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Neves, Nedy Maria Branco Cerqueira; Boaventura, Camila Silva; Costa, Maria Alice Freitas; Bitencourt, Almir Galvão Vieira

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Ethical implications of genetic testing of susceptibility to breast cancer

Nedy Maria Branco Cerqueira Neves[1], *Camila Silva Boaventura*[2], *Maria Alice Freitas Costa*[2], *Almir Galvão Vieira Bitencourt*[2]

1. Universidade Salvador, Salvador/BA, Brasil. **2.** A. C. Camargo Cancer Center, São Paulo/SP, Brasil.

Abstract

Breast cancer is a public health problem because it is the malignant neoplasm with the highest incidence in women worldwide. The hereditary form corresponds to about 5% to 10% of all cases and is directly related to the inheritance of genetic mutations. The main ones occur in the BRCA1 and BRCA2 tumor suppressor genes. The identification of these mutations is extremely important because of the high risk of breast cancer development in this population, allowing differentiated screening strategies and the adoption of risk reduction measures. However, reflections on the ethical aspects related to the indiscriminate use of genetic testing are important and necessary. The objective of this study was to evaluate the knowledge and opinion of physicians of an oncology reference center on the indication of genetic tests for susceptibility to breast cancer given the ethical dilemmas to which they are submitted in medical practice.

Keywords: Breast neoplasms. Genetic testing. Genes, BRCA1. Genes, BRCA2. Ethics, medical.

Resumo

Implicações éticas dos testes genéticos de suscetibilidade ao câncer de mama

O câncer de mama representa um problema de saúde pública por ser a neoplasia maligna de maior incidência em mulheres no mundo. A forma hereditária corresponde a cerca de 5% a 10% de todos os casos e está diretamente relacionada à herança de mutações genéticas, sendo as principais nos genes supressores de tumor BRCA1 e BRCA2. A identificação dessas mutações é de extrema importância pelo elevado risco de desenvolvimento de câncer de mama nessa população, permitindo estratégias de rastreamento diferenciado e adoção de medidas de redução de risco. Entretanto, é importante e necessário refletir sobre os aspectos éticos relacionados ao uso indiscriminado de testes genéticos. O objetivo deste trabalho foi avaliar o conhecimento e a opinião de médicos de um centro de referência oncológico sobre a indicação dos testes genéticos de suscetibilidade ao câncer de mama mediante dilemas éticos aos quais são submetidos na prática médica.

Palavras-chave: Neoplasias da mama. Testes genéticos. Genes BRCA1. Genes BRCA2. Ética médica.

Resumen

Implicaciones éticas de las pruebas genéticas de susceptibilidad al cáncer de mama

El cáncer de mama es un problema de salud pública por ser la neoplasia maligna más frecuente en mujeres a nivel mundial. La forma hereditaria representa entre un 5% y un 10% de los casos de esta neoplasia, relacionada directamente con las mutaciones genéticas heredadas, principalmente, en los genes supresores de tumores BRCA1 y BRCA2. La identificación de estas mutaciones es muy importante debido al alto riesgo de desarrollar cáncer de mama en esta población, pues facilita la aplicación de estrategias de cribado diferenciadas y la adopción de medidas de reducción del riesgo. Sin embargo, es importante y necesario reflexionar sobre los aspectos éticos relacionados con el uso indiscriminado de pruebas genéticas. Este estudio pretende evaluar el conocimiento y perspectiva de médicos de un centro de referencia oncológico sobre la indicación de pruebas genéticas para detectar el cáncer de mama a través de dilemas éticos a los que se ven sometidos en la práctica médica.

Palabras clave: Neoplasias de la mama. Pruebas genéticas. Genes BRCA1. Genes BRCA2. Ética médica.

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Research

Breast cancer (BC) represents a public health problem as it is both the most common malignant neoplasia and the leading cause of cancer mortality in women worldwide. BC etiology is multifactorial, related to genetic and environmental factors. The hereditary form corresponds to about 5% to 10% of all cases and is directly related to the inheritance of genetic mutations, and the main ones occur in the tumor suppressor genes, BRCA1 and BRCA2 [1,2].

