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44. Harris, R.E., Alshafie, G.A, Abou-Issa, H. & Seibert, K. Chemoprevention of breast cancer in rats by celecoxib, a cyclooxygenase 2 inhibitor. *Cancer Res.* **60**, 2101–2113 (2000).
45. Torrance, C.J. *et al.* Combinatorial chemoprevention of intestinal neoplasia using an NSAID and an EGFR-kinase inhibitor. *Nature Med.* **6**, 1024–1028 (2000).
46. Vadlamui, R. *et al.* Regulation of cyclooxygenase-2 pathway by HER2 receptor. *Oncogene* **18**, 305–314 (1999).
47. Hynes, N.E. & Stern, D.F. The biology of erbB-2/neu/HER-2 and its role in cancer. *Biochim. Biophys. Acta* **119**, 165–184 (1994).
48. Perou, C.M. *et al.* Molecular portraits of human breast tumours. *Nature* **406**, 747–752 (2000).
49. Alizadeh, A.A. *et al.* Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* **403**, 503–511 (2000).
50. Houston, S.J. *et al.* Overexpression of c-erbB2 is an independent marker of resistance to endocrine therapy in advanced breast cancer. *Br. J. Cancer.* **79**, 1220–1226 (1999).
51. Sjogren, S., Inganas, M., Lindgren, A., Holmberg, L. & Bergh, J. Prognostic and predictive value of c-erbB-2 overexpression in primary breast cancer, alone and in combination with other prognostic markers. *J. Clin. Oncol.* **16**, 462–469 (1998).
52. Archer, S.G. *et al.* Expression of ras p21, p53 and c-erbB-2 in advanced breast cancer and response to first line hormonal therapy. *Br. J. Cancer* **72**, 1259–1266 (1995).
53. Berns, E.M. *et al.* Oncogene amplification and prognosis in breast cancer: relationship with systemic treatment. *Gene* **159**, 11–18 (1995).
54. Leitzel, K. *et al.* Elevated serum c-erbB-2 antigen levels and decreased response to hormone therapy of breast cancer. *J. Clin. Oncol.* **13**, 1129–1135 (1995).
55. Nicholson, R.I. *et al.* Epidermal growth factor receptor expression in breast cancer: association with response to endocrine therapy. *Breast Cancer Res. Treat.* **29**, 117–25 (1994).
56. Borg, A. *et al.* ERBB2 amplification is associated with tamoxifen resistance in steroid-receptor positive breast cancer. *Cancer Lett.* **81**, 137–144 (1994).
57. Wright, C. *et al.* Relationship between c-erbB-2 protein product expression and response to endocrine therapy in advanced breast cancer. *Br. J. Cancer* **65**, 118–121 (1992).
58. Jarvinen, T.A., Holli, K., Kuukasjarvi, T. & Isola, J.J. Predictive value of topoisomerase IIα and other prognostic factors for epirubicin chemotherapy in advanced breast cancer. *Br. J. Cancer* **77**, 2267–2273 (1998).
59. Rozan, S. *et al.* No significant predictive value of c-erbB-2 or p53 expression regarding sensitivity to primary chemotherapy or radiotherapy in breast cancer. *Int. J. Cancer* **79**, 27–33 (1998).
60. Paik, S. *et al.*, erbB-2 and response to doxorubicin in patients with axillary lymph node-positive, hormone receptor-negative breast cancer. *J. Natl. Cancer Inst.* **90**, 1361–1370 (1998).
61. Jacquemier, J. *et al.* Breast cancer response to adjuvant chemotherapy in correlation with erbB2 and p53 expression. *Anticancer Res.* **14**, 2773–2778 (1994).
62. Allred, D.C. *et al.* Overexpression of HER-2/neu and its relationship with other prognostic factors change during the progression of in situ to invasive breast cancer. *Hum. Pathol.* **23**, 974–979 (1992).
63. Gusterson, B.A. *et al.* Prognostic importance of c-erbB-2 expression in breast cancer. International (Ludwig) Breast Cancer Study Group. *J. Clin. Oncol* **10**, 1049–1056 (1992).

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Breast cancer results from genetic and environmental factors leading to the accumulation of mutations in essential genes. Genetic predisposition may have a strong, almost singular effect, as with *BRCA1* and *BRCA2*, or may represent the cumulative effects of multiple low-penetrance susceptibility alleles. Here we review high- and low-penetrance breast-cancer-susceptibility alleles and discuss ongoing efforts to identify additional susceptibility genes. Ultimately these discoveries will lead to individualized breast cancer risk assessment and a reduction in breast cancer incidence.

