Supplemental data

Summary

Figure S1. Subgroup analysis of progression-free survival in ER+ gBRCA breast cancer treated with a PARPi in a phase III trial

Metastatic setting

Olympiad n = 152 — 0.82 (95%CI 0.55-1.26)

Embraca n = 241 — 0.47 (95%CI 0.32-0.71)

Brocade 3 n= 266 — 0.69 (95%CI 0.52-0.92)

Adjuvant

Olympiad n = 325 — 0.70 (95%CI 0.38-1.27)
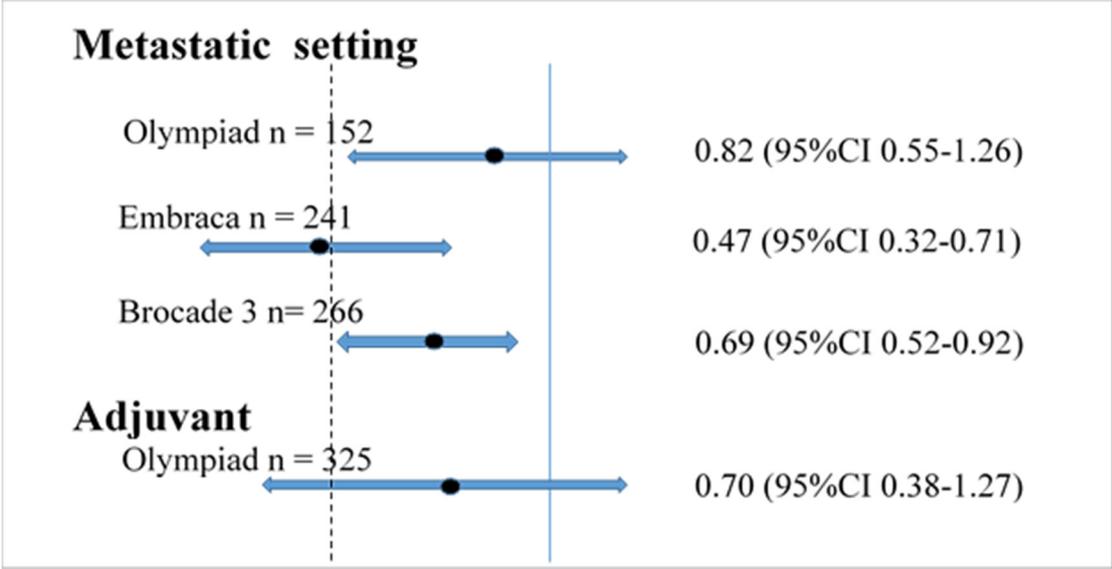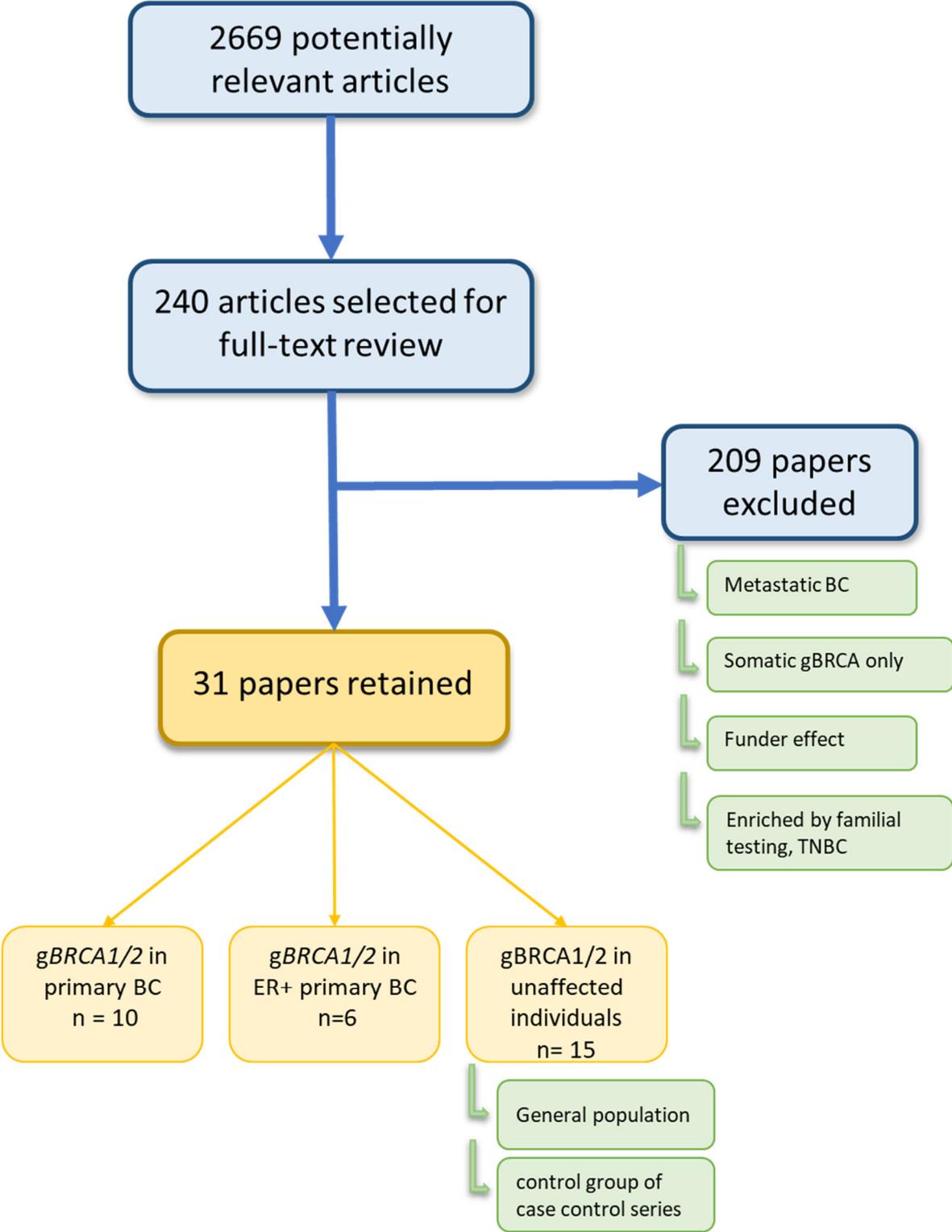
Figure S2. Quoron flowchart