It is estimated that less than 1% of the general population has mutations in the BRCA1 and BRCA2 genes; however, identifying these mutations is extremely important, since this population is at high risk of developing BC. Among patients known to carry mutations that increase the risk for BC, early differentiated screening or the adoption of risk reduction measures—such as prophylactic bilateral mastectomy—are recommended. From this perspective, genetic testing is paramount to corroborate the strengthening of preventive medicine, which aims to predict, avoid, and alleviate the diseases not yet manifested [3].

Current recommendations suggest that all women, by age 30, should undergo an assessment of risk for BC to guide counseling on screening, genetic testing, and risk-reducing treatments [4]. In general, patients with a personal or family history of ovarian cancer at any age, BC under age 50, bilateral BC or triple-negative subtype at any age, male BC, or Ashkenazi Jewish ancestry, should be considered for genetic counseling [5]. The medical geneticist will determine whether to perform the test and which test would be appropriate for each patient, after discussing the procedure risks and benefits.

In this context, the molecular approach to detecting pathogenic mutations has become crucially important. Nevertheless, ethical, social, and legal problems arise simultaneously. Some issues are worth discussing, such as: the right to test healthy individuals; rights related to employers and health insurers; prejudice and embarrassment towards family, friends, and society; psychological implications of the advance knowledge of a serious pathology in the future; advantages and disadvantages involved in the process, and diagnosis reliability [2,6].

In view of this, investigating and reflecting on the problematization of the recommendation for genetic testing are necessary actions. Screening for certain diseases can include the use of high-tech medical equipment on patients, or exclude them from the social and working life, causing stigma. The objective of this study was to evaluate the knowledge and opinion of physicians from a cancer reference center about recommending genetic testing for BC susceptibility in view of ethical dilemmas to which they are subjected in medical practice.

Method

This is a descriptive, cross-sectional study carried out by the application of a questionnaire to physicians working at a cancer reference center. The research was approved by the Institution's Research Ethics Committee and all participants signed the informed consent form. The physicians included are specialists in genetics, breast disease, oncology, radiology, pathology, and gynecology.

The instrument applied was a self-administered questionnaire, adapted from the one used by Thies, Bockel and Bochdalofsky [7], consisting of 28 objective questions and two cases, which aimed to trace their sociodemographic data. The participants were also asked about their knowledge of and opinions on genetic testing for BC susceptibility and its ethical implications in reducing the risk for BC.

Data tabulation and analysis were made on the SPSS software version 20.0, considering statistical significance of $p<0.05$. The study used the parameters of descriptive statistics to characterize the findings, and chi-square and Fisher's exact tests for the correlation between categorical variables.

Results

Seventy-five physicians participated in the study, with 41.2 years as the mean age (ranging from 28 to 68 years); 40 were men (53.3%) and 35 were women (46.7%). The sample was composed of 31 radiologists (41.3%), 17 oncologists (22.7%), 11 pathologists (14.7%), seven specialists in breast disease (9.3%), six gynecologists (8%) and three geneticists (4%). Most respondents (42.7%) had more than 15 years of training, 32% had between 10 and 15 years, and 21.3%, between five and 10 years.

When asked if they knew the criteria for recommending counseling and genetic testing, 47 replied affirmatively (62.7%), and 28 replied negatively (37.3%). Radiologists (74.2%) and pathologists (45.5%) (p<0.001) were the specialists who most reported not knowing the criteria.

The main benefit from carrying out genetic testing was to guide screening, recommendations and prevention (n=57; 76%), obtain more accurate estimates of risk of developing cancer (n=25; 33.3%), and confirm or not if BC is hereditary (n=19; 25.3%). Regarding the testing limitations, 47 (62.7%) considered that a negative result does not exclude mutations in other genes (variants of uncertain significance), and 28 respondents (37.3%) said that the main limitation is that a negative result does not exclude the risk of developing sporadic cancer.

Regarding the problems that may arise as genetic testing is performed, the main one was the negative psychological effect on the patient, pointed out by 71 respondents (94.7%), followed by negative social reaction (employment loss, stigma about the disease, etc.), and problems with health and life insurance plans, both mentioned by 14 respondents (18.7%); problems related to protecting the privacy of personal information, pointed out by 13 respondents (17.3%); increased risk of suicide, mentioned by six respondents (8%); and only one respondent (1.3%) believed that no problems would arise.

