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PRINT: ISSN 0972-3757 ONLINE: ISSN 2456-6330

Int J Hum Genet, 24(3): 251-257 (2024)
DOI: 10.31901/24566322.2024/24.03.719

Genetic Counseling Experience of Patients Referred for Hereditary Cancer Panel Testing

Kanay Yararbas[1, 2] and Ugur Ozbek[1]

[1]Acibadem Mehmet Ali Aydinlar University Medical School, Department of Medical Genetics, Kayisdagi Street 32, K. Bakkalkoy, Atasehir, Istanbul, Turkey
[2]Acibadem Labgen Genetic Diagnosis Center, Istanbul, Turkey
E-mail: [1]<kanayyararbas@gmail.com>, [2]< ugur.ozbek@acibadem.edu.tr

KEYWORDS BRCA1. BRCA2. Breast Cancer. Genetic Counseling. Hereditary. Ovarian Cancer

ABSTRACT At least 10 percent of cancers occur in patients who carry a mutation in a known cancer susceptibility gene. This makes screening the at-risk individuals necessary in order to make it possible to offer risk-reducing options. This kind of susceptibility testing makes genetic counseling a necessity. The aim of the present paper is to report some properties obtained from the pre-test and post-test genetic counseling sessions; along with basic distribution statistics and to document the genetic counseling aspects of 500 patients referred to the Medical Genetics clinic in order to obtain genetic counseling and if performed, genetic testing. The genetic counseling aspects were documented with respect to demographic data of the patients, the test results and responses to these results were evaluated. The data obtained from this study support the need for detailed genetic counseling.

INTRODUCTION

At least 10 percent of cancers may be ascribed to mutation(s) in known cancer susceptibility gene(s) in affected patients who carry these mutations (AlHarthi et al. 2020). Hereditary cancers occur in individuals with at least a single genetic mutation. Genetic counseling is helpful in the management and possible prevention of the hereditary cancer in the patients who are suspected to have cancer susceptibility genes. Carriers of these type of mutations are at significantly higher risk of cancer compared with the general population (Chavarri-Guerra et al. 2020). Thus in order to reduce the cancer risk in the patients who are genetically predisposed, it is necessary to implement genetic screening as well as counseling approaches in people at hereditary cancer risk. Medical geneticists employ genetic counseling not only to identify the individuals and family members at hereditary cancer risk, but also to select appropriate testing methods for the proband and potential carriers of the mutated susceptibility genes in the entire family. Genetic counseling helps in explaining the details of genetic testing to the proband and family members by pre-test counseling, and also makes it easier for the physician to elaborate the meaning of test results in a post-test counseling session, so that cancer risk is reduced in the family members carrying the mutation. Genetic counseling is the most appropriate way to prepare the patients to make informed decision on the basis of their carrier status (Meiser et al. 2002; Schmeler et al. 2006; Jarvinen et al. 2009; Domchek et al. 2010; Walsh et al. 2011; Cancer Genome Atlas Network 2012; kanser.gov.tr. 2018).

Address for correspondence:
Kanay Yararbas
Acibadem Mehmet Ali Aydinlar University Medical School,
Department of Medical Genetics,
Kayisdagi Street 32,
K. Bakkalkoy, Atasehir, Istanbul, Turkey
Telephone: +90216 5004785
E-mail: kanayyararbas@gmail.com

Objectives

The aim of the present work is to report the pre-test and post-test genetic counseling sessions along with basic distribution statistics and documentation of the genetic counseling of 500 patients referred to the Medical Genetics clinic to obtain genetic counseling and genetic testing, on need basis.

MATERIAL AND METHODS

Ethical Issues

This study was approved by the Ethical Committee of Acibadem Mehmet Ali Aydinlar Universi-

ty (2018-6/22). Informed consent was obtained from all the included individual participants in the study.

Subjects and Related Counseling Issues

The present retrospective study aimed to report the featured aspects of pre-test and post-test genetic counseling sessions. The study included 500 patients who were referred to the Medical Genetics clinic to obtain genetic counseling and genetic testing, if needed.

Documentation of Genetic Counseling and Testing

The researchers documented important demographics of the patients, and the outcomes of the counseling sessions. Hereditary Cancer Panel of Multiplicom (BRCA Hereditary Cancer MASTR Plus; For Next-Generation Sequencing, Agilent Tech, US) containing 26 genes was chosen as the screening test. After the test, the DNA variations of 26 individual genes were classified into five groups according to ACMG criteria (Richards et al. 2015): Pathogenic, likely pathogenic (these two classes are given in the Results section), variant of unknown significance (VUS) (these were reported as "additional findings," and include details on patients being followed-up, and updated analysis in accordance with the current literature and guidelines, every 6 months), likely benign and benign (these two classes are not reported).