Breast cancer genetics: What we know and what we need

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Although the last decade has seen many important advances in understanding genetic susceptibility to breast cancer, there remains much to learn. Unanswered questions include the number and nature of genetic variants that predispose women to breast cancer, the interplay between those variants and environmental factors, and the optimal use of that information to reduce both the personal and social costs of breast cancer. Germline mutations in *BRCA1* and *BRCA2* and a few other rare variants account for only 15–20% of breast cancer that clusters in families and less than 5% of breast cancer overall. So what are we looking for, how can we find it and how will we best use the information, once available?

The most widely accepted model of breast cancer susceptibility is that it is due to a small number of highly penetrant mutations (such as in *BRCA1* and *BRCA2*) and much larger number of low-penetrance variants (Fig. 1). Interaction between these genetic variants and environmental exposures is also important. Current efforts are aimed at identifying and characterizing these variables, but the complexities of these studies are considerable. Here we review what is known about genetic variants that predispose to breast cancer and consider ongoing efforts to identify additional high- and low-penetrance susceptibility genes.

High-penetrance mutations in known susceptibility genes

Germline mutations in *BRCA1* have been identified in 15–20% of women with a family history of breast cancer and 60–80% of women with a family history of both breast and ovarian cancer[1,2]. Female mutation carriers have a lifetime breast cancer risk of 60–80% (refs. 3,4), although penetrance estimates as low as 36% have been reported in a series of Jewish breast cancer cases selected without regard to family history[5] (Fig. 1). The median age of diagnosis in mutation carriers is 42 years, more than 20 years earlier than the median for unselected women in the US and Western Europe[6]. Lifetime ovarian cancer risks are estimated at 20–40%, but, unlike breast cancer, age-specific penetrance is not heavily skewed toward early onset disease[7,8]. Increased risk[5] for prostate and colon cancer have also been reported, with relative risks of 4.1 and 3.3, respectively[9], and *BRCA1* mutations are found in excess in women with multiple primary cancers of any type who have both a personal and family history of breast cancer[10].

BRCA1 is a large gene, with 22 exons encoding a 220-kilodalton nuclear protein with a zinc-binding RING domain at the amino terminus, and a conserved acidic carboxyl terminus[11] that functions in transcriptional co-activation[12]. The main downstream targets identified so far are p53-responsive genes, including *p21* and *BclX*[13]. BRCA1 binds to BRCA2, p53, RAD51 and many other proteins involved in cell cycling and DNA-damage response[14,15] (Fig. 2a). The involvement of BRCA1 in response to DNA damage is supported by extensive data, including evidence that BRCA1 is phosphorylated by the ataxia telangiectasia mutated (ATM) and checkpoint kinase 2 (CHK2) proteins in response to DNA damage[16,17], that cells without functional BRCA1 do not arrest in G2 after DNA damage and are deficient in transcription-coupled repair[18,19], and that BRCA1 is part of the RAD50–MRE11–p95 complex, an essential component of recombination-mediated repair of DNA double-stranded breaks[20]. Thus, specific involvement of BRCA1 in DNA-damage response pathways is well-documented, but the specificity of cancer risk,

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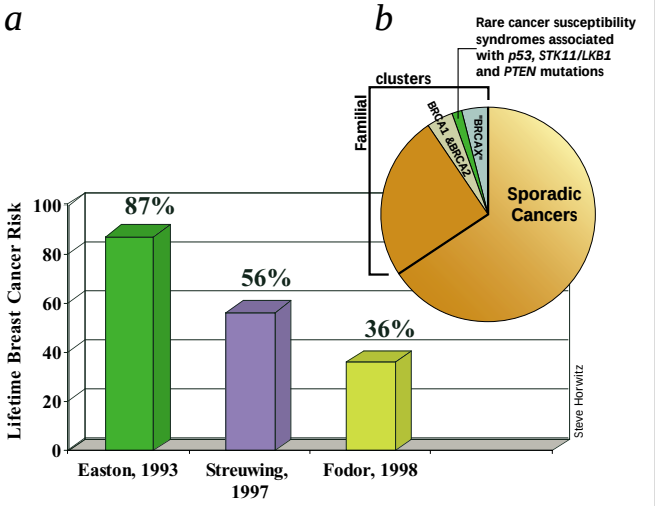

Fig. 1 ***a***, Penetrance estimates for breast cancer risk in women with germline *BRCA1* mutations vary depending on the population used for analysis. A study for The Breast Cancer Linkage Consortium (BCLC) estimated 87% penetrance using linkage results in a cohort of large families with multiple affected women[3]. A lifetime penetrance of 56% was estimated using Ashkenazi volunteers in Washington, DC, a cohort skewed toward the presence of family history of breast cancer, but weighted less heavily toward high-penetrance families than the BCLC family set[4]. A penetrance of 36% was estimated based on consecutive Ashkenazi breast cancer cases with no selection for family history[5]. These penetrance estimates could vary because of genotype-specific effects, but another explanation is that there are modifiers of breast cancer penetrance, both genetic and environmental. ***b***, Breast cancer can be divided into cases that occur in the presence (familial clusters) or absence (sporadic cases) of other cases in female relatives. Familial clusters range from large families with as many as half of the women affected with breast cancer to a single first- or second-degree relative pair. Sporadic cases may be isolated events or may be part of an unrecognized familial cluster. In all cases, it is likely that both genetic and environmental factors are involved, with the relative importance of each ranging from strongly genetic, or strongly environmental.

mostly limited to breast and ovarian cancer, has not been explained.

