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Review

The influence of breast cancer susceptibility genes on radiotherapy efficacy and adverse toxicities

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ABSTRACT

Breast cancer is a prevalent malignancy, with 5%–7% of cases hereditary, attributed to susceptibility gene mutations. Radiotherapy is vital in its treatment, but current guidelines lack consideration for genetic status. This review explored the relationships between breast cancer susceptibility genes such as BRCA1/2, CHEK2, ATM, etc. and radiotherapy efficacy and adverse toxicity. Findings showed that BRCA1/2 mutations do not change the therapeutic index of radiotherapy. The impact of CHEK2 mutations on radiotherapy remains uncertain. For ATM, radiotherapy may still be appropriate despite conflicting evidence on efficacy. PALB2 mutation carriers can receive standard adjuvant radiotherapy, while data on BARD1 and radiotherapy are scarce. RAD51 mutations may enhance radiotherapy efficacy with tissue-specific side effects. TP53 mutations are linked to poor radiotherapy outcomes and increased toxicity, suggesting caution in using radiotherapy for related patients. PTEN mutations may decrease tumor response to radiotherapy while increasing normal tissue toxicity. The roles NF1, CDH1, and STK11 play in breast cancer radiotherapy need to be further studied. In summary, breast cancer susceptibility genes exert heterogeneous effects on radiotherapy, underscoring the clinical significance of personalized treatment tailored to genetic profiles.

1. Introduction

Breast cancer is one of the most prevalent malignancies worldwide, ranking the first both in incidence rate and mortality rate among women.[1] Its development results from multifactorial interactions involving genetic predisposition, lifestyle factors, and environmental exposures. While the majority of breast cancers arise from acquired non-hereditary somatic mutations that accumulate over an individual's lifetime, 5%–7% of cases are classified as hereditary.[2–4] Population-based Cancer Risk Estimates Related to Susceptibility (CARRIERS) consortium studies have demonstrated that pathogenic mutations in susceptibility genes such as BRCA1, BRCA2, ATM, CHEK2, and PALB2 are correlated with an increased risk of breast cancer. Notably, specific pathogenic variants in genes like BARD1, RAD51C, and RAD51D show a stronger association with estrogen receptor (ER)-negative breast cancer compared to ER-positive subtypes in mutation carriers.[5]

Radiotherapy is a crucial treatment modality in the management of breast cancer, with approximately 50%–65% of patients requiring radiation therapy.[6–8] It reduces the 10-year risk of any first recurrence (local or distant) from 35.0% to 19.3% and decreases overall mortality by 10%–20%.[9,10] Current guidelines primarily determine radiotherapy indications based on disease stage, surgical approach, and patient-specific factors, without differentiating between patients with and without susceptibility gene mutations. However, emerging evidence has shown significant differences in treatment efficacy, adverse effects, and prognosis between these two groups.[3,11]

For instance, studies have shown that among unilateral breast cancer patients, the 10-year cumulative risk of contralateral breast cancer (CBC) is 15.5%–17.5% in BRCA1/2 germline mutation carriers, compared to 3.2% in non-carriers.[12] After breast-conserving surgery (BCS) with radiotherapy, this risk increases to 26% in mutation carriers but remains at 3% in non-carriers.[13] This disparity may be due to incidental radiation exposure to the contralateral breast during treatment.[14] Furthermore,

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