RESULTS

There were 482 female and 18 male individuals who obtained genetic counseling. From those, 451 cases were already diagnosed with cancer, the remaining 31 individuals were family members suspected as potential carriers. Among these 451 cases, the distribution of various cancers was as follows: breast 401 (88.9%), ovarian 22 (4.88%), colon 17 (3.77%) and 11 (2.44%) were diagnosed with other types of cancers (Brain, Kidney, Skin, Bone, Lung, Prostate) (Table 1). Most of the patients were suffering from breast – ovarian tumors, and that's why female / male ratio is high.

The demographic characteristics of the patients at the time of admission were summarized in Table 2.

Education levels of the recruited patients are classified in Table 3. The survey showed majority of the studied subjects (n = 450) had university level education.

Table 1: Distribution of type of cancers diagnosed in the patient cohort (n = 451)

Breast	88.9%
Ovarian	4.88%
Colon	3.77%
Other	2.44%

Table 2: The characteristics of the patients at the time of admission

Patient type	*N (%)*
Newly Diagnosed As Having Cancer	202 (40.4)
Previously Diagnosed And Operated	249 (49.8)
Not Diagnosed With Cancer	
- Family history	
- Known mutation in family members	40 (8)
Not Diagnosed With Cancer	
- Decision making for a lesion	
- Curiosity, Just to get information	9 (1.8)

Table 3: If we look at educational levels, 450 of the patients were at university or higher education level, whereas 44 of them had lower degrees

University or higher education level	450
Lower level	44
Other levels	NA

The researchers asked the patients to classify the reasons for their referral to the Medical Genetics Outpatient Clinic from two different perspectives: the referring clinician (n = 491) and Self-interpretation of patients (n = 360).

The clinician's referral reason was either directly due to the test request (n = 441), or genetic counseling (n = 50). The test was requested because of one of the two following reasons:

a- In accordance with the NCCN criteria (NCCN 2024a), the clinicians thought it was necessary to investigate the cancer's heritability (including the relatives of the individuals with mutated gene(s)) (n = 426);

b- The use of drugs such as PARP-I (n = 15)

The rationale for the self-interpretation of patients to apply for genetic counseling was as follows:

- To help my children to know the possibility of heritability (n = 240)
- It can be useful for my treatment (n = 202)
- Both (n = 110)
- Don't know (n = 28)

After Genetic Counseling, a test request was made to test 425 patients from Medical Genetics

Outpatient Clinic according to NCCN criteria. Another 15 patients were tested to support the treatment approach with drugs such as PARP-I. Hereditary cancer panel testing containing 26 genes (BRCA1, BRCA2, CDH1, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, PTEN, STK11, TP53, ATM, BRIP1, CHEK2, NBN, RAD51C, RAD51D, BARD1, BLM, FAM175A, MRE11, RAD50, XRCC2) was chosen for the screening.

In 35 patients, no test was requested either by the clinician or by self-assessment. Among these, 19 individuals were without cancer and the cancer patient in the family was alive and accessible; five patients were tested at another center and were waiting for the results; for economic reasons nine patients did not want to be tested; and two patients gave up later.

Within the total, 201 patients were asked if they found genetic counseling helpful. All answered yes.

The most striking observation during the genetic counseling was a misunderstanding of inheritance pattern of familial breast and ovarian cancers in a significant proportion of the recruited patients. It was noticed that out of the 190 individuals who had exchanged ideas on this issue, 90 believed that hereditary susceptibility to breast and ovarian cancer would be inherited only from the mother.

Post-test Counseling Issues

Among the 425 cases included in this study and tested, 66 cases were positive for a pathogenic genetic variation associated with a hereditary cancer susceptibility. They received genetic counseling about the detected genetic mutation and its heritability.

The majority of individuals (n = 359), who tested negative for hereditary cancer predisposition, displayed satisfaction with the genetic testing results. However, the level of satisfaction decreased in the patients whose tests indicated potential cancer susceptibility and who had strong family history of cancer incidence. Common reactions of these unsatisfied patients were:

- Why did we do it then?
- What will happen now? reflecting their feeling of such uncertainty.

In people who had negative results (n = 359), there was a common misperception that the cancer is not associated with any genetic background or genetic characteristics. Fifty patients thought that as cancer is "not genetic, no risk for my relatives." On the other hand, 40 patients stated that cancer had emerged through genetic mechanisms and that they considered genetic heredity and risk to the families through pre-test genetic counseling.

Genetic counseling was given to the siblings in 31 cases, as these patients wanted the genetic test to be done in their families for detecting the mutation. Discussions were conducted in a total of nine positive cases who were over 18 years of age. Seven of these patients wanted to be tested, whereas 2 individuals (both under 20) did not want to take a test.

