

Inherited genetic susceptibility to breast cancer

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Inherited genetic susceptibility to breast cancer can be due both to genes which confer a high degree of risk and to polygenes which have a smaller effect on disease risk. An estimated 5–10% of breast cancer is considered to be due to mutations in genes conferring high risk which results in hereditary patterns of disease. Two major breast cancer susceptibility genes, *BRCA1* and *BRCA2*, which were identified using linkage analysis in large extended breast and/or ovarian cancer pedigrees, are estimated to account for the majority of large families with breast/ovarian cancer predisposition and about two-thirds of large breast cancer families. The associated lifetime risk for breast cancer in mutation carriers ranges from 40% to 90%, depending on the extent of family history and the population. Other genetic factors, such as *HRAS* or *CAG* repeats of *AR*, as well as reproductive and hormonal factors may therefore modify cancer risk.

Women at particularly high risk of developing breast cancer represent a group in whom expensive and rigorous screening programmes are cost-effective and who may benefit from trials of chemoprevention. There are only preliminary data on the efficacy of increased surveillance and on risk reduction due to prophylactic surgery. However, for chemoprevention to be equivalent to prophylactic mastectomy, it will be necessary to strive for an equivalent reduction. The efficacy of chemoprevention in this high-risk population is unknown. Existing and new agents for chemoprevention need to be carefully assessed in properly designed clinical trials among such women. In the process, other factors modifying the penetrance in mutation carriers need to be taken into account in order to evaluate the true effect of the chemopreventive agents.

Polygenes confer much lower levels of risk and may be relevant for risk assessment when the effects of multiple loci, possibly in conjunction with environmental factors, are understood and quantified. At present, it seems unlikely that the genetic information at single polygenes will be clinically relevant for risk assessment and management.

Introduction

The occurrence of a complex disease such as breast cancer can be attributed to joint effects of genetic and environmental factors. The genetic factors can include inherited genetic susceptibility due to major genes and polygenes as well as acquired somatic genetic aberrations. Major genes usually have a strong effect on disease risk and although disease-associated (mutated) alleles occur at relatively low frequency, they confer a high risk of disease to the individual. These 'highly penetrant' alleles are therefore associated with multiple occurrences of disease in a family, often in a Mendelian pattern of an autosomal dominant trait. Hereditary

breast cancer is characterized by early age at onset and multifocal disease. An estimated 5–10% of breast cancer is considered to be due to the presence of a mutation in an autosomal dominant susceptibility gene. The majority of breast cancer which occurs in the absence of a strong family history and with later age at onset is likely to be due to the joint effects of several genes and environmental factors. Polygenes usually have a smaller effect on disease risk to the individual. However, the disease-associated alleles are relatively common in the population and may account for a larger attributable proportion of breast cancer than major genes in the general population.

Major susceptibility genes for breast cancer

Several major genes for breast cancer susceptibility have been identified, as shown in Table 1. They have been cloned as predisposing genes for different cancer syndromes in which breast cancer is a constituent tumour. Mutation analysis has confirmed that the cancer occurrence in these syndromes can be largely explained by the genes identified. However, there remains a proportion of such families in which the disease-associated allele has not been identified. This can be attributed to both the imperfect sensitivity of the mutation detection method and the existence of additional as yet unidentified susceptibility genes.

Mutations in several of the highly penetrant genes of the cancer syndromes associated with hereditary breast cancer, such as *TP53* (Li-Fraumeni syndrome), *MSH2* (Muir-Torre syndrome), *PTEN* (Cowden syndrome), *STK11* (Peutz-Jeghers syndrome), are extremely rare in the general population (Li *et al.*, 1988; Malkin *et al.*, 1990; Birch *et al.*, 1994; Li *et al.*, 1997; Spigelman *et al.*, 1989; Jenne *et al.*, 1998) (Table 1). They are unlikely to contribute to inherited breast cancer susceptibility manifested in families with elevated incidence of breast cancer and are

considered to account for less than 1% of all breast cancer.

