variáveis na análise multivariada foram selecionadas por eliminação retrógrada. As variáveis com valores de $p < .2$ permaneceram no modelo final. Todas as análises foram realizadas usando SAS, versão 9.4 (SAS Institute, Cary, NC).

O desfecho primário foi a proporção de pacientes submetidos à GGT. A medida de desfecho secundário foi a identificação das variáveis associadas à realização de GGT.

Esta análise segue as diretrizes para relatórios de estudos transversais de estudos transversais (STROBE).

5.7 CONSIDERAÇÕES ÉTICAS

Esse projeto não apresenta riscos para as pacientes e não prevê armazenamento de amostras. Além disso, não existe um questionário a ser entregue para as pacientes, pois prevê análise de dados coletados do estudo AMAZONA III, previamente aprovado pelos CEP do Hospital de cada centro. Esse projeto foi autorizado pelo grupo GBECAM/LACOG, responsável pelo Projeto AMAZONA III.

5.8 FINANCIAMENTO/APOIO

O estudo AMAZONA III foi financiado pelo Latin American Cooperative Oncology Group (LACOG) e pelo Brazilian Breast Cancer Study Group (Grupo Brasileiro de Estudos em Câncer de Mama - GBECAM). O GBECAM recebeu financiamento do Instituto AVON e do

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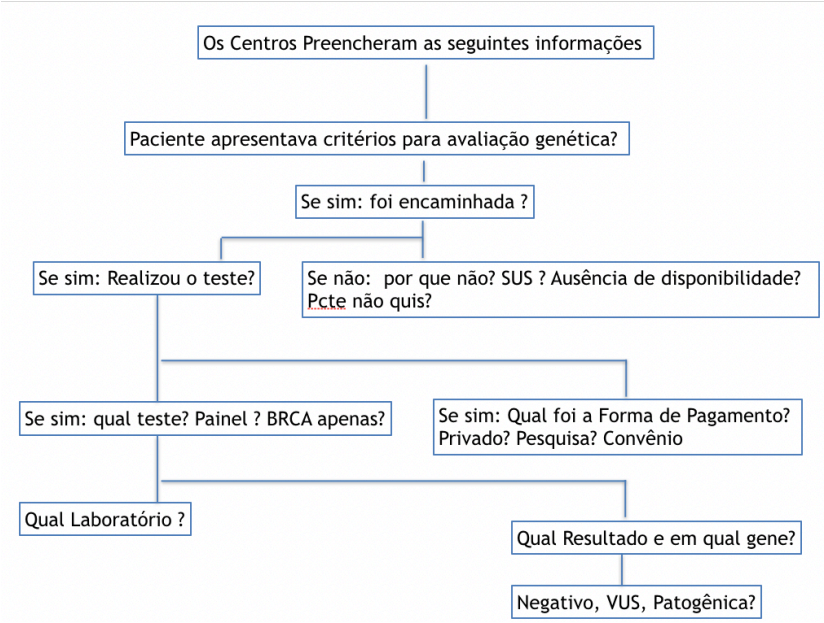

FIGURA 2: Fluxograma para os dados sobre acesso ao teste genético

6 RESULTADOS

6.1 RESULTADO EM FORMATO DE ARTIGO

Germline Genetic Testing in Breast Cancer: Utilization and Disparities in a Middle-Income Country

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Key Points

Question: In what percentage of patients is germline genetic testing (GGT) for breast cancer performed, and what factors represent barriers to its performance in a middle-income country?

Findings: Only 9% of this large Brazilian multicenter cohort of 2,974 breast cancer patients underwent GGT: 3% of high-risk patients treated within the public healthcare system and 43.2% of those treated in the private sector. Socioeconomic conditions and institutional characteristics were significantly associated with lower testing rates.

Meaning: This study highlights the worrisome fact that GGT is rarely performed in this middle-income country, with possible implications on global efforts to improve GGT.

Abstract

Importance*:* Adjuvant poly (ADP-ribose) polymerase (PARP) inhibitors have been approved for germline *BRCA* mutation carriers, reflecting a need to identify this population and discuss implications. Low rates of germline genetic testing (GGT) have been reported globally for breast cancer (BC) patients, while no data are available for low- and middle-income countries (LMIC), including on the assessment of genetic risk.

Objective: To analyze the GGT rate in a middle-income country and identify barriers to testing.

Design: A cross-sectional analysis from a large cohort of BC patients.

Setting: Patients enrolled in AMAZONA III, the largest Brazilian multicenter prospective cohort study in BC.

Participants: A total of 2,974 newly diagnosed BC patients participating in the AMAZONA III study.

Main Outcomes and Measures: To determine GGT rates and identify women at a high risk of hereditary breast cancer based on National Comprehensive Cancer Network criteria; identify potential barriers to GGT uptake according to the characteristics of the patients and of the healthcare systems; and identify factors associated with undergoing GGT in a multivariate Poisson regression model. *P*-values <.05 were considered statistically significant.

Results: In the AMAZONA III cohort, 1,476/2,974 patients (49%) were classified as high-risk and met the criteria for GGT. Genetic counseling was recommended for 521 patients (17%). Only 282 (9%) actually underwent GGT. In the high-risk group of patients, 97% of those in the public healthcare system and 56% of those in the private system did not undergo GGT. Age, education level, occupation, monthly income, availability of genetic counseling on site, and being treated at a teaching center were factors associated with undergoing GGT (*P*<.05). Fifty of the patients tested (17%) had a germline pathogenic or likely pathogenic variant.

Conclusions and Relevance: Few patients in this large cohort underwent GGT. Even in the private healthcare system in which testing is available, fewer than half of the high-risk patients were tested. Disparities and the barriers identified reinforce the need for education and strategies to improve access to genetic counseling and testing. GGT for BC patients remains an unmet need that should be prioritized to improve breast cancer management in LMIC.

Introduction

Breast cancer (BC) is the leading cause of cancer-related death in women worldwide, with more than two million new cases annually.[1] Around 5%-10% of all BC cases are associated with high- and moderate-risk BC genes.[2,3] Identifying this small proportion of hereditary BC patients using germline genetic testing (GGT) is critical, as it affects decisions on treatment management.[4] Currently, numerous guidelines recommend GGT in patients at risk of hereditary BC.[5–8] Until 2021, GGT results were used to discuss risk-reducing surgery, decisions regarding surveillance, and family counseling. Recent reports suggest that this information may also affect systemic treatment for early-stage and advanced BC.[9]

The OlympiA trial reported a significant benefit in overall survival with adjuvant poly (ADP-ribose) polymerase (PARP) inhibitors in high-risk patients with the germline *BRCA* mutation (gBRCAm). This finding was considered practice-changing[9] and provided a rationale for offering GGT to all BC patients.[10,11] Although GGT is widely recommended, a limited number of mutation carriers have been identified. GGT is offered even less frequently in deprived communities such as among racial minorities and in developing countries.[12–16] In low-resource countries, the cost of testing and the non-availability of genetic counseling represent significant barriers to BC genetic testing, meaning that universal testing is far from being achieved in low- and middle-income countries (LMIC).[15]

Brazil is a large, heterogenous, upper middle-income country (MIC) with 74,000 new BC cases expected annually.[17] Regional socioeconomic differences and variability in the quality of healthcare services impact diagnosis, treatment and clinical outcome. While low rates of GGT

have been reported in high-income countries (HIC), the prevalence of hereditary BC and the rate of GGT in LMIC are unknown.[12,13]

The different structures in Brazil make the present complex multicenter cohort an important source of data on BC in the country. This article evaluates the use of GGT in an MIC where the comprehensive public healthcare program does not offer it for BC and the private healthcare system only provides it in certain specific cases.[18] Around 75% of the Brazilian population depends exclusively on the public healthcare system; therefore, analyzing barriers to testing rather than simply failure to provide GGT is essential in devising strategies to improve testing rates.

This study aimed to determine the GGT rate in women with BC enrolled in a large Brazilian cohort and the potential barriers to its performance.

Methods

AMAZONA III cohort

This study consists of an analysis of the AMAZONA III study (GBECAM 0115/ ClinicalTrials.gov identifier: NCT02669373), a prospective multicenter study involving around 3,000 women in Brazil ≥18 years of age who had recently been diagnosed with invasive BC. Twenty-two sites participated in the study between January 2016 and March 2018, with patients treated in the public and private healthcare systems being included. Although previous studies on this cohort analyzed 2,950 women, using valid data for specific objectives, the current analysis included 2,974 patients.[19–21]

Sociodemographic, clinical and pathology data were collected during the AMAZONA III study, including whether there was a family history of cancer. Patients' medical records were reviewed yearly for five years to collect follow-up data on treatment patterns, disease recurrence, disease progression, and survival outcome. The internal review board of each participating institution approved the protocol of the study, which was conducted according to the good clinical practices guidelines and those of the International Council of Harmonization (ICH) for human research. All participants gave their signed informed consent prior to inclusion.

Variables evaluated

Patients meeting the criteria for hereditary BC testing according to the 2019 National Comprehensive Cancer Network (NCCN) criteria[7] were defined as having a high risk of hereditary BC. The following characteristics were analyzed: age ≤45 years at diagnosis, triple-negative BC prior to 60 years of age, bilateral BC, personal history of ovarian cancer, any family member with ovarian cancer, and patient <50 years of age at diagnosis with a family history or previous personal history of BC. Some of the over twenty NCCN criteria for recommending GGT could not be assessed due to the non-availability of information in the AMAZONA III database, including a history of other types of cancer such as prostate or pancreatic cancer in the family, being of Ashkenazi Jewish descent or family history being unknown.

Genetic data collection

During the 2019 and 2020 patient reviews, the investigators collected data on GGT, including referrals for genetic evaluation, performance of GGT, results of genetic testing (variant of uncertain significance, pathogenic or likely pathogenic variant, or negative) and type of genetic testing (panel or individual gene test) **(eFigure 1 in the Supplement)**.

Health center characteristics

The 22 centers involved in the study provided information on whether professional genetic counseling was available, whether it was available within the public healthcare system, whether the healthcare center was located in a teaching hospital, and which healthcare systems were accepted.

Statistical analyses

All patients with available data were included in this analysis. Quantitative variables were described as means and standard deviations. Categorical variables were expressed as frequency percentages and compared using a t-test. Qualitative variables were described as absolute and relative frequencies and compared using the chi-square test. Adjusted residuals were calculated whenever necessary. *P*-values <.05 were considered statistically significant.

Univariate and multivariate Poisson regression analysis with robust variance was adjusted to assess the characteristics associated with the GGT rate. Variables in the multivariate analysis were selected by backward elimination. Variables with *P*-values <.2 remained in the final model. All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

The primary outcome measure was the proportion of patients who underwent GGT. The secondary outcome measure was identification of the variables associated with undergoing GGT. This analysis follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cross-sectional studies.[22]

Results

Patients Characteristics

Entire cohort

Overall, 2,974 patients were enrolled in the AMAZONA III cohort study. **Table 1** shows patients' sociodemographic characteristics and those of the tumor at baseline. Briefly, the median age at diagnosis was 53.9 years and 63.01% were treated in the public healthcare system. The majority of patients were white (58.72%), postmenopausal (59.35%), either illiterate or having only elementary schooling (46.47%), unemployed (56.84%), and with a family history of ovarian or breast cancer (62.37%). Data have previously been published on young patients and healthcare systems in the AMAZONA III cohort.[19,21]

High-risk group

Of the 2,974 patients enrolled in the original cohort, 49% (n=1,476) met the 2019 NCCN criteria for genetic testing for hereditary BC, constituting the high-risk group (Figure 1).

In the high-risk group the median age at diagnosis was 44.0 years; 60% of patients (n=874) were treated within the public healthcare system and 40% (n=588) in the private healthcare system (data missing for the remaining cases); 64% had no more than high school education; 83% earned a monthly salary of less than five minimum wages, and 52.34% reported being employed. The majority of patients were white (58.70%), premenopausal (65.53%), and had a family history of ovarian or breast cancer (69.91%) **(Table 1)**. According to the NCCN criteria for GGT identified by the oncology team at each institution, 826 patients (55.96%) met the criteria, while 289 (19.58%) did not, and in 361 cases (24.46%) the data were missing.

