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Cohorts With Familial Disposition for Colon Cancers in Chemoprevention Trials

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Abstract Colon cancer provides an attractive setting for chemoprevention trails because of the frequency and variation of familial predisposition that is observed in this malignancy. Additionally, the adenomatous polyp, the precursor of colon cancer, is a valuable intermediate marker for judging the effectiveness of candidate chemopreventive agents.

Inherited colon cancer susceptibility varies from mild to severe. Conditions with extreme susceptibility include the autosomal dominantly inherited syndromes of familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). These are highly penetrant syndromes with extreme cancer risk. FAP arises from mutations of the APC gene and HNPCC from mutations of the mismatch repair genes. Specific and individual genetic diagnosis is now possible in both syndromes, thus allowing identification of genetically affected individuals for chemoprevention trials.

FAP accounts for less than 1% of colon cancers, while HNPCC may be present in up to 5% of cases. Familial clustering is common in the remainder of cases, which are often referred to as sporadic, but probably arise in part from inherited susceptibility. Epidemiologic studies have shown that first-degree relatives have a two- to four-fold increased risk of acquiring colon cancer compared to the general population. Ten percent of individuals in the U.S. have a first-degree with colon cancer. This clinically identifiable higher risk group thus constitutes a large potential cohort for chemoprevention trials.

The common familial cases of colon cancer can be further stratified by severity. A relative diagnosed under the age of 50 or two first-degree relatives affected with colon cancer confers an even greater risk for this malignancy, estimated to be four to six times that of the general population. Adenomatous polyps also precede the development of colon cancer in these categories, thereby providing a readily identifiable clinical endpoint to judge the effectiveness of chemoprevention.

It is expected that genetic markers will soon be available for more precise identification of common colon cancer susceptibility. Candidate markers include mild mutations of the APC and mismatch repair genes, glutathione transferase isoenzymes, acetylator status, and phospholipase A2 expression. Bile acid concentrations of the bowel may be genetically and/or environmentally determined and likely have a role in colon cancer susceptibility.

We recently identified a large kindred with polyp and cancer susceptibility arising from a mild mutation of the APC gene. There are over 4,000 kindred members and mutational testing has demonstrated 140 gene carriers to date. We expect to institute chemoprevention trials in this kindred using adenomatous polyp number as an endpoint of effectiveness. J. Cell. Biochem. 25S:131–135.

Key words: adenomatous polyp; colon cancer; colonic polyp; familial polyposis; familial risk; inherited risk

Familial risk is common among cases of colorectal cancer and varies from mild to severe. The most severe familial risk arises from the syndromes of familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer. These conditions are rare and together account for probably less than 5% of colon cancer cases. The risk for colon cancer in individuals who have a first-degree relative with this malignancy is two- to three-fold increased over the population risk. This group is much more common, however, and may involve up to 20% of colon cancer cases. Individuals who have even a second- or third-degree relative with colon cancer have a 30% to 50% increased risk. This group may account for a large fraction and possibly even the majority of colon cancer cases.

Each of these risk categories represents persons with defined risks for colon cancer who

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might benefit from chemoprevention. Each category could therefore also serve as a source of appropriate cohorts for chemoprevention trials. This section will describe each of risk categories and suggest how they might be involved in chemoprevention.

RARE SYNDROMES

The rare syndromes include familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). FAP has several variants including Gardner syndrome, Turcot syndrome and attenuated adenomatous polyposis coli.

Familial Adenomatous Polyposis

FAP is an autosomal dominantly inherited syndrome characterized by the development of hundreds to thousands of colonic adenomatous polyps at a mean age of 16 years [1]. On average, 50% of untreated individuals will develop colon cancer by age 39 years, and colon cancer is inevitable if the large bowel is not removed. Two-thirds of those who present with symptoms will have colon cancer on evaluation.

Extracolonic manifestations of FAP include gastric fundic gland polyps in 50% to 100%, and duodenal adenomas in 90% to 100% of affected persons. The gastric polyps have little, if any, malignant potential, but a 10% to 12% lifetime risk of periampullary duodenal cancer is observed. Other benign lesions include osteomas, soft tissue tumors of the skin, supernumerary teeth, desmoid tumors, and congenital hypertrophy of the retinal pigment epithelium (CHRPE). Other malignancies are unusual but include CNS tumors, hepatoblastomas and thyroid carcinomas.

