Incidental Histopathological Findings in Risk-Reducing Mastectomies: A Cross-Sectional Study

Thaysa Estevão Fernandes[1]; Daniel Imbassahy de Sá Bittencourt Câmara e Silva[1]; Augusto Ostermann Magalhães[1]; Mariana Decco Faucz[1]; Monique Possari Minari[1]; Thiago Gaspar[1]; Renato Torresan[1]; Fabrício Brenelli[1]; Geisilene Russano de Paiva Silva[1]; Bárbara Narciso Duarte[1]; Christine Elisabete Rubio Alem[1]; Leonardo Roberto da Silva[1]; Susana Oliveira Botelho Ramalho[1]; Sandra Regina Campos Teixeira[1]; Ana Elisa Ribeiro da Silva Cabello[1]; Cesar Cabello[1].

1 State University of Campinas of Affiliation

Introduction

Breast cancer is the most common malignancy in women worldwide (1) and represents a significant global health burden, especially among high-risk populations such as carriers of pathogenic germline variants (e.g., BRCA1 e BRCA2) and/or individuals meeting NCCN Guidelines criteria for hereditary breast cancer syndromes (2). For patients at high hereditary risk, risk-reducing surgery is an effective preventive strategy. However, histopathological analysis of the surgical specimens often reveals incidental findings (IFs), such as occult carcinomas and precursor lesions, with a reported prevalence ranging from 1.6% to 11.3% (3, 4). The clinical significance and correlation of these findings with specific risk profiles remain understudied.

Objective

This study aimed to estimate the prevalence of incidental histopathological findings in risk-reducing mastectomy specimens and identify associated risk factors in a Brazilian cohort.

Methods and Materials

This cross-sectional study analyzed risk-reducing breast surgery (RRBS) specimens from Women's Hospital "Prof. Dr. José Aristodemo Pinotti"— Center for Integral Attention to Women's Health (CAISM/ UNICAMP), between 2013–2025. Eligible patients carried pathogenic/likely pathogenic germline variants and/or fulfilled NCCN high-risk criteria (NCCN version 3.2021). Histopathological assessment followed an institutional protocol with extensive tissue sampling. Logistic regression models evaluated demographic, clinical, and surgical predictors of IFs.

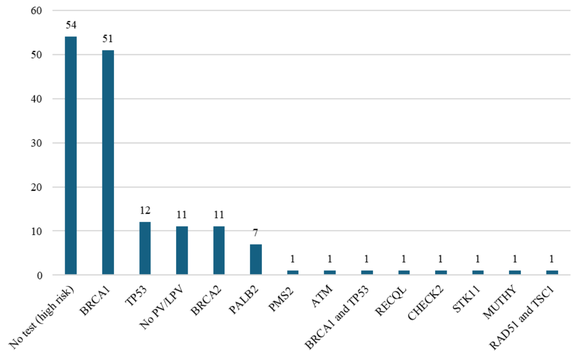


Fig 1. Distribution of pathogenic/likely pathogenic variants of the population

Results

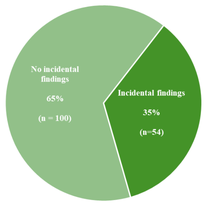
100 patients have undertaken a genetic panel for hereditary breast cancer, with 63 (40,9%) presenting a PV/LPV in BRCA1 or BRCA2 genes, 26 (16,8%) with a PV/LPV in other high, moderate or low penetrance genes and 11 (7%) had a no PV/LPVs test (including no variants, benign variants or VUS). Figure 1 summarizes this distribution.

IFs were identified in 35% (54/154) of patients, including atypical proliferations (70%), DCIS (22%), and invasive neoplasia (8%). On multivariate analysis, older age (OR 1.071) and bilateral mastectomy (OR 3.27) were significant independent predictors of IFs. For invasive and DCIS findings, age was the only significant factor (OR 1.069). Genetic status showed no significant association. Figure 2, table 1 summarizes this distribution.

