

Breast cancer risk associated with *BRCA1* and *BRCA2* in diverse populations

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Abstract | Germline mutations in the *BRCA1* or *BRCA2* tumour-suppressor genes are strong predictors of breast and/or ovarian cancer development. The contribution of these mutations to breast cancer risk within any specific population is a function of both their prevalence and their penetrance. Mutation prevalence varies among ethnic groups and may be influenced by founder mutations. Penetrance can be influenced by mutation-specific phenotypes and the potential modifying effects of the patient's own genetic and environmental background. Although estimates of both mutation prevalence and mutation penetrance rates are inconsistent and occasionally controversial, understanding them is crucial for providing accurate risk information to each patient.

Penetrance

A measure of the proportion of genetically similar individuals that show any phenotypic manifestation of a mutation that they have in common.

Numerous epidemiological factors affect the likelihood of developing breast and ovarian cancer, but no other predictor is as powerful as an inherited mutation in the tumour-suppressor genes *BRCA1* or *BRCA2*. Even though hereditary breast cancer accounts for only 5–10% of all breast cancer cases, individuals carrying mutations in one of these genes have a 40–80% chance of developing breast cancer, making these mutations the strongest breast cancer predictors known^{1–3}.

BRCA1 and *BRCA2* were molecularly identified in 1994 and 1995, respectively, and since then patients with strong personal and/or family history of breast and/or ovarian cancer have been counselled to seek molecular genetic testing for germline mutations in these genes^{4,5}. In the context of this Review, the term 'mutation' will be used to refer to a disease and/or risk-associated deleterious genetic lesion. Indicators of inherited breast and/or ovarian cancer syndromes include early age of cancer onset, multiple affected individuals within a family (especially multiple first-degree relatives), the development of bilateral disease and males with breast cancer. It has been estimated that 0.7–29% of such families are accounted for by mutations in *BRCA1*, and 1.5–25% are accounted for by mutations in *BRCA2* (REFS 6–9). Although these reports represent a wide range of population proportions, most evidence suggests that, in general, germline mutations in known breast cancer risk genes account for ~20% of breast cancers associated with family history^{10,11} (previously reviewed by Szabo and King¹²). It is therefore crucial to understand the

contribution of *BRCA1* and *BRCA2* mutation-associated risks to these breast cancer populations.

Studies of *BRCA1* and *BRCA2* mutation frequencies have revealed great differences in populations from different geographic regions and ethnicities. For example, 34% of Swedish high-risk families carry deleterious *BRCA1* mutations, and 69% of these are a single mutation. However, only 2% carried mutations in *BRCA2* (REF. 13). By contrast, 32% of similarly high-risk Sardinian families carry one of two common *BRCA2* mutations, and 11% carry a single *BRCA1* mutation¹⁴. In Poland, 64% of high-risk families carry a *BRCA1* mutation (one of nine recurring mutations), but rarely any *BRCA2* mutations¹⁵ (similar ranges are reviewed by Szabo and King¹²). As we approach the goal of personalized medicine, it is important to recognize the contribution of an individual patient's genotype to her (or his) breast cancer risk, as well as the gene–gene and gene–environment relationships that may modify mutation penetrance in each individual.

Mutation prediction and detection

Patients seeking genetic counselling for breast and/or ovarian cancer risk will be assessed for the likelihood of carrying a *BRCA1* or *BRCA2* mutation. Knowing the frequency and range of mutations in a given population can therefore be an important factor in deciding whether to seek genetic testing.

Patients seeking *BRCA1* or *BRCA2* genetic testing in a clinical setting will be tested by complete sequencing of

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At a glance

- Inherited mutations in the *BRCA1* and *BRCA2* tumour-suppressor genes are the strongest indicators of breast and/or ovarian cancer risk.
- Understanding the limitations of the various mutation ascertainment methods is crucial when assessing the literature reporting *BRCA1* and *BRCA2* mutation frequencies in different populations.
- Prevalence of *BRCA1* and *BRCA2* mutations among high-risk cancer patients may vary by ethnicity, study inclusion criteria and mutation detection techniques.
- Many studies focus on the prevalence of *BRCA1* and *BRCA2* mutations in different ethnic populations. However, the cancer risks associated with these mutations are a function of mutation penetrance.
- Founder mutations in some populations may affect the prevalence of inherited *BRCA1* and *BRCA2* mutations. The limited genetic variability in members of founder populations can help reduce the variability in penetrance of *BRCA1* and *BRCA2* mutations, providing a more reproducible assessment of true *BRCA1* and *BRCA2*-associated cancer risk in these populations.
- Clinicians who are interested in providing personalized cancer-risk counselling for patients should understand the contributions of *BRCA1* and *BRCA2* mutations in diverse populations, *BRCA1* and *BRCA2* mutation penetrance, and potential modifying factors that are particular to a patient's ethnicity, family history and environmental influences.

coding regions in most cases (BOX 1); however, the basic and translational research literature reports a variety of different mutation detection methods, each with its own strengths and weaknesses. As a result, there are significant inconsistencies between studies. Most detection strategies begin with a rapid determination of which exons or exon fragments carry sequence variations, then only those fragments are sequenced. Most of these methods identify PCR fragments with variant base sequences or heteroduplex denaturation–reassociation products resulting from mismatched strands at points of heterozygosity. Because most *BRCA1* and *BRCA2* mutations are protein truncating, many investigators have used a protein truncation test (PTT) to identify truncated *in vitro* transcription and/or translation products from patient complementary DNAs or large exons from genomic DNA. The sensitivities and specificities of the various detection methods have been reviewed and compared elsewhere^{16,17}.

According to the [Breast Cancer Information Core](#) (BIC; version modified 31 January 2007), the deleterious mutations clinically identified in *BRCA1* and *BRCA2* so far include a small number of missense mutations and a much larger number of protein-truncating mutations.

