North Clin Istanb 2024;11(4):302–308
doi: 10.14744/nci.2023.93196

Original Article RADIATION ONCOLOGY

General analysis of breast cancer patients tested for BRCA mutations and evaluation of acute radiotherapy toxicity

Sule Karabulut Gul,[1] Huseyin Tepetam,[1] Berrin Benli Yavuz,[2] Ozge Kandemir Gursel,[3] Ayse Altinok,[4] Irem Yuksel,[1] Omar Alomari,[5] Banu Atalar,[6] Ilknur Bilkay Gorken[7]

[1]Department of Radiation Oncology, University of Health Sciences, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkiye
[2]Department of Radiation Oncology, Necmettin Erbakan University, Meram Faculty of Medicine, Konya, Turkiye
[3]Department of Radiation Oncology, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkiye
[4]Department of Radiation Oncology, Medical Park Bahcelievler Hospital, Istanbul, Turkiye
[5]University of Health Sciences, Hamidiye Faculty of Medicine, Istanbul, Turkiye
[6]Department of Radiation Oncology, Acibadem University Faculty of Medicine, Istanbul, Turkiye
[7]Department of Radiation Oncology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkiye

ABSTRACT

OBJECTIVE: The objective of our study is to evaluate breast cancer patients with BRCA1 or BRCA2 gene mutations and compare them with patients without these mutations. Specifically, we aim to assess the acute side effects of radiotherapy in both groups.

METHODS: Data were collected from four participating centers, comprising information from 73 patients who underwent known mutation analysis and had complete data. Patients were monitored on a weekly basis throughout their treatment for acute toxicity, which was evaluated using the Radiation Therapy Oncology Group (RTOG) acute toxicity criteria.

RESULTS: The median age of the 73 patients included in our study was 43. Among them, 17 had BRCA1-positive mutations and 19 had BRCA2-positive mutations. Invasive ductal carcinoma was present in 67 patients, all of whom underwent surgery. Of the patients, 57 received conventional radiotherapy doses, while 16 received hypofractionated radiotherapy doses. During follow-up, metastasis occurred in three patients. In BRCA-positive patients, those under 40 years of age ($p<0.001$), with high nodal positivity ($p=0.008$), grade 2–3 ($p=0.022$), and lymphovascular invasion ($p=0.002$) were significantly more frequent compared to BRCA-negative patients ($p<0.001$). The median survival was 35.8 months. Grade 1 dysphagia developed in seven BRCA-negative patients and four BRCA-positive patients, with no significant difference observed between the two groups ($p=0.351$). There was also no statistical difference observed in the occurrence of grade 2–3 skin reactions, with 11 BRCA-negative patients and eight BRCA-positive patients experiencing these side effects.

CONCLUSION: Our study supports existing literature by identifying an association between the presence of BRCA mutations and young age, nodal status, grade, and lymphovascular invasion. Additionally, we found no significant difference in the occurrence of radiotherapy toxicity between BRCA-positive and BRCA-negative patients. These findings suggest that radiotherapy can be safely administered to BRCA-positive patients after breast-conserving surgery or mastectomy. Keywords for our study include breast cancer, BRCA mutation, radiotherapy, and side effects.

Keywords: BRCA mutation; breast cancer; radiotherapy; side effects.

Cite this article as: *Karabulut Gul S, Tepetam H, Benli Yavuz B, Kandemir Gursel O, Altinok A, Yuksel I, et al. General analysis of breast cancer patients tested for BRCA mutations and evaluation of acute radiotherapy toxicity. North Clin Istanb 2024;11(4):302–308.*

Received: May 09, 2022 *Revised:* August 10, 2023 *Accepted:* August 30, 2023 *Online:* August 01, 2024

Correspondence: Sule KARABULUT GUL, MD. Saglik Bilimleri Universitesi, Dr. Lutfi Kirdar Kartal Sehir Hastanesi, Saglik Uygulama Merkezi, Istanbul, Turkiye.
Tel: +90 532 397 48 40 e-mail: sulegul2003@yahoo.com

