Family Cancer Group
St Mark's Hospital

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Introduction

The aim of our group is to define the inherited predispositions to colorectal cancer and to refine our management of familial risk in order to prevent familial colorectal cancer.

Clinical Resource

The Bobby Moore Oracle Database includes the clinical details of 3130 families at increased risk of familial colorectal cancer. 3413 at-risk family members have undergone a surveillance colonoscopy. These individuals are flagged by the NHS Information Centre. 868 tumour blocks and 1634 blood samples have been collected. We have 150 new referrals each year.

Molecular genetic studies

Hereditary Mixed Polyposis Syndrome

Hereditary mixed polyposis syndrome was originally described at St Mark's in an Ashkenazi Jewish family. In collaboration with Professor Ian Tomlinson (Welcome Trust Centre for Human Genetics, Oxford) we have identified a DNA duplication upstream of GREM1 (a BMP antagonist) which leads to its increased and ectopic expression in individuals with HMPS (Jaeger et al 2012). In collaboration with the Kennedy Galton Regional Genetic Laboratory we have developed a genetic test that we are using for presymptomatic diagnosis in at-risk family members.

Polymerase Proofreading-associated Polyposis

In collaboration with Professor Ian Tomlinson whole genome sequencing was undertaken in families from St Mark's with multiple colorectal adenomas and cancers in whom no genetic alterations had been detected in known colorectal cancer genes. Five families were identified with germline mutations in the proofreading domains of DNA polymerases POLD1 and POLE (Palles et al, 2013). These mutations result in

genetic instability and the development of colonic adenomas and cancers. A clinical genetic test has been developed with Kennedy Galton Regional Genetic Laboratory for presymptomatic diagnosis of Polymerase Proofreading-associated Polyposis.

Assessment of familial risk and prospective outcome of colonoscopic surveillence

Definition of the phenotype and management of Familial Colorectal Cancer

In collaboration with five other European centres (The Netherlands Foundation for Detection of Hereditary Tumours, The German consortium for Hereditary Non Polyposis Colorectal Cancer, The Danish HNPCC-register, Karolinska Institut Sweden, Manchester Regional Genetic Service) and Professor Peter Sasieni (Wolfson Institute for Preventative Medicine, Queen Mary College, University of London) we have collected prospective data on the outcome of colonoscopic surveillance in families with at least three affected individuals with colorectal cancer consistent with dominant inheritance and in whom Lynch syndrome has been excluded.

We have shown that at-risk individuals do develop high-risk colonic adenomas but not until a later age and with no evidence of accelerated tumourigenesis. We have recommended that five yearly colonoscopic surveillance is started from around the age of 40 (Mesher et al, In Press)

Chemoprevention Studies

Colorectal Adenoma/carcinoma Prevention Programme 2 (CAPP2)

We have previously recruited patients to this international randomised study of dietary and aspirin intervention in hereditary colorectal cancer. Further follow-up of the patient cohort has demonstrated a significant reduction in the incidence of colorectal cancer in the group taking 600mg of aspirin daily and also a reduction in the incidence of extra-colonic Lynch syndrome-associated cancers (Burn et al 2011). There was no effect from resistant starch (Mathers et al 2012). A dose-ranging study of aspirin therapy (CaPP3) will be launched in 2014.

European guidelines for the Management of Lynch syndrome

The Mallorca Group, of which I am a member, has published European guidelines for the management of Lynch syndrome (Vasen et al 2013)

Colonoscopic surveillance

Professor Brian Saunders has published a description of an endoscopic technique that he used on one of our patients to remove a large rectal polyps using retraction (Saunders et al 2013)

Teaching and Patient Information

We have held two well-attended information evenings for individuals with Lynch syndrome. We continue to provide teaching and research projects to students undertaking a BSc in Gastroenterology at Imperial College School of Medicine.

Publications

Papers

Burn J, Gerdes A-M, McCrea F, Mecklin J-P, Moeslein G, Olschwang S, Eccles D, Evans DG, Maher ER, Bertario L, Bisgaard M-L, Dunlop M, Ho JWC, Hodgson SV, Lindblom A, Lubinski J, Morrison PJ, Murday V, Ramesar R, Side L, Scott RJ, Thomas HJW, Vasen HF, Barker G, Crawford G, Elliott F, Movahedi M, Pylvanainen K, Wijnen JT, Fodde R, Lynch HT, Mathers JC, Bishop DT on behalf of the CAPP2 Investigators. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2011: 378; 2081-7

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Saunders BP, Tsiamoulos ZP, Thomas H, Warusavitarne. Rectal endoscopic submucosal dissection made easy: A solution to the retraction problem. Gastroenterology 2013; 145: 939-941
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