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PROPHYLACTIC MASTECTOMY IN PATIENTS WITH SPECIFIC HLA GENE VARIANTS: BENEFITS AND CONTROVERSIES

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Abstract: INTRODUCTION Prophylactic mastectomy is an established preventive strategy for individuals carrying BRCA mutations, yet its role in patients with specific HLA gene variants remains uncertain. While some HLA polymorphisms have been associated with increased breast cancer susceptibility, others appear to confer protection. The immunological mechanisms involved in tumor surveillance and immune evasion suggest that HLA variants may contribute to breast cancer risk, but their clinical significance in surgical prevention has not been fully determined. Current risk stratification models do not routinely incorporate HLA genotyping, leading to uncertainty in decision-making regarding prophylactic surgery in this subgroup. **OBJETIVE** To evaluate the necessity, effectiveness, and clinical rationale for prophylactic mastectomy in patients with specific HLA gene variants, considering genetic predisposition, immunological mechanisms, and surgical outcomes. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: "Prophylactic mastectomy" AND "HLA gene polymorphisms" OR "Breast cancer risk assessment" OR "Genetic counseling" OR "Immune surveillance" in the last years. **RESULTS AND DISCUSSION** The results highlight the lack of definitive evidence supporting prophylactic mastectomy in HLA-positive individuals. Unlike BRCA carriers, for whom mastectomy significantly reduces cancer incidence, the variable risk associated with HLA variants complicates surgical recommendations. Psychological distress and decisional conflict are common among patients faced with uncertain genetic risk, and disparities in access to genetic counseling further exacerbate these challenges. Breast reconstruction options and postoperative quality of life were also analyzed, with findings indicating that while many patients report satisfaction, others experience regret, particularly when risk estimates are ambiguous. **CONCLUSION** Given the current gaps in evidence, prophylactic mastectomy in HLA--positive patients should be approached with caution. Future research should prioritize large-scale studies to determine the true oncogenic impact of HLA polymorphisms and assess whether surgical intervention provides a survival benefit. Until more conclusive data are available, risk reduction strategies should focus on individualized counseling, enhanced surveillance, and potential non-surgical interventions tailored to the specific genetic profile of each patient.

Keywords: Prophylactic mastectomy; HLA gene polymorphisms; Breast cancer risk assessment; Genetic counseling; Immune surveillance.

INTRODUCTION

Prophylactic mastectomy has long been a pivotal strategy in managing individuals at elevated risk for breast cancer[1]. Historically, this surgical intervention was primarily considered for patients with significant family histories or those diagnosed with hereditary breast cancer syndromes, notably mutations in the BRCA1 and BRCA2 genes[1]. These mutations are well-documented for their substantial increase in breast cancer risk, leading many carriers to opt for bilateral prophylactic mastectomy to mitigate this threat[1]. Studies have demonstrated that such preventive measures can reduce the incidence of breast cancer by approximately 90% in these high-risk populations[2].

However, the emergence of data implicating specific human leukocyte antigen (HLA) gene variants in breast cancer susceptibility has introduced new dimensions to risk assessment and prophylactic strategies[2]. The HLA system,

integral to immune function, presents antigens to immune cells, thereby influencing the body's ability to recognize and combat malignancies[2]. Certain HLA polymorphisms have been associated with either increased susceptibility or resistance to various cancers, including breast cancer[3]. This association suggests that HLA typing could become a valuable tool in stratifying breast cancer risk, potentially guiding decisions regarding prophylactic interventions[3].

The mechanisms by which HLA gene variants modulate cancer risk are complex and multifaceted[3]. It is postulated that specific HLA alleles may alter antigen presentation, thereby affecting immune surveillance and tumor recognition[3]. For instance, certain HLA polymorphisms might impair the presentation of tumor-associated antigens, allowing malignant cells to evade immune detection and proliferate unchecked[4]. Conversely, other variants may enhance immune recognition of neoplastic cells, conferring a protective effect[4]. Understanding these mechanisms is crucial, as it could inform the development of personalized prophylactic strategies and immunotherapeutic approaches[4].

Epidemiological studies have sought to elucidate the prevalence of specific HLA gene variants across different populations and their correlation with breast cancer incidence[5]. These investigations have revealed notable variations in HLA allele frequencies among ethnic groups, which may contribute to disparities in breast cancer risk[5]. For example, certain HLA alleles associated with increased breast cancer susceptibility are more prevalent in specific populations, suggesting a genetic predisposition modulated by HLA genotype[5]. Such findings underscore the importance of incorporating HLA typing into genetic screening programs to identify individuals who may benefit from enhanced surveillance or prophylactic interventions[6]. Current guidelines for prophylactic mastectomy primarily focus on individuals with BRCA mutations or a strong family history of breast cancer[6]. However, the recognition of HLA gene variants as potential risk modifiers necessitates a reevaluation of these recommendations[6]. Incorporating HLA typing into risk assessment models could refine patient selection for prophylactic mastectomy, ensuring that those at genuine high risk receive appropriate counseling and intervention[7]. This approach aligns with the principles of personalized medicine, tailoring preventive strategies to the individual's genetic risk profile[7].

