

SPECIAL ARTICLE

Polygenes, Risk Prediction, and Targeted Prevention of Breast Cancer

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ABSTRACT

BACKGROUND

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New developments in the search for susceptibility alleles in complex disorders provide support for the possibility of a polygenic approach to the prevention and treatment of common diseases.

METHODS

We examined the implications, both for individualized disease prevention and for public health policy, of findings concerning the risk of breast cancer that are based on common genetic variation.

RESULTS

Our analysis suggests that the risk profile generated by the known, common, moderate-risk alleles does not provide sufficient discrimination to warrant individualized prevention. However, useful risk stratification may be possible in the context of programs for disease prevention in the general population.

CONCLUSIONS

The clinical use of single, common, low-penetrance genes is limited, but a few susceptibility alleles may distinguish women who are at high risk for breast cancer from those who are at low risk, particularly in the context of population screening.

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EMPIRICAL GENOMEWIDE ASSOCIATION studies have identified six breast-cancer susceptibility alleles that are common in the general population. These findings have brought us a step closer to a polygenic approach to the prevention of breast cancer. The risks conferred by individual loci are small, but risk alleles seem to act multiplicatively. As a result, the risk of breast cancer is approximately six times as great among women carrying 14 risk alleles as among those carrying no risk alleles at these loci. Overall, there is an approximately log-normal distribution of relative risk in the population on the basis of combinations of genotypes at these loci. The efficiency of population-based preventive programs such as screening mammography could be improved by targeting women who are at the greatest risk for breast cancer according to genotype.

An improved understanding of genetic risk factors and their interactions with the environment would allow accurate predictions of disease and facilitate prevention through measures directed toward persons at high risk.^{1,2} Nevertheless, whether molecular testing for common genetic variants can have sufficient predictive power to be of practical use has been questioned.³⁻⁵

We examined the implications of findings concerning the risk of breast cancer based on common genetic variation, using data on family history from a population-based series of women with breast cancer.⁶ We found that the data were compatible with a log-normal distribution of genetic risk in the population and that the distribution of risk was sufficiently wide for useful discrimination between high-risk and low-risk groups.

We concluded that genetic risk profiles would improve population-based programs of intervention for breast cancer if common alleles could be identified. At the time of our study, however, such alleles were unknown. Here, we review progress in unraveling the basis of inherited susceptibility to breast cancer, and we explore the implications of recent findings for counseling women regarding their individual risk and for guiding public health policy.

METHODS

GENETIC SUSCEPTIBILITY TO BREAST CANCER

Breast cancer tends to cluster in families; the disease is approximately twice as common among

first-degree relatives of patients as among women in the general population.⁷⁻⁹ The higher rate of breast cancer among monozygotic twins of patients than among dizygotic twins or siblings suggests that genetic variation, rather than lifestyle or environmental factors, accounts for most of the familial clustering.^{10,11}

Familial clustering of breast cancer occurs in specific inherited breast-cancer syndromes in which single genes confer a high risk. Several such genes, including *BRCA1*, *BRCA2*, *PTEN*, and *TP53*, have been identified by means of family-based linkage studies. The susceptibility alleles of these genes are rare in the general population, and they account for less than 25% of the inherited component of breast cancer.¹² Other genes that confer a risk equivalent to that of *BRCA1* and *BRCA2* are unlikely to exist, since most families with four or more cases of breast cancer can be accounted for by *BRCA1* or *BRCA2*,¹³ and extensive attempts to identify similar genes with the use of family-based linkage studies have failed.

Genetic association methods have long been used to map cancer-susceptibility alleles,¹⁴ but until very recently, these efforts were largely unsuccessful. Initially, moderate-risk alleles were identified in family-based studies by sequencing candidate genes in women from families with multiple cases of breast cancer that was not due to mutations in the known high-penetrance genes. One of these alleles is the 1100delC protein-truncating variant in the cell-cycle-checkpoint kinase gene (*CHEK2*).¹⁵⁻¹⁸ This variant confers a relative risk of breast cancer of 2.3 and has a higher prevalence among patients with a family history and a diagnosis of breast cancer at a young age than among unselected patients.¹⁸ Assuming a constant relative risk with age, the estimated absolute risk of breast cancer among carriers of 1100delC would be 13% by 70 years of age, as compared with an estimated absolute risk of 5.7% among noncarriers. These estimates are based on data on the incidence of breast cancer in England and Wales¹⁹ (see the Table in the Supplementary Appendix, available with the full text of this article at www.nejm.org). All subsequent absolute risks presented in this article are based on the same incidence data. The *CHEK2* 1100delC makes only a small contribution to the overall burden of breast cancer, however, since it accounts for only 1.4% of the excess risk among

first-degree relatives. Similar approaches identified rare variants in the ataxia–telangiectasia mutated (*ATM*) gene²⁰ (confirming observations in families with ataxia–telangiectasia^{21,22}), the *BRCA1*-interacting protein C-terminal helicase 1 (*BRIP1*) gene,²³ and the partner and localizer of *BRCA2* (*PALB2*) gene,²⁴ which confer relative risks of 2.0 to 2.5. However, these variants combined explain less than 1% of the genetic risk.