Missense mutations. There have been 27 *BRCA1* missense mutations reported, affecting 15 codons (FIG. 1). These lie primarily in regions encoding the *BRCA1* protein RING and BRCT domains, which are known to be involved in functionally important protein–protein interactions. Ten missense mutations affecting eight codons have been reported for *BRCA2*. Four mutations in the first codon of *BRCA1* (M1I, M1R, M1T and M1V) and three in the first codon of *BRCA2* (M1R, G-to-T M1I and G-to-A M1I) are included with the list of known missense mutations, but the effects of the base changes in the first codon are more likely to be related to translation initiation than amino-acid substitution *per se*.

Additionally, several missense mutations are categorized as such by their predicted amino-acid substitutions, yet the base changes may have more to do with splicing defects because of their proximity to intron–exon junctions.

Truncating mutations. These include nonsense mutations, frame-shift mutations due to small insertion and/or deletion events, and mutations within splice sites. Over 670 truncating mutations have been reported for *BRCA1*, and over 730 for *BRCA2*. These mutations occur throughout the lengths of the two genes¹⁸. In both genes, truncating mutations are far more frequently observed than deleterious missense mutations.

Larger genomic alterations. In addition to point mutations that can be detected within a PCR fragment, *BRCA1* and *BRCA2* are both known to have germline mutations resulting from larger-scale genomic rearrangements that result in duplications or deletions of one or more exons, usually producing premature stop codons. Depending on the selection criteria and the nationality of the study group, large-scale rearrangements in *BRCA1* have been reported as frequently as 2–12% among high-risk families^{19,20}, and might represent 7–40% of all *BRCA1* mutations identified^{21,22}. More recently, such mutations have been identified in *BRCA2* in 2–8% of high-risk families, again varying with the selection criteria and the population studied^{20,23,24}. Such mutations could not be detected by traditional methods, so their contribution to mutation frequencies in different populations might not always be reported.

Patient prevalence. Dozens of studies examining 100 or more subjects have been reported, showing the frequency of deleterious *BRCA1* and/or *BRCA2* mutations in individuals considered at high risk for carrying mutations by reason of family history in different ethnic and geographical populations. Nearly the same number of studies have been performed on cohorts of fewer than 100 subjects. Although the contribution of *BRCA1* and *BRCA2* mutations to cancer risk is clearly different in different populations, the true extent of these differences is difficult to gauge given the wide variety of patient inclusion criteria and mutation ascertainment methods used in different studies. For example, one study of high-risk patients in the Czech Republic found frequencies of 23.6% *BRCA1* and 11.6% *BRCA2* mutation carriers in a large population²⁵, whereas an earlier study of Czech patients with similar inclusion criteria suggested only 2% *BRCA1* and 2% *BRCA2* mutation carriers²⁶. There could be several explanations for these differences, but one likely possibility is that the more recent study ascertained mutations using complete sequencing of all *BRCA1* and *BRCA2* exons and intron–exon boundaries, whereas the earlier study identified variants using PTT and heteroduplex analysis, then sequenced only potential positives from these assays. Such pre-screening methods could reduce detection sensitivity. In another example, a study of high-risk Latina women from the United States showed a 0.7% frequency of *BRCA1* mutations⁷, whereas another study published the same year on another large

Protein truncation test (PTT). A method of identifying truncating mutations from PCR-amplified cDNA or genomic exons using coupled *in vitro* transcription and translation followed by gel electrophoresis of labelled polypeptides.

High-risk patient
A patient from a high-risk family, or a family with multiple (especially first-degree) affected members. Such families with breast cancer may also be associated with ovarian cancer, bilateral breast cancer, male breast cancer and/or early-onset disease. These families are considered more likely than average to carry a high-penetrance (or high-risk) mutation in *BRCA1* or *BRCA2*.

Heteroduplex analysis (HA). A rapid method to detect mutations that relies on the fact that double-stranded DNA molecules with a single base-pair mismatch mutation migrate in gel electrophoresis to a different location compared with molecules that do not have a mismatch mutation.

Box 1 | Mutation screening in patients

Several models have been devised, on the basis of personal and family cancer history and mutation-prevalence tables, to predict a patient's likelihood of carrying a *BRCA1* or *BRCA2* mutation. The BRCAPRO model assumes Mendelian inheritance of the autosomal dominant *BRCA1* or *BRCA2* mutations^{133,134}, whereas the breast and ovarian analysis of disease incidence and carrier estimation algorithm (BOADICEA) estimates the likelihood of *BRCA1* and *BRCA2* mutations in a way that accounts for polygenic, low-penetrance factors and *BRCA1* and *BRCA2* modifiers that are known to contribute to some familial breast and/or ovarian clusters^{129,135}. These and other models have been compared and reviewed elsewhere^{133,136–138}. As always, the most useful models for predicting patient risk will include estimates of both mutation frequency and mutation penetrance (see below), and these may differ in different ethnic or geographic populations¹³⁹. Parameters for each model should be adjusted accordingly in different clinical settings.

Individuals seeking genetic testing for *BRCA1* and *BRCA2* mutations in the United States are screened by Myriad Genetics, or in laboratories with rights licensed by Myriad. Unless patients are specifically interested in a known family mutation or high-frequency mutations that are specific to certain ethnic groups, both genes are typically sequenced entirely and, additionally, tested for some recurring *BRCA1* rearrangements^{19,140–142}. Outside of the United States, mutation screening is not necessarily performed by Myriad, but in different laboratories that are established according to guidelines of individual countries. In the United Kingdom, for example, *BRCA1* and *BRCA2* mutation testing is offered by regional clinics run by the National Health Service in cases in which patients meet family history criteria set by a national standard, as determined by their physicians.

cohort of high-risk Latina individuals showed a 23% frequency²⁷. Both studies used complete sequencing to identify mutations, but the first study included patients with two or more affected first-degree relatives (breast or ovarian cancer) with no selection for age of onset, while the second study used more stringent criteria for high-risk status, including age of disease onset.

