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REVIEW

A systematic review of the international prevalence of *BRCA* mutation in breast cancer

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Abstract: A systematic review was conducted, summarizing international *BRCA 1* or *2* (*BRCA1/2*) mutation prevalence in breast cancer. Databases (eg, Medline and Embase; N=7) and conferences were searched (January 2012 to December 2017). From 17,872 records, 70 studies were included. In 58 large (N>100) studies, *BRCA1/2* mutation prevalence varied widely from 1.8% (Spain) in sporadic breast cancer to 36.9% (United States) in estrogen receptor/progesterone receptor low+ (1–9% on immunohistochemistry/human epidermal growth factor receptor 2–negative [HER2-]) breast cancer. In 2 large studies unselected for family history, ethnicity, sex, or age and no/unclear selection by breast cancer stage or hormone receptor (HR) status, germline *BRCA* (g*BRCA*) mutation prevalence was 2.9% (Italy) to 3.0% (South Korea). In the 4 large unselected triple-negative breast cancer studies, g*BRCA* mutation prevalence varied from 9.3% (Australia) to 15.4% (United States). g*BRCA* mutation prevalence in 1 large unselected HR positive/HER2- early breast cancer study was 5% (United States). In 2 large unselected metastatic breast cancer studies, g*BRCA* mutation prevalence was 2.7% (France) and 4.3% (Germany). Locally advanced breast cancer studies were small and not in unselected populations. Poor reporting of g*BRCA* status and basis of selection implies a need for further large well-reported *BRCA* mutation prevalence studies in breast cancer.

Keywords: BRCA1, BRCA2, prevalence, systematic review, chemotherapy

Introduction

Breast cancer is a major health burden globally; it is the second most common cancer worldwide and the most common cause of cancer death in women.[1] The disease is multifactorial and thought to result from interactions between a number of different environmental, lifestyle, hormonal, and genetic factors, including a family history of breast cancer (hereditary breast cancer). A wealth of evidence indicates that mutations in the key tumor suppressor genes—the breast cancer susceptibility genes 1 or 2 (*BRCA1/2*)—predisposes an individual to developing breast cancer.[2] Such mutations may be inherited (germline) or arise as a result of a combination of genetic and environmental factors (somatic).[2] Specific subgroups have been identified as having a higher proportion of individuals who carry a *BRCA* mutation, including those who have been diagnosed with triple-negative breast cancer (TNBC) and those from different ethnic groups, including Black populations and those of Ashkenazi Jewish heritage.[3,4]

BRCA proteins play a key role in the DNA damage response, an essential pathway that ensures the survival of both normal and malignant breast cells.[5] Patients who carry a high-risk mutation in 1 or both of the *BRCA* genes (*BRCA1* or *BRCA2*) have a significantly increased risk of developing breast cancer and other

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cancers (eg, ovarian or prostate cancer).[2,4] For those who go on to develop advanced breast cancer (aBC), the newly developed poly adenosine diphosphate–ribose polymerase inhibitors (PARPi) offer a new targeted approach to specifically treat those with germline *BRCA1/2* mutations.[6] Recently, olaparib became the first of the PARPi drugs to receive approval by the United States Food and Drug Administration (FDA) for use in the treatment of patients with germline *BRCA* (g*BRCA*) mutation and human epidermal growth factor receptor 2–negative (HER2-) metastatic breast cancer; talazoparib was approved by the FDA in 2018 and as of this writing is undergoing review by the European Medicines Agency.

Given recent developments in the management of those with *BRCA*-mutated breast cancer,[4,7–10] it is important that international healthcare providers and decision makers are kept informed of the burden of *BRCA*-mutated disease and the prevalence of the population that would potentially benefit from current and future *BRCA* mutation-targeted therapeutic options.

The objective of this systematic review was to identify and summarize the latest prevalence of *BRCA* mutations (including g*BRCA* mutations wherever specified) in the breast cancer population, focusing on those individuals who are potential targets for *BRCA* mutation-targeted therapies across a number of countries, specifically Australia, Canada, France, Germany, Israel/Palestine, Italy, Japan, Russia, South Korea, Spain, United Kingdom, and United States.

Methods

This systematic review followed the recommendations of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in healthcare and the Cochrane Handbook for Systematic Reviews of Interventions.[11,12] This systematic review was also conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S1).

A range of electronic databases was searched (N=7), including Medline, Embase, EconLit, and the Cochrane Database of Systematic Reviews. Searches used a combination of text and database thesaurus terms. Searches of gray literature sources, including conference abstracts, were also conducted. Full details of resources and strategies used are available Appendix 1 in the Supplementary materials.

This manuscript includes observational studies reporting on the prevalence of *BRCA* mutations (*BRCA1, BRCA2*, or *BRCA1/2*), including germline mutations (wherever specified) in male or female breast cancer patients. The prevalence of any mutation was included regardless of whether the mutation was a founder mutation or not. Also, where study authors did not clearly state that mutations were germline or somatic and/or deleterious, pathogenic, or clinically relevant, the mutation was classified as not reported/unclear in order to avoid any misinterpretation. Study inclusion was not limited by language. Only data that were publicly available and reported from January 2012 to December 2017 were eligible for inclusion. This ensured that data were as relevant to current clinical practice as possible, given the rapidly evolving nature of the management of patients with breast cancer associated with *BRCA* mutation.

Data from the included studies were extracted, stored, and analyzed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) spreadsheets. The principal summary measure that was extracted was percentage prevalence. Given the large amount of data in the topic area, we focused our findings on data from 12 countries: United States, Canada, United Kingdom, Germany, France, Spain, Italy, Australia, Japan, South Korea, Russia, and Israel. Details of the study methods, population characteristics, risk of bias, and prevalence data were extracted and summarized from each study by 1 reviewer and checked for accuracy against the original publication by a second reviewer. Any discrepancies were resolved through consensus or consultation with a third reviewer. Criteria used to assess the risk of bias were taken from the critical appraisal checklist for studies reporting prevalence data of the Joanna Briggs Institute, which assesses the risk at the study level.[13]

Studies were grouped by country. In addition, within the broader population of interest (patients with g*BRCA* mutation breast cancer), data have been highlighted and discussed separately for subgroups of patients that were of particular interest: locally advanced/metastatic TNBC and locally advanced/metastatic HR–positive (HR+) and HER2- breast cancer.