When families exhibit common and prominent benign extra-intestinal lesions, particularly osteomas and soft tissue tumors, the condition has been typically referred to as Gardner syndrome. The presence of CNS malignancies in affected families has been termed Turcot syndrome. An attenuated variant of FAP has now also been recognized and is called attenuated adenomatous polyposis coli (AAPC). Persons with AAPC have an average of 30 colonic adenomas, rather than hundreds or thousands, and have an approximate 10-year delay in adenoma and cancer development compared to typical FAP.

The gene that is mutated in FAP is found on the long arm of chromosome 5 and is called the adenomatous polyposis coli (APC) gene [2]. The exact function of the gene is not known, but it appears to be involved with the cell adhesion complex. Eighty percent of affected families have a different and distinct mutation of the APC gene but virtually all mutations that are disease causing are ones that result in termination of the protein at or near the mutation.

The location of the mutations in the APC gene bears some relation to the disease phenotype. Mutations in the proximal four exons of the APC gene result in AAPC. The CHRPE lesions are observed in families with mutations distal but not proximal to exon 9 [3]. Greater numbers of colonic adenomas are found if the mutations are in the mid portion of exon 15 [4]. Why some families exhibit a more prominent expression of extra-intestinal lesions is not known, however. Furthermore, some families with Turcot syndrome arise from mutations of the APC gene, while others are associated with mutations of the genes relating to HNPCC [5].

Linkage testing, in vitro detection of APC protein fragments and direct detection of the mutation have all been used investigationally for the diagnosis of at-risk family members in FAP families. Linkage and in vitro protein fragment testing are now commercially available and are widely applied clinically for the diagnosis of FAP [6,7]. Readily available genetic testing makes FAP families particularly attractive for use as cohorts in chemoprevention trials. Individuals with FAP, in fact, have already been extensively employed in the evaluation of sulindac for polyp regression [8]. Presymptomatic diagnoses by genetic testing can now allow agents to be evaluated for their ability to prevent even the initial emergence of colonic adenomas in gene carriers. The possible regression of gastric polyps and duodenal adenomas is also an important clinical issue that requires investigation. Even the less common tumors of the thyroid and brain may provide opportunity for chemoprevention.

We are presently examining a large kindred with AAPC and a known mutation of the APC gene [9]. Mutational testing has been developed that allows highly accurate genetic diagnosis. Genetic testing in over 1,000 kindred members has revealed almost 200 mutant gene carriers. Colonoscopy and upper gastrointestinal endoscopy is being carried out in gene carriers to define the phenotype and develop appropriate management guidelines. The number of adenomas in gene carriers has been found to be

extremely variable, and to average 30. The variability suggests environmental and/or modifying genetic influences. The smaller number of polyps and their variability also suggest that AAPC kindreds could provide a very applicable setting for chemoprevention trials. A specific genetic diagnosis, a more approachable number of polyps for assessment and the already known possibility of modulating polyp expression all add to the attractiveness of employing such families for chemoprevention.

Hereditary Nonpolyposis Colorectal Cancer

HNPCC is also an autosomal dominantly inherited disease with an extremely high risk for colon cancer [10]. Affected persons with this condition, however, usually develop only a few colonic adenomas. But the adenomas occur on average at a younger age than expected in the population and are larger and exhibit more villous histology that those in control groups. The average age of colon cancer diagnosis in HNPCC is about 45 years. Uterine cancer appears to be associated with this syndrome and some families also have exhibited an excess of gastric, pancreatic, ovarian, renal, and other malignancies. The exact frequency of this condition is not known, but it appears that between 1 and 5 % of colon cancer cases in the U.S. arise as a part of HNPCC.

Until the recent identification of the genes mutated in this syndrome, the diagnosis was based primarily on family history. The lack of specific clinical features made this approach necessary. The agreed upon clinical criteria for the condition included three relatives with colon cancer, two of them being first-degree relatives of the third, two affected generations and one of the cases having a diagnosis at age 50 years or younger. Over 70% of the families that meet these criteria are now found to have a disease causing mutation in one of the four identified mismatch repair genes [11]. These mutations also usually cause truncation of the resultant protein. Commercial genetic tests have just become available for the genetic diagnosis of at-risk members in families with HNPCC.

