A Familial Gastrointestinal Cancer Clinic: Organization, Aims and Activities, 2004–2007

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Abstract

Background: Dedicated, organ-specific screening clinics have been shown to significantly reduce cancer morbidity and mortality.

Objectives: To establish a dedicated clinic for Clalit Health Service patients at high risk for hereditary gastrointestinal cancer and to provide them with clinical and genetic counseling, diagnostic screening and follow–up.

Results: During the 3 years of the clinic's activity, 634 high risk families, including 3804 at-risk relatives, were evaluated. The most common conditions were hereditary colorectal syndromes, Lynch syndrome (n=259), undefined young-onset or familial colorectal cancer (n=214), familial adenomatous polyposis (n=55), and others (n=106). They entered follow-up protocols and 52 underwent surgical procedures.

Conclusions: Consistent public and professional education is needed to increase awareness of hereditary colorectal cancer and the possibility of family screening, early diagnosis and therapy. The public health services – i.e., the four health management organizations – should provide genetic testing for these patients who, at present, are required to pay for almost all of these available but costly tests. Dedicated colorectal surgical units are needed to provide the specialized therapeutic procedures needed by patients with familial colorectal cancer. Our future plans include adding psychosocial support for these at-risk patients and their families as well as preventive lifestyle and dietary intervention.

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In Israel, colorectal cancer has increased rapidly in recent decades to become the most common cancer in both men and women, with more than 3000 new patients diagnosed in the year 2002. Israel has a high incidence of CRC; this is especially true for Jews of European origin, with recent immigrants from the former Soviet Union at the highest risk. This has been attributed to the interaction of environmental risk factors with an innate genetic susceptibility due to generations of intermarriage within a closed community [1,2]. The Arab population is known to have a high incidence of right-sided CRC, young age at onset, and genetic changes consistent with generations of intermarriage within a closed community. As their lifestyle becomes more typically Israeli, they too now have an increasing incidence of left-sided colorectal cancer, which is more typical of sporadic CRC [3].

It is estimated that more than 15% of CRC patients are predisposed to the disease due to a genetic defect [4]. The largest group, < 10%, comprises first-degree relatives of CRC patients. This is attributed to the interaction of their undefined recessive risk factors with commonly occurring environmental conditions. The importance of these recessive risk factors is illustrated by the declining CRC incidence in the Israeli born who are increasingly the descendants of inter-ethnic marriages and have a more Mediterranean lifestyle [1,2].

In about 5% of CRC patients the cause is a dominant genetic risk factor. The two main types of hereditary colorectal cancers are Lynch (hereditary non-polyposis colorectal cancer) and familial adenomatous polyposis syndromes [4]. They are caused by germline mutations of the mismatch repair (MMR) and adenomatous polyposis coli (APC) genes, respectively. Less common are the Peutz-Jeghers, juvenile and hyperplastic polyposis syndromes, and the recessive mutation of the base-excision repair MYH gene. Members of these families have a 25–50% chance of inheriting the diseased gene, predisposing them to CRC and sometimes to cancers in other sites such as brain, stomach, duodenum, female organs and the urinary tract. In addition, there are specific syndromes due to oncogenetic mutations identified in the Jewish population. These include the hereditary mixed polyposis syndrome and the I1307K APC variant [1,4,5]. Moreover, recent findings of commonly occurring founder mutations in Jews have facilitated the genetic diagnosis in some [1,5,6]. These mutation carriers tend to develop cancers early in life. The psychological, somatic, social and economic burdens on these families are profound [7,8].

Recent advances in molecular technology have enabled detection of some of the abnormal genes that cause the common syndromes. For these high risk individuals, pre-symptomatic detection and treatment of precancerous adenomas or early cancers by regular surveillance is the most effective and economic way to prevent HCRC and its associated morbidity and mortality [4,9-12].

With predictive genetic testing and diagnosis it is now possible to distinguish the diseased-gene carriers from those who have not inherited the defective gene within affected families, thus allowing the accurate risk assessment of all at-risk family members. Those not harboring the diseased gene are spared the psychological burden as well as the chore of continuous surveillance. Resources can then be concentrated on counseling and vigilant surveillance of those carrying the defective gene in order to prevent the development of cancer [4,12-14].

CRC = colorectal cancer

HCRC = hereditary CRC

Management of these HCRC families requires a multidisciplinary approach and, based on previous experience of the first author (P.R.) at the Tel Aviv Medical Center, is best performed by a dedicated unit [15,16]. Since its establishment in 2004, the Hereditary Gastrointestinal Cancer Unit has developed a unique service for these HCRC families, who are members of Clalit Health Services.

Activities and aims

The mission of the Hereditary Gastrointestinal Cancer Clinic is to achieve cancer prevention in at-risk individuals and high risk families through early detection, timely treatment, education and ongoing research. Our clinic provides service for Clalit Health Services families suspected or proven to have familial-hereditary colorectal and other cancers. The latter includes familial esophageal, gastric and pancreatic cancers; since they are not common this report addresses only HCRC. The aim of this article is to demonstrate the clinic's usefulness so that it, and similar units, will be accepted as an integral part of the national medical services.