In order to focus on the most robust data, we have centered our report mainly on the results of 58 large studies (N>100). Nevertheless a full set of results from all 70 studies that met the inclusion criteria is reported in Appendix 2 of the Supplementary materials.

Results

Study selection

A total of 17,872 titles and abstracts were retrieved from the literature searches and an additional 6 from hand

searching reference lists, background papers, and systematic reviews. From these, full papers were obtained for 269 citations. After further review, 88 papers were excluded; the reason(s) for exclusion are listed in Appendix 3 of the Supplementary materials.

From the remaining 181 papers, 73 papers reported *BRCA* mutation prevalence data for 70 studies across the 12 countries. A summary of the study selection process is reported in Figure 1.

Prevalence studies

Risk of bias of prevalence studies

Only 3 of the 70 prevalence studies were assessed as at low risk of bias (green shading in Figure 2) on all 10 criteria according to the Joanna Briggs Institute checklist.[13–16] Twenty-seven studies of the 70 (37.5%) had no criteria at high risk of bias (blue shading in Figure 2), but there was at least 1 criterion for which the risk of bias was unclear (red shading in Figure 2).[14–40] Particular areas of concern across the studies reporting on *BRCA* status that may affect the cumulative evidence on *BRCA* prevalence included no adequate description of the source population and setting (n=28; 40.0% of studies), inadequate sample size (n=12; 17.1 of studies), and sample population not necessarily representative of the total population of patients (n=11; 15.7% of studies).

A summary of the risk of bias and further details are reported in Appendix 4 in the Supplementary materials.

Overview of prevalence studies

Seventy studies reported the prevalence of *BRCA1* and/or *BRCA2* mutations in patients with breast cancer in the following countries: United States (33 studies), Canada (2 studies), United Kingdom (4 studies), Germany (3 studies), France (2 studies), Spain (4 studies), Italy (3 studies [including 1 study from Sardinia]), Australia (2 studies), Japan (1 study), South Korea (11 studies), Russia (2 studies), and Israel (3 studies [including 1 study from Palestine]).

g*BRCA* mutation prevalence was reported explicitly in only 32 of the 70 studies; the majority of studies did not make it clear whether mutations were germline or somatic. Also, only 45 of the 70 studies specified whether the *BRCA* mutations were deleterious (or clinically significant) or not. Forty-four of the 70 studies reported separate prevalence data for *BRCA1* and *BRCA2*, including whether a proband carried both *BRCA1* and *BRCA2* mutations. Also, 4 of these 44 studies did not report this information fully for all subgroups.[14,18,41,42] Most studies (62) reported the prevalence of any *BRCA* mutation, ie, *BRCA1* or *BRCA2* as opposed to only *BRCA1* or only *BRCA2*.

Nine of the studies failed to report in sufficient detail how individuals were selected for inclusion in the study population. A total of 17 studies reported data for a population explicitly stated to be unselected for family history of breast cancer, 7 studies categorized patients as mixed (some with and others without a family history of breast cancer), 7 studies purely focused on patients with a family history of breast cancer, and 38 studies reported that

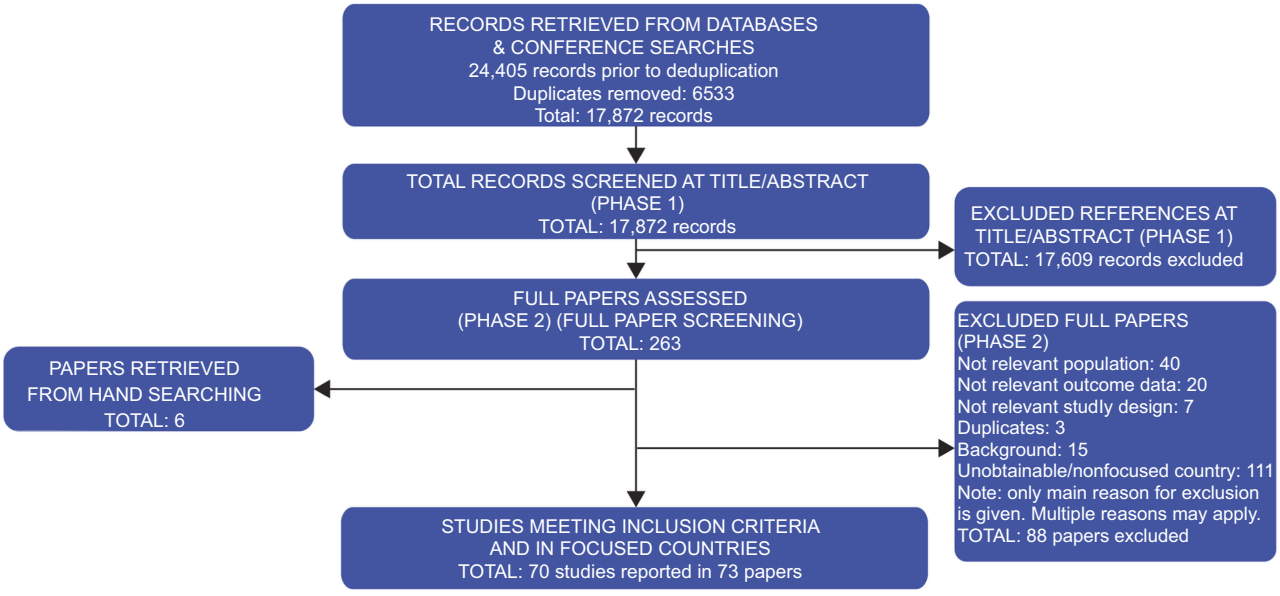

Figure 1 PRISMA flow chart detailing literature searches and inclusion screening.