Candidate-gene searches for common risk alleles (minor-allele frequency, >0.05) have generally been performed in patients who were unselected for family history and in unrelated controls.¹⁴ The only common breast-cancer susceptibility locus to emerge from this work is the coding variant D302N in caspase 8 (*CASP8*), the common D allele, which is associated with a per-allele odds ratio of 1.13 (95% confidence interval, 1.08 to 1.18) for breast cancer as compared with the N allele.²⁵ The failure to find more genes is, in retrospect, unsurprising since the total number of candidate genes evaluated has been small as compared with the number of genes in the human genome.

In contrast to candidate-gene studies, the results of genomewide association studies in breast cancer and other complex diseases have been encouraging. Three genomewide association studies in breast cancer have reported six new breast-cancer susceptibility loci at highly stringent levels of statistical significance^{26–28} (Table 1). These loci are all single-nucleotide polymorphisms (SNPs) with two alleles: a high-risk allele and a low-risk allele. Since there are two copies of each locus in the genome, there are three possible combinations of alleles: two low-risk alleles, one low-risk and one high-risk allele, or two high-risk alleles. The risk conferred by each of these loci appears to be allele-dose–dependent with a multiplicative effect on the relative-risk scale (log-additive), but the magnitude of the relative risk is small. The high-risk allele of the SNP rs2981582 in intron 2 of *FGFR2* (the fibroblast growth factor receptor 2 gene) has the largest effect of all the known common susceptibility loci, with a per-allele relative risk of 1.26 as compared with the low-risk allele. It has a frequency of 38% in the general population, and the low-risk allele has a frequency of 62% in the general population. The population attributable risk of this variant is 19%, but it accounts for only approximately 2%

of the genetic risk of breast cancer (Supplementary Appendix).

Preliminary results have shown no evidence of interactions (on the log scale) among the seven loci identified so far (unpublished data), suggesting that the combined effect of these seven loci may be adequately described by a simple multiplicative (log-additive) model. The multiplicative model is consistent with the polygenic model of disease susceptibility.²⁶ With this model, the seven loci in combination would explain just 5% of the genetic risk.²⁶

CLINICAL RELEVANCE OF INDIVIDUAL LOW-PENETRANCE ALLELES

How could the identification of genetic risk factors influence prevention for an individual woman or a population? Individual susceptibility alleles are unlikely to contribute much to prevention in the population, even though they may have important implications for the individual woman.⁵ Consider a hypothetical allele with a carrier frequency of 0.003 that confers an increase in risk among carriers by a factor of 10, with a corresponding lifetime risk of disease in a carrier of 60%.²⁹ Such an allele would be similar to deleterious alleles of *BRCA1* and *BRCA2*, which have a combined carrier frequency of about 0.003 in the United Kingdom, where there are no common founder mutations.³⁰ This allele would be present in 3% of all cases of breast cancer. An intervention such as chemoprevention, which reduces the risk of disease by 40%, would reduce the absolute risk among carriers by 24% (i.e., 40% of 60%). A screening program to detect and treat carriers would reduce the disease burden in the population by only 0.7% (i.e., 24% of 3%) if the testing and treatment were complete. The *CHEK2* 1100delC is only slightly more common than 0.003 (carrier frequency, 0.007), but it confers a substantially smaller risk (relative risk, 2.3). With an intervention that reduces the risk by 40%, the absolute reduction would be 5.6%. A population-screening program to detect and treat *CHEK2* 1100delC carriers would reduce the total disease burden by 0.7% if the testing and treatment were complete.