Clearly, evaluating the literature describing prevalence of *BRCA1* and *BRCA2* mutations among high-risk patients requires an assessment of both cohort selection criteria and also mutation ascertainment methods, but does one have a greater influence than the other? Obviously the answer could be different in every case, but one example illustrates the power of limited methodologies to overwhelm other factors. Two studies from two American cancer risk clinics showed very different frequencies of *BRCA2* mutations in cohorts of high-risk patients. Nanda *et al.* reported a 25% frequency of *BRCA2* mutations in patients from families with two or more cases of breast and/or ovarian cancer among first- or second-degree relatives²⁸, whereas Vaziri *et al.* reported only a 1.9% frequency of *BRCA2* mutations in patients from families with three or more affected first-degree relatives, weighted toward early-onset disease and disease occurrence in two or more generations²⁹. Interestingly, the study with the less stringent criteria for at-risk status²⁸ showed a higher frequency of *BRCA2* mutations than the study with the more stringent inclusion criteria. It may be that the different results in these and numerous other studies are influenced by demographic differences between cohorts that make reproducibility difficult. However, it is worth noting that Nanda *et al.* used complete sequencing as the mutation detection method, whereas the Vaziri *et al.* study used a combination of pre-selection techniques to limit the number of exons sequenced directly.

Sporadic breast cancer. Mutations in *BRCA1* or *BRCA2* have become associated with high-risk families, yet it is important to understand the likelihood of these mutations occurring in individuals who are not from high-risk families. As breast and ovarian cancer occurring in the same family is a hallmark for *BRCA1* and/or *BRCA2* mutation carriers, several investigators have sought to address the frequencies of *BRCA1* and *BRCA2* mutations in ovarian cancer patients unselected for family history or age of disease onset. The results suggest *BRCA1* mutation frequencies ranging from 4 to 29% and *BRCA2* mutation frequencies from 0.6 to 16% (TABLE 1). Similarly, several groups have investigated the frequencies of these mutations in early-onset breast cancer cases, again unselected for family history (TABLE 1), finding *BRCA1* mutation frequencies from 0.7 to 10% and *BRCA2* mutation frequencies from 1 to 6% (TABLE 1). Interestingly, one analysis of a cohort of breast cancer cases diagnosed at age 40 years or younger from the Australian Breast Cancer Study showed that roughly 5% of these early-onset cases carried either a *BRCA1* or a *BRCA2* mutation³⁰. This study confirmed other studies that showed that the likelihood of finding a mutation in either *BRCA1* or *BRCA2* increases in line with the number of affected first-degree relatives. However, this study also showed that most early-onset patients in whom *BRCA1* and *BRCA2* mutations were identified had no family history of breast cancer. Thus, although the frequency of mutations among individuals with strong family history may be greater than the frequency in patients with no family history, in a clinical setting the proportion of patients with family history may be small compared with that of patients without family history³⁰. The important conclusion for clinicians is that it is likely most *BRCA1* and *BRCA2* mutations occurring in a clinical setting will be present in individuals with no family history of breast cancer.

Finally, the observation that male breast cancer is the single inherited breast cancer susceptibility phenotype not associated with *BRCA1* mutations (the observation that prompted the search for *BRCA2*), inspired several studies that examined the frequencies of *BRCA2* mutations in male patients with breast cancer unselected for family history or age of onset, revealing *BRCA2* mutation frequencies of 7–14% (TABLE 1).

The studies listed in TABLE 1 indicate that identifying the prevalence of *BRCA1* and *BRCA2* mutations in patients without strong family histories would be informative. By examining cohorts that retain isolated features of high-risk families (ovarian cancer, early-onset breast cancer or male breast cancer), these studies begin to address the relative predictive values of individual high-risk familial phenotypes for identifying *BRCA1* and *BRCA2* mutations. In general, patients unselected for family history but who nonetheless have ovarian cancer, early-onset breast cancer or male breast cancer, are more likely than sporadic cases to harbour *BRCA1* and *BRCA2* mutations. Overall, it is likely that the true frequency of *BRCA1* and *BRCA2* mutations, with the exception of high-frequency founder mutations (see below), cannot be shown rigorously to differ between

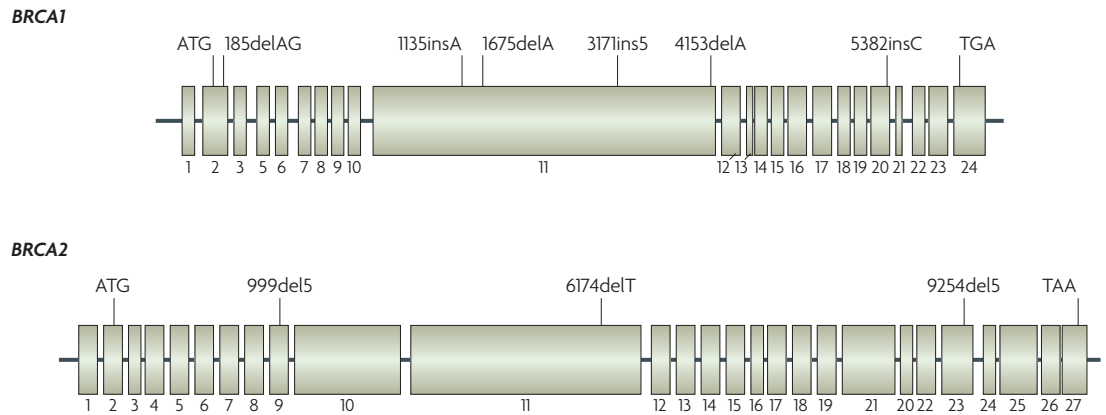


Figure 1 | Position of several founder mutations within *BRCA1* (top) and *BRCA2* (bottom). Exons are indicated by shaded boxes. Exon numbers are shown beneath. Note that *BRCA1* has no exon 4, owing to a correction made after the initial description. The open-reading frames are indicated by ATG in exon 2 of both genes, and the termination codons by TGA (*BRCA1*) and TAA (*BRCA2*). Positions of founder mutations described in TABLE 3 are indicated above.