BC, breast cancer

Table S1: Frequency of gBRCA1 and gBRCA2 carriers among unselected breast cancer patients

Study	Breast cancer n	BRCA1 n	BRCA2 n
Tung 2016	488	18	12
Hu 2021	32,247	275	417
Chen 2020	524	11	18
Pereira 2016*	2433	30	33
Beitsch 2019	959	2	13
Abugattas 2015	266	11	2
Li 2019	5,099	50	42
Malone 2006	1,628	52	44
Kurian 2019	18,522	536	477
Dorling 2021	48,826	515	754
Total	**108,699**	**1,496 (46%)**	**1,776 (54%)**

* from tumor mutation study;

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Pathogenic Variants in a Large, Unselected Breast Cancer Cohort. *Int. J. Cancer* **2019**, *144*, 1195–1204.

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Table S2. Frequency of gBRCA1 and gBRCA2 carriers by ER status among unselected breast cancer patients

Study	Country/ Ethnicities	ER+ *	BRCA1/ ER+ n	BRCA2/ ER+ n	ER-	BRCA1/ ER-	BRCA2/ ER-
Tung 2016	United States: Boston, MA / 7.8% Ashkenazi Jewish 81.4% non-Ashkenazi white	364	5	11	124	13	1
Hu 2021	United States: 4% Asian, 12.3% Non-Hispanic black, 3.2% Hispanic, 78.9% Non-Hispanic white, 1.7% Other	18,428	73	201	3805	114	82
Chen 2020	South China	363	4	15	139	7	1
Li 2019	Sweden : Stockholm	3637	17	30	643	30	7
Kurian 2019	United States: California and Georgia	11642	227	365	7060	309	112
Dorling 2021	16 European countries, 5 Asian countries, 3 American countries 2 Oceania countries	*30466*	120	446	7766	269	149
TOTAL		**66680**	**457**	**1085**	**20190**	**761**	**368**

* including ER+PR- and ER+HER2+++ tumors;

Table S3. Frequency of gBRCA carriers among unaffected individuals

Type of study	Type of analysis	n	BRCA1	BRCA2	Reference
Genome-wide population					
	exome	50,726	95 (36%)	172 (64%)	Manickam 2018
	exome	30,223	86 (39%)	131 (61%)	Abul-Husn 2020
Bio bank data					
	exome and whole genome	125,747	332 (43%)	447 (57%)	gnomAD Karczewski2020
Case–control					
	large panel	32,544	37(32%)	78 (68%)	Hu2020 (CARRIERS)
	large panel	50,703	58 (30%)	135 (70%)	Dorling 2021
Total		**238,973 (1/173)**	**550 (40%) (1/434)**	**828 (60%) (1/288)**	

*https://gnomad.broadinstitute.org;

Table S4. Frequency of gBRCA carriers in gnomAD* exome sequencing database**

	Count		BRCA ratio		Prevalence			BRCA type prevalence difference
	BRCA1	BRCA2	BRCA1	BRCA2	BRCA1/2	BRCA1	BRCA2	P value***
Complete cohort (n=125,747)								
	332	447	43%	57%	0.62%	0.26%	0.36%	2*10-5
Femalecohort (n=57,786)								
	152	219	41%	59%	0.64%	0.26%	0.38%	3*10-4
Male cohort (n=67,21961)								
	180	228	44%	56%	0.60%	0.26%	0.34%	1*10-2

*v2.1.12; **using ClinVar August 2021. This database contains 7268 constitutive samples of individuals with cancer (5.7% of total, 3332 males and 3936 females). ***µFisher's exact test

References
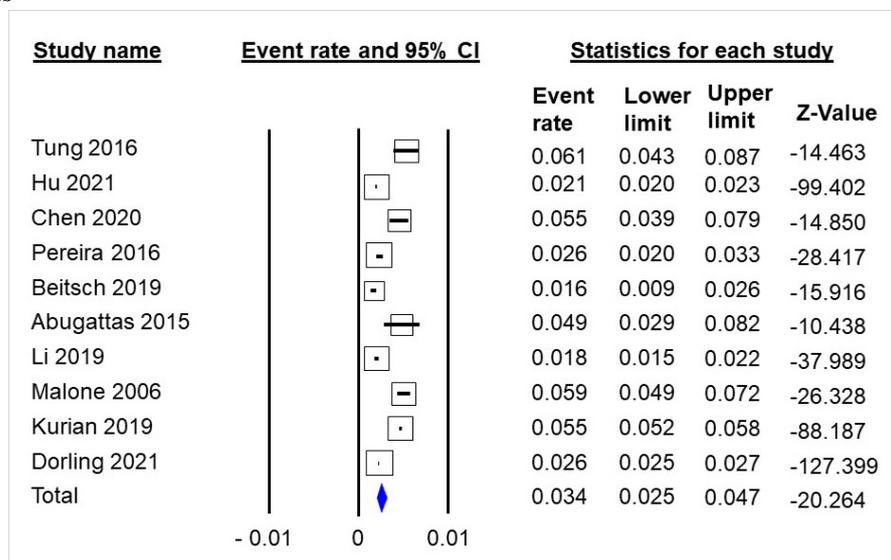
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Table S5. Meta-analysis of gBRCA carriers among unselected breast cancer patients

