S3. Genetics and Prevention in Relation to Oesophagal Adenocarcinoma

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Gastric cancer has been declining for more than half a century, whereas the incidence of oesophageal cancer is increasing rapidly. The histopathological subtype is also changing with a predominance of oesophageal adenocarcinoma compared with squamous carcinoma. The reasons for these epidemiological changes are not clear although population based data have implicated gastro-oesophageal reflux disease as a risk factor. In susceptible individuals reflux of duodeno-gastric contents can lead to the development of a columnar-lined oesophagus, commonly called Barrett's oesophagus. This can then progress to adenocarcinoma via a metaplasia-dysplasia-carcinoma sequence. At the current time the mortality from oesophageal adenocarcinoma is >80% at 5 years. Therefore endoscopic surveillance programmes have been generally recommended for patients with Barrett's oesophagus in an attempt to detect early, curable lesions. Unfortunately these programmes are cumbersome and costly and have not yet been proven to reduce population mortality. In order to improve patient outcomes we need to be able to identify patients at high risk and to understand the triggers for disease progression. Identification of high risk individuals There is mounting evidence that there is an underlying genetic susceptibility to Barrett's oesophagus and oesophageal adenocarcinoma. However, this is likely to be as a result of multiple low penetrance susceptibility genes which have yet to be identified. Once patients are identified as having Barrett's oesophagus their chance for developing adenocarcinoma is in the order of 0.5 to 1% per year. The histological assessment of dysplasia as a predictor of cancer development is highly subjective. Therefore, multiple, specific somatic mutations in the tissue have been investigated as potential biomarkers. The most promising markers to date are the presence of aneuploidy, loss of heterozygosity of p53 and cyclin D1 overexpression. However, a study of evolutionary relationships suggest that mutations occur in no obligate order. Combinatorial approaches are therefore being advocated which include genomic profiling or the use of a panel of molecular markers in order to define the common molecular signatures that can then be used to predict malignant progression. An alternative approach would be to use markers for the final common pathway following genetic instability, which is the loss of proliferative control. We have demonstrated an increase in expression of a novel proliferation marker, Mcm2, occurs during the malignant progression of Barrett's oesophagus. These Mcm2 expressing cells are detectable on the surface and hence a cytological approach may be applicable. Chemoprevention strategies In view of the role of reflux components in the pathogenesis of Barrett's oesophagus the effect of acid and bile on the cell phenotype have been studied. These studies have demonstrated that pulsatile acid and bile exposure induce cell proliferation. The mechanism for the hyperproliferative response appears to involve p38 mitogen activated protein kinase (MAPK) pathways as well as protein kinase C (PKC and cyclo-oxygenases. A clinical implication of the laboratory studies is that suppression of acid and bile may need to be profound in order to suppress cell proliferation and by inference, to ultimately prevent the development of dysplasia. There is some support for this concept from short-term clinical studies and a large randomised chemoprevention trial is being instigated which will evaluate the effect of proton pump inhibitors with or without aspirin. Given the epidemic increase in oesophageal adenocarcinoma and the dismal 5-year mortality rate, a radical approach is necessary to prevent cancer development in individuals with pre-malignant lesions.