Analysing Of Genotype-Fenotype Correlation Of Patients With Hereditary Cancer Syndrome With BRCA1 And BRCA2 Mutations

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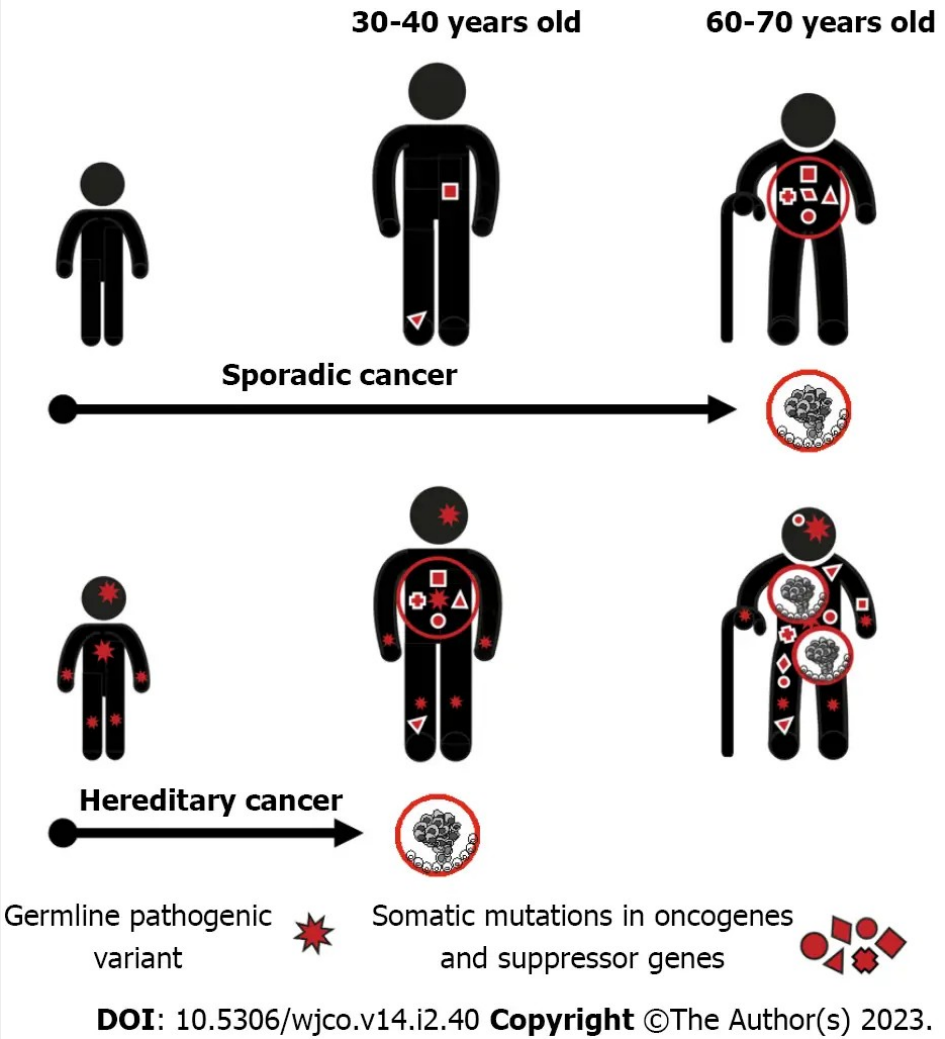
- Although all cancers occur as a result of genetic damage, genetic damage is not always passed down through families.

- Approximately 10-15% of breast and ovarian cancers are due to germline mutations in the BRCA1 or BRCA2 genes.