Data

	Study Name	Events	Sample size	Event rate	Logitevent rate	Std Err
1	Tung 2016	30	488	0.061	-2.726	**0.188**
2	Hu 2021	692	32247	0.021	-3.820	**0.038**
3	Chen 2020	29	524	0.055	-2.837	**0.191**
4	Pereira 2016	63	2433	0.026	-3.628	**0.128**
5	Beitsch 2019	15	959	0.016	-4.142	**0.260**
6	Abugattas 2015	13	266	0.049	-2.968	**0.284**
7	Li 2019	92	5099	0.018	-3.997	**0.105**
8	Malone 2006	96	1628	0.059	-2.770	**0.105**
9	Kurian 2019	1013	18522	0.055	-2.850	**0.032**
10	Dorling 2021	1269	48826	0.026	-3.624	**0.028**

Results
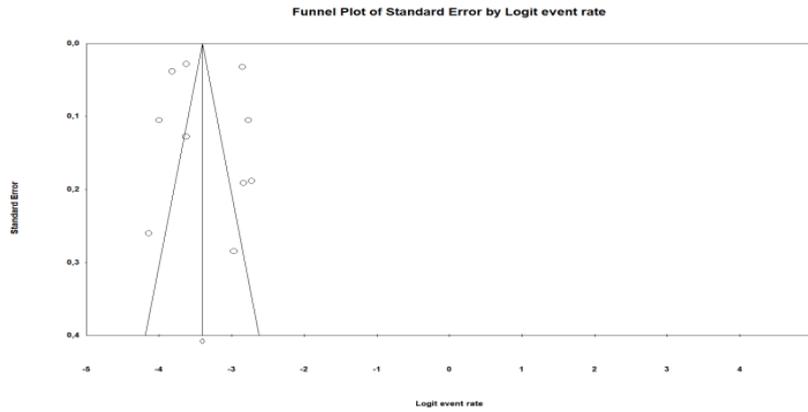
| Study name	Event rate	Lower limit	Upper limit	Z-Value
Tung 2016	0.061	0.043	0.087	-14.463
Hu 2021	0.021	0.020	0.023	-99.402
Chen 2020	0.055	0.039	0.079	-14.850
Pereira 2016	0.026	0.020	0.033	-28.417
Beitsch 2019	0.016	0.009	0.026	-15.916
Abugattas 2015	0.049	0.029	0.082	-10.438
Li 2019	0.018	0.015	0.022	-37.989
Malone 2006	0.059	0.049	0.072	-26.328
Kurian 2019	0.055	0.052	0.058	-88.187
Dorling 2021	0.026	0.025	0.027	-127.399
Total	0.034	0.025	0.047	-20.264

Heterogeneity analysis:
I2 statistic (%)= 94.7, Phet =0.000 (I2>40% p<0.05) ➔ heterogeneity ➔ random-effects model
Forest plot: gBRCA=3.4%, 95% CI 2.5-4.7

Selection Bias

			Random	
N studies	Eggers Test	Duval &Tweedie (DT) Method	DT Event rate	DT event rate IC 95%
10	0.88	0	0.034	0.025 – 0.047

Funnel plot log gBRCA

Funnel Plot of Standard Error by Logit event rate
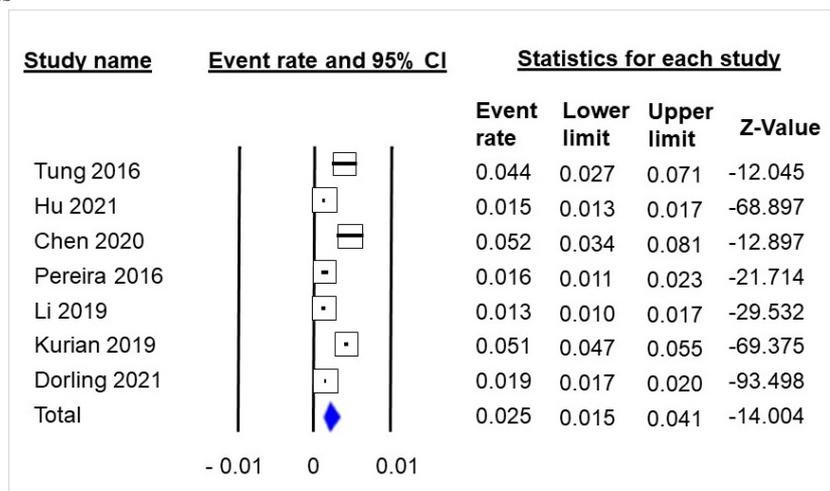
Results based on 10 studies retained (open circles). No additional studies identified by "trim and fill" (Egger et al, 1997; Duval & Tweedie, 2000). Egger's test does not show publication bias (p=0.88).

Table S6. Meta-analysis of gBRCA carriers among ER+ breast cancer patients

Data

	Study Name	Events	Sample size	Event rate	Logitevent rate	Std Err
1	Tung 2016	16	364	0.044	-3.080	**0.256**
2	Hu 2021	274	18428	0.015	-4.194	**0.061**
3	Chen 2020	19	363	0.052	-2.896	**0.236**
4	Pereira 2016	28	1780	0.016	-4.136	**0.190**
5	Li 2019	47	3637	0.013	-4.336	**0.147**
6	Kurian 2019	592	11642	0.051	-2.927	**0.042**
7	Dorling 2021	566	30466	0.019	-3.967	**0.042**