Regarding the role of genetic counseling, 58 professionals (77.3%) answered that the counselor should only inform and not persuade, respecting the patient's individuality, whereas 14 (18.7%) believe that the counselor is in the best position to make a decision.

After the survey on genetic counseling, 55 respondents (73.3%) stated that the results are confidential, even if this attitude jeopardizes third parties' health or physical integrity, whereas 20 respondents (26.7%) agreed that it is lawful to disclose certain genetic data to third parties, regardless of the patient's wishes, whenever their health is at stake. Most respondents (93.3%) agree that employers and health insurance companies should not have access to testing results.

Most respondents believe that the molecular result with a pathogenic mutation for BC should only be delivered to the patient in the presence of a geneticist (90.7%), and that this diagnosis should only be performed by services that have a multidisciplinary team able to offer users genetic counseling, psychosocial support, and medical follow-up (97.3%). After receiving the genetic testing result, 61.3% of respondents believe that only patients who test positive should undergo follow-up, whereas 37.3% believe that all patients should undergo medical and/or psychological follow-up.

In the case of an asymptomatic patient with a pathogenic mutation, 38 professionals (50.7%) indicated that they would recommend risk-reducing bilateral mastectomy and adnexectomy; 33 (44%) would recommend performing periodic imaging exams, and four (5.3%), none of the options. While most gynecologists, oncologists, geneticists and specialists in breast disease (83.3%, 82.4%, 66.7% and 57.1%, respectively) would recommend prophylactic mastectomy and adnexectomy, most pathologists and radiologists (81.8% and 64.5%, respectively) would recommend periodic imaging testing for early diagnosis (p<0.001).

Discussion

The evolution of new technologies in biomedical sciences has allowed clear and increasingly early diagnoses. From human genome mapping, genetic testing became a reality, revealing the DNA constitution and enabling certain pathologies to be predicted[8]. The initial questions concern the need to carry out predictive genetic testing—that is, who, when, and why to do them. All technology ends up being appropriate, especially in the health area, even if transitory.

Thus, learning whether the patient bears or not mutations in the BRCA1 and BRCA2 genes is increasingly present in medical practice, and validating the test among women is common[9]. This trend makes treatment in the early stages of diseases easier, allowing for a better prognosis. However, despite these advances, reflecting on the indiscriminate use of genetic testing results is necessary. Careless disclosure of this information can harm the patient, hindering their socio-labor activities due to prejudice.

The contribution of genetic testing to the prevention of many diseases is undeniable, aligning them in modern routine research.

However, multiple questions stemming from individual, family, social, psychological, and ethical consequences are raised [2,10].

This study, carried out by field research, presented relevant results regarding the topic to be debated. The following analysis contemplates the intersection between the results found and the literature, considering bioethical and legal principles, from the perspective of human dignity.

Initially, the wide range of medical specialties related to the care of women with BC must be consulted to better understand the professionals' opinion and knowledge of genetic testing. According to the literature, a group of professionals working in a transdisciplinary manner can encompass a deeper knowledge and allow a better patient reception [2,11].

In the sample evaluated, no significant difference regarding sex was found, that is, 53.3% were men and 46.7% were women. Most of the physicians included in the study had significant training time and, consequently, experience in their area of expertise and competence to understand and discern the consolidated knowledge in this field.

The vast majority reported being aware of the criteria for recommending genetic counseling and testing. Pathologists and radiologists are among the minority that reported being uninformed on the subject. It is believed that this result is because, generally, in these specialties, physicians do not have direct contact with the patient. These professionals are more involved with diagnostic and anatomopathological diagnosis, which may justify the lower commitment to knowledge of the criteria for recommending genetic testing.

The benefits from genetic testing mentioned by the physicians are related to screening, recommendations and prevention, followed by the possibility of obtaining more accurate estimates of the risk of developing BC, and confirmation or not of inherited cancer genes. These data are in line with the recommendations for the use of genetic testing to identify pathogenic variations and inherited genes [12,13]. Genetic testing related to knowledge, attitudes and communication behavior is primary care in BC prevention, considering that it can inform stratified risk [14,15].

