E18. Management of high-risk women; assessing the risk

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Assessing risk

Risk assessment for breast cancer can take place on two different levels. In healthy women, it refers to establishing the risk of developing breast cancer within the next few year(s). In patients, it refers to the risk of developing a recurrence after treatment, i.e. the ability to predict therapeutic failure. In both areas, major progress has been made in establishing the factors that contribute to or predict this risk, and this has already impacted upon the way in which we treat breast cancer.

The past 10–15 years were witness to the identification of several breast cancer susceptibility genes, mostly through linkage analysis in families followed by positional cloning. As mutations in these genes were identified in large families with multiple cases of early-onset breast cancer, the cancer risks conferred by these mutations are generally high, and their prevalence in the general population is very low (<0.01%).

BRCA1 and *BRCA2* are the most well known of these genes, and the breast cancer risks conferred by mutations in these genes are now well established [1,2]. A female carrier of a *BRCA1* or *BRCA2* mutation has an approximately 50–80% risk of developing breast cancer by the age 70 years. In addition, the risk of several other cancers also appears to be elevated, in particular the risk of ovarian cancer. There is also good evidence that these risk estimates depend on a woman's reproductive history, oral contraceptive usage, position of the mutation in the gene, or genetic variation at other genes [3]. This makes an individual risk assessment in a *BRCA1* carrier extremely difficult. Nevertheless, it can be safely concluded that the breast cancer risk is high (e.g., >50% in a life time).

It has been estimated that mutations in *BRCA1* and *BRCA2* can explain only a small proportion of the overall excess familial risk seen among unselected cases and their relatives [4]. This has been taken as evidence that other breast cancer susceptibility genes still remain to be identified. Several genetic models have been proposed to explain this residual familial risk, ranging from a rare dominant, moderately penetrant gene, to a common, high penetrance, recessive gene [5]. Linkage to a third major breast cancer gene (*BRCA3*) has thus far not been decisively claimed, although it should be emphasised that detecting linkage in the presence of locus heterogeneity will require a large set of families (>200) to exclude the possibility that *BRCA3* is capable of explaining a small proportion of families.

Another genetic model receiving increasingly more attention is one in which several common, low penetrance genes with multiplicative effects on risk may account for the residual non-*BRCA1/2* familial aggregation. Using data from a population-based series of individuals with breast cancer, a log-normal distribution of genetic risk in the population that is sufficiently wide to provide useful discrimination of high- and low-risk groups, has been derived [6]. Assuming all of the susceptibility factors could be identified, the half of the population at the highest risk would account for 88% of all affected individuals. Of course, not all the factors constituting the risk profile will be genetic, but these results suggest that it will eventually be possible to identify individuals as susceptible by their genotype profile and to prevent disease by targeting interventions to those 'at risk'. Breast cancer incidence data on twins, the contralateral breast and on first-degree relatives of patients also suggests that most breast cancer occurs in a minority of women susceptible women [7].

The biggest immediate challenge now is two-fold: 1) to identify the genetic factors that compose the risk profile, and 2) to design cost-effective, non-invasive, preventive interventions. Without the latter, population-based gene testing for breast cancer risk assessment will never be acceptable, although knowing all the breast cancer risk genes will be interesting from a pharmacogenetic standpoint.

At the level of prognosis, much progress has been made by the use of gene expression profiling of breast tumours on microarrays. This has revealed combinations of gene expression that predict the metastatic potential of the tumour. In one study, this expression profile strongly outcompeted lymph node status as a prognostic indicator [8] (see also the abstract by Van de Vijver *et al* at this meeting). However, further work is required to establish whether this technology measures metastatic capability or response to therapy. Nonetheless, it is clear that it will have a profound impact on breast cancer treatment, in that it will allow a more personalised evaluation of the different treatment options.

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Management of high-risk patients

It is presently not clear whether or not breast cancer in high-risk women has a different prognosis [9]. Hence, breast cancer in *BRCA1/2* carriers is treated in the same way as sporadic breast cancer of the same grade and stage. Depending on the age of the patient, prophylactic surgery of the other breast may be considered, since the risk of contralateral breast cancer is very high in these patients.

For healthy carriers, the situation is more difficult. The most definitive risk reduction is accomplished by bilateral prophylactic surgery [10], but the uptake of this type of prevention is low in many countries, despite overall good cosmetic results after breast reconstruction. Chemoprevention by tamoxifen, although effective to some extent in preventing sporadic breast cancer, does not seem to have a major effect in BRCA carriers [11], although larger studies are needed. The efficacy of standard mammography to detect breast cancer at early stages and reduce breast cancer mortality is largely unknown in this group of women. Magnetic resonance imaging (MRI) might increase the effectiveness of screening in women with a familial or genetic predisposition, and trials to establish the efficacy of MRI compared with mammography, cost-effectiveness of regular screening and quality of life during surveillance are underway.

References

[1] Antoniou A, Pharoah PDP, Narod S, Risch HA, Eyfjord JE, Hopper JL et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: A combined analysis of 22 studies. Am J Hum Genet 2003; 72(5): 1117–1130.

[2] King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003; 302(5645): 643–646.

[3] Narod S. Modifiers of risk of hereditary breast and ovarian cancer. Nature Reviews Cancer 2002; 2(2): 113–123.

[4] Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N et al. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst 1999; 91(11): 943–949.

[5] Antoniou AC, Pharoah PDP, McMullan G, Day NE, Stratton MR, Peto J et al. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. Br J Cancer 2002; 86(1): 76–83.

[6] Pharoah PDP, Antoniou A, Bobrow M, Zimmern RL, Easton DF, Ponder BAJ. Polygenic susceptibility to breast cancer and implications for prevention. Nature Genet 2002; 31(1): 33–36.

[7] Peto J, Mack TM. High constant incidence in twins and other relatives of women with breast cancer. Nature Genet 2000; 26: 411–414.

[8] Van de Vijver MJ, He YD, van 't Veer L, Dai H, Hart AAM, Voskuil DW et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002; 347(25): 1999–2009.

[9] Phillips KA, Andrulis I, Goodwin PJ. Breast carcinomas arising in carriers of mutations in BRCA1 or BRCA2: are they prognostically different? J Clin Oncol 1999; 17(11): 3653–3663.

[10] Meijers-Heijboer H, van Geel B, Van Putten WLJ, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MBE et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2001; 345(3): 159–164.

[11] King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2 – National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 2001; 286(18): 2251–2256.