Results

Study name	Event rate and 95% CI	Event rate	Lower limit	Upper limit	Z-Value
Tung 2016		0.044	0.027	0.071	-12.045
Hu 2021		0.015	0.013	0.017	-68.897
Chen 2020		0.052	0.034	0.081	-12.897
Pereira 2016		0.016	0.011	0.023	-21.714
Li 2019		0.013	0.010	0.017	-29.532
Kurian 2019		0.051	0.047	0.055	-69.375
Dorling 2021		0.019	0.017	0.020	-93.498
Total		0.025	0.015	0.041	-14.004

Heterogeneity analysis:
I^2 statistic (%)= 98.7, P_{het} =0.000 (I^2>40% p<0.05) ➔ heterogeneity ➔ random-effects model
Forest plot:
gBRCA=2.5%, 95% CI 1.5-4.1
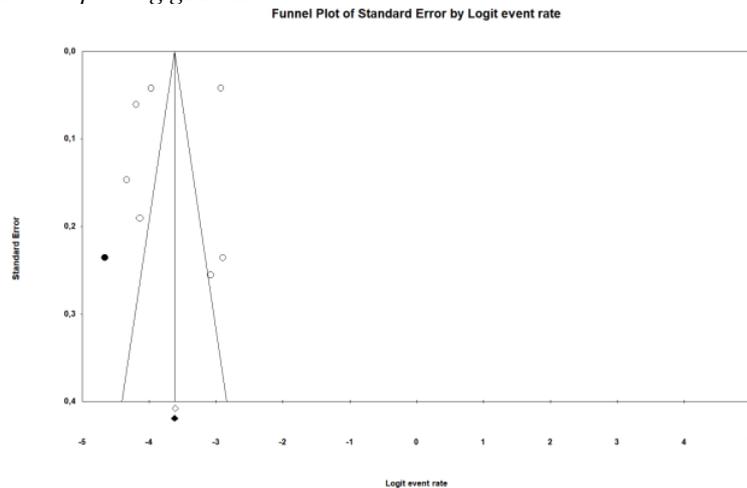
Selection Bias

			Adjusted value : Random	
N studies	Eggers Test	Duval &Tweedie (DT) Method	DT Event rate	DT event rate IC 95%
7	0.77	1	0.022	0.014 – 0.036

Funnel plot log gBRCA
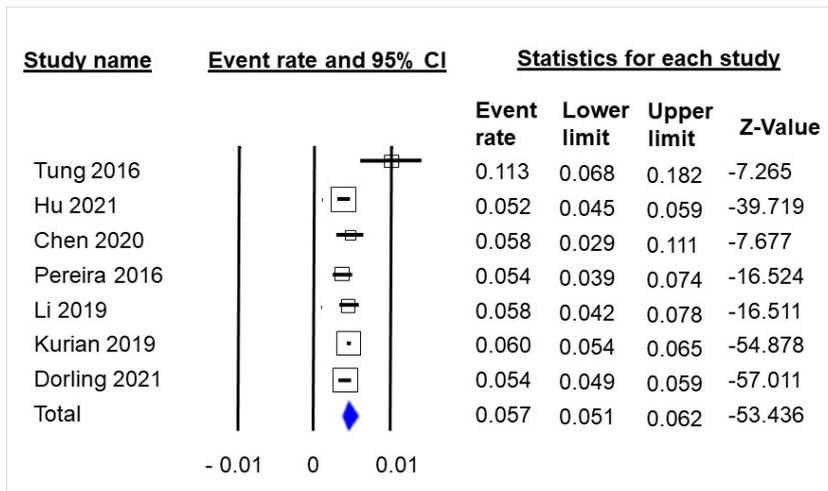
Results based on 7 studies retained (open circles). 1 additional study identified by "trim and fill" analysis (Egger et al, 1997; Duval & Tweedie, 2000). Egger's test does not show publication bias (p=0.77).

Table S7. Meta-analysis of gBRCA carriers among ER- breast cancer patients

Data

	Study Name	Events	Sample size	Event rate	Logitevent rate	Std Err
1	Tung 2016	14	124	0.113	-2.061	**0.284**
2	Hu 2021	196	3805	0.052	-2.913	**0.073**
3	Chen 2020	8	139	0.058	-2.796	**0.364**
4	Pereira 2016	35	653	0.054	-2.871	**0.174**
5	Li 2019	37	643	0.058	-2.796	**0.169**
6	Kurian 2019	421	7060	0.060	-2.758	**0.050**
7	Dorling 2021	418	7766	0.054	-2.867	**0.050**

Results

Study name	Event rate and 95% CI	Event rate	Lower limit	Upper limit	Z-Value
Tung 2016		0.113	0.068	0.182	-7.265
Hu 2021		0.052	0.045	0.059	-39.719
Chen 2020		0.058	0.029	0.111	-7.677
Pereira 2016		0.054	0.039	0.074	-16.524
Li 2019		0.058	0.042	0.078	-16.511
Kurian 2019		0.060	0.054	0.065	-54.878
Dorling 2021		0.054	0.049	0.059	-57.011
Total		0.057	0.051	0.062	-53.436

Heterogeneity analysis:

I^2 statistic (%)= 46.6, P_{het} =0.0810 ➔ heterogeneity ➔ random-effects model
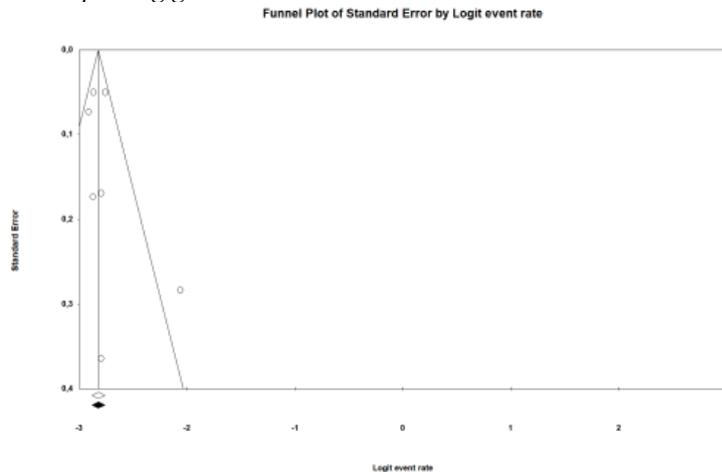
Forest plot:

gBRCA=5.7%, 95% CI 5.1-6.2

Selection Bias

|			Adjusted value : Random	
N studies	Eggers Test	Duval &Tweedie (DT) Method	DT Event rate	DT event rate IC 95%
7	0.43	0	0.057	0.051 – 0.062