Germline Genetic testing in the entire sample population and in the high-risk group

Overall, 17% of patients in the entire cohort (n=521) were referred for genetic counseling, and 9% (n=282) actually underwent GGT **(Figure 1 and eTable1)**. In the high-risk group, 64% (n=955) were not offered genetic evaluation and of those referred for genetic counseling only 54% underwent GGT.

Only 3% of high-risk patients in the public healthcare system and 43.2% in the private healthcare system underwent GGT (**Table 2**). Of the 282 tested patients, 9% (n=26) were treated in the public healthcare system. The type of test performed was genetic panel testing in 63% (n=175) of the patients, irrespective of the healthcare system. In the tested group, 17% (n=50) of the women had a germline pathogenic variant, including 35 in *BRCA1* or *BRCA2* and 15 in other related BC genes (**Table 3**).

Of the participating centers, 40% did not have professionals qualified to perform genetic counseling. Of those offering this service, only 30% provided it within the public healthcare system. Around 55% of centers were situated within a teaching institute. Only 18% of the centers received patients exclusively within the public healthcare system **(eTable 2).**

Clinical and pathological characteristics and the likelihood of undergoing GGT

Patients under 40 years of age had a significantly greater chance of undergoing GGT (RR 6.82, 95%CI: 4.13-11.27, *P<.0001*) compared to those over 50 years of age. Patients with poorer education levels, including illiterate patients or those with only elementary school education, were less likely to undergo GGT than those with a university degree (RR=0.47, 95%CI: 0.22-0.96, *P*=.0379). Patients earning 2-5 minimum wages had a significantly higher chance of undergoing GGT compared to those earning 0-2 minimum wages (RR=2.22, 95%CI: 1.30-3.75, *P*=.0002).

No association was found between undergoing GGT and tumor characteristics, type of surgery, menopausal status or ethnicity. Being treated in a teaching center and having access to genetic counseling were factors significantly associated with a greater likelihood of undergoing GGT (RR=1.64, 95%CI: 1.02-2.64, *P*=.0406 and RR 2.27, 95%CI: 1.34-3.83, *P*=.0022, respectively). The univariate and multivariate analyses of all factors are shown in **Table 4**.

Table 1. Characteristics of the patients, treatment centers, and tumors in the AMAZONA III cohort.

Patient characteristics	Allpatients (n=2,974)	High-risk (n=1,476)	Tested (n=282)
Age (years)			
≤35	237 (8.61)	237 (17.10)	76 (29.46)
35 – 45	546 (19.83)	546 (39.39)	91 (35.27)
45 – 50	423 (15.36)	229 (16.52)	32 (12.40)
50 – 65	1000 (36.31)	287 (20.71)	52 (20.16)
>65	548 (19.90)	87 (6.28)	7 (2.71)
Healthcare System			
Public	1855 (63.01)	874 (59.78)	26 (9.29)
Private	1089 (36.99)	588 (40.22)	254 (90.71)
Menopausal status			
Premenopausal/Perimenopausal	1122 (40.65)	886 (65.53)	179 (75.85)
Postmenopausal	1638 (59.35)	466 (34.47)	57 (24.15)
Ethnicity/skin color			
White	1701 (58.72)	847 (58.70)	233 (85.35)
Non-white	1196 (41.28)	596 (41.30)	40 (14.65)
Education level			
Illiterate - Completed elementary school	1245 (46.47)	469 (35.29)	17 (7.23)
Completed high school	679 (25.35)	384 (28.89)	48 (20.43)
University or postgraduate degree	755 (28.18)	476 (35.82)	170 (72.34)
Monthly household income			
No income - 2 minimum wages (R$ 880 to	959 (46.44)	443 (44.70)	6 (5.56)
2 to 5 minimum wages (R$ 2640 to R$ 4400)	801 (38.79)	388 (39.15)	59 (54.63)
5 to 10 minimum wages (R$ 4400 to R$ 8800)	198 (9.59)	97 (9.79)	28 (25.93)
> 10 minimum wages (over R$ 8800)	107 (5.18)	63 (6.36)	15 (13.89)
Employment status			
Employed	1240 (43.16)	749 (52.34)	221 (81.85)
Unemployed	1633 (56.84)	682 (47.66)	49 (18.15)
Marital status			
Yes	1699 (58.79)	931 (64.34)	194 (70.55)
No	1191 (41.21)	516 (35.66)	81 (29.45)
Family history of cancer [a]			
Yes	2757 (92.77)	1379 (93.49)	253 (89.72)
No	215 (7.23)	96 (6.51)	29 (10.28)
Family history of breast and ovarian cancer			
Yes	1855 (62.37)	1032 (69.91)	216 (76.59)

Children			
Yes	2386 (85.43)	1146 (83.22)	188 (74.90)
No	407 (14.57)	231 (16.78)	63 (25.10)
Type of surgery performed			
Breast-conserving surgery	791 (44.97)	339 (35.72)	46 (33.09)
Mastectomy, NSM,[b] SSM[c]	800 (45.48)	390 (41.10)	78 (56.12)
Other	168 (9.55)	81 (8.54)	15 (10.79)
Neoadjuvant treatment			
Yes	1045 (38.01)	613 (45.11)	105 (42.68)
No	1704 (61.99)	746 (54.89)	141 (57.32)
Region of the country			
South	1002 (34.12)	501 (34.50)	142 (51.45)
Southeastern	615 (20.94)	328 (22.59)	101 (36.59)
Midwest	568 (19.34)	235 (16.18)	13 (4.71)
North	6 (0.20)	2 (0.14)	1 (0.36)
Northeast	746 (25.40)	386 (26.58)	19 (6.88)
Characteristics of the treatment center			
Teaching hospital			
Yes	1060 (38.45)	490 (36.00)	112 (39.72)
No	1697 (61.55)	871 (64.00)	170 (60.28)
Healthcare sector covered at the institution			
Both (Public and private)	1606 (58.25)	795 (58.41)	86 (30.50)
Private	845 (30.65)	444 (32.62)	181 (64.18)
Public healthcare system	306 (11.10)	122 (8.96)	15 (5.32)
Genetic counseling availability			
Yes	1441 (52.27)	760 (55.84)	261 (92.55)
No	1316 (47.73)	601 (44.16)	21 (7.45)
Tumor characteristics			
ECOG performance status			
0	1671 (75.92)	881 (80.90)	193 (93.69)
1	471 (21.40)	195 (17.91)	12 (5.83)
2	48 (2.18)	12 (1.10)	0 (0.00)
3	8 (0.36)	1 (0.09)	1 (0.49)
4	3 (0.14)	0 (0.00)	0 (0.00)
Clinical stage of cancer at initial diagnosis			
I	500 (24.27)	217 (21.11)	50 (26.32)
II	859 (41.70)	439 (42.70)	90 (47.37)
III	630 (30.58)	325 (31.61)	40 (21.05)
IV	71 (3.45)	47 (4.57)	10 (5.26)
Molecular subtype - surgery			
Luminal A	1062 (48.05)	533 (47.04)	99 (47.14)
Luminal B - HER-2 negative	267 (12.08)	115 (10.15)	27 (12.86)
Luminal B - HER-2 positive	377 (17.06)	167 (14.74)	40 (19.05)
HER-2 positive	161 (7.29)	77 (6.80)	16 (7.62)
Triple-negative	343 (15.52)	241 (21.27)	28 (13.33)
Tumor Grade (biopsy)			
1	398 (17.87)	166 (15.16)	28 (12.50)
2	1190 (53.44)	566 (51.69)	101 (45.09)
3	639 (28.69)	363 (33.15)	95 (42.41)
Moment of breast cancer detection			
At screening	941 (34.01)	445 (32.36)	113 (44.84)
From symptoms	1826 (65.99)	930 (67.64)	139 (55.16)
Molecular subtype – biopsy			
Luminal A	1062 (48.05)	533 (47.04)	99 (47.14)
Luminal B - HER-2 negative	267 (12.08)	115 (10.15)	27 (12.86)
Luminal B - HER-2 positive	377 (17.06)	167 (14.74)	40 (19.05)
HER-2 positive	161 (7.29)	77 (6.80)	16 (7.62)
Triple-negative	343 (15.52)	241 (21.27)	28 (13.33)
Molecular subtype - biopsy			
Hormone receptor-positive	1329 (60.14)	648 (57.19)	126 (60.00)

HER-2 positive	538 (24.34)	244 (21.54)	56 (26.67)
Triple-negative	343 (15.52)	241 (21.27)	28 (13.33)

N.B.: Data were missing in some cases. [a] Family history included all tumor types in first-, second- or third-degree relatives. [b] NSM: nipple-sparing mastectomy; [c] SSM: skin-sparing mastectomy.

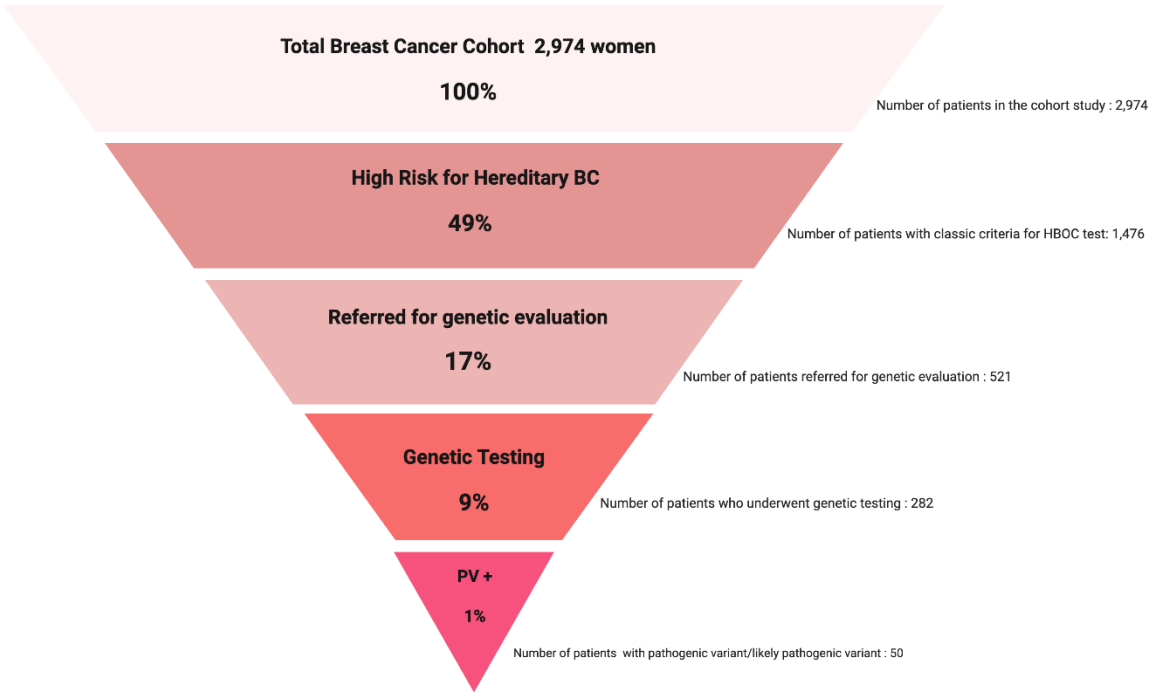

Figure 1. Numbers of patients in the high-risk group who were referred for genetic evaluation, underwent genetic testing, and tested positive.

(Footnote:)

HBOC: Hereditary breast and ovarian cancer; PV: Pathogenic variant.

All percentages are relative to the total number of patients in the cohort. This graph highlights the gaps in genetic testing for breast cancer and missed cases through failure to identify high-risk patients who would ultimately require genetic counseling and testing.

Table 2. Missed opportunity for germline genetic testing in high-risk patients according to the healthcare system.

Healthcare system	Total number of high-risk patients (n=1,462)	Total number of tested patients (n=280)	Proportion of high-risk patients not tested (%)
Public [a]	874	26	97%
Private [b]	588	254	56.8%

N.B.: Data were missing in some cases. [a] The public healthcare system does not offer coverage for germline genetic testing. [b] The private healthcare system covers germline genetic testing.