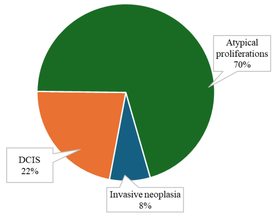
Table 2 presents the results of the univariate and multivariate logistic regression analysis (using the stepwise variable selection method) to examine the association between the factors studied and the presence of incidental findings for the whole population of the study.

Age and type of surgery were identified as variables significantly associated with the presence of incidental findings. Women at higher risk of findings were those of older age, with a 7.1% increase in risk per year of age (OR =1.071; CI 95% 1.029 – 1.115, p < 0.001) and those who underwent bilateral mastectomy with 3.3-fold higher risk (OR =3.27; CI 95% 1.50–7.11, p = 0.003).3

a) Incidental findings



b) Pathology of findings



c) Table 1

Finding	N	% of total	% of findings
No incidental findings	100	64.9%	
Invasive ductal carcinoma	3	1.9%	8%
Malignant Phyllodes tumor	1	0.6%	
DCIS	11	7.1%	22%
DCIS + LCIS	1	0.6%	
ADH	12	7.8%	
ADH + ALH/LCIS	2	1.3%	
ALH/LCIS	9	5.8%	70%
FEA	8	5.2%	
ADH + FEA	7	4.5%	

Fig 2. Incidental histopathological findings at the study's population. a) Proportion of incidental findings; b) and c) Pathological analysis of each finding, categorized as invasive neoplasia, ductal carcinoma in situ and atypical proliferations. *ADH - atypical ductal hyperplasia; ALH - atypical lobular hyperplasia; DCIS – ductal carcinoma in situ; FEA - flat epithelial atypia; LCIS - lobular carcinoma in situ.*

Table 2. Results of univariate and multivariate regression analysis of all study population

		Univariate analysis (n=154)			Multivariate analysis (n=143)		
Variable	**Category**	p-value	O.R.*	95% CI*	p-value	O.R.*	CI 95% O.R.*
Age	<40 years (ref.)	--	1.00	---	--	--	--
	≥40 years	**0.010**	2.45	1.24 – 4.83	--	--	--
Age	Continuous variable	**0.04**	1.056	1.018 – 1.096	**<0.001**	1.071	1.029 – 1.115
Race	White (ref.)	---	1.00	---	--	--	--
	Non-white	**0.014**	3.21	1.27 – 8.10	--	--	--
Menopausal status	Pre-menopausal	---	1.00	---	--	--	--
	Postmenopausal	0.356	1.40	0.69 – 2.84	--	--	--
BMI	Continuous variable	**0.008**	1.107	1.027 – 1.195	--	--	--
BMI	<25 (ref.)	---	1.00	---	--	--	--
	25-29.9	**0.010**	2.97	1.29 – 6.84	--	--	--
	≥30	**0.013**	3.56	1.38 – 9.13			
Family history	None (ref.)	---	1.00	---	--	--	--
	First-degree	0.430	1.64	0.48 – 5.59	--	--	--
	Second/third degree	0.975	0.98	0.24 – 3.94	--	--	--
Surgery	Unilateral mastectomy (ref.)	---	1.00	---	---	1.00	---
	Bilateral mastectomy	**0.014**	2.40	1.19 – 4.85	**0.003**	3.27	1.50 – 7.11
	Mammoplasty	0.138	4.04	0.64 – 25.53	0.083	6.00	0.79 – 45.58
Indication for surgery	No PV/LPVs(ref.)	---	1.00	---	--	--	--
	High-risk	0.173	3.09	0.61 – 15.72	--	--	--
	BRCA	0.541	1.66	0.33 – 8.49	--	--	--
	Non-BRCA	0.086	4.50	0.81 – 24.99	--	--	--

*OR (Odds Ratio) = Risk ratio for the presence of findings. 95% CI = 95% confidence interval for the risk ratio. Stepwise variable selection criterion. Ref.: reference category.