Advancements in surgical techniques have significantly improved the outcomes of prophylactic mastectomy[7]. Options such as skin-sparing and nipple-sparing mastectomies, combined with immediate reconstruction, have enhanced aesthetic results and patient satisfaction[7]. These developments are particularly pertinent for individuals considering prophylactic surgery based on genetic risk factors, as they may mitigate some of the psychological and quality-of-life concerns associated with mastectomy[8]. Nevertheless, the decision to undergo prophylactic mastectomy is complex, involving considerations of surgical risk, potential complications, and the psychological impact of body image alterations[8]. The psychological ramifications of prophylactic mastectomy are profound and multifaceted[8]. While the procedure offers significant risk reduction, it also entails irreversible changes to body image and potential impacts on sexual health[8]. Patients may experience feelings of loss, altered self-perception, and concerns about femininity and attractiveness[9]. These psychological factors must be carefully weighed against the potential benefits of risk reduction[9]. Comprehensive preoperative counseling, including discussions with mental health professionals, is essential to support patients in making informed decisions and to provide strategies for coping with the emotional consequences of surgery[9].

A critical component of the decision--making process for prophylactic mastectomy is the risk-benefit analysis, particularly in individuals identified as HLA-positive[10]. While the presence of certain HLA gene variants may confer an increased risk of breast cancer, the absolute risk and the potential benefit of prophylactic surgery must be carefully evaluated[10]. This assessment should consider the individual's overall health, life expectancy, and personal values[10]. In some cases, enhanced surveillance or chemoprevention may be appropriate alternatives to surgery[11]. Shared decision-making, incorporating patient preferences and values, is paramount in developing a personalized risk reduction strategy[11].

Lifestyle and environmental factors also play a significant role in modulating genetic risk for breast cancer[11]. Factors such as diet, physical activity, alcohol consumption, and exposure to environmental carcinogens can influence the penetrance of genetic risk factors, including HLA gene variants[11]. For instance, regular physical activity and maintaining a healthy weight have been associated with a reduced risk of breast cancer, potentially mitigating the increased risk conferred by certain genetic profiles[12]. Therefore, risk reduction strategies should adopt a holistic approach, combining genetic risk assessment with lifestyle modifications to optimize outcomes[12].

Ethical considerations are integral to the discourse on recommending prophylactic surgery based on genetic risk factors[12]. The potential for genetic discrimination, issues of informed consent, and the psychological impact of genetic risk information must be carefully navigated[12]. Patients should be fully informed of the limitations of genetic testing, including the possibility of variants of uncertain significance and the fact that not all individuals with high-risk gene variants will develop cancer[13]. Moreover, the potential for coercion, whether perceived or real, should be minimized, ensuring that patients' autonomy in decision-making is respected[13]. The impact of prophylactic mastectomy on overall survival and cancer recurrence rates is a critical consideration[13]. While the procedure significantly reduces the risk of developing breast cancer, it does not eliminate it entirely, as residual breast tissue may harbor malignant potential[13]. Furthermore, the survival benefit of prophylactic mastectomy must be weighed against the risks associated with surgery and the potential for postoperative complications[14]. Long-term studies are needed to quantify the survival benefit, particularly in populations with specific genetic risk factors such as HLA gene variants[14].

OBJETIVES

To evaluate the necessity, effectiveness, and clinical rationale for prophylactic mastectomy in patients with specific HLA gene variants, considering genetic predisposition, immunological mechanisms, and surgical outcomes.

SECUNDARY OBJETIVES

1. To analyze the oncogenic mechanisms linking HLA polymorphisms to breast cancer risk.
2. To compare the risk profiles of HLA-positive patients versus BRCA mutation carriers.
3. To assess the psychological and quality-of-life impact of prophylactic mastectomy in this population.
4. To investigate disparities in access to genetic testing and surgical prevention.
5. To propose future research directions for refining risk stratification and clinical decision-making.

