

# Predominance of BRCA2 mutation and estrogen receptor-positive breast cancer among BRCA1/2 mutation carriers.

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**Research Article**

**Keywords:** BRCA1, BRCA2, breast cancer, estrogen receptor

**Posted Date:** February 11th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1301478/v1>

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# Abstract

**Background:** PARP inhibitor (PARPi) agents can improve progression-free survival of patients with breast cancer (BC) who carry a germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant (gBRCA1/2) in both the metastatic and adjuvant setting. Therefore, we need to redefine the criteria of women and tumor phenotype that should be tested for gBRCA1/2.

**Objective:** We studied the relative distribution of gBRCA1 and gBRCA2 in unselected populations of women with BC and in unaffected individuals. We also analyzed the proportion of estrogen receptor (ER)-positive (ER+) tumors in unselected BC patients with gBRCA1/2.

**Design:** We performed a meta-analysis of studies of unselected BC that analyzed the relative contribution of gBRCA1 versus gBRCA2 and ER+ tumors among gBRCA1/2 carriers. We then performed a meta-analysis of gBRCA1/2 carriage in unaffected individuals, from genome-wide population studies, the gnomAD databank, and case-control studies.

**Results:** The *BRCA2* gene was involved in 54% of BC in unselected patients with gBRCA1/2 (n=108,699) and 59% of unaffected individuals (n=238,973) as compared with 38% of gBRCA1/2 family cohorts (n=29,700). The meta-analysis showed that 1.66% (95% CI 1.08-2.54) and 1.71% (95% CI 1.33-2.2) of unselected BC patients carried a gBRCA1 and gBRCA2, respectively. In unaffected individuals, the frequency of heterozygosity for gBRCA1 and gBRCA2 was estimated at 1/434 and 1/288, respectively. Nearly 0.5% of unaffected individuals in the studied populations carried a gBRCA1/2. Overall, 58% of breast tumors occurring in women carrying a gBRCA1/2 were ER+ (n=86,870).

**Conclusion:** This meta-analysis showed that gBRCA2 carriage is predominant in unselected BC and in unaffected individuals. ER+ tumors among women with gBRCA1/2-related BC is predominant and has been underestimated. Because PARPi agents improve progression-free survival with ER+ gBRCA1/2 BC in both the adjuvant and metastatic setting, BC should be considered regardless of ER status for BRCA1/2 screening for therapeutic purposes.

## Key Points

- This metanalysis shows that in unselected breast cancer (BC) patients, 3.4% have a *BRCA1* or *BRCA2* germline pathogenic or likely pathogenic variant (gBRCA1/2), with gBRCA2 more frequent than gBRCA1.
- In unaffected individuals, gBRCA2 is more frequent than gBRCA1. The frequency of heterozygosity is estimated at 1/288 and 1/434, respectively.
- In unselected BC patients with gBRCA1/2, more than half of tumors are estrogen receptor-positive.

## Introduction

Poly (ADP-ribose) polymerase inhibitor (PARPi) agents have been found effective for treating high-risk and metastatic breast cancer (BC) related to germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant (gBRCA1/2, <sup>1-4</sup>). Therefore, we need to identify which BC patient and which tumor type could benefit from genetic screening.

In 70% of cases, BC related to gBRCA1 has an estrogen receptor negative (ER-) phenotype (<sup>5</sup>). Also, from the largest available families cohorts, among identified families with gBRCA1/2, gBRCA1 is the predominant molecular form, implicated in 62% of 29,700 identified families (<sup>6</sup>). Because of these features and other therapeutic options available for ER+ BC, screening for gBRCA1/2 in ER+ BC has not been prioritized, and most attention has been paid to genetic testing of ER- tumors for theragnostic purposes.

However, in patients with metastatic hormone-resistant ER+ BC, PARPi agents have increased both progression-free survival and quality of life as compared with chemotherapy (<sup>2-4</sup>; Fig. 1 supplement). In the adjuvant setting, progression-free survival was also improved in high-risk ER+ BC patients receiving olaparib (<sup>1</sup>). Therefore, the question of using PARPi agents in ER+ gBRCA1/2 BC is of major clinical relevance.

We performed a meta-analysis of available cohorts of unselected BC in the literature addressing the relative contribution of gBRCA1 and gBRCA2 and ER+ tumors in gBRCA1/2 patients overall. We then evaluated the prevalence of gBRCA1/2 carriage in unaffected individuals by a meta-analysis of genome-wide population studies, the gnomAD sequencing aggregation database and control groups of BC case-control studies.

