

Chapter 4
Breast Cancer and Genetic Predisposition

The relation between the occurrence of a cancer and the existence of genetic alterations is now well established. In breast cancer as in the majority of cancers, these alterations are mostly somatic. Genetic alterations observed in the course of the malignant transformation are varied: chromosomal deletions, translocations, amplifications and rearrangements, duplications or whole chromosome losses (aneuploidy), and point mutations. Some of these alterations lead to the modification of the expression and/or the structure of the product of the gene implied by these alterations.

It will result in:

- activating genes in a dominant way: the alteration of only one of the two copies of the gene is required and these genes have been called oncogenes.
- inactivating genes whose loss of function participates to tumorigenesis; these genes have been called tumor suppressor genes (TSG).
- activating or inactivating genes whose products interfere with the genome stability: genes regulating the processes of mitosis and DNA repair enzymes. The alteration of these genes will help the occurrence of alterations of the more directly implicated genes (i.e. oncogenes and tumor suppressor genes).
- finally, the above mentioned gene expression modifications can result, not from the direct alteration of the gene itself, but from alteration of genes acting on the “modeling” of the chromatin or on the DNA methylation status. Such mechanisms are called epigenetic.

The activation or inhibition of only one of these genes is not sufficient to convert the phenotype of a normal cell into a tumor one: multiple mutational events are required. The accumulation of these genetic alterations, which interact and cooperate between themselves, is necessary to lead to the tumor phenotype. During this multi-stage process, each new genetic alteration acquired by the cell will give it new properties, favoring the selection of this clone and thus converging to the tumoral phenotype. The understanding of carcinogenesis requires the identification of these numerous genetic alterations or mutations, of which all or part of it is responsible for the initiation and the tumor progression. In due time, the identification of the responsible genetic alterations have repercussions on diagnosis, prognosis and therapeutic.

Somatic alterations in breast tumors

At the chromosomal level, the most frequently observed somatic genetic alterations are deletions affecting in particular the chromosomes 1p, 3p, 6q, 8p, 9p, 11q, 13q, 16q, 17p; these chromosomal regions may thus contain TSGs, with a decreased or lost expression in tumor tissues. Other chromosomal regions are amplified, notably 1q, 8q, 11q13, 17q, 20q13... Several amplified oncogenes have been identified within these regions like HER2 on 17q, MYC on 8q24, or Cyclin D1 on 12q13. Other alterations include point mutations, notably those affecting the tumor suppressor gene TP53, present in 20 to 40% of breast cancer or those of the oncogene PI3K –Phosphatidyl Inositol 3 Kinase-, in about 25% of breast tumors. Other TSGs are mutated less frequently like PTEN, a tumor suppressor gene inhibiting PI3K, or CDKN2A, a negative regulator of the cell cycle. Epigenetic alterations are frequent in breast tumors; for example the methylation of the promoters of several TSGs results in a loss or decreased of their expression level.

At the RNA level using DNA microarray –also called transcriptomics-, five molecular subtypes with distinct gene expression profiles have been evidenced. One major ER negative class contains HER2 positive, basal-like (HER2 and ER negative) and normal-like breast tumors. The ER positive tumors can be subdivided in luminal and B subtypes. Moreover, this molecular classification clearly influences the prognosis and response to treatments of breast tumors, with the best prognosis for luminal A and the worse for basal-like tumors.

Hereditary cancer predisposition

Genetic alterations may occur by chance, but may be enhanced by mutagenic and/or mitogenic factors, both endogenous and environmental. In 4 to 10% of breast cancers, a germline mutation predisposes to breast cancer, easing the occurrence of specific other somatic genetic alterations. Knudson in 1971 postulated that the development of retinoblastoma results from two mutations in retinoblast. The two-hit model assumed that one mutation spontaneously occurs and the second could be the consequence of a constitutional –also called germ-line- mutation.

Comings in 1973 focused the Knudson hypothesis to a particular gene which should regulate the cellular growth. This explains why a recessive mutation can have a dominant phenotype in cancer predisposition. The analysis of LOH -for Loss of Heterozygosity- in retinoblastoma showed that the wild allele was prone to be more frequently lost in the tumor tissue than the mutated one. That explains also why the probability to a child to inherit a parent's mutation is 50%. There is no sex discrimination, so risk can be transmitted by either men or women. Some suppressor genes have been implied in inherited predisposition to breast cancer. In genetic susceptibility, all cells carry a mutation responsible for the disease. The transmission mode is mainly autosomal dominant. Then, the offsprings have 50% risk to have the deleterious mutation.