populations, as no single definition of ‘high-risk family’ or ‘early-onset disease’ is equally applicable to all populations, and penetrance modifiers of mutations (a major influence in the appearance of affected family members) will not be similar in all genetic and environmental backgrounds. However, understanding the role of *BRCA1* and *BRCA2* mutations as risk factors in patients with no particular personal or family cancer history is crucial to understanding breast and ovarian cancer risk factors in general populations, although the low frequency of these mutations in general populations makes risk difficult to determine with statistical rigour. To overcome these challenges, several groups have taken advantage of multi-institutional collaborative studies to identify *BRCA1* and *BRCA2* mutation frequencies in large cohorts of breast and ovarian cancer patients unselected for family history, age of onset or other indicators of high-risk status (TABLE 2). As anticipated, the mutation frequencies in different populations are generally low (0–7% for *BRCA1* and 1–3% for *BRCA2*; TABLE 2).

Thus, some *BRCA1* and *BRCA2* mutation carriers without family history of disease may have comparatively low (but still clinically significant) mutation-associated penetrance, whereas others may have uninformative family structures that do not reveal family history regardless of mutation penetrance, such as small size, few female relatives or patrilineal inheritance of the mutation. In the future, genetic counsellors advising patients on whether to seek genetic testing may cooperate with pathologists and molecular biologists to take advantage of other biological indicators of *BRCA1* and *BRCA2* mutation status. For example, it has been demonstrated that the gene expression profiles of sporadic and *BRCA1*-associated tumours are distinct³¹ and the immunohistopathological profile of *BRCA1*-associated tumours, phenotypically a subset of basal-like tumours (having molecular markers that are characteristic of basal epithelial cells; see below), are also distinguishable from other tumour subtypes^{32,33}. Such distinguishing characteristics are already providing the basis for future predictions of *BRCA1* and

BRCA2 mutation status. For example, women with ‘triple negative’ — ER⁻, PR⁻ and HER2⁻ — breast cancer are candidates for *BRCA1* testing, and new genomic technologies are being developed to make it more practical to carry out large numbers of predictive tests in a clinical setting, as those with a family history probably represent only a fraction of mutation carriers.

Once a mutation has been identified, patients need to be counselled on their likelihood of developing cancer, that is, they need to know the penetrance of their mutations in the context of their own genetic and environmental backgrounds. Although penetrance estimates for *BRCA1* and *BRCA2* mutations are vital to risk assessment, they remain highly controversial. Some studies examined penetrance in very high-risk families (four or more breast cancer cases) with a *BRCA1* or *BRCA2* mutation carrier proband. Age-specific cumulative risks by 70 years were typically high in these families, with *BRCA1* or *BRCA2* mutation carriers having an 80–87% likelihood of developing breast cancer, and a 27–63% likelihood of developing ovarian cancer^{34–36}. One study showed a lower risk of breast cancer (67%) among *BRCA2* mutation carriers in families with four or more cases of breast or ovarian cancer³⁷. A more recent study using families from high-risk counselling clinics with varying inclusion criteria found even lower penetrance for *BRCA1* and *BRCA2*, with breast cancer risks of 46% and 43%, respectively, and ovarian cancer risks fell within the broad ranges reported previously, 39% and 22%, respectively.

To ascertain the true penetrance of *BRCA1* and *BRCA2* mutations in more general populations, several laboratories have worked to determine the penetrance of mutations found in large hospital-based cohorts that have not been selected for family history or ethnicity. As the frequency of *BRCA1* and *BRCA2* mutations in such unselected populations is typically so low that it precludes meaningful statistical analysis, some of these studies used populations selected for age of onset, anywhere between 40 and 55 years of age, in order to enrich for *BRCA1* and *BRCA2* mutations.

Proband
The affected person that identifies a family for study.

Table 1 | Mutation frequencies in non-family-history cohorts

Population	BRCA1 mutation frequency, %	BRCA2 mutation frequency, %	Refs
Ovarian cancer, unselected			
Czech Republic	10	Not determined	144
Japan	3.9	Not determined	145
Norway	4	Not determined	146
Pakistan	13.3	2.5	147
Sweden	7.4	0.6	148
Turkey	9.8	6.9	149
USA	8.6	0.9	150
USA (Ashkenazim)	28.6	15.6	151
Breast cancer, early onset			
Australia	3.3	Not determined	152
Britain	2.6	2.3	9
	0.7	1.3	38
Germany	3.3	2.2	153
Iran	3.6	2.4	154
Korea	10	8.3	155
Spain	0.8	4	156
	0.7	5.9	157
Sweden	6.8	2.1	158
USA	10.5	6.5	125
	5.9	3.4	159
Male breast cancer			
Iceland	Not determined	7.1	160
Poland	Not determined	11	161
Spain	Not determined	5.9	162
USA	Not determined	14	163

Results from these studies, again, show risks of breast cancer that are associated with deleterious mutations in *BRCA1* or *BRCA2* to be somewhat lower (47–57% and 31–56%, respectively, by the age of 70 years) than the risks ascertained from studies of high-risk families^{38–40}. The ranges of ovarian cancer risks in these studies narrowed considerably for mutations in *BRCA1* and *BRCA2* (36–39% and 10–11%, respectively, by the age of 70 years)^{38,39}. Risch *et al.* estimated a *BRCA1*-mutation-associated risk by the age of 80 years of 68% for breast cancer and 36% for ovarian cancer⁴¹. Other studies evaluated the cancer risks associated with *BRCA1* and *BRCA2* mutations together, finding a 40% risk of breast cancer by the age of 70 years³⁰ or risks of breast or ovarian cancer of 73.5% and 27.8%, respectively, by the age of 80 years⁴². Again, these studies show that the penetrance of deleterious *BRCA1* and *BRCA2* mutations is lower overall in a general population than in high-risk families, but the variability is broad and the confidence intervals are wide. Reasons for this variability may include different cut-off ages used to define early onset in different populations,

pedigree-specific genetic and/or environmental modifiers, or different ethnically-defined genetic mixes in the different populations studied.