The lifetime breast cancer risk for carriers of *BRCA2* mutations also is estimated to be 60–85%, and the lifetime ovarian cancer risk is estimated to be 10–20%. However, unlike the situation with *BRCA1*, men with germline mutations in *BRCA2* have an estimated 6% lifetime risk of breast cancer, representing a 100-fold increase over the male population risk. *BRCA2* mutations also may be associated with an increase in colon, prostate and pancreatic cancers, gallbladder and bile duct cancer, stomach cancer and malignant melanoma[21]. The Ashkenazi founder mutation 6174delT seems to be an example of a low-penetrance breast cancer mutation, with estimates as low as 28% (ref. 22).

BRCA2 is even larger than *BRCA1*, with a 10.3-kilobase open reading frame encoding a 384-kilodalton nuclear protein. *BRCA2* bears no obvious homology to any known gene, and the protein contains no well-defined functional domains[23,24] (Fig. 2b). In fact, no *BRCA2* missense mutations have been unequivocally designated as disease-associated because of the paucity of data on functional domains. BRCA2 binds to BRCA1 and to RAD51, indicating involvement of BRCA2 as well in recombination-mediated repair of double-stranded breaks and the maintenance of chromosome integrity[25]. Moreover, mice homozygous for truncated *BRCA2* grow poorly compared with heterozygous littermates, do not produce germ cells and develop thymic lymphomas. Mouse embryo fibroblasts (MEFs) from *BRCA2*-null cells develop gross chromosomal abnormalities within a few cell divisions, with spontaneous double-stranded breaks, tri-radials and quadri-radials, again emphasizing the essential involvement of BRCA2 in genomic stability[26–29]. These abnormalities in BRCA2-deficient cells indicate a function for BRCA2 not just in double-stranded break repair but also in chromosome segregation, which requires an intermediate complex of chromosome association that may be homology-mediated[30].

STK11/LKB1 is a serine–threonine kinase; mutations in this gene cause Peutz-Jegher syndrome (characterized by hamartomatous polyps in the small bowel and pigmented macules of the buccal mucosa, lips, fingers and toes) and are associated with a relative risk for breast cancer of 20.3 compared with non-carriers[31]. Mutations in phosphatase and tensin homolog (*PTEN*), a dual-specificity phosphatase, cause Cowden syndrome (adenomas and follicular cell carcinomas of the thyroid gland, polyps and adenocarcinomas of the gastrointestinal tract, and ovarian carcinoma) and also are associated with a 20–30% lifetime risk of breast cancer[32]. Two germline mutations in the androgen receptor gene have been reported as susceptibility alleles for male breast cancer, both in the zinc finger and both in families with clinical evidence of androgen insensitivity, but analysis of larger series has not identified additional mutations, indicating that this is a rare cause of male breast cancer[33,34]. Finally, germline mutations in *p53* cause Li-Fraumeni syndrome. Initially described as a syndrome of childhood leukemias, brain tumors, adrenal carcinomas and soft tissue sarcomas, breast cancer penetrance in mutation carriers that survive childhood approaches 100% (ref. 35). However, all of these susceptibility alleles are rare in the population, with mutations in these genes accounting for a very small fraction of heritable susceptibility for breast cancer.

One area of particular controversy has been the role of *ATM* mutations in breast cancer susceptibility. Homozygous germline mutations in *ATM* cause ataxia telangiectasia, an autosomal recessive disorder characterized by cerebellar ataxia, oculocutaneous telangiectasias, radiation hypersensitivity and an increased incidence of malignancy, including a lifetime risk for non-Hodgkin lymphoma that approaches 100% and an increased risk of breast and ovarian cancer[36]. Heterozygous mutations in *ATM* were initially thought to confer an increased breast cancer risk, a finding that could be particularly relevant, given that *ATM* heterozygotes represent up to 7% of the general population, and that screening mammography, a source of ionizing radiation, could theoretically increase the penetrance of such mutations[37]. Subsequent studies have been contradictory, and the association remains controversial. Supporting the hypothesis are data indicating that family members of ataxia telangiectasia patients are at increased risk of breast cancer (relative risk, 1.5–9)[38–40] and one study showing an increased rate of *ATM* mutations in patients diagnosed with breast cancer before age 45 (ref. 41). In the latter study, 40% of cases had contralateral disease, and all had been exposed to low-dose radiation at a young age. Refuting the hypothesis are several studies showing that in women diagnosed with breast cancer before age 40, *ATM* mutation frequency did not differ from controls[42–45]. Similar findings were reported in a recent Norwegian study of 150 breast cancer cases diagnosed before age 55 (ref. 46). These data indicate that in the absence of additional exposures, any increased breast cancer risk due to truncating mutations in *ATM*, if any, is likely to be minimal.

