Risk stratification for colorectal cancer and implications for screening

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Abstract

In addition to the well-recognized syndromes described (FAP, HNPCC) clusters of colorectal cancers occur in families much more often than would be expected by chance. This familial clustering in about 10-20% of colorectal cancers has implications for screening because the immediate family members of a patient with apparent sporadic colorectal cancer have a twofold to threefold increased risk of the disease. The magnitude of the risk depends on the age at diagnosis of the index case, the degree of kinship of the index case to the at-risk case, and the number of affected relatives. In addition to screening the easily identifiable high-risk groups such as FAP and HNPCC, care should be taken to recognize intermediate-risk patients and to provide them with appropriate screening recommendations. Because the molecular basis and the natural history of these intermediate-risk patients are largely unknown, screening recommendations are as yet more empirical. If a person has a first degree relative with colon cancer, average risk colon cancer screening is recommended, but starting at age 40 years. The decreased age is given because the risk at age 40 for those with an affected first-degree relative is similar to the risk at age 50 for the general population. An individual with two first-degree relatives affected with colon cancer or one first-degree relative diagnosed under the age of 60 y should have colonoscopy beginning at age 40, or 10 years younger than the earliest case in the family. Colonoscopy should be repeated every five years if negative. An even stronger family history of colon cancer syndromes of colon cancer.should suggest the consideration of one of the inherited syndromes.. (Acta gastroenterol. belg., **2005**, 68, **241-242**).

Background

In addition to the well-recognized autosomal dominant colorectal cancer syndromes such as Familial Adenomatous Polyposis (FAP) and Hereditary Non-Polyposis Colorectal Cancer (HNPCC), clusters of colorectal cancers occur in families much more often than would be expected by chance (1). Postulated reasons for this increased risk include 'mild' and undetected mutations of APC and mismatch repair genes, as well as yet unknown polymorphisms in genes involved in nutrient or carcinogen metabolism (2). Candidate alleles that have been shown to be associated with modest increased frequencies of colon cancer include the APC I1207K and E1317Q polymorphisms and loss of imprinting of the IGF2 gene. However, none of these alleles have been characterized well enough to support its routine use in a clinical setting at this time. This familial clustering in about 10-20% of colorectal cancers has implications for screening because the immediate family members of a patient with apparent sporadic colorectal cancer have a twofold to threefold increased risk of the disease. The magnitude of the risk depends on the age at diagnosis of the index case, the degree of kinship of the index case to the at-risk case, the number of affected relatives, and the age of the screenee (3). Because the molecular basis and the natural history of these intermediate-risk patients are largely unknown, screening recommendations are as yet more empirical. Most recommendations are based on the findings of the study by Fuchs *et al.* that provided relative risks for colorectal cancer according to number of affected relatives (1). This study was a prospective cohort study were individuals were followed over years for the development of colorectal cancer and provided information on their family history. For persons with a family history the relative risk was higher if they were young, and approached the population risk as they got older. Future research into the molecular basis of these syndromes should allow more definite risk evaluation.

Screening guidelines

Screening strategies have been developed to address the familial risk of commonly observed colon cancer. Screening recommendations are empiric and combine the known effectiveness of available screening tools with the observed risks associated with family history (4). If a person has a first degree relative with colon cancer, average risk colon cancer screening is commended, but starting at age 40 years. The decreased age is given because the risk at age 40 years for those with an affected first-degree relative is similar to the risk at age 50 years for the general population. An individual with two first-degree relatives affected with colon cancer or one first-degree relative diagnosed under the age of 60 years should have colonoscopy beginning at age 40 years, or 10 years younger than the earliest case in the family. Colonoscopy should be repeated every five years if negative. An even stronger family history of colon cancer should suggest the consideration of one of the inherited syndromes of colon cancer. The necessity to offer colorectal cancer screening, to first degree relatives of colorectal cancer patients, may become a legal duty of the consulting physician (5).

There are several reasons why these first degree relatives of patients with colorectal cancer may be difficult

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to reach by a conventional direct population screening system.

First, the presence of colorectal cancer in a relative of a subject, may not be known to the physician (most often a general practitioner), because familial history was not taken. For example, even in a highly sensitised population of physicians, such as colorectal oncologists in a tertiary care centre, and of patients, i.e. colorectal cancer patients themselves, only in 59% of the cases the oncologists filed a comprehensive familial history of cancer (6). Paradoxically, young age and a first degree relative with colorectal cancer were not associated with a more comprehensive family history assessment and even worse : an increasing number of cancers per family was a strong predictor of a less comprehensive family history assessment. It appears therefore, that a screening programme trying to reach this population should not be based on history taking by a physician. Secondly, patients with a first degree relative with colorectal cancer tend to develop their own colorectal cancer at a younger age (1). This observation, may lead to the fact that the younger subjects with a familial history of colorectal cancer may develop colorectal cancer themselves, before the age at which mass screening programs are initiated (e.g. age 50) is reached. Thirdly, there may be psychological reasons to refuse screening. Fourthly, screening programmes for colorectal cancer, may be hampered by referring bias. This means that only individuals with strong interest for health issues are interested in participating, whereas the risk of these individuals may be lower, due to a more healthy lifestyle.

Psychosocial aspects

The number of individuals participating in cancer prevention programs is increasing and includes healthy high-risk individuals. Awareness of increased risk of colorectal cancer through risk estimates, knowledge of positive mutation status, and participation in surveillance programs could cause physical and psychological distress. Misunderstanding of risk estimates and increased psychological distress may lead to a less strict adherence to surveillance. It is therefore of major importance to evaluate psychological aspects related to genetic counselling and the influence of a surveillance program in at-risk individuals. Such testing has already been performed in high risk HNPCC kindreds in Belgium (7). The following issues could be studied in this intermediate elevated risk population : perception of benefits of prevention, perception of discomfort associated with colonoscopies, risk perception, health-related quality of life and level of anxiety and depression, and knowledge of why surveillance with colonoscopies has been recommended. A cross sectional study of screened individuals reported a beneficial experience of the surveillance and colonoscopies and that the level of discomfort from the colonoscopies was low (8). A lower level of depression was found as compared with a reference study. An increased number of colonoscopies resulted in lower values of discomfort but did not affect the values of benefit. Individuals who recalled earlier polypectomies even reported improved perception benefit. These results imply that the detection of polyps may increase the experience of benefit and that most individuals experience less discomfort the longer they have participated in the program. In the risk group with a life time risk ranging from 10 to 20%, most individuals overestimated their risk of colorectal cancer. In fact, 20% of the low-risk individuals believed their lifetime risk of colorectal cancer to be 80%. One possible explanation could be that the findings of colon polyps during surveillance could lead to an increased risk perception in low-risk individuals. The information given to HNPCC mutation carriers is precise in terms of an 80% lifetime risk. In intermediate risk groups, the information is more complex, and thus, more likely to be subject to personal interpretation. The finding of overestimation of risk in these groups is in accordance with previous observations finding worry to be a motivating factor for attendance, and consequently, these individuals could be expected to report a higher lifetime risk of colorectal cancer. The adherence to surveillance is important in this population and is facilitated if individuals at risk are well aware of the reason for the prevention procedure, although their risk perception might still be incorrect.

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