Some of the variability within and between studies may be due to real biological differences between populations. For example, several studies have shown that the penetrance for some deleterious mutations in some populations has actually increased several-fold over recent decades, so the ages of the subjects in a given study could affect the outcome of the penetrance estimates considerably^{39,43,44}. Other studies describe the importance of determining whether subjects within affected families have had prophylactic oophorectomies or mastectomies. These procedures have been shown to have benefits in *BRCA1* and/or *BRCA2* mutation carriers in both reduced cancer risk and prolonged life expectancy^{45–47}, and it has been demonstrated that individuals who test positive for *BRCA1* and *BRCA2* mutations seek prophylactic surgeries in large numbers^{48,49}. This can have a great effect on risk estimates ascertained through prospective studies^{50,51}. Yet information relating to prophylactic surgeries is not always collected from study populations used to determine penetrance.

Some discrepancies between penetrance estimates in different studies may also be due to differences in statistical analyses of results. For example, although most agree that *BRCA1* and *BRCA2* mutation penetrance may appear higher in carriers from high-risk families using raw data, there are different methods used to make statistical corrections for these overestimates^{37,51}, and there may be different results when reporting relative versus absolute risks³⁹. Differences may also occur when important parameters are estimated rather than measured directly. For example, most studies use statistical models to estimate the number of mutation carriers in families with a proband, whereas King *et al.* (2003) used direct sequencing to determine the mutation status of members in affected families. Unlike other studies, this study concludes that mutation carriers with no family history of breast and/or ovarian cancer have as great a cancer risk as those from high-risk families⁴⁴. Likewise, penetrance estimates may seem different in prospective versus retrospective studies of family members carrying deleterious *BRCA1* and/or *BRCA2* mutations⁴⁰.

Different penetrance estimates have also been described for specific *BRCA1* and *BRCA2* mutations^{52,53}. Among the most extensively described of these different mutation-specific phenotypes are those associated with mutations that fall within the proposed *BRCA2* ovarian cancer cluster region (OCCR) — a region of ~3.3 kb in exon 11 in which truncating mutations are associated with a higher incidence of ovarian cancer compared with breast cancer, relative to truncating mutations in other regions of *BRCA2* (REFS 41,54–56). As these are truncating mutations, it would be expected that the mutant transcripts would be subject to nonsense-mediated mRNA decay (NMD), resulting in reduced mRNA levels from the mutant allele^{57,58}. However, NMD has varying levels of efficiency, and it is certainly possible that these

Oophorectomy
Surgical removal of the ovaries.

Nonsense-mediated mRNA decay
(NMD). The process by which mRNA molecules carrying stop codons in any but the 5'- or 3'-most exon are degraded by a regulated pathway.

Table 2 | Mutation frequencies in general breast cancer populations

Population	BRCA1 mutation frequency, %	BRCA2 mutation frequency, %	Refs
China	1.1	1.1	164
The Netherlands and Belgium	2.2	Not determined	165
Finland	0.4	1.4	166
Pakistan	4.4	2.3	147
Poland	3	Not determined	167
Sweden	7	Not determined	168
	<1	Not determined	169
USA	2.4	2.3	124
	3.3	Not determined	123
USA — African Americans	0	Not determined	123
	1.4	2.6	124

suggested mutation-specific phenotypes reflect some amount of mRNA that escapes NMD in the pre-cancerous cells in which these causative mutations exert their deleterious effects, or that NMD itself is misregulated in cancer cells, affecting the aetiology of tumours in a BRCA2-mutation-specific manner. Still, the phenotypes reported for the OCCR are not reproducible in all populations⁵⁹, and NMD has been observed to affect mRNA containing BRCA2-OCCR-truncating mutations⁶⁰. As yet, no truncated BRCA2 protein has ever been demonstrated to accumulate in cells carrying OCCR mutations.

Different mutation-specific phenotypes have been ascribed to some BRCA1 mutations but, again, no truncated proteins have yet been observed. Indeed, NMD has been examined directly in BRCA1 (REF. 61) using lymphoblastoid cell lines from affected families. In this regard, perhaps the most informative BRCA1 mutations are the set of large-scale rearrangements that remove both promoter sequences and the first exon of BRCA1 (REFS 22,62). These mutations may be thought of as true molecular nulls, as they are not transcribed. So far there has been no observed phenotypic difference between these mutations and many other truncating BRCA1 mutations, providing a phenotypic standard for their null status.

Founder mutations

One of the most useful ways to approach penetrance estimates is to examine founder mutations, or high frequency individual alleles that are particular to a specific population. The concept of a founder effect was described by Ernst Mayr⁶³ to explain the reduced genetic variability of some small populations relative to their parent populations. He proposed that, in cases where the small population was founded by a small number of individuals, they would carry only a small subset of the genetic variability of the parent population. Such a geographically isolated subpopulation (or parent population that suffers a dramatic decrease or bottleneck) could then give rise to larger populations with a conspicuous lack of overall genetic diversity, regained as new variants occur spontaneously or migrate in from other populations^{64,65}.

The founder effect has been used to explain the high frequencies of disease-associated mutations in specific human populations. Classic examples include the high frequencies of the Tay–Sachs mutation in Jewish populations from eastern Europe (Ashkenazi Jews)⁶⁶. It has been estimated that the average individual carries four recessive-lethal mutations in the heterozygous state⁶⁷, so a founder population of 40 individuals isolated from a larger parent population would be expected to carry over 100 deleterious mutations⁶⁶. Likewise, a mutation that immigrated or arose *de novo* within a small population would be likely to have a higher frequency among descendants than if it had occurred in a larger population. Such founder mutations would therefore appear as high-frequency, deleterious mutations in unrelated families from closed populations that exhibit overall low genetic diversity.