Inherited predisposition to breast cancer and family history

A family history of breast cancer is clearly accepted as a risk factor and for a long time. When there is a family history, the breast cancer risk is increased by 3 to 4 times. And this increase is positively correlated to the number of first and second degree relatives with a breast cancer and the precocity of these cancers. Breast cancer is a very frequent disease and that explain the difficulty to associate multiple breast cancers in a family and predisposition to breast cancer. Familial aggregate and genetic susceptibility to cancer are not synonymous. At the breast cancer diagnosis, 15-20% of women have a first degree parent with a breast cancer and only 5% have a genetic susceptibility. However, in breast cancer, there is, up to now, few other factors than a family history to decide a gene screening. Nowadays, some family histories can be associated to a specific gene. A germline mutation in the *BRCA1* and *BRCA2* gene is most frequent cause. However, less than 30% of families with solely multiple breast cancers have a mutation in those two genes. The population-based cases of breast cancer and familial clusters have favored the polygenic model where multiple genetic factors act independently. Some studies are assessing the effect of multiple gene alteration.

Genes involved in breast cancer predisposition

Susceptibility genes can be classified by the risk and the penetrance. The penetrance is the frequency of the disease expression associated to a deleterious mutation. In high penetrance genes, individuals with a deleterious mutation have a risk in the lifetime close to 80%. Schematically, the breast cancer risk is by 80% at 80 years old.

High penetrance genes : BRCA1 and BRCA2

Discovery

Linkage studies were used to find those two genes. Linkage studies the transmission of some markers in families with a predisposition to cancer. Some significant marker can identify a sensible area in genome which transmitted exclusively to the individual with a phenotype of breast cancer. The correlation with the *BRCA1* and *BRCA2* genes has been between 35% and 50% of the familial cases. The attempt to find another genes to explain the families without any mutation in *BRCA1/2* failed. *BRCA1* gene was localized at the chromosome 17q21 in 1990 and identified in 1994. This gene can explain the majority of familial predisposition. *BRCA2* gene, localized in chromosome 13p12.1 have been identified in 1995. This gene is mainly associated to families with solely breast cancer and/or with male breast cancer.

Molecular function

BRCA1 and *BRCA2* are genetically distinct but both of them are involved in the maintenance of genome stability. The role of *BRCA1* looks complex : E3 ubiquitin ligase involved in the DNA damaging signal, reparation of double stranded DNA breaks, chromatin remodelling and implication in the transcription. There is no biallelic mutation reported and no viable animal with null *BRCA1* allele. *BRCA2* intervenes also in the reparation of double stranded DNA breaks and homologous recombination in the direct association of *RAD51*. A biallelic mutation in *BRCA2* have been associated Fanconi's anemia (FANC-D1). In this disease, the consequences are an extreme sensitivity to chemotherapy and irradiation with spontaneous chromosomal instability.

Epidemiology

In general population with breast cancer, the proportion of mutations in those two genes are very low. One women by 400 is a *BRCA1/BRCA2* mutation carrier. The average frequency is between 2 and 6% in young onset of breast cancer in different population. In a british study, 6% of women with a breast cancer diagnosed before 36 years have a mutation either in *BRCA1* or *BRCA2*. With the most penetrance estimates, the respective proportions of *BRCA1* and *BRCA2* mutation carriers are 3% of patients with breast cancer and younger than age 50 years, 0.4-0.8% of patients with breast cancer and age 50 years or older, and 0.1% of women in the general population. All those statistics have been evaluated on Caucasian women in Europe and United States, African women seem to have a lower rate of deleterious mutations, but much more unclassified variants with unknown significance and have a higher frequency of young onset of the disease (studies on African American women). In all ovarian cancer, *BRCA1* and *BRCA2* mutations occur in 10-20% in unselected patients.