METHODS

This is a narrative review, in which the main aspects of the necessity, effectiveness, and clinical rationale for prophylactic mastectomy in patients with specific HLA gene variants, considering genetic predisposition, immunological mechanisms, and surgical outcomes in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Prophylactic mastectomy" AND "HLA gene polymorphisms" OR "Breast cancer risk assessment" OR "Genetic counseling" OR "Immune surveillance" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case--control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION

Prophylactic mastectomy in patients with specific HLA gene variants remains an evolving field of study, with recent findings suggesting a complex interplay between genetic predisposition and immune surveillance[15]. The strength of evidence linking HLA polymorphisms to breast cancer risk varies, with some alleles appearing to confer increased susceptibility, while others demonstrate protective effects[15]. HLA-DRB1*03, for instance, has been associated with a reduced risk of breast cancer, whereas HLA-DRB1*12 has been linked to an elevated incidence of the disease[15]. Comparative risk analyses between HLA-positive individuals and BRCA mutation carriers have highlighted distinct oncogenic pathways[16]. While BRCA mutations lead to defective DNA repair and genomic instability, HLA-associated risks are mediated through alterations in immune recognition[16]. This suggests that while BRCA mutation carriers benefit significantly from prophylactic mastectomy, the same cannot be definitively concluded for HLA-positive patients without further risk stratification[16].

Immunological mechanisms play a fundamental role in the pathogenesis of HLA--associated breast cancer[17]. Aberrant antigen presentation due to specific HLA variants may result in impaired immune surveillance, allowing malignant cells to evade detection[17]. Furthermore, some HLA alleles have been implicated in chronic inflammation, which can contribute to carcinogenesis by fostering a tumor-promoting microenvironment[17]. The clinical utility of HLA testing in breast cancer risk assessment remains under investigation[18]. Unlike BRCA testing, which has clear predictive value and therapeutic implications, the role of HLA typing in clinical practice is less established[18]. As more data become available, incorporating HLA genotyping into risk models may refine patient selection for prophylactic interventions[18].

Genetic counseling protocols must adapt to incorporate HLA testing where relevant, ensuring that patients receive accurate risk estimates[19]. The interpretation of HLA-related breast cancer risk is complex, requiring integration with other genetic, environmental, and familial factors[19]. Without clear guidelines, there is a risk of overestimating or underestimating the actual danger posed by specific HLA polymorphisms[19]. The psychological effects of HLA testing and risk disclosure warrant careful consideration[20]. Patients identified as high risk may experience anxiety and decisional conflict regarding prophylactic

surgery[20]. The uncertainty surrounding the implications of HLA positivity further complicates decision-making, underscoring the need for robust pre-test counseling[20].

Outcomes of prophylactic mastectomy in HLA-positive versus BRCA-positive patients remain poorly defined[21]. While BRCA carriers exhibit a well-documented survival benefit from risk-reducing mastectomy, similar data for HLA-positive individuals are lacking[21]. The absence of definitive risk estimates makes it challenging to determine whether prophylactic mastectomy offers a tangible advantage in this population[21]. Patient satisfaction and regret following prophylactic mastectomy are key indicators of procedural success[22]. While most high-risk patients report relief from cancer-related anxiety postoperatively, a subset experiences regret, often due to surgical complications or unexpected psychological distress[22]. The likelihood of regret appears to be higher in patients whose preoperative risk assessment was ambiguous or inadequately communicated[22].

Survival and recurrence rates following prophylactic mastectomy in HLA-positive individuals require further study[23]. Given that the oncogenic mechanisms in HLA-associated breast cancer are distinct from those in BRCA-driven malignancies, the effectiveness of surgical prevention may differ[23]. Long-term follow-up studies are necessary to establish whether prophylactic mastectomy translates to a significant reduction in breast cancer incidence in this group[23]. The role of breast reconstruction following prophylactic mastectomy is critical in improving patient outcomes[24]. Advances in reconstructive techniques, including autologous tissue transfer and implant-based approaches, have enhanced cosmetic results and quality of life[24]. However, surgical complications such as capsular contracture and implant failure remain concerns, particularly in patients with prior radiation exposure[24].

Disparities in access to genetic testing and prophylactic mastectomy persist, particularly in lower-income populations[25]. Socioeconomic status, healthcare literacy, and geographic barriers influence the likelihood of undergoing genetic screening and subsequent risk-reducing surgery[25]. Addressing these inequities through policy interventions and financial support programs is crucial for ensuring equal access to preventive care[25]. The debate over surveillance versus prophylactic mastectomy in HLA-positive patients remains unresolved[26]. While enhanced screening protocols, including MRI-based surveillance, offer an alternative to surgery, their long-term efficacy in reducing mortality is unclear[26]. Individualized decision-making, taking into account patient preferences and comorbid conditions, is essential for optimizing risk management[26].

Ethical considerations surrounding prophylactic mastectomy recommendations in HLA-positive individuals must be addressed[27]. Given the uncertainty in risk prediction, physicians must balance the potential benefits of surgery with the risks of overtreatment[27]. Informed consent processes should emphasize the limitations of current knowledge to support truly autonomous patient decision-making[27]. The economic burden of genetic screening and prophylactic mastectomy on healthcare systems is significant[28]. While cost-effectiveness analyses support BRCA testing and preventive surgery, similar evaluations for HLA testing are lacking[28]. Determining the financial viability of incorporating HLA genotyping into routine breast cancer risk assessment is an area requiring further research[28].

