Concerning the interpretation of QL scores, it is not yet clear how to understand a given difference or change in scores. Is a statistically significant improvement of 7 points in 'emotional functioning' important to patients? A number of different approaches are being explored to better understand the importance of different magnitudes of change. One of these is the Subjective Significance Questionnaire, developed by Osoba as a means of better understanding changes measured by the EORTC QLQ-C30 QL questionnaire. Other approaches use wellknown clinical 'events' (e.g. the impact of a given treatment) as 'anchors': the effect of the wellknown treatment on QL scores can then be compared to the impact of a new treatment.

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Update on BRCA1 and BRCA2: Molecular biology and genetics

B.L. Weber[1]. [1]*University of Pennsylvania, Medicine and Genetics, Philadelphia, United States*

Women with an inherited alteration in one copy of BRCA1 or BRCA2 are at very high risk of developing breast cancer. Recent data suggest that BRCA1 plays a critical role in the cellular response to DNA damage. This may occur by BRCA1 participating in signals to stop cell cycling so that repair can take place, or to induce cell death if the damage is too great to be repaired. The end result of cell replication in the presence of damaged DNA is malignant transformation, thus these insights offer an explanation of the role of BRCA1 in preventing cancer.

We have identified a link between BRCA1 and three other important proteins – the cell cycle inhibitor p21, the tumor suppressor/DNA repair gene p53 and the regulator of cell death gene Bax. We have shown that BRCA1 plays a role in modulating the ability of p53 to induce these genes, possibly serving as a cellular switch after DNA damage. In addition, we have completed studies of the kinetics of BRCA1 regulation in response to DNA damaging agents, further supporting the role of BRCA1 as a sensor of damage that then functions as a switch after damage occurs. As BRCA2 interacts with BRCA1, it is likely that both genes function in a similar pathway.

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Genetic heterogeneity of hereditary breast cancer

P. Devilee. *Department of Human & Clinical Genetics, Leiden University Medical Centre, Leiden, Netherlands*

Between 6 and 19% of women with breast cancer have at least one affected relative at the time of diagnosis, but not all of them are expected to be true genetic cases. Families with inherited breast cancer are characterized by multiple early-onset and/or bilateral cases, and frequent occurrence of specific other malignancies (notably ovarian cancer). The most likely model explaining the observed familial clustering is one incorporating the transmission of an autosomal dominant susceptibility locus. Yet the observed risk to siblings can be equally well explained by either an infrequent high-risk gene, or a low-risk gene with high population frequency. In fact, it is now clear that inherited breast cancer is determined by a number of genes conferring a range of penetrances. Rare high-risk genes are most amenable for detection by linkage analysis, and this has led to the discovery of BRCA1 and BRCA2. They jointly explain the large majority of families with either the breast-ovarian cancer syndrome, with at least one case of male breast cancer, or with at least 6 cases of breast cancer diagnosed under 60. However, roughly 60% of the families with 4 or 5 cases of breast cancer diagnosed under 60, and no cases of ovarian cancer, are not accounted for by these genes. Other genes, such as PTEN and TP53, cause primarily specific cancer syndromes, of which breast cancer forms just one constituent. Hence more breast cancer susceptibility genes remain to be identified, which are probably of lower penetrance than BRCA1 and BRCA2, although they still predispose to breast cancer at a young age.

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Clinical management of the *BRCA* heterozygote

Mark Robson. *Memorial Sloan-Kettering Cancer Center, New York, NY, United States*

Significant progress has been made in defining the genetic epidemiology of hereditary breast cancer, but the clinical approach to individuals with an inherited predisposition continues to evolve. Different questions arise for women who are already affected with breast cancer and for those who have not yet developed the disease. In approaching the affected heterozygote, the central clinical question is whether cancer arising in the setting of a germline mutation requires a different clinical approach from that arising without such a predisposition. *BRCA1*-associated breast cancers are usually rapidly proliferating, aneuploid, infiltrating ductal carcinomas of high histologic grade, lacking hormone receptors, with a relatively high frequency of somatic *p53* mutations. *HER2* overexpression appears to be uncommon. Although there are fewer data, *BRCA2*-associated cancers may have a histologic appearance and immuno-phenotypic profile more closely resembling "sporadic" cancer. Early studies suggested that the prognosis of *BRCA*-associated cancer was similar to that of sporadic cancers, but recent unselected series suggest that outcomes are actually worse, as would be expected from the prognostic factor profile.

In approaching the unaffected heterozygote, the major issue is the relative effectiveness of screening strategies compared to primary prevention approaches with surgery or chemoprevention. Current guidelines are based on expert opinion alone. The level of cancer risk in this population justifies aggressive screening, but the effectiveness of mammography and ovarian cancer screening remains undefined. Risk-reducing surgery appears to be effective, but failures do occur and the acceptance of procedures varies. Studies of new screening and prevention methods are underway.

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Prophylactic interventions – Effective, harmful or of unproven benefit?

P.A. Daly. *St. James's Hospital and Trinity College, Dublin 8, Ireland*

Most knowledge relating to the genetic basis of cancer and particularly inherited cancer predisposition has only recently been discovered. Inevitably there is major interest in risk assessment, genetic testing and strategies which may be used to reduce morbidity and mortality among those who carry mutations conferring inherited cancer risk. A futuristic vision of cancer care takes us towards a circumstance where advanced disease is no longer seen. Instead we can focus on detection of high-risk individuals and employ effective screening strategies, chemoprevention or prophylactic surgery to reduce or eliminate risk of cancer death. Unfortunately life is not so simple and care must be taken to inform patients and others presenting for genetic testing of the limitations and complexity of issues surrounding hereditary cancer predisposition. Each site presents specific issues with regard to screening, chemoprevention and surgery. For HNPCC carriers, for instance, screening through colonoscopy can improve survival for at-risk individuals but screening of female carriers for extracolonic malignancy is of unproven benefit. There is no evidence for the use of chemoprevention and prophylactic colectomy, while an option for some, is also of unproven benefit. Issues such as this are similarly complex for breast and ovarian cancer. The major beneficiaries at present from genetic testing are those who have a negative test where a known, disease-related mutation exists within a family. Noncarriers can be released from the anxieties which prevail and do not need the increased surveillance now recommended for those carrying mutations or those with a high risk based on family history data. Information regarding prophylactic interventions is steadily accumulating but, as yet, efficacy remains limited for many strategies, potential for harm exists and much proof remains to be gathered.

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Role of chemotherapy (CT) in non metastatic head and neck squamous cell carcinoma (HNSCC): Results of an international meta-analysis

J.P. Pignon, C. Domenge, S. Gueérin, L. Designé, M. Luboinski, J. Bourhis. *On behalf of the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) Collaborative Group; Institut Gustave-Roussy, France*

Purpose: In 1994 an International Collaborative Group (MACH-NC) was set up to perform a meta-analysis of randomized trials in order to evaluate the role of CT on survival of patients with HNSCC.

Methods: 10 741 patients (pts) randomized between 1965 and 1993 in 63 trials comparing loco-regional treatment to same treatment plus CT were included. Nasopharynx and "organ preservation" trials were excluded. Collection of individual patient data, updated for 2/3 of the trials, allowed extensive checking. Logrank test stratified by trial was used.

Results: A small (4% at 5 years), but significant ($p < 0.0001$) **survival** benefit in favor of CT was shown. However the observed benefit was dependent upon the type of CT used ($p = 0.005$): no significant benefit for **adjuvant** CT (benefit 1%, 8 trials*, 1 854 pts*) as well as **neoadjuvant** CT