The distribution of mutated genes in 66 positive cases is summarized in Table 4.

Table 4: The distribution of 66 positive results

BRCA 1-2	44
BRCA + Another Gene	2
Other Genes	20

The following conclusions directly affected the genetic counseling features:

- If you were only looked at BRCA1-2; In ~ 10 percent of cases, the test would be considered positive.
- The number of positive cases with panel testing changed to ~15 percent.
- Two patients had two additional pathogenic mutations in different genes besides BRCA, and this could only be revealed by the use of the panel for testing.

Genetic Consultation Timings

Pre-test genetic counseling took longer time than the post-test counseling sessions. Standard duration was 30 minutes for each pre-test counseling session, whereas 15 minutes for post-test visits. In the case of negative results, specifically, the duration of genetic counseling after the test is shorter. The longest session took 65 minutes in an individual after a positive test result.

In five cases, there was more than one request for genetic counseling for the same result. Four out of these five cases had genetic counseling due to positive results.

In some cases, the referring clinician also provided feedback and requested a consultation with

a Medical Genetics specialist. In this way, the reasons for the interview with the clinicians of 36 cases were as follows: For the presence of VUS (n = 21), because of the pathogenic test result (n = 11), as there are findings in the genes with little or no literature data (n = 2), and the calculation of 5-year and lifetime risks with percentages, and reporting (n = 2).

In 89 cases, only VUS was reported. Two cases were pregnant and one of them was disease-free, but had family history (her mother died due to young breast carcinoma). This later patient had pathogenic mutation of RAD50, but her husband didn't take a carrier scan. The patient's pregnancy was still going on, and it was decided to establish a follow-up plan after the pregnancy (Surgeon). No pathogenic mutation was detected in the other case and no follow-up information is available.

DISCUSSION

This is the first study to analyze and report the genetic counseling data before and after the test in a large number of Turkish oncology patients suspected of cancer susceptibility. In a recent study on 123 pediatric patients visiting a Turkish hospital, it was determined that parental consanguinity together with >2 malignancies during the parents' childhood to be the most common indication for genetic counseling (Demirsoy et al. 2021). These authors suggested the significance of genetics counseling selection tools for better differentiation of probable cancer susceptible patients. Thus, nearly 10 percent of pediatric cancer cases were found to have germline mutations within cancer predisposition genes in genome-wide sequencing studies, and a recent work reported an extended family in Turkey with multiple affected members carrying a missense CD70 variation with combined immune deficiency and malignancy (Khodzhaev et al. 2020). However, in any of these studies the importance of the genetic counseling before and after the test was described, which is the focus of this study.

According to literature only half of the individuals tested for cancer susceptibility have the chance to receive genetic counseling (Ropka et al. 2006). A recent study summarized the multi-gene panel application with considerations for pre-/ post- testing and described the clinical aspects of genetic counseling on the basis of panel testing results (Lee et al. 2021). In our center, it is clear that more than these 500 people have opted to receive genetic counseling according to NCCN criteria over the period of one year. Such need for genetic counseling is even more evident for ovarian cancer, as only 22 ovarian cancer patients received genetic counseling. Some of these patients should probably only be referred for PARP inhibitor treatment. They were asked to be tested for BRCA genes. In other studies also it was suggested that there should be an improvement for the referral of ovarian cancer patients (Maria et al. 2015). In one study with nearly 1000 breast cancer patients, it has been observed that approximately half of the patients with pathogenic/ likely pathogenic mutations were missed by the selection of patients for genetic testing in accordance with NCCN guidelines, emphasizing the need for genetic screening in all the suspected cancer patients (Beitsch et al. 2019).

Half of the present cases (249 out of 500) were treated by surgery. These individuals would have been able to avoid the additional risk-reducing surgical burden if they had the chance to undergo genetic counseling at the time of initial diagnosis. Some of the follow-up patients were probably referred to the geneticist when an additional diagnosis was made in their families or recurrence was detected. The researchers noticed that discussion of genetic testing and genetic counseling before and after surgery, had an impact on the psychology of the patient. Of course, studies on this subject need to be expanded. Understanding the genetic predisposition as soon as cancer is diagnosed, and understanding that it can create a condition that concerns the rest of the family can increase the patient's psychological stress. This may adversely affect the patient compliance (Christie et al. 2012; Wevers et al. 2015). The potential anxiety and stress from the impending results of a genetic test often make the patients to seek in-person disclosures with the clinician rather than an informal telephone disclosure (Beri et al. 2019).

