

Evaluation of Pathology Results of Patients with a History of Breast Cancer who were Operated on for Gynecological Pathologies or Prophylaxis

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OBJECTIVES: The present study aimed to evaluate the operation results of patients who were followed up due to breast cancer and were operated on due to gynecological pathologies or for prophylactic purposes, and determine the distribution of gynecological pathologies in breast cancer patients

STUDY DESIGN: Patients with breast cancer who had gynecological surgery in our institution between December 2015 and January 2023 were retrospectively analyzed in this cross-sectional study. The pathological reports and medical records of the included patients were obtained from the gynecologic oncology electronic database system and the patient files. The study is approved by the institution's local ethics committee.

RESULTS: Totally 57 patients with a history of breast cancer had gynecological operations between December 2015 and January 2023. The median age of the patients was 49. Benign pathologies were detected in the majority of patients with a history of breast cancer, this rate was found to be 87.7%. The pathology revealed malignant/premalignant disease in seven (12.2%) patients. Among these seven patients, four patients had malignant disease one patient had microinvasive cervical cancer, one patient had ovarian serous cancer, one patient had cervical and ovarian metastasis of breast cancer, and one patient had ovarian metastasis of breast cancer.

CONCLUSIONS: Patients with a history of breast cancer have increased rates of gynecological pathology development compared to the normal population.

Keywords: Breast cancer, Gynecological pathologies

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Introduction

Breast cancer is the most common type of cancer in women. It is responsible for 11.7% of all female cancers (1 to 4 cancer cases) and is the fifth leading cause of cancer-related deaths (1).

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Many risk factors associated with breast cancer have been identified. Breast cancer risk factors can be divided into two groups: modifiable and non-modifiable risk factors. Modifiable risk factors: body mass index (BMI), physical activity, smoking, alcohol, parity, oral contraceptive use, and hormone replacement therapy. Non-modifiable risk factors: age at menarche, age at menopause, menopausal status, family history of breast cancer, and the presence of genetic mutations, especially Breast cancer type 1 susceptibility protein (BRCA1), BRCA2 gene mutations, and history of radiotherapy to the thoracic region (2).

The risk of breast cancer increases with age, 80% of the patients are over the age of 50 (3), and the risk of gynecological pathology development increases with increasing age, too. Since the development of breast cancer has similar risk factors with gynecological pathologies (e.g. obesity, nulliparity), the risk of gynecological pathology is increased in patients with breast cancer compared to the normal population (4).

Adnexal masses can frequently be seen in patients with a history of breast cancer. Breast cancer is the most common primary tumor that metastasizes to gynecological organs after colorectal cancer (5,6).

Gynecologic follow-up in breast cancer patients is very

important for the early detection of benign, premalignant, and malignant pathologies. Early diagnosis and treatment can be possible with the presence of symptoms such as abnormal uterine bleeding, pelvic-abdominal pain, abdominal distension, and examination findings.

In the present study, we aimed to evaluate the operation results of patients who were followed up due to breast cancer and were operated on due to gynecological pathologies or for prophylactic purposes and determine the distribution of gynecological pathologies in breast cancer patients.

Material and Method

Patients with breast cancer who had gynecological surgery in our institution between December 2015 and January 2023 were retrospectively analyzed in this cross-sectional study. Clinico-pathological characteristics of patients such as age, tamoxifen history, BRCA status, an indication of surgery, pathology results, and Ca-125 level were evaluated. The pathological reports and medical records of the included patients were obtained from the gynecologic oncology electronic database system and the patient files. The study was initiated with the approval of the Health Sciences University Antalya Training and Research Hospital Ethics Committee on May 04, 2023, with the approval number 2023-097. The principles stated in the Helsinki Declaration were adhered to in the study.

Patients who were between 20-75 years old were included. All patients who had abnormal uterine bleeding had a preoperative endometrial biopsy. Patients with known endometrial and ovarian cancer were excluded. Patients with a history of cancer other than breast cancer were excluded.