The search for additional high-penetrance genes

Traditional linkage studies are still being used in the search for

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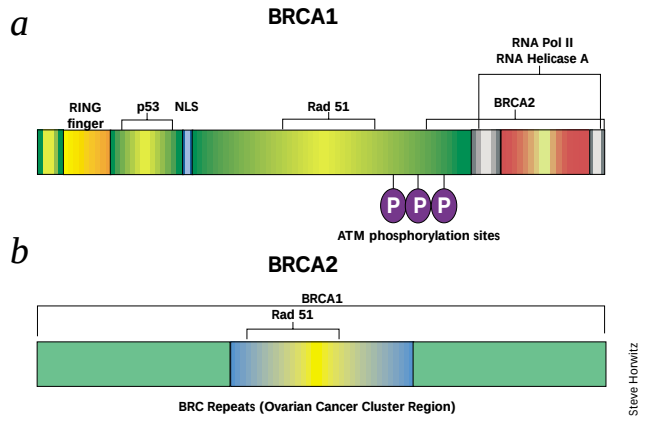

Fig. 2 ***a***, BRCA1 protein. The zinc-binding RING finger domain is near the amino terminus, where many protein partners interact. NLS, nuclear localization signal; p53 (ref. 13) and RAD51 (ref. 14) binding site; BRCT, the BRCA1 carboxy-terminus domain. This domain, found in more than 40 proteins associated with response to DNA damage, is required for the transcriptional co-activation activity of BRCA1 (ref. 12). Point mutations in both the RING and BRCT domains have been found in association with early onset breast cancer in many families. P, serines phosphorylated by ATM in response to DNA damage[16]. ***b***, BRCA2. Little is known about structure–function relationships for BRCA2; it interacts with BRCA1, but a specific domain has not been identified[15]. RAD51 interaction site. The central portion of BRCA2 has been called the ovarian cancer cluster region (OCCR), based on what seems to be both a reduced penetrance for breast cancer and an increased penetrance for ovarian cancer associated with mutations in this region; this region includes the Ashkenazi founder mutation 6174delT.

high-penetrance breast cancer susceptibility genes, with one recent report indicating a locus for '*BRCA3*' on chromosome 13q, distinct from *BRCA2* and *Rb* (ref. 47). However, overwhelming evidence against this locus was found in a collection of 119 families with a lod score at this locus of –33.0 (ref. 48). Although hampered by the possibility that additional genes are of lower penetrance than are *BRCA1* and *BRCA2*, and the likelihood that remaining families are more heterogeneous than those used to identify *BRCA1* and *BRCA2*, these positional cloning efforts are greatly facilitated by the detailed sequence information now available for the human genome. The associated ordered set of polymorphic genetic markers is an essential resource for initial gene localization and a denser map of markers useful for fine mapping has become available through the Single-Nucleotide Polymorphism (SNP) Consortium. Moreover, '*in silico*' gene prediction efforts have become more sophisticated, and the time-consuming task of experimental exon identification may soon be of mainly historical interest.

So why can't we find '*BRCA3*', more than 6 years after the identification of *BRCA1* and *BRCA2*? First, the clues afforded by other phenotypes in the families are missing: Ovarian cancer and male breast cancer were recognized as component tumors of breast-cancer-susceptibility syndromes before either *BRCA1* or *BRCA2* were isolated, allowing for targeted ascertainment of genetically homogenous families. In addition, the likelihood of success using this approach is enhanced if the families being analyzed have multiple cases of early-onset breast cancer and strong evidence against involvement of both *BRCA1* and *BRCA2*. However, the larger the families are, the more likely they are due to either *BRCA1* or *BRCA2* (ref. 49), and those that are not may represent multiple susceptibility alleles (genetic heterogeneity), reducing the power of linkage analysis. Attempts have been made to cluster families using traditional histopathological classifications, and although significant differences between sporadic breast cancers, those due to *BRCA1* and *BRCA2* and those found in families without such mutations have been found, the associations are not strong enough to use in stratifying linkage data[50]. Larger family sets to increase statistical power are needed, as well as new ways to cluster families into subgroups most likely to represent single-gene disorders. One such approach being developed is the stratification of breast cancer families based on a molecular profile of the associated tumors. These analyses can use either expression profiling or array-based comparative genomic hybridization, both providing unique molecular signatures. The first example of this approach showed that transcriptional profiling using cDNA arrays can separate sporadic tumors from those found in women with *BRCA1* mutations[51]. Nonetheless, hundreds of small pedigrees may needed to localize '*BRCA3*', fortunately aided by technological advances such as automated capillary-based fragment analysis, making the analysis of large numbers of samples much faster than during the search for *BRCA1* and *BRCA2*.

