Case Report

GENEALOGY OF FAMILIES WITH BREAST CANCER – A TOOL TO IDENTIFY WOMEN AT RISK

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Summary

Breast cancer (BC) is the most common malignancy in Bulgarian women. The incidence varies according to age, exogenous factors (diet, socioeconomic status, oral contraceptive, etc.) and endogenous factors (family history of BC, age at menarche and menopause, etc.). Familial clustering is accounting for 20% of all BC cases. About 5-10% of all BCs are due to inheritance of highly penetrant gene mutations. Family history and gene mutations increase the risk of BC two-tree fold and 65-80%, respectively. We present six pedigrees of family BC. In two of these cases there is a strong clustering of BC. Other cases reveal an association of BC with ovarian, pancreatic, prostate and gastric cancer. We pay attention to healthy first-degree relatives at high risk of developing BC during their lifetime. Genetic testing for mutation in highly penetrant genes and preventive procedures to decrease the risk of BC should be offered to these relatives.

Key words: breast cancer, family history, risk of breast cancer, genetic counselling

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and a leading cause of cancer death in females in Bulgaria (34.1 per 100 000 women in 2011). In 2009, 3809 new cases of BC have been diagnosed [1].

It is estimated that 1 in 14 women in Bulgaria will develop BC, with a life expectancy of 77 years. This statistics accounts for an approximate 7% average population risk for Bulgarian women.

There are three types of BC, depending on the genetic basis of BC – inherited/hereditary, familial and sporadic.

Hereditary BC (5-10% of all cases) occurs in women with an alteration in a BC susceptibility gene, which has been inherited through the germline cells, sporadic BC (70-80%) occurs in women without such predisposition. Familial BC refers to BC occurring in a woman with at least one relative with BC and accounts for about 15% of all cases [2].

Current measures to reduce BC in women of average-population risk include annual clinical

breast examination (starting at the age of 30) and screening mammography (usually starting at the age of 40).

Some women are at a risk higher than the average population risk, based on certain factors in their personal and/or family history [3]. Some specific measures for assessment of BC risk could be an integral part of medical practice. A patient's family history and 2 empiric tools (Gail and Claus models) should be used in practice to accurately calculate the risk for BC [4].

A family history increases the risk. For example, a woman with one first-degree relative with BC is at a risk twice as high for developing the disease.

An accurate family history is useful to identify women with inherited predisposition. Approximately 5% to 10% of BC is due to the inheritance of a mutation in highly penetrant cancer susceptibility genes, mainly in BRCA1 and BRCA2. The carrier of these mutations is at high risk (about 60-85%) of BC and at an increased risk of other associated cancers (ovarian, Fallopian tube, prostate, male breast, pancreatic, gastric and peritoneum cancer) [5].

Strategies, based on risk assessment tools (personal and family history), are available to reduce the risk of BC.

Materials and Methods

Family history was used as a tool to identify family members at a risk higher than average for developing BC. We drew pedigrees of six families, and in each of them the proband was a patient that had been already diagnosed with BC. All patients were registered at the Department of Surgical Oncology, University Hospital of Pleven.

We applied two of the most commonly used models to assess the risk for developing BC in healthy relatives of a proband. The Gail model is a tool that provides BC empiric risk based upon age, age at first period, age at the time of birth of a first child /nulliparous, family history of BC (mother, sister or daughter), number of past breast biopsies, number of breast biopsies showing atypical hyperplasia, race/ethnicity. The Claus model is an empiric model that estimates BC risk based only on family history [6].

Genetic counseling was performed on probands and healthy relatives at BC risk and genetic testing was recommended to those that were found to be at increased risk.

Results

We report six families with multiple affected members with BC or other associated cancers.

In **pedigree 1** (Figure 1), III – 2 is 43-year-old woman, with an increased risk of BC. She has a first-degree relative (II-2) with bilateral BC (first cancer diagnosed at age 45), and first-degree relative (III-1) with ovarian cancer (diagnosed at age 43). Based on family history, using detailed BC risk calculator, her risk was assessed at 29.3% within her lifetime. Clinical and self-examinations every six months (beginning at the age of 18) and annual mammography (beginning at the age of 35-40) were recommended to this woman.