Funnel plot log gBRCA
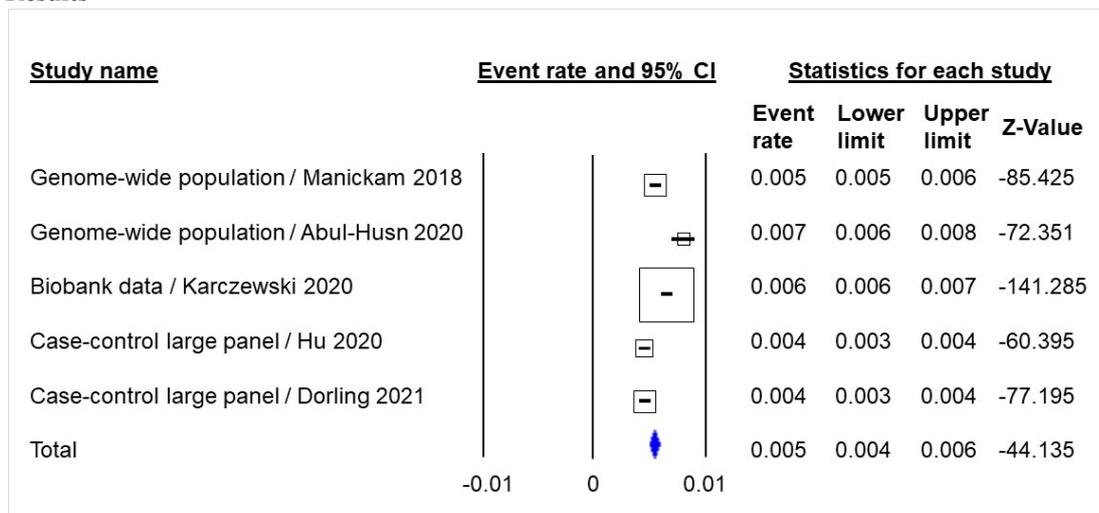
Results based on 7 studies retained (open circles). 1 additional study identified by "trim and fill" analysis (Egger et al, 1997; Duval & Tweedie, 2000). Egger's test does not show publication bias (p=0.43).

Table S8. Meta-analysis of gBRCA carriers among unaffected individuals

Data

	Study Name	Events	Sample size	Event rate	Logitevent rate	Std Err
1	Genome-wide population / Manickam	267	50726	0.005	-5.242	**0.061**
2	Genome-wide population / Abul-Husn	217	30223	0.007	-4.929	**0.068**
3	Bio bank data / Karczewski 2020	779	125747	0.006	-5.078	**0.036**
4	Case-control large panel / Hu 2021	115	32544	0.004	-5.642	**0.093**
5	Case-control large panel / Dorling 2021	193	50703	0.004	-5.567	**0.072**

Results

Study name	Event rate and 95% CI	Event rate	Lower limit	Upper limit	Z-Value
Genome-wide population / Manickam 2018		0.005	0.005	0.006	-85.425
Genome-wide population / Abul-Husn 2020		0.007	0.006	0.008	-72.351
Biobank data / Karczewski 2020		0.006	0.006	0.007	-141.285
Case-control large panel / Hu 2020		0.004	0.003	0.004	-60.395
Case-control large panel / Dorling 2021		0.004	0.003	0.004	-77.195
Total		0.005	0.004	0.006	-44.135

Heterogeneity analysis:
I^2 statistic (%)= 94.7, P_{het} =0.000 ➔ heterogeneity ➔ random-effects model
Forest plot:
gBRCA=0.5%, 95% CI 0.4-0.6
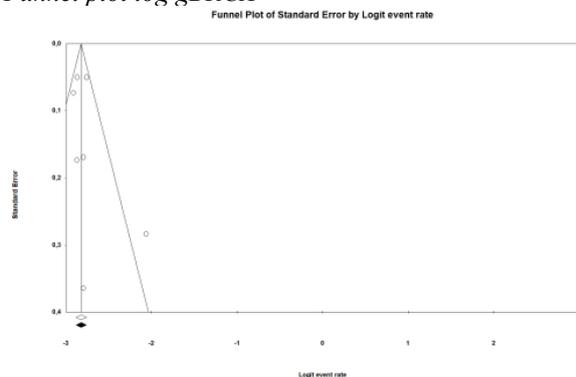
Selection Bias

|			Adjusted value : Random	
N studies	Eggers Test	Duval &Tweedie (DT) Method	DT Event rate	DT event rate IC 95%
5	0.23	0	0.005	0.004 – 0.006