Families with hereditary breast cancer have been clinically recognized as multiple cases of early-onset cancer over several generations of close relatives with ovarian cancer as well as other cancer sites also involved. Two breast cancer susceptibility genes, *BRCA1* and *BRCA2*, have been identified using linkage analysis in large extended breast and/or ovarian cancer pedigrees and subsequent molecular cloning (Miki *et al.*, 1994; Wooster *et al.*, 1995; Tavtigian *et al.*, 1996). Mutations in *BRCA1* or *BRCA2* account for the majority of high-risk families in which multiple cases of breast and/or ovarian cancer occur as an autosomal dominant trait. Based on data from 237 families with four or more breast cancer cases occurring before 60 years of age (regardless of ovarian cancer) collected by the international Breast Cancer Linkage Consortium, Ford *et al.* (1998) estimated that overall 52% of hereditary breast cancer in such families was explained by mutations in the *BRCA1* gene, 32% by mutations in the *BRCA2* gene, and the remainder by one or more as yet unidentified genes. Genetic heterogeneity appears to be greater among families with breast cancer only, since the

Table 1. Genes conferring high risk for breast cancer

Associated syndrome	Clinical manifestation	Gene
Hereditary breast/ovarian cancer	Breast cancer, ovarian cancer	<i>BRCA1, BRCA2</i>
Li-Fraumeni syndrome	Sarcoma, brain and breast cancer cancer of breast and thyroid	<i>TP53</i>
Cowden's disease	Multiple hamartomatous lesions of skin, mucous membrane, cancer of breast and thyroid	<i>PTEN/NMAC1</i>
Peutz-Jeghers syndrome	Melanocytic macules of lips, multiple polyps, tumours of intestinal tract, breast, ovaries etc.	<i>STK11</i>
Hereditary nonpolyposis colorectal cancer	Colorectal cancer, predominantly also tumours of endometrium, ovaries, intestinal tract and breast	<i>MSH2, MLH1, PMS1, PMS2</i>
Ataxia telangiectasia	Progressive cerebral ataxia, hypersensitivity to radiation, increased cancer risk	<i>ATM</i>

majority of breast/ovarian cancer families have mutations in *BRCA1* (81%) and *BRCA2* (14%), compared with only two thirds of families with breast cancer only. On the other hand, familial breast cancer occurring in both males and females is mainly attributed to *BRCA2* (76%). More recent studies, using direct mutation screening, have included a broader spectrum of families seen at genetic clinics, with a larger proportion of families having only two or three breast and/or ovarian cancer cases. These studies suggest that *BRCA1* mutations are responsible for only 10–20% of breast cancer in such families, with *BRCA2* mutations accounting for about half of this fraction (Gayther *et al.*, 1997; Hakansson *et al.*, 1997; Serova Sinilnikova *et al.*, 1997; Struewing *et al.*, 1997). However, up to 45% of families with both breast and ovarian cancer may be associated with mutations in the *BRCA1* gene (Gayther *et al.*, 1995; Serova Sinilnikova *et al.*, 1997; Shattuck-Eidens *et al.*, 1995; Couch *et al.*, 1997; Stoppa-Lyonnet *et al.*, 1997; Dong *et al.*, 1998; Frank *et al.*, 1998).

Recent population-based studies of early-onset breast cancer suggest that *BRCA1* and *BRCA2* may be responsible for equal fractions of early-onset breast cancer and that these two genes together account for only about 6–10% of early-onset breast cancer in the general population (Hopper *et al.*, 1999; Peto *et al.*, 1999). Furthermore, only about 10% of patients with a first-degree family history of breast or ovarian cancer in the general population harbour a germline mutation in *BRCA1* or *BRCA2*. Based on mutation screening in ovarian cancer families, the allele frequencies of mutant *BRCA1* and *BRCA2* alleles have been estimated to be 0.0013 and 0.0017 (Antoniou *et al.*, 2000). This is compatible with the estimate of allele frequency of 0.0033 for dominant breast cancer-predisposing genes from segregation analysis, indicating that these disease-causing alleles are relatively rare in the general population (Claus *et al.*, 1991). On the other hand, in founder populations with recurrent mutations, such as among Ashkenazi Jews and in the Icelandic population, disease allele frequencies can be as high as 2.5% (Struewing *et al.*, 1995; Tonin *et al.*, 1995, 1996; Johannsdottir *et al.*, 1996; Roa *et al.*, 1996; Fodor *et al.*, 1998; Thorlacius *et al.*, 1997).