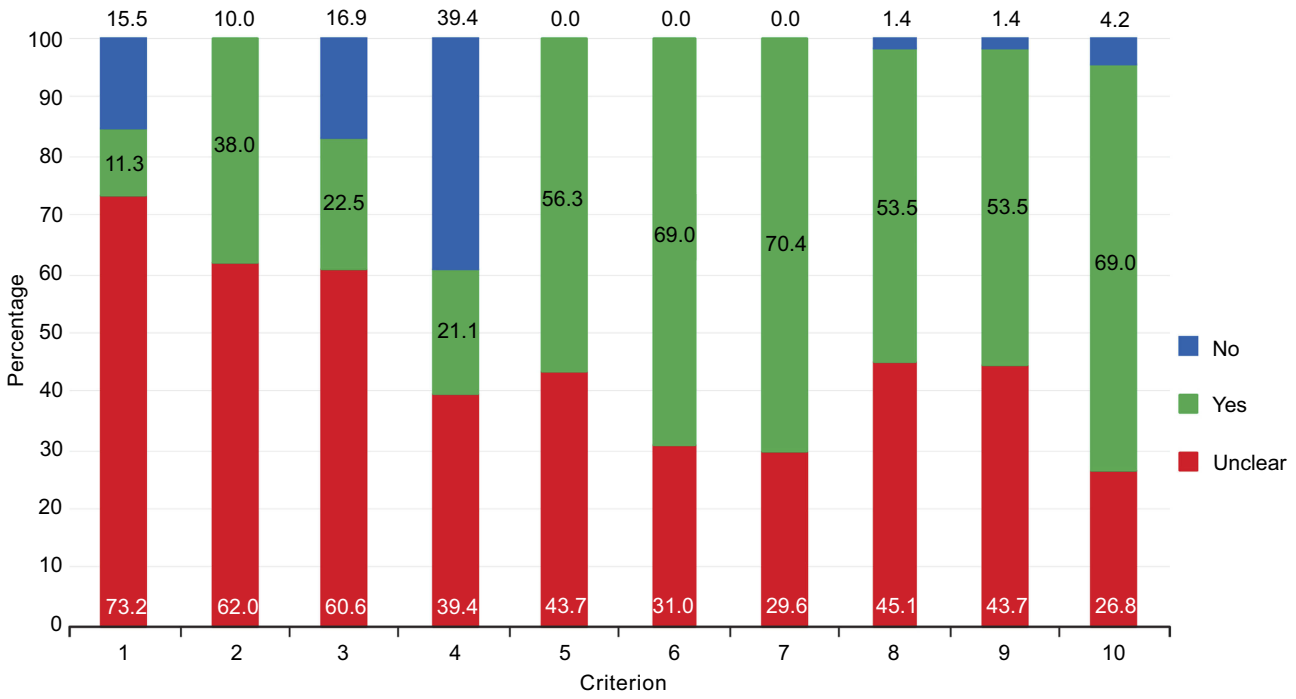

Figure 2 Summary of JBI risk of bias assessment for prevalence studies.
Abbreviations: JBI, Joanna Briggs Institute.

probands were selected on criteria other than only family history, such as sex, ethnicity, and age at breast cancer diagnosis. When studies were reported as mixed, they included both those individuals with and those without a family history of breast cancer, but they did not report that probands were unselected for family history. Such mixed studies reported on samples that might not have the same proportion of those individuals with a family history as those designed specifically to be unselected for family history. No study reported *BRCA* mutation prevalence solely in men, 31 reported data for TNBC patients, and 4 reported data for patients with HR+/HER2- disease (2 of which were in a subgroup of those with HR low+ [1–9% on immunohistochemistry]). Seven studies reported on the prevalence of metastatic breast cancer, and only 2 reported on locally aBC. Three studies reported prevalence for multiple subgroups.[18,43,44] Eighteen studies did not report data on either HR status or breast cancer stage.

Of the 31 studies reporting on TNBC, there was variation in terms of breast cancer stage, including populations of mixed cancer stages and those for whom the stage of disease was not reported. Twelve studies included populations that were unselected on the basis of family history or mixed (with and without) family history. Only 1 study[45] reported *BRCA* mutation for aBC, and these data were only for a small subgroup of United States patients with metastatic breast cancer (metastatic TNBC), including those with and without a family history of breast cancer.

For the 4 studies that reported *BRCA* mutation in patients with HR+/HER2- breast cancer, none was in the same population in terms of criteria used to select patients. One of the studies required patients to fulfill a complex set of selection criteria in accordance with the National Medical Insurance Reimbursement in South Korea,[15] and another only included females with early breast cancer.[46]

The 7 studies that reported *BRCA* mutation in metastatic breast cancer included only 1 study in a population with a specific HR status, which was in TNBC[45] (as mentioned above) in the United States.

Neither of the 2 studies in patients with locally aBC reported on the HR status of participants. One United States study[43] included patients who varied with respect to their family history of breast cancer, and the other study (from Israel[44]) included data reported according to the different *BRCA* mutation proband (*BRCA1* and *BRCA2*) for patients who were female, of Ashkenazi Jewish descent, and diagnosed with early onset breast cancer.

Twenty-five studies reported details on the method used to screen for *BRCA* mutations. Where reported, most studies used either direct sequencing (8 studies) or next-generation sequencing (NGS) methods (8 studies). Seven studies

reported testing for only a subset of *BRCA*-associated mutations .[3,31,44,47–51]

A summary of the key study characteristics is provided in Table 1.[3,14–22,24–82] Further characteristics of the included studies are provided in Appendix 2 of the Supplementary materials.

