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THE IMPORTANCE OF GENETIC TESTING IN CANCER PREVENTION

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ABSTRACT

The present article describes patient with the BRCA1 5382insC mutation in location 17q21. The patient was referred for genetic counselling because of infertility. While consulting the patient for infertility and collecting family tree the patient told that her mother, grandmother and aunt had or still has an ovarian cancer. So patient received genetic test for six most often BRCA1 and BRCA2 gene mutations. Test showed that patient has the mutation of BRCA1 5382insC gene. BRCA1 5382insC mutation 10 times increases risk to get breast cancer and 20 times ovarian cancer, compared with the general population. To reduce risk of breast and ovarian cancer patient received advices about healthy life style, screening tests for ovarian cancer and was offered to oncologist to consult prophylactic oophorectomy. Genetic testing is connected with patent law. World patent system is based on the main characteristics of patenting, i.e., inventions must meet the general details – invention novelty, utility and nonobviousness. In addition, it is important to comply with the requirements to public orde and morality, which are becoming essential on isolated human genes and cells patenting. Moral and Ethical issues in Europe and the U.S. are different scope. According to the European system, the question of when morality may be used as a basis to exclude patents on biotechnological inventions is an ethical question and also closely interconnected with fundamental constitutional issues.

Key words: Patent system, legislation, cancer, genetic screening.

INTRODUCTION

Breast cancer (BC) is one of the most common cancer in the world. There are many risc factors: estrogen exposure, alcohol consumption, radiation exposure, obesity, chronic stress [1]. Also the risk of cancer increases with patient age: 80% of cancer cases occurs in pacients who are over 50 years old. Human genome and identify genes led to the establishment of the Human Genome Project (HBP). The HGP estimates that the human genome consists of 20,000 to 25,000 genes. The US Patent and Trademark Office (USPTO) issues thousands of patents for human genes identified by HGP and it is reasonable to believe that this trend will continue as the HGP isolates and identifies more human genes . This increase is not only evident in the United States, but also and in the EU. Deoxyribonucleic acid (DNA) is a molecule that encodes the genetic instructions used in the development and functioning of all known living organisms and many viruses. DNA is well-suited for biological information storage. The DNA backbone is resistant to cleavage, and both strands of the double-stranded structure store the same biological information. Certain genes mutations like BRCA1 and BRCA2 increase the risk of cancer [2,3]. BRCA1 and BRCA2 are human genes that produce tumor suppressor proteins. Like many other tumor suppressors, the proteins produced from the BRCA1 and BRCA2 genes helps prevent cells from growing and dividing too rapidly or in an uncontrolled way. In women who have a BRCA1 or BRCA2 gene mutation there is an increased risk of getting breast cancer and ovarian cancer [4]. So it is important to ask patients about family history of breast cancer so as to find it on an earlier [5]. Among women, breast cancer is the most commonly diagnosed cancer after nonmelanoma skin cancer, and it is the second leading cause of cancer deaths after lung cancer.

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In 2012 worldwide there were 1692000 breast cancer report cases.

The most common genes mutations associated with BC are four:

- BRCA1
- BRCA2
- TP53
- PTEN

But researchers have found other common genes that can slightly increase a woman's risk of developing breast cancer.

Unfortunately no tests are available for these genes yet but they include:

- CASP8
- FGFR2
- TNRCP
- MAP3K1
- rs4973768
- LSP1

BRCA1 gene cytogenetic location is 17q21. In addition to female breast cancer, mutations in the *BRCA1* gene increase the risk of several types of cancer: fallopian tube cancer, male breast cancer, and pancreatic cancer. Many of these mutations change one of the amino acids used to make the BRCA1 protein, resulting in a protein that cannot perform its normal DNA repair function, and cells become proliferate in an uncontrolled way. BRCA1 gene mutation increases risk of BC from 60% to 85%, and fallopian tube cancer from 40% to 60% [6]. BRCA2 gene cytogenetic location is 13q12.3.Mutations in one copy of the *BRCA2* gene can lead to an increased risk of ovarian cancer, prostate cancer, pancreatic cancer, fallopian tube cancer, male breast cancer, and an aggressive form of skin cancer called melanoma.