AIM OF GENETIC SCREENING IN HEREDITARY CANCER SYNDROMES



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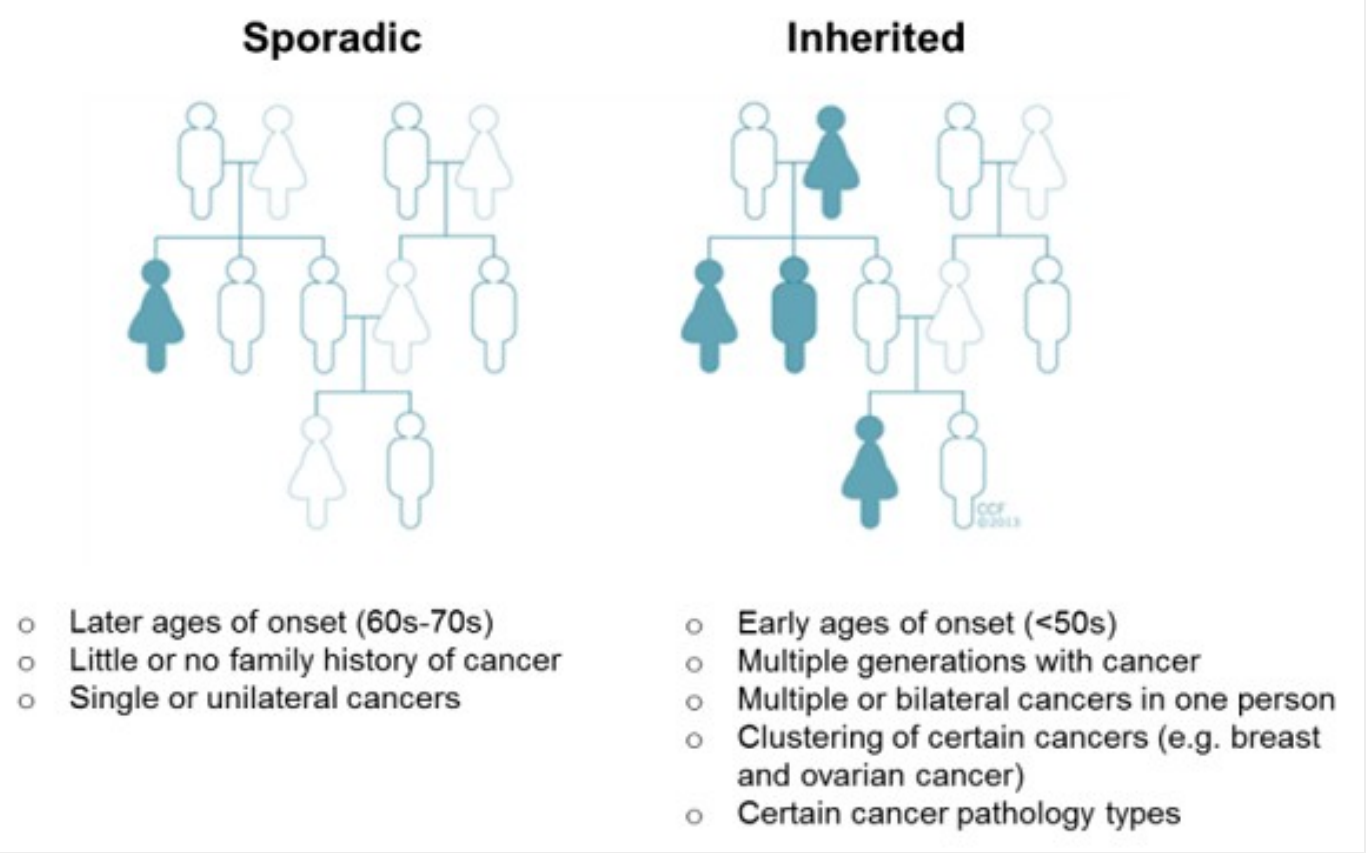
- Detection of these cancers is very important in terms of directing systemic or surgical treatment because they appear at an earlier age than their sporadic equivalents, can be more aggressive, and have different drug sensitivities and responses to treatment.

Examples of some symptoms that raise suspicion of hereditary cancer:

- Earlier age of onset,
- Multiple primary tumors,
- Bilateral involvement,
- Rare malignancies,
- Tumor groups specific to a defined syndrome