In **pedigree 2** (Figure 2), V-2 was found at increased risk of BC, because she has one second-degree relative (III-2) and three other relatives (III-3, II-6, I-1) with BC, all of them on the paternal lineage. We might suspect a hereditary BC in this family and genetic counseling and BRCA mutations testing for should be recommended to V-2.

In **pedigree 3** (Figure 3), family members IV-7 and IV-9 are at high risk of BC. Each of them has one first-degree relative (III-6 and III-7, respectively) and two second-degree relatives (III-7, II-7 and III-6, II-7, respectively) with BC, diagnosed before age 50. In addition, IV-7 and IV-9 have one relative (III-4) with BC and one (I-1) with gastric cancer. Gastric cancer could be associated with BRCA mutation too.

On the other hand, IV-1 and IV-2 are at risk higher than the average population risk for developing BC because of their first-degree relative (III-4) with BC and other degree relatives (I-1, II-7, III-6, III-7) with BC and other cancers. Family members IV-7, IV-9, IV-1 and IV-2 should be referred for BRCA mutation testing due to the strong family history of BC and gastric cancer. These relatives were suspected for a potential BRCA mutation.

In **pedigree 4** (Figure 4), family member IV-1 is at a risk higher than average for developing BC. Her mother (III-2) has had BC with early onset - 36 years. Her grandfather (II-5) died of pancreatic cancer at 50, and her great-grand father (I-5) died of prostate cancer, both relatives being on the maternal lineage. Pancreatic and prostate cancers are associated with BRCA mutation too. IV -1 should be referred for BRCA mutation testing due to her family history of BC, pancreatic and prostate cancer.