Risk

In familial aggregate, *BRCA1* and *BRCA2* are the two archetypes for high penetrance genes. In Breast Cancer Linkage Consortium, those two genes were responsible for 95% of families with ovarian and breast cancers (at least 4 cases before 60 years old). Recent estimates of breast-cancer risk by the age of 80 years are 90% for *BRCA1* mutation carriers and 40% for *BRCA2* mutation carriers. Some studies have tried to identify genotype-phenotype correlation. For *BRCA2*, there is the ovarian cancer cluster region, central region between nucleotide 3035 and 6629. There, the risk of ovarian cancer is multiplied twice and breast cancer risk divided. Other attempt to find other correlation was unsuccessful. Now, some studies try to understand the reason why some positive *BRCA1/2*-mutation families have a higher incidence of breast cancers. Some polymorphisms in other genes could facilitate the increase in the breast cancer risk. *RAD51* have been the first gene identified as a modifier of risk among *BRCA1/2* mutation carriers. The gene *RAD51*, a partner of both *BRCA1* and *BRCA2* in the double-stranded DNA-repair mechanisms, have a polymorphism in the 5' untranslated region (UTR) 135G>C which has been suggested as a possible modifier of breast cancer risk in *BRCA1* and *BRCA2* mutation carriers. For CC homozygotes in *BRCA1/BRCA2* mutations carriers, the hazard ratio is increased by 1.92. Moreover, in *BRCA2* mutations carriers and CC homozygote, the hazard ratio is 3.18. A single nucleotide polymorphism have reported for the *MDM2* gene to increase the risk for breast and ovarian cancer in the Ashkenazi *BRCA1* and *BRCA2* mutation carriers. There are also strong evidences to suggest increases in penetrance of breast cancer related to *BRCA1* and *BRCA2*. Environmental and lifestyle factors could play a role in this trend.

High penetrance genes with a specific spectrum of cancer

Other genes have been implied in predisposition to breast cancers with a high penetrance rate. In those genes, breast-cancer is not the main phenotype. No other high penetrance genes have been found through large genome-wide association study.

TP53 gene (17p13) is responsible for Li-Fraumeni syndrome with the following associated cancers : soft-tissue sarcoma, osteosarcoma, brain tumors, adrenocortical carcinoma, leukemia and colon cancers. In this type of familial aggregation, a mutation in *TP53* is found in 50% of cases. 1% of breast-cancer before 40 years old would be associated to a mutation in this gene. The relative risk of

breast cancer is 1,46 overall, but from 5,46 between 15 and 29 year-old. The risk by age of 70 years is more than 90.

PTEN gene is responsible for several syndromes: Cowden's disease, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome and Proteus like syndrome. Major cancers associated are thyroid, endometrial and genito-urinary cancers. Breast-cancer cover 0,1% . PTEN is associated to cutaneous and muquous hamartome. Half of mutation carriers have mastopathie which lead in 50% of cases to breast cancer. The relative risk of breast cancer is 2-4. The risk by age of 70 years is more than 25-50.

STK11/LKB1 gene is responsible for Peutz-Jeghers syndrome. The spectrum of tumours are from small intestine, colorectal, uterine, testicular, ovarian sex cord and others. The relative risk of breast cancer is 15 and the risk by age of 70 years is 45-54.

CDH1 gene, E-cadherin, is responsible mainly for hereditary diffuse gastric carcinoma. The risk of breast cancer is 3,25 and the risk by age of 70 years is 39. The cytology of the breast cancer associated to CDH1 is very specific with a lobular type. Some family have been described without any diffuse gastric carcinoma.

Intermediate penetrance genes

Four intermediate-penetrance breast cancer genes have been identified : CHEK2, ATM, BRIP1 and PALB2. Mutations are rare and confer a relative risk to breast cancer of 2 to 4. Those four genes are implied in the cell cycle regulation and DNA reparation. They interact directly or indirectly with *BRCA1* or *BRCA2*.

CHEK encodes CHK2 protein implied in the phosphorylation of both p53 and *BRCA1* during DNA double-strand breaks reparation. The mutation reported is 1100delC. A meta-analysis conclude to a direct odds ratio of breast cancer between 1,72 and 3,2. Some studies associated this gene with other cancers as prostate and Li-Fraumeni syndrome, but without any convincing evidence.

ATM occupies a central role in the response to double-strand DNA breaks. It is associated to ataxia telangectasia when biallelic mutations. However, the heterozygous women have an increase in breast cancer between 1,51 and 3,78.