Istanbul Provincial Directorate of Health - Available online at www.northclinist.com

Breast cancer is a prevalent and widespread disease affecting a large number of women worldwide [1]. While various factors such as lifestyle and environmental influences contribute to the majority of breast cancer cases, hereditary factors also play a significant role in the development of certain forms of the disease [2]. Among hereditary breast cancers, mutations in the BRCA1 and BRCA2 genes are the most frequently observed. These genes play a critical role in DNA repair and cell cycle regulation, and mutations in these genes substantially increase the risk of developing breast and other types of cancer [3]. Consequently, the identification of BRCA mutations in breast cancer patients holds great importance for genetic counseling, treatment decision-making, and family screening.

Furthermore, genetic testing for BRCA mutations is strongly recommended for individuals with a personal or family history of breast or ovarian cancer, as well as those who meet other criteria indicative of an inherited predisposition to cancer. By undergoing genetic testing, individuals can gain valuable insights into their potential genetic risk factors, enabling them to make informed decisions regarding preventive measures and tailored treatment plans.

The treatment of breast cancer often involves the inclusion of radiotherapy, which is typically administered after surgery. The primary objective of radiotherapy is to induce DNA damage in cancerous cells using ionizing radiation. This damage hinders cell division and growth, ultimately leading to tumor reduction or elimination [4]. However, despite its effectiveness, radiotherapy can also give rise to a range of side effects, both acute and late in nature [5]. This occurs because normal tissues near the tumor area may also be exposed to radiation, which can result in long-term damage. Therefore, it is crucial to carefully monitor patients undergoing radiotherapy to minimize the potential for adverse side effects.

Studies have indicated that BRCA1 and BRCA2 gene mutations may enhance the response of tumor cells to radiotherapy by increasing their sensitivity to ionizing radiation and DNA damage [6]. However, it is essential to acknowledge that these mutations can also influence the susceptibility of patients to complications associated with radiotherapy. This underscores the importance of carefully evaluating toxicity profiles in patients with BRCA mutations who undergo radiotherapy. By considering the potential risks and benefits of radiotherapy in this specific population, healthcare professionals can strive to optimize treatment outcomes while minimizing the potential for adverse side effects.

Highlight key points

- BRCA1 and BRCA2 gene mutations are critical genetic factors that significantly increase the risk of breast and ovarian cancer.
- Breast cancer patients carrying BRCA mutations may be more sensitive to radiotherapy toxicity.
- The detection of patients' BRCA mutations and the assessment of radiotherapy toxicity play a crucial role in making appropriate treatment decisions.
- Understanding the relationship between BRCA mutations and radiotherapy toxicity can contribute to the development of more personalized treatment approaches for breast cancer patients.
- More research on the relationship between BRCA mutations and radiotherapy toxicity is needed.

By assessing the acute side effects of radiotherapy in breast cancer patients with BRCA mutations, this study will significantly contribute to our understanding of the potential benefits and risks associated with radiotherapy in this specific patient population. The findings will assist healthcare professionals in making informed decisions regarding the use of radiotherapy in the treatment of breast cancer patients with BRCA mutations, allowing for the optimization of treatment strategies tailored to this group of patients. Furthermore, the study results may have broader implications for the development of new therapeutic approaches and the design of future clinical trials in breast cancer research. Ultimately, the study aims to advance our knowledge of treating breast cancer patients with BRCA mutations and contribute to the improvement of patient outcomes in this population.

MATERIALS AND METHODS

This is a multicenter retrospective cohort study that was presented as a project at the Radiation Therapy Oncology Group (RTOG) workshop. Data regarding the toxicity profiles of breast cancer patients with and without BRCA1/2 mutations between 2019–2022 have been collected from four different centers collaborated in this study.

