Presymptomatic diagnosis of hereditary colorectal cancer

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Findings by SBU Alert

People with a hereditary disposition for colorectal cancer are at high risk for developing cancer during their lifetime. Methods are available both to determine whether such a predisposition exists and to detect early stages of cancer. Given this information, patients can be screened via regular examination of the colon (coloscopy) and in some cases be offered preventive surgery, which substantially reduces the risk for cancer.

There is good* evidence concerning the association between the prevalence of certain genes and the risk for cancer. There is moderate* evidence regarding the effects of preventive interventions in individuals at high risk. Assessments are lacking on how total programs affect survival, quality-of-life, and costs.

Due to ethical and practical considerations, there are limited opportunities to use randomized studies to evaluate screening for hereditary disposition for disease. Hence, it is important to use model analyses to illuminate the full range of patient benefits and economic consequences from all types of preventive programs aimed at healthy individuals.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see “Grading of evidence”.

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Technology

The lifetime risk for acquiring colorectal cancer is approximately 5 per cent. For individuals who carry a hereditary disposition for colorectal cancer the risk is substantially higher (80 to 100 per cent). Hereditary colorectal cancer is expressed mainly in two ways. One type, familial polyposis (FAP), is characterized by formation of a large number of polyps in the colon. The other, and considerably more common, type is Hereditary Non-Polyposis Colorectal Cancer (HNPCC). This disorder is characterized by isolated polyps, tumors, in the first part of the colon and is associated with a higher risk for other types of cancer, mainly cancer in the endometrium, stomach, and the mucosal epithelium of the urinary tract.

Programs to prevent hereditary colorectal cancer are based on five interrelated components:

1. identification of families with hereditary cancer
2. genetic counseling
3. regular check-ups
4. preventive surgery
5. genetic testing.

Most commonly, families are identified when patients diagnosed with colorectal cancer present with clinical signs of hereditary disease. These include early debut of cancer, the presence of multiple tumors or a large number of polyps, and several first-degree relatives (parents, siblings, children) with the disease. Approximately 10 per cent of all patients with colorectal cancer have one or more first-degree relatives who have or have had the disease [1]. All clinical departments that treat cancer patients do identification of patients with suspected hereditary disease.

When it has been established that hereditary colorectal cancer exists in a family it may be appropriate to offer genetic testing to determine which member, or members, of the family are predisposed, and offer these individuals preventive, targeted interventions. Common blood tests are used in genetic testing to isolate the DNA. The DNA is then analyzed to identify the change (mutation) in the affected gene that has caused the disease. Often, different (private) mutations exist in different families. Therefore, one must identify the mutation that has caused the disease in a confirmed case in each family. When the mutation is determined, others in the family undergo genetic testing aimed at analyzing the mutation. The analyses are complicated and expensive. There are several different genes responsible for colorectal cancer, and their configuration is complex. Hence, genetic testing is conducted on strict criteria at only a few special laboratories in Sweden.

Complementary genetic counseling and different types of followup, and in some cases prophylactic surgery, are offered to individuals where hereditary predisposition has been identified. Special followup programs involving regular check-ups are started at a relatively early stage since hereditary forms of colorectal cancer often presents already at 30 to 50 years of age.

Target group

Approximately 5000 new cases of colorectal cancer are reported in Sweden annually. Between 5 and 10 per cent have a hereditary disposition for the disease. Many of the 250 to 500 individuals who are affected annually by hereditary colorectal cancer are related to each other, the number of newly detected families is substantially lower. Approximately 400 families in Sweden are known to have hereditary colorectal cancer, but this figure is increasing with the increased attention given the disease in recent years. Less than 1000 persons are targeted for some type of routine check-ups or other interventions.

Relation to other technology

Another way to reduce morbidity and mortality from disease is general screening for colorectal cancer in certain age groups in the population. Such programs are being assessed, but have not yet demonstrated that mortality can be reduced at a reasonable cost and without major ethical consequences.

Patient benefits

The purpose of programs to prevent hereditary colorectal cancer is to identify a group consisting of healthy individuals who are at high risk for developing the disease. Through preventive interventions, morbidity and mortality from colorectal cancer in this risk group can probably be eliminated. If this risk group is not identified, the gene carriers have a high probability (over 80 per cent) of contracting colorectal cancer. If one only identifies families at risk without conducting genetic testing, the risk group offered preventive interventions would be twice the size. The risk for each person in this group would also be lower (approximately 40 per cent) [1]. If no preventive measures are taken, treatment would be given to gene carriers at a later stage after several of them had acquired cancer symptoms. At later stages in the disease, treatment results are worse, i.e., approximately the same as in sporadic colorectal cancer.