High-throughput somatic mutation analysis for gene searches

The availability of the human genome sequence also makes possible a bold approach to cancer gene discovery based on high-throughput analysis of somatic changes in sporadic tumors. Strategies that detect gains and losses (both loss of heterozygosity and homozygous deletions) as well as small intragenic mutations have been central to cancer gene identification in the past, but now we have the capacity to analyze thousands of tumors across the entire genome. Although cost and technical problems remain obstacles, techniques that move away from gel-based systems, using capillaries or high-performance liquid chromatography platforms, provide the high-throughput while maintaining specificity and sensitivity.

Using these approaches, the Cancer Genome Project at The Sanger Centre is designed to identify cancer-related genes based on homozygous deletions in a comprehensive panel of more than 1,500 cell lines, as well as mutation analyses of every gene in the human genome in a set of common primary tumors, including breast cancers. This high-throughput approach, using the facilities and expertise assembled for the sequencing of whole genomes, should ultimately identify all genes that are frequently altered in cancer. A subset of these genes will have predisposing germline mutations, so these efforts will also provide a complete list of cancer-related genes to be screened through cancer families and large case-control studies to fully define the basis of cancer susceptibility due to mutations in moderate- and high-penetrance genes.

Low-penetrance cancer susceptibility genes

Although efforts to identify high-penetrance susceptibility alleles continue, it has become apparent that much of the breast cancer that clusters in families will not be explained by these mutations. Using families with at least four cases of early-onset breast cancer, 67% of families with four or five cases of breast cancer were found to be not linked to *BRCA1* or *BRCA2* (ref. 49) and other, more common susceptibility alleles, by definition of lower penetrance, may be responsible for a large fraction of these families. In addition, two population-based series indicated that only 15% of the excess breast cancer risk to sisters and mothers of the cases was attributable to mutations in *BRCA1* and *BRCA2* (refs. 2,52). Finally, family history remains a predictive factor for breast cancer risk in women without

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BRCA1 or *BRCA2* mutations[53]. Thus, cumulative evidence indicates that there are common elements of risk in the population that are shared between women with breast cancer and their relatives, and low-penetrance susceptibility alleles are prime candidates.

One of the implicit problems in isolating low-penetrance genes is that such genes will rarely produce multiple-case families that can be used in traditional linkage studies, making association studies a more tenable approach. As large population-based case control studies are expensive and time-consuming, one approach has been to evaluate candidate low-penetrance susceptibility genes as modifiers of high-penetrance genes. In these studies, age of diagnosis in carriers of *BRCA1* and *BRCA2* mutations is used as a surrogate for penetrance, and association of a genetic variant with a significant difference between age at diagnosis is analyzed. Candidate 'modifying genes' are selected on the basis of biological plausibility. Candidate genes from many cellular pathways have been investigated using this approach, including hormone metabolism, carcinogen detoxification, DNA-damage response and immune surveillance. *HRAS1* and the androgen receptor represent candidates with evidence for modification of the BRCA1 phenotype.

The proto-oncogene *HRAS1* encodes a protein involved in mitogenic signaling. A 'minisatellite' of 30–100 units of a 28-base-pair repeat is located approximately 1 kilobase downstream of *HRAS*. Individuals with rare alleles (population frequency, less than 5%) have an increased risk of breast cancer[54]. An association study of carriers of *BRCA1* mutations indicated that in women with one or two rare *HRAS* alleles, the risk for ovarian cancer was increased 2.11-fold over women with common alleles[55]. As this variant exists outside the *HRAS*-coding region, it may be an example of a marker in linkage disequilibrium with an adjacent, unrecognized gene, rather than a variant with a direct effect on HRAS function.

In another study of carriers of *BRCA1* mutations, women with at least one long androgen receptor allele (more than 28, 29 or 30 CAG repeats in exon 1) were diagnosed with breast cancer 0.8, 1.8 and 6.3 years earlier, respectively, than women with shorter alleles[56]. BRCA1 may interact with and can act as a co-activator of the androgen receptor promoter, providing a plausible explanation for the finding that allelic variation in the androgen receptor affects breast cancer penetrance in *BRCA1* mutation carriers.[57]

Many other genetic variants have been tested, often with conflicting results when evaluated by more than one group or when variants with an apparent effect in carriers of *BRCA1*/*BRCA2* mutations are tested in a conventional case-control cohort. Whether any of the genes now being investigated will ultimately be viewed as low-penetrance susceptibility alleles remains to be determined, and considerable work remains in this area. Nonetheless, the recognition that these genetic variants may be important in disease susceptibility is a useful step forward.