The study includes a total of 73 breast cancer patients from four participating centers which provided complete requested clinical data with known BRCA1/2 mutation analyses. Also, acute radiation toxicity data collected during treatment were recorded. All patients had undergone surgery. Demographic information, clinical characteristics, and data collected

Table 1. Shows the RTOG acute toxicity grades for dysphagia and esophagitis during breast cancer treatment

Grade	Dysphagia	Esophagitis
0	None	None
1	Mild, discomfort	Mild, asymptomatic
2	Moderate, soft diet	Moderate, symptomatic, analgesic use
3	Severe, liquid diet	Severe, nasogastric tube feeding or hospitalization required
4	Parenteral nutrition only	Esophageal perforation, fistula, bleeding, or surgical intervention required
5	Death	Death

RTOG: Radiation therapy oncology group.

Table 2. Shows the RTOG acute toxicity grades for skin toxicity during cancer treatment

Grade	Skin toxicity
0	None
1	Faint erythema or dry desquamation
2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
4	Life-threatening consequences; full-thickness skin necrosis or ulceration of the dermis, spontaneous bleeding from involved site, skin graft indicated
5	Death

RTOG: Radiation therapy oncology group.

before and during treatment of the patients were recorded. The selection criteria encompassed individuals with a confirmed diagnosis of breast cancer, who had undergone radiotherapy treatment and BRCA1/2 mutation analysis. Furthermore, patients were included in the study based on the availability of accurate and complete data records, ensuring the robustness of the data collection process. It is important to note that patients with co-positive BRCA1 and BRCA2 mutations were not included in the study. In the analysis, patients with positive BRCA1 and/or BRCA2 mutations were collectively referred to as "BRCA positivity" to account for the evaluation of these mutations together. However, the specific consideration of BRCA1 and BRCA2 co-positivity was not taken into account in this study. During the radiotherapy treatment, the patients were closely monitored, and their acute toxicity was evaluated on a weekly basis. The evaluation of acute toxicity was done using the RTOG acute toxicity criteria, which is a widely recognized system used to assess the severity and frequency of acute tissue reactions resulting from radiotherapy [7]. The toxicity criteria are explained in Table 1 and Table 2.

Statistical Analysis

The statistical analysis was conducted using IBM SPSS Statistics for Windows, version 20 software (IBM Corp., Armonk, New York, USA). Categorical variables were presented as percentages, while continuous variables were reported as median values with corresponding ranges. The demographic and clinical characteristics of the patients were compared between the two groups using either the chi-square test or Fisher's exact test for categorical variables. Continuous variables were compared using the Mann-Whitney U test. Furthermore, the association between the incidence and severity of toxicity was assessed using Spearman correlation analysis. A significance level of $p<0.05$ was considered statistically significant for all analyses.

Table 3. Characteristics of included patients in our study

Variable	n=73 (%)	Variable	n=73 (%)
Age		RT dose technique	
≤40	37	Conventional	78.1
>40	63	Hypofractionated	21.9
Triple negative (TNBC)		RT field	
TNBC	26	Breast	30.1
Non-TNBC	74	Breast + lymphatic	17.8
Breast Surgery		Chest wall	6.8
BCS	50.7	Chest wall + lymphatic	45.2
MRM	37	Boost	
MRM reconstruction	12.3	Absent	50.7
Axillary surgery		Present	49.3
None	1.4	RT technique	
SLNB	46.6	Conformal	20.5
ALND	28.8	FIF IMRT	49.3
SLNB + ALND	23.3	Tomotherapy	30.1
T stage		RT hormonal therapy	
Tis + 1 + 2	86.3	Absent	69.9
T3 + 4	13.7	Present	30.1
N stage		Skin reaction	
N0.1	79.5	Absent	32.9
N2.3	20.5	Grade 1	41.1
Grade		Grade 2	17.8
Grade 1	6.8	Grade 3	8.2
Grade 2–3	93.2	Dysphagia	
Histology		Absent	84.9
Invasive ductal	91.8	Present (Grade 1)	15.1
Invasive lobular	8.2	BRCA	
ECE		Negative	50.7
Absent	89	BRCA1+	23.3
Present	11	BRCA2+	26
LVI		Metastasis	
Absent	79.5	Absent	95.9
Present	20.5	Present	4.1
Chemotherapy		Final status	
Absent	5.5	Alive	97.3
Present	94.5	Deceased	2.7

ALND: Axillary lymph node dissection; BCS: Breast-conserving surgery; BRCA1+: BRCA1 positive; BRCA2+: BRCA2 positive; ECE: Extracapsular extension; FIF IMRT: Field-in-field intensity-modulated radiotherapy; LVI: Lymphovascular invasion; MRM: Modified radical mastectomy; PNI: Perineural invasion; RT: Radiotherapy; SLNB: Sentinel lymph node biopsy; TNBC: Triple-negative breast cancer.