Detection of *BRCA1* and *BRCA2* mutations is considered to be of clinical importance because of

the associated high lifetime risk of disease. Earlier estimates based on large extended pedigrees used for linkage analysis indicated that *BRCA1* mutations confer an 87% risk of developing breast cancer by the age of 70 years and a 40–60% risk of developing ovarian cancer (Easton *et al.*, 1994). Affected mutation carriers also have an estimated lifetime risk of 65% of developing a second breast cancer (Ford *et al.*, 1994). The risk for breast cancer was thought to be similar for *BRCA2* mutations, whereas the lifetime ovarian cancer risk was estimated to be lower at 27% (Ford *et al.*, 1998). Risk of breast cancer among males is also highly elevated in *BRCA2* families. In addition, mutations in both genes confer increased risks for cancers at other sites, such as prostate, pancreas and colon (Ford *et al.*, 1994; Easton *et al.*, 1997).

Population-based studies in Australia as well as in founder populations such as Ashkenazi Jews and the Icelandic population, however, have estimated much lower risks to mutation carriers (Struewing *et al.*, 1997; Levy-Lahad *et al.*, 1997; Thorlacius *et al.*, 1998; Hopper *et al.*, 1999). Lifetime breast cancer risk for female carriers was estimated to be 37% for the *BRCA2* 999del5 mutation in Iceland and 56% for breast cancer risk and 16.5% for ovarian cancer associated with any of the three common *BRCA1* and *BRCA2* mutations among Ashkenazi Jews.

There is substantial variation in the age of onset and the site of cancer occurrence in carriers of *BRCA1* and *BRCA2* mutations between as well as within families. This variability is also observed for founder mutations (Levy-Lahad *et al.*, 1997; Thorlacius *et al.*, 1996). Therefore, suggestions that different variants may be associated with different disease severity or may predispose differentially by cancer site cannot be the sole explanations for the variability. *BRCA1* and *BRCA2* are considered to be tumour-suppressor genes and, therefore, changes in both alleles are required for complete loss of normal gene function. Even in individuals with an inherited mutation in one gene copy, loss or aberration of the normal gene copy later in life will be required for the development of disease. Other factors, both genetic and environmental, may therefore modify cancer risk.

Several other gene loci have been reported to modify the penetrance of *BRCA1* mutations. Mutation carriers harbouring rare 'variable number of tandem repeats' (VNTR) alleles of the *HRAS*

proto-oncogene have been found to have a 2.1-fold higher risk for ovarian cancer than carriers with only common alleles, but breast cancer risk was not increased (Phelan *et al.*, 1996). Rebbeck *et al.* (1999) reported that genotypes with long CAG repeats at the androgen receptor gene were associated with earlier age at diagnosis of breast cancer in *BRCA1* mutation carriers. A few studies have addressed the question of modifying effects of known reproductive risk factors on the *BRCA1*-associated risk. Some indicate similar effects of reproductive and hormonal risk factors on breast or ovarian cancer risk and others suggest that effects in mutation carriers may be different from those seen in breast and ovarian cancer in the general population (Narod *et al.*, 1995; Chang-Claude *et al.*, 1997; Ursin *et al.*, 1997; Jernstrom *et al.*, 1999). Most of these studies suffer from very small sample size and/or survival bias due to the fact that prevalent cases were used. To appropriately address these questions, an international prospective cohort study among *BRCA1/2* mutation carriers is being carried out under the coordination of the International Agency for Research on Cancer. Knowledge gained about risk modifiers in mutation carriers may be useful for refining individual risk estimation and may provide further insight into the pathways of breast cancer tumorigenesis.