SELECTION OF PATIENTS FOR GENETIC SCREENING

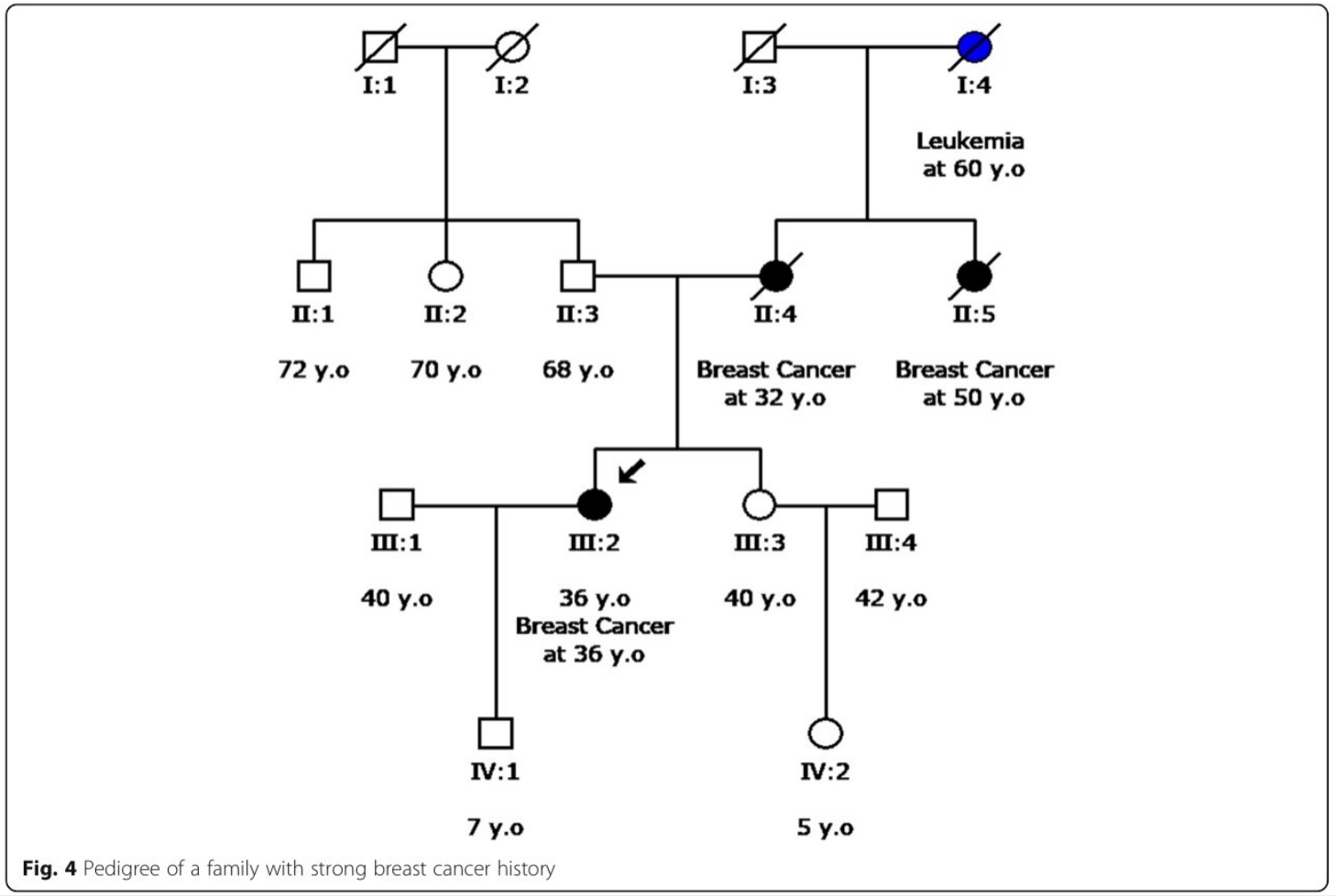


Fig. 4 Pedigree of a family with strong breast cancer history

Obtaining information about at least 3 generations is valuable in terms of accurate evaluation of family history.

COMMON HEREDITARY CANCER SYNDROMES

- **Hereditary breast / ovarian cancer (BRCA1 , BRCA2)**
- Hereditary non-polyposis colorectal cancer (MLH1 , MSH2 , MSH6, PMS1, PMS2)
- Multiple endocrine neoplasias (RET)
- Cowden syndrome (PTEN)
- Li-Fraumeni syndrome (TP53)

According to research, the most common hereditary cancer syndromes are;

- Hereditary breast and ovarian cancers
- Lynch Syndrome (HNPCC)

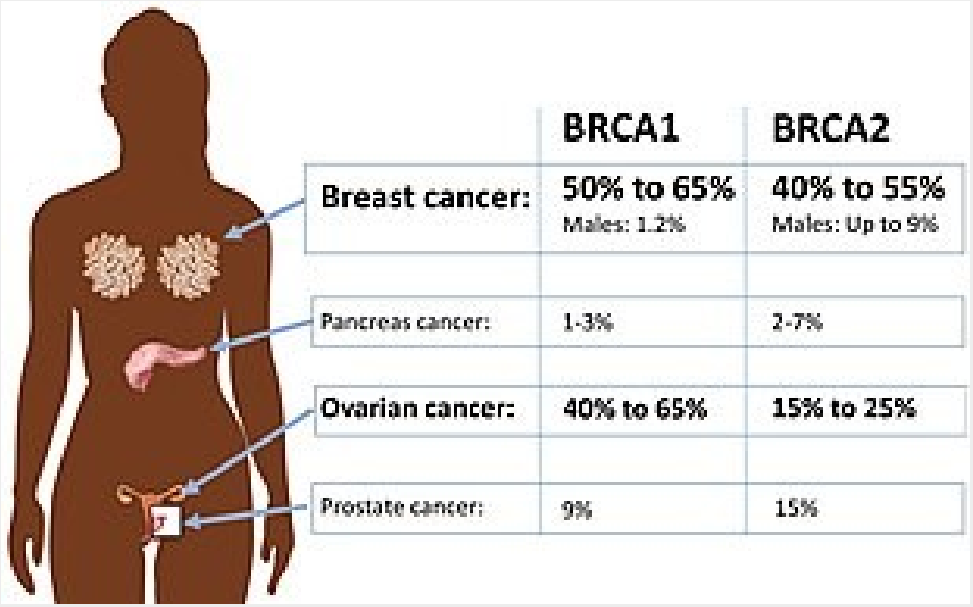
TABLE 4.