Funnel plot log gBRCA
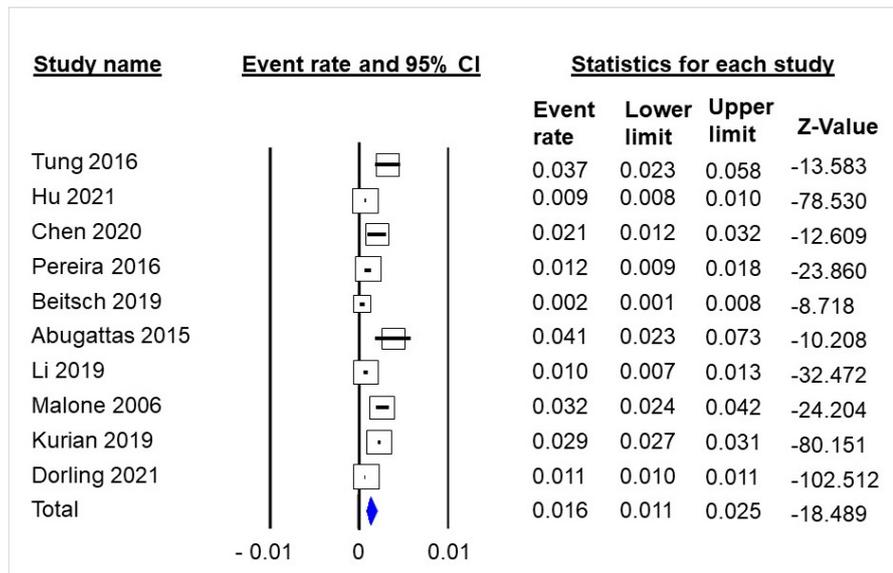
Results based on 5 studies or databases retained (open circles). No additional study identified by "trim and fill" analysis (Egger et al, 1997; Duval & Tweedie, 2000). Egger's test does not show publication bias (p=0.23).

Table S9. Meta-analysis of gBRCA1 carriers among unselected breast cancer patients

Data

	Study Name	Events	Sample size	Event rate	Logitevent rate	Std Err
1	Tung 2016	18	488	0.037	-3.262	**0.240**
2	Hu 2021	275	32247	0.009	-4.756	**0.061**
3	Chen 2020	11	524	0.021	-3.842	**0.305**
4	Pereira 2016	30	2433	0.012	-4.383	**0.184**
5	Beitsch 2019	2	959	0.002	-6.171	**0.708**
6	Abugattas 2015	11	266	0.041	-3.143	**0.308**
7	Li 2019	50	5099	0.010	-4.615	**0.142**
8	Malone 2006	52	1628	0.032	-3.411	**0.141**
9	Kurian 2019	536	18522	0.029	-3.513	**0.044**
10	Dorling 2021	515	48826	0.011	-4.541	**0.044**

Results

Heterogeneity analysis:
I^2 statistic (%)= 98, P_{het} 0.000 (I^2>40% p<0.05) ➔ heterogeneity ➔ random-effects model
Forest plot:
    gBRCA1=1.66%, 95% CI 1.08-2.54
Selection Bias
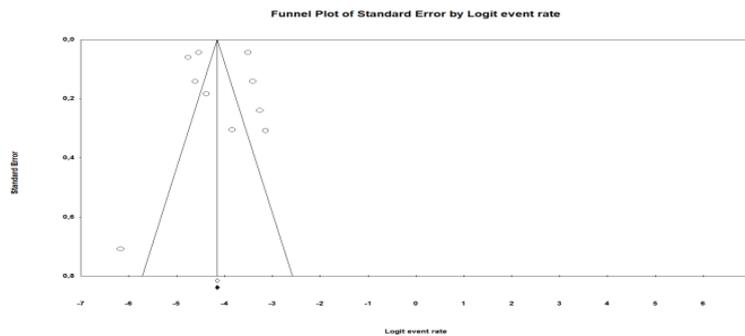
			Random	
N studies	Eggers Test	Duval &Tweedie (DT) Method	DT Event rate	DT event rate IC 95%
10	0.92	0	0.0166	0.0108 – 0.0254

Funnel plot log gBRCA1
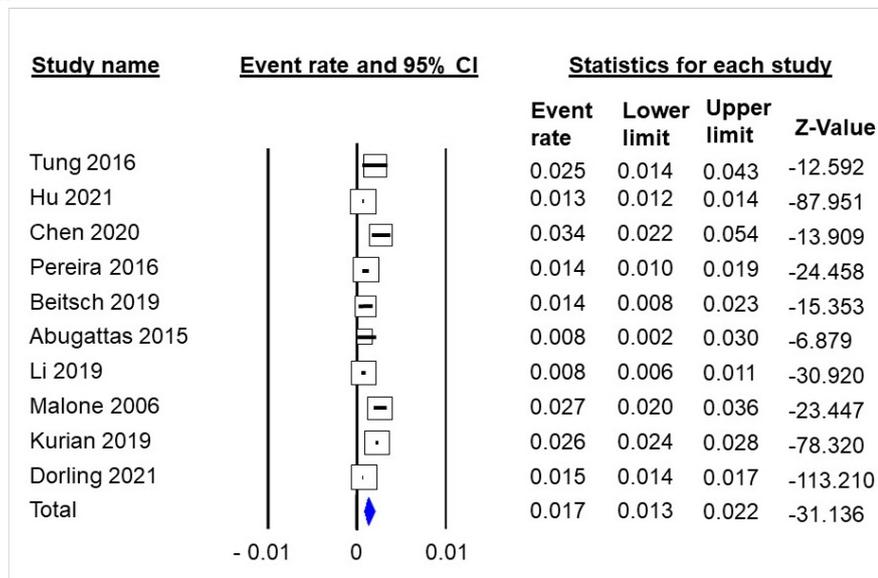
Funnel Plot of Standard Error by Logit event rate

Results based on 10 studies retained (open circles). No additional study identified by "trim and fill" analysis (Egger et al, 1997; Duval & Tweedie, 2000). Egger's test does not show publication bias (p=0.92).