In surgery, primarily minimally invasive surgery was preferred and laparotomy was applied to patients with large pelvic masses, and large myomas, and who did not prefer laparoscopic surgery.

Prophylactic surgery was recommended for patients who do not have a medical indication but come with a request for hysterectomy due to the concern of the patient or the doctor who primarily follows the patient, and hysterectomy +/- Bilateral salpingoophorectomy (BSO) was performed if they still have a request after being informed in detail.

Hysterectomy+BSO was recommended for patients who were BRCA positive. Hysterectomy+BSO was recommended for those whose age was over 35-40 years old with BRCA1 and for those over 40-45 years old with BRCA2 mutation. Hysterectomy after endometrial biopsy was recommended for patients who had recurrent abnormal uterine bleeding since these patients shouldn't use hormonal therapy. BSO is added to surgery according to the patient's age and wish.

In patients with BRCA mutation, a detailed examination of fallopian tubes was done by applying the "Sectioning and

Extensively Examining the Fimbriated End (SEE-FIM)" protocol.

Statistical analysis

Statistical analyses were performed using the SPSS (Statistical Package for Social Sciences) software version 22. Descriptive analyses were presented using medians and range. The proportions were presented as percentages.

Results

Totally 57 patients with a history of breast cancer had gynecological operations between December 2015 and January 2023. The median age of the patients was 49 (range, 34-65) years old. Parities of 52 patients were known. Forty-seven (94%) patients had at least one child. Five patients had diabetes mellitus (DM), four patients had hypertension (HT) and one patient had DM+HT. The indication for surgery was prophylaxis in 24 (42.1%) patients and BRCA positivity in 14 (24.5%) patients. Totally 36 (63.1%) patients underwent laparoscopic surgery. Details of patients' characteristics and operation data are presented in Table I.

Among 57 patients, 52 (91.2%) patients had endometrial pathology reports, and details of endometrial pathology distribution are given in Table II. Thirty-six (63.2%) of 52 patients who had endometrial pathology reports used tamoxifen. Details of tamoxifen use and endometrial pathologies distribution are given in Table III. Endometrial intraepithelial neoplasia was detected in only 2 (5.5%) of the patients using tamoxifen.

The pathology revealed malignant/premalignant disease in seven (12.2%) patients. Among these seven patients, one patient had microinvasive cervical cancer, one patient had ovarian serous cancer, one patient had cervical and ovarian metastasis of breast cancer, one patient had serous tubal intraepithelial carcinoma (STIC), two patients had endometrial intraepithelial neoplasia, and one patient had ovarian metastasis of breast cancer. The patient with cervical cancer had hysterectomy+BSO due to margin positivity in conization material and final pathology revealed microinvasive cervical cancer. The patient with cervical and ovarian metastasis came to the outpatient clinic with a PET CT revealing high retention of F-fluorodeoxyglucose (FDG) in the uterine cervix and ovaries. She had type B radical hysterectomy and BSO. STIC was detected in one of 14 patients with positive BRCA mutation (0.7%) and the patient with STIC had hysterectomy and BSO due to BRCA1 positivity. Endometrial intraepithelial neoplasia was detected in two of the patients, and both patients were using tamoxifen. One of the patients diagnosed with endometrial intraepithelial neoplasia (EIN) had a hysterectomy and BSO due to abnormal uterine bleeding, another patient had a hysterectomy and BSO for prophylaxis. The last patient had USO due to an adnexal mass and pathology revealed breast cancer metastasis. Clinico-pathological details of these seven patients are shown in Table IV.