Table 3. Number of patients with pathogenic variant or likely pathogenic variant in genetic test results and proportion of genes with pathogenic variant/likely pathogenic variant in the group of patients with positive results.

Genes	Patients with pathogenic variant/ likely pathogenic variant (n)	(%)
BRCA1	22	44
BRCA2	13	26
ATM	4	8
PALB2	3	6
TP53	2	4
BRIP1	2	4
MUTHY	2	4
PTEN	1	2
MSH6	1	2
Total	**50**	**100**

Table 4. Univariate and multivariate regression analysis to evaluate factors associated with undergoing germline genetic testing.

Parameter	Tested (%)	Univariable analysis			Multivariable analysis		
		Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value
Health insurance				<.0001			
Public	26 (1.45)	0.05	0.03 to 0.08				
Private	254 (27.88)	1.00	-				
Status Female				<.0001			
Premenopausal/Perimenopausal	179 (17.33)	1.00	-				
Postmenopausal	57 (3.74)	0.22	0.16 to 0.29				
Race				<.0001			
White	233 (15.45)	4.5	3.25 to 6.24				
Non white	40 (3.43)	1.00	-				
Educational level				<.0001			0.0379
Illiterate - Completed first degree	17 (1.44)	0.06	0.03 to 0.09		0.47	0.22 to 0.96	
Completed second degree	48 (7.43)	0.29	0.21 to 0.39		0.58	0.36 to 0.94	
Completed superior degree or higher	170 (26.07)	1.00	-		1.00	-	
Laboral activity				<.0001			0.0546
Yes	221 (19.84)	6.19	4.59 to 8.36		1.61	0.99 to 2.63	
No	49 (3.20)	1.00	-		1.00	-	
Age in years				<.0001			<.0001
≤40	128 (28.64)	6.93	5.18 to 9.26		6.82	4.13 to 11.27	
40 - 50	71 (10.60)	2.56	1.83 to 3.58		2.92	1.71 to 4.97	
≥50	59 (4.13)	1.00	-		1.00	-	
Region				<.0001			
South	142 (16.47)	0.88	0.69 to 1.11				
Southeastern	101 (18.70)	1.00	-				
Midwest	13 (2.31)	0.12	0.07 to 0.22				
North	1 (20.00)	1.07	0.18 to 6.23				
Northeast	19 (2.60)	0.14	0.08 to 0.23				
Molecular subtype				0.5403			
Hormone receptor positive	126 (10.31)	1.16	0.78 to 0.72				
HER-2 positive	56 (11.22)	1.27	0.82 to 1.95				
Triple negative	28 (8.86)	1.00	-				
Household income per month				<.0001			0.0002
No income - 2 minimum wages (R$ 880 to R$1760)	6 (0.65)	0.04	0.01 to 0.11		0.56	0.20 to 1.52	
2 to 5 minimum wages (R$ 2640 to R$ 4400)	59 (7.87)	0.52	0.30 to 0.88		2.22	1.30 to 3.75	
5 to 10 minimum wages (R$ 4400 to R$ 8800)	28 (14.97)	0.99	0.55 to 1.77		1.92	1.10 to 3.32	
More than 10 (more than R$ 8800)	15 (15.15)	1.00	-		1.00	-	
Clinical stage of cancer at initial diagnosis				0.0098			
I	50 (11.55)	1.12	0.58 to 2.13				
II	90 (11.28)	1.09	0.58 to 2.04				
III	40 (6.75)	0.65	0.33 to 1.27				
IV	10 (10.31)	1.00	-				
Family history of cancer				0.0243			
Yes	253 (9.90)	0.60	0.42 to 0.86				
No	29 (16.38)	1.00	-				
Does the patient have children?				<.0001			
Yes	188 (8.45)	0.49	0.37 to 0.64				
No	63 (17.40)	1.00	-				
Surgery type				0.0141			
Mastectomy, Adenomastectomy, Skin sparing mastectomy	78 (10.58)	1.00	-				
Breast-conserving surgery	46 (6.43)	0.61	0.42 to 0.87				
Other	15 (9.80)	0.93	0.54 to 1.57				
Did the patient undergo any neoadjuvant treatment?				0.2755			
Yes	105 (10.45)	1.14	0.90 to 1.46				
No	141 (9.13)	1.00	-				
Is the patient currently married or lives in common-law marriage?				<.0001			
Yes	194 (12.54)	1.72	1.34 to 2.21				
No	81 (7.30)	1.00	-				
Private and public systems?				<.0001			0.0003
Both	86 (5.87)	1.18	0.69 to 2.02		0.76	0.31 to 1.84	
Private practice	181 (23.94)	4.82	2.89 to 8.03		3.99	1.91 to 8.32	
Public health system	15 (4.97)	1.00	-		1.00	-	
Presence of genetic counselor in the institution?				<.0001			0.0022

Yes	261 (21.10)	12.91	8.33 to 20.00		2.27	1.34 to 3.83	
No	21 (1.63)	1.00	-		1.00	-	
Academic center?				0.2746			0.0406
Yes	112 (12.10)	1.14	0.90 to 1.43		1.64	1.02 to 2.64	
No	170 (10.65)	1.00	-		1.00	-	

Discussion

To our knowledge, this is the first study with multicenter real-world data on the accessibility and performance of genetic testing in MIC. The rate of GGT was very low in this large cohort of BC patients, and significant disparities were found in the management of patients within the same country. Although low rates of GGT in HIC have been reported, data for LMIC remain very limited.[12,13,23–25] While testing was expected to be low in the public healthcare system, which does not cover GGT, less than half of high-risk patients treated in the private healthcare system underwent testing, which is disappointing since the test is available in that setting.

A state-of-the-art program in BC should include cancer risk assessment, genetic counseling and testing.[26] Test results enable counseling by multidisciplinary teams to be provided to BC patients with mutations, and specific treatments and preventive strategies to be recommended.[4,27] Advances in next-generation sequencing technology have led to a reduction in the costs and an increase in the use of multi-gene panel testing.[23,28] Although the criteria for selecting patients for testing remain controversial, patients considered at a high risk of a *BRCA* mutation should indeed be tested.[29]

The large randomized OlympiA study resulted in a significant overall survival benefit (HR of 0.68; *P*=.0009) in patients with gBRCAm HER2-negative BC at a high risk of recurrence who were treated with olaparib,[9] highlighting the importance of identifying these patients to provide them with the benefits of appropriate treatment. Although referring to a small proportion of BC patients with a particular targetable molecular abnormality, this approach is in accordance with the principles of personalized medicine. This discussion has evolved from a focused approach centered on the testing of patients with high-risk characteristics to a broader testing strategy potentially involving all patients.[30–32]

Clearly, rates of *BRCA1/2* testing in BC patients remain suboptimal. According to Kurian et al., only 24.1% of BC patients diagnosed in 2013-2014 in California and Georgia underwent GGT.[13] Another US study estimated GGT rates using pooled cross-sectional data from three Cancer Control Modules. Although 35.6% of women with BC met one or more of the eligibility criteria for testing, only 20.2% were advised to undergo testing and 15.3% were actually tested.[25] Recently, reported real-world data for 2,527 patients with advanced BC showed that in HR+/HER2- patients, the *BRCA* testing rate was 99% in Israel, 68% in the US and 37% in the European Union. In advanced triple-negative BC patients, the testing rate was 100% in Israel, 93% in the US and 78% in the EU.[33] However, in another recent multi-country report (France, Germany, Italy, Spain, the UK and the US), *BRCA* testing in advanced HER-2-BC patients was only 28%.[34]

Two large case-control studies involving 113,000 women from the Breast Cancer Association Consortium and 64,791 women from the Cancer Risk Estimates Related to Susceptibility Consortium clearly showed the value of information on genetic predisposition. Some genes such as *BRCA1/2*, *PALB2*, *CHEK2* and *ATM* have been consistently associated with BC. For

the *BARD1*, *RAD51C* and *RAD51D* mutations, associations with estrogen receptor-negative BC are also robust.[2,3] In Latin America, China, India and other LMICs, different retrospective single-center or single-laboratory analyses are available, with 9-30% of patients being found to have a pathogenic variant in BC genes.[35–41] However, data on GGT in these countries remain scarce. A recent retrospective report from Chile involving 3,955 BC patients from the public and private healthcare systems reported similar results to those found here. While 48.3% of patients met the NCCN high-risk criteria, only 15.7% were tested: 19.6% in the private healthcare network versus 10.3% in the public healthcare service.[42]

AMAZONA III is a multicenter trial with data from 22 centers in 14 cities in Brazil (**eFigure 2**), including patients from the public and private healthcare sectors. Most patients were treated within the public healthcare system in which testing is not covered; therefore, the low rate of testing in this group was expected. The small number of patients in the public healthcare group that were tested either paid for the test themselves (19%) or were tested through research programs (38%). This is consistent with some of the barriers experienced by Latin American women living in the US, including the high cost of testing, lack of awareness and competing life concerns.[43]

Surprisingly, this analysis identified a considerable proportion of high-risk patients treated within the private healthcare system who failed to undergo GGT. As these patients have access to testing, lack of information on its importance or the lack of formal genetic counseling may be the main reason for the low rates of GGT. In 2016, the Brazilian National Health Agency made *BRCA1/2* testing available for some high-risk cancer patients. In 2018, an expanded panel test was also authorized.[44] The present findings indicate a missed opportunity to recognize

patients with hereditary BC who could benefit from risk-reducing surgeries and ultimately, a missed opportunity to identify asymptomatic carrier family members.

Reported barriers to testing high-risk patients include physician education and awareness of genetic testing.[45] Dusic et al. proposed solutions at provider level that included education on genetics, communication with genetic counselors, and training in identifying high-risk patients. At individual level, the perceived cost and preconceived ideas about GGT were cited as barriers that needed to be tackled.[46] Our findings consistently showed that patients' socioeconomic factors such as high educational level, high family income and young age were significantly associated with a greater likelihood of undergoing testing. Concomitantly, factors related to where the patients received care, i.e. in a teaching hospital, and the availability of genetic counseling increased the likelihood of identifying high-risk characteristics and of referral for testing.

Genetic risk assessment is only one of many challenges in healthcare systems in Brazil and other LMICs. Fragmented healthcare systems with insufficient resources, ineffective payment systems and services, care of inconsistent quality, and lack of integration among health specialties result in significant discrepancies in outcomes.[22] Lourenção et al. evaluated a Brazilian cohort and reported data on *BRCA* pathogenic mutation in 275 index cases and in 356 carriers who were relatives of the index patients. The analysis was conducted from a payer perspective, considering the Brazilian public healthcare system. The *BRCA1/2* testing and preventive strategies were shown to be cost-effective to the healthcare system in an upper MIC.[47] Although it is difficult to make definitive assumptions on how to use limited resources in a specific country context, GGT for patients with high-risk criteria seems a reasonable option.

However, it should be taken into account that around 30% of pathogenic variants in high and moderate BC gene carriers are missed when these criteria are used to evaluate hereditariness.[48]

Access to testing is a significant barrier. Awareness and access to information remain major obstacles to identifying these patients. Strategies to identify patients need to be addressed, including use of the FHS-7 questionnaire, a simple instrument for identifying the most common hereditary BC syndrome phenotypes that was validated in southern Brazil as a family history screening tool in primary care to refer at-risk individuals for genetic evaluation.[49] In this context, educational events and information campaigns targeting both the general public and the medical community are extremely important. To integrate GGT into routine medical care, barriers must be addressed at individual, provider, clinical and societal levels with tailored approaches.[12,13,46] Achatz et al. have proposed realistic strategies for improving genetic counseling, testing and the management of hereditary breast and ovarian cancer in Brazil, including regulatory actions.[50] This is certainly a complex issue, with multiple context-dependent dimensions.

The strength of this national, multicenter real-world study includes the fact that a large number of patients were recruited and data were collected prospectively. This large, heterogeneous cohort is representative of MIC. Nevertheless, some limitations need to be taken into consideration, including missing sociodemographic and clinical data that prevented a full analysis of the whole set of NCCN criteria from being performed.