The selection of candidate low-penetrance susceptibility genes is inherently limited by what we now think of as biologically plausible. As there is relatively little information available about potential candidates for breast-cancer-susceptibility alleles, an unbiased approach to define areas of the genome that may contain low-penetrance susceptibility alleles is very appealing.

Again using the hypothesis that genes that modify the penetrance of *BRCA1* and *BRCA2* are good candidates for low-penetrance susceptibility alleles in general, non-parametric linkage analysis is being used to identify genomic regions shared by women affected with breast cancer (all with *BRCA1* mutations) more frequently than would be expected due to chance. To prioritize areas of the genome to search for potential modifiers of *BRCA1*, data were used on regions of chromosomal loss in breast cancers from carriers of *BRCA1* mutations and selected for study both arms of chromosome 4 (4p, 64% loss; 4q, 81% loss) and 5q (86% loss), all of which had no more than a loss rate of 11% in sporadic tumors[58]. Initial analysis did not identify any significant candidate loci on chromosome 4; however, it did provide modest evidence of a locus on 5q more commonly shared by affected than unaffected women. This association was further strengthened when only women with a breast cancer diagnosis before age 45 were considered (K.N. & B.L.W., unpublished data). This region can now be analyzed for known and predicted genes that may be suitable candidates for traditional association studies.

These pilot data provide the basis for a complete genome-wide search in a large set of relative pairs with *BRCA1* mutations, and indicate that other related approaches may yield useful results as well. However, an essential component in the success of genome-wide association studies is marker density, as the power of any association test will decrease rapidly within a short distance of the gene of interest (linkage disequilibrium effect), or with differences in the relative allele frequency of flanking markers. A recent analysis of linkage disequilibrium indicated that 500,000 single-nucleotide polymorphisms would be required for whole-genome studies (if linkage disequilibrium does not extend beyond an average distance of 3 kilobases)[59]. However, these studies are becoming increasingly more feasible with the availability of high-density single-nucleotide polymorphism maps and high-throughput genotyping, making such an approach using large breast cancer case-control studies likely in the near future.

Although it is unlikely that the final list of breast-cancer-susceptibility alleles will be neatly divided into high- and low-penetrance genes, and will more likely represent a spectrum of penetrance with each modified by multiple gene–gene and gene–environment interactions, it is now apparent that most familial breast cancer risk is not accounted for by mutations in the high-penetrance susceptibility genes *BRCA1* and *BRCA2*. Thus, efforts are underway to identify additional high- and low-penetrance genes. The search for other cancer-susceptibility genes, particularly prostate cancer-associated genes, are beset with the same challenges of heterogeneity, the possibility of reduced penetrance, and many sporadic cases complicating ongoing linkage studies and producing conflicting results from different groups. However, whereas the challenge of identifying these genes is daunting, and the cost not trivial, the benefits will be enormous. Management guidelines available for women with germline *BRCA1* and *BRCA2* mutations appear to reduce the risk of breast and ovarian cancer by at least 60% and 90%, respectively[60]. Moreover, screening protocols targeted to high-risk women are evolving, which will likely reduce the mortality of the tumors that do occur. Finally, statistical models indicate that most of the risk of breast cancer may occur in a minority of women[61]. Thus, as the genetics of breast cancer are fully elucidated, tools will be developed to indicate who to screen and how, as well as who may not need screening, reducing health care costs and associated morbidity. Preventative and therapeutic targets will also be developed that will considerably reduce the incidence and mortality of breast cancer, benefiting women, their families and society as a whole.

1. Couch, F.J. *et al.* BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. *N. Engl. J. Med.* **336**, 1409–1415 (1997).
2. Peto, J. *et al.* Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer [see comments]. *J. Natl. Cancer Inst.* **91**, 943–949 (1999).
3. Easton, D.F., Bishop, D.T., Ford, D. & Crockford, G.P. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. *Am. J.Hum. Genet.* **52**, 678–701 (1993).
4. Struewing, J.P., Tarone, R.E., Brody, L.C., Li, F.P. & Boice, J.D.Jr. BRCA1 mutations in young women with breast cancer. *Lancet* **347**, 1493 (1996).
5. Fodor, F.H. *et al.* Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients. *Am. J. Hum. Genet.* **63**, 45–51