## Patients And Methods

The search strategy used variations and Boolean connectors of key terms and is given in supplementary data. We retained only unselected BC studies analyzing gBRCA1/2. To avoid potential selection bias, we thus excluded studies of BC women undergoing genetic testing under specific criteria such as family history, young age and screening for therapeutic trials with potential enrichment for triple-negative BC, studies of metastatic cancer, and studies of BC in specific ethnicities (e.g., French Canadian or Ashkenazi Jewish heritage). Studies of somatic mutation were retained only if gBRCA1/2 data were available.

We used Comprehensive Meta-Analysis software to estimate the pooled values of the parameters as well as their 95% confidence intervals (CIs). We estimated heterogeneity by using the Cochran Q test with the point estimate  $I^2$ . If heterogeneity was present (Q statistic significant at 5%), we took it into account by using a random-effects model. Publication bias was visually estimated with funnel plots and quantified with the Egger test and the “trim-and-fill” method of Duval and Tweedie. Details on the meta-analyses are given in the supplement. gBRCA1/2 carriage was explored in the exome cohort (n=125,747) of gnomAD v2.1.1 (<sup>7</sup>). gBRCA1 and gBRCA2 were identified in the ClinVar database (<sup>8</sup>, August 2021 release).

## Results

### ***gBRCA1 and gBRCA2 carriage in unselected BC patients***

Meta-analysis of unselected BC series showed that 3.4% of BC occurred in patients with gBRCA1/2 (n = 108,699, 95% CI 2.5-4.7, Figure 1a, supplement). gBRCA1 and gBRCA2 status accounted for 1.66% (95% CI 1.08-2.54) and 1.71% (95% CI 1.33-2.2) of BC (Figure 1b, 1c, supplement). Among BC patients with gBRCA1/2, 46% (n=1,496) carried a gBRCA1 and 54% (n=1,776) a gBRCA2 ( supplement) .

### ***Frequency of gBRCAm carriers in unaffected individuals***

We performed a meta-analysis of available data from genome-wide population studies and the gnomAD databank and for unaffected individuals of case-control studies of genetic testing in BC (<sup>9, 10</sup>). The frequency of gBRCA1 and gBRCA2 was 0.18% (95% CI 0.12-0.25) and 0.32% (95% CI 0.27-0.38), respectively (supplement). Carriage of gBRCA1/2 in the general population was 0.5% (95% CI 0.4-0.6) (Figure 2a, supplement). The frequency of heterozygous gBRCA1 and gBRCA2 was estimated at 1/434 and 1/288, respectively (supplement). The *BRCA2* gene accounted for 59% of total gBRCA1/2 carriers in the general population (Figure 2b, supplement).

### ***Frequency of ER+ tumors in unselected BC patients with gBRCAm***

The meta-analysis showed that 2.5% of patients with ER+ tumors (95% CI 1.5-4.1, Figure 3a) and 5.7% with ER- tumors (95% CI 5.1-6.2) carried a gBRCA1/2 (Figure 3b, supplement). Among gBRCA1 carriers, 38% (457/1218) had ER+ tumors, whereas among gBRCA2 carriers, 75% (1085/1453) had ER+ tumors. Overall, 58% (1542/2671) of breast tumors with gBRCA1/2 carriage were ER+ (n=86,870; Figure 3c; supplement).

## Discussion

Our overall finding of a higher gBRCA2/gBRCA1 ratio in the BC population agrees with the most recent and largest studies of BRCA screening of unselected BC (<sup>9, 10</sup>). Because most BRCA1 cases of BC are ER- and most BRCA2 cases are ER+ (5), the frequency of ER+ tumors among the overall BC BRCA patients depends on the relative contribution of gBRCA2 incidence in unselected BC. In several published reports describing the frequency of gBRCA in BC series, the bias of selection on family criteria but also on age or triple-negative phenotype may have underestimated the frequency of gBRCA2.

Our finding of a predominant prevalence of gBRCA2 versus gBRCA1 in the general population also agrees with recent unselected population-genomic screening showing a higher-than-expected prevalence of

gBRCA2 versus gBRCA1 in individuals of predominant European ancestry (<sup>11,12</sup>). Further studies in other populations are needed to precise the prevalence of gBRCA1/2 by ancestry.