Autosomal Dominant Hereditary Cancer Syndromes

Syndrome	Penetrance	Gene	Associated Cancers/Features
Breast/ovarian	85%	BRCA1 at 17q21 BRCA2 at 13q21	Breast (female and male), ovary, colon, prostate BRCA2 only: pancreatic, gallbladder, bile duct, stomach cancer, and melanoma
Cowden	100%	PTEN at 10q23	Breast, thyroid (especially papillary), renal cell, and uterine fibroids
Familial adeomatous polyposis (Gardner syndrome, Turcot syndrome)	Close to 100%	APC gene at 5q21	Greater than 100 polyps Gardner syndrome is associated with sebaceous cysts and lipomas; Turcot syndrome is also associated with brain tumors
Hereditary nonpolyposis colon cancer (Lynch syndrome)	Up to 90%	MSH2 at 2p22 MLH1 at 3p21 PMS1 at 2q31 PMS2 at 7p22 MSH6 at 2p16	Colon, stomach, small intestine, ureter and kidney, endometrial, and ovarian cancer
Li-Fraumeni syndrome	Up to 90%	TP53 at 17p13.1	Osteosarcomas, soft tissue sarcomas, breast cancer, brain cancer, adrenocortical carcinomas, and acute leukemia
Familial melanoma	Up to 100%	CMM1 TP16 at 9p21 CDK4 at 12q14	Melanoma; often have 10 to hundreds of dysplastic nevi
Multiple endocrine neoplasia type 1	Up to 90%	MEN1 at 11q13	Parathyroid and pancreatic tumors (both benign and malignant), thyroid carcinomas, pheochromocytomas
Multiple endocrine neoplasia type 1	Nearly 100%	RET at 10q11.2	Medullary thyroid carcinomas, pheochromocytomas, and benign parathyroid tumors
Neurofibromatosis type 1	100%	NF1 at 17q11.2	Café au lait spots, opticgliomas, neurofibrosarcomas, astrocytomas
Neurofibromatosis type 2	100% by age 60	NF2 at 22q12	Multiple spine and skin tumors
Nevoid basal cell carcinoma syndrome	97%	PTC at 9q22.3	Basal cell carcinomas, jaw cysts, palmer planter pits, ovarian fibromas, and hamartous polyps of the stomach
Peutz-Jeghers syndrome	100%	STK11 at 19p13.3	Harartomatous polyps throughout the gastrointestinal tract; colon, breast, pancreas, uterus, and ovarian cancer
Familial retinoblastoma	90%	BR1 at 13q14.1	Retinal tumors, osteosarcomas, Ewing sarcoma, leukemia, lymphoma
Von Hippel Lindau syndrome	90%	VHL at 3025	Clear cell renal carcinomas, pheochromocytomas, retinal angiomas, pancreatic tumors
Wilm's tumor	100%	Wt1 at 11p13 WP2 at 11p15.5 FWT1	Wilm's tumor

Data from www.geneclinics.org and references 8, 11, 12, 31, and 32.

BRCA1 AND BRCA2 MUTATIONS



	BRCA1	BRCA2
Breast cancer:	50% to 65% Males: 1.2%	40% to 55% Males: Up to 9%
Pancreas cancer:	1-3%	2-7%
Ovarian cancer:	40% to 65%	15% to 25%
Prostate cancer:	9%	15%

- BRCA 1 and BRCA 2 are penetrance genes for breast and ovarian cancers and tumor predisposition syndromes.
- Approximately 10-15% of breast and ovarian cancers occur through hereditary transmission.
- As a result of mutations in these tumor suppressor genes, cell proliferation cannot be controlled and the risk of cancer, especially in the breast and ovaries, increases.

AIM OF TE STUDY

- With our study, we aim to list those with BRCA1 and BRCA2 gene mutations detected in patients who applied to Bezmialem Vakıf University Medical Genetics Department with a diagnosis of hereditary cancer, to match the gene mutation we found with the clinical and laboratory findings of these patients and to make a genotype-phenotype correlation.

METHOD

- 55 patients with hereditary cancer syndrome who applied to medical genetics polyclinic, those with BRCA1 and BRCA2 gene mutations will be included in the study. Data such as the patient's gender, type of cancer, age at diagnosis, which mutation was detected in which gene, and cancer history in relatives will be obtained from family history of patients.

