whether or not intensified surveillance will be effective in terms of reducing morbidity and mortality remains to be seen. This lack of evidence must be communicated to individuals at increased genetic risk, and this lack of proven outcome needs to be considered in the decision making process for appropriate management strategies in each individual case.

201 Invited

Prophylactic surgery and oophorectomy in the management of high risk individuals

Abstract not received.

202 Invited

Optimal genetic testing in 2006

D. Stoppa-Lyonnet. *Genetics Department, Institut Curie, Paris, France*

Genetic testing for breast cancer predisposition was greatly improved during these ten past years thanks to the identification of breast cancer predisposing genes. At the present time, 4 genes may be tested in the setting of a cancer genetic clinic: *BRCA1*, *BRCA2*, *TP53*, and *PTEN*; 3 genes may be tested, but still in a research setting: *ATM*, *CHK2*, and *STK11*. All these genes are associated with an increased risk of breast cancer through a germ-line mutation transmitted according to a dominant mode and leading to a biological inactivated protein. At the tumour level, a second mutation event has, in most cases, inactivated the second allele, leading some people to call these genes "tumour suppressor genes" (TSG). However, the *BRCA1, BRCA, and ATM* genes must be regarded as caretaker genes as there are involved in the maintenance of the genome stability rather than in the negative control of cell cycle.

Due to the high number of different mutations scattered in the coding sequence of each gene and due to the lack of information brought by a negative result at the end of a complete gene screening, two types of tests have to be considered: index case test which aim is to understand the family history by the identification of a causal mutation and thus to allow a genetic test in the relatives. The index case test needs the complete screening of the chosen genes; the test in relatives is tagged on the mutation identified in the index case. In order to be in the best situation to understand the origin of the family history and thus to identify a mutation, the index case is in general a women previously affected with breast or ovarian cancer. The indication of genetic testing and the choice of the gene to be tested rely on the personal and family history of breast cancer patients. In front of a family history of breast and/or epithelial ovarian cancer without any other phenotypic features, the *BRCA1* and *BRCA2* genes are screened.

The strategy chosen for the identification of mutations in index cases must be able to identify both point and small size mutations located in the coding sequence of the gene or at the exon-intron junctions and large gene rearrangements (partial or complete gene deletion or duplication). Indeed, at the present time, it is estimated that 10 to 20% and 5 to 10% of mutations are large rearrangements of the respectively *BRCA1* or *BRCA2* genes. We will review the different techniques that may be used for the detection of point mutations and large gene rearrangements.

One of the greatest difficulties in breast cancer genetic testing is that the number of expected mutations is unknown. At the present time, about 80% of women affected with breast cancer and tested for *BRCA1/2* gene mutation are not found to be mutation carrier. Many reasons may explain these results: lack of sensitivity of mutation detection methods, detection of gene variants of unknown significance (unknown variant, UV), test of a sporadic case in a family where a *BRCA1/2* mutation is running, test of familial aggregation occurring by chance. Conversely, women whose personal and family history does not meet genetic testing criteria may be carrier of *BRCA1/2* mutation.

Altogether, the improvement of genetic testing and the identification of a tumour signature indicating the involvement of a specific predisposing gene are urgently needed to optimise breast cancer risk estimation and thus the management of women at risk of breast cancer.

Thursday, 23 March 2006 09:00–12:45

PLENARY KEYNOTE

Local and regional treatment

203 Invited

Molecular prediction of local behaviour

M.J. Van de Vijver. *The Netherlands Cancer Institute, Department of Pathology, Amsterdam, The Netherlands*

In this abstract, the clinical and pathological aspects of locoregional recurrence are discussed separately for chestwall recurrence after mastectomy and for local recurrence after breast conserving treatment; followed by a discussion of genetic techniques that can be used to find additional risk factors for local recurrence.

1. Local recurrence after mastectomy.

It has been shown that risk factors for local recurrence after mastectomy include young age, the presence of lymph node metastases and large tumor size. At present, there is still heated debate on which patient subgroups should receive postoperative radiotherapy to the chestwall.

It has been shown in a number of studies that radiotherapy to the chestwall decreases the percentage of chestwall recurrences. It depends on the population of breast cancer patients what the magnitude of the benefit from radiotherapy is. For example, for some populations of breast cancer patients the chestwall recurrence rate may decrease from 10% to 5% by giving radiotherapy. This is an important improvement of local control, but goes at the cost of treating 90% of the patients with radiotherapy without providing benefit. At present, there are no molecular markers of local recurrence after mastectomy. At present, a prospective clinical trial (termed the SUPREMO trial) is being started, in which patients after mastectomy will be randomised between radiotherapy and no radiotherapy to the chestwall. The collection of tumor tissue for genetic testing will be part of the trial; this will provide the possibility to identify risk factors for local recurrence after mastectomy; and identify subgroups of patients that will benefit from radiotherapy after mastectomy.

2. Local recurrence after breast conserving therapy.

Nowadays, 60–70% of patients undergo breast-conserving therapy. As the status of the resection margins is a very important factor determining risk of local recurrence, optimal work up of surgical specimens is extremely important.

It has also been shown that an extensive component of intraductal carcinoma (EIC) which has been incompletely excised, is an important risk factor for local recurrence after breast conserving therapy. For this reason the ductal carcinoma in situ (DCIS) component in and around the tumour should be assessed.

The reason that EIC is a risk factor for local recurrence is that a large amount of DCIS may be left behind in the breast after excision in some patients. For this reason, the most important task for the pathologist in this respect is to estimate the likelihood that a large amount of DCIS is left behind in the breast.

In most published series, only poorly differentiated DCIS has been evaluated as a risk factor for local recurrence. Much less is known about residual well differentiated DCIS left behind in the breast; it is likely that also an extensive component of well differentiated DCIS is a risk factor for local recurrence, but after a much longer interval.

Lobular carcinoma in situ (LCIS) adjacent to invasive disease has not been associated with an increased risk of local recurrence.

When the margins are free or only focally involved, young age is the most important risk factor for local recurrence. We have previously found that patients younger than 40 years of age have a 6-fold increased risk of local recurrence compared to patients older than 60 years. For this reason, our research to identify risk factors for local recurrence is mostly aimed at patients younger than 50 years.

3. Genetic techniques to predict local recurrence.

For the treatment of breast cancer, especially the choice of adjuvant systemic treatment, determining oestrogen receptor status, progesterone receptor status and HER2 status is extremely important.

In the past 20 years, much research has been devoted to identity prognostic and predictive factors, especially to guide adjuvant systemic therapy.

All this research has resulted in thousands of scientific papers, but only recently, some of these assays are starting to be used in day-to-day clinical decision-making, mainly in the form of incorporation of these assays into clinical trails. It is to be expected that in the coming years the process of bringing this knowledge from scientific research into the clinic will be proceeding at a higher speed than we have seen in the past 20 years.