The inclusion of GGT in clinical practice remains a significant challenge worldwide. A very low rate of GGT was found in this large prospective multicenter cohort of Brazilian BC patients, and disparities between public and private healthcare systems were clear. This represented a

lost opportunity to prevent cancer deaths in carriers of mutations and their families. Also, to offer advances in understanding cancer genetic features in a miscegenated population. Older age, low educational level and low monthly income were factors significantly associated with low GGT uptake in this MIC cohort.

Prioritization, strategic planning, and sensible resource allocation are important elements in moving forward. Focusing on educating both the general public and the medical community is mandatory. More than addressing the universal testing controversy, offering the test to all women identified as having high-risk criteria is a critical first step towards improving BC care.

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Supplementary content

This supplementary material has been provided by the authors to give readers additional information on their work.

Some considerations with respect to the AMAZONA III cohort

To compare between healthcare systems, patients who were treated under the Brazilian National Healthcare System (*Sistema Único de Saúde - SUS*) were considered to be publicly insured (public healthcare system), while those with private health insurance or who paid for their treatment themselves were classified as being in the private healthcare sector.

Data on breast cancer subtypes (estrogen receptor [ER]-positive, progesterone receptor [PR]-positive and human epidermal growth factor receptor 2 [HER2] status) and tumor grade were collected from immunohistochemistry reports at local pathology laboratories. The tumors were then classified as luminal A-like tumors, luminal B/HER2-negative-like tumors, luminal B/HER2-positive-like tumors, HER2-positive (non-luminal)-like tumors, and triple-negative tumors.

eTable 1. Genetic testing rate in the cohort analyzed. [a]

Description	Number of patients (n)	(%)
Total sample in the AMAZONA III study	2974	100
High risk for hereditary breast/ovarian cancer	1476	49
Referred for genetic evaluation	521	17
Genetic testing performed	282	9
Findings of pathogenic or likely pathogenic variants	50	1

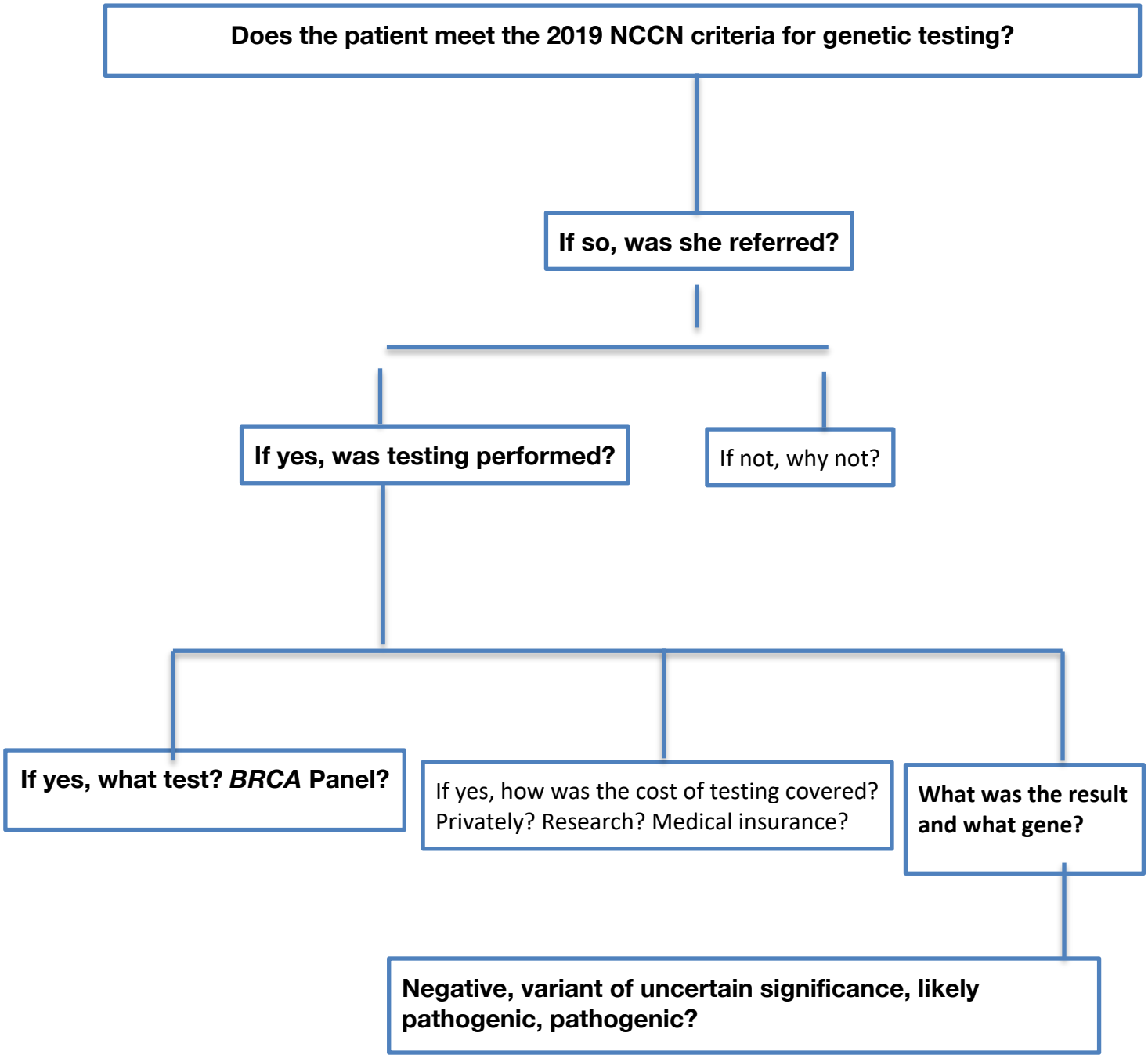
[a] eTable 1 is related to Figure 1.

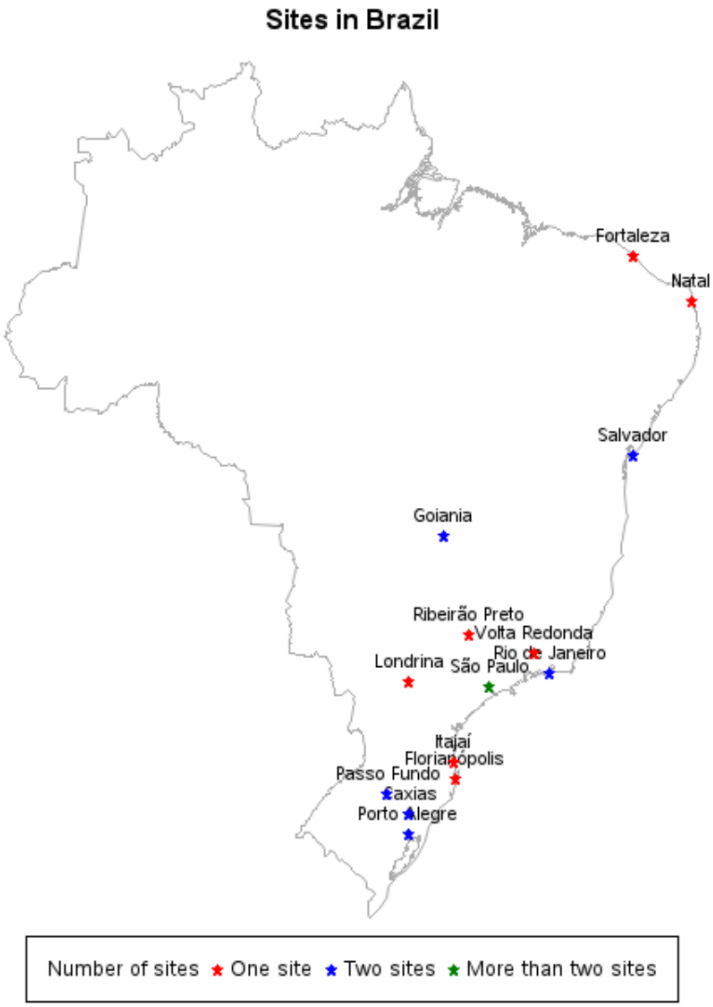
eTable2: Survey of all participating centers in the AMAZONA III study. [a]

Center	Teaching Hospital (Yes/No)	Healthcare System (Public/Private/Both)	Availability of genetic counseling (Yes/No)
1	Yes	Both	Yes
2	Yes	Public	Yes
3	No	Private	Yes
4	No	Private	No
5	Yes	Private	Yes
6	No	Both	No
7	No	Private	Yes
8	Yes	Both	Yes
9	No	Both	No
10	Yes	Private	No
11	Yes	Both	Yes
12	No	Both	No
13	Yes	Both	No
14	Yes	Both	Yes
15	No	Private	Yes
16	No	Private	Yes
17	Yes	Both	No
18	Yes	Public	No
19	Yes	Public	Yes
20	No	Private	Yes
21	Yes	Both	Yes
22	No	Public	No

[a] eTable 2 is related to eFigure 2.

eFigure 1. Flowchart on genetic testing in the AMAZONA III Cohort





eFigure 2. The geographical distribution of the 23 sites participating in the AMAZONA III trial. [a]

[a] One site failed to include any patients.

7 DISCUSSÃO

Existe um imperativo clínico para expandir o acesso ao GGT para pacientes com CM, a identificação de VP deve ser ponderada em todos os aspectos do manejo sobre o câncer, desde a prevenção até o tratamento. Na era da oncologia de precisão, o tratamento do câncer pode ser personalizado e a identificação de VP cumpre o mandato dessa abordagem de medicina personalizada atual, identificando uma pequena população de pacientes definida por uma anormalidade molecular específica, permitindo uma estratégia de gerenciamento direcionada com impacto[61,62].

Abordar a lacuna no acesso ao GGT exige avaliações de necessidades específicas de cada local para determinar a melhor abordagem. No nosso estudo, o não reconhecimento de pacientes de alto risco pela equipe de tratamento em torno de 20%, a ausência de profissionais que recomendem os testes nos centros de tratamento, assim como, a baixa escolaridade das mulheres com CM foram alguns dos fatores que merecem atenção de um programa de educação, tanto para equipe multidisciplinar de tratamento quanto para as pacientes com CM, sobre a importância do GGT. Apenas aumentar a oferta, sem orientação e sem capacidade do sistema de cuidar desses indivíduos não é produtivo. No AMAZONA III, menos de 50% das mulheres consideradas de alto risco tratadas pelo sistema privado e com acesso ao GGT, realizaram o mesmo.

Os estudos em diferentes países podem contribuir para o entendimento, manejo e reconhecimento de barreiras locais. Um estudo realizado na Nigéria avaliou o conhecimento das pacientes com CM. Noventa por cento (90%) responderam que ouviram falar sobre CM mas não sabiam sobre do que se tratava exatamente e nem as possíveis causas. Quase 1/5 das pacientes acreditavam que o CM era um ataque espiritual e 91% não sabiam sobre CM hereditário [63]. Outro estudo nos EUA, revelou também, através de uma pesquisa em 2.529 mulheres com CM os principais motivos para a não realização do GGT: A razão mais comum para os pacientes de alto risco relatarem não fazer o teste foi a não oferta pelo médico (56,1%), alto custo do teste (13,7%), o não desejo de realizar (10,7%) e a negativa pela família sobre o pagamento do teste" (0,2%) [23]. Esse presente estudo brasileiro não conseguiu avaliar com as pacientes o motivo da não realização do GGT e essa é umas das limitações.

Estudo publicado recente no Chile realizado em dois centros de Santiago analisou 3.955 mulheres com CM e demonstrou: 48.3% (1.911) preenchiam critérios NCCN para realização

de GGT e apenas 7% (300) realizaram o GGT, sendo que 268 realizaram o teste de painel. Os nossos dados confirmam esses achados, compreendendo 2,974 mulheres com CM de 22 centros aonde 49% (1.476) preenchiam os critérios NCCN e apenas 9% (282) realizaram o GGT. Um fator a ser ponderado é que a nossa atual coorte pode ter ainda mais pacientes com critérios de indicação de testagem, uma vez que não foi possível analisar todos os critérios na base de dados, como por exemplo história familiar de câncer de próstata ou pâncreas[64].