When describing a recurring mutation as a potential founder mutation, it is important to show the mutation occurred only once in history. There are several examples of recurring mutations in BRCA1 and BRCA2 that arose multiple times in different populations because their particular local DNA-sequence environments create mutational hot spots. Such recurring mutations do not represent founder mutations. To make the distinction between single and multiple historical occurrences of the same mutation, it is necessary to look at genetic marker variants that are close enough to the mutation to remain associated through numerous generations, with little or no separation by meiotic recombination. Useful markers include single nucleotide polymorphisms and

Box 2 | Using founder mutations to identify disease-associated genes

As founder mutations occur in the context of single haplotypes, and founder populations have less genetic diversity than more outbred populations, it is efficient to use founder populations in which certain diseases are unusually prevalent to identify genes that are associated with inherited disease predisposition. In such populations, the common haplotypes that are linked to causative mutations may be detected not only in affected members of high-risk families, but also, to some extent, in unrelated families within the population. This reduction of genetic variability of causative mutations has proved fruitful in identifying disease-associated genes in founder populations. The Finnish population, for example, is descended from a small number of founders and there has been little immigration over the past 80–100 generations. As a result, the Finnish population have an unusually high frequency of several inherited diseases (reviewed by de la Chapelle and Wright¹⁴³). This population has enabled the identification of founder mutations and the cloning of genes responsible for several disorders, such as diastrophic dysplasia, progressive myoclonus epilepsy and chloride diarrhoea¹⁴³.

Tay–Sachs

A genetic disorder found in East European Jewish families. It is a lysosomal disease in which there is a deficiency of hexosaminidase A, an enzyme that degrades ganglioside GM2. The build-up of GM2 affects the brain and nerves leading to the death of affected children by 5 years of age.

Table 3 | *BRCA1* and *BRCA2* founder mutations identified in various populations

Nationality (ethnicity, if specified)	<i>BRCA1</i> mutation	<i>BRCA2</i> mutation	Comments	Refs
Germany	5382insC	–	Found in 4% of cases with family history and 1% of unselected BrCa cases	170
Iceland	–	999del5	4.1% of OvCa cases	86
Israel (Ashkenazim)	185delAG 5382insC	6174delT	Of BrCa and/or OvCa examined: 185delAG, 33%; 5382insC, 0%; 6174delT, 29%	76
Norway	1675delA 1135insA	–	Of unselected OvCa cases examined: 1675delA, 2.1%; 1135insA, 0.8%	171
Poland	5382insC 4153delA	–	Of high-risk families: 5382insC, 9.4% Of unselected ovarian cancer cases, 5382insC, 7.7%; 4153delA, 2.2%	172–174
Spain	–	9254del5	9254del5 found in 1% of high-risk families examined	175
Sweden	3171ins5	–	3171ins5 found in 23–26% of high-risk families examined	176,177
USA (Ashkenazim)	185delAG 5382insC	6174delT	Of high-risk families: 185delAG, 41.1%; 5382insC, 5.9%; 6174delT, 5.9% Of unselected OvCa cases: 185delAG, 19–61%; 5382insC, 9%; 6174delT, 30% Of early-onset BrCa: 185delAG, 6.3%; 5382insC, 1.9%; 6174delT, 2–7.5% Of unselected BrCa cases: 185delAG, 3–23%; 5382insC, 0.75%; 6174delT, 3%	73,74,77, 178–182

microsatellite markers, also known as short tandem repeats. A series of nearby markers that segregate together as a unit through generations constitutes a haplotype. A recurrent mutation that occurs on a single haplotype in a population may be considered a founder mutation, while a mutation that occurs on more than one haplotype is considered to have occurred multiple times in the population history and is not a founder mutation.

Although founder populations in general are especially useful for gene discovery, founder mutations in *BRCA1* and *BRCA2* have been useful in defining mutation-associated risks in specific populations (BOX 2). Three of the best-characterized *BRCA1* and *BRCA2* founder mutations are found in Ashkenazi Jewish populations (TABLE 3). The Ashkenazim are European Jews, historically separated from other major groups in Africa and the Middle East, though they generally trace their origins to the Near East before the Roman exile⁶⁸. Ashkenazi Jewish populations have an unusually high prevalence of more than 20 known recessive disease-associated mutations, and genetic evidence suggests this reflects a founder effect resulting from a population bottleneck within the last millennium that resulted in a low number of maternal ancestors^{69,70}. The mutations *BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT have been identified in 0.8–1%, 0.1–0.4% and 1–1.5%, respectively, of Ashkenazi Jewish populations^{71,72}. Among Ashkenazi breast cancer cases, these three founder mutations combined account for 6.7–11.7% of all patients^{73,74}, 59% of patients from high-risk breast cancer families⁷⁵, 30% of cases diagnosed under the age of 40 years⁷⁶, and 24–62% of ovarian cancer cases occurring in patients that have not been selected on the basis of family history^{75–77}. Although these three founder mutations are not identified in all high-risk breast and/or ovarian cancer families, they do represent the majority of germline *BRCA1* and *BRCA2* mutations found in Ashkenazi Jewish populations^{78,79}. Indeed, one study has found only 16 out of 74 (21%) *BRCA1* and *BRCA2* mutations identified in an Ashkenazi population were non-founder *BRCA1* and *BRCA2* mutations⁸⁰.