Summary of BRCA mutation prevalence data

Prevalence between individual studies varied widely. In the 58 large (N>100) studies, the lowest prevalence was reported as 1.8% for deleterious g*BRCA* mutation in a Spanish study (N=495) of sporadic breast cancer cases within a population with no family history or other criteria warranting hereditary breast cancer screening and a mixture of patients with different HR profiles.[18] In contrast, the highest reported prevalence was 36.9% for germline deleterious *BRCA* mutation in a United States study (N=314).[76] The patients in this study were described as having an estrogen receptor/progesterone receptor low+ status (ie, 1–9% on immunohistochemistry) and to have HER2- breast cancer; other risk criteria used to select the study population were not clearly reported.

Figure 3 summarizes the prevalence of any type of *BRCA* mutation (*BRCA1* or *BRCA2*) in the 19 largest (N>500) included studies. Generally, *BRCA* mutation prevalence was lowest in those populations that were not selected on the basis of family history and highest in those that were selected on the basis of at least 1 or more criterion, including family history of breast cancer, early onset breast cancer, or male breast cancer. In the 7 largest studies that also reported that mutations were germline, g*BRCA* mutation prevalence varied from 2.9% in a Sardinian study[77] (unselected population) to 26.5% in a German study[78] (selected for family history of breast cancer).

Among those studies reporting on patients with TNBC, there was a clear trend for studies to report higher *BRCA* mutation prevalence levels. For example, in the unselected population, *BRCA* mutation prevalence was 11.2% in a study by Couch et al[79] versus 2.9% in a mixed HR-status study by Palomba et al[77].

In those studies that fully reported *BRCA* mutation prevalence according to the *BRCA1* and *BRCA2* probands, 26 out of 43 reported that mutations in *BRCA1* were more common than in *BRCA2*.

gBRCA mutation prevalence in those unselected on any basis other than hormone receptor status or breast cancer stage

Table 2 summarizes the g*BRCA* mutation prevalence in 10 large (N>100) studies that included individuals who were unselected on the basis of family history of breast cancer, age, sex, or ethnicity.

g*BRCA* mutation prevalence was similar in 2 studies of populations[26,77] with mixed breast cancer HR status or in which the HR status was not reported and the breast cancer stage was not reported or unclear. g*BRCA* mutation prevalence was 2.9% in a Sardinian study[77] and 3.0% in a South Korean study.[26]

In populations with metastatic breast cancer, 2 studies reported similar g*BRCA* mutation prevalence data (2.7%[80] and 4.3%[81]). Higher g*BRCA* mutation prevalence values were reported in the United States study by Tung et al,[46] but these data were from a single academic center that only included patients with early breast cancer; this study reported that *BRCA* mutation prevalence for a subgroup of patients with HR+/HER2- breast cancer was 5.0%.

In 4 studies of TNBC patients that reported on g*BRCA* mutation prevalence, values ranged from 9.3% in an Australian study (N=439)[82] to 15.4% in a United States study (N=207).[42] Both of these studies included populations with both early and advanced stages of breast cancer.

BRCA mutation prevalence in advanced breast cancer

Table 3 reports data from 4 large (N>100) studies reporting on *BRCA* mutation prevalence in patients with metastatic breast cancer. Mutations in *BRCA1* were less common than mutations in *BRCA2* in 2 studies.[80,81] However, in contrast, the prevalence of *BRCA1* mutations was more common than *BRCA2* in 1 study.[45]

BRCA mutation prevalence of any kind varied widely across the 4 studies in metastatic breast cancer. g*BRCA* mutation prevalence was reported to be as low as 2.7% in a French study (N=407)[80] in which the population was unselected for family history of breast cancer and patients with breast cancer varied in their HR status. In a large German study (N=1462)[81] in a population unselected by family history of breast cancer, the prevalence of g*BRCA* mutation was also comparatively low (4.3%), but it was not reported whether this included deleterious *BRCA* mutations. In contrast, g*BRCA* mutation prevalence was as high as 21.0% in a study (N=195) of patients with a family history of breast cancer and in which patients varied with respect to their HR status.[45]

Table 3 also shows the studies in locally aBC. Only 1 small study (N=13)[44] in Israel reported the prevalence of mutation of any *BRCA* gene, in a population of Ashkenazi Jewish women with early onset breast cancer.

Table 1 Summary of key study characteristics

Germline *BRCA* reported	Deleterious/ pathogenic/clinically significant mutation reported	Country	Study ID	Population selection criteria	Hormone receptor status	Breast cancer stage	N at risk of *BRCA* mutation
Yes	Deleterious	United States	Bayraktar, 2013[45]	Mixed	Mixed	Metastatic	195
					TNBC		44
			Couch, 2015[79]	Unselected		NR/unclear	1824
			De La Cruz, 2012[74]	NR/unclear	Mixed	Invasive	196
			Guerra, 2017[25]	Hispanic	NR/unclear	NR/unclear	2329
			Keung, 2012[43]	Mixed	Mixed	Metastatic	1
						Mixed	26
						Locally advanced	4
					TNBC	NR/unclear	3
			Rummel, 2013[33]	Unselected		Mixed	182
			Sanford, 2014[35]	NR/unclear		NR/unclear	122
					HR low+, HER2-		144
			Sanford, 2015[76]		TNBC		238
					HR low+, HER2-		314
			Sharma, 2014[42]	Unselected	TNBC	Mixed	207
				Family history			128
			Stadler, 2012[50]	Ashkenazi, family history of pancreatic cancer	NR/unclear	NR/unclear	211
			Tung, 2015[16]	Ashkenazi excluded			1781
			Tung, 2016[46]	Unselected, female	HR+/HER2-	Stages I to III	301
					Mixed		488
					TNBC		87

(*Continued*)

Table 1 (Continued).