METHODS

In this case report, patient was send for genetic molecular testing for detecting BRCA1 and BRCA2 genes mutations. The test is done by extracting DNR from the leukocytes, according to standard methodic. Molecular testing is based on PCR reaction and DNA analysis by scanning BRCA1 and BRCA2 genes and looking for structure mutations. Usually BRCA1 and BRCA2 mutation analysis is targeted only for coding exons and has implicated protein-truncating mutations in BRCA1 and BRCA2 inactivation. Also mutations can be attributed to other exonic mutation, mutations in introns and untranslatable regions.Usually searching is performed for six most common BRCA1 and BRCA2 genes mutations: *BRCA1 185delAG,* BRCA1 300>G(C61G), BRCA1 2080delA, BRCA1 415delA, BRCA1 5382insC, BRCA2 6174delT.

For each mutation, three primers (one common, one specific for the mutant, and one specific for the wild-type allele) were used. The competing wild-type and mutant primers were designed to differ by ~20 bp size, allowing detection of the PCR products by standart electrophoresis and ultraviolet illumination after ethidium bromide staining. The wild-type (shortand) mutant (long) primers both contain a mismatched base sequence near the 3′ end. In the early cycles of amplification, the mismatched sequences generate mutagenized PCR products that are refractory to cross-amplification by the competing primer, thereby ensuring specificity of the reaction. The long (mutant) primer also incorporates two additional mismatched bases at two contiguous positions corresponding to the 5′ end of the short (wild-type) primer. The primer sequences and sizes of corresponding amplicons are shown in Table 1.

RESULTS

In this graph we want to present rare case report, share patients clinical data and discuss the latest published results about BRCA1/A2 genes mutation, from 2009 to 2014, importance in breast and ovarian cancer. A 40-year-old female patient (born August 15, 1973) was consulted by physician because of infertility. Physician sent patient to geneticist to make the frequent test because of infertility. The karyotype test was done and it didn't show any changes (46XX). During the collection of family tree patient mentioned that her grandmother and mother died of ovarian cancer. Then the patient was tested for 6 most frequent BRCA gene mutations:

- BRCA1 185delAG
- BRCA1 300>G(C61G)
- BRCA1 2080delA
- BRCA1 415delA
- BRCA1 5382insC
- BRCA2 6174delT

The test matched our suspicious. Genetic test showed that patient has germinal mutation of BRCA1: 5382insC gene. BRCA1 5382insC mutation 10 times increases risk to get breast cancer and 20 times ovarian cancer, compared with the general population.

Family history

Fig. 1 shows family members who had or has ovarian cancer. It is seen that proband had tendency to have BRCA1 gene mutation, because her mother, grandmother and her aunt had ovarian cancer.

DISCUSSION

A BRCA1 and BRCA2 genes mutation typically increases the risk of breast and ovarian cancer about 90% [7]. The BRCA1 and BRCA2 genes provides instructions for making a protein that is directly involved in repairing damaged DNA. In the nucleus of many types of normal cells, the BRCA1 and BRCA2 proteins interacts with several other proteins, including the proteins produced