Cancer risk, especially breast cancer risk, has been reported in epidemiological studies to be highly increased (4- to 8-fold) in blood relatives (thus obligate heterozygous gene carriers) of patients with the recessive disease ataxia telangiectasia (Swift *et al.*, 1987; Easton *et al.*, 1994). After the cloning of the *ATM* gene, studies based on mutation screening and haplotype analysis yielded lower estimates of about a threefold increase in the risk for breast cancer among heterozygous carriers (Athma *et al.*, 1997; Janin *et al.*, 1999). In contrast to previous estimates, heterozygosity for germline *ATM* mutations appears to be rarely observed in unilateral breast cancer in the general population and in families, but may be more prevalent among non-familial early-onset bilateral breast cancer (Vorechovsky *et al.*, 1996; FitzGerald *et al.*, 1997; Chen *et al.*, 1998; Broeks *et al.*, 2000). Most studies have screened for truncating *ATM* mutations, because missense mutations are technically more difficult to identify, and they may have therefore

underestimated the prevalence. Further studies aimed at identifying germline missense mutations and rare allelic variants of the *ATM* gene may provide better estimates of the contribution of *ATM* variants to early-onset breast cancer (Izatt *et al.*, 1999; Vorechovsky *et al.*, 1999).

Polygenes in the etiology of breast cancer

Genetic variants with low penetrance are unlikely to cause extensive familial aggregation. The association between specific genetic variants and breast cancer risk is studied by comparing the allele frequency or the distribution of genotypes among unrelated cases and unrelated controls with the same genetic background. When using the traditional epidemiological study designs of case-control and cohort studies, particular attention should be paid to the genetic composition of the comparison groups, since a positive association can arise as an artefact of population admixture (Lander & Schork, 1994). To prevent spurious associations, studies could be carried out within relatively homogeneous populations or should use family-based ('internal') controls, such as parents of the affected individuals (Terwilliger & Ott, 1992). Although association studies can be performed for any random DNA polymorphism, the search for etiologically relevant genes is more likely to be rewarding if directed at functionally significant variants in genes known or assumed to be biologically related to the disease of interest.

An increasing number of studies have investigated the relationship between common allele variants and breast cancer risk. Some 20 different genes have been examined, but none of the common alleles studied was clearly shown to modify the risk of breast cancer. Such genes include those involved in steroid hormone metabolism, which may modulate the levels of bioavailable steroid hormones, such as the catechol-O-methyltransferase (*COMT*), aromatase cytochrome P450 genes *CYP19*, *CYP17* (steroid 17 α -hydroxylase/17,20 lyase) and *CYP11B* and the steroid hormone receptor genes, such as those for the estrogen receptor (*ER*), progesterone receptor (*PR*) and androgen receptor (*AR*) as well as the vitamin D receptor (*VDR*). Genes involved in carcinogen metabolism may also modify breast cancer risk. These include genes coding for phase I enzymes such as *CYP1A1*,

CYP1A2 and *CYP2D6*, which act on tobacco smoke-associated carcinogens, *CYP2E1* which metabolizes ethanol, as well as genes for phase II enzymes such as the glutathione S-transferases μ (*GSTM1*), π (*GSTP1*) and θ (*GSTT1*), and the N-acetyltransferases *NAT1* and *NAT2*. In addition, common alleles of high-penetrance genes such as *TP53*, *BRCA1* and *ATM* can affect the integrity of cell-cycle checkpoint and DNA repair and thus modify cancer risk. Table 2 shows examples of genetic polymorphisms studied for association with breast cancer risk.

The results of the majority of the studies have

been summarized recently by Dunning *et al.* (1999). Statistically significant associations were reported in about a quarter of the 46 studies reviewed, but none was seen in more than one study. This can be explained largely by the lack of power in the majority of the studies. Less than a quarter of the studies had sufficient power to detect a relative risk of 2.5 for a rare allele homozygote if the rare allele frequency was 0.2. Dunning *et al.* (1999) performed a meta-analysis of 17 allele variants in 13 genes in order to obtain more precise estimates. Statistically significant differences in genotype frequencies were found for

Table 2. Examples of genetic polymorphisms studied for association with breast cancer risk^a