Ethics Committee Approval and Patient Consent

This study was carried out in compliance with the principles outlined in the Helsinki Declaration. The research protocol received approval from the ethics committee of Kartal Dr. Lutfi Kirdar Training and Research Hospital on December 6, 2019, with the reference number 2019/514/167/16. Informed consent was obtained from all participating patients, who provided their consent by signing the appropriate consent forms prior to their involvement in the study. To safeguard patient confidentiality, all data utilized in the study were anonymized.

RESULTS

Among the 73 patients included in this study, the median age was 43 years. Out of these patients, 17 were identified as BRCA1-positive (+), while 19 were identified as BRCA2-positive (+). Among the cases, 67 patients were diagnosed with invasive ductal carcinoma (IDC). Ten patients had T3-T4 stage tumors, and 15 patients had lymph node involvement classified as N2-3. In terms of radiotherapy, 57 patients received conventional doses, while 16 patients received hypofractionated doses. Radiotherapy was administered to the breast in 22 patients, to the breast and lymphatics in 13 patients, to the chest wall and lymphatics in 33 patients, and solely to the chest wall in 5 patients. Detailed patient characteristics are presented in Table 3.

During the follow-up period, metastases were detected in 3 patients, all of whom had invasive ductal carcinoma and tested negative for BRCA mutations. Among patients under the age of 40, those with BRCA mutations exhibited significantly higher rates of high node positivity, grade 2–3 tumors, and lymphovascular invasion compared to BRCA-negative patients ($p<0.001$). The median survival time was calculated to be 35.8 months. Grade 1 dysphagia was observed in 7 BRCA-negative patients and 4 BRCA-positive patients, with no significant difference between the two groups ($p=0.351$). Similarly, the occurrence of grade 2–3 skin reactions did not differ significantly between BRCA-negative patients (11 patients) and BRCA-positive patients (8 patients). Regarding the distribution of BRCA status, 37 patients (50.7%) were BRCA-negative, 17 patients (23.3%) were BRCA1 positive, and 19 patients (26%) were BRCA2 positive. Further details and a summary of these findings can be found in Table 4.

Although the distribution of BRCA-positive and BRCA-negative patient groups in this study is not perfectly balanced, the overall proportion of BRCA-negative patients is slightly higher than that of BRCA-positive patients. Furthermore, the distribution between BRCA1 and BRCA2 positive patient groups is relatively even. Table 2 provides a comprehensive comparison of demographic, clinical, and treatment factors between BRCA-negative and BRCA-positive breast cancer patients, with corresponding p-values indicating the presence of significant differences between the two groups for each factor. It is crucial to acknowledge that further research with larger sample sizes is necessary to ascertain whether this distribution accurately represents the entire population.

Table 4. Various demographic, clinical, and treatment factors between BRCA (-) and BRCA (+) breast cancer patients