from the BRAC51 and BARC1 genes, to mend breaks in DNA. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer. The inheritance way of this cancer, that is regulated by BRCA1 and BRCA2 genes mutation is autosomal dominant [8]. Research suggests that the BRCA1 protein also regulates the activity of other genes and plays a critical role in embryonic development [9]. As we can see it might be a reason why our patient with BRCA1 gene mutation has fertility problems. The findings of a large international prospective study suggest for the first time that women with *BRCA1* mutations should have preventive ovarian surgery (prophylactic oophorectomy) by age 35, as waiting until a later age appears to increase the risk of ovarian cancer before or at the time of the preventive surgery. Women with BRCA2, however, do not appear to be at an increased risk of cancer by 35 years, so the prophylactic oophorectomy may be delayed to later age [10]. Moreover, women with *BRCA1* and *BRCA2* mutations who had this surgery experienced a 77 percent reduction in their overall risk of death by age 70. Also patient with BRCA1 or BRCA2 mutations must have routine screening for breast cancer (self-exams, mammograms, doctor visits) like all women who are older than 50 years old [11,12]. Men who test positive for BRCA1 and BRCA2 gene mutations are considered to be at higher-than-average risk for prostate cancer. They should talk with their doctors about beginning screenings, including an annual digital rectal examination and prostate-specific antigen (PSA) blood test between ages 40 and 50. Men risk for breast cancer stays very low, but it is still higher than it is for men who do not have the mutations of BRCA1 or BRCA2 genes. So if men notes any unusual breast changes or lumps to their doctors immediately.

To avoid breast cancer for all the women, they should try to change the lifestyle and make it healthy that means:

- Limit alcohol
- Do not smoke
- Control your weight
- Be physically active
- Breast-feed
- Limit dose and duration of hormone therapy
- Avoid oral contraceptive
- Avoid exposure to radiation and environmental pollution

EU Directive individual articles are identified potential inventions, i.e. biological material (EU Directive art.2, part.2), a way, a method which makes it possible to get the material to the specific features. All these inventions are recognized as patentable if they meet the general requirements of patentability - . However, although the biological material or a particular way will be recognized as inventionsthey can get to the list of unpatentable objects, enshrined in EU Directive and in few EPC articles. These documentations provides that „the human body cannot constitute patentable inventions, an element isolated from the human body or a partial sequence of a gene“ . Unpatentable are „processes for cloning human beings, processes for modifying the germ line genetic identity of human beings, uses of human embryos for industrial or commercial purposes, processes for modifying the genetic identity of animals“ . Moreover, bearing in mind that patents are mostly acquired for the economic benefit of the invention, possible to state that pliuripotencial human embryonic stem cell patenting is not possible.

Comparing US and European legislative and judicial approaches to the grant of patents on isolated human genes and cells, in the author point of view the worldwide general patentability details are similarand its content reflects nearly the same characteristics of patentability, differs only the word identification of particulars. The main and the biggest difference is noticeable in the moral and ethicalpatentability assessments, there is a difference between general and civil law in countries. United States, as belonging to the first group fall into the sphere of moral neutrality. The author believes that the Europe patent legal system is more appropriate for its approach to human morality and dignity. Human is valuable in itself, created by nature. There are other ways and methods to heal the human being or disease, not only patenting inventions, which supposedly created by human diseases. U.S. does not give importance to the moralityand focuses on the economy and social welfare by allowing people to get well in this way, not making any reservations to the patenting of human stem cell.