Gene	Polymorphism	Functional effect	Frequency of risk-associated allele (controls)	Range of risk estimates
<i>Steroid hormone metabolism genes</i>				
<i>COMT</i>	Val158Met	Reduced activity	0.35–0.52	0.80–2.20
<i>CYP17</i>	Promoter T→C	May increase transcription	0.38–0.42	0.81–2.52
<i>CYP19</i>	(TTTA) ₁₀	Unlikely	0.008–0.02	1.07–4.84
<i>PR</i>	306 bp insertion in intron 7	Unlikely	0.13–0.18	0.77–1.39
<i>Carcinogen metabolism genes</i>				
<i>CYP1A1</i>	Ile462Val	Possible increase in enzyme activity	0.04–0.09	0.88
<i>CYP2D6</i>	A, B, C alleles	Nonfunctioning enzyme	0.04–0.12	0.66–2.09
<i>CYP2E1</i>	Intron 6	Unlikely	0.08	1.01–1.04
<i>GSTM1</i>	Gene deletion	No enzyme	0.40–0.51	0.77–2.50
<i>GSTP1</i>	Ile105Val	Reduced activity	0.28	1.58–1.97
<i>GSTT1</i>	Gene deletion	No enzyme	0.21–0.28	0.63–1.50
<i>NAT1</i>	A1088T	Possible increased activity	0.17–0.46	1.00–1.20
<i>NAT2</i>	(several)	Low activity	0.51–0.62	0.70–2.08
<i>Other genes</i>				
<i>TP53</i>	Arg72Pro	Unknown	0.26–0.35	1.07–1.47
	Intron 6 G→A	Unlikely	0.10–0.13	0.28–1.08
	16 bp insertion in intron 3	Unlikely	0.12–0.16	0.51–2.08
<i>BRCA1</i>	Pro871Leu	Unknown	0.37	1.17
	Gln356Arg	Unknown	0.07	0.88
<i>ATM^b</i>	Pro → Arg	Unknown	0.016	3.0

^a Dunning *et al.* (1999)

^b Larson *et al.* (1999)

CYP19 (TTTA)₉ polymorphism ((TTTA)₁₀ carrier odds ratio (OR) = 2.33, 95% confidence interval (CI) = 1.36–4.17), the *GSTP1* Ile105Val polymorphism (Val carrier OR = 1.60, 95% CI = 1.08–2.39) and the *TP53* Arg72Pro (Pro carrier OR = 1.27, 95% CI = 1.02–1.59). There was evidence for heterogeneity with the *GSTM1* gene deletion, which showed a significant association only for postmenopausal breast cancer (null homozygote OR = 1.33, 95% CI = 1.01–1.76). In addition, some evidence of protection against breast cancer was found for homozygotes of the *PR* PROGINS allele (OR = 0.41, 95% CI = 0.15–0.95). Table 3 presents some low-penetrance alleles showing significant associations with breast cancer risk in joint analyses.

Some positive associations of allele variants have been found in conjunction with environmental exposures, for example, cigarette smoking and variant alleles of genes encoding carcinogen-metabolizing enzymes, *CYP1A1*, *NAT2*, *CYP2E1* and *GSTM1*. Although major effects of variant genotypes were not always found, some interactions with smoking were reported but within inconsistent results across studies (Ambrosone *et al.*, 1996; Shields *et al.*, 1996; Hunter *et al.*, 1997; Kelsey *et al.*, 1997; Ishibe *et al.*, 1998; Millikan *et al.*, 1998). A few other studies have investigated the possibility of gene–gene interaction involving *CYP1A1*, *GSTM1*, *GSTT1*, *COMT* and *CYP17* (Lavigne *et al.*, 1997; Bailey *et al.*, 1998; Helzlsouer *et al.*, 1998; Huang *et al.*, 1999). The interactions reported have yet to be confirmed by other studies (Lavigne *et al.*, 1997; Huang *et al.*, 1999).