Variable	BRCA (-) (n=37)	BRCA (+) (n=36)	p
Age			<0.001
≤40	16.2	58.3	
>40	83.8	41.7	
Smoking			0.854
No	70.3	72.2	
Yes	29.7	27.8	
TNBC			0.384
Non-TNBC	78.4	69.4	
TNBC	21.6	30.6	
T stage			0.467
Tis+1+2	89.2	83.3	
T3+4	10.8	16.7	
N stage			0.008
N0.1	91.9	66.7	
N2.3	8.1	33.3	
Grade			0.022
Grade 1	13.5	0	
Grade 2–3	86.5	100	
Histology			0.012
Invasive ductal	83.8	100	
Invasive lobular	16.2	0	
ECE			0.967
No	89.2	88.9	
Yes	10.8	11.1	
LVI		0.002	
No	91.9	61.1	
Yes	8.1	38.9	
PNI		0.818	
No	78.4	80.6	
Yes	21.6	19.4	
Chemotherapy			0.042
No	10.8	0	
Yes	89.2	100	
RT dose technique			0.078
Conventional	86.5	69.4	
Hypofractionated	13.5	30.6	
RT hormone therapy			0.665
No	67.6	72.2	
Yes	32.4	27.8	
Skin reaction grade			0.465
Gr0-1	70.3	77.8	
Gr2-3	29.7	22.2	
Desquamation			0.013
No	73	94.4	
Yes	27	5.6	
Dysphagia			0.058
No	91.9	100	
Yes	8.1	0	

T stage: Tumor stage; N Stage: Lymph node stage; ECE: Extracapsular extension; LVI: Lymphovascular invasion; PNI: Perineural invasion; RT: Radiotherapy; Gr: Grade.

DISCUSSION

The presence of BRCA mutations is a genetic factor that has been linked to an elevated risk of breast cancer and increased mortality rates [8]. The findings of our study align with previous research [9], indicating that BRCA-positive patients tend to be younger and exhibit higher rates of nodal involvement, tumor grade, and lymphovascular invasion. Despite variations in the administration of radiotherapy, including dosage and fractionation methods, our results demonstrate that these factors do not significantly influence the occurrence of toxicity between BRCA-positive and BRCA-negative patients. Therefore, careful consideration should be given to the application of radiotherapy in patients with a genetic predisposition [10].

Hypofractionated doses of radiotherapy are characterized by shorter treatment durations but higher doses administered per session. This approach has been proposed as a potential strategy to reduce side effects in certain cases compared to conventional fractionated radiotherapy [11]. However, the results of this study suggest that the use of hypofractionated doses did not have a significant impact on the occurrence of toxicity in both BRCA-positive and BRCA-negative patients.

In conclusion, the treatment of patients with BRCA mutations requires careful consideration of various factors. However, the findings of this study suggest that factors such as T stage, nodal involvement, the irradiated area, and the use of hypofractionated doses do not significantly influence the occurrence of toxicity between BRCA-positive and BRCA-negative patients. Therefore, it is essential to individualize radiotherapy approaches based on patient characteristics and long-term follow-up data [12].

Furthermore, this study revealed no significant difference in terms of dysphagia and skin reactions between the BRCA-positive and BRCA-negative patient groups, which is consistent with some existing studies in the literature [13]. To gain a more precise and comprehensive understanding of the factors influencing radiotherapy toxicity, larger-scale, multicenter studies are needed.

The primary objective of the current study was to explore the disparities in toxicity outcomes between BRCA-positive and BRCA-negative patients receiving radiotherapy, and our findings align with the existing literature. Our results demonstrated that all BRCA-positive patients had invasive ductal carcinoma and were under the age of 40, in contrast to BRCA-negative patients. These findings indicate that the presence of BRCA1 and BRCA2 mutations is associated with more aggressive breast cancer characteristics, including increased nodal involvement and earlier disease onset [14].

The present study found no significant difference in radiotherapy-related toxicity between the BRCA-negative and BRCA-positive patient groups. Similar findings have been reported in some studies in the literature [15], suggesting that radiotherapy is a safe and effective treatment option for patients with BRCA1 and BRCA2 mutations. However, it is important to acknowledge that a more robust understanding of the differences in toxicity can be attained through larger-scale, multicenter studies, which would provide more definitive evidence regarding the safety and efficacy of radiotherapy in this specific patient population. Furthermore, ongoing research efforts should focus on developing strategies to mitigate radiotherapy-related toxicity and exploring potential treatment modifications that could enhance outcomes for individuals with BRCA1 and BRCA2 mutations [16].