Consider a low-penetrance variant that doubles the risk of breast cancer, confers a lifetime risk of 18%, and occurs in 5% of the population. Such an allele has not yet been identified for

Table 1. Established Common Breast-Cancer Susceptibility Alleles.*

dbSNP No.	Gene†	Chromosome	Risk-Allele Frequency‡	Relative Risk per Allele‡	Fraction of Total Variance in Risk Explained§	Population Attributable Risk§	Study
					%		
rs2981582	<i>FGFR2</i>	10q	0.38	1.26	1.7	19	Easton et al., ²⁶ Hunter et al. ²⁷
rs3803662	<i>TNRC9, LOC643714</i>	16q	0.25	1.20	0.9	10	Easton et al. ²⁶
rs889312	<i>MAP3K1</i>	5q	0.28	1.13	0.4	7	Easton et al. ²⁶
rs3817198	<i>LSP1</i>	11p	0.30	1.07	0.1	4	Easton et al. ²⁶
rs13281615	None known	8q	0.40	1.08	0.2	6	Easton et al. ²⁶
rs13387042	None known	2q	0.50	1.20	1.2	19	Stacey et al. ²⁸
rs1053485	<i>CASP8</i>	2q	0.86	1.13	0.3	20	Cox et al. ²⁵

* *CASP8* denotes caspase 8, dbSNP database of single-nucleotide polymorphisms, *FGFR2* the fibroblast growth factor receptor 2 gene, *LOC643714* a hypothetical protein LOC643714, *LSP1* lymphocyte-specific protein 1, *MAP3K1* mitogen-activated protein kinase kinase kinase 1, and *TNRC9* trinucleotide repeat containing 9.

† These genes are within the linkage-disequilibrium block or blocks defined by the associated variant and are plausible candidates for the causal gene.

‡ Values are from published data cited in the Study column.

§ See the Supplementary Appendix for details.

breast cancer, and it is unlikely to exist. The variant would be present in 9.5% of all patients. An intervention that reduces the risk by 40% (absolute risk reduction, 7.2%) could reduce the total disease burden by 4%. The alleles identified by recent genomewide association studies confer smaller risks. For *FGFR2* rs2981582, the relative risks of breast cancer as compared with the average risk in the population are 0.83 for carriers of two low-risk alleles (common-allele homozygotes), 1.05 for carriers of one high-risk and one low-risk allele (heterozygotes), and 1.38 for carriers of two high-risk alleles (rare-allele homozygotes). These risks are based on the published per-allele relative risk of 1.26,²⁸ with the genotype-specific risks adjusted to be relative to the average risk in the population. The estimated frequencies of these three groups in the population are 38%, 47%, and 14%, respectively, and the lifetime risks of breast cancer are 10% for women who carry one risk allele and 13% for women who carry two risk alleles. Thus, if we were to genotype 100 persons for rs2981582 and apply a preventive measure to heterozygotes and homozygotes, we would identify 47 heterozygotes and 14 homozygotes, among whom the number of cases of breast cancer over a lifetime would be reduced from 4.6 in heterozygotes (10% of 47 heterozygotes) and 1.8 in homozygotes (13% of

14 homozygotes) to 2.8 and 1.1, respectively. The total reduction in cases of breast cancer would be 2.6 per 100 women screened.

RESULTS

On the basis of the seven risk alleles listed in Table 1, there are 2187 possible combinations of genotypes. In the United Kingdom, 56 of 10 million women carry two copies of the low-risk allele for each gene. Assuming a multiplicative model for interaction between these alleles, the relative risk of breast cancer in this group is 0.43, as compared with the population average, and the lifetime risk of breast cancer is 4.2% as compared with a population average of 9.4%. In the United Kingdom, 7 of 10 million women carry two copies of the risk allele for each gene. Their relative risk is 2.7, which is equivalent to a 23% lifetime risk. The risk for women at highest risk is 6.3 times as great as that for women at lowest risk. Figure 1 shows the distribution of the population according to the relative risk of breast cancer. The risk distribution on a log relative risk scale is close to a normal distribution, with a mean just below 0, as predicted by the polygenic model. The distribution of cases is shifted to the right, with a mean of slightly more than 0.

The population in the top half of the risk

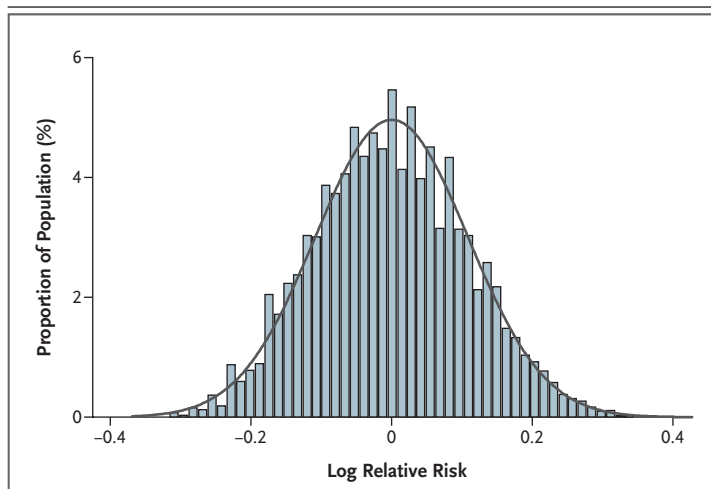


Figure 1. Distribution of Genetic Risk in the Population.