Table I: Patients' characteristics and operation data

	Mean	Range
Age	49	34-65
	Number	Percentage
Parity		
0	3	5.2%
1 child	10	17.5%
2 children	22	38.5%
3 or more children	17	29.8%
Unknown	5	8.7%
BRCA Status		
BRCA 1, 2 +	14	24.5%
Negative/Unknown	43	75.5%
Indications		
Prophylaxis	24	42.1%
BRCA positivity	14	24.5%
Adnexal mass	10	17.5%
Abnormal uterine bleeding	9	15.7%
Tamoxifen Use		
Yes	36	63.1%
No	18	31.5%
Unknown	3	5.2%
Operation		
Hysterectomy+BSO	52	91.2%
USO	2	3.5%
BSO	3	5.2%
Minimally invasive surgery		
Yes	36	63.1%
No	21	36.8%
Patients History		
Hypertension	4	7%
Diabetes Mellitus	5	8.7%
Hypertension+Diabetes Mellitus	1	1.7%
No	47	82.4%
Complication		
Yes	3	5.2%
No	54	94.7%

Table II: Distribution of endometrial pathologies

Endometrial Pathologies	Number	Percentage
Benign	40	76.9%
Endometrial polyps	10	19.2%
Endometrial Intraepithelial Neoplasia	2	3.8%

Table III: Tamoxifen use and distribution of endometrial pathologies

Endometrial Pathologies	Benign	Endometrial polyps	Endometrial Intraepithelial Neoplasia
Tamoxifen Use (Total 36 patients)	27 (75%)	7 (19.4%)	2 (5.5%)

Three patients had intraoperative complications which were surgical site infection in two patients and a ureteral injury in one patient.

Totally 52 (91.2%) patients had hysterectomy and bilateral salpingo-oophorectomy, one patient had type B radical hysterectomy+BSO, three patients had BSO, and two patients had unilateral salpingo-oophorectomy (USO).

Ten patients were operated on with the diagnosis of adnexal mass. Four patients had benign cysts, one patient had mature cystic teratoma, one patient had ovarian fibroma, two patients had ovarian breast cancer metastases, and one patient had ovarian serous carcinoma. Details of adnexal mass and pathologies are shown in Table V.

The ca-125 level of 29 patients was known. The median Ca-125 level was 11 IU/ml (range, 4-56). The Ca-125 level of only one patient was above 35 IU/mL and there was no gynecological pathology in that patient. The ca-125 level of the patient with secondary ovarian cancer was 15 IU/mL and it was 17 IU/mL and 10 IU/ml for the patient with ovarian metastasis of breast cancer.

Table IV: Clinico-pathological details of patients with malignant/premalignant pathology

Patient	Age	Tmx Hx	Indication of Surgery	Pathology	BRCA
1	59	-	CIN 3	Microinvasive cervical cancer	*
2	44	-	BRCA+	STIC	+
3	54	*	Abnormal uterine bleeding	Endometrial intraepithelial Neoplasia	-
4	50	*	Prophylaxis	Endometrial intraepithelial Neoplasia	-
5	47	*	Adnexal mass	Ovarian serous cancer	+
6	65	*	Uterine Cervical and Ovarian Retention in PET CT	Cervical and ovarian metastasis of breast cancer	-
7	34	+	Adnexal mass in Ultrasound	Ovarian metastasis of breast cancer	*

*BRCA status not known

Table V: Pathologies of patients operated with an indication of adnexal mass

Adnexal mass	Mature cystic teratoma	Ovarian Fibroma	Serous ovarian carcinoma	Breast cancer metastasis	Benign serous cystadenoma
Number	2 (20%)	1 (10)	1 (10%)	2 (20%)	4 (40%)

Discussion

The incidence of benign, premalignant, and malignant gynecological pathologies in patients with a history of breast cancer increases compared to the normal population (4). In the present study, benign pathologies were detected in the majority of patients with a history of breast cancer. This rate was found to be 87.7%, while Uysal et al. reported it as 83.7%.(7).