Germline *BRCA* reported	Deleterious/ pathogenic/clinically significant mutation reported	Country	Study ID	Population selection criteria	Hormone receptor status	Breast cancer stage	N at risk of *BRCA* mutation
		Spain	de Juan Jimenez, 2012[18]	Sporadic BC (no family history or other criteria for hereditary BC screening)	Mixed	Metastatic	23
						Mixed	495
			Gonzalez-Rivera, 2016[24]	Unselected	TNBC	Stages II-III	105
			Zugazazoitia, 2014[73]	Mixed	Mixed	Mixed	341
					TNBC		57
		Australia	Wong-Brown, 2015[82]	Unselected			439
		France	Tunon De Lara, 2017[72]	Decided with each patient, based on age, family history, and tumor histology	Mixed	NR/unclear	25
		South Korea	Jung, 2016[71]	Family history		Invasive	181
				Mixed			411
		Sardinia/Italy	Palomba, 2014[77]	Unselected		NR/unclear	726
							49

(*Continued*)

Table 1 (Continued).

Germline *BRCA* reported	Deleterious/ pathogenic/clinically significant mutation reported	Country	Study ID	Population selection criteria	Hormone receptor status	Breast cancer stage	N at risk of *BRCA* mutation
	Pathogenic	United States	Rummel, 2017[34]	Unselected, early onset (age <40 years)	Mixed	Mixed	118
			Ross, 2017[70]	Female with multiple BC primaries	NR/unclear	NR/unclear	65
			Ellsworth, 2017[21]	Females with TNBC	TNBC		196
		Spain	Andres, 2014[69]	No family history, diagnosed at age <50 years			92
		France	Meynard, 2017[80]	Unselected	NR/unclear	Metastatic	407
		Germany	Kast, 2016[78]	Family history		NR/unclear	59,304
		South Korea	Kim, 2012[26]	Unselected			471
				NR/unclear			2139
				High risk (early onset BC, bilateral BC, male BC, or cancer of multiple organs that include breast)			1668
		Israel/Palestine	Lolas Hamameh, 2017[68]	Diagnosis at age ≤40 years, or with family history	Mixed	Mixed	453
					TNBC		44
	Clinically significant	South Korea	Seong, 2014[67]	Family history, female	Mixed		221
					TNBC		42
	NR/unclear	United States	Vidula, 2017[39]	Metastatic BC	Mixed	Metastatic	178
		Germany	Fasching, 2017[81]	Unselected	NR/unclear		1462
		Italy	Musolino, 2012[29]			NR/unclear	55
		Russia	Cherdyntseva, 2014[47]	Family history			765

(*Continued*)

Table 1 (Continued).

Germline *BRCA* reported	Deleterious/ pathogenic/clinically significant mutation reported	Country	Study ID	Population selection criteria	Hormone receptor status	Breast cancer stage	N at risk of *BRCA* mutation
No	Deleterious	United States	Beck, 2017[66]	Young age (<50 years) at diagnosis	TNBC		199
			Hartman, 2012[65]	Unselected			
			Weitzel, 2013[51]	Family history, Hispanic	NR/unclear		610
			Welinsky, 2016[64]	Unselected			191
		Germany	Rhiem, 2016[63]	Without family history	TNBC		750
		South Korea	Han, 2013[84]	Family history	NR/unclear		775
		Japan	Kitagawa, 2014[27]	NR/unclear	TNBC		123
	Pathogenic	United States	Buys, 2017[62]	Mixed	Mixed		35,409
					TNBC		4797
			Pal, 2015[14]	Female, black, diagnosed age ≤50 years	Mixed	Invasive	396
					TNBC		66
			Susswein, 2016[61]	Female, no known previous *BRCA* testing	NR/unclear	NR/unclear	3315
		United Kingdom	Eccles, 2017[60]	Age <40 years at diagnosis	TNBC		542
		South Korea	Kang, 2015[41]	Family history	Mixed		1228
				Family history of breast or ovarian cancer or diagnosis age ≤40 years with bilateral BC or BC with other primary malignancy or male BC, in accordance with the standard of National Medical Insurance Reimbursement in Korea			2403
			Yoon, 2017[40]	Mixed	NR/unclear	Mixed	328

(*Continued*)

Table 1 (Continued).

Germline *BRCA* reported	Deleterious/ pathogenic/clinically significant mutation reported	Country	Study ID	Population selection criteria	Hormone receptor status	Breast cancer stage	N at risk of *BRCA* mutation
	NR/unclear	United States	Biskupiak, 2017[59]	NR/unclear	Mixed	Invasive	816
			Emborgo, 2016[22]	Unselected	TNBC	NR/unclear	377
			Greenup, 2013[3]	NR/unclear			450
			Pal, 2012[58]	Black women with early onset BC	NR/unclear	Invasive	48
			Pal, 2014[30]	Female, black, diagnosed age ≤50 years	Mixed		283
			Petersen, 2016[57]	Age <60 years at diagnosis	TNBC	NR/unclear	87
			Skandan, 2016[36]	NR/unclear	Mixed	Mixed	32
			Vidula, 2017[39]	Metastatic BC		Metastatic	178
		United Kingdom	Rahman, 2017[56]	BC diagnosis at age <40 years or bilateral BC diagnosed at age <60 years or TNBC or breast + ovarian cancer or male BC	NR/unclear	NR/unclear	1020
				Family history, other[a]			368
			Robertson, 2012[32]	Unselected	TNBC		159
				Family history and/or young age at diagnosis			149
		Australia	Duffy, 2012[19]	Age <31 years at diagnosis	NR/unclear		91
		Canada	Ghadirian, 2014[49]	Family history 51+, all women 50-	Mixed	Mixed	1093
			Vanstone, 2012[38]	NR/unclear	NR/unclear	NR/unclear	1003

(*Continued*)

Table 1 (Continued).