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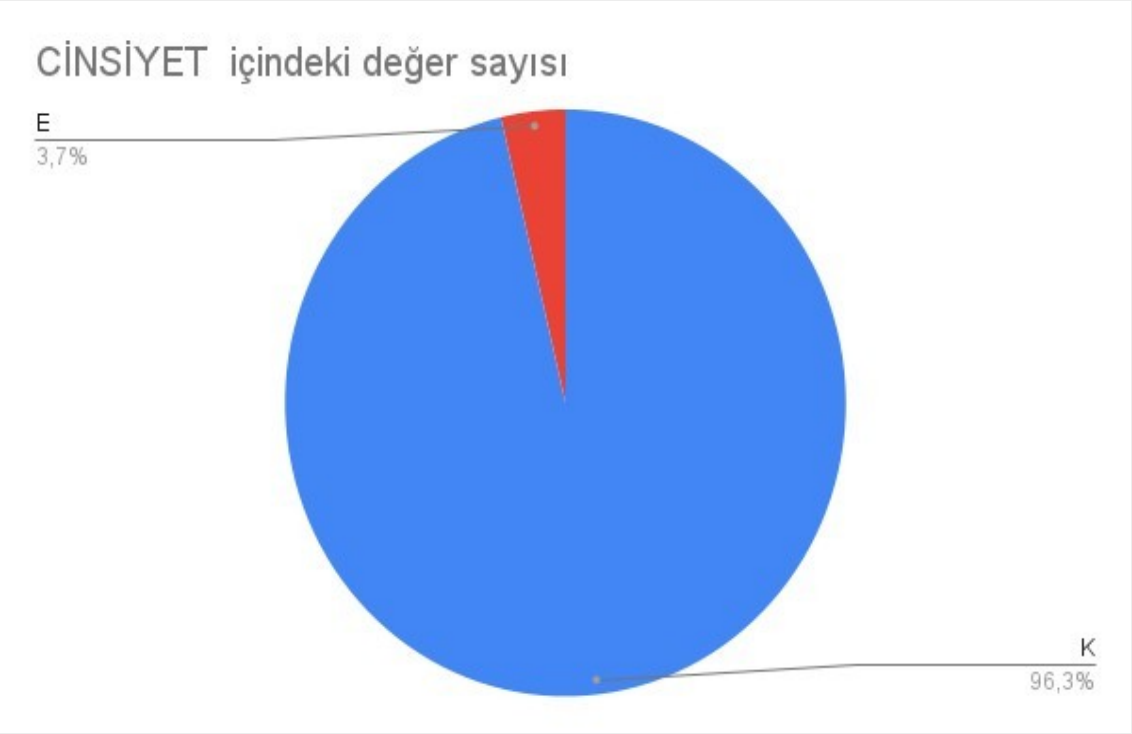
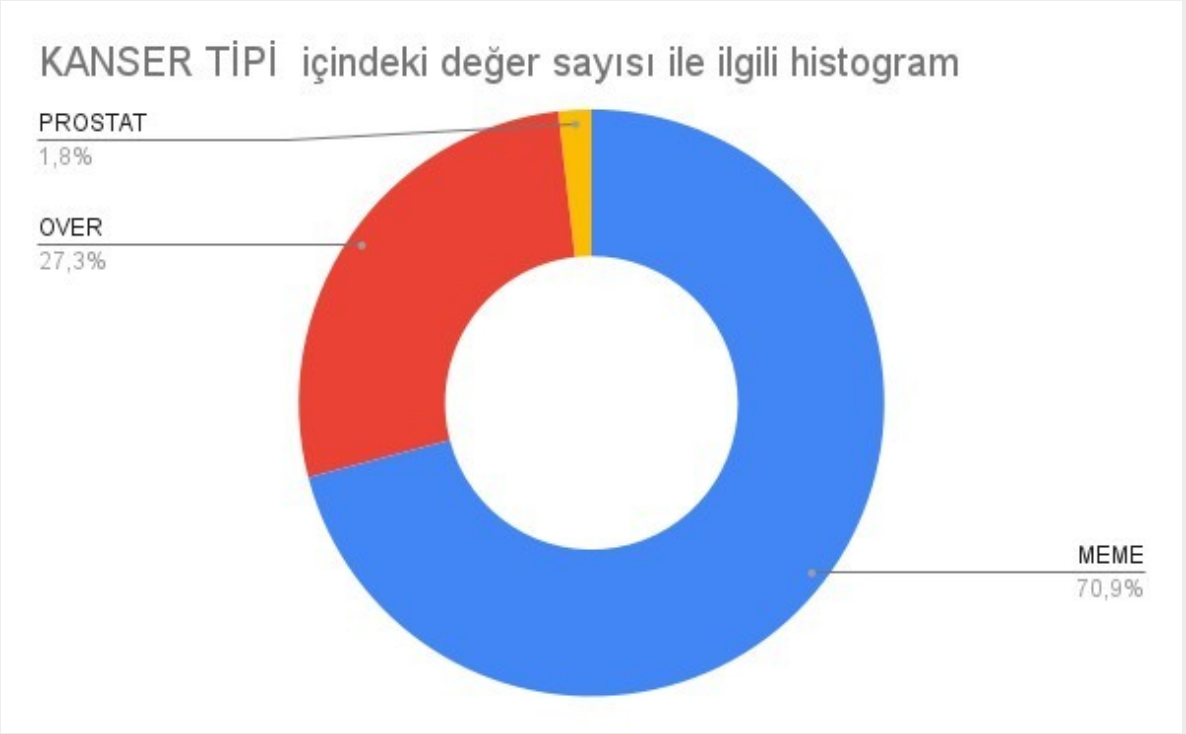
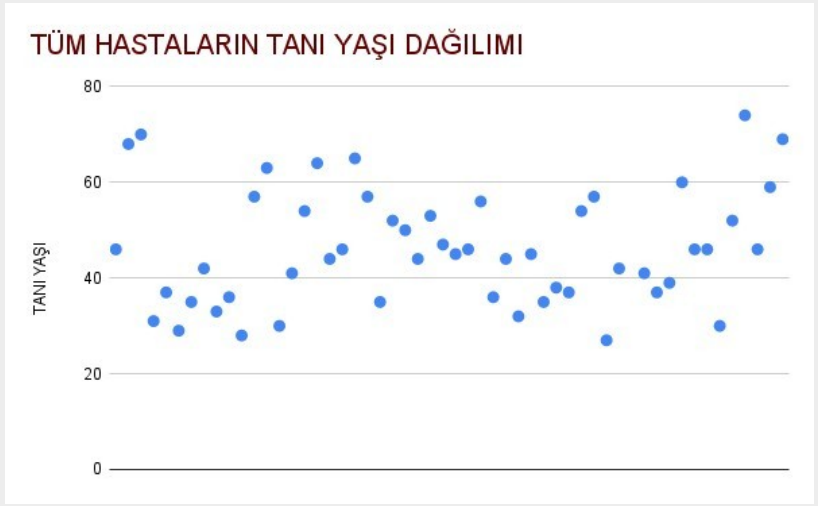
- **Name**
- **Gender**
- **Age**
- **Type of cancer**
- **Pathology**
- **Cancers seen in the patient's 1st, 2nd, 3rd degree relatives**