The higher incidence of gBRCA1 found in the largest international cohort of identified gBRCA1/2 carriers (CIMBA <sup>6</sup>) could be due to lack of penetrance of BC with gBRCA2 carriage. However, the prospective study by Kuckenbacher et al.<sup>(13)</sup> does not support this hypothesis because the cumulative lifetime risk is similar (cumulative BC risk to age 80 years: 72% and 69% for BRCA1 and BRCA2 carriers, respectively). More likely, because the occurrence of BC in gBRCA2 women is time-delayed as compared with gBRCA1 women, the older age of women at diagnosis could result in lack of testing for gBRCA2 carriage. Another potential explanation is that the higher incidence of ovarian cancer with gBRCA1 versus gBRCA2 carriage (cumulative risk to age 80 years is 44% and 17%, respectively) could also lead to more active BRCA testing in women with this criterion. Finally, the well-known triple-negative phenotype of BRCA1 tumors could also result in more referral for genetic testing for BRCA1 versus BRCA2 BC patients.

Our data strongly suggest that the frequency of gBRCA2 carriage and ER+ tumors among women with BC is underestimated because classical genetic testing criteria are often missing in gBRCA2 families. In a previous review of the literature, we found that 50% of overall BRCA1/2 BC cases are missed when genetic testing criteria are used (<sup>14</sup>). Accordingly, the study by Li et al. (<sup>15</sup>) showed that a higher percentage of BRCA2 versus BRCA1 carriage (81% vs 46%) was missed by clinical screening. In the study of unselected BC cases by Beitsch et al.<sup>(16)</sup>, which excluded patients who had previously been tested, 86% of the gBRCAm cases were gBRCA2.

This study shows that more than half of BC cases occurring in women with gBRCA1/2 are in fact ER+. It also shows that the frequency of gBRCA2 carriage is higher than expected in both unselected BC patients and in the general population. Because of the important benefit of identifying gBRCA1/2 carriage for PARPi treatment and prevention, ER+ BC should be considered fully for BRCA screening.

## Declarations

## Funding:

This work was commissioned and supported by the French Society of Predictive and Personalized medicine an independent nonprofit learned society.

## Acknowledgements:

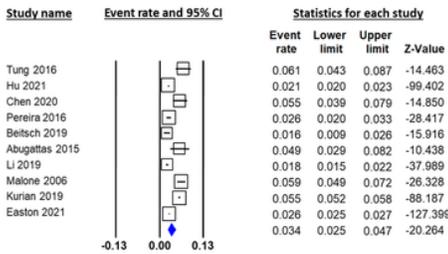
The authors acknowledge the contribution of patient advocacy from “BRCA France” and “*Sapins de Noël des créateurs*” associations. Dr. Pujol discloses attending Advisory Board Membership meetings for AstraZeneca, Pfizer, Roche, Novartis and Exact Science. Dr Hughes discloses honoraria from Hologic Inc, Myriad Genetics and CRA Health LLC.

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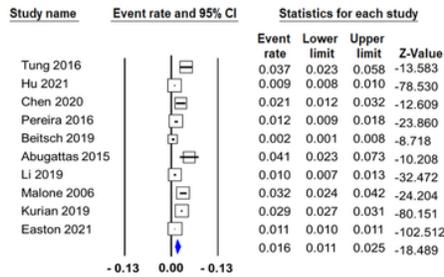
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# Figures

1a. gBRCA1/2



1b. gBRCA1



1c. gBRCA2

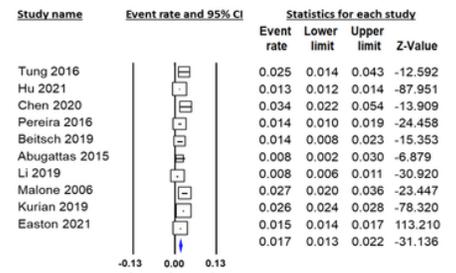
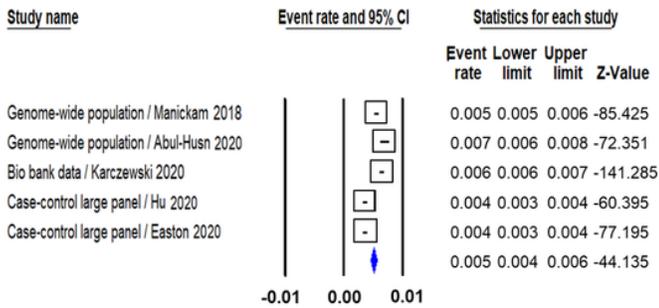