Germline *BRCA* reported	Deleterious/ pathogenic/clinically significant mutation reported	Country	Study ID	Population selection criteria	Hormone receptor status	Breast cancer stage	N at risk of *BRCA* mutation
		Israel	Asleh-Aburaya, 2015[17]	Family history	TNBC	Mixed	30
			Dagan, 2017[44]	Female, Ashkenazi, early onset	Mixed	Metastatic	3
						Mixed	149
						Locally advanced	13
		South Korea	Lee, 2015[28]	NR/unclear	TNBC	NR/unclear	534
			Sohn, 2016[55]	Unselected	NR/unclear		358
			Son, 2012[37]	High risk (early onset BC defined as diagnosis age ≤40 years, bilateral BC, personal history of breast and ovarian cancer, male BC, or cancer of multiple organs that include breast)			758
		Italy	Loi, 2017[87]	High individual or familial BC risk (age at diagnosis <50 years, contralateral BC, personal or family history of male BC/*BRCA* mutation/ovarian cancer)	Mixed	Mixed	86
		Russia	Polonikov, 2015[31]	NR/unclear	NR/unclear	NR/unclear	217

(*Continued*)

Table 1 (Continued).

Germline *BRCA* reported	Deleterious/ pathogenic/clinically significant mutation reported	Country	Study ID	Population selection criteria	Hormone receptor status	Breast cancer stage	N at risk of *BRCA* mutation
Unsure	Deleterious	United States	Pal, 2014[54]	Female, black, diagnosed age ≤50 years	Mixed	Invasive	144
	Pathogenic		Pal, 2013[53]		NR/unclear		46
		United Kingdom	Eccles, 2016[20]	Mixed	HER2+, HR status unknown	Mixed	101
		South Korea	Park, 2017[15]	Family history of breast or ovarian cancer or diagnosis at age ≤40 years with bilateral BC or BC with other primary malignancy or male BC, in accordance with the standard of National Medical Insurance Reimbursement in Korea	HR+/HER2-		252
					Mixed		478
					TNBC		76
	NR/unclear	United States	Ellsworth, 2012[48]	Female, mixed		NR/unclear	154
		South Korea	Noh, 2013[52]	Family history of breast or ovarian cancer or <40 years of age at diagnosis or bilateral BC, or male sex	Mixed		209

Notes: [a]Not fulfilling any of the following criteria: BC <40 years; bilateral BC <60 years; TNBC; BC + ovarian cancer; male BC.

Abbreviations: +, positive; -, negative; BC, breast cancer; *BRCA*, BC susceptibility gene; HER2+, human epidermal growth factor receptor 2–positive; HER2-, human epidermal growth factor receptor 2–negative; HR+, hormone receptor–positive; ID, identification; low+ indicates 1–9% on immunohistochemistry; NR, not reported; TNBC, triple-negative BC.

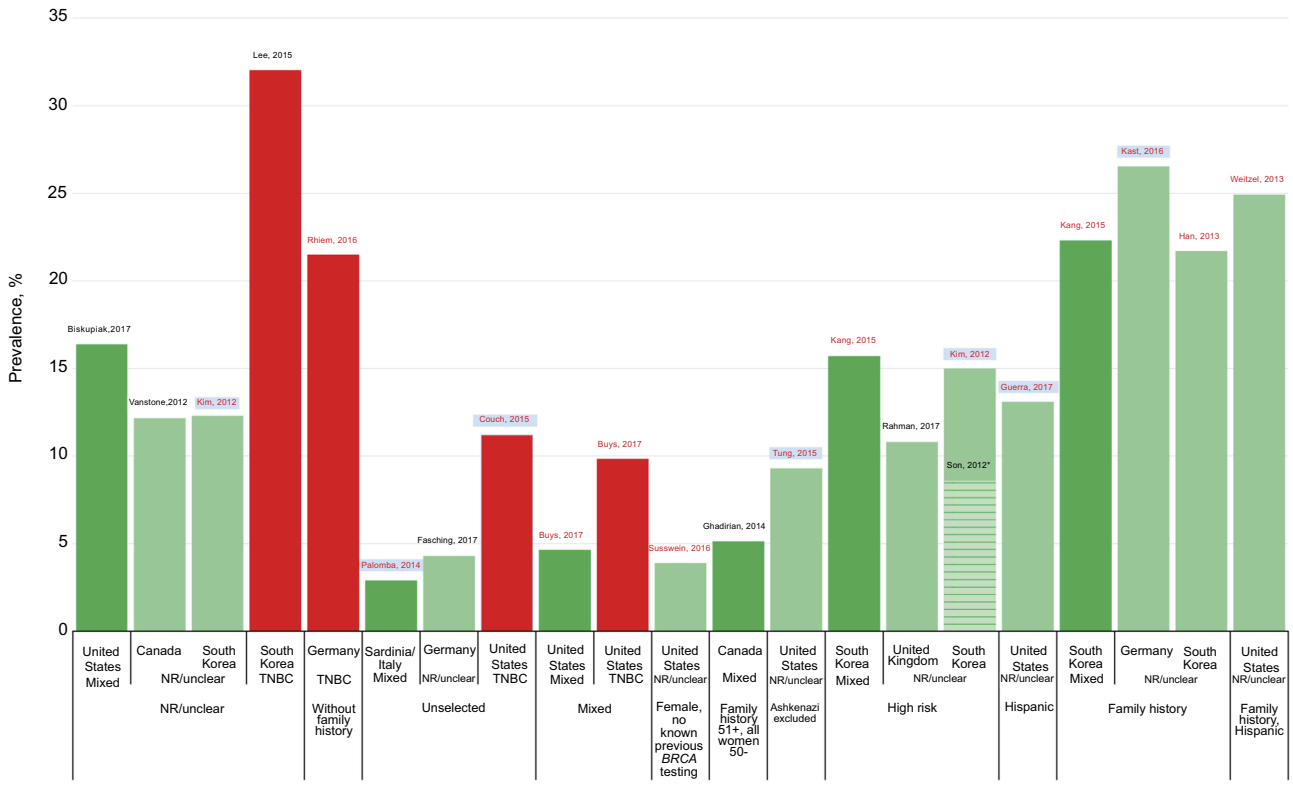

Figure 3 Prevalence (%) in largest (N>500) studies.