Half of the cases in the present study consisted of individuals with university and higher level education. It may cause prolongation of genetic counseling duration as they probably ask more questions. Many educated people do research on the subject of heritable cancer and susceptibility on the internet before coming to the clinic. Many educated individuals research heritable cancer and susceptibility on the internet before their clinic visits,

enhancing their understanding of genetic risks and contributing to a more informed decision-making process during genetic counseling, as emphasized in recent outcomes research (NCCN 2024b). and can help in their better understanding of their genetic situation, even though the time spent by the genetic counselor is likely to be more.

Normally, it is the clinician who refers his or her patient to the medical geneticist in order to obtain genetic counseling, but such expertise may not be readily available in many clinics/ hospitals. Therefore, it is not always possible to employ a genetic counselor in oncology clinics. Because of the scarcity of such expertise in countries like Turkey, not only for oncology but for many other medical specialties, including perinatology, the clinician himself/herself tries to give genetic counseling. In the researchers' series, only 10 percent of the cases were referred for genetic counseling purposes. The other cases were sent directly with a test request. Actually, after the influence of "Angelina Jolie effect" and the impact of individualized medicine, the specialty of Medical Genetics has become more popular among the patients and other clinicians in Turkey. Also in Turkey, as globally, the integration of genetic counselors into oncology and other medical specialties has been enhanced by advancements in genomic medicine, making genetic counseling more accessible and crucial for patient care (National Cancer Institute 2023; Perspectives in Genetic Counseling 2023).

The clinician's perspective in terms of clinical judgment of a cancer patient can be variable, especially for invasive intervention or more radical surgery. Oncologists and surgeons were observed to have conflicts in 27 out of 66 positive cases in the present study. While oncologists tend to decide in accordance with NCCN guidelines, surgeons have been shown to offer a risk-reducing surgical option. The NCCN guideline recommends the evaluation of some genes in the presence of a family history, and the family history of these cases may be poor. Genes that do not generate high risk factors are also frequently reported.

A significant number of patients were aware of the fact that they came to the medical genetic outpatient clinic for genetic testing. After their last visit with the referring clinician, it is obvious that they want to have the test done for themselves as well as for their children. This may not be compatible with the results reported in other publications. However, it is not surprising that the patient who is diagnosed with cancer is under such a under psychological stress and considers the healthy living of the rest of his/her family members. Some patients have no idea why they are seeing the geneticist and this may complicate genetic counseling (Brandt et al. 2008; Novetsky et al. 2013; Trepanier et al. 2014).

The testing of BRCA1 and BRCA2 genes has been replaced by panel tests, and VUS detection rates have increased. It is a condition that requires appropriate genetic counseling as well as patient follow-up. The researchers report VUSs as "other findings" and follow their patients every 6 months for reanalysis. The literature is also very controversial in this regard (Leblond et al. 2011; Culver et al. 2013).

Genetic counseling is a challenge for pregnant women. It is the clinician's job to determine the urgency of the situation. In elective conditions, detailed counseling visit may be planned with the patient after pregnancy (Kanishka et al. 2016).

CONCLUSION

The most significant difficulty encountered during genetic counseling in the context of present study is the general lack of familiarity with medical terminology among Turkish population. Counseling sessions should be reevaluated since the patients with cancer predisposition need clear explanation of their health status. In addition, accurate information is essential, as genetics contains some more specialized knowledge. The fact that the patients' predisposition to breast cancer is believed to be inherited from the mother and that the risks are completely eliminated if the genetic test result is negative, supports the need for detailed genetic counseling.

RECOMMENDATIONS

It is necessary to place the indications for genetic evaluation in the cancer clinic and not to deprive the selected patients and their families of the genetic counseling option. For this purpose, it would be useful to follow a guideline such as NCCN's Genetic/Familial High Risk Assessment guidelines. It must be kept in mind that genetic "counseling" and genetic "testing" indications differ in NCCN criteria. Counseling experience ensures appropriate measures are taken to prevent/monitor occurrence in patients at-risk and family members

with similar mutations but does not reduce risk. Informed decisions that shall be taken by the patients need to be specified as decisions based on the carrier status.

LIMITATIONS

The results of this study should be interpreted carefully. There are some limitations. First is the limited number of patients. Although the number of patients seems sufficient for such a study, it is a restricted group. For example, patients only comply with NCCN criteria for genetic testing. In addition, the number of ovarian and other cancers is quite insufficient; this restricts the data obtained from patients suspected to have hereditary breast and ovarian cancer syndrome and Lynch syndromes. Rather, the data mostly reflects the characteristics of breast cancer patients. This study was not designed to distinguish the perspectives of oncologists and surgeons. There should be no misunderstandings in this respect.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ACKNOWLEDGMENT

We would like to thank to Dr. Ozkan Ozdemir, PhD. for his kind help for statistical evaluation of the paper.

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Paper received for publication in February, 2019
Paper accepted for publication in April, 2024