Because of majority of gynecological pathologies are benign in breast cancer patients, routine hysterectomy+/-BSO should not be recommended for all breast cancer patients. Patients' risk factors should be taken into consideration and surgery should be recommended for certain indications. For example, surgery is recommended for BRCA-positive cases, patients with abnormal uterine bleeding, and patients with pelvic masses. Apart from these, BSO can generally be recommended to patients with metastatic breast cancer for castration purposes, upon the recommendation and request of medical oncology, and to patients who cannot use tamoxifen for some reasons and treatment will switch to aromatase inhibitors.

Tamoxifen used in breast cancer patients with its low estrogenic effect on the uterine corpus, may cause epithelial and non-epithelial uterine corpus lesions such as polyps, hyperplasia, cancer, and uterine sarcoma (8,9). Mostly seen endometrial pathology in breast cancer patients using tamoxifen has been reported as endometrial polyp, this rate is approximately 8-44% in the previous studies (8,10). In the present study, this rate was found to be 19.4% and is compatible with the literature. Also in patients using tamoxifen, the endometrial intraepithelial neoplasia rate was found to be 0.9-2.5% (11), and the endometrial cancer risk increased 1.5-6.9 fold (12). In the present study, the rate of endometrial intraepithelial neoplasia was found to be 5.5% and no endometrial cancer was detected. The reason why endometrial cancer was not detected in the present study was that patients with preoperative endometrial cancer diagnoses were not included in the present study. In previous studies, abnormal uterine bleeding was the most important factor associated with the presence of gynecological pathologies in breast cancer patients using tamoxifen (13). Therefore, in the presence of abnormal uterine bleeding, the patient should undergo further evaluation in addition to annual examinations.

In previous studies, STIC was generally investigated in patients with known BRCA mutation or a strong family history of breast or ovarian cancer, and the rate of STIC in these patients was between 0.6% to 6% (14-16). In the present study, this rate was found to be 0.7%, which is similar to the literature.

In the present study, ovarian malignancy was detected in 3 of 10 patients who were operated on with the diagnosis of adnexal mass (30%). When looking at the literature, this rate was found to be between 12% and 50% (17).

Breast cancer patients have an increased risk of developing secondary primary female genital tract cancer (18). Studies have found that the risk of endometrial and ovarian cancer in breast cancer patients is increased by 30% (19). In our research, one patient was diagnosed with secondary ovarian cancer, and two patients were diagnosed with metastasis of breast to ovary. Therefore, the rate of primary ovarian cancer was 1.7% in our population.

Additionally, female genital system involvement can be observed in metastatic breast cancer patients. Although genital system metastases are rare in breast cancer patients, the most frequently affected areas were found to be the ovary and vagina (20,21). In the present study, breast cancer metastasis was detected in a total of 2 (3.5%) patients, and two metastases were detected in the ovaries. Additionally, cervical metastasis was detected in one patient in addition to ovarian metastasis, although for extra genital malignancies, the cervix is rarely the metastasis site due to its small size, dense fibromuscular structure, limited blood flow, and afferent lymphatic drainage alone (22). When the breast cancer pathology reports of both patients with ovarian metastases were examined, both patients had invasive lobular carcinoma and estrogen and progesterone receptors were found to be positive. When the literature was reviewed, it was reported that the rate of lobular carcinoma in ovarian metastases was found to be higher, as in our study (23-25).

Ca-125 value has a prognostic importance in predicting recurrence in breast cancer patients. However, the preoperative Ca-125 value does not have a prognostic importance in breast cancer patients (26). In the present study, the median value of Ca-125 in breast cancer patients was found to be within normal limits.

In conclusion, patients with a history of breast cancer have increased rates of gynecological pathology development compared to the normal population, and these patients should undergo annual gynecological examinations and be further evaluated in the presence of symptoms.

Declarations

Ethics approval and consent to participate: Since the present study was retrospective, informed consent was not obtained. The study was reviewed and approved by the ethics committee of the Health Sciences University Antalya Training and Research Hospital (Ethics approval reference number: 2023-097 date 04/05/2023). All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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