The emergence of personalized medicine offers new opportunities for refining prophylactic mastectomy recommendations[29]. Integrating genetic, hormonal, and environmental risk factors into predictive algorithms may allow for more precise patient stratification[29]. The use of machine learning models to analyze large

genomic datasets holds promise in identifying novel biomarkers for breast cancer susceptibility[29]. Hormone receptor status is a critical factor influencing prophylactic surgery decisions[30]. In BRCA mutation carriers, estrogen receptor--negative tumors are more common, justifying aggressive preventive measures[30]. However, the relationship between HLA polymorphisms and hormone receptor expression remains poorly understood, highlighting the need for additional molecular studies[30].

Adherence to follow-up care after prophylactic mastectomy is essential for early detection of residual or new malignancies[31]. Despite the perception that risk is eliminated post-surgery, cases of residual breast cancer have been documented[31]. Comprehensive post-mastectomy surveillance strategies should be emphasized in patient education to mitigate late-stage cancer diagnoses[31]. Prophylactic mastectomy has significant implications for body image and sexual function[32]. While many patients adjust positively over time, others experience persistent distress related to changes in physical appearance[32]. Psychological interventions, including cognitive behavioral therapy and peer support programs, may facilitate better coping mechanisms in affected individuals[32].

The need for standardized guidelines on HLA-based risk reduction strategies is increasingly evident[33]. Current recommendations lack specificity regarding the role of prophylactic mastectomy in this subset of patients[33]. International consensus efforts should prioritize evidence-based protocols that consider the nuanced risks associated with different HLA variants[33]. Future research directions should focus on elucidating the precise oncogenic mechanisms of HLA-associated breast cancer[34]. Large-scale, multicenter studies are necessary to clarify the clinical significance of various HLA polymorphisms[34]. Expanding research efforts in this field will be instrumental in refining preventive strategies and optimizing patient outcomes[34].

CONCLUSION

Prophylactic mastectomy in patients with specific HLA gene variants remains a complex and evolving topic, with current evidence indicating both potential benefits and considerable uncertainties. While BRCA mutations have well-established guidelines for risk-reducing surgery, the role of HLA polymorphisms in breast cancer predisposition is less clear. The immunological mechanisms underlying HLA-associated oncogenesis suggest a possible influence on tumor surveillance and immune evasion, but definitive risk stratification remains challenging. Without robust predictive models, determining which HLA-positive individuals might benefit from prophylactic surgery continues to be a subject of debate.

The lack of standardized genetic counseling for HLA-positive patients further complicates clinical decision-making. Unlike BRCA carriers, who receive clear recommendations based on decades of research, individuals with high-risk HLA variants face greater uncertainty regarding their actual cancer risk. Current risk prediction models do not yet incorporate HLA typing, which limits the ability of clinicians to offer precise guidance on prophylactic interventions. Until more comprehensive data are available, counseling should emphasize individualized risk assessment, incorporating family history, environmental factors, and other genetic predispositions.

Psychological and quality-of-life considerations are central to discussions about prophylactic mastectomy in this patient population. The anxiety associated with a perceived high cancer risk can drive some individuals toward surgery, even in the absence of definitive risk estimates. However, post-mastectomy regret, body image disturbances, and sexual dysfunction remain important concerns. Ensuring that patients have access to psychological support and realistic expectations regarding both risk and surgical outcomes is crucial in guiding informed decision-making.

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Healthcare disparities in genetic testing and prophylactic surgery access continue to present challenges in preventive oncology. Socioeconomic factors, geographic barriers, and healthcare system limitations affect whether high-risk individuals receive appropriate risk assessment and intervention. Expanding access to HLA genotyping, refining its clinical utility, and integrating it into comprehensive cancer prevention programs will be critical in addressing these disparities.

Future research should prioritize large--scale, longitudinal studies to determine the true oncogenic significance of HLA polymorphisms in breast cancer. Further investigation is needed to establish whether prophylactic mastectomy offers a survival benefit in HLA-positive patients or whether alternative risk-reduction strategies, such as enhanced surveillance or immunomodulatory therapies, would be more appropriate. Advances in personalized medicine and machine learning models may help refine risk stratification, ultimately improving decision-making for this subgroup of patients.

In conclusion, while prophylactic mastectomy remains a crucial option for patients with well-defined genetic risk factors, its role in HLA-positive individuals is not yet fully understood. Until more robust evidence supports its effectiveness, decisions regarding surgical prevention in this group should be made cautiously, emphasizing individualized counseling and shared decision-making. Ongoing research will be instrumental in clarifying whether HLA genotyping should become a routine component of breast cancer risk assessment and whether surgical intervention is a justified strategy in this unique patient population.

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