A evolução dos estudos sobre CM hereditário desde a década de 90 que incluíam indivíduos predominantemente com história familiar de câncer de mama e análises de genes únicos até os dias atuais com grandes estudos caso controles de pacientes com GGT permitiu um aumento do nosso conhecimento e manejo do CM hereditário. Nesse contexto, o presente estudo se torna relevante devido ao grande número de pacientes numa coorte multicêntrica em LMICs avaliando a frequência de realização do GGT não só no grupo de alto risco definido pelos critérios NCCN como em toda a coorte.

8 CONCLUSÃO

Esse estudo demonstrou o número de apenas 9% de mulheres com CM que realizaram GGT, assim como as disparidades no acesso ao GGT entre as pacientes tratadas pelo sistema de saúde público e pelo sistema de saúde privado foram documentadas. Globalmente, o acesso ao GGT permanece inadequado, apesar das importantes implicações para o manejo clínico quando uma VP é identificada. A disparidade no acesso aos testes é particularmente evidente em LMICs, onde o GGT geralmente não está disponível nos sistemas de saúde público. Idade avançada, baixo nível educacional e baixa renda mensal foram fatores significativamente associados à baixa captação de GGT nesta coorte MIC.

As disparidades relacionadas ao CM devem ser consideradas como uma questão importante. A falha em identificar indivíduos com VP acionáveis e poder oferecer a eles os cuidados necessários é uma oportunidade perdida. Nos LMICs, com estimativas de crescente aumento de incidência de câncer nas próximas décadas e com taxa de mortalidade relacionadas ao câncer ainda inadequadas, reconhecer indivíduos com CM hereditário é uma estratégia de medicina personalizada. Essa estratégia tem resultados eficazes de redução de mortalidade, redução de incidência de novos cânceres, detecção precoce de novos canceres com impacto em redução de morbidade e identificação de familiares não afetados que podem se beneficiar em redução de incidência e mortalidade relacionadas ao CM. Priorização, planejamento estratégico e alocação sensata de recursos são elementos importantes para avançar. Concentrar-se em educar o público em geral e a comunidade médica é obrigatório.

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ANEXOS

ANEXO A – Resultados do artigo em tabelas

Tabela 1Anexo A: Acesso ao Teste Genético (tabela representativa da figura 1 do artigo)

Descrição relacionada ao acesso ao teste genético	Número de pacientes (%)
Total coorte AMAZONA III	2974 (100%)
Alto risco para câncer de mama hereditário	1476 (49%)
Referenciada para aconselhamento genético	521 (17%)
Realizaram o teste genético	282 (9%)
Variantes patogênicas identificadas	50 (1%)

Tabela 2 Anexo A: Oportunidade perdida ao Teste Genético. Tabela representativa da tabela 2 do artigo.

Sistema de Saúde	Pacientes Alto Risco (N)	Total de Pacientes Testadas (N)	Pacientes de Alto Risco Não Testadas (%)
Público	874	26	97%
Privado	588	254	56.8%
Total	1,462	280	19,15%

Tabela 3 Anexo A: Forma de testagem genética das pacientes do SUS.

SUS testadas no AMAZONA III	N (%)
Seguradora de saúde	1 (3,85%)
Protocolo de Pesquisa	10 (38,46%)
Pagamento privado	5 (19,23%)
Unknow	10 (38,46%)

ANEXO B – Folha de Parecer Consubstanciado do CEP-PUCRS

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: AVALIAÇÃO PROSPECTIVA DA CASUÍSTICA DE CÂNCER DE MAMA EM INSTITUIÇÕES DE SAÚDE BRASILEIRAS ¿ estudo AMAZONA III

Pesquisador: Carlos Henrique Escosteguy Barrios

Área Temática:

Versão: 2

CAAE: 48573015.5.2007.5336

Instituição Proponente: UNIAO BRASILEIRA DE EDUCACAO E ASSISTENCIA

Patrocinador Principal: GRUPO BRASILEIRO DE ESTUDOS DO CANCER DE MAMA

DADOS DO PARECER

Número do Parecer: 1.463.980

Apresentação do Projeto:

Título: AVALIAÇÃO PROSPECTIVA DA CASUÍSTICA DE CÂNCER DE MAMA EM INSTITUIÇÕES DE SAÚDE BRASILEIRAS – estudo AMAZONA III

Pesquisador responsável: Dr. Carlos Henrique Escosteguy Barrios

Assistente: Franciele de Almeida Menegat

Objetivo da Pesquisa:

Primário:

- Descrever a epidemiologia do câncer de mama na população brasileira.

Secundários:

- Avaliar o perfil demográfico, socioeconômico, comorbidades e os fatores de risco reprodutivos, familiares e antropométricos das pacientes incluídas;- Caracterizar o perfil imunofenotípico (subtipos) dos tumores de mama através dos dados anatomopatológicos (laboratório da instituição) tais como: grau tumoral, ER, PgR, HER2, Ki67;- Descrever os exames de rastreamento, sintomas principal e estágio do câncer de mama no momento do diagnóstico; - Descrever o tratamento realizado para câncer de mama inicial e localmente avançado tais como cirurgia, radioterapia, quimioterapia, terapia endócrina;- Descrever o tratamento paliativo realizado para

Endereço: Av.Ipiranga, 6681, prédio 40, sala 505
Bairro: Partenon **CEP:** 90.619-900
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3320-3345 **Fax:** (51)3320-3345 **E-mail:** cep@pucrs.br

ANEXO C – Carta de Aprovação SIPESQ-PUCRS do Projeto AMAZONA III

SIPESQ

Sistema de Pesquisas da PUCRS

PROPESQ

Código SIPESQ: 7116 Porto Alegre, 26 de janeiro de 2016.

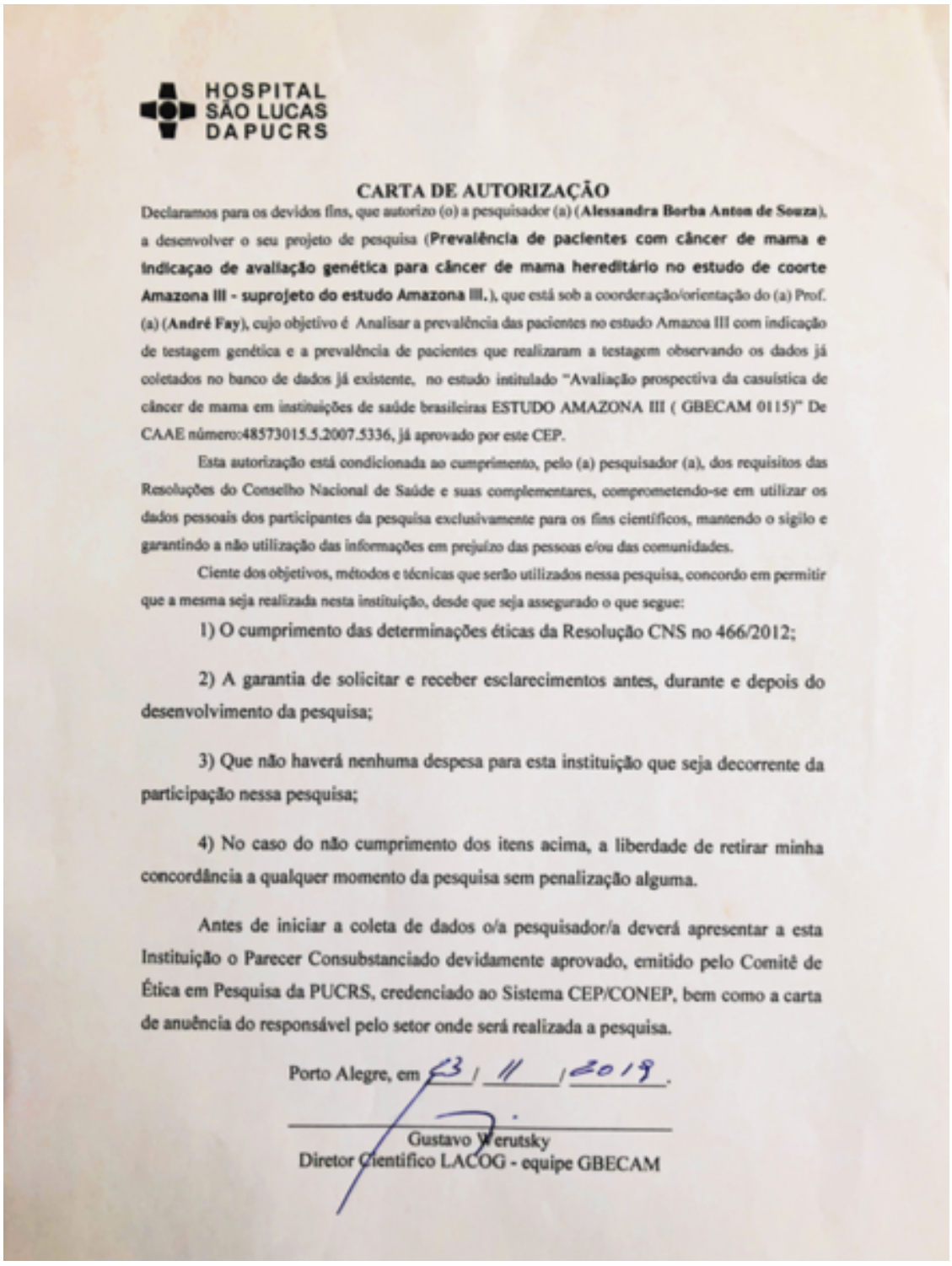
Prezado(a) Pesquisador(a),

A Comissão Científica da FACULDADE DE MEDICINA da PUCRS apreciou e aprovou o Projeto de Pesquisa "AMAZONA III - GBECAM 0115 - AVALIAÇÃO PROSPECTIVA DA CASUÍSTICA DE CÂNCER DE MAMA EM INSTITUIÇÕES DE SAÚDE BRASILEIRAS." coordenado por CARLOS HENRIQUE E BARRIOS. Caso este projeto necessite apreciação do Comitê de Ética em Pesquisa (CEP) e/ou da Comissão de Ética no Uso de Animais (CEUA), toda a documentação anexa deve ser idêntica à documentação enviada ao CEP/CEUA, juntamente com o Documento Unificado gerado pelo SIPESQ.

Atenciosamente,

Comissão Científica da FACULDADE DE MEDICINA

ANEXO D – Carta de Autorização do Hospital São Lucas da PUCRS



HOSPITAL SÃO LUCAS DA PUCRS

CARTA DE AUTORIZAÇÃO

Declaramos para os devidos fins, que autorizo (o) a pesquisador (a) (**Alessandra Borba Anton de Souza**), a desenvolver o seu projeto de pesquisa (**Prevalência de pacientes com câncer de mama e indicaçao de avaliação genética para câncer de mama hereditário no estudo de coorte Amazona III - suprojeto do estudo Amazona III.**), que está sob a coordenação/orientação do (a) Prof. (a) (**André Fay**), cujo objetivo é Analisar a prevalência das pacientes no estudo Amazoa III com indicação de testagem genética e a prevalência de pacientes que realizaram a testagem observando os dados já coletados no banco de dados já existente, no estudo intitulado "Avaliação prospectiva da casuística de câncer de mama em instituições de saúde brasileiras ESTUDO AMAZONA III (GBECAM 0115)" De CAAE número:48573015.5.2007.5336, já aprovado por este CEP.

Esta autorização está condicionada ao cumprimento, pelo (a) pesquisador (a), dos requisitos das Resoluções do Conselho Nacional de Saúde e suas complementares, comprometendo-se em utilizar os dados pessoais dos participantes da pesquisa exclusivamente para os fins científicos, mantendo o sigilo e garantindo a não utilização das informações em prejuízo das pessoas e/ou das comunidades.