The log relative risk scale of -0.4 to 0.4 is equivalent to 0.4 to 2.5 on the relative risk scale.

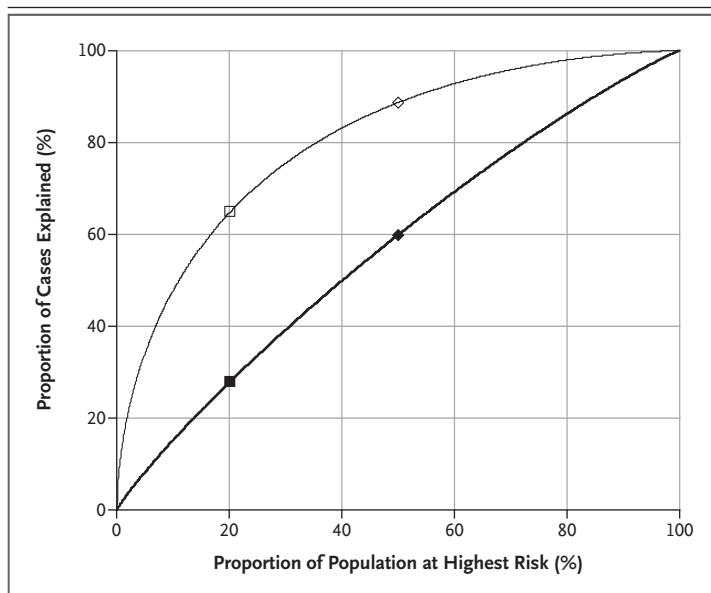


Figure 2. Proportion of Cases of Breast Cancer Explained by the Proportion of the Population at Highest Risk for the Disease.

Estimates based on currently known susceptibility alleles are indicated by the thick line. Estimates based on the best-case scenario, in which all possible breast-cancer susceptibility alleles are known, are indicated by the thin line.⁶ The graph shows that the half of the population at highest risk for breast cancer on the basis of the genotype at seven known susceptibility loci accounts for 60% of all cases of breast cancer (solid diamond) and the 20% at the highest risk account for 28% of all cases (solid square). If all possible susceptibility alleles were known, the respective proportions, based on the genotype, would be 88% (open diamond) and 64% (open square).

distribution accounts for 58% of all cases of breast cancer, and 10% of the population at highest risk accounts for 15% of all cases. Figure 2 shows the proportion of cases accounted for by a given proportion of the population above a specified risk, based on the risk distribution generated by the seven known common alleles. For comparison, the thin line in Figure 2 shows the predicted risk distribution if all the alleles that influence breast-cancer risk were known.⁶

Thus, the risk profile generated by these common moderate-risk alleles apparently does not provide sufficient discrimination to warrant individualized prevention. Useful risk stratification may be possible, however, in prevention programs for a population. For example, the United Kingdom's National Health Service breast-screening program is currently offered to all women 50 years of age and older, irrespective of family history or other risk factors. A 50-year-old woman in the general population in the United Kingdom has a 2.3% risk of breast cancer within the next 10 years of her life. If we assume that 2.3% is the threshold at which the screening program has a net benefit, it makes sense to offer screening to all women with that level of risk, irrespective of age. Similarly, women at lower risk would not be eligible for screening, also irrespective of age. A 40-year-old woman with a 10-year risk of 2.3% would be offered screening, whereas a 55-year-old woman with a 10-year risk of 1% would not. If such a strategy were implemented, the efficiency of the screening program would increase because it would be targeted at women at highest risk. The cost of a genetic test for purposes of risk profiling would be minimal as compared with the costs of a lifetime screening program. Similar arguments concerning absolute risk provide support for the United Kingdom's National Institute for Health and Clinical Excellence (NICE) guidelines for women with a family history of breast cancer. These guidelines recommend mammographic screening for women 40 years of age or older if their 10-year risk is more than 3% on the basis of family history alone. This moderate-risk group of women with an affected first-degree relative younger than 40 years of age or two affected first-degree relatives accounts for less than 5% of the population.

