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Family medicine and gynaecologic pathology

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It may seem at first glance as though Pathology has little to do with Family Medicine. Pathology studies the causes of diseases and the ways in which disease processes affect the body. Its application provides essential information for the diagnosis and monitoring of disease. A better understanding of what has gone wrong helps treatments to be devised and preventative measures to be put in place.

Pathology has six main branches: anatomical pathology, microbiology, haematology, clinical biochemistry, immunology and forensic pathology. The Hong Kong College of Pathologists has established professional examinations which are now internationally recognised for each of these disciplines and it is now working towards setting up accreditation of all pathology laboratories in Hong Kong. It would be difficult to briefly cover yet adequately in one article each discipline in turn. We have chosen from the smaller branch of gynaecologic pathology, and will look at some aspects of recent developments in molecular pathology which would be of relevance to the family physicians.

Cervical cancer

Cervical cancer is the second most common cancer among women worldwide. In Hong Kong, it ranks 7th among female cancer deaths. Family physicians contribute significantly to cervical cancer screening in Hong Kong, doing a lot of cervical cytology sampling performed in their clinics. Understanding between the family physicians and pathologists is essential to ensure efficient detection of cervical cancer and its precursors.

The reporting of a cervical smear includes assessment of the specimen adequacy and giving a concise description of cells in precisely defined and generally accepted cytological terms. This may be followed, if appropriate, by a prediction of a histological condition based on the overall picture, and should include a recommendation for further management of the patient.[1,12]

Besides continuous evolution of the cervical cytology reporting system to improve correlation with histologic findings, modern cytology practice also

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encompasses introduction of quality control system and improvement of the organisation of a cervical cytology screening laboratory.[16] Routine and systematic rescreening, regular histologic correlation as well as periodic proficiency testing are important to promote an adequate standard of cervical smear reporting. Modernisation of the laboratory organisation also includes careful planning of staff structure with close scrutiny of the training and qualification of laboratory staff, setting a suitable level of workload, arrangement of proper flow of smears and cautious design of the information system. Appropriate accommodation of the laboratory with sufficient facilities is also necessary for ensuring the standard of cervical smear reporting.

Cervical cancer screening by examination of Papanicolous smear has proved to be efficient and cost-effective. However, with increased expectations from the general public as well as pressure from medicolegal aspect of screening, new devices have been promoted in recent years in an attempt to improve the accuracy of cervical smear reporting by improving the quality of the sample and increasing the efficiency of screening for abnormal cells.[13-15]

Conventional smears obscured by blood, inflammation, thick areas, poor fixation and air-drying artefact preclude proper interpretation of epithelial cells. The ThinPrep Pap Test and Autocyte Prep™ system are two devices approved by the Food and Drug Administration (FDA) available for the practice of liquid based cytology. Thin layered or "monolayer" smears with relatively clean background may be produced to facilitate the searching for abnormal cells.

Traditionally, primary screening and rescreening of cervical smears are performed manually by cytotechnicians. The Papnet system allows a semi-automated approach by selecting the most suspicious fields in a smear to be considered by cytotechnicians. FDA has approved the Papnet system for quality control. Another device, the AutoPap 300QC system, can automatically classify cervical smears into normal smears and smears that need human review either because of the quality of the smear or because of the presence of abnormal cells. It was FDA-approved for quality control rescreening and later for primary screening as well. However, at present stage, only a portion of the smears can be excluded from primary manual screening.

Breast cancer susceptibility genes

The family physician dealing with entire families would have had the opportunity to discover familial clustering of certain cancer types. Hereditary cancer is used to refer to a cancer which occurs in an individual who is believed to carry and transmit a mutation of a gene which predisposes to developing that cancer.

The earliest well known hereditary cancer syndromes were those of hereditary retinoblastoma and colon cancer in polyposis coli. Studies of familial breast and ovarian cancer have further identified several other hereditary cancer syndromes, namely: the breast-ovarian cancer syndrome, site-specific breast cancer, site-specific ovarian cancer, the Li-Fraumeni syndrome and hereditary non-polyposis colon cancer. Each of these groups requires the identification of 3 to 5 members of that family to be affected by the specific cancer type.

It has been estimated that about 5-10% cases of breast and ovarian cancers are due to autosomal dominant hereditary syndromes. Germline mutations in the breast cancer susceptibility genes, BRCA1 and BRCA2,[2] appear to account for the majority of hereditary ovarian cancer cases and at least half of hereditary breast cancers.

The distinctive clinical features observed for these hereditary breast and ovarian cancer cases include younger age of onset, bilaterality and the presence of associated tumors. Transmission of cancer through a single lineage can be documented in most families and associated tumors include those of colon, prostate, pancreatic, endometrial cancers and sarcomas, as well as male breast cancer. Extended family histories may be difficult to obtain especially with small nuclear families, thus early age of onset (under 45 years) may be the only clue to inherited breast cancer in a family.

Mutations of the BRCA1 and BRCA2 genes have been reported largely in familial cases, particularly of Caucasians with a strong family history or early onset disease. The proportion of breast cancer families with BRCA1 mutations varies from 7% in breast cancer only families to 40% in the breast and ovarian cancer families.[3,4] A wide variation in incidence of BRCA mutations has been observed amongst the various populations.[5] These ethnic differences may be partly due to founder mutations which presumably arose in a single ancestor of a specific ethnic group initially established by

a small number of people which later expanded. Thus even in the absence of a strong family history, one of the three known Ashkenazi founder mutations occur at an incidence of 30% and 40% amongst Jewish women with breast cancer and ovarian cancer respectively.[6]

Unique BRCA1 and BRCA2 mutations have been found in Chinese breast cancer families and sporadic breast cancer patients respectively.[7,8] A relatively high incidence of 11.3% for BRCA1 germline mutations in sporadic Chinese ovarian cancer has been recently reported.[9] Although there is much evidence to implicate the BRCA1 and BRCA2 genes in sporadic cancers, somatic mutations in these genes are rare.[10,11]

In families where mutations in BRCA1 and BRCA2 have been identified, estimates of breast cancer risk can be made with greater accuracy. The lifetime risk of cancer in BRCA carriers ranges from 56-84%. The optimal medical management strategy for the unaffected BRCA mutation carrier is however not known. Women at increased risk of breast cancer are currently offered the options of increased surveillance or prophylactic surgery, and may be eligible for chemoprevention as part of an approved research protocol.

For an individual from a family with a known mutation, a negative test result is very meaningful, as the woman can be reassured that she does not carry that familial mutation. She should however be under routine surveillance for sporadic breast cancer. A negative result from families where no mutation has yet been identified on the other hand is less meaningful. This may mean genes other than that of BRCA1 or BRCA2 are involved in the family, or that the mutation could not be found by the laboratory technique used for screening. Adverse psychological consequences, as well as the social implications including insurance and employment discrimination, remain a potential risk. Thus careful genetic counselling should be given and the benefits and limitation of genetic testing considered carefully beforehand.

In Hong Kong, a Hereditary Breast and Ovarian Cancer Program has been set up in The University of Hong Kong, in collaboration with Mount Sinai Hospital, The University of Toronto. The purpose of this program is to identify suitable high risk families and to make available genetic testing to suitable individuals. ■

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