BRIP1 and PALB2, both encodes for proteins which interacts one with *BRCA1* and the other with *BRCA2*. In case of biallelic mutation, both result in Faconi Anemia. BRIP1 mutations have a relative risk close to 2 (95% CI 1,2-3,2). PALB2 mutations have a relative risk close to 2,3 (CI 95% 1,4-3,9).

Low-penetrance genes and alleles

Other pathways have been reported sterodien hormone (AR), hormonal metabolism (CYP17, CYP19) detoxification system (GSTM1, GSTP1, NAT2). In recent publications, some specific single nucleotide polymorphisms could increase the breast-cancer risk or protect carriers to this cancer as the gene CASP8. An interesting review have explored all the variant described in those gene and the level of risk associated. In candidate gene studies and genome-wide association studies, many polymorphisms were studied and some new genes were connected to BC susceptibility. Unfortunately, the odd ratio were all close to 1 to 2 (as the following table).

Locus	Gene	Homozygote OR (95% CI)
10q26	FGFR2	1,63 (1,53-1,72)
16q12	TNRC9	1,64 (1,45-1,85)
2q35		1,44 (1,30-1,58)
2q33	CASP8	0,74 (0,62-0,87)
11p15	LSP1	1,17 (1,08-1,1,25)
6q22.33	ECHDC1	1,41 (1,25-1,59)

Table : Summary of known low-penetrance breast cancer predisposition variants

The increase is so moderate that they can not be used alone. One can imagine a combination of several SNP to determine an individual risk. Since the penetrance can be modulated by external factors, a notion of individual susceptibility is now assumed to explain a risk of cancer associated to many factors in which there is the genetic factor.

Finally, only *BRCA1/2* is proposed as a routine screening in a breast/ovarian cancer familial history, but high penetrance genes with specific phenotype.

BRCA1/BRCA2 tumor characteristics

Infiltrating ductal carcinoma is the most common histological subtype in hereditary breast cancers, although several subtypes are associated with hereditary breast tumors. This is the case of medullary breast carcinoma that is observed in 11% of *BRCA1* tumors, whereas only 1-2% of sporadic and *BRCA2* tumors belong to this subtype.

BRCA1 tumors have characteristic pathological features. They often show atypical medullary features, 'pushing margins' and lymphocytic infiltrate, and are less likely to have coincident *in situ* carcinoma. *BRCA1* tumors are usually of high histological grade, highly proliferative, and ER/PR and HER2 negative (referred to as 'triple-negative' tumors).

At the biological level, frequent somatic mutations of TP53 and/or p53 immuno overexpression are observed. *BRCA1* tumors often express basal cytokeratins (CK 5/6 and/or 14 and 17) and EGFR^{43,44}. Altogether *BRCA1* tumors share morphological and immunohistochemical features of basal-like breast tumors. Also at the RNA level using DNA microarray, the tumors arising in *BRCA1* carriers segregate together with sporadic basal-like breast cancers.

Unlike *BRCA1* tumors, *BRCA2* tumors do not have specific morphological and biological properties. They are of a low or intermediate grade (60%). They express ER and PR in the same proportion than not otherwise specified sporadic breast tumors and are mainly HER2 negative.

Oncogenetic consultancy

Organization and role

Some important points should be stressed during the consultancy: best limits, impact on social life and personal point of view, medical management, information diffusion in the family... The time to get the result should be clearly described. Time for reflection and decision should also be given to the patient.

Consultancy is an important time to discuss about the familial history and disease risk. Now it should be also a point of entry for a multidisciplinary carryover.

Family test is well codified :

- 1- General information and family history discussion
- 2- information about a genetic test and its limits
- 3- a choice given with an informed consent
- 4- two independent blood samples collected at two different days
- 5- a psychological and multidisciplinary management

Indications

A molecular screening should be proposed when a family history can evoke a predisposition to breast or ovarian cancers. Two levels of clinical intervention can be assessed. For healthy patient, the detection of a deleterious mutation in a family can help to assess their own risk toward the cancer. For cancer patient, that can also be a help to decide a surgery intervention and to plan a regular surveillance.

Since *BRCA1* and *BRCA2* have a very high penetrance, a molecular screening should be prescribed specifically to those two genes. In fact, genes associated to low-to-moderate risk have no clear management guideline up to now. In case of asymptomatic individual, the decision to perform a molecular screening should be assessed in a multidisciplinary staff to take into account all the impact connected to this analysis.