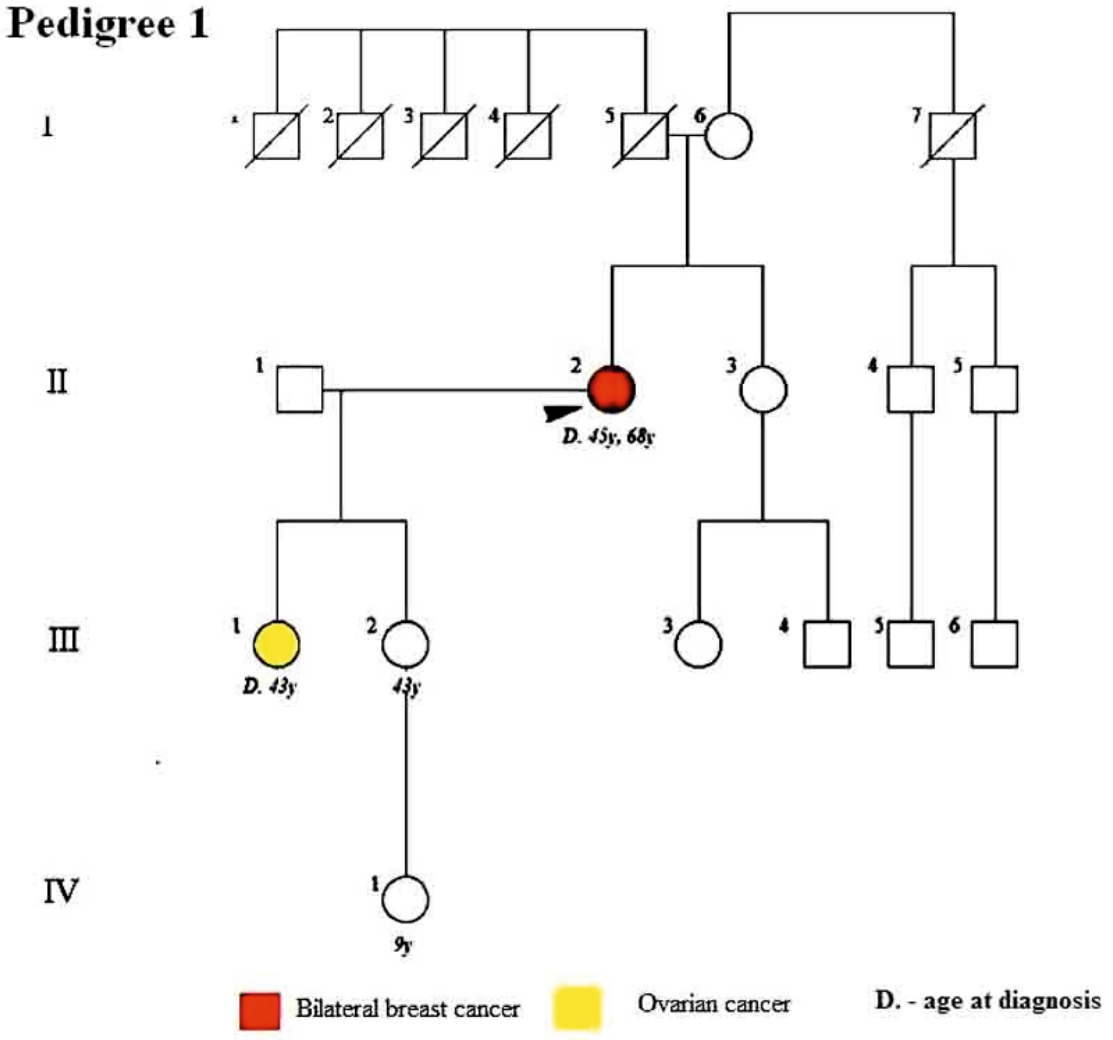

Figure 1. Family pedigree of proband. The proband (II-2) is indicated by an arrow

In **pedigree 5** (Figure 5), IV-5 and IV-6 are at high risk for developing BC. They have one first-degree relative with BC (III-5), two other close relatives with BC (II-4 and III-8) and one relative (I-2) with prostate cancer. Relatives IV-5 and IV-6 should be referred for BRCA mutation testing, based on the strong family history of BC and prostate cancer (associated with BRCA mutations).

In **pedigree 6** (Figure 6), III - 3 is 44-year-old female with an increased risk of BC. Her menarche was at age 13 and she is not menopausal yet. She has a history of two breast biopsies: one - benign and one - with atypical lobular and ductal hyperplasia. Her sister (III-2) has been diagnosed with BC at age 47. The proband (III – 3) also has relatives with gastric cancer – (I-4) on the maternal lineage and (I-1) on the paternal lineage. Based on her medical and family history, using detailed BC risk calculator, her risk was assessed at 48 % within her lifetime. This woman should be referred for genetic testing for BRCA mutation testing.