Discussion

To our knowledge this is the paper in the literature with the highest prevalence of incidental findings (IF) in RRBS. As we are inserted in a public health setting in Brazil, in which there is limited access to genetic testing, personal risk has a crucial role tailoring the decision of a risk reducing procedure. Interestly, according to our results, age greater than 40 years and bilateral mastectomy were independent risk factors for IF in RRBS. Furthermore, there was no significant association with a negative test and the risk of IF (table 1). Those findings emphasize that in resource-limited scenarios, considering only personal history compatible with NCCN's high risk criteria over documented genetic risk should have an importance in the decision making process of RRBS, especially in patients with less than 40 years, possibly avoiding development of a silent disease.

In addition, our institutional protocol, which mandates extensive macroscopic evaluation and increased sampling (e.g., 4 blocks per quadrant and 2 from the retroareolar region, totaling 18 initial blocks), significantly contributes to the high prevalence of IFs. This meticulous approach ensures that even subtle or early-stage lesions, such as incidental foci of ductal carcinoma in situ with microinvasion, are detected, thereby enhancing diagnostic accuracy and potentially impacting patient management. The practice of obtaining additional sections for paraffin blocks from suspicious areas further underscores the value of comprehensive macroscopic examination in uncovering clinically significant pathologies that might otherwise be missed.

In our cohort, 90.4% (n = 133) of patients reported a family history of breast cancer, including 68.7% (n = 101) with a first-degree relative and 21.7% (n = 32) with a second- or third-degree relative (Table 1). This high prevalence highlights the central role of detailed family history in determining eligibility for risk reducing breast surgery. Evidence from large cohorts indicates that RRBS substantially decreases breast cancer incidence even in the absence of genetic testing. Moreover, the presence of atypical hyperplasia - which was found in 19,4% of our cohort - further amplifies this risk, particularly when combined with a positive family history, with relative risks exceeding fourfold compared with women without these features.

This study has several limitations that should be considered. First, its retrospective nature and its single-center and tertiary-care setting at a referral institution may limit the generalizability of the results, as our population may represent a particularly high-risk group. Second, the cross-sectional design does not allow for the inference of causality from the associations found. The limited use of preoperative MRI and the definition of IF based on clinical and imaging reports may introduce classification bias. Additionally, the statistical power to analyze factors specifically associated with malignant neoplasms (invasive or in situ) was limited by the small number of these events (n=16). Finally, the lack of long-term follow-up data prevents the assessment of the clinical impact of these incidental findings on the survival of these patients. Although prospective studies provide more robust evidence, they are not ethically feasible in the context of RRBS —a procedure with established benefits for this high-risk population. Therefore, to validate and generalize our results, we recommend conducting multicenter studies, which could add sufficient statistical power to establish more precise and personalized clinical guidelines based on individual pathological risk.

Conclusions

This study reports the highest prevalence of IFs in RRBS specimens to date, largely attributable to the comprehensive sampling protocol. Associations with clinical characteristics, particularly age, contrast with the absence of correlation between negative genetic testing and reduced risk. These findings highlight the importance of integrating detailed clinical and familial risk assessment into surgical decision-making, especially in resource-limited systems with restricted access to genetic testing

Contact

Thaysa Estevão Fernandes
State University of Campinas
Email: thaysaefernandes1996@gmail.com
Phone: + 55 (31) 99717-5082.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024; 74(3): 229-263. doi:10.3322/caac.21834.
2. NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate. Versão 1.2026, 10 jul. 2025. © 2025 National Comprehensive Cancer Network, Inc. Todos os direitos reservados. Disponível em: https://www.nccn.org/guidelines/breast-ovarian-2026. Acesso em: 5 ago. 2025.
3. Wong, SM. Ferroum, A., Apostolova, C. et al. Incidência de câncer de mama oculto em portadoras de BRCA1/2 ou outras variantes patogênicas de alta penetrância submetidas a mastectomia profilática: quando a biópsia do linfonodo sentinela é indicada?. Ann Surg Oncol 29 , 6660–6668 (2022).
4. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 1999;340:77-84. http://www.ncbi.nlm.nih.gov/pubmed/9887158.

This presentation is the intellectual property of the Thaysa Estevão Fernandes. Contact them at thaysaefernandes1996@gmail.com for permission to reprint and/or distribute.

© Poster Template by Genigraphics® 1.800.790.4001 www.genigraphics.com