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SYMPOSIUM

Genetics – where are we?

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A proportion of breast cancer cases arise due to a genetic predisposition; the exact proportion is unknown. A significant proportion of cases could occur due to low penetrance genes and this proportion will not be confirmed until such genes are discovered. Less than 5% is due to mutations in *BRCA1* and *BRCA2* although these genes are probably the most important of the highly penetrant breast cancer predisposition genes. Since their discovery, there are several pertinent issues in the *BRCA1/2* field.

What are the cancer risks from BRCA1 and BRCA2? *BRCA1* and *BRCA2* predispose to breast and ovarian cancer. The lifetime penetrance figures in families with multiple cases of these cancers are 80–85% for breast cancer for both genes and 44–60% for *BRCA1* and 27% for *BRCA2* for ovarian cancer. These genes also predispose to other cancers: *BRCA2:* fallopian tube, prostate, pancreas, melanoma, head and neck, stomach and gall bladder cancer. *BRCA1*: colon, cervix, endometrium, pancreas and prostate cancer (but the latter to a lesser extent than *BRCA2*). There is debate about the penetrance in certain populations: it may be lower in the Ashkenazim (although one study refutes this) and mutations found in population-based single cases of breast cancer with no family history. This raises the possibility of modifier effects, either from environment and/or modifier genes.

Tumour genetic/pathological profiling: Breast cancers developing in *BRCA1* carriers have a different somatic genetic expression profile from non-carriers. It has also been reported that breast cancers from *BRCA1* carriers are more likely to be ER/PR negative and HER2 negative. Recently, positivity for cytokeratin expression has been described in *BRCA1* and this may be able to be used to determine which individuals with ER negative tumours should be offered germline *BRCA1* analysis in the future.

Issues in genetic counselling, testing and treatment: The issues surrounding penetrance are important for genetic counselling. At present, most testing, at least in Europe, occurs in cancer genetics clinics. The discoveries of specific pathological profiles for *BRCA1* tumours could alter this by bringing germline testing into clinical management of the primary tumour in the oncology clinic. There is an increased risk of contralateral breast cancer in germline *BRCA1/2* mutation carriers and some such women opt for bilateral mastectomy as their primary surgical management.

Is there a fingerprint of the presence of a germline BRCA mutation? We have found a set of about 50 genes that have differential expression in normal cells from *BRCA1* carriers after irradiation induced DNA damage. No difference is seen in unirradiated cells. This has implications for the use of DNA-damaging agents in screening and treatment of *BRCA1* carriers and could have application to distinguish pathogenic mutations from normal variants (polymorphisms).

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Use of oral contraceptives and risk of breast cancer in BRCA1/2 mutation carriers

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In the general population women who are currently using oral contraceptives are known to have a slightly increased (24%) risk of breast cancer. Stronger associations have been found for BRCA1/2 mutations carriers. However, the sparse literature is inconsistent.

We investigated the association between use of oral contraceptives (OC) and risk of breast cancer among BRCA1/2 mutation carriers in the International BRCA1/2 Carrier Cohort Study (IBCCS study). Out of a sample of 1579 BRCA1/2 mutation carriers we selected 202 cases who completed a standard mailed questionnaire within five years after diagnosis and matched them with 303 controls for a nested case-control analysis. Both groups were matched on age, cohort, and country group, and analyses were adjusted for gene mutation, parity and prophylactic oophorectomy.

Women who currently used OC or women who had used OC in the past had a risk of breast cancer comparable with never users (Odds Ratio (OR)=1.22, 95% Confidence Interval (CI): 0.61–2.43 for current users, OR=1.05, 95% CI: 0.64–1.71 for ex users, respectively). Though a long duration of use was associated with an increased risk, this was not statistically significant (OR=1.87, 95% CI: 0.88–3.96 for OC use of 13 years or longer). Women who started OC use before age 20 had a similar risk as never users (OR=1.09, 95% CI: 0.69–1.75).

So far, no indication was found that the association between OC use and the risk of breast cancer among BRCA1/2 mutation carriers strongly differs from what is known for the general population. However, with the higher background rates among BRCA1/2 mutation carriers comparable relative risks imply higher absolute risks.

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First steps in the test process

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The testing process begins with identification of an at-risk individual and referral to a genetic clinic. Genetic counselling is an essential component of genetic testing and should include at least two individualized sessions. The first step in counselling is to assess the patient's concerns and motives for seeking help and to guarantee that where possible and appropriate his/her personal needs and priorities will be met. It is important for all health professionals to remember that the principal goal of cancer genetics care is to prevent death from cancer. Another important step is to compile an accurate family history. The family history or pedigree should include three generations and include all cases of cancer on both the paternal and maternal side. Unaffected family members need to be documented too as this enables an assessment of potential inheritance patterns. All malignancies should be confirmed through medical and/or death records, with relevant consent from relevant individuals within the family. During the counselling session risk assessment is undertaken and discussed. There are several risk models available for breast cancer that incorporate family history. Accurate analysis of the pedigree is essential when classifying individuals into high, moderate and low-risk groups.

Individuals at high risk of carrying a mutation on the basis of their family history can be offered genetic testing. Genetic testing is a two-stage process. The first step is to identify the altered gene in the family. The second is to offer genetic predictive testing to unaffected individuals in that family once the mutation has been found. Predictive testing is highly specific, and unaffected people in the family who are tested and who carry the pathogenic mutation are at increased risk of developing malignancy. The cancer risk of individuals who have a negative test for a known, deleterious mutation within their family is reduced to that of the normal population, and they should avail of screening and health promotion guidelines applicable to the general population. Individuals who harbour deleterious mutations in BRCA 1 and BRCA2 need information regarding medical management so they can make informed choices. These management strategies include prophylactic surgical interventions chemoprevention and surveillance programmes. Uncertainty remains around interventions for this group, and thus up-to-date results of clinical trials and consensus views of expert panels are essential for women if they are to make informed choices.

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The issues for women following risk communication

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For the majority of women, risk communication significantly improves women's perceptions of their personal risk without an adverse effect on psychological well being, irrespective of wide variations in the provision of cancer genetic services. However, women who continue to overestimate their risk have higher levels of anxiety, and those who continue to underestimate may engage in sub optimal health care behaviour. Cancer worries are increased in women with a family history of breast cancer, especially those bereaved in adolescence, compared to women in the population, but evidence is inconsistent as to the impact of risk counselling on cancer worry. Unresolved grief or difficulties in adult relationships resulting from early bereavements may be highlighted by confronting a personal risk, and family relationships may be disrupted by the impact of breast cancer and bereavements, so that diffusing risk information can be problematic. With respect to risk management, women may have unrealistic expectations about the availability of pre-symptomatic genetic testing, and uptake of chemoprevention trials and risk-reducing mastectomies is low, so that women perceive a number of difficulties with these options. At risk women place high priority on access to regular mammographic