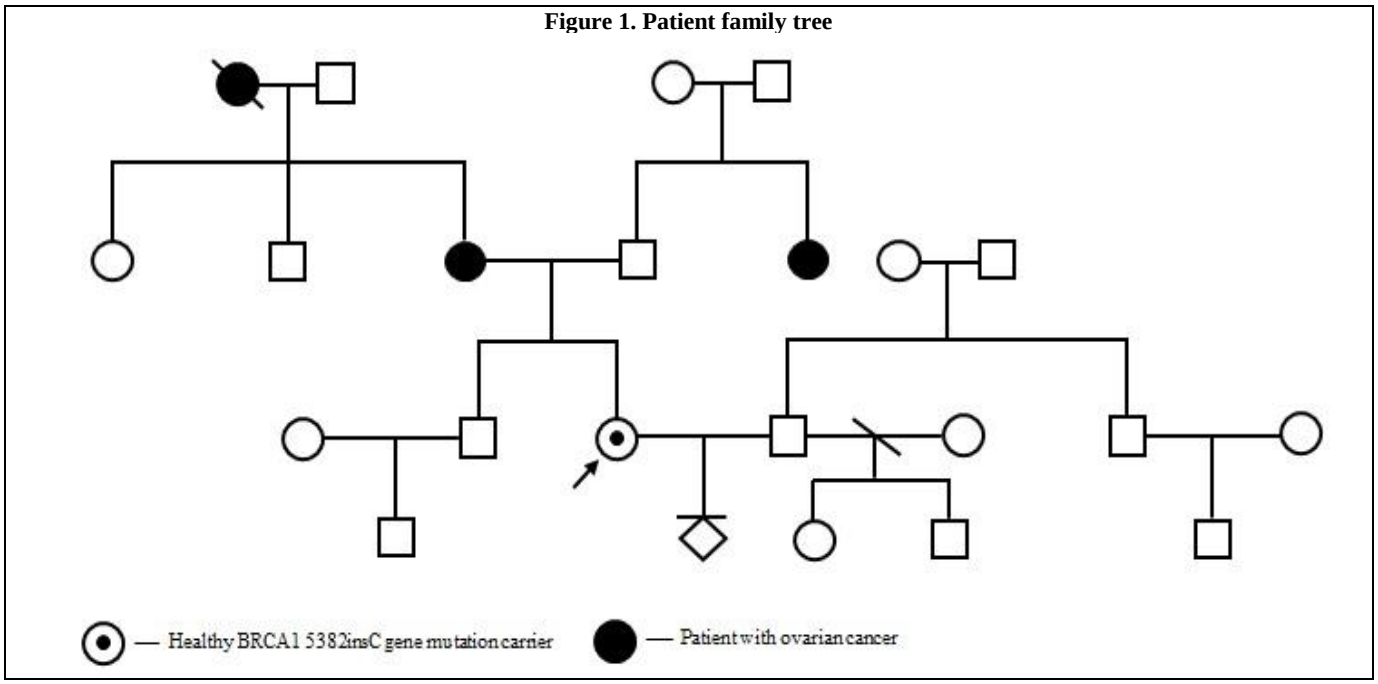
After the genetic testing patients should be referred to genetic counseling, so as to be informed about prophylactic. What do geneticist should advice for women who has the mutation on BRCA1 or BRCA2 genes:

- As it is already mentioned in the discussion, discuss possible prophylactic (including preventive (prophylactic) surgical removal of your ovaries, breast, or even both before cancer has an opportunity to form [13-15]. Talking about breast removing (mastectomy) many women tries to avoid it because of bad looking. But after all there is a reconstruction possibility after mastectomy. Current breast reconstruction techniques are diverse and may involve the use of an autologous tissue flap, a prosthetic implant, or both. So patient appearance would be normal [16]. Also women can chose breast-conserving therapy which is alternative to mastectomy for the treatment of invasive breast cancer but it is not applicable to all patients [17].
- Offer to discuss with your physician about taking a hormonal therapy medicine such as tamoxifen, raloxifen, or exemestane. These drugs could reduce the risk of developing breast cancer. To low the risk of ovarian cancer, doctors should offer to take ten oral contraceptives. While data is not clear on the safety of oral contraceptives

in people at high risk for breast cancer, some doctors do recommend them for carriers of BRCA1 and BRCA2 mutations. This recommendation depends on factors including which mutation you carry and how much breast or ovarian cancer is in your family.

- Also there is chemotherapy treatment which is effective, because research shows that with multimodality therapy 5-year local recurrence-free survival rate was 95% [18].

Figure 1. Patient family tree



CONCLUSIONS

We point the importance if there are cases of breast or ovarian cancer in family, there is need for genetic test of BRCA1 or BRCA2 genes mutation, even in healthy subjects at least I-st degree relatives in order to know if the patient is in high risk group. If the test is positive the patient is followed by self-exams, ultrasound examination, mammograms, MRI and specific blood tests.

After discussing with physician the patients also should consider about preventive (prophylactic) surgical removal of ovaries or breasts.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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