As for the limitations of the genetic testing, 62% of the respondents signaled being concerned about the negative result. Individuals must be advised that undergoing genetic testing does not exclude mutations in other unassessed genes or variants that do not yet have an established pathogenic relationship, known as variants of uncertain significance (VUS). In addition, a negative genetic testing does not mean that the patient is not at risk of developing BC, and this should be made clear so that conventional screening is not impaired [16].

Regarding problems arising from genetic testing, 94.7% indicated that the main one was the negative psychological effect on the patient, followed by negative social reaction, such as job losses, stigma about the disease, and problems related to health care and life insurance plans.

Some concepts related to predictive genetic testing should be mentioned to better clarify the understanding of the advantages and disadvantages of applying it in contemporary times.

Romeo-Malanda and Nicol [17] indicate that, according to 1997 recommendation 5 of the Council of Europe, medical and genetic data have different conceptions: the former consist of any information relating to a person's health, while the latter are hereditary characteristics of an individual or a group of people. As provided for in item XII of article 2 of the *International Declaration on Human Genetic Data* [18], genetic testing is conceived as a method that allows detecting the presence, absence, or change in a particular chromosome.

The inappropriate use of predictive genetic testing results can compromise and violate an individual's fundamental rights [19], which are embedded in the principle of human dignity and are a premise of the democratic rule of law [20]. In this regard, many countries do not have regulations on the matter, and the legal system must legitimize health care properly, stop abuse, and stress ethical and moral values.

This study shows that regarding the role of genetic counseling, 77.3% of responses were favorable to information without persuading the patient, thus respecting their autonomy. Genetic counseling is the procedure of explaining the likely consequences of the results of a genetic testing or screening, mentioning its risks and benefits [18]. This concept refers to the principles of bioethics related to beneficence, and non-maleficence, for the patient's physical and psychological health, due to the impact that the positive result can have on their psyche [8,21].

In genetic counseling, it is imperative to provide clear, objective, adequate, and appropriate information, in addition to prior request for free, informed, express, and revocable consent [8]. The absence of counseling may constitute an omission in the risk assessment process. This orientation is usually indicated in the guidelines and protocols of professionals who perform predictive genetic testing.

In the survey performed, 73.3% of respondents agreed that the results should be kept confidential, even if this attitude puts the patient's health and third parties' physical integrity at risk. This result contradicts the ethical and legal postulates of most medical ethics codes worldwide, according to which the physician is obliged to break confidentiality in order to safeguard human life. In this regard, the constitution of most countries, under the aegis of the democratic rule of law, defends that life is a supreme good in its integrality and universality, as an essential presupposition.

However, there are controversies on this topic due to the concept of autonomy, considered the ability of a rational individual to make an unforced decision based on available information. In bioethics, this principle allows the patients, being lucid and oriented, to deliberate about the diagnostic and therapeutic conducts of their lives [21]. Therefore, the best conduct, according to the established protocols, can go against the patient's will, making the decision-making process by the team complex and paradoxical.

Although the person has the right to receive information regarding their health and illness, as Carvalho [22] indicates, according to the 1997 Human Rights Convention, there is also the opposite right. To explain it better: if the patient does not want to be clarified, this is a right they have—the right not to know. Likewise, the patient has the right to refuse to undergo tests that reveal their genetic identity, and the denial must be duly documented and signed by the patient.

Most respondents (93.3%) believe that employers and health insurance companies should not have access to testing results. This is in line with the postulates transcribed from the ethics and bioethics manuals and the legislation in force in democratic rules of law. It is pertinent to enshrine this principle to protect the patient and the information generated by genetic testing, which can marginalize them and cause all kinds of discrimination and prejudice by health insurance providers, besides difficulties in integrating into social and working life.

Regarding the delivery of a molecular result with a pathogenic mutation for BC, 97.3% of respondents said that tests should only be performed by services that have a multidisciplinary team able to offer users genetic counseling, psychosocial support, and medical follow-up. When comparing the data obtained in this research, it is noted that they are consistent with those found in the literature, and all results point to the necessity of referring families with genetic diseases to genetic counseling, and that professionals in this area should invest more in care humanization, with attention to the psychological dimensions [11].

Psychological, psychotherapeutic, or psychosocial approaches should be used to support and minimize the distress of knowing the positive genetic testing results. Among the justifications for using therapeutic support, it can be described that *physicians perceive that the information provided in Genetic Counseling is not neutral from a psychological point of view, but rather threatening to the ego; the occurrence of a genetic disease in a family triggers a process of mourning or suffering* [23].

