Genetic testing and surgical decision making in hereditary colorectal cancer

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Abstract

Hereditary colorectal cancer results from specific genetic alterations. The causative genes for familial adenomatous polyposis, juvenile polyposis, Peutz-Jeghers syndrome, and hereditary nonpolyposis colorectal cancer have been cloned and characterized within the past decade. Genetic testing has therefore become more widely used to confirm the clinical diagnosis of each of those syndromes, to provide adequate surveillance, to allow screening of at-risk family members, and to help the surgeon in surgical decision making. The aim of this review is to analyze the importance of genetic testing in view of the clinical and surgical management of those gene-carriers individuals, and to discuss how should the surgeon integrate genetic testing in the evaluation of such patients.

Keywords

Genetic testing · Familial adenomatous polyposis · Hereditary nonpolyposis colorectal cancer · Juvenile polyposis · Peutz-Jeghers syndrome · Surgical decision making

Introduction

In 1988 Vogelstein et al. [1] first described the multistep genetic alterations in colorectal carcinogenesis [1]. Within the past decade some of the causative genes for hereditary colorectal cancer syndromes such as familial adenomatous polyposis (FAP), juvenile polyposis (JP), Peutz-Jeghers syndrome (PJS), and hereditary nonpolyposis colorectal cancer (HNPCC) have been cloned and characterized [2–15]. It is therefore not surprising that molecular genetic testing has become part of the work-up of patients with hereditary and/or familial colorectal cancer [16, 17]. Because of the rapid and continuous development in basic and clinical medicine of hereditary colorectal cancer, medical and legal experts have urged surgeons to play an active role in the decision to use molecular genetic testing, focusing on the patient’s diagnosis, personal and family history [18, 19].

Colorectal cancer (CRC) results from interactions between genes and environment. CRC is the second most common malignancy in developed countries; epidemiologic data suggest that sporadic CRC accounts for approximately 80% of all CRC cases, while FAP, HNPCC, and familial CRC account for 1%, 5%, and 15–20%, respectively [20]. Individuals have an increased risk of CRC if one or more first-degree relatives have developed
CRC, or if CRC was diagnosed before 45 years of age [21]. Factors such as gene penetrance, cumulative absolute risk for CRC, clinical criteria for hereditary cancer (i.e., Amsterdam criteria in HNPCC), and specific genotype-phenotype correlations need to be evaluated when molecular genetic testing is to be used for preventive and/or therapeutic management of those affected individuals and their at-risk relatives [22, 23]. The best setting to provide clinical and genetic screening is within a familial cancer registry in which surgeons, genetic counselors, molecular biologists, oncologists, and gastroenterologists interact to give adequate guidelines for the management of these patients. This setting allows accrual of clinical data, stimulates research, and provide adequate family support [24].

The aim of this review is to provide an update on hereditary colorectal cancer syndromes with emphasis on molecular genetic testing and its use in surgical decision making.

Familial adenomatous polyposis

FAP is an inherited, autosomal dominant precancerous syndrome with close to 100% penetrance, characterized by the development of 100 or more colorectal adenomatous polyps [25, 26]. The frequency at birth is estimated to be 1:10,000. Up to 30% of FAP patients are isolated cases due to spontaneous mutations in the adenomatous polyposis coli (APC) gene. Although the age at onset is variable, ranging from age 10 to 60 years, most patients are diagnosed in their late teens. If left untreated, one or more of the colorectal adenomas will progress to colorectal cancer, typically by the age of 40 years. The severity of disease is variable for the development and progression of extracolonic manifestations such as desmoid tumors and perianal carcinoma, two leading causes of mortality in FAP [27].

FAP is caused by germline mutations of the APC gene [3, 4]. APC is a tumor suppressor gene and inactivation of the APC gene leads to neoplastic tumor growth [28, 29]. Although the exact function of the APC protein is not fully understood, it interacts with β-catenin, E-cadherin, and/or microtubules, and it is apparently involved with the regulation of cell growth and adhesion, as well as with the cell signaling pathway [30]. Since the majority of APC mutations germline mutations result in a truncated APC protein, the most commonly used molecular test is the protein truncation test (PTT) which detects up to 80% of APC mutations [31]. Other tests such as the in vivo yeast fusion protein assay may be used as an alternative test to PTT [32, 33]. DNA sequencing is then performed to characterize the germline mutation.

It is worth emphasizing that if an APC mutation is identified in an affected family, gene testing for first-degree relatives is considered 100% accurate. Gene testing is initiated with a surviving relative who has FAP. A caveat about the pitfall of commercial APC gene testing comes from a recent survey of 177 cases referred for APC analysis [34]. Inappropriate clinical criteria were used in 17% of cases, that is, either an at-risk relative or someone without a histologically confirmed diagnosis of FAP. Molecular results were misinterpreted in 31.6% of patients who were told that their APC gene test was negative when in fact no gene mutation was demonstrated, and the genetic test was uninformative [34]. Few patients received genetic counseling or gave informed consent prior to gene testing. The implications of these findings and the potential screening discharge of patients with an uninformative result emphasize the need for better understanding of gene tests.

APC gene testing is cost effective when compared to ongoing flexible sigmoidoscopy until age 60 [35, 36]. If a first-degree relative does not carry the causative APC gene mutation in the family, the patient is not considered at risk for FAP and does not require repeat flexible sigmoidoscopy for FAP. The patient remains at population risk for CRC. However, acceptance of molecular technology in clinical practice has been mixed to date. A recent survey of 30 international FAP Registries confirmed that 63.3% would alter their clinical recommendations for APC gene-negative carrier, but 26.7% would maintain screening despite the clearcut absence of genetic mutation [37].

More recently, it has been suggested that molecular gene tests can be used as a guide to surgical management of FAP patients [38]. One should first make the distinction between prophylactic colectomy, intended as a procedure to prevent cancer, and therapeutic colectomy, aimed at already affected individuals. In FAP prophylactic colectomy is part of the surgical management, because of the known adenoma-carcinoma sequence [25]. Specific genotype-phenotype correlations exist for the number and location of colorectal adenomas: attenuated FAP or attenuated APC (AAPC), clinically diagnosed on the basis of fewer than 100 adenomas present at endoscopy, is associated with mutations in three regions of the APC gene (5’ end, exon 9, and 3’ end), whereas classical FAP (>100 adenomas) is associated with mutations in other regions of the gene [39].

Vasen et al. [38] observed that APC mutations in the APC gene 3’ of codon 1250 are associated with an increased risk for rectal cancer, and consequently that restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) was the operation of choice for patients with such mutations. However, the authors did not specify the number of adenomas, specific location of the APC mutations, or the age at colectomy, all known risk factors for rectal cancer. Variation in polyp severity from confluent to spare adenomas in patients with 3’ mutations has already been demonstrated [40, 41]. Patient compliance with follow-up surveillance should be factored into sur-