Several models exist for the decision to screen those genes. Family history remains the main factor to select individual for a genetic screening. Some model were developed but no have been fully validated. Moreover, the population used for those models were mainly occidental (BRACAPRO, MANCHESTER). BRACAPRO appears to perform with the best performance, but in small families, it is necessary to have direct criteria of selection.

The indicators can include with a 10% detection probability of mutations :

- early age of cancer onset before 35 years-old
- multiple affected individuals within a family :
 - o at least 3 cases of breast or ovarian cancer in the same parental branch and with first degree relative. If the first degree relative is a male, the second degree can be taken into account.
 - o Two cases of breast cancer in first degree relatives in whom one breast cancer occur before 40 years-old, or one cancer is ovarian cancer, or one breast cancer is for a male.
- bilateral disease
- association of a breast cancer and an ovarian cancer
- males with breast cancer

Here, a rapid table for compute the best indication:

<i>BRCA1/2</i> mutations identified	5
Breast cancer in a woman under 30 years-old	4
Breast cancer in a woman between 30-39 years-old	3
Breast cancer in a woman between 40-49 years-old	2
Breast cancer in a woman between 50-70 years-old	1
Breast cancer in a man	4
Ovarian cancer	3

In a parental branch, all the event have to be added with the weight associated. If it is superior to 5, it is an excellent indication. Between 3 and 4, indication is possible. Under 3, the medical use is reduced. As quoted before, ovarian cancer is an important weight in any assessment for a mutation in families. Deleterious mutation in *BRCA1/BRCA2* account for 1 to 30% of family with those indicators. The screening of mutations should characterise the mutation responsible for the familial aggregate of cancer. Due to the large spectrum of mutations, many families bear its own private mutation. Any strategy to screen only a panel of specific mutation in a country has not been generalised.

Confirm a genetic predisposition

To maximise the the yield, the first analysis should be performed only with a person getting the most reliable clinical history to predisposition. If possible, the person with the breast cancer should be the first person to undergo a genetic testing. Some medical doctors can be directly contact by someone in the family with healthy. In those cases, it is better to ask for contacting the person with breast cancer.

Detection strategy begins mostly with a rapid first screening to select suspicious exons. Since all mutations are heterozygous, the techniques performed in routine look for heteroduplex (dHPLC, HRM). Then, a direct sequence of some suspicious exons can be done. Two independent blood samples should be collected to check any positive result on another independent sample from the patient. The result should be given only to the person associated to the medical consultation. What ever the result, there given directly to the patient. Any mail, fax or e-mail should be avoided.

If positive, the patient is encouraged to diffuse the result toward his family. Specific surveillance and preventive treatment can then be proposed to the patients. If the result is negative, the existence of the genetic predisposition cannot be cancelled only with these results. The interpretation to a negative result is either the lack of sensibility in the technique used or the responsibility laid on another unknown gene. Some case without any mutation can also be phenocopy that means they have a non hereditary cancer. That is why, it can be valuable to test an other patient with a breast or ovarian cancer in the family. With a negative result, the residual risk of predisposition has then to be assessed only with the family history.

In between, some result would conclude to a polymorphism which has no impact on the disease history. There is would get an unclassified variant which should be analysed further to conclude to any responsibility. Some methods have proposed to better classify those unclassified variants with unknown significance in the risk of cancer⁵⁰. Only deleterious mutation will lead to genetic tests for all the family members.

Test other family members

When a deleterious mutation is found in a family, the genetic tests proposed to other members of the family is only focused on the deleterious mutation identified. The time to get the result is shortened. In those other member of the family if the test is negative, they can be considered with a risk equal to the risk of the general population. However, a recent study have raised a disturbing possibility that even with a negative-mutation result, women in those families still have between two and five times more risk to develop a cancer than women in general population⁵¹. In fact, since there are a large number of individuals with a breast cancer in those families, individuals are usually under a high level of surveillance and often fully aware of the risks.

If the test is positive, medical follow-up can be proposed. Then a negative test result is a very important information for an individual in family with a deleterious mutation.

Database and interpretations

In the international database (Breast Information Cancer / <http://research.nhgri.nih.gov/bic/>), a large panel of mutations has been described. For *BRCA1*, 1643 different mutations have been reported with 52% reported once. For *BRCA2*, 1643 mutations have been reported with 54% reported once.