Many of the earlier association studies suffer from both small and/or poorly designed samples. Careful consideration for selection of controls was often neglected. While the meta-analysis of published studies by Dunning *et al.* (1999) provides an apparently precise estimate, the inclusion of all studies without consideration for their quality does not necessarily produce a summary estimate which is accurate and relevant, thus limiting the inferences that can be drawn about the role of these gene variants in the etiology of breast cancer. Much larger studies are required to elucidate the complex interplay between many genes and environmental factors.

Implications for breast cancer risk assessment, management and prevention

With the identification of major genes for inherited breast cancer, it is now possible to screen for germline mutations in high-risk families. When a test result is positive, family members can be identified as carriers or non-carriers based on the germ-line mutation specific to the family. The genetic diagnosis improves risk assessment, since carriers will suffer from a high lifetime cancer risk, while non-carriers have only the population level of risk. Except for certain founder populations, it may at present be appropriate to cite a range of risk estimates for carriers until more data are available to differentiate risk to carriers dependent upon the extent of family history and other modifying factors. In the case of a negative test result, it may be difficult to interpret the finding for an affected woman with high *a priori* probability of carrying a susceptibility gene. All routinely available tests fail to detect a minimum of 10% of the mutations in both *BRCA1* and *BRCA2* (Stoppa-Lyonnet *et al.*, 1999). The identification of women at particularly high risk of developing breast cancer will provide a group among whom expensive and rigorous screening programmes are likely to be cost-effective, as well as a cohort of women who may benefit from chemoprevention.

At present, there is still uncertainty about recommendations for management of women with inherited susceptibility to breast cancer, although guidelines have been proposed (Eisinger *et al.*, 1998; Møller *et al.*, 1999a). There are only preliminary data suggesting that increased surveillance will reduce breast cancer mortality through detection of early tumours in high-risk women (Møller *et al.*, 1999b; Macmillan, 2000; Tilanus-Linthorst *et al.*, 2000). The appropriateness of breast and ovarian cancer screening schedules as well as the effectiveness of magnetic resonance imaging (MRI) of the breast need to be evaluated. The question of breast-conserving therapy is also not resolved, in view of the high risk of second primary breast cancer, as well as a possibly higher risk of ipsilateral breast tumour recurrence and increased radiation sensitivity in *BRCA1* and *BRCA2* mutation carriers (Robson *et al.*, 1999; Turner *et al.*, 1999).

Table 3. Some low-penetrance alleles showing significant associations with breast cancer risk in joint analyses

Gene	Polymorphism	Frequency of risk-associated allele in controls		Risk estimates for carrier	Study size No. cases/No. controls	Reference
CYP19	(TTTA) _H ₁₀	0.018		1.07 (0.35–3.91)	348/145	Siegelmann-Danieli <i>et al.</i> , 1999
		0.008		1.56 (0.59–4.57)	599/433	Healey <i>et al.</i> , 2000
		0.005		4.84 (1.87–14.8)	464/619	Haiman <i>et al.</i> , 2000
				2.33 (1.36–4.17)	Combined	Dunning <i>et al.</i> , 1999
GSTP1	Ile105Val	0.29	heterozygous	1.48 (0.81–2.73)	110/113	Helzlsouer <i>et al.</i> , 1998
			homozygous	1.97 (0.77–5.02)		
		0.28	heterozygous	1.53 (0.83–2.84)	62/155	Harries <i>et al.</i> , 1997
			homozygous	1.58 (0.49–5.06)		
			heterozygous	1.61 (1.10–2.34)	Combined	Dunning <i>et al.</i> , 1999
	homozygous	1.83 (0.95–4.48)	Combined			
TP53	Arg72Pro	0.76		1.10 (0.69–1.75)	107/305	Wang-Gohrke <i>et al.</i> , 1998
		0.37		1.47 (1.08–2.00)	212/689	Sjalander <i>et al.</i> , 1996
		0.35		1.07 (0.66–1.76)	93/347	Kawajiri <i>et al.</i> , 1993
				1.27 (1.02–1.59)	Combined	Dunning <i>et al.</i> , 1999
GSTM1	Deletion	0.46	postmen	2.50 (1.34–4.65)	110/113	Helzlsouer <i>et al.</i> , 1998
		0.50	postmen	1.10 (0.73–1.64)	177/233	Ambrosone <i>et al.</i> , 1995
		0.51	≥ 50yr	1.99 (1.19–3.37)	361/437	Charrier <i>et al.</i> , 1999
				1.33 (1.01–1.76)	Combined	Dunning <i>et al.</i> , 1999
PR	Progens	0.13		0.90 (0.38–2.09)	68/101	Lancaster <i>et al.</i> , 1998
		0.14		0.77 (0.50–1.18)	292/220	Manolitsas <i>et al.</i> , 1997
		0.18		1.39 (0.79–2.45)	187/90	Garrett <i>et al.</i> , 1995
			homozygous	0.41 (0.15–0.95)	Combined	Dunning <i>et al.</i> , 1999