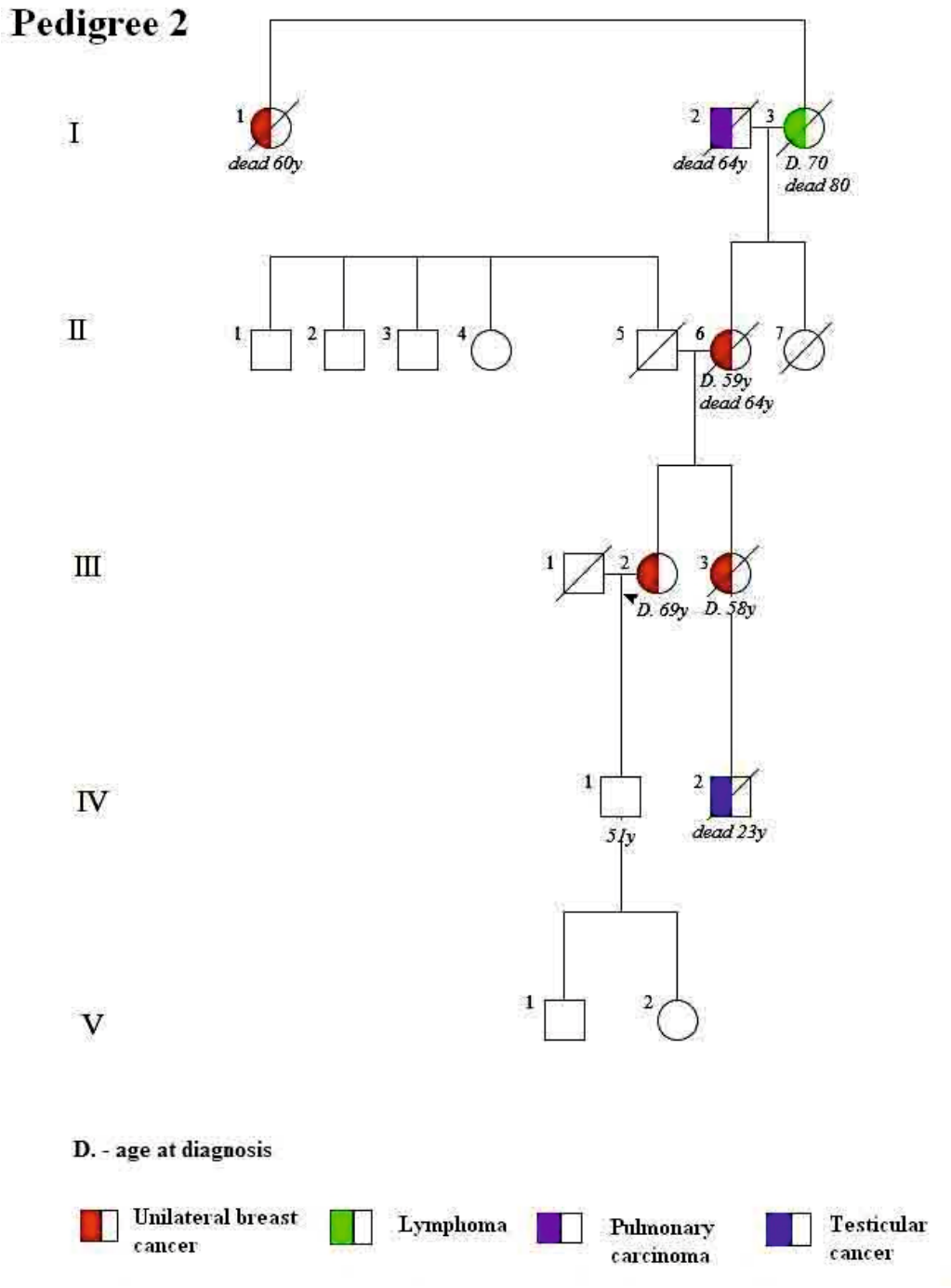

Figure 2. Family pedigree of proband. The proband (III-2) is indicated by an arrow