Figure 1

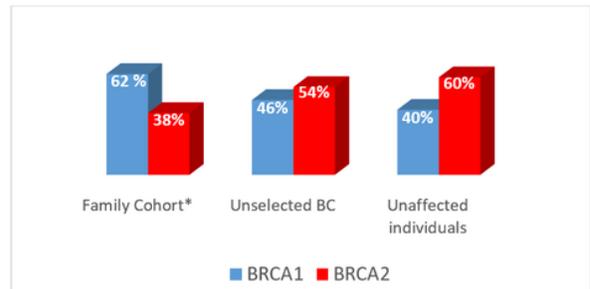
## Meta-analysis of gBRCA1 and gBRCA2 in unselected breast cancer

1a. gBRCA1/2

2a. gBRCA1/2 carriers in unaffected individuals



2b. Comparison of gBRCA1 and gBRCA2 frequency in family cohort, unselected BC and unaffected individuals

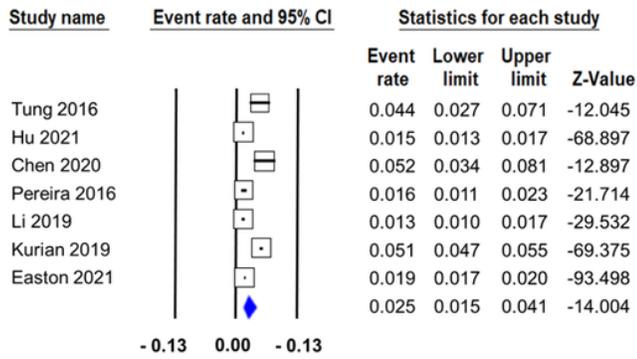


\*Family cohort : from 29,700 gBRCA1/2 families from the CIMBA cohort (6)

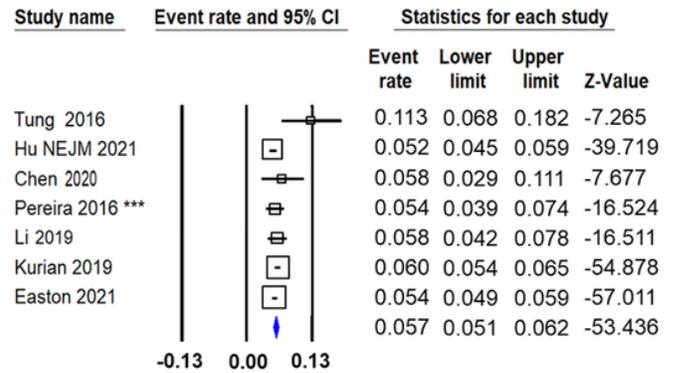
Figure 2

## Meta-analysis of gBRCA1 and gBRCA2 in unaffected individuals

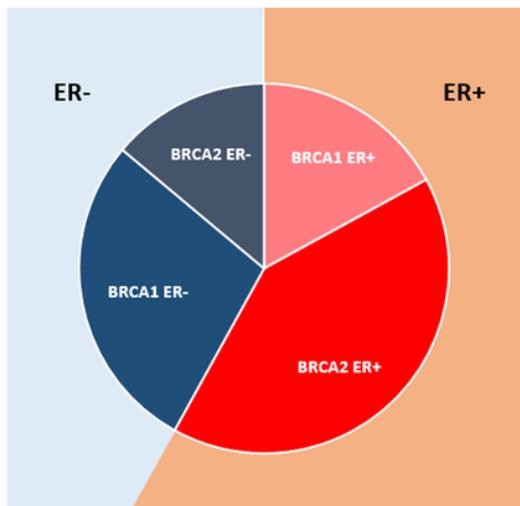
**3a. gBRCA1/2 carriers in ER+ unselected BC**



**3b. gBRCA1/2 carriers in ER- unselected BC**



**3c. Frequency of ER+ and ER- tumors in unselected BC patients with gBRCA1/2**



**Figure 3**

**Meta-analysis of gBRCA1 and gBRCA2 in unselected BC by ER status**

**3a. gBRCA1/2 carriers in ER+ unselected BC**