It is worth noting that *BRCA1* 185delAG is not found exclusively in Ashkenazi patients. This mutation has been found in patients of Spanish ancestry as well as other ethnic groups, sometimes with frequencies similar to those in Ashkenazi populations^{81–83}, suggesting that this mutation may have existed before the Jewish diaspora. That is, because of the history of the Ashkenazi Jews, it is to be expected that this founder mutation may be identified in populations that do not identify themselves as historically Ashkenazi. That this variant has been found in patients of Spanish ancestry is probably because many Sephardic Jews were forced to convert to Roman Catholicism, and it is probably a marker for Jewish ancestry among Spaniards. Additionally, it has been suggested that microsatellite markers flanking 185delAG are consistent with it having arisen independently in at least two populations or subpopulations⁸³, but these results have not been tested further with higher-resolution assays.

Another well-studied founder mutation is the Icelandic founder mutation *BRCA2* 999del5. Genetic evidence, in accordance with demographic data, suggests the Icelandic population was subject to a greater level of genetic drift than other European populations, resulting in reduced genetic variation. The founder effect is evident from the comparatively small number of mitochondrial lineages, mostly originating from Scandinavia and the British Isles⁸⁴. The *BRCA2* 999del5 mutation, the sole high-frequency founder mutation in Iceland, was found in 0.4–0.6% of unaffected Icelanders, 7.7–8.5% of breast cancer cases that had not been selected on the basis of family history or age of onset, 6–7.9% of ovarian cancer cases^{85–87} and 40% of breast cancers occurring in males⁸⁸.

Founder mutations and penetrance. The Ashkenazi founder mutations (*BRCA1* mutations 185delAG and 5382insC, and *BRCA2* mutation 6174delT) and the Icelandic founder mutation (*BRCA2* 999del5) have been used for penetrance analysis. In addition to the

Short tandem repeat

A chromosomal region containing variable tandem repeat numbers of single or short nucleotide repeat sequences.

Genetic drift

Random changes in allele frequencies over generations. This dynamic of random sampling has a greater effect in smaller populations.



Figure 2 | Mercator projection of the Earth illustrating the “out of Africa” theory of early human migrations. It is suggested that human origins were in eastern Africa, and then different groups migrated to populate other parts of Africa, Europe and Asia, Australia and the Americas.

increased likelihood of finding a statistically useable number of *BRCA1* and/or *BRCA2* mutations in these populations, these founder mutations also allow examination of penetrance in a minimally heterogeneous genetic background, providing insights into potential genetic and/or environmental modifiers of *BRCA1* and *BRCA2* mutation-associated cancer risks. In most studies, cancer risks in carriers of these founder mutations are indeed lower when patients are not selected for family history, although the range of penetrance estimations in different studies is broad. Some show age-specific cumulative risks for breast cancer in these carriers to be 26–60%^{74,75,89–93}, whereas others found higher risks, up to 80%^{43,44,85,93}. These four founder mutations are associated with a similarly broad range of ovarian cancer risks (12–40%) by the age of 70 years^{44,89,93,94}.

Such population-specific genetic risk assessments already affect the clinical testing options available to high-risk families. For example, individuals of Ashkenazi Jewish ancestry may be advised to seek genetic testing for only three high-frequency *BRCA1* and *BRCA2* founder mutations before considering the more expensive complete sequence analysis of both genes^{95,96}. The efficiency of this strategy has prompted numerous hunts for similar high-frequency mutations in other ethnic groups, with some success.

Mutations in non-founder populations

Although founder populations can be useful for studying genetic diseases with minimal background heterogeneity, not all cancer patients are descended from such populations. For example, patients of African ancestry have less frequent but more aggressive breast cancers than other populations, whether they live in Africa or elsewhere in African diaspora populations^{97,98}. Yet understanding the contribution of *BRCA1* and *BRCA2* to populations of African ancestry poses unique challenges that cannot be completely anticipated from the assumptions practiced in analysis of founder populations.

Traditionally, modern humans were thought to have arisen from a small population in Africa during the late Pleistocene, replacing other archaic *Homo* taxa^{99–101}. However, more recent evidence from mtDNA and non-recombining Y-chromosome sequences suggest a more complex ‘mosaic’ of multiple origins of the modern *Homo*¹⁰². In all cases, models suggest one or more bottleneck events associated with human migrations out of Africa^{100,103} (FIG. 2), such that emigrating populations carry only subsets of the genetic diversity in Africa-originating populations.

African populations show significantly higher levels of genetic diversity than other populations, reflected in over 2,000 distinct ethnic groups and languages^{104–106}. Indeed, there is greater genetic diversity within and between different African populations than between African and Eurasian populations^{107,108}. During the Atlantic slave trade from the 15th to the 19th century, over 45 ethnic groups were brought to the Americas from African regions ranging from Senegambia to west Central Africa, and even some groups from south-east Africa. Additionally, modern descendants from these groups carry genetic admixtures of roughly 20% non-African origin^{109,110}.

Founder mutations have been difficult to identify in African and African-American populations, perhaps partly due to the potentially high background genetic diversity of the populations examined, and possibly in part because of the paucity of studies focused on these populations. One potential founder mutation, *BRCA1* 943ins10, has been identified in patients from Washington DC, Florida, South Carolina and Côte d’Ivoire (formerly known as the Ivory Coast)^{111,112}. Although haplotype analysis demonstrates that this mutation probably has a single origin and does not represent a mutational hot spot, no study has determined the prevalence of this mutation in any African or African-American population. Several other potential founder mutations have been proposed because of anecdotal recurrence, but few have been examined for shared haplotypes, and none has been examined for population prevalence. If one does emerge as a true founder mutation, it is unlikely that it will constitute a large proportion of all *BRCA1* and *BRCA2* mutations within a population, in contrast to the founder mutations associated with the Ashkenazi and Icelandic populations.