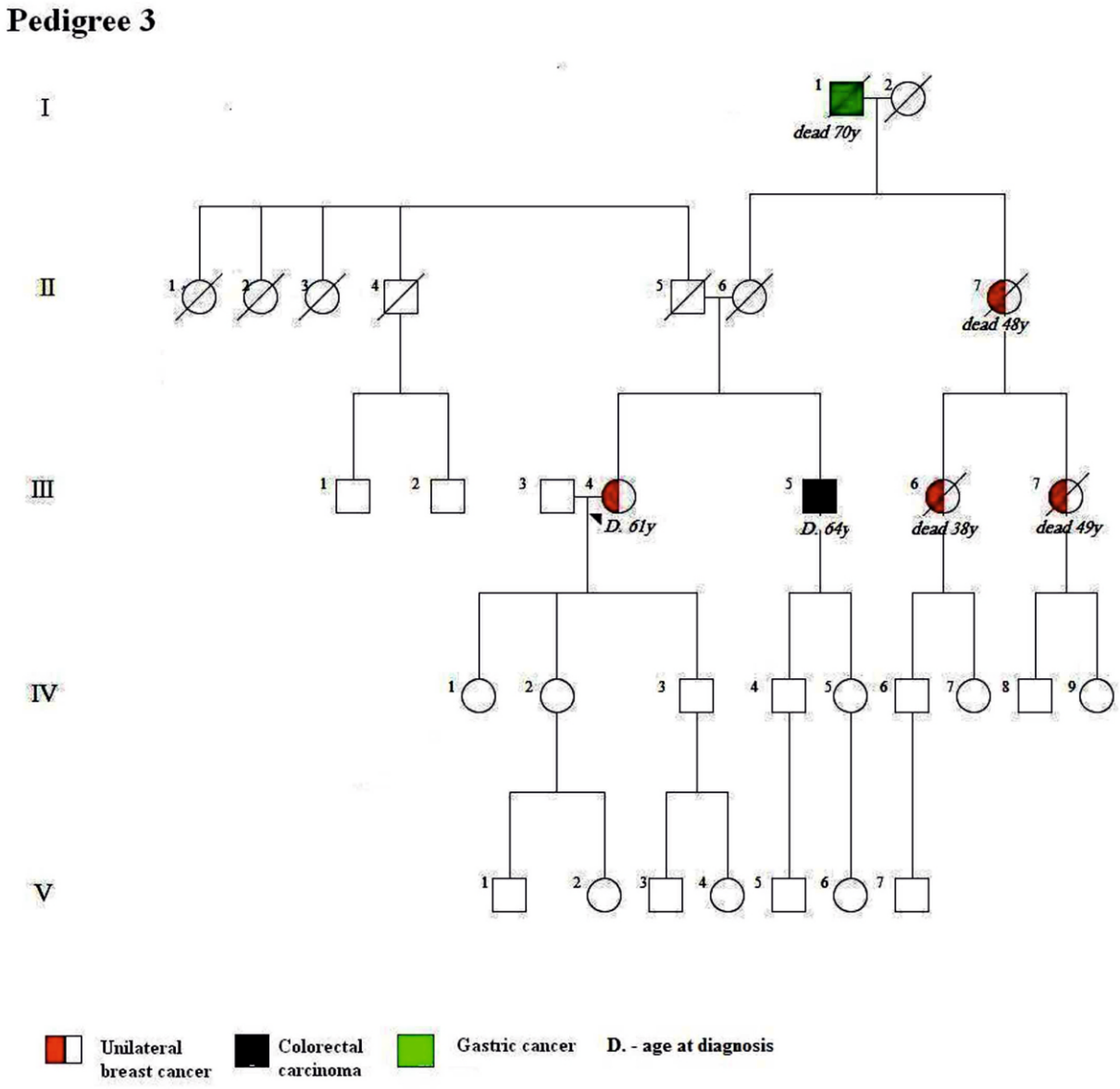

Figure 3. Family pedigree of proband. The proband (III-4) is indicated by an arrow

Discussion

It has been estimated that about 70% of all primary BCs are sporadic forms, 15-20% are familial and the remainder 5-10% are hereditary forms.

Family history is one of the strongest risk factors for developing BC. Although a woman in the general population has a 7% risk of BC in her lifetime, in a woman with a family history the risk is estimated as 30%. However, when she carries the BRCA mutation, the risk for cancer rises to 65-80%. In order to assess the likelihood of a predisposing gene in family, it is necessary to assess the family tree [7].

A family history may be described as significant only when on the same side of the family there are:

- two or more close (first, second and third degree) relatives who have had BC;
- one or more close relatives who have had BC before the age of 40;
- close relatives who have had BC and others who have had ovarian cancer;

