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Preface

Thematic issue on the molecular biology of hereditary ovarian cancer

Ovarian cancer is a complex heterogeneous disease defined by histopathology, somatic molecular genetic attributes, and hereditary context. About 90% of ovarian cancers are of the epithelial type and within this group an estimated 5% are attributed to the inheritance of a highly penetrant allele that confers a significant life-time risk for developing ovarian cancer. In most developed countries, epithelial ovarian cancer is the fifth most common cause of death and is the most lethal form of gynecologic malignancy. Regardless of hereditary context, most cases are diagnosed at an advanced disease stage, where it has spread to other pelvic organs. Management is usually by surgical cytoreduction followed by platinum-based and taxane-based chemotherapy. Advanced disease is effectively managed in a minority of patients as evidenced by an overall 5-year survival of 10–30%. In stark contrast to breast cancer, there are no effective ovarian cancer surveillance protocols in routine use. Although, oral contraceptive use, pregnancy, lactation, and tubal ligation are associated with decreased risk, family history of breast and/or ovarian cancer remains one of the most significant factors conferring increased risk to the disease. In this issue we review the latest advances in the field of hereditary ovarian cancer and introduce new avenues of genetic research aimed at addressing overall risk to this disease.

Henry Lynch's group at Creighton University first reported hereditary transmission of an autosomal dominant trait predisposing women to ovarian cancer in the early 1970s. The ovarian cancer cases were found in families with an unusually large number of women diagnosed with breast cancer at a young age. These breast and ovarian cancer syndrome families, as they are now called were investigated and instrumental in the identification of the BRCA1 and BRCA2 breast-ovarian cancer susceptibility genes in the mid-1990s. Henry Lynch and colleagues review the historical context for the field of hereditary predisposition to ovarian cancer. It is estimated that 90% of hereditary ovarian cancer are due to germline mutations in one of two genes, BRCA1 and BRCA2, associated with hereditary breast and ovarian cancer syndromes. In recent years, it has become increasingly apparent that specific histopathological subtypes of ovarian cancer, such as the serous subtype, which also account for the majority of malignant sporadic cases, are more often associated with germline

BRCA1 mutations. The review also describes the estimated 10% of hereditary ovarian cancers associated with the genes involved in repairing errors in DNA replication, such as MLH1 or MSH2, found in cancer syndromes featuring colorectal cancers. The identification of hereditary genetic factors affords the opportunity to clinically manage the disease by identifying women at increased risk for cancer. Cancer surveillance and cancer prevention options for high risk women and the genetic counseling issues surrounding such management and intervention strategies are discussed. Although the heterogeneity of epithelial ovarian cancer is reflected in the spectrum of histopathological subtypes observed in hereditary cancer families, it has become increasingly apparent that specific subtypes are underrepresented in each of breast-ovarian cancer and colorectal cancer syndrome families. The review discusses the 'dualistic model of ovarian tumorigenesis' based on somatic molecular genetic attributes observed in specific histopathological subtypes and pathologies of epithelial ovarian cancer. This review sets the tone for the more specialized ones that follow in the series.

The BRCA1 and BRCA2 breast-ovarian cancer susceptibility genes represent the most well characterized genetic risk factors for ovarian cancer. Susan Ramus and Simon Gayther review their genetic contribution to ovarian cancer. Although germline mutations in these genes have been reported in all populations worldwide that have been investigated, the frequency, spectrum and nature of mutations can vary significantly. The spectrum of mutations is complex, but specific mutations have been reported to recur in defined populations, which has enabled genetic testing for carrier detection. The genetic analysis of common mutations in historically well-defined populations (the Ashkenazim, as an example) has enabled estimates of the 'age' of such mutations, such as proposed for the 5383insC BRCA1 mutation, which was estimated to arise 38 generations ago in the Baltic region. Variation in ovarian cancer risk associated with each gene is discussed, such as the evidence suggesting that mutations that occur within the 'ovarian cancer cluster region' confer a higher risk to ovarian cancer in BRCA2 mutation carriers. Research aimed at elucidating genetic factors that may modify risk in BRCA1 and BRCA2 mutation carriers to account for variability in penetrance is also presented.

Although BRCA1 and BRCA2 were identified over 10 years ago much remains unknown about the biological role they play in the etiology of hereditary ovarian cancer. It is not clear if hereditary ovarian cancers develop and progress through molecular pathways that intersect those occurring in sporadic disease or by independent paths. The analyses of global molecular genetic events associated with hereditary disease have been applied to BRCA1/2 mutation carriers in only a limited number of studies. Loss of heterozygosity analyses in ovarian cancer samples has suggested that BRCA1 and BRCA2 behave as tumor suppressors, as it is often the mutated allele inherited through the germline that is retained in tumor tissues. To elucidate molecular pathways associated with the disease, whole genome transcriptome profiling of hereditary ovarian cancers has been performed. As reviewed by Amir Jazaeri, interesting results have emerged linking BRCA1 and BRCA2 implicated ovarian cancers with sporadic (non-mutated) disease. It appears that the transcriptomes of sporadic cases overlap those of BRCA1 or BRCA2 implicated cancers. These results are intriguing given the rarity of deleterious somatic mutations occurring in these genes in sporadic cases. This review presents recent evidence to reconcile these observations, which include alternative mechanisms of inactivation of BRCA1 involving epigenetic modification and pathways that affects BRCA2 partners/interactors (such as members of Fanconia anemia pathway) that could mimic BRCA2 loss in sporadic cases. Unfortunately, there have been no systematic surveys of global genomic aberrations of hereditary ovarian cancers that would complement transcriptome profiling. As reviewed by Kylie Goringe and Ian Campbell, ovarian cancers frequently exhibit complex genomic aberrations. The frequency of specific genomic rearrangements and the observation that they often contain cancer related genes, lends support to the notion that these events are not random. Also reviewed are the merits of applying the latest technologies, which are based on surveying both copy number and allelic content.