Ciente dos objetivos, métodos e técnicas que serão utilizados nessa pesquisa, concordo em permitir que a mesma seja realizada nesta instituição, desde que seja assegurado o que segue:

1) O cumprimento das determinações éticas da Resolução CNS no 466/2012;

2) A garantia de solicitar e receber esclarecimentos antes, durante e depois do desenvolvimento da pesquisa;

3) Que não haverá nenhuma despesa para esta instituição que seja decorrente da participação nessa pesquisa;

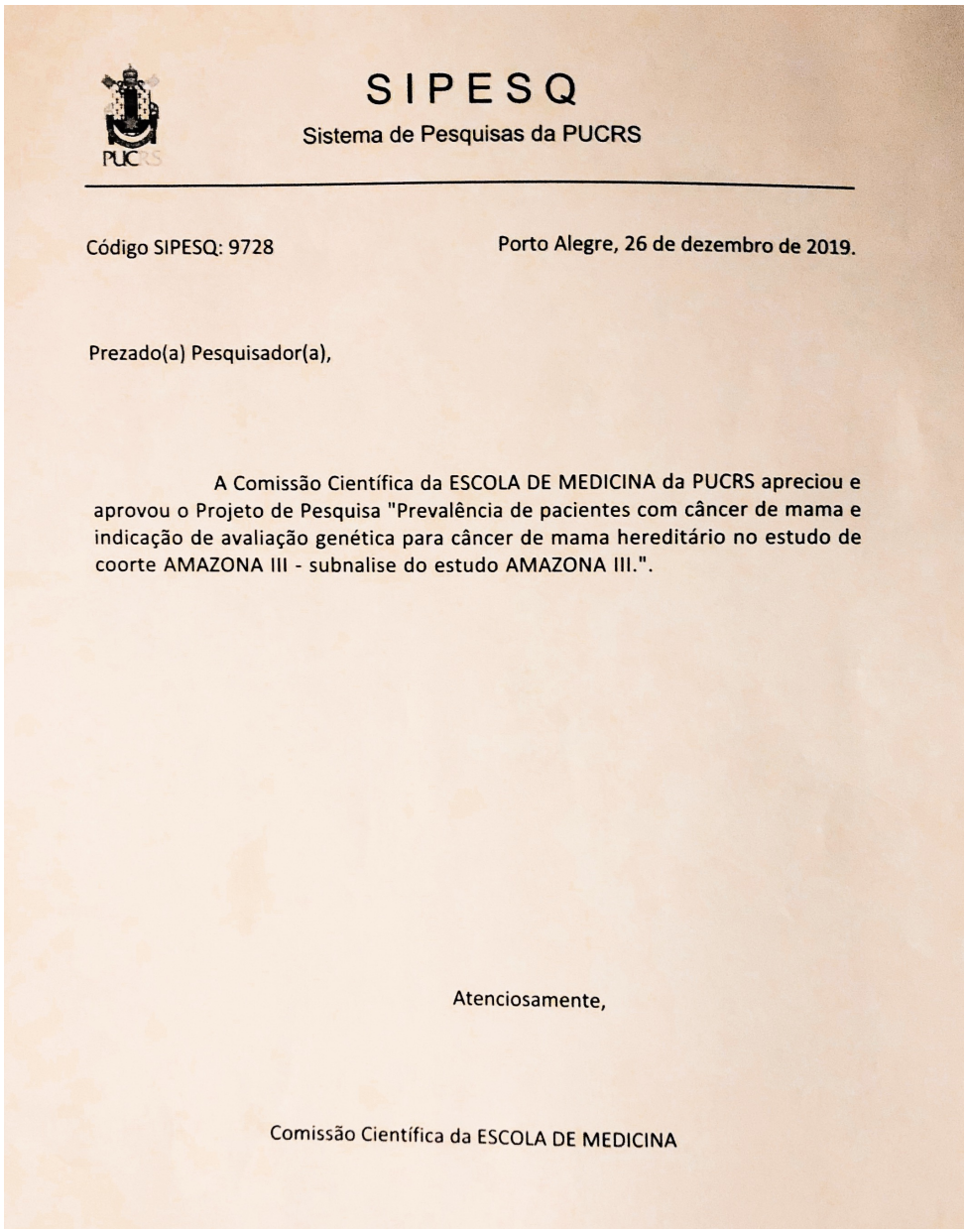
4) No caso do não cumprimento dos itens acima, a liberdade de retirar minha concordância a qualquer momento da pesquisa sem penalização alguma.

Antes de iniciar a coleta de dados o/a pesquisador/a deverá apresentar a esta Instituição o Parecer Consubstanciado devidamente aprovado, emitido pelo Comitê de Ética em Pesquisa da PUCRS, credenciado ao Sistema CEP/CONEP, bem como a carta de anuência do responsável pelo setor onde será realizada a pesquisa.

Porto Alegre, em 13 / 11 / 2019.

Gustavo Werutsky
Diretor Científico LACOG - equipe GBECAM

ANEXO E – Carta de Aprovação SIPESQ-PUCRS da atual análise



SIPESQ

Sistema de Pesquisas da PUCRS

Código SIPESQ: 9728

Porto Alegre, 26 de dezembro de 2019.

Prezado(a) Pesquisador(a),

A Comissão Científica da ESCOLA DE MEDICINA da PUCRS apreciou e aprovou o Projeto de Pesquisa "Prevalência de pacientes com câncer de mama e indicação de avaliação genética para câncer de mama hereditário no estudo de coorte AMAZONA III - subnalise do estudo AMAZONA III.".

Atenciosamente,

Comissão Científica da ESCOLA DE MEDICINA

ANEXO F – Comprovante de Submissão em Revista Indexada - QUALIS

JAMA Network

JAMA Network | Open

Detailed Status Information

Manuscript #	JNO23-8202
Current Revision #	0
Submission Date	07-02-2023 22:34
Current Stage	In Quality Control
Title	Germline Genetic Testing in Breast Cancer: Utilization and Disparities in a Middle-Income Country
Manuscript Type	Original Investigation
Study Type	Cross-sectional Study
Corresponding Author	Andre Fay (CAPES Research Fellowship, Postgraduate Program, School of Medicine, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil; Latin American Cooperative Oncology Group (LACOG), Porto Alegre, RS, Brazil)
Coauthors	Alessandra Souza , Carlos Barrios , Rafaela Gomes , Tomas Reinert , Juliana Giacomazzi , Daniela Rosa , Eduardo Cronemberger , Gustavo Werutsky , José Bines , Geraldo Queiroz , Vladmir de Lima , Ruffo Freitas Junior , Jose Couto , Karla Emerenciano , Heloisa Resende , Susanne Crocamo , Brigitte Van Eyli , Yeni Neron , Vanessa Dybal , Nicolas Lazaretti , Rita Costamillan , Diocesio Pinto de Andrade , Clarissa Mathias , Giovana Vacaro , Giuliano Borges , Alessandra Morelle , Carlos Sampaio Filho , Max Mano , Sergio Simon , Andre Fay (corr-auth)
Visual Abstract Required?	
Abstract	Importance: Adjuvant poly (ADP-ribose) polymerase (PARP) inhibitors have been approved for germline BRCA mutation carriers, reflecting a need to identify this population and discuss implications. Low rates of germline genetic testing (GGT) have been reported globally for breast cancer (BC) patients, while no data are available for low- and middle-income countries (LMIC), including on the assessment of genetic risk. Objective: To analyze the GGT rate in a middle-income country and identify barriers to testing. Design: A cross-sectional analysis from a large cohort of BC patients. Setting: Patients enrolled in AMAZONA III, the

ANEXO G – Outros Artigos Publicados Durante o Período do Doutorado

ARTIGO 1

Ann Surg Oncol
https://doi.org/10.1245/s10434-021-10812-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

The Attitudes of Brazilian Breast Surgeons on Axillary Management in Early Breast Cancer—10 Years after the ACOSOG Z0011 Trial First Publication

Eduardo Camargo Millen, PhD[1], Francisco Pimentel Cavalcante, MD[2], Felipe Zerwes, PhD[3], Guilherme Novita, MD, MSc[4], Alessandra Borba Anton de Souza, MD, MSc[5], João Henrique Penna Reis, MD[6], Helio Rubens de Oliveira Filho, MD, MSc, FACS[7], Luciana Naíra de B. L. Limongi, MD[8], Barbara Pace Silva de Assis Carvalho, PhD[9], Adriana Magalhães de Oliveira Freitas, MD[10], Monica Travassos Jourdan, MD[11], Vilmar Marques de Oliveira, PhD[12], and Ruffo Freitas-Junior, PhD[13]

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ABSTRACT

Purpose. To evaluate the impact of the ACOSOG Z0011 trial on axillary breast cancer surgery management in Brazil following publication of that study (2010) and again in 2020.

Patients and Methods. A survey of members of the Brazilian Society of Mastology.

Results. Of 1627 breast surgeons, 799 (49.1%) completed and returned the questionnaire. For patients with the Z11 inclusion criteria, following detection of a positive sentinel lymph node (SLN), axillary dissection (AD) was recommended by 99.2% of respondents before publication of the study, 47.5% in 2010 and 18.5% in 2020 ($p < 0.001$). In breast-conserving surgery, if there were micro-metastases, 2.6% would perform AD, 30.3% axillary radiotherapy, and 67.1% no additional axillary treatment, while with macrometastases, these proportions were 21.3%, 52.2%, and 26.5%, respectively. In cases of mastectomy and of nodal extracapsular extension, 43.4% and 36% of surgeons, respectively, recommended AD. For clinically negative axilla and suspicious findings at ultrasonography, 69% of the surgeons would apply the Z11 approach. Most applied the Z11 criteria in cases of younger patients (83.6%) and triple-negative and/or HER2 positive tumors (74%). AD was significantly more likely to be recommended by surgeons who did not work in academic institutes, who worked in locations other than capital cities, who were not board-certified, and who were ≥ 50 years old.

Conclusions. This survey revealed substantial changes in axillary surgery management in cN0/pathologically positive SLN, particularly following publication of the updated Z11 results and other similar studies. A better education environment and long-term follow-up were factors associated with the incorporation of Z11-related changes in practice.

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Accepted: 3 September 2021

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ARTIGO 2

Breast Cancer Research and Treatment (2021) 186:753–760
https://doi.org/10.1007/s10549-020-06076-5

CLINICAL TRIAL

Real-world data on neoadjuvant endocrine therapy in ER-positive/HER2-negative breast cancer

Leonardo Roberto da Silva[1] · Camila Annicchino de Andrade[1] · Fabrício Brenelli[1] · Susana Ramalho[1] · Tomás Reinert[2,3] · Alessandra Borba Anton de Souza[4] · Ana Elisa Ribeiro da Silva[1] · Maria Beatriz de Paula Leite Kraft[1] · Vivian Castro Antunes de Vasconcelos[1] · Antônio Luiz Frasson[4] · Renato Zochio Torresan[1] · Cesar Cabello[1] · Matthew J. Ellis[5] · Luiz Carlos Zeferino[1]

Received: 28 October 2020 / Accepted: 23 December 2020 / Published online: 4 February 2021

Abstract

Purpose Neoadjuvant endocrine therapy (NET) has been shown to be effective in ER-positive/HER2-negative breast cancer in clinical trials. However, adoption in clinical practice is still limited. Real-world data may provide useful insights into effectiveness, toxicities and quality of care, potentially rendering clinical trial results to the real-world setting. Our purpose was to report real-world data of a cohort of postmenopausal patients submitted to NET.

Methods This prospective cohort study evaluated 146 postmenopausal female patients with ER-positive/HER2-negative breast cancer treated with NET at three tertiary hospitals between 2016 and 2018. Clinicopathological information were collected prospectively. Preoperative Endocrine Prognostic Index (PEPI) score was calculated for tumors submitted to at least 16 weeks of NET.

Results Median age was 67 years old, and 87.8% had stage I-II disease. Most tumors had histological grade II (76.1%). Median pretreatment Ki67 expression was 10%. Aromatase inhibitor was used in 99.5% of patients, and median treatment duration was 21.0 weeks. No tumor progressed during NET. Breast-conserving surgery was performed in the majority of patients (63.0%), as well as sentinel lymph-node biopsy (76.7%). Pathological complete response rate was 1.0%. 43 patients (29.5%) had PEPI score 0, and 26% had PEPI scores 4–5. Posttreatment Ki67 median expression was 3.0%, and only five tumors (3.4%) showed marked increase in Ki67 expression during treatment. Seven patients (4.8%) had HER2-positive residual disease, and were treated with adjuvant chemotherapy plus trastuzumab.