For both *BRCA1* and *BRCA2*, there is a large diversity. In some populations, one or few mutations are associated with the large majority of predisposition breast cancer associated to *BRCA1* and *BRCA2*. For instance, in the Dutch families, two large rearrangements represent 36 per cent of the described mutations. This phenomenon is described as a founder effect. In the Ashkenazic families, they are three recurrent mutations. In Iceland, *BRCA2*, 999del5 covers most of the mutations.

Usually, clearly deleterious *BRCA1* and *BRCA2* mutations are frameshift or non-sense mutations. Because the real function of those two genes just begins to be understood, there is few clues to classify missense mutations.

Surveillance of a inherited breast-cancer background

The follow-up of individuals at risk is managed after a precise quantification of the cancer risk. Generally, those preventive actions target only individuals bearing in *BRCA1/BRCA2* mutation and those with a high probability to bear any mutation. It should be mentioned here that the use of an oral contraceptive is allowed. Up to now, no clear increase in breast cancer has been associated to in general population. In contrast, hormone replacement therapy (HRT) should be discussed in this population. Certainly, high level of estrogens/progestins should be avoided in this population, but the exact consequences are undefined. However, short term HRT for women who undergo prophylactic bilateral salpingo-oophorectomy at early age should be considered. Short term HRT does not seem to decrease the risk reducing effect of PBSO.

Screening for breast cancer

The surveillance of women with high risk of Hereditary Breast Cancer should be done in multidisciplinary state-of-the-art breast centers. Monthly self-breast examination starting at age 18 has been recommended, although no significant reduction in breast cancer mortality has been shown.

Semiannual clinical breast examination at age of 25 is usually recommended; the proportion of cancers detected by clinical breast exam varies from 0 to less than 5%. Until recently, only clinical breast exam and annual mammography from age 25 was recommended. Nowadays, the most sensitive screening approach uses four modalities to detect breast tumors early on: clinical breast exam, mammography, breast ultrasonography, or MRI. The screening interval is usually 6 months and combines one or more of these modalities.

Mammography

A meta-analysis of the efficacy of screening mammography had shown a reduction in breast cancer mortality by 16% in women whatever their age. The first criteria to measure the efficacy of screening mammography is the number of interval cancers which raise in between two screenings and present as a palpable mass after a normal screening examinations. Among 10 series, 29% of incident tumors were interval cancers. Those interval cancers were found more commonly in the women younger than 40 years of age. The sensitivity of mammography is influenced by age, breast density and the time of development of breast tumors.

In BRCA mutation carriers, the sensitivity of mammography is low, with a high risk to have interval cancer, of up to 50%. One explanation may be the rapidly growing “basal-like” phenotype found in *BRCA1*-associated cancers⁴⁴. Due to its high specificity, from 90 to 100%, annual mammography is recommended in high-risk women, but in association with other modalities of surveillance.

Ultrasonography

Annual screening ultrasonography has been found to add sensitivity to mammography, particularly for women with dense breasts.

Magnetic Resonance Imaging

Unlike mammography, breast density does not influence magnetic resonance image quality. Contrast-enhanced MRI has been reported to have 70 to 100% sensitivity in BRCA mutation carriers (compared to about 40% for mammography) and a specificity ranging from 80 to 95%^{57,58}. Annual bilateral MRI starting at age 25, as an adjunct to mammography, is now recommended. Using these modalities interval breast cancers are equal or less to 10%.

Screening for ovarian cancer

Twice-yearly transvaginal ultrasonography and serum CA 125 measurements are usually performed although they have not shown to downstage ovarian tumors or improve survival. The management of Hereditary Breast Cancer as well as ovarian cancer has been reviewed.

In France, the modalities for the follow-up of predisposed women were proposed by a group of experts in 1998 and revised in 2004:

- Clinical breast examination two to three time a year, from the age of 20
- Yearly bilateral mammography from the age of 30 -year-old, even 25
- Yearly breast ultrasonography, moreover with high density breast
- Yearly MRI. Due to its high sensitivity, bilateral MRI every year in comparison to mammography, has been introduced in routine practice in 2004.

Strategy for reducing risk

Other preventive options than surveillance include chemoprevention and surgery.

Surgery

Preventive surgery aims to reduce cancer risk and mortality. Risk-reducing options are prophylactic bilateral mastectomy (PBM) and prophylactic bilateral salpingo-oophorectomy (PBSO).