It would be possible to genotype every woman at all known susceptibility loci and, on the basis

Table 2. Absolute Risks of Breast Cancer According to Percentile of Population.*

Percentile of Population	Relative Risk	Lifetime Risk†	10-Yr Risk at 50 Yr	Age at Which 10-Yr
			of Age†	Risk ≥2.3%
			%	yr
5	0.63	6.1	1.5	NA‡
10	0.69	6.7	1.6	NA‡
20	0.77	7.4	1.8	NA‡
40	0.90	8.6	2.1	53
60	1.03	9.7	2.4	49
80	1.20	11.0	2.7	45
90	1.35	12.0	3.0	43
95	1.49	14.0	3.4	41

* The relative risks are based on the risk distribution of seven known breast-cancer susceptibility loci.

† The absolute risks (lifetime risk and 10-year risk at 50 years of age) are estimated from the relative risks and age-specific breast-cancer incidence and all-cause mortality in England and Wales in 2004.

‡ NA denotes not applicable. The 10-year risk of breast cancer increases with age and peaks at approximately 60 years of age.²⁹ It then decreases because the mortality from other causes increases faster than the incidence of breast cancer. Thus, the maximum 10-year risk among some women is less than the 2.3% threshold.

of her breast-cancer risk profile, offer a personalized screening program in which the starting age would vary. Table 2 shows the absolute risks of breast cancer per centile of the population. These absolute risks are based on the predicted risk distribution of the seven known breast-cancer susceptibility loci. Table 2 also shows the age at which women in different risk categories will have a specified absolute risk of breast cancer in the next 10 years. Women in the 5th percentile of the risk distribution (relative risk, 0.63) have a 10-year risk at 50 years of age of 1.5%, and, because of the effects of competing causes of death, they never reach a threshold 10-year risk of 2.3%.

In contrast, women in the 95th percentile have a 10-year risk of 2.3% after 41 years of age. Only the top 0.1% of the population would reach the threshold for moderate risk according to the NICE guidelines, for whom annual screening after 40 years of age is recommended. As more alleles are identified, the precision of the risk estimates would improve, but the principle would remain the same. For example, if two further sets of seven loci conferring the same relative risks were identified, women in the 95th percentile would have a relative risk of 1.91, and approximately 3.5% of the population would be included in the NICE moderate-risk category. However, no women would be included in the high-risk category as defined by NICE (i.e., 8%

risk between 40 and 50 years of age); magnetic resonance imaging (MRI) or prophylactic oophorectomy or mastectomy would be appropriate for women in this category. Even if all susceptibility loci were known,⁶ only 2% of the population would be included in this category. Thus, it is likely that this high-risk category will remain restricted largely to carriers of *BRCA1* and *BRCA2* mutations. In practice, risk prediction could be improved by incorporating information on lifestyle risk factors or other markers (e.g., mammographic density), but risk classification with the use of genetic profiling could improve the current classification.

DISCUSSION

Although the clinical use of single, common low-penetrance genes is limited, a small number of susceptibility alleles could distinguish women at high risk for breast cancer from women at low risk, particularly in the context of population-screening programs. Moreover, stratifying women according to genetic risk may improve the efficiency of screening programs.

There are many questions to be answered and barriers to be overcome, however, before such potential could be realized. The simple models we described make several assumptions, some of which may not be robust. For example, the as-

sumption that the benefit of mammographic screening for an individual woman is merely a function of absolute risk is clearly an oversimplification. The sensitivity of mammography is reduced in women younger than 50 years of age, and the true benefit is more likely to be a complex interaction between age and absolute risk. Furthermore, the complexity of a population-oriented prevention program that is based on individual risk might outweigh its marginal improvement in efficiency. As more risk alleles are identified, however, our ability to predict risk will improve, and the gain in efficiency will increase.

If it were feasible to implement a program for women with a genetic risk of breast cancer, public (and professional) education would be necessary, and even then the concept might not be acceptable. However, new and expensive forms of screening or screening tests with marginal clinical benefits to the individual woman may be possible only in subgroups of the population at high risk. Screening for breast cancer by means of MRI

may be more effective than mammography, but it would be prohibitively expensive unless it was targeted to patients at highest risk.

Effective use of genetic profiling depends on the best available set of markers. Most reported genetic associations have been false positive results and would be worthless for risk prediction.³¹ The evidence providing support for some loci that were recently identified in genomewide studies, such as those used in the above calculations, is strong, but it will still be important to base profiling on accurate estimates of the risks associated with these loci, either singly or in combination.

Our understanding of the genetic susceptibility to breast cancer and other complex diseases is likely to change rapidly over the next decade. Policymakers should start to consider how this knowledge could be used to make a polygenic approach to disease prevention a reality.

No potential conflict of interest relevant to this article was reported.

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