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(1998).
6. Easton, D.F., Narod, S.A., Ford, D. & Steel, M. The genetic epidemiology of BRCA1. Breast Cancer Linkage Consortium. *Lancet* **344**, 761 (1994).
7. Easton, D.F., Ford, D. & Bishop, D.T. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Am. J. Hum. Genet.* **56**, 265–271 (1995).
8. Struewing, J.P. *et al.* The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N. Engl. J. Med.* **336**, 1401–1408 (1997).
9. Ford, D., Easton, D.F., Bishop, D.T., Narod, S.A. & Goldgar, D.E. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Lancet* **343**, 692–695 (1994).
10. Shih, H. *et al.* BRCA1 and BRCA2 mutations in breast cancer families with multiple primary cancers. *Clin Cancer Res* **6**, 4259–4264 (2000).
11. Miki, Y. *et al.* A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* **266**, 66–71 (1994).
12. Chapman, M.S. & Verma, I.M. Transcriptional activation by BRCA1. *Nature* **382**, 678–679 (1996).
13. Zhang, H. *et al.* BRCA1 physically associates with p53 and stimulates its transcriptional activity. *Oncogene* **16**, 1713–1721 (1998).
14. Scully, R. *et al.* Association of BRCA1 with Rad51 in mitotic and meiotic cells. *Cell* **88**, 265–275 (1997).
15. Scully, R. & Livingston, D.M. In search of the tumour-suppressor functions of BRCA1 and BRCA2. *Nature* **408**, 429–432 (2000).
16. Cortez, D., Wang, Y., Qin, J. & Elledge, S.J. Requirement of ATM-dependent phosphorylation of brca1 in the DNA damage response to double-strand breaks. *Science* **286**, 1162–1166 (1999).
17. Lee, J.S., Collins, K.M., Brown, A.L., Lee, C.H. & Chung, J.H. hCds1-mediated phosphorylation of BRCA1 regulates the DNA damage response. *Nature* **404**, 201–204 (2000).
18. Larson, J.S., Tonkinson, J.L. & Lai, M.T. A BRCA1 mutant alters G2-M cell cycle control in human mammary epithelial cells. *Cancer Res.* **57**, 3351–3355 (1997).
19. Gowen, L.C., Avrutskaya, A.V., Latour, A.M., Koller, B.H. & Leadon, S.A. BRCA1 required for transcription-coupled repair of oxidative DNA damage. *Science* **281**, 1009–1012 (1998).
20. Zhong, Q. *et al.* Association of BRCA1 with the hRad50-hMre11-p95 complex and the DNA damage response. *Science* **285**, 747–750 (1999).
21. Easton, D.F. & Consortium, T.B.C.L. Cancer risks in BRCA2 mutation carriers. *J. Natl. Cancer Inst.* **91**, 1310–1316 (1999).
22. Warner, E. *et al.* Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst* **91**, 1241-1247 (1999).
23. Wooster R *et al.* Identification of the breast cancer susceptibility gene BRCA2. *Nature* **378**, 789-92 (1995).
24. Tavtigian, S.V. *et al.* The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. *Nature Genet.* **12**, 333–337 (1996).
25. Chen, J.J., Silver, D., Cantor, S., Livingston, D.M. & Scully, R. BRCA1, BRCA2, and Rad51 operate in a common DNA damage response pathway. *Cancer Res.* **59**, 1752s–1756s (1999).
26. Connor, F. *et al.* Tumorigenesis and a DNA repair defect in mice with a truncating Brca2 mutation. *Nature Genet.* **17**, 423–430 (1997).
27. Friedman, L.S. *et al.* Thymic lymphomas in mice with a truncating mutation in Brca2. *Cancer Res.* **58**, 1338–1343 (1998).
28. Patel, K.J. *et al.* Involvement of Brca2 in DNA repair. *Mol. Cell* **1**, 347–357 (1998).
29. Sharan, S.K. *et al.* Embryonic lethality and radiation hypersensitivity mediated by Rad51 in mice lacking Brca2. *Nature* **386**, 804–810 (1997).
30. Nasmyth K. Peters JM. Uhlmann F. Splitting the chromosome: cutting the ties that bind sister chromatids. *Science*. **288**,1379–1385 (2000).
31. Boardman, L.A. *et al.* Increased risk for cancer in patients with the Peutz-Jeghers syndrome. *Ann. Int. Med.***128**, 896–899 (1998).
32. Liaw, D. *et al.* Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nature Genet.* **16**, 64–67 (1997).
33. Wooster, R. *et al.* A germline mutation in the androgen receptor gene in two brothers with breast cancer and Reifenstein syndrome. *Nature Genet.* **2**, 132–134 (1992).
34. Lobaccaro, J.M. *et al.* Androgen receptor gene mutation in male breast cancer. *Hum. Mol. Genet.* **2**, 1799–1802 (1993).
35. Malkin, D. *et al.* Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* **250**, 1233–1238 (1990).