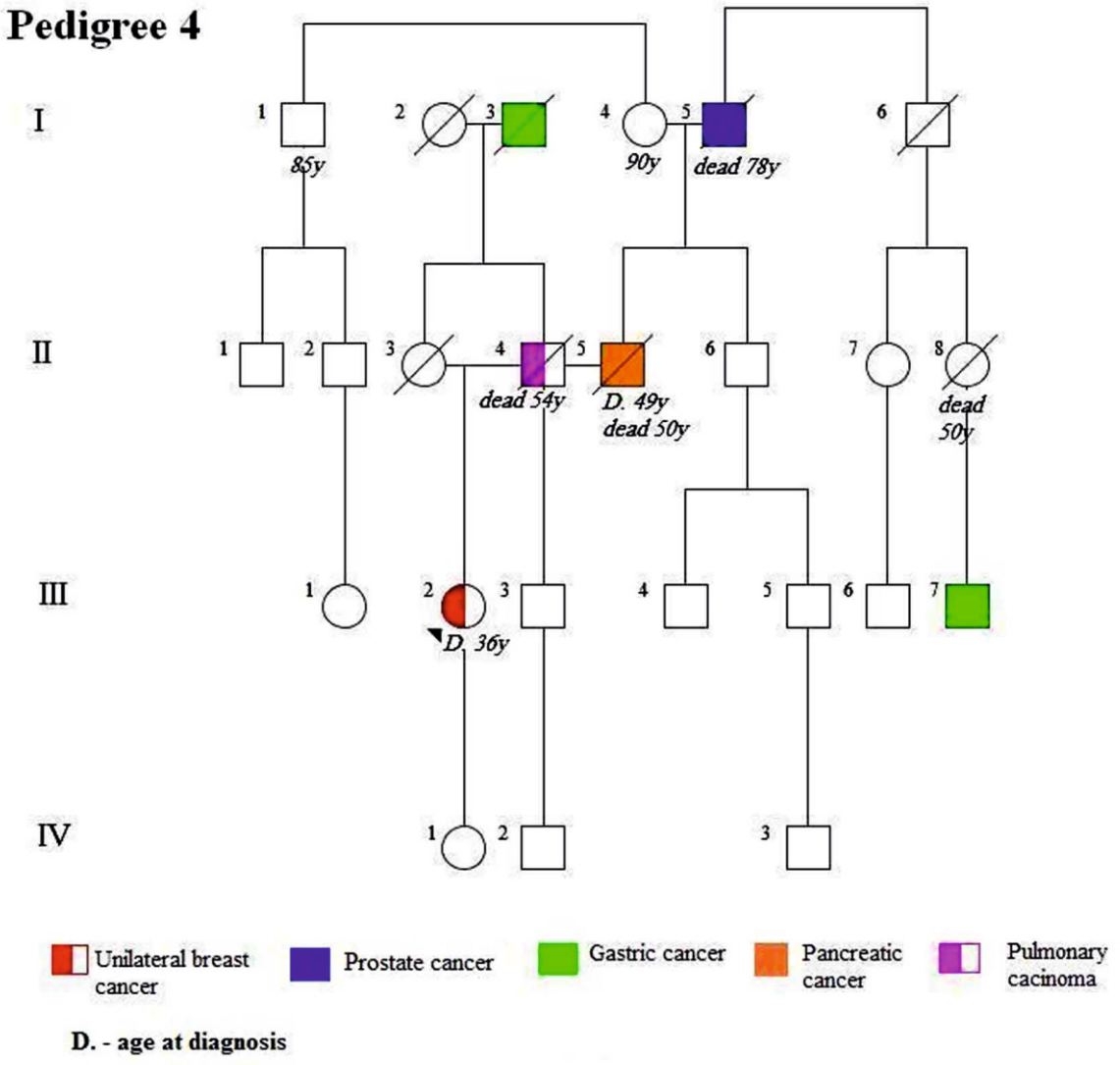

Figure 4. Family pedigree of proband. The proband (III-2) is indicated by an arrow

- one close relative who has had BC in both breasts (bilateral) or who has had breast and ovarian cancer;
- other related tumors, such as ovarian, Fallopian tube, prostate, male breast, pancreatic, gastric and peritoneum cancer [8].

There is a consideration that the cumulative risk of BC (to age 50 years) in sisters, mother, and aunts of the case patient, respectively, is 6, 3 and 2 times the population risk, if the case patient is younger than 40 at diagnosis, but is considerably lower if the case patient is older at diagnosis [9].

On the other hand, large epidemiological data worldwide has found that the probability for a woman to develop BC increases according to the number of affected first-degree relatives. The risk increases four to six times if two first degree relatives develop the disease. For example, the probability for a woman aged 20 to develop BC (by the age of 80) who has no affected relatives is 7.8%, one affected relative – 13.3% and 2 affected relatives – 21.1% [10].

There is evidence that the family history of ovarian cancer can also increase BC risk, and this effect is confined to relatives of patients not only with bilateral BC. Studies have indicated that family history of prostate cancer increases BC