Conclusions Our real-world data shows that NET is effective and safe in postmenopausal patients with ER-positive/HER2-negative breast cancer. Postmenopausal status and low-risk luminal tumor features (luminal A-like) should be used as selection criteria to ensure the best results with NET.

Keywords Neoadjuvant therapies · Breast neoplasms · Sentinel lymph node biopsy · Aromatase inhibitors

Leonardo Roberto da Silva and Camila Annicchino de Andrade are co-first authors.

✉ Luiz Carlos Zeferino
zeferino@fcm.unicamp.br

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[2] Centro de Pesquisa da Serra Gaúcha (CEPESG), Caxias do Sul, Brazil

[3] Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil

[4] Breast Cancer Center, Hospital São Lucas, Pontifical Catholic University of Rio Grande Do Sul (PUCRS), Porto Alegre, Brazil

[5] Lester and Sue Smith Breast Cancer Center, Baylor College of Medicine, Houston, TX, USA

ARTIGO 3

ecancermedicalscience

Management of the positive sentinel lymph node following neoadjuvant chemotherapy: results of a survey conducted with breast surgeons

Francisco Pimentel Cavalcante[1,a], Felipe Zerwes[2,b], Eduardo Camargo Millen[3,c], Guilherme Novita[4,d], Alessandra Borba Anton de Souza[5,e], João Henrique Penna Reis[6,f], Helio Rubens de Oliveira Filho[7,g], Luciana Naíra de B L Limongi[8,h], Barbara Pace Silva de Assis Carvalho[9,i], Adriana Magalhães de Oliveira Freitas[10,j], Monica Travassos Jourdan[11,k], Vilmar Marques de Oliveira[12,13,l], Ruffo Freitas-Junior[14,m]

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[3]Instituto Oncoclinicas, Rio de Janeiro, RJ 22440040, Brazil
[4]Breast Unit, Hospital Israelita Albert Einstein, São Paulo, SP 01321001, Brazil
[5]Oncology Research Group-CNPq, PUCRS, Porto Alegre, RS 90610000, Brazil
[6]Breast Center, Instituto Orizonti and Hospital Mater Dei, Belo Horizonte, Minas Gerais, MG 30210080, Brazil
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[h]https://orcid.org/0000-0001-9014-4793
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[k]https://orcid.org/0000-0003-0910-0270
[l]https://orcid.org/0000-0002-9478-5616
[m]https://orcid.org/0000-0003-4145-8598

Research

Abstract

Introduction: Despite the lack of randomised evidence, there is a current trend towards omitting axillary surgery in cases of positive sentinel lymph node (SLN) following neoadjuvant chemotherapy (NACT). This study evaluated practice patterns of Brazilian breast surgeons when managing positive SLN following NACT.

Methods: This was a nationwide electronic survey of breast surgeons affiliated with the Brazilian Society of Mastology. Management approaches for positive SLN after NACT (axillary dissection (AD), regional nodal irradiation (RNI) or no additional treatment) were evaluated as a function of residual disease volume in the SLN (macro-metastasis, micro-metastasis or isolated tumour cells (ITC)).

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Email: fpimentelcavalcante@gmail.com

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https://doi.org/10.3332/ecancer.2022.1357

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Received: 24/09/2021

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ARTIGO 4

Published online: 2022-02-24

Original Article

Salvage Nipple-sparing Mastectomy for Patients with Breast Cancer Recurrence: A Case Series of Brazilian Patients

Mastectomia preservadora de mamilo para pacientes com recidiva de câncer de mama: Uma série de casos de pacientes brasileiras

Antônio Luiz Frasson[1] Martina Lichtenfels[2] Fernanda Barbosa[1] Alessandra Borba Anton de Souza[2] Ana Beatriz Falcone[1] Isabela Miranda[2] Betina Vollbrecht[2] Carolina Malhone[1] José Yoshikazu Tariki[1]

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Address for correspondence Antônio Luiz Frasson, MD, PhD, rua Ipiranga 6.690, sala 714, Porto Alegre, RS, 90610-000, Brazil (e-mail: alfrasson.af@gmail.com).

Rev Bras Ginecol Obstet

Abstract

Objective Few studies analyzed the safety of salvage nipple-sparing mastectomy (NSM) for local relapse treatment. We evaluated the outcomes of patients with indications for mastectomy who chose to undergo NSM for ipsilateral breast tumor recurrence (IBTR).

Methods Between January 2001 and December 2018, we evaluated 24 women who underwent NSM for local relapse after conservative surgery.

Results The patients were followed up for a mean time of 132 months since the first surgery. After the NSM, 5 (20.8%) patients were diagnosed with local recurrence and only 1 (4.2%) patient died. The patients presented 4.8% (2) of partial and 2.4% (1) of total nipple necrosis.

Conclusion In this long-term follow-up since the first surgery, we observed low rates of complication and good survival, although associated with high local recurrence in patients diagnosed with IBTR undergoing NSM as salvage surgery. We demonstrated that NSM may be considered after IBTR for patients who did not want to undergo total mastectomy.

Keywords
- neoplasm recurrence
- subcutaneous mastectomy
- segmental mastectomy

Resumo

Objetivo Há poucos estudos sobre a segurança de se realizar adenomastectomia (*nipple-sparing mastectomy*, NSM, em inglês) para tratamento de recidiva local. O objetivo deste estudo foi avaliar os resultados de pacientes com indicação para mastectomia que optaram por se submeter a NSM para o tratamento de recorrência local.

Métodos Foram analisadas 24 pacientes submetidas a NSM para tratamento de recidiva local após tratamento conservador entre janeiro de 2001 e dezembro de 2018.

Palavras-chave
- neoplasias da mama
- mastectomia subcutânea
- mastectomia segmental

received
July 13, 2021
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November 18, 2021

DOI https://doi.org/10.1055/s-0042-1743098.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

ARTIGO 5

ORIGINAL ARTICLE
DOI: 10.29289/259453942019000418

AESTHETIC OUTCOME AND ONCOLOGICAL SAFETY OF NIPPLE-SPARING MASTECTOMY

Resultado estético e segurança oncológica da mastectomia poupadora do mamilo

Janaina Ferreira Viegas[1]*, Martina Lichtenfels[2], Alessandra Borba Anton de Souza[3], Betina Vollbrecht[3], Francisco Laitano Neto[3], Felipe Pereira Zerwes[3], Antônio Luiz Frasson[3]

ABSTRACT

Background: Nipple-sparing mastectomy (NSM) has been performed for breast cancer treatment and for women at high risk. NSM provides better aesthetic outcomes; however, its oncological safety is still controversial. **Objective:** To evaluate the surgical complications, oncological safety and aesthetic satisfaction of breast cancer patients undergoing NSM with immediate breast reconstruction operated by the same medical team in a Breast Cancer Center in Brazil. **Method:** From 2004 to 2011, an aesthetic satisfaction questionnaire was administered to women undergoing NSM followed by immediate breast reconstruction 30 or 60 days after surgery. Aesthetic satisfaction, complication rates and oncological safety were analyzed. **Results:** Thirty-six breast cancer patients who underwent NSMs followed by immediate reconstruction answered the questionnaire. Most of them considered their results good (51%) or great (43%) and all patients will recommend NSM as a therapeutic treatment for other women with breast cancer. Only one patient presented infection and loss of the mammary implant, and recurrence rates were satisfactory (5.5%). **Conclusion:** Our findings showed low complication rate, oncological safety and good aesthetic outcome related to NSM with immediate reconstruction in patients from a Breast Cancer Center in Brazil. Despite the limitations of our study, we support the use of NSM with immediate reconstruction for a better aesthetic outcome with oncological safety.

KEYWORDS: breast neoplasms; esthetics; subcutaneous mastectomy; treatment outcome.

RESUMO

Introdução: A Mastectomia Poupadora do Mamilo (MPM)tem sido realizada em tratamentos de câncer de mama e em mulheres em situação de risco. A cirurgia traz melhores resultados estéticos; todavia, a sua segurança oncológica ainda é controversa. **Objetivo:** Avaliar as complicações cirúrgicas, a segurança oncológica e a satisfação estética de pacientes com câncer de mama submetendo-se à MPM com reconstrução imediata da mama operadas pela mesma equipe médica em um centro de câncer de mama no Brasil. **Método:** De 2004 a 2011, um questionário de satisfação estética foi administrado a mulheres submetidas à MPM seguida de reconstrução imediata de mama 30 ou 60 dias após a cirurgia. Foram analisadas a satisfação estética, as taxas de complicações e a segurança oncológica. **Resultados:** Trinta e seis pacientes com câncer que se submeteram a MPMs seguidas de reconstrução imediata responderam ao questionário. A sua maioria considerou os resultados bons (51%) ou ótimos (43%) e todos os pacientes a recomendarão como tratamento terapêutico a outras mulheres com câncer de mama. Apenas uma paciente apresentou infecção e perda do implante mamário, e as taxas de recorrência foram satisfatórias (5,5%). **Conclusão:** Nossas descobertas mostraram baixa taxa de complicação, segurança oncológica e bom resultado estético relacionado à MPM com reconstrução imediata em pacientes de um centro de câncer de mama no Brasil. Apesar das limitações do nosso estudo, nós apoiamos o uso da MPM com reconstrução imediata para um melhor resultado estético com segurança oncológica.

PALAVRAS-CHAVE: neoplasias da mama; estética; mastectomia subcutânea; resultado do tratamento.

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ARTIGO 6

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Research Article

The Impact of Bone Metastasis Location in the Clinical Outcome of Patients with Metastatic Renal Cell Carcinoma (mRCC): An Analysis from the Latin American Renal Cancer Group (LARCG)

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ARTIGO 7

Breast Cancer Research and Treatment
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CLINICAL TRIAL

Risk-reducing mastectomy: a case series of 124 procedures in Brazilian patients

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Abstract

Purpose Women with mutations in breast cancer predisposition genes have a significantly higher lifetime risk of developing breast cancer and can opt for risk-reducing mastectomy. Women with positive family history of cancer can also opt for prophylactic surgery as a preventive method in selected cases. Current studies showed reduced risk of developing breast cancer after prophylactic nipple-sparing mastectomy, however, despite the good clinical outcomes, one of the main concerns regarding nipple-sparing mastectomy (NSM) is the oncological safety of nipple-areola complex preservation. In this study, we aimed to evaluate the indications, complication rates, and unfavorable events of 62 Brazilian patients that underwent risk-reducing NSM from 2004 to 2018.

Methods Patient data were reviewed retrospectively and descriptive statistics were utilized to summarize the findings.

Results The mean patients age was 43.8 years. The main indication for risk-reducing NSM was the presence of pathogenic mutation (53.3%), followed by atypia or lobular carcinoma in situ (25.8), and family history of breast cancer and/or ovarian cancer (20.9%). There were four (3.2%) incidental diagnosis of ductal carcinoma in situ and one invasive ductal carcinoma (0.8%). From the 124 prophylactic NSM performed, two (1.6%) complications had occurred: one (0.8%) infection and one (0.8%) partial nipple necrosis. In a mean follow-up of 50 months, there was one (1.6%) newly diagnosed breast cancer in the 62 patients undergoing prophylactic NSM.

Conclusions Our findings demonstrated efficacy and safety to perform NSM as prophylactic surgery with good oncological outcomes and low complication rates in a case series of Brazilian patients.

Keywords Prophylactic surgical procedures · Genetic predisposition to disease · Subcutaneous mastectomy · Breast neoplasm

Introduction

Approximately 40–50% of hereditary breast and ovarian cancer syndromes are associated with mutations in the *BRCA1* and *BRCA2* genes, while only 10% is related to mutation in other moderate and high-risk genes, such *TP53*, *PTEN*, *PALB2*, *CHECK2*, and *STK11* [1, 2]. Women with mutations in *BRCA* genes have a significant increased lifetime risk of developing breast cancer. The risk of breast cancer at the age of 80 years is 72% for *BRCA1* mutation carriers and 69% for *BRCA2* mutation carriers [3].

