Alteration in estrogen receptor status in metachronous contralateral breast cancer among unilateral early breast cancer patients with *BRCA 1/2* mutations

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Introduction

- CBC risk is substantially higher in *BRCA1/2* carriers, with 20-year risks of 40% for *BRCA1* and 26% for *BRCA2*, compared with about 8% in non-carriers [1].
- ER status shapes prognosis and treatment choice; ER discordance between primary and metachronous CBC complicates adjuvant decisions [2].
- The impact of *BRCA1/2* mutations on ER status change in metachronous CBC is not well defined, limiting individualized planning [3].
- This study evaluates how *BRCA1/2* mutation status relates to ER alteration to support improved counseling and personalized management.

Methods and Materials

- **Study design:** Retrospective review of unilateral early breast cancer patients who underwent *BRCA1/2* testing and later developed metachronous CBC (≥2 years), treated between 2004–2020 at Samsung Medical Center, Seoul National University Hospital, and Gangnam Severance Hospital.
- **Patient groups:** *BRCA1* carriers, *BRCA2* carriers, *BRCA1 or BRCA2* carriers, and *BRCA1/2*-negative.
- **Exclusion criteria:** Distant metastasis at diagnosis, bilateral breast cancer at presentation, or CBC diagnosed <2 years after the primary cancer.
- **Statistical analysis:** ER status changes analyzed using Fisher's exact test and logistic regression.

Figure 1. Schematic diagram

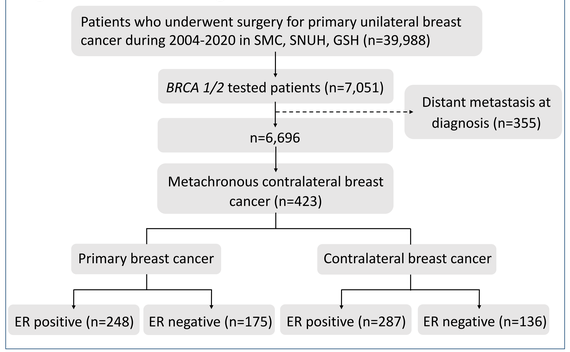
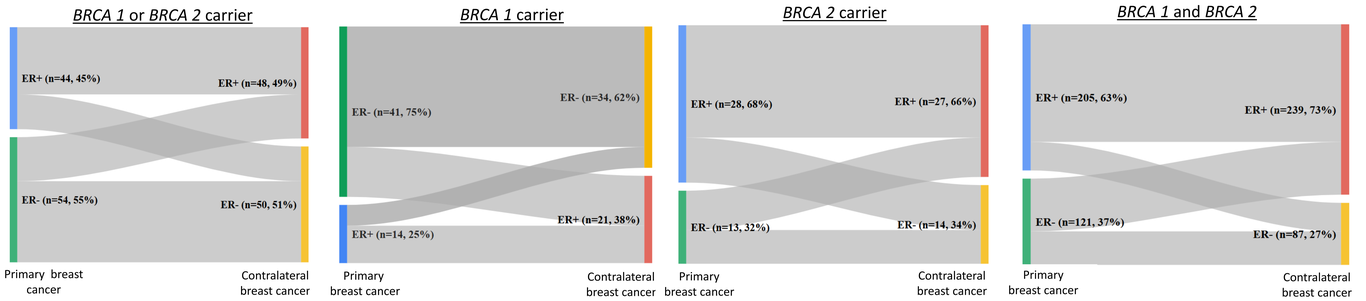


Figure 2. Sankey diagram of estrogen receptor alteration



Results

Table 1. Rate of estrogen receptor negative status in contralateral breast cancer based on *BRCA 1/2* status

	Primary breast cancer ER positive (n=248)				Primary breast cancer ER negative (n=175)			
	Total n	Number of ER negative CBC (%)	Odds ratio (95% CI)	*p-value*	Total n	Number of ER negative CBC (%)	Odds ratio (95% CI)	*p-value*
BRCA1 or BRCA2 carrier	43	14 (32.6%)	1.99 (0.96-4.11)	0.069	54	35 (64.8%)	2.9 (1.49-5.65)	0.002
BRCA1 carrier	14	5 (35.7%)	2.29 (0.73-7.21)	0.171	41	29 (70.7%)	3.8 (1.77-8.18)	< 0.001
BRCA2 carrier	28	8 (28.6%)	1.65 (0.68-4.02)	0.318	13	6 (46.2%)	1.35 (0.43-4.26)	0.767
BRCA1/2 negative	205	40 (19.5%)	(ref)		121	47 (38.8%)	(ref)	

Table 2. Change in adjuvant chemotherapy status from primary to contralateral breast cancer based on ER alteration

		CTx+ → CTx+	CTx+ → CTx-	CTx- → CTx+	CTx- → CTx-
Primary breast cancer ER positive (n = 248)	Total n	31	75	32	110
	Number of ER negative CBC (%)	10 (32.3%)	15 (20.0%)	7 (21.9%)	22 (20.0%)
Primary breast cancer ER negative (n = 175)	Total n	62	51	24	38
	Number of ER negative CBC (%)	41 (66.1%)	14 (27.5%)	15 (62.5%)	12 (31.6%)

[a]CTx+ and CTx– indicate the presence or absence of adjuvant chemotherapy, respectively; → indicates the change in adjuvant chemotherapy status from primary to contralateral breast cancer.

ER, estrogen receptor; CBC, contralateral breast cancer; CTx, chemotherapy.

Conclusion

- This multicenter analysis identified that *BRCA1* mutation carriers with ER negative primary breast cancer have a markedly higher likelihood of developing ER negative metachronous contralateral breast cancer.
- These findings highlight the clinical value of genetic counseling for high-risk patients.
- They also support considering risk-reducing strategies, including prophylactic mastectomy, for *BRCA1* carriers with ER negative disease.

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