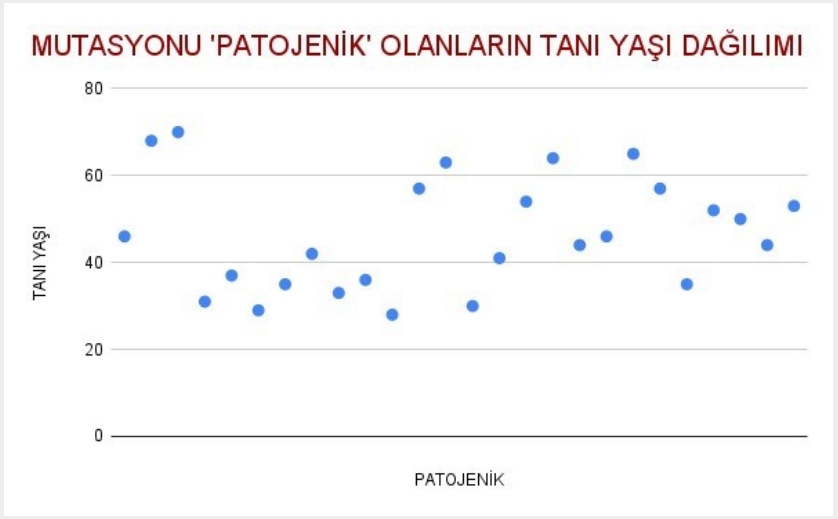
RESULTS:

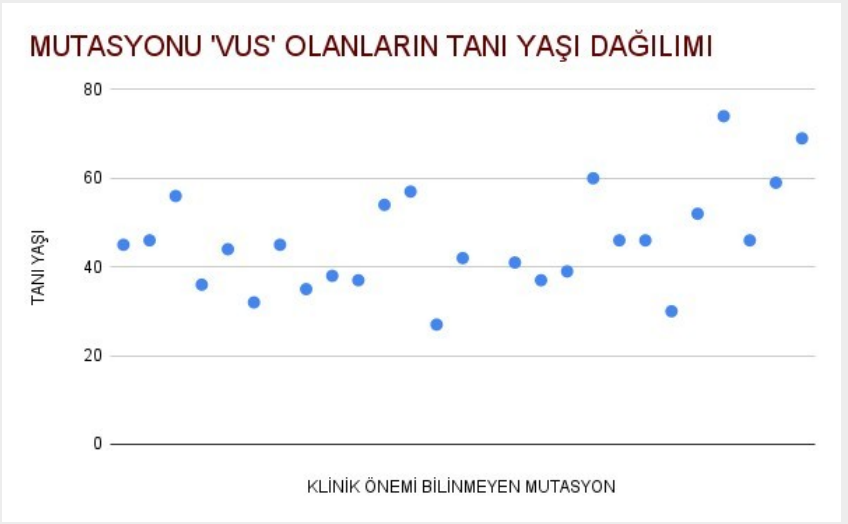
55 patients evaluated in the study, the average age at diagnosis was 46.8 years. Of the 39 breast cancer patients in the study, 13 carried the BRCA1 mutation, 26 carried the BRCA2 mutation; 10 of the 15 ovarian cancer patients carried the BRCA1 and 5 carried the BRCA2 mutation.