The findings from this study are in alignment with the existing literature, highlighting the consistent differences observed between BRCA-positive and BRCA-negative groups. The more aggressive clinical features observed in BRCA-positive patients emphasize the necessity for a cautious and tailored approach to their treatment. Individualizing radiotherapy applications based on patient characteristics and relying on comprehensive, long-term follow-up data are essential for making informed clinical decisions. By adopting such an approach, clinicians can strive to provide optimal care for patients with BRCA1 and BRCA2 mutations while minimizing the potential risks of treatment-related complications.

In this study, we acknowledge certain limitations that should be considered. One limitation is the challenge of finding and including an adequate number of both BRCA-positive and BRCA-negative patients, which may have impacted the statistical power and generalizability of our results due to the small sample size. However, despite these limitations, our study provides valuable insights into the significance of BRCA1 and BRCA2 gene mutations in breast cancer treatment. We have demonstrated the strong relationship between BRCA mutations and breast and ovarian cancer risk, as well as the potential increased sensitivity of BRCA-positive patients to radiotherapy toxicity. Our findings emphasize the importance of BRCA testing in making informed treatment decisions and the potential for more personalized approaches in breast cancer treatment. Nevertheless, further research is needed to explore the intricate relationship between BRCA mutations and radiotherapy toxicity in greater depth.

Conclusion

In summary, our study confirms the association of BRCA mutation with young age, nodal status, grade, and lymphovascular invasion. Additionally, it indicates that BRCA positivity does not impact treatment toxicity, and radiotherapy can be safely administered after BCS or mastectomy for BRCA-positive patients. These findings hold important implications for clinical practice, facilitating more personalized and effective approaches to the treatment of BRCA-positive patients.

Ethics Committee Approval: The Kartal Dr. Lutfi Kirdar Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 06.12.2019, number: 2019/514/167/16).

Authorship Contributions: Concept – SKG; Design – SKG; Supervision – SKG; Materials – SKG, HT, BBY, OKG, AA, IY, OA, BA, IBG; Data collection and/or processing – SKG, HT, BBY, OKG, AA, IY, OA, BA, IBG; Analysis and/or interpretation – SKG; Literature review – SKG; Writing – SKG; Critical review – SKG.

Conflict of Interest: No conflict of interest was declared by the authors.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424. [CrossRef]
2. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994;266:66–71. [CrossRef]
3. Roy R, Chun J, Powell SN. BRCA1 and BRCA2: different roles in a common pathway of genome protection. Nat Rev Cancer 2011;12:68–78. [CrossRef]
4. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005;104:1129–37. [CrossRef]
5. Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. Nat Rev Cancer 2011;11:239–53. [CrossRef]
6. Venkitaraman AR. Cancer suppression by the chromosome custodians, BRCA1 and BRCA2. Science 2014;343:1470–5. [CrossRef]
7. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6. [CrossRef]
8. Narod SA, Foulkes WD. BRCA1 and BRCA2: 1994 and beyond. Nat Rev Cancer 2004;4:665–76. [CrossRef]
9. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al; BRCA1 and BRCA2 Cohort Consortium. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317:2402–16. [CrossRef]
10. Telli ML, Gradishar WJ, Ward JH. NCCN Guidelines updates: breast cancer. J Natl Compr Canc Netw 2019;17:552–5.
11. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513–20. [CrossRef]
12. McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, et al; EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383:2127–35. [CrossRef]
13. Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010;376:235–44. [CrossRef]
14. Mavaddat N, Barrowdale D, Andrulis IL, Domchek SM, Eccles D, Nevanlinna H, et al; Consortium of Investigators of Modifiers of BRCA1/2. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomarkers Prev 2012;21:134–47. [CrossRef]
15. Pijpe A, Andrieu N, Easton DF, Kesminiene A, Cardis E, Noguès C, et al; GENEPSO; EMBRACE; HEBON. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). BMJ 2012;345:e5660. [CrossRef]
16. Bernstein JL, Thomas DC, Shore RE, Robson M, Boice JD Jr, Stovall M, et al; WECARE Study Collaborative Group. Contralateral breast cancer after radiotherapy among BRCA1 and BRCA2 mutation carriers: a WECARE study report. Eur J Cancer 2013;49:2979–85. [CrossRef]