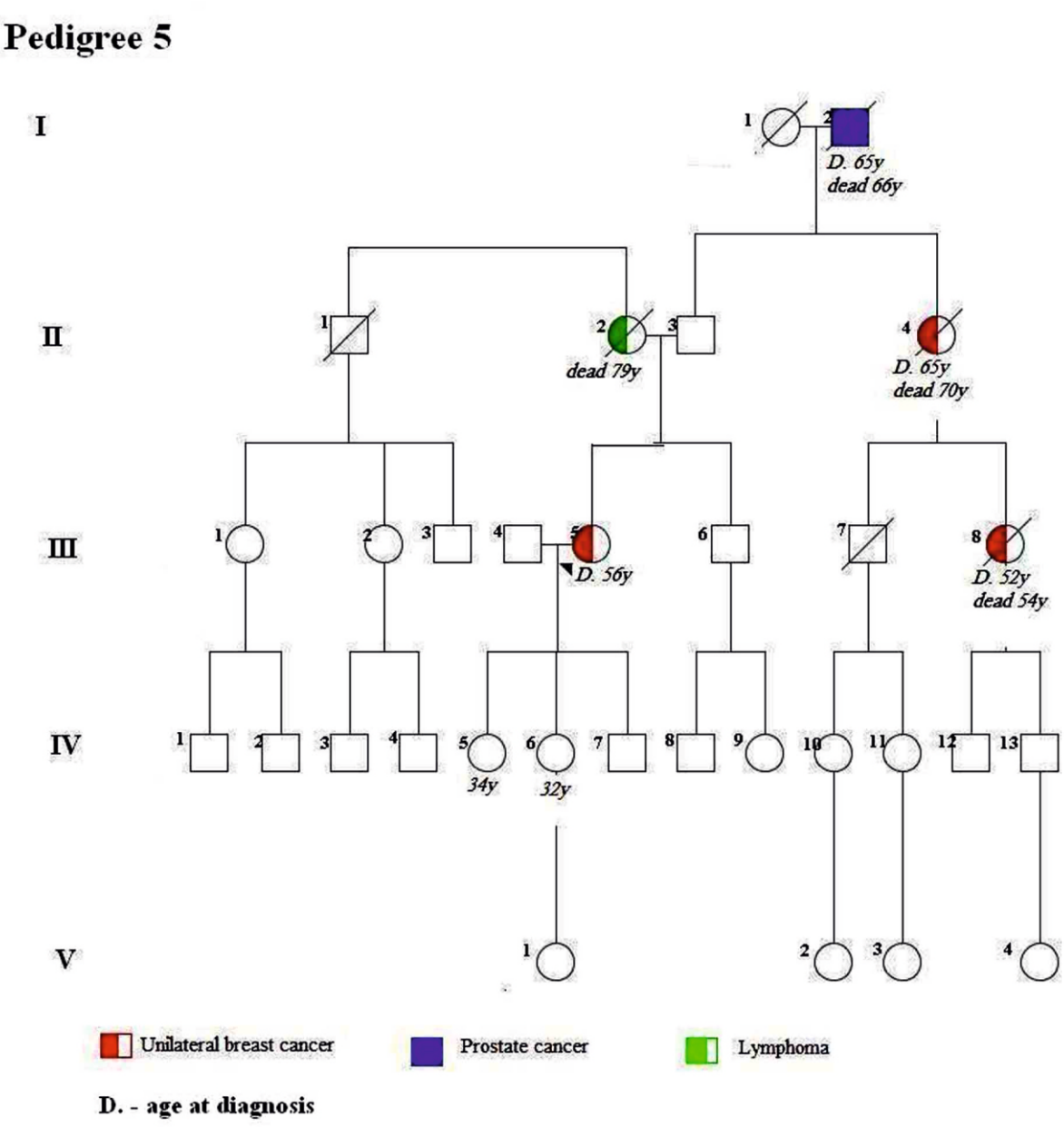

Figure 5. Family pedigree of proband. The proband (III-5) is indicated by an arrow

risk in first-degree relatives of a proband more than the risk based only on a family history of BC [10, 11].

Currently, there is a general consensus that patients with bilateral BC, those who develop a combination of BC and another epithelial cancer, and women with early onset of the disease are most likely to be carrying a genetic mutation predisposing to BC. Literature reviews have presented families with BC that show an excess of ovarian, colon, prostatic, and other cancers attributable to the same inherited mutation [10].

In this context, identification of the mutations in BRCA1 and BRCA2 susceptibility genes has provided a molecular basis for genetic testing. Genetic testing of women at increased risk of BC, based on strong family history, allows to precisely estimate the risk for developing BC. This could favour the use of surveillance measures in relatives at moderate or high risk of cancer [7].