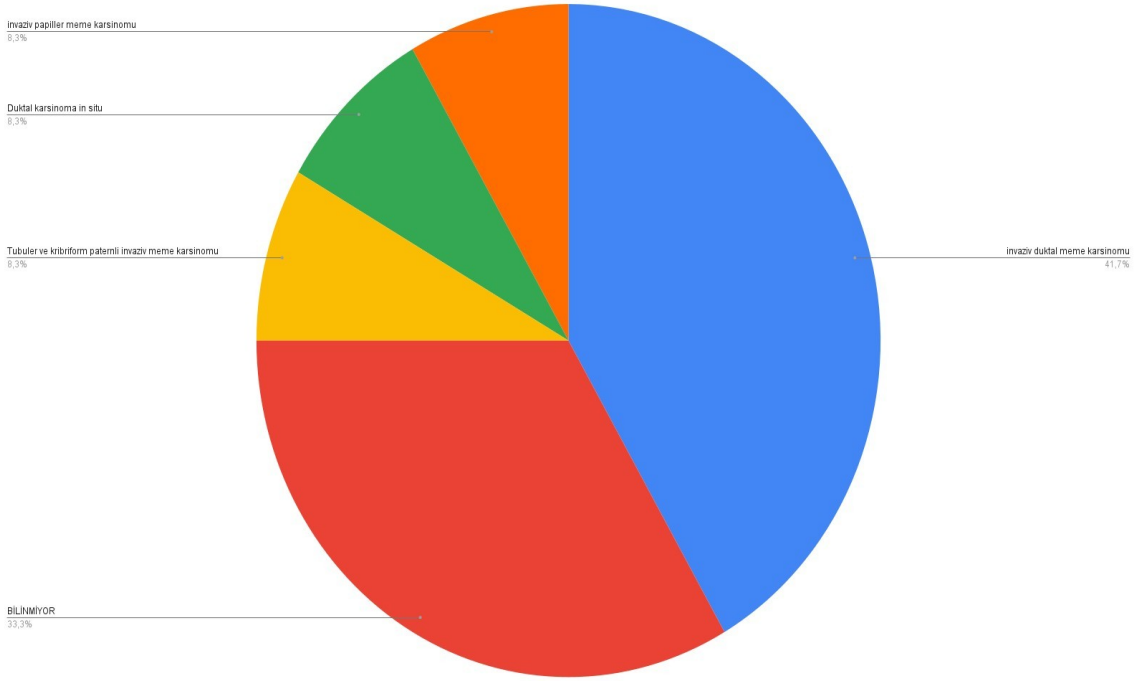




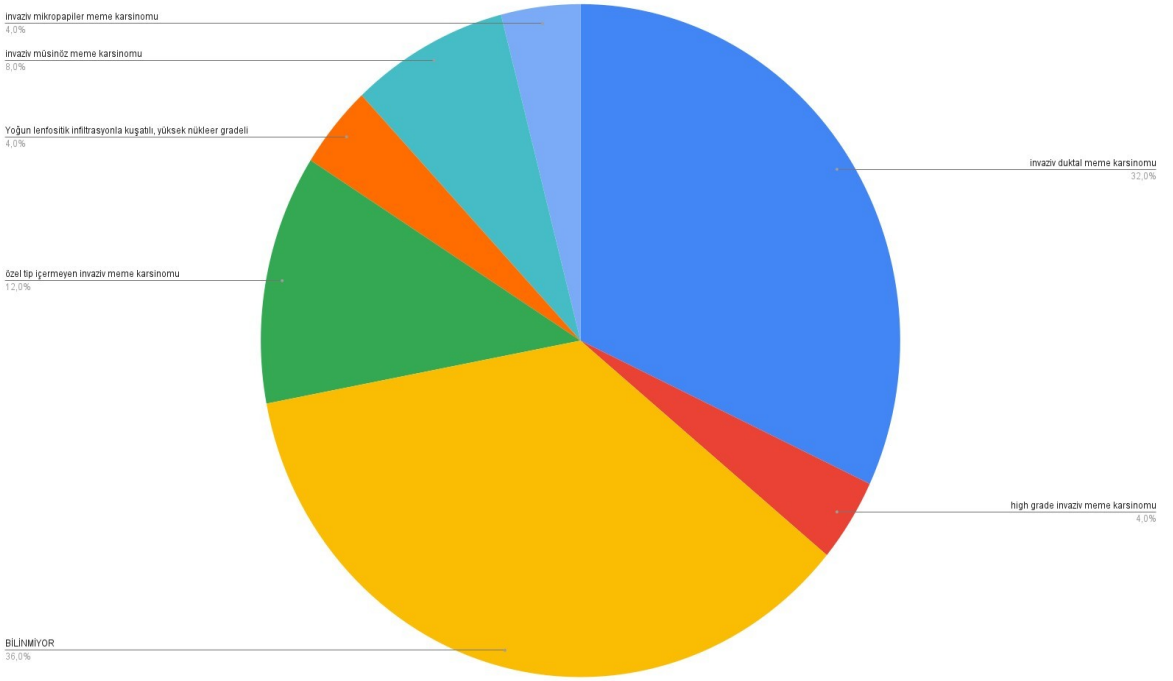
- It was observed that whether the mutations seen in the patients were reported as pathogenic (27) or VUS (28) according to the literature record did not affect the age of diagnosis.

- 3 mutations were detected in different unrelated individuals.
- The cancer history of the patients' first, second and third degree relatives was questioned and a total of 117 relatives with cancer were found to have a history of 25.6% breast cancer, 12.8% lung cancer and 11.1% ovarian cancer.
- When the exons were examined, the majority of mutations were detected in exon 11 and exon 20.
- Both mutations resulted in a higher rate of breast cancer.

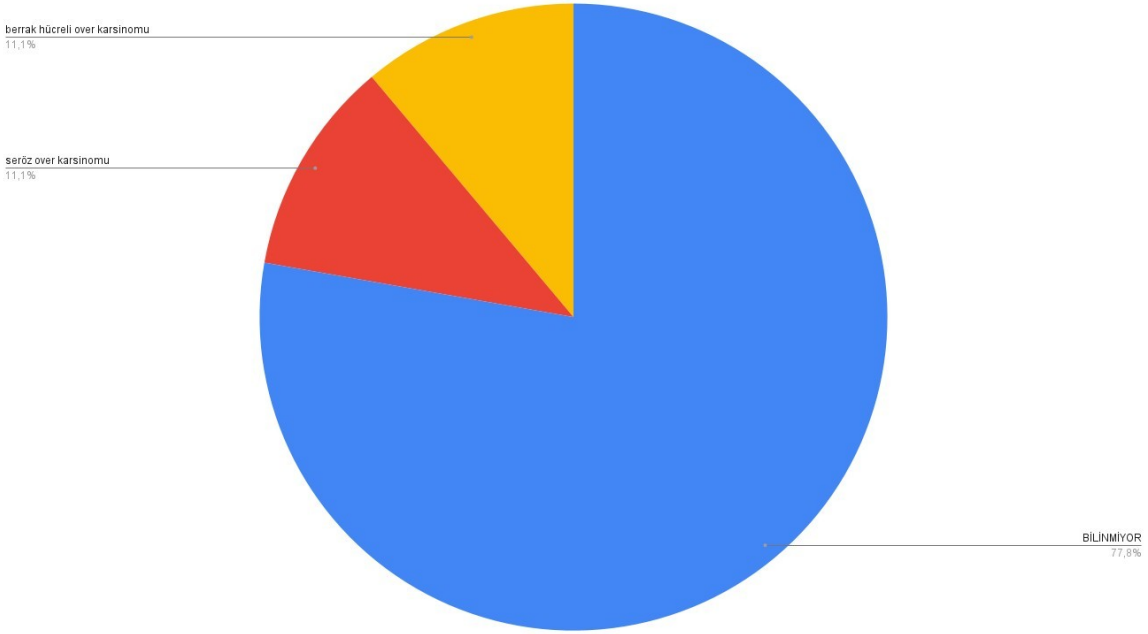
BRCA1 + MEME CA PATOLOJİ



BRCA2 + MEME CA PATOLOJİ



BRCA1 + OVER CA PATOLOJİ



BRCA2 + OVER CA PATOLOJİ

This study showed that the presence of a genetic mutation lowers the age of cancer diagnosis. Patients’ close relatives should also be examined genetically and followed up clinically.

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