The cellular origins of epithelial ovarian cancer remain unknown. A prevailing hypothesis is that they arise from epithelial cells of the ovarian surface or ovarian inclusion cysts. For some histopathological subtypes, endometriotic tissue has also been proposed as possible origin. However, recent studies of prophylactic salpingo-oophorectomies of BRCA1 implicated cases suggest an alternative hypothesis involving the distal fallopian tube. In early studies, surveys of cancer phenotypes occurring in hereditary breast and ovarian cancer families have reported an unusual number of fallopian tube cancers. Christopher Crum reviews the evidence implicating the distal fimbria as a possible origin of hereditary ovarian cancer. Also reviewed is evidence suggesting that sporadic serous subtype cancers regardless of their BRCA1/2 mutation status, could also originate from the fallopian tube. This review also reiterates an emerging model for the origins of epithelial ovarian cancer that implicate both distal fallopian tube and surface epithelial cells of the ovary as plausible sites for the origins of epithelial ovarian cancer that takes into account the various histopathological subtypes of the disease.

There is evidence to suggest that ovarian cancer susceptibility is also affected by low penetrance genetic polymorphisms. Peter Fasching and colleagues on behalf of the Ovarian Cancer Association Consortium has reviewed this

emerging new field of study by describing the application of large-scale genetic assays to survey single nucleotide polymorphisms in association with studies to identify risk associated genetic markers. As pointed out in this review, the success of such studies requires large well-defined cohorts. A survey of the reported literature reveals a number of promising candidates that warrant further investigation. The present challenge of such studies is to incorporate the heterogeneity of the epithelial ovarian cancer into study design. Only few studies, for example have associated risk with specific histopathological subtypes of ovarian cancer.

Genetic testing for BRCA1 and BRCA2 mutations in the context of familial breast and/or ovarian cancer has become standard practice in genetic counseling units for assessing risk. As the risk for ovarian cancers is significantly reduced by prophylactic salpingo-oophorectomy in carriers of deleterious mutations, this approach for cancer prevention has the potential to significantly reduce ovarian cancer mortality. However, it is clear that much remains unknown about the etiology and biology of hereditary ovarian cancer. Not all familial ovarian cancer cases can be attributed to the known highly penetrant cancer susceptibility genes and the penetrance of the known genes is highly variable. Epidemiological evidence and genome-wide association studies point to other genetic factors that may contribute to ovarian cancer risk in both hereditary and sporadic contexts. The molecular genetic characterization of somatic events in ovarian cancer suggests the possibility that distinct pathways may be involved in the development and progression of ovarian cancer, some of which overlap events observed in hereditary disease attributed to germline mutations in BRCA1 and BRCA2. Other than the clinical benefit of carrier detection for BRCA1/2 mutation carriers, it is the study of hereditary ovarian cancers that has contributed to the emergence of a new model encompassing the origins of most histopathological subtypes epithelial ovarian cancers. It is clear that major advances in the molecular genetic understanding of hereditary ovarian cancer have come through the efforts of collaborative studies involving scientists with diverse expertise. For over 30 years, geneticists from around the world have studied the hereditary cancer families so patiently and diligently collected by Henry Lynch and his colleagues. A paucity of molecular genetic data remains for hereditary ovarian cancers, and perhaps this can be reconciled through collaborative endeavors as has been successfully demonstrated with the recent efforts of association studies of polymorphic alleles in ovarian cancer. A puzzling question remains. What accounts for the apparent tissue specificity associated with the known highly penetrant ovarian cancer susceptibility genes? Addressing this question remains a significant challenge as presently there are few models that adequately mimic the development of human epithelial ovarian cancer.

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the Montreal General Hospital Research Institute before joining the McGill University in 1995. She was part of both international research teams that discovered the BRCA1 and BRCA2 breast-ovarian cancer susceptibility genes. Research in her laboratory leads to the discovery of recurring BRCA1 and BRCA2 mutations in French Canadian cancer families which has facilitated genetic testing and clinical management of high risk families from this population. She continues to research the contribution of these genes in high risk breast and/or ovarian cancer families. She also leads research studies aimed at elucidating the chromosome 3 and 17 genes associated with ovarian tumorigenesis which incorporate assays that survey allelic aberrations and large-scale expression microarrays, and functional complementation strategies using whole or fragmented chromosome transfer techniques into ovarian cancer cell lines that would alter their growth and tumorigenic potential. A major research endeavour with members of the Cancer Network affiliated with the Fonds du Recherche en Santé du Québec aims to identify gene expression signatures

associated with poor outcome of epithelial ovarian cancer patients.

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