Patients presenting inherited breast cancer syndromes can opt for intensive clinical surveillance or prophylactic surgery with the aim of early detection and of reducing cancer development and mortality. Nipple-sparing mastectomy (NSM) has been successfully performed for the treatment of breast cancer and for women at high risk of developing breast cancer [4, 5]. The number of prophylactic mastectomies have been increasing after the press noticed worldwide that actress Angelina Jolie performed a bilateral risk-reducing mastectomy (BRRM) due to an inherited pathogenic *BRCA1* mutation [6]. However, not only mutation carriers can choose the surgery as a preventive method. Women with strong family history of breast and/or ovarian cancer,

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ARTIGO 8

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ORIGINAL ARTICLE

The Breast Journal WILEY

Effect of intraoperative radiotherapy for early breast cancer on 10-year recurrence rates and overall survival

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Abstract

The aim of this study was to evaluate 10-year local control and overall survival of IORT for early breast cancer treatment. We analyzed 68 patients submitted to breast conservative surgery and IORT, in the accelerator room of the Radiotherapy Service in South Brazil. In the long-term follow-up, we had 17.6% of patients with ipsilateral breast cancer recurrence, 2.9% with regional recurrence, 2.9% with contralateral breast recurrence, and 5.9% with distant metastasis. The 10-year overall survival was 82.8%. Our data show high local recurrence rates, however, good overall survival in early breast cancer patients treated with breast-conserving surgery and intraoperative radiotherapy with electron beams in the long-term follow-up.

KEYWORDS
breast cancer, conserving surgery, intraoperative radiotherapy

1 | INTRODUCTION

Intraoperative radiotherapy with electrons (IORT) after conservative surgery for breast carcinoma allows the substitution of conventional breast irradiation for one session of radiotherapy with the equivalent dose during surgery.

Data from previous trial showed that local relapse in breast carcinoma conservatively treated are in the same quadrant initially involved by the tumor and the delivery of radiotherapy directly to the tumor bed after the quadrantectomy should be adequate to ensure a good local control.[1] The presence of certain drawbacks, such as the length of overall treatment time, social and economic distress, and integration with systemic therapy, has led to an increased use of accelerated partial-breast irradiation in clinical practice.

Previously we published results of 40 patients submitted to breast-conserving surgery (BCS) and IORT. In the short-term follow-up, median of 18 months, six patients (15%) presented with some grade of fibrosis under the scar and only one patient (2.5%) presented local recurrence. Our data showed that intraoperative radiotherapy with electron beams can be safely conducted in the linear accelerator room with a conventional machine.[2] However, one of the main concerns remains the lack of long-term follow-up.[3] Here, we report the 10-year outcomes of patients submitted to BCS and IORT utilizing a low-cost self-developed collimator and an existing radiotherapy equipment.

2 | METHODS

2.1 | Eligible patients

We analyzed 75 patients submitted to BCS and IORT in the linear accelerator room of the Radiotherapy Service at the São Lucas Hospital of the Pontifical Catholic University of Rio Grande do Sul (PUCRS) from January 2004 to April 2009. Patients with unifocal breast carcinoma clinical smaller than 25 mm, aged over 44 years, who were candidates for conservative surgery and subsequent conventional radiotherapy, were selected. Five patients with largest lesion size, pathologic 30 mm and candidates for conservative treatment, and six patients with previous cancer (3 breast cancer, lymphoma, colon cancer, and melanoma), were also included in this

ARTIGO 9

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RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

Axillary management for patients with breast cancer after neoadjuvant chemotherapy: Results of a survey among Brazilian breast surgeons

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Abstract

Background: Currently, there are broadly differing patterns in the management of the axilla after neoadjuvant chemotherapy (NAC) and no consensus with clinically strong evidence on the subject. A survey was performed to assess the current axillary management after NAC among Brazilian breast cancer surgeons.

Methods: The Brazilian Society of Mastology members were invited by email to complete an anonymous online survey and a total of 426 responses were collected.

Results: The majority of responders (67%) indicated performing routine axillary staging by physical exam, ultrasound, and fine needle biopsy in case of a suspicious node before NAC. Among breast surgeons working in the Brazilian Public Unified Health System, 11.3% answered that sentinel lymph node biopsy (SLNB) is not reasonable after NAC in their services. Seventy-seven responders (18.2%) reported performing SLNB instead of axillary lymph node dissection (ALND) only in patients who are clinically node-negative before NAC. Axillary complete pathologic response is necessary to omit ALND for 42.8% of responders. The molecular profile of a breast tumor is not considered when choosing axillary management after NAC for 73.7% of responders.

Conclusions: Our survey highlighted the trend towards de-escalation of axillary surgery and observed high heterogeneity in axillary management after chemotherapy in a group of brazilian breast surgeons.

KEYWORDS
breast neoplasm, neoadjuvant therapy, sentinel lymph node

1 | INTRODUCTION

Neoadjuvant chemotherapy (NAC) is increasingly administered to women with breast cancer and currently applied to decrease tumor size, allowing breast-conserving surgery instead of mastectomy and also reverting inoperable tumors into operable ones.[1,2] Although, de-escalation of breast surgery is a reality in patients with early-stage breast cancer minimalizing surgery morbidity and increasing quality of life,[3] axillary conservative management in the era of NAC remains controversial.[4] The identification of negative lymph nodes in a patient with cN1 disease at diagnosis might be difficult using sentinel lymph node biopsy (SLNB) after NAC, the false-negative rates of SLNB being one of the main concerns. Identification of

ARTIGO 10

Perspectives on the Systemic Staging in Newly Diagnosed Breast Cancer

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Abstract

Breast cancer is a complex disease, and accurate systemic staging is an essential aspect of the evaluation of a patient with newly diagnosed breast cancer. Considering that the chance of having metastatic disease at breast cancer diagnosis is different in each patient and depends on a variety of anatomic and biologic factors, it is crucial to understand that some populations may benefit from more intensive staging because their pretest probability of metastatic disease is higher than that of the average patient. Identifying these patients with de novo stage IV breast cancer is associated with substantial prognostic and therapeutic implications. Unfortunately, recent advances in understanding breast cancer heterogeneity and molecular biology have not been incorporated in the international guidelines and recommendations about imaging examinations for detecting de novo metastatic breast cancer. This review article discusses important issues regarding the rationale for performing systemic staging, addresses current and innovative imaging methods, and proposes an algorithm for systemic staging in patients with newly diagnosed breast cancer.

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Keywords: Breast neoplasm, Cancer staging, Metastasis, Positron emission tomography, de novo

Introduction

Breast cancer is a heterogeneous disease with a complex diversity of anatomic and biological features that makes personalized care very challenging. Cancer staging is an essential aspect of the diagnosis and serves to summarize disease extent and prognosis accurately and concisely. Additionally, accurate staging is useful in comparing the results of different therapeutic strategies and selecting treatment of individual patients. In patients with newly diagnosed breast cancer, evaluation for metastatic disease before primary therapy initiation remains a somewhat controversial topic.

With the implementation of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual eight edition, prognostic estimates for early-stage breast cancer have been refined by incorporating both anatomic and biologic factors into a prognostic staging system.[1] However, these factors have not been routinely incorporated into the recommendations of systemic staging examinations in newly diagnosed cases.

Available guidelines do not recommend routine use of systemic imaging staging procedures in patients with newly diagnosed early-stage breast cancer based on the infrequent incidence of metastatic disease in this setting. However, most of the available recommendations are not evidence-based, and for the most part, do not contemplate breast cancer heterogeneity and the benefits of newly available therapies. Although most patients presenting with early-stage breast cancer diagnosis have a small chance of having metastatic disease, a not insignificant proportion of patients with stage II and III breast cancer have metastatic disease that could go undetected without adequate imaging. Identifying these patients with de novo stage IV breast cancer is associated with substantial implications regarding prognosis and therapeutic alternatives. Differently from the clinical scenario of a few years ago, there are now clearly different recommendations for each breast cancer subtype according to the disease setting with a variety of effective first-line therapies. Therefore failure to identify a stage IV de novo disease due to suboptimal staging could be particularly detrimental to the patient's quality of life and survival outcomes. At the same time, we need to recognize the caveats associated with a more intensive evaluation of patients for metastasis before primary therapy. Among others, these include the chance of false-positive results, resulting in increased health care costs and the delay of essential treatments.

This article aims to critically evaluate the current staging recommendations for detecting breast cancer metastasis, highlighting emerging staging strategies applicable to patients with breast cancer. We will also discuss important issues about the use of prognostic classifications to allow personalized oncologic care. We should acknowledge that our focus will be on the systemic staging of patients with newly diagnosed disease. We will not cover follow-up strategies and will not address the locoregional staging of breast cancer.

Rationale for Performing Systemic Staging in Early-Stage Breast Cancer

Knowledge of cancer anatomic extent and biological behavior is key to defining optimal care.[2] Over the last decades, we have established strategies for staging cancers to better categorize patients with

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ARTIGO 11

ecancermedicalscience

Highlights of the 17th St Gallen International Breast Cancer Conference 2021: customising local and systemic therapies

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Abstract

The 17th edition of the St Gallen International Breast Cancer Conference was held in March 2021 in an entirely virtual mode. More than 3,300 participants took part in this important bi-annual critical review of the 'state of the art' in the multidisciplinary care of early-stage breast cancer (BC). Seventy-four experts from all continents discussed and commented on the previously elaborated consensus questions as well as numerous interrogations on early-BC diagnosis and treatment asked by the audience. The theme of this year's Conference was 'Customising local and systemic therapies'. This paper summarises the results of the 2021 international panel votes as a quick news update. We discuss the most important issues on genetics, pathology, surgery, radiotherapy and systemic therapies presented and debated throughout the conference. We selected the topics based on applicability into the personalised care of BC patients and focused on questions that have a clear impact on our current clinical practice.

Keywords: *breast cancer, 17th St Gallen Consensus Conference 2019, adjuvant, neoadjuvant, consensus*

Conference Report

Introduction

The 17th St Gallen International Breast Cancer Conference was held between 17 and 21 March 2021. Due to the COVID-19 pandemic, this edition was conducted in an entirely virtual mode. More than 3,300 participants from over 94 countries joined the live scientific sessions and the consensus meeting. Around 70 experts (detailed in Table 1) from all continents discussed and commented on an extended set of thoughtfully prepared questions as well as numerous questions on early-breast cancer (BC) diagnosis and treatment asked by the live audience. Some changes were introduced in the Conference's chairmanship and the consensus panel composition, including 21 new panelists since 2017.

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ARTIGO 12

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BMC Cancer

RESEARCH Open Access

Management of early-stage triple-negative breast cancer: recommendations of a panel of experts from the Brazilian Society of Mastology

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Abstract

Background: Triple-negative breast cancer (TNBC) is a heterogenous subtype involving different patterns of behavior and clinical course, demanding a complex, individualized sequence of treatment. The knowledge and attitudes of the affiliated members of the Brazilian Society of Mastology regarding TNBC were evaluated and a consensus regarding management and treatment was reached.

Methods: Affiliates completed a survey involving 44 objective questions. In addition, a specialist meeting was held with 27 experts and 3 ad hoc consultants. The panelists completed the survey before and after brainstorming. Answers achieving 70% of agreement were considered consensual. The chi-square test was used to compare answers between panelists and affiliates and the Kappa coefficient to calculate agreement.

Results: Consensus among the panelists increased from 26 (59.1%) to 32 questions (72.7%) following brainstorming ($p = 0.17$), including 7/10 questions on systemic treatment. Among the affiliates, consensus was achieved for 24 questions (54.5%), resulting in moderate agreement ($\kappa = 0.445$). Neoadjuvant chemotherapy should be indicated for almost all cases (except cT1a-b N0) and should include platinum agents. When indicated, immunotherapy is part of the standard of care. The panel reaffirmed the concept of *no ink on tumor* as indicative of adequate margins and the

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