Extensive experience with check-up programs in FAP families has shown that the risk for developing colorectal cancer and dying from the disease is lower among those who have had the colon removed (colectomy). One study has shown that check-ups in healthy family members in HNPCC families also provide the opportunity for earlier detection of cancer [2]. During a 10-year period, 118 people with an estimated risk of 50 per cent for developing colorectal cancer were examined every third year via coloscopy, or sigmoidoscopy (sigmoideum = the distal part of the colon), plus x-ray imaging of the colon. The group was compared to a similar sized group at equally high risk but who refused check-ups. In the group checked, the occurrence of colorectal cancer was 4.5 per cent in contrast to 11.9 per cent in the group not undergoing check-ups. This difference reflected that detected polyps could be removed before they developed into cancer. In the group not undergoing check-ups, mortality was 4 per cent during the 10-year period, while none of the subjects who underwent check-ups died from colorectal cancer.

Complications and side effects

Genetic testing for hereditary cancer has a special place in laboratory diagnostics since the test aims to identify individuals who carry a gene for a disease that presents much later in life. A false test result could mean that individuals who should be offered preventive interventions are not given this opportunity. It could also mean that healthy individuals receive false information that they are at higher risk for developing a severe cancer. Families at higher risk for cancer need genetic counseling that should also include supportive counseling, for those who want it.

Check-ups of the colon involving repeated coloscopy examinations when hereditary predisposition exists are often uncomfortable for the patient, but essentially harmless. Preventive surgery such as colectomy is a major procedure, but the risk for serious complications is low.

Costs and cost-effectiveness

A targeted mutation analysis in families where mutations are identified costs approximately 5000 SEK per person. When the test can eliminate a person from a control program this represents substantial savings. Searching for a specific mutation in a family costs up to 20 000 SEK per family. These analyses must therefore be conducted on strict criteria.

The costs for coloscopy check-ups every second year should be weighed against the high risks (over 80 per cent) for gene carriers to develop cancer. Each examination costs approximately 3000 SEK. In preventive surgery, an organ is removed which would otherwise probably have to be surgically removed due to a tumor. A major operation in the small or large intestine costs, on average, 66 745 SEK (1998) [3]. With the less common disease, FAP, the probability of developing cancer is so high that preventive colectomy is most likely cost-effective.

A model for cost-effectiveness has been used to study two strategies for following gene carriers. The strategies were: regular check-ups with coloscopy at 2 to 3 year intervals, or no regular check-ups [6]. According to registry data from the Netherlands and data from the scientific literature, life expectancy for a gene carrier was 7 years longer in the group who received check-ups. The total costs were lower for this alternative. A model analysis from the United States that covered 12 different strategies for followup of treatment in gene carriers (HNPCC) confirmed that expected survival increased between 13 to 15

years with prophylactic surgery or regular check-ups compared to the "no check-up" alternative [5]. Costs were not analyzed.

Structure and organization of health services

Genetic counseling and check-up programs directed at healthy gene carriers are prerequisites for preventing hereditary colorectal cancer. A network of clinics at the university departments in Sweden has contact with affected family members. Nevertheless, it is often difficult for healthy family members to receive a referral to specialists for counseling and check-up programs if the family is spread around the country, particularly since preventive work is directed toward healthy individuals who have not previously been treated at their local hospital.

Organizational problems and difficulties in identifying who should be responsible for the costs sometimes means that check-up programs do not function satisfactorily. The National Swedish Board of Health and Welfare has developed national guidelines on the investigation, followup, and care of individuals suspected to be at increased risk for hereditary cancer, including colorectal cancer [4].

Ethical aspects

Family studies and genetic counseling raise ethical questions regarding personal integrity. In Sweden, there is a generally accepted principle that a family study is based on trust between the care seeker and the physician. All contact with the family goes through the person seeking care, so that confidentiality concerning individual family members is not violated. Healthcare personnel are not allowed, on their own initiative, to contact members of a family to inform them that they are at higher risk for cancer. It is also important to recognize that everyone has the right to refuse information about whether they have a hereditary predisposition that may cause disease.

In situations where prophylactic surgery is used, it should always be performed with the patient's expressed consent after he or she has been informed in an appropriate manner. The same applies to genetic testing which should be offered only by physicians who are sufficiently knowledgeable about the hereditary nature of the disease, in order to provide adequate genetic counseling in conjunction with the test results.

Diffusion in Sweden

Special programs for preventing hereditary colorectal cancer are available at the onco-genetic departments at the university hospitals in Sweden. Check-up programs are administered by special clinics, whereas the check-ups are performed at the local hospitals.

Current evaluation research

SBU Alert is not aware of any ongoing major assessments of this method.

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