Notes: Horizontal axis has 3 levels: bottom – selection (family history/sex/ethnicity); middle – hormone receptor status (red = TNBC, dark green = mixed, light green = NR/unclear); top – country. BC stage not shown because NR/unclear for all but 2 studies (1 mixed and 1 invasive); *Bar for Son, 2012[37] is striped in order to distinguish it from bar for Kim, 2012: it is of mixed hormone receptor status.[26] Pale blue = germline reported; red text = deleterious/pathogenic/clinically significant reported. High risk: based on fulfilment of at least 1 of a set of criteria, including family history, early onset, or male BC, which vary by study (See Table 1). Mixed: implies that the study included both those individuals with and without a family history of breast cancer, but the study did not report that probands were unselected.

Abbreviations: BC, breast cancer; NR, not reported; TNBC, triple-negative breast cancer.

Discussion

To our knowledge, this is the first systematic review that utilized rigorous review methods[11,12] to comprehensively report on the international prevalence of *BRCA* mutation (including g*BRCA* [*BRCA1* and/or *BRCA2* wherever specified] mutation) in breast cancer patients across a broad range of populations. Prevalence was also analyzed according to HER2 status, HR status, and stage of breast cancer (including locally advanced or metastatic).

In the 58 large studies (N>100), the prevalence of *BRCA* mutation of any kind between individual studies varied very widely from 0.6% to 36.9%. However, in contrast, the prevalence of g*BRCA* mutation appeared to vary little (≈3%) between studies in a general (unselected) population.[26,77] g*BRCA* mutation prevalence appeared to be unaffected by metastatic breast cancer stage, ranging from 2.7%[80] to 4.3%.[81] Our results are consistent with a publication by Nelson et al,[83] regarding a meta-analysis of 70 studies. None of these 70 studies was published after 2011 and as a result the studies were not included in our review; germline status was also not explicitly reported. The meta-analysis[84] reported a *BRCA* mutation prevalence of 3% in women with breast cancer and 20% in high-risk families. This was consistent with our reported *BRCA* mutation prevalence results among large studies, where family history was associated with a *BRCA* mutation prevalence of more than 20% (range of 21.7%[84] to 26.5%[78]). Consistency of our results can be further ascertained with a recent April 2019 publication by Kurian et al who reported germline *BRCA1/2* mutation prevalence among United States breast cancer patients in the Georgia and California SEER registries (HR+/HER2-: 5.2% and TNBC: 15.4%); these numbers are largely aligned to what we have summarized in this systematic literature review.[85]

There did appear to be evidence of a selection effect in our review according to some risk characteristics of breast cancer. This included an increase in *BRCA* prevalence in those populations selected on the basis of high-risk criteria

Table 2 Germline *BRCA* mutation prevalence in those unselected for family history, age, sex, or ethnicity

Country	Study ID	Breast cancer stage	N at risk of mutation	% *BRCA1*	% *BRCA2*	% *BRCA1/2*
TNBC						
United States	***Sharma, 2014***[42] ***Couch, 2015***[79] Rummel, 2013[33]	***Mixed*** ***NR/unclear*** Mixed	***207*** ***1824*** 182	***11.1*** ***8.5*** 9	***4.3*** ***2.7*** NA	***15.4*** ***11.2*** NA
Spain	***Gonzalez-Rivera, 2016***[24]	***Stages II-III***	***105***	***12.4***	***1.9***	***14.3***
Australia	***Wong-Brown, 2015***[82]	***Mixed***	***439***	***5.9***	***3.4***	***9.3***
HR+/HER2-						
United States	***Tung, 2016***[46]	***Stages I-III***	***301***	***1.7***	***3.3***	***5.0***
Mixed hormone receptor status						
Sardinia/Italy United States Germany *France*	***Palomba, 2014***[77] ***Tung, 2016***[46] ***Fasching, 2017***[81] ***Meynard, 2017***[80]	***NR/unclear*** ***Stages I-III*** ***Metastatic*** ***Metastatic***	***726*** ***488*** ***1462*** ***407***	***1.0*** ***3.7*** ***1.4*** ***0.7***	***1.9*** ***2.5*** ***2.9*** ***2.0***	***2.9*** ***6.1*** ***4.3*** ***2.7***
Hormone receptor status NR/unclear						
South Korea	***Kim, 2012***[26]	***NR/unclear***	***471***	***1.5***	***1.5***	***3.0***

Notes: Bold = germline reported; *Italics* = deleterious/pathogenic/clinically significant reported. Mixed: implies that the study included both those with and without a family history of breast cancer, but the study did not report that probands were unselected.
Abbreviations: *BRCA1/2*, BC susceptibility gene 1 or 2; HER2-, human epidermal growth factor receptor 2–negative; HR+, hormone receptor–positive; ID, identification; NA, not applicable; NR, not reported; TNBC, triple-negative breast cancer.

Table 3 *BRCA* mutation prevalence in advanced breast cancer

Country	Study ID	Selection	Hormone receptor status	N at risk of mutation	% *BRCA1*	% *BRCA2*	% *BRCA1* and 2	% *BRCA1/2*
Metastatic BC								
United States	***Bayraktar, 2013***[45] Vidula, 2017[39]	***Mixed*** NR/unclear	***Mixed***	***195*** 178	***15.0*** NR	***6.0*** NR	***0.00*** NR	***21.0*** 15.2 **0.6**[a]
Germany	**Fasching, 2017**[81]	**Unselected**	**NR/unclear**	**1462**	**1.4**	**2.9**		**4.3**
France	***Meynard, 2017***[80]	***Unselected***	***Mixed***	***407***	***0.7***	***2.0***	***0.00***	***2.7***
Locally advanced BC								
United States	***Keung, 2012***[43]	***Mixed***	***Mixed***	***4***	***NA***	***75.0***	***NA***	***NA***
Israel	Dagan, 2017[44]	Female, Ashkenazi, Early onset		13	23.1	30.8	0.0	53.8

Notes: Bold = germline reported; *italics* = deleterious/pathogenic/clinically significant reported. [a]Within this study, 1/178 (0.6%) probands were identified as having a mutation that was germline. Mixed: implies that the study included both those individuals with and without a family history of breast cancer, but the study did not report that probands were unselected.
Abbreviations: BC, breast cancer; *BRCA1/2*, BC susceptibility gene 1 or 2; ID, identification; NA, not applicable; NR, not reported.