Methods

Clinical services

- *Personnel*: These include two medical interviewers, three physicians and a genetic counselor.
- *Record keeping*: Pedigrees of affected and at-risk families are generated and updated. To maintain patient confidentiality a locked database is kept for pedigrees and genetic information.
- *Genetic-guided screening program*: An individual-tailored screening program for at-risk family members is formulated and organized using a combination of the genetic and clinical information obtained.
- *Counseling*: Genetic counseling is provided and, in the future, lifestyle and psychosocial support will be offered to affected families.

Education

Information is provided to both the medical profession and the public about HCRC to ensure proper referral and adherence to a screening/surveillance program.

Research

Clinical, psychosocial, laboratory and molecular genetic research is planned to improve our understanding and management of HCRC.

International collaboration

The participation of the clinic's personnel in international meetings and collaborative research efforts facilitates exchange of information and involvement in multicenter studies.

Entry criteria

The clinic accepts referral of families throughout Israel, from family physicians, internists, general and colorectal surgeons, pediatricians and gastroenterologists, satisfying the following criteria (it should be noted that because of the Holocaust, wars, dispersion and small sized families it is often difficult to obtain all the clinical criteria):

1. Families affected by histologically proven familial adenomatous polyposis or other polyposis syndromes. This includes index patients and at-risk first-degree relatives above the age of 12 years.
2. Families affected by Lynch syndrome, satisfying the modified Amsterdam or Bethesda criteria and/or with proven mismatch repair gene mutation [17,18]. This includes index patients and at-risk first-degree relatives from the age of 20 years.
3. Families satisfying one of the following (American Cancer Society) criteria:
   - One first-degree family member who has histologically proven CRC or adenoma diagnosed before the age of 60 years
   - Two or more first-degree family member having histologically proven CRC or adenoma diagnosed at any age

   These include index patients and at-risk first-degree relatives 10 years younger than the youngest affected relative [4].

Results

To date, the clinic has recruited 634 families with confirmed or suspected HCRC. Specialists referred most of these families, while a few were self-referred. To date 711 of 3804 family members have received or are receiving our service [Table 1]. Our clinical screening/surveillance program has detected treatable lesions, for timely intervention, by identifying precancerous or early cancerous conditions in these patients. Most of them have already received the appropriate management and/or are under surveillance to choose the appropriate time and therapy [Table 2].

Surgical procedures were performed in 52 patients; a few of them were operated by a unit specializing in surgery for HCRC patients. In most cases, only after a standard surgical procedure was the patient recognized as being at high risk for familial cancer. Because of the increasingly frequent detection of gynecological malignancy in our HNPCC female gene carriers, the clinic has taken measures to increase these women's awareness about this condition, including ongoing gynecological surveillance; the question of prophylactic surgery as an alternative to clinical surveillance

Table 1. Total number of families and individuals at risk recruited to the clinic until August 2007

	No. of families	No. of alive index patients	No. of alive at-risk relatives
Familial CRC or < 60 yrs old	214	230	1,049
FAP	55	67	336
Lynch syndrome	259	299	1,991
Juvenile polyposis	3	3	16
Hyperplastic polyposis	9	9	51
MYH	2	4	17
Cowden syndrome	4	8	20
Other	88	91	324
Total	634	711	3804

MYH = mutation of the base-excision repair MYH gene

HNPCC = hereditary non–polyposis colorectal cancer

Table 2. Positive clinical findings and interventions: cumulative results until August 2007

Positive findings	No. of events	Treatment/ No. of patients
Colorectal		
Adenocarcinoma	3	Surgery
FAP, all	55	Genetic consult/Surveillance; Surgery (n=6)
FAP rectal stump adenoma	1	Surgery
FAP with cancer*	3	Surgery
Lynch syndrome	259	Genetic consult/Surveillance; Surgery, (n=28)
Juvenile polyposis/ Cowden syndrome	12	Genetic consult/Surveillance; Surgery (n=1)
Hyperplastic polyposis	9	Surveillance/Surgery (n=1)
Extra colonic		
Significant duodenal adenoma	2	Polypectomy
Desmoid tumor	3	Chemopreventive treatments
TCC ureter*	2	Surgery
Endometrial neoplasia*	3	THBSO
Brain tumors*	1	Surgery
Sebaceous skin neoplasia*	1	Chemotherapy/surgery

* Occurred before enrolling in the Familial Cancer Clinic
FAP = familial adenomatous polyposis, Lynch syndrome = hereditary non-polyposis colorectal cancer (HNPCC), TCC = transitional cell carcinoma, THBSO = total hysterectomy and bilateral salpingo-oophorectomy

Table 3. Report on laboratory genetic diagnosis: cumulative results until August 2007