In our study, we report six families with aggregation of breast and/or other associated cancers (ovarian, pancreatic, prostatic and gastric cancer). Based on the personal family histories and taking into account the risk factors mentioned above, we identified the healthy relatives of probands as being at a risk higher than

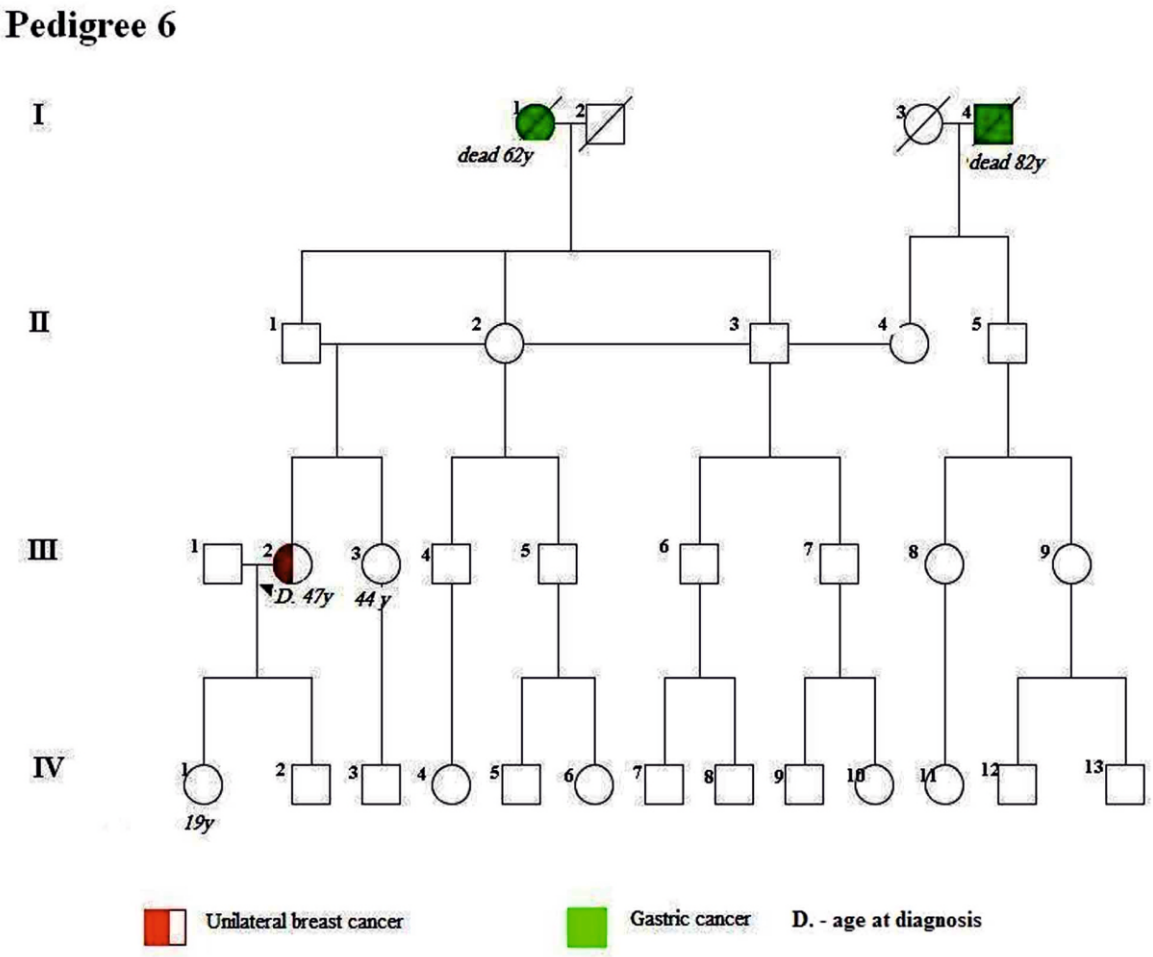

Figure 6. Family pedigree of proband. The proband (III-2) is indicated by an arrow

average. We offered them to take some prophylactic measures such as breast self examination (starting at the age of 18) and mammography (starting at the age of 35) and to undergo genetic testing (mainly for BRCA1and BRCA2).

The relatives without confirmed BRCA mutation were considered at a risk as high as the population risk – about 7%. In relatives with confirmed BRCA mutation status, the risk was estimated at 65-80% and they were referred for prophylactic measures such as chemoprevention and risk- reducing mastectomy.

Conclusion

Our study highlights the role of family history assessment for identifying women at high risk of BC. Based on revealed risk factors in family history, these women should be referred for earlier screening interventions and risk-reducing therapies.

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