In view of the extreme cancer risk in HNPCC, and with the availability of genetic testing, this group provides an important resource for chemoprevention trials. Furthermore, chemoprevention for persons with a genetic diagnosis of HNPCC could hopefully delay or even eliminate the need for colectomy. The emergence, or lack thereof, of polyps can be used as a study endpoint, just as in FAP. The close follow-up clinically required for individuals with HNPCC (biannual colonoscopy) provides a ready method for evaluation of the effectiveness of an agent under study.

COMMON FAMILIAL RISK FOR COLON CANCER

Epidemiologic investigations have consistently demonstrated a two- to four-fold increased risk (over the general population) for colon cancer in persons who have a first-degree relative with this malignancy [12,13]. Kindred studies have further indicated that this familial risk likely arises from mildly to moderately penetrant inherited susceptibility factors [14,15]. The genes that give rise to this purported type of inherited risk have not yet been identified.

Stratifying Common Familial Risk

Despite the lack of specific genetic information, several clinical factors have been identified that allow stratification of familial risk. The most important are the number of affected first-degree relatives and the age of colon cancer diagnosis [12,13]. Having two relatives with colon cancer increases the risk of this malignancy 3-6–fold over the general population. Estimates of lifetime risk for colon cancer in this situation range from 25% to 35%. A similar risk is observed if a first-degree relative is diagnosed with colon cancer at or under the age of 50 years. It is estimated that 10% to 15% of colon cancer cases will fall into this "very high" risk group, and only a small fraction of them will be found to have FAP or HNPCC.

The risk of colon cancer is increased 30% to 50% even if a second- or third-degree relative has this cancer [16]. Some increased risk is also observed in both men and women if a first-degree relative is found to have breast, prostate, uterine, or ovarian cancer. There is likewise risk conferred if a first-degree relative has adenomatous polyps. The degree of risk in this situation is less certain, however, and probably depends on the size and number of polyps and the age of the person at polyp diagnosis.

Any of the common risk categories outlined could be used to generate cohorts for chemoprevention trials. In each situation it also appears that adenomatous polyps are the precursors of colon cancers, thus providing an accessible and

reasonably short-term end point. The lack of specific genetic diagnoses in these common settings would weaken the power of studies because some fraction of those under study would not actually have an increased risk. Nonetheless, these populations would be ideal for some of the less toxic agents, particularly micro- or macro-nutrients. Furthermore, the increased cancer risk would substantially increase study power compared to intervention trials in the general population.

Metabolic Phenotypes and Common Familial Risk

It is hypothesized that a number of "metabolic polymorphisms" are involved in the common type of familial risk in colon cancer. These include acetylator status, certain p450 isoenzymes, N-oxidation status, glutathione-*S*-transferase isoenzymes, phospholipase A2 expression and others [17,18]. Some of these have been associated with colon cancer in population studies, while others are hypothesized to be because of their relation to the processing of certain carcinogens or promoters important to colon cancer pathogenesis. As more information becomes available concerning the cancer predisposition associated with these metabolic polymorphisms, certain of them may provide a means of identifying cohorts with increased risk. It is also expected that specific genetic or biochemical tests will become available to determine the presence of any of the specific polymorphisms with great accuracy.

SUMMARY

The accuracy of genetic diagnosis in the rare syndromes of colon cancer make these conditions important resources for chemoprevention trials. The commonly observed familial risk also provides an important resource for chemoprevention. Although specific genetic diagnoses are not yet possible in this setting, stratification of risk on clinical grounds is possible. Large numbers of subjects with common familial risk could be identified for testing of lower-risk chemopreventive agents. Better study power can also be expected in these groups compared to the general population because of the increased disease risk. Also important is that the adenomatous polyp can be used as a reasonably short-term endpoint in each of the colon cancer categories.

In all, colon cancer in families provides an attractive setting for identification of cohorts for chemoprevention trials. Familial risk is common and reasonably well defined. Specific genetic diagnosis is also now possible in some of the rare inherited syndromes.

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