However, this opinion does not have support when the testing result is negative: 61.3% of the physicians responded that psychological counseling should be indicated only to patients who test positive.

Finally, 50.7% of the professionals reported that they were in favor of radical procedures in patients with a genetic mutation, even if asymptomatic. In this regard, a study carried out in France in 2000 with 700 surgeons, gynecologists and obstetricians revealed that about 90% recommended mammography for BC cancer screening, while 18.7% found it acceptable to perform prophylactic mastectomy in cases of women with gene mutation for BC, but only 10.9% indicated this procedure from 30 years of age [24]. In the United States, there is a greater acceptance of prophylactic mastectomy, as 29% of a group of obstetricians/gynecologists and about 50% of a group of general surgeons declared that they would recommend this alternative to women who tested positive for the BC genes [25].

In view of the above, it is concluded that mastectomy has an aggressive, mutilating, and traumatic character for women's lives and health,

since it influences the biopsychosocial dimension of the female spectrum [9]. In addition, prophylactic mastectomy is a personal decision, due to possible surgical complications and psychological problems.

Regarding surgery, 30% of women have complications at the time and during the surgical follow-up, and some studies show regret in 49% of patients [9]. On the other hand, studies have shown that most women who underwent prophylactic mastectomy did not show significant changes in terms of their self-esteem, satisfaction with their appearance, feeling of femininity, and in relation to stress and emotional stability [26].

Despite so many controversies in the medical field, there is a consensus that the mastectomy procedure reduces the incidence of breast carcinoma in women with mutations in the BRCA1 and BRCA2 genes [9]. When performed prophylactically, it is less invasive and causes less suffering if the reconstruction is immediate, probably due to the aesthetic result achieved. Since this technique has begun to be used, several changes have occurred: initially, a more invasive and traumatizing radical mastectomy was performed; recently, the so-called modified mastectomy is performed, which is less aggressive.

Final considerations

Concisely, it can be concluded that the theme addressed in this work presents conflicting opinions about recommending predictive genetic testing. The central axis of the research design is aligned with the opinion of physicians, from different specialties, who are part of the teams of a unit dedicated to the diagnosis and treatment of cancer, especially BC.

With technological progress, performing predictive genetic testing is a worldwide reality. The uncertainties relate to whom should undergo it and when to recommend the tests, in addition to the indication of treatment. From this perspective, the guiding ideology consists of the greatest possible benefit with the least feasible risk, both for the indicated behaviors and for the information on the results.

The disclosure of testing results is a threat to the patient, causing anguish, depression, and grief in the psychological dimension. From the perspective of confidentiality, it exposes the patient to the risk of exclusion from health insurance plans and unemployment due to prejudice and discrimination.

Genetic counseling, through multiprofessional teams, has been identified as a preponderant factor for placing the patient within the new reality, embracing their pain and helping their difficulties. It is essential to re-conceptualize current models so that teams can commit to the patient, being aware of the complexity of the problem.

In the light of bioethics, prophylactic mastectomy remains a controversial issue, being surrounded by ambiguities, with strong ethical questions and no consensus between physicians and the scientific community. The decision about the procedure is inexorably personal, after the patient knows and becomes aware of the alternatives and their consequences.

In view of the aspects observed, it is believed that the questions raised here can help guide the decision on recommending genetic testing and its effects. Therefore, it is suggested that the physicians who work in these teams be prepared with broader knowledge of the content addressed, seeking to reduce suffering and improve the patients' quality of life.

Research

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Nedy Maria Branco Cerqueira Neves – PhD – nedyneves@yahoo.com
0000-0002-6383-3320
Camila Silva Boaventura – PhD – milasb2004@yahoo.com.br
0000-0002-5268-8084
Maria Alice Freitas Costa – Master – marialicefc@gmail.com
0000-0002-8501-4713
Almir Galvão Vieira Bitencourt – PhD student – almirgvb@yahoo.com.br
0000-0003-0192-9885

Correspondence
Almir Bitencourt – Rua Professor Antonio Prudente, 211, Liberdade CEP 01509-010. São Paulo/SP, Brasil.

Participation of the authors
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Research