Most studies that have described the population and family risks associated with inherited *BRCA1* and *BRCA2* mutations have used primarily Caucasian populations, leaving patients of African ancestry understudied. Additionally, phenotypic similarities between breast cancers in Africans and African Americans and in *BRCA1* mutation carriers suggest a potential distinctive genetic contribution to breast cancer risk and/or aetiology in patients of African ancestry. Although breast cancers occur less frequently in patients of African ancestry than in other groups, they tend to occur at earlier ages and are more frequently associated with aggressive tumour features, such as comparatively high frequencies of medullary or atypical medullary carcinoma, poor differentiation, aneuploidy, p53 mutations and oestrogen

receptor-negative and progesterone receptor-negative status (reviewed previously^{112,113}). These features are in many ways similar to features associated with *BRCA1* mutation carriers^{32,114–116}.

Some of these general descriptions of *BRCA1*-associated tumours have been associated with tumour categories defined by microarray analysis. Perou and colleagues examined the expression pattern of thousands of genes from numerous breast tumours, and found that they fell into discrete clusters: one that looked like normal breast cells, one that was associated with overexpression of the growth factor receptor gene *ERBB2* (also known as HER2 and neu), one associated with a basal epithelial cell-type expression pattern, and two associated with luminal epithelial cell-type patterns^{117,118}. Strikingly, tumours from *BRCA1* mutation carriers have predominantly basal-like expression patterns, consistent with immunohistological patterns and poor prognoses¹¹⁹, and sporadic tumours with basal-like expression patterns frequently exhibit reduced levels of *BRCA1* expression^{120,121}. Likewise, these aggressive basal-like tumours occur with higher frequency in premenopausal African-American patients than other groups, potentially explaining, at least in part, the higher frequency of breast cancer mortality among African Americans¹²². Thus, although *BRCA1* mutations seem to occur with similar or lower frequency among African Americans than in other groups^{7,80,123–126}, *BRCA1*-associated pathways may have an especially important role in breast cancer development in patients of African ancestry, perhaps pointing the way to genetic or epigenetic modifiers of *BRCA1* activity.

Conclusions

The benefits of population genetic analysis of *BRCA1* and *BRCA2* could lie well beyond the hunt for high-frequency founder mutations. These studies could be the keys to several outstanding problems in risk assessment and genetic analysis. First, the option of genetic testing for *BRCA1* and *BRCA2* mutations is underused by some ethnic groups, in part because of cultural attitudes toward health care. It is therefore of great importance to be able to describe the genetic risks and testing benefits particular to every ethnicity, particularly underserved groups¹²⁷.

Second, most reported deleterious mutations in *BRCA1* and *BRCA2* are exonic lesions that are predicted to result in protein truncation. Others might be mutations in consensus splice donor or acceptor sites, or one of the few known deleterious missense mutations¹²⁸. Yet in many populations the majority of patients will also carry one or more clinically unclassified genetic variants with unknown effects on gene function. It is vital to determine which of these variants are benign polymorphisms and which could contribute to cancer risk.

Third, several statistical models can be used to predict the likelihood of carrying a *BRCA1* or *BRCA2* mutation on the basis of personal and family history of breast and/or ovarian cancer. Yet most tested individuals that are predicted to have a high probability of being mutation carriers have no identifiable *BRCA1*

or *BRCA2* mutations²⁸. In the absence of evidence for other high-penetrance cancer risk mutations^{129,130}, this could be due partly to the inadequacy of current testing methods to detect all potential deleterious mutations²⁰. As discussed previously, most *BRCA1* and *BRCA2* mutations are predicted to result in protein truncation or to disrupt canonical splice-site sequences, whereas some result from large genomic rearrangements and a few represent known missense mutations. To date, there has been no systematic study to identify non-obvious mutations that affect *BRCA1* or *BRCA2* gene transcription or mRNA processing, either because such mutations could lie far from the genes' exons, or because the potential deleterious effect is not always clear from the nature of the base substitution. Although there is little evidence that such potential categories of mutation have a significant role in *BRCA1*-associated and *BRCA2*-associated breast cancer risk, these mutation categories have been identified in other disease-associated genes, and there is interest in characterizing the potential protein functional effects of many unclassified sequence variants identified during genetic testing. Additionally, there are elegant models suggesting much inherited breast cancer risk could come from non-Mendelian, polygenic effects of low-penetrance genes not necessarily linked to *BRCA1* or *BRCA2* (REFS 10,131). Although such mutations are unlikely to explain much non-*BRCA1*-associated or non-*BRCA2*-associated familial relative risk, they could contribute significantly to the population-attributable fraction of cancer risk¹³². Population genetic studies could be the key to identifying deleterious mutations with hidden locations or hidden significance, determining whether low-penetrance mutations in *BRCA1* or *BRCA2* exist and whether they contribute to cancer risk through different aetiologies, and identifying genetic modifiers that affect *BRCA1* and *BRCA2* mutation penetrance.

Fourth, much of our current understanding of the variety and penetrance of deleterious *BRCA1* and *BRCA2* mutations has come from studies in which test cohorts that have the greatest likelihood of including many mutation carriers, because of early age of onset or multiple affected family members, were chosen. Yet in a typical clinical setting *BRCA1* and *BRCA2* mutation testing is recommended for patients with a range of mutation likelihoods, from moderate to high. Surprisingly, little information is available for gauging the prevalence of *BRCA1* and *BRCA2* mutations in cancer patients in a typical risk-assessment setting. The tools of population genetics are necessary to determine the true contribution of *BRCA1* and *BRCA2* mutations to cancer risk in the most relevant populations.

The *BRCA1*-associated and *BRCA2*-associated risks are different in geographical and historically defined groups. These differences make clear the importance of assessing a patient's risk with respect to her (or his) own genetic context. As the genetic stories of different populations are unfolded, we will see how evolving scientific tools and changing working assumptions of population genetics can help guide our understanding of clinically relevant *BRCA1* and *BRCA2* gene functions.

Polygenic

A model of genetic determinism in which genetic variants of multiple genes function in combination to produce a phenotype.

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DATABASES

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