Preventive options being discussed for high-risk women are prophylactic surgery and chemoprevention. Recent reports from retrospective follow-up and emerging data from prospective follow-up suggest that prophylactic mastectomy and prophylactic oophorectomy can reduce the risk of breast cancer in high-risk women (Evans *et al.*, 1999; Hartmann *et al.*, 1999; Rebbeck *et al.*, 1999). A cohort of high-risk women who underwent prophylactic mastectomy at the Mayo Clinic experienced an 81% reduction in incident breast cancer compared with their sisters (Hartmann *et al.*, 1999). However, long-term prospective follow-up on an extended group of women will be necessary to fully address the risk of subsequent breast cancer and the psychological sequelae. The risk reduction conferred by oophorectomy reported in 122 *BRCA1* mutation carriers was 47% and increased with longer duration of follow-up (Rebbeck *et al.*, 1999). The use of compounds that reduce the production of ovarian hormones may provide a non-surgical alternative to prophylactic surgery.

Effective chemoprevention would reduce the need for prophylactic surgery. If mammographic screening is not effective in this high-risk group, chemoprevention will become a higher priority. Tabar *et al.* (1999) reported that there was no reduction in mortality in women aged 40–49 years with grade 3 ductal carcinoma in the Swedish two-county study. Women with *BRCA1* and *BRCA2* germline mutations typically present with early-onset tumours of higher grade (grade 3) (Eisinger *et al.*, 1996; Lakhani *et al.*, 1998). However, if chemoprevention is to be equivalent to (the gold standard of) prophylactic mastectomy, it will be necessary to strive for an 80% reduction. The approximately 50% reduction in the risk of developing breast cancer due to tamoxifen treatment in a trial in the United States (Fisher *et al.*, 1998) was not reproduced in two smaller European trials (Powles *et al.*, 1998; Veronesi *et al.*, 1998). Raloxifene, another selective estrogen receptor modulator (SERM), decreased the risk of estrogen receptor-positive breast cancer by 90%, but not estrogen receptor-negative invasive breast cancer (Cummings *et al.*, 1999). However, the issues relating to the use of SERMs as chemopreventive agents will have to include the estrogen receptor-negativity of *BRCA1* tumours (Lidereau *et*

al., 2000). The synthetic retinoids are another class of compounds being explored for chemoprevention (IARC, 1999; Lippman & Lotan, 2000). Fenretinide, a synthetic retinoic acid derivative, may decrease the occurrence of a second breast malignancy in premenopausal women (Veronesi *et al.*, 1999).

Chemoprevention is still in its infancy and the efficacy of chemoprevention in this high-risk population is unknown. The efficacy of new as well as existing agents for chemoprevention needs to be carefully assessed in properly designed clinical trials of women with increased risk of breast cancer. In the process, other modifying factors of penetrance in mutation carriers should be accounted for in order to evaluate the true effect of the chemopreventive agents.

Polygenes confer much lower levels of risk and may be relevant for risk assessment when the effects of multiple loci, possibly in conjunction with environmental factors, are understood and quantified. At present, it is unlikely that the genetic information about single polygenes will be clinically relevant for risk assessment and management. However, the knowledge gained on the role of different single polygenes and their interaction with environmental factors may help to direct research efforts towards identifying different pathways in breast cancer carcinogenesis which may be amenable for preventive measures, including chemoprevention.

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