Polyposis (FAP, MYH and PJS)	No.
Families with germline mutation in the APC, MYH or PJS gene identified	7
Individuals tested positive for germline APC, MYH or PJS mutation	23
At-risk individuals proven negative for mutated APC, MYH or PJS gene	51
Lynch syndrome (HNPCC)	
Microsatellite instability analysis performed	47
Tumors proven to be microsatellite unstable	13
Families with germline MMR gene mutation identified	7
Individuals tested positive for carrying germline MMR mutation	19
At-risk individuals proven negative for carrying a MMR gene mutation	105*

*The majority of these were only tested for 1906G>C in MSH2 (Ashkenazi founder mutation)
APC = adenomatous polyposis coli, MMR = mismatch repair, PJS = Peutz-Jeghers syndrome

is under discussion [19]. For young women with FAP, we also try to delay colectomy and recommend that they complete their families before undergoing surgery because of the risk for reduced fecundity and/or to also consider *in vitro* pre-implantation genetic testing [4,20].

During the genetic counseling session a detailed personal and family history is obtained and an in-depth discussion is held on the genetics of the specific disorder as well the options of genetic testing and its consequences. Genetic testing for HCRC is not available through the HMOs and patients are obliged to pay for most tests [Table 3]. This is illustrated by the small number of patients undergoing costly genetic evaluation for Lynch syndrome. Post-test genetic counseling is provided to all individuals who had genetic testing. During this session the various options are discussed for prevention, treatment and surveillance [13,14]. The close working relationship between the departments of genetics and gastroenterology is essential for the success of the familial high risk clinic.

Discussion

The results presented in Tables 1–3 demonstrate that, within a short time, our specialized clinic has successfully enrolled HCRC patients, providing screening, therapy and counseling. This success will depend on our continued educational efforts to decrease the overall incidence of mortality from HCRC in the near future.

To achieve the clinic's mission in educating the public and the medical profession about HCRC we prepared information pamphlets that provide an overview of HCRC, detailed information on both FAP and Lynch syndrome, and a description of the service provided by the clinic. The booklets are distributed to recruited families, to health care professionals collaborating with the clinic and to related organizations. With the help of the Israel Cancer Association and a donor contribution, an international multi-authored book for advising families of HCRC patients has been translated into Hebrew and is available, gratis, from the Association.

Continuous support of recruited family members is an important task of the clinic. To improve communication of mutual support, for both the FAP and HNPCC patients, we have organized meetings in the past few years. We shall continue our commitment to raising awareness and educating the public on issues regarding HCRC as well as CRC in general by means of public lectures and distribution of our publications. We need to increase the medical profession's awareness of HCRC and cancer of the large bowel in general, and this is facilitated by presenting results of our research at scientific meetings.

As reported in the literature and from our experience, the importance of taking a simple family history of illnesses, such as cancer, is frequently ignored [21,22]. In the United States this has actually let to court cases claiming medical negligence by not informing individuals and their families of their cancer risk [23]. The possibility to consult with our specialty clinic needs to be brought to the attention of the family physicians. We will also continue to interact with the colorectal surgeons who are our natural collaborators. Whenever possible, patients at risk for HCRC should be identified *before* surgical procedures are performed and these should be done by surgeons who have specialist training.

Through continuous new genetic test development and our collaboration with local and international genetics laboratories, we aim to provide a more comprehensive genetic diagnostic service for all HCRC syndromes. Currently, genetic diagnostic tests for FAP and Lynch syndrome have been well established, but only the former is partially covered by our HMOs. The most common genetic mutations are those causing Lynch syndrome. These tests are not covered by the HMOs, therefore these patients are required to pay for genetic evaluation *even when the results will help to identify*

FAP = familial adenomatous polyposis
HMO = health management organizations

persons needing intense follow-up while the 50% *who do not need this will be spared unnecessary invasive and expensive screening tests* [4]. In addition, identifying persons with CRC due to Lynch syndrome influences the choice of oncological chemotherapy [24]. This can significantly influence their survival and prevent inappropriate therapy. We shall also focus our efforts on making these tests available through the HMOs, and help to identify the underlying genetic defects for those families in whom pathogenic mutations cannot be detected using conventional methods.

HCRC patients undergo frequent invasive and expensive screening and follow-up endoscopic tests. We are examining the possibility of supplementing these tests with sensitive non-invasive tests that might help determine when colonoscopy should be performed. These patients and their families suffer from anxiety and frequently have guilt feelings because of their genetic disorder [7]. We will add a dedicated psychologist-social worker to the service who can help us and the patients. We will also include in the team a dedicated nutritionist who can give preventive education to the individuals and families at risk since it has been shown that even genetic disorders can be modulated by preventive dietary and lifestyle changes. This will likely lead to chemopreventive studies and therapies that have been proven useful for suppressing the growth of neoplasia [4,25].

Finally, the clinic and staff need to be recognized as a unique service. The staff should be able to dedicate their time and services to the HCRC patients and not be dependent on research grants and donations

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