Table S10. Meta-analysis of gBRCA2 carriers among unselected breast cancer patients

Data

	Study Name	Events	Sample size	Event rate	Logitevent rate	Std Err
1	Tung 2016	12	488	0.025	-3.681	**0.292**
2	Hu 2021	417	32247	0.013	-4.335	**0.049**
3	Chen 2020	18	524	0.034	-3.336	**0.240**
4	Pereira 2016	33	2433	0.014	-4.287	**0.175**
5	Beitsch 2019	13	959	0.014	-4.287	**0.279**
6	Abugattas 2015	2	266	0.008	-4.883	**0.710**
7	Li 2019	42	5099	0.008	-4.791	**0.155**
8	Malone 2006	44	1628	0.027	-3.584	**0.153**
9	Kurian 2019	477	18522	0.026	-3.633	**0.046**
10	Dorling 2021	754	48826	0.015	-4.155	**0.037**

Results:

Study name	Event rate and 95% CI	Event rate	Lower limit	Upper limit	Z-Value
Tung 2016		0.025	0.014	0.043	-12.592
Hu 2021		0.013	0.012	0.014	-87.951
Chen 2020		0.034	0.022	0.054	-13.909
Pereira 2016		0.014	0.010	0.019	-24.458
Beitsch 2019		0.014	0.008	0.023	-15.353
Abugattas 2015		0.008	0.002	0.030	-6.879
Li 2019		0.008	0.006	0.011	-30.920
Malone 2006		0.027	0.020	0.036	-23.447
Kurian 2019		0.026	0.024	0.028	-78.320
Dorling 2021		0.015	0.014	0.017	-113.210
Total		0.017	0.013	0.022	-31.136

Heterogeneity analysis:
I^2 statistic (%)= 94.7, P_{het}=0.000 (I^2>40% p<0.05)) ➔ heterogeneity ➔ random-effects model
Forest plot:
gBRCA2=1.71%, 95% CI 1.33-2.2

Selection Bias

N studies	Eggers Test	Duval &Tweedie (DT) Method	Random	
			DT Event rate	DT event rate IC 95%
10	0.99	0	0.017	0.0133 – 0.022

Funnel plot log gBRCA2
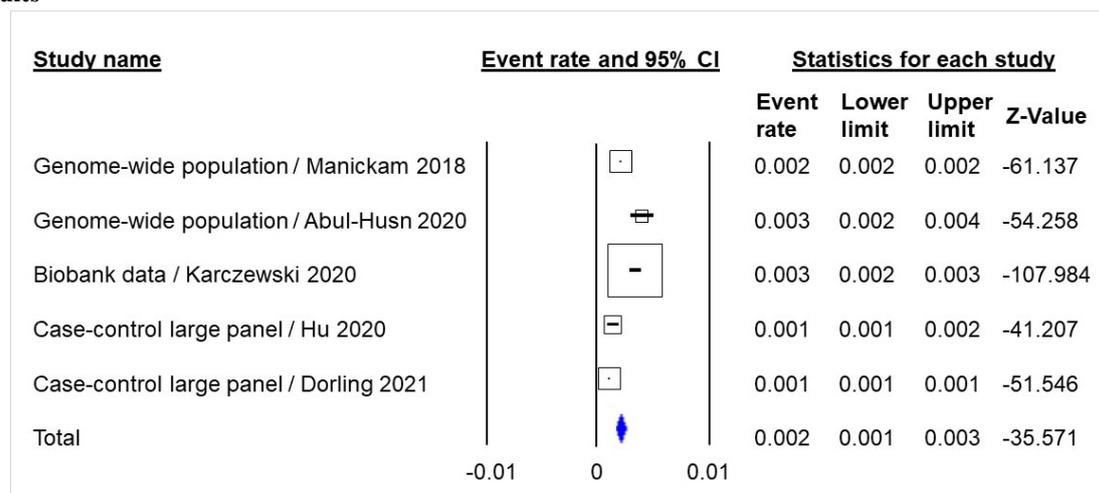
Funnel Plot of Standard Error by Logit event rate

Results based on 10 studies retained (open circles). No additional study identified by "trim and fill" analysis (Egger et al, 1997; Duval & Tweedie, 2000). Egger's test does not show publication bias (p=0.99).

Table S11. Meta-analysis of gBRCA1 carriers among unaffected individuals

Data

	Study Name	Events	Sample size	Event rate	Logit event rate	Std Err
1	Genome-wide population exome 1	95	50726	0.002	-6.278	**0.103**
2	Genome-wide population exome 2	86	30223	0.003	-5.859	**0.108**
3	Bio bank data exome and whole genome	332	125747	0.003	-5.934	**0.055**
4	Case-control large panel 1	37	32544	0.001	-6.778	**0.164**
5	Case-control large panel 2	58	50703	0.001	-6.772	**0.131**

Results

Study name	Event rate and 95% CI	Event rate	Lower limit	Upper limit	Z-Value
Genome-wide population / Manickam 2018		0.002	0.002	0.002	-61.137
Genome-wide population / Abul-Husn 2020		0.003	0.002	0.004	-54.258
Biobank data / Karczewski 2020		0.003	0.002	0.003	-107.984
Case-control large panel / Hu 2020		0.001	0.001	0.002	-41.207
Case-control large panel / Dorling 2021		0.001	0.001	0.001	-51.546
Total		0.002	0.001	0.003	-35.571