(based on the fulfillment of at least 1 of a set of criteria, including family history, early onset, or male breast cancer), when compared with those who were not selected on the basis of family history. In the 7 largest studies that also reported on prevalence of g*BRCA* mutation, g*BRCA* mutation prevalence varied from 2.9% to 26.5%, but it was

difficult to determine any trends in the data as the populations varied widely with respect to their selection criteria. However, a trend was evident in the prevalence of *BRCA* mutation between those populations with versus those without TNBC; those with TNBC tended to have a higher prevalence of *BRCA* mutation in line with previous research. There was also a suggestion that in a small majority (26 of 44 studies), mutations in *BRCA1* were more common than in *BRCA2*. However, this trend was reversed among patients with TNBC, in whom the majority of mutations were *BRCA1*. A published meta-analysis, by Tun et al,[86] of prevalence of *BRCA1* mutation in female patients with breast cancer, regardless of germline status, found that those with high-risk (including family history and early onset breast cancer) TNBC are much more likely to have *BRCA1* mutation compared with those with a non-TNBC phenotype (relative risk 5.65 [95% confidence interval 4.15–7.69]), and that approximately 2 in 9 (≈22%) women with TNBC harbor *BRCA1* mutation. Our review also found *BRCA1* mutation to be more common than *BRCA2* mutation in TNBC, although our estimates of *BRCA1* mutation prevalence were mostly (11 of 14 studies) lower than the estimate by Tun et al, ie, 22%.[86] There was no obvious explanation for this difference except that very few of the studies included in our review were included in the review by Tun et al[86]. Indeed, the only study in common between our review and that by Tun et al[86] was the study by Bayraktar et al[45]. This was because all other studies included by Tun et al[86] were outside of our scope: 8 of the 12 studies were published before 2012 and the other 3 were China-based population studies.[86]

The content of any systematic review is dependent on the quality of the included research. We focused on those studies whose specific aim was to investigate the prevalence of *BRCA* mutation, rather than studies that happen to report ad hoc data on prevalence or data that could be used to calculate prevalence. Nonetheless, some studies had a small sample size and/or poor reporting of study data and methods, which hampered our assessment. Wherever possible, we have provided information regarding the strength of the evidence and have also highlighted any general weaknesses or omissions in the data. In particular, studies often failed to report whether *BRCA* mutations were germline or somatic and which specific *BRCA* genes were under investigation (including fully reporting data for *BRCA1* and *BRCA2* mutations separately and whether a proband carried both *BRCA1* and *BRCA2* mutations). In addition, it was not clear whether the mutations were deleterious/pathogenic/clinically significant or not and which sequencing method was used (ie, direct or NGS). The HR status of patients (beyond that of TNBC) was similarly poorly described. Where this was not clearly reported by the authors of the primary studies, we labeled the study as unclear to avoid any misinterpretation. This was identified as a weakness in many of the included studies, and researchers should ensure that these details are clearly reported in future studies. In estimating *BRCA* mutation prevalence, it is also important for the purposes of collating and comparing data across studies that future studies clearly identify how they select their study populations and report on key baseline characteristics such as family history, ethnicity, and personal history of cancer (type, stage, and HR status). Consistency in reporting these variables will help to avoid the issues of heterogeneity raised in this review, including problems in summarizing the overall findings and identifying trends in the data. Studies should also follow the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement[75] to improve reporting standards in epidemiological studies.

None of the studies included in our review reported prevalences in the main population of interest (g*BRCA* mutation in HR+/HER2- or TNBC locally advanced/metastatic disease unselected for family history, sex, age, and ethnicity), ie, those individuals who are potentially eligible for PARPi. This implies a challenge for healthcare providers and policy makers who need to estimate the size of the population eligible for PARPi. Future epidemiological studies need to target this specific population of interest to assist healthcare decision makers, policy makers, and payers quantify the population and make informed decisions.

Conclusions

To our knowledge this is the first systematic review to comprehensively report on the international prevalence of *BRCA* mutations in breast cancer patients across a broad range of populations. *BRCA* mutation prevalence varied widely within key clinical and demographic subgroups and across countries. Among TNBC populations, the percentage prevalence of g*BRCA* mutations ranged from 9.3% to 15.4%, and amongst patients with metastatic breast cancer, from 2.7% to 4.3%. Within larger studies the prevalence of *BRCA* mutations appeared higher for those studies that selected patients based on their family history and the presence of TNBC. However, the interpretation of the prevalence data was hampered by poor reporting on the nature of *BRCA* mutations (eg, germline versus somatic) and key baseline characteristics of

the patients. Further large, well-reported, epidemiological studies of *BRCA* prevalence are warranted.

Abbreviation list

aBC, advanced breast cancer; *BRCA1/2*, breast cancer susceptibility genes 1 or 2; CRD, Centre for Reviews and Dissemination; FDA, Food and Drug Administration; g*BRCA*, germline *BRCA*; HER2-, human epidermal growth factor receptor 2–negative; HR+, hormone receptor–positive; NGS, next-generation sequencing; PARPi, poly ADP-ribose polymerase inhibitors; TNBC, triple-negative breast cancer.

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Author contributions

All authors made substantial contributions to the conception and design, data acquisition and data analysis and interpretation; drafted the article; provided final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

NA, SR, CF, and JR are employees of Kleijnen Systematic Reviews Ltd., who were paid consultants to Pfizer in connection with the development of this manuscript. RGWQ is an employee of and owns stocks from Pfizer Inc. The authors report no other conflicts of interest in this work.

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