36. Morrell, D., Cromartie, E. & Swift, M. Mortality and cancer incidence in 263 patients with ataxia-telangiectasia. *J. Natl. Cancer Inst.* **77**, 89–92 (1986).
37. Swift, M., Reitnauer, P.J., Morrell, D. & Chase, C.L. Breast and other cancers in families with ataxia-telangiectasia. *N. Engl. J. Med.* **316**, 1289–1294 (1987).
38. Swift, M., Morrell, D., Massey, R.B. & Chase, C.L. Incidence of cancer in 161 families affected by ataxia-telangiectasia. *N. Engl. J. Med.* **325**, 1831–1836 (1991).
39. Inskip, H.M., Kinlen, L.J., Taylor, A.M., Woods, C.G. & Arlett, C.F. Risk of breast cancer and other cancers in heterozygotes for ataxia-telangiectasia. *Br. J. Cancer* **79**, 1304–1307 (1999).
40. Janin, N. *et al.* Breast cancer risk in ataxia telangiectasia (AT) heterozygotes: haplotype study in French AT families. *Br. J. Cancer* **80**, 1042–1045 (1999).
41. Broeks, A. *et al.* ATM-heterozygous germline mutations contribute to breast cancer-susceptibility. *Am. J. Hum. Genet.* **66**, 494–500 (2000).
42. FitzGerald, M.G. *et al.* Heterozygous ATM mutations do not contribute to early onset of breast cancer. *Nature Genet.* **15**, 307–310 (1997).
43. Izatt, L. *et al.* Identification of germline missense mutations and rare allelic variants in the ATM gene in early-onset breast cancer. *Genes Chrom. Cancer* **26**, 286–294 (1999).
44. Chen, J., Birkholtz, G.G., Lindblom, P., Rubio, C. & Lindblom, A. The role of ataxia-telangiectasia heterozygotes in familial breast cancer. *Cancer Res.* **58**, 1376–1379 (1998).
45. Vorechovsky, I. *et al.* ATM mutations in cancer families. *Cancer Res.* **56**, 4130–4133 (1996).
46. Laake, K. *et al.* Screening breast cancer patients for Norwegian ATM mutations. *Br. J. Cancer* **83**, 1650–1653 (2000).
47. Kainu, T. *et al.* Somatic deletions in hereditary breast cancers implicate 13q21 as a putative novel breast cancer susceptibility locus. *Proc. Natl. Acad. Sci. USA* **97**, 9603–9608 (2000).
48. Thompson, D. *et al.* Chromsome 13q: Two genes too many? *Proc. Am. Assoc. Cancer Res.* (2001).
49. Ford, D. *et al.* Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am. J.Hum. Genet.* **62**, 676–689 (1998).
50. Lakhani, S.R. *et al.* The pathology of familial breast cancer: histological features of cancers in families not attributable to mutations in BRCA1 or BRCA2. *Clin. Cancer Res.* **6**, 782–789 (2000).
51. Hedenfalk, I. *et al.* Gene-expression profiles in hereditary breast cancer. *N. Engl. J. Med.* **344**, 539 (2001).
52. Anonymous. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br. J. Cancer* **83**, 1301–1308 (2000).
53. Claus, E.B., Schildkraut, J., Iversen, E.S., Berry, D. & Parmigiani, G. Effect of BRCA1 and BRCA2 on the association between breast cancer risk and family history. *J. Natl. Cancer. Inst.* **90**, 1824–1890 (1998).
54. Krontiris, T.G., Devlin, B., Karp, D.D., Robert, N. J. & Risch, N. An association between the risk of cancer and mutations in the HRAS1 minisatellite locus. *N. Engl. J. Med.* **329**, 517–523 (1993).
55. Phelan, C.M. *et al.* Ovarian cancer risk in BRCA1 carriers is modified by the HRAS1 variable number of tandem repeat (VNTR) locus. *Nature Genet.* **12**, 309–311 (1996).
56. Rebbeck, T. *et al.* Modification of BRCA1-associated breast cancer risk by the polymorphic androgen receptor CAG repeat. *Am. J. Hum. Genet.* **64**, 1371–1377 (1999).
57. Park, J.J. *et al.* Breast cancer susceptibility gene 1 (BRCAI) is a coactivator of the androgen receptor. *Cancer Res.* **60**, 5946–5949 (2000).
58. Tirkkonen, M. *et al.* Distinct somatic genetic changes associated with tumor progression in carriers of BRCA1 and BRCA2 germ-line mutations. *Cancer Res.* **57**, 1222–1227 (1997).
59. Kruglyak, L. Prospects for whole-genome linkage disequilibrium mapping of common disease genes. *Nature Genet.* **22**, 139–144 (1999).
60. Eisen, A., Rebbeck, T.R., Wood, W.C. & Weber, B.L. Prophylactic surgery in women with a hereditary predisposition to breast and ovarian cancer. *J. Clin. Oncol.* **18**, 1980–1995 (2000).
61. Peto, J. & Mack, T.M. High constant incidence in twins and other relatives of women with breast cancer. *Nature Genet.* **26**, 411–414 (2000).

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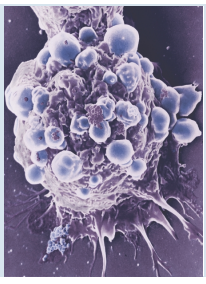

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