Heterogeneity analysis:
I^2 statistic =93%, p value 0.000 (I^2>40% p<0.05) ➔ heterogeneity ➔ random-effects model
Forest plot:
gBRCA1==0.182%, 95% CI 0.128-0.257
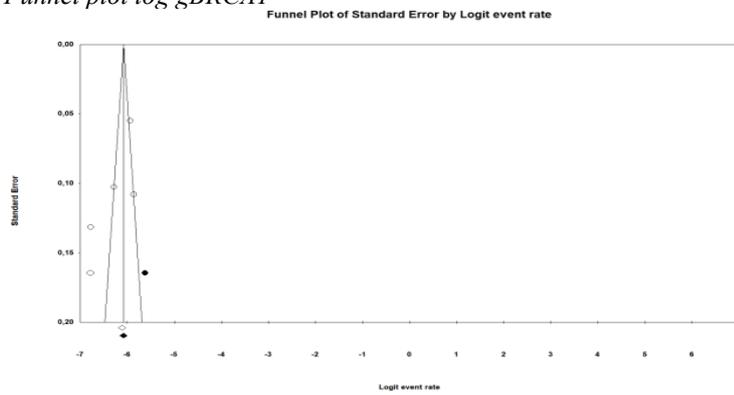
Selection Bias

|				Random	
N studies	Eggers Test	Duval &Tweedie (DT) Method	DT Event rate	DT event rate IC 95%	
5	0.22	0	0.00202	0.00147–0.00278	

Funnel plot log gBRCA1
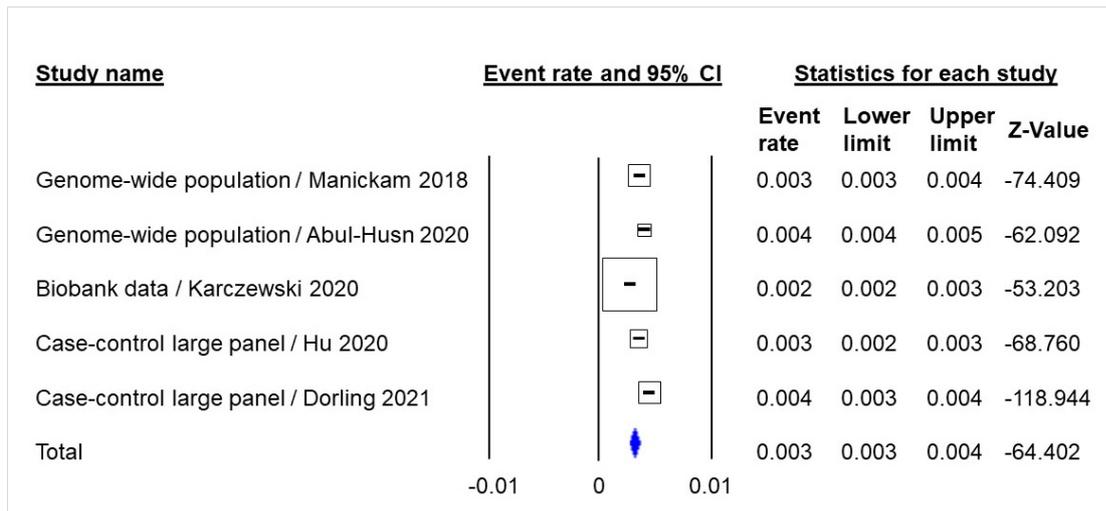
Results based on 5 studies or databases retained (open circles). 1 additional study identified by "trim and fill" analysis (Egger et al, 1997; Duval & Tweedie, 2000). Egger's test does not show publication bias (p=0.22).

Table S12. Meta-analysis of gBRCA2 carriers among unaffected individuals

Data

	Study Name	Events	Sample size	Event rate	Logit event rate	Std Err
1	Genome-wide population exome 1	172	50726	0.003	-5.683	**0.076**
2	Genome-wide population exome 2	131	30223	0.004	-5.437	**0.088**
3	Bio bank data exome and whole genome	447	125747	0.004	-5.636	**0.047**
4	Case-control large panel 1	78	32544	0.002	-6.031	**0.113**
5	Case-control large panel 2	135	50703	0.003	-5.926	**0.086**

Results

Study name	Event rate and 95% CI	Statistics for each study			
		Event rate	Lower limit	Upper limit	Z-Value
Genome-wide population / Manickam 2018		0.003	0.003	0.004	-74.409
Genome-wide population / Abul-Husn 2020		0.004	0.004	0.005	-62.092
Biobank data / Karczewski 2020		0.002	0.002	0.003	-53.203
Case-control large panel / Hu 2020		0.003	0.002	0.003	-68.760
Case-control large panel / Dorling 2021		0.004	0.003	0.004	-118.944
Total		0.003	0.003	0.004	-64.402

Heterogeneity analysis:

I^2 statistic =84.7%, p value 0.000 (I^2>40% p<0.05) ➔ heterogeneity ➔ random-effects model
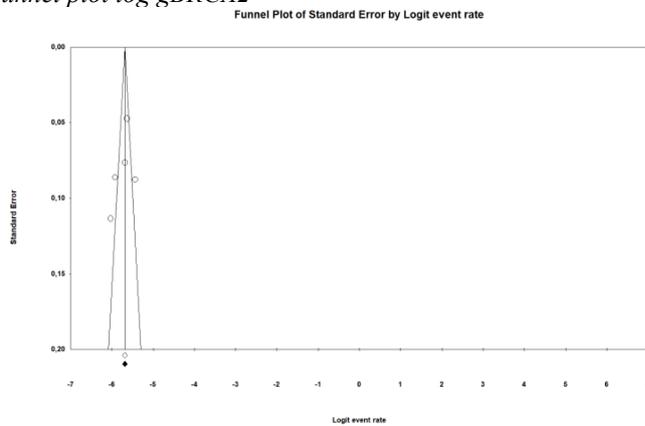
Forest plot:

gBRCA2=0.323%, 95% CI 0.271-0.384

Selection Bias

			Random	
N studies	Eggers Test	Duval &Tweedie (DT) Method	DT Event rate	DT event rate IC 95%
5	0.42	0	0.00323	0.00271-0.00384

Funnel plot log gBRCA2

Results based on 5 studies or databases retained (open circles). No additional study identified by "trim and fill" analysis (Egger et al, 1997; Duval&Tweedie,2000).Egger test do not show publication bias publication bias (p=0.42).