No randomised, controlled trials of prophylactic surgery have been conducted. Most of studies are retrospective or prospective cohort studies.

Mastectomy cut the risk of breast cancer by 90% in mutation carriers. Other studies of prophylactic bilateral mastectomy in high-risk women have been published. All studies results are consistent with a high risk reduction of breast cancer, ranging from 85-100%.

Salpingo-oophorectomy is an important preventive intervention for mutation carriers and cut the risk of gynaecologic cancer by 80 to 96 per cent. Furthermore, with this intervention, the risk of breast cancer is approximately cut by 50 per cent probably due to the induction of premature menopause. This intervention is recommended for women older than 40 years old and with a familial project closed. However the earlier the PBSO is performed, the greater is beneficial effect. Hormone replacement therapy should be considered in these young women. A short hormone replacement therapy after a salpingo-oophorectomy does not seem to modify the risk reduction.

Although highly effective, PBM and PBSO do not entirely prevent the risk of subsequent breast or ovarian cancer. For example, a 0.2% annually risk of peritoneal cancer after PBSO has been reported.

Chemoprevention

The development of SERMs like Tamoxifen has improved survival in breast cancer. In the primary prevention setting, Tamoxifen given for five years was shown to reduce the incidence of breast cancer by 43% in woman at increased risk. Other trials have shown a reduction in breast cancer incidence in high risk women. There is some evidence in the reduction in the risk of contralateral breast cancer both in *BRCA1* and *BRCA2* carriers. The results of trials tamoxifen are contradictory and several studies have not proven a risk reduction in breast cancer incidence. Moreover, concerns over the side effects discourage widespread implementation of tamoxifen. All trials indicated increased risk for thromboembolic events (OR = 2,21 [CI 1,01-2,24]), endometrial cancer (OR=2,42 [CI 1,46-4,03]) and stroke (OR = 1,50 [CI 1,01-2,24]). Another SERM, Raloxifen may confer a similar risk reduction with lower side effects.

In France, no official indication has been approved by a national drug agency. In contrast, the FDA has approved the use of Tamoxifen as a preventive agent for high risk women only. Other anti-estrogens like Aromatase Inhibitors (AIs) have been proposed in control trials. They seem to surpass Tamoxifen in terms of both efficacy and tolerance. However, it should be underscored that AIs will be effective only in post-menopausal women. Randomized trials are in development.

No randomised controlled trials of oral contraceptives to prevent breast and ovarian cancer have been published. Observational studies indicate associations between oral contraceptives and reduced ovarian cancer in the general population as well as *BRCA1/2* mutation carriers. Case-control studies have demonstrated a substantially lower risk in women with have had three or more years of exposure to oral contraceptives (up to 60%).

Treatment

The great majority of studies on survival in hereditary breast cancer do not identify a survival difference between mutation carriers and non carriers. Currently, mutation carriers are treated with the same protocols than all the patients with breast cancer, particularly with adjuvant therapy. The

existence of a mutation does not seem to have an impact on the efficacy or on toxicity of treatment. However, due to the high incidence of in-breast tumor recurrence as well as of second ipsilateral primary tumor, the indication of a full mastectomy should be discussed.

The high risk of contralateral breast cancer –25 to 30% at 10 years- shall be taken into account and a prophylactic mastectomy can be also proposed, although this risk may partly be reduced by PBSO and/or chemoprevention.

Novel therapeutic approaches are now proposed. Several preclinical data support the hypothesis that BRCA-deficient cells are more sensitive to particular chemotherapies. The reason for that may be the role of BRCA genes in DNA repair, especially DNA double-strand break repair⁷⁷. Thus, BRCA deficient cells may be more sensitive to alkylating-agents like cisplatin and mitomycin. Clinical trials addressing these issues are ongoing. Other strategies that may also take advantage of the specific DNA repair defect in BRCA-deficient cells are currently being tested, like poly(ADP)-ribose polymerase (PARP) inhibitors. Actually, the inhibition of PARP results in accumulation of double-strand breaks in BRCA-deficient cells. Phase I and II studies are in development.

Altogether, BRCA-associated cancers should be treated like sporadic breast cancers bearing comparable clinical and pathological features. However, local treatment should be discussed regarding the high of second primary breast tumors.