Are we making progress in diagnosing and preventing gastrointestinal cancers?

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Introduction

By measures of mortality and morbidity gastrointestinal (GI) cancers are leading the field of oncology. Between one fifth and one quarter of all human cancers arise in the digestive system. Many patients with cancer of the digestive system present with incurable disease. As locally advanced cancer often goes with distant metastases, treatment options are mostly limited to systemic treatment or local palliation only. Despite the many enhancements in cytotoxic therapy and novel biologic agents, overall progress in the outcome of metastatic disease is poor [Sabharwal and Kerr, 2007; Bouvier *et al.* 2006].

The fact that most GI cancers are for long preceded by recognizable, treatable precursor lesions has posed great challenges. Primary prevention strategies seek to prevent the formation of cancer in an otherwise healthy population. Secondary prevention activities are aimed at early disease detection, thereby increasing the opportunities for interventions to prevent progression of the disease. Advanced diagnostic and therapeutic tools have been developed to detect and treat cancerous lesions at the earliest stage. With these tools and increased awareness of their impact, early treatment and prevention have become a major task for the modern gastroenterologist. In this review we focus on recent developments in cancer prevention, detection and the approach to early cancer.

Risk factors and precursor lesions

Pathogenesis of most GI cancers follows a sequential, multistep process with well-defined biological stages, developing from low-grade dysplasia to high-grade dysplasia, and finally to invasive carcinoma [Raza, 2000; Fearon and Vogelstein, 1990]. This is a complex process in which various acquired and inborn genetic factors are involved. Chronic injury and inflammation play a critical role in the majority of GI cancers. The inflammatory process induces oxidative stress, and initiates replacement of injured and damaged cells by a continual regenerative process with risk of DNA damage and uncontrolled cell proliferation [Orlando, 2002].

There are numerous well-recognized conditions in the GI tract that predispose to cancer. Such premalignant conditions include Barrett's metaplasia and achalasia of the esophagus, atrophy and metaplasia of the stomach, chronic inflammation of the biliary tract and pancreas, chronic inflammatory bowel disease, and colonic polyp syndromes.

The use of biomarkers for risk identification may have infinite potential. There have been several attempts to identify markers of tumor DNA shed from tumors into stool. Although there is evidence that this noninvasive approach is useful, there are still important barriers in terms of sensitivity, specificity, and cost. At present, a panel of DNA markers can identify over 50% of patients with colorectal cancer (CRC) and many patients with advanced adenomas [Imperiale *et al.* 2004].

Risk scores based on simple clinical, histological, and serological parameters can already serve as

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a practical tool to select patients for surveillance endoscopy. Intragastric extent of intestinal metaplasia is an example of an indicator for gastric cancer risk that can be assessed by a score based on individual risk factors [de Vries *et al.* 2009a].

Screening and surveillance

The key purpose of screening and surveillance protocols is the detection of presymptomatic curable disease. It is of crucial importance for the efficacy of screening and surveillance programs that the natural history of the target disease consists of a sequential process with well-defined biological stages, and that in this sequence a so-called critical point along its natural history is identified. This critical point is best described as the point during the multistep process before which treatment is either more effective than afterwards, or equally effective but easier to apply [Craanen and Kuipers, 2001]. This critical point should be noticeable by a reliable and efficient screening technique. Furthermore, the critical point has to lie between the earliest possible time of diagnosis and the usual time of clinical diagnosis.

Some GI cancers in various risk areas do not satisfy the basic conditions, whereas others are unbiased candidates for effective large-scale screening and surveillance programs. For those candidates, such as Barrett's, gastric premalignant lesions and colon adenomas, the effect of surveillance on the incidence of advanced cancer and mortality has to be proven before launching large-scale stratified screening and surveillance programs [Reid *et al.* 2010; de Vries *et al.* 2008; Levin *et al.* 2008; Everett and Axon, 1998]. The availability of mass screening programs in high-risk countries for gastric cancer has substantially decreased mortality [Tsubono *et al.* 2000]. In contrast, in North America and Europe where such programs are lacking and few gastric cancers are detected at an early stage, cancer survival is significantly worse [Verdecchia *et al.* 2003]. For CRC in the Western world a trend towards such reduction is documented [Hoff *et al.* 2009]. For esophageal cancer, even in the setting of Barrett's metaplasia, survival benefit has not convincingly been shown.

Chemoprevention

To reduce the incidence and outcome of GI cancer, chemoprevention strategies represent an alternative approach to screening and surveillance programs [Half and Arber, 2009]. This can be achieved for various tumors with a variety of methods, some of which required maintenance treatment whereas others only require a single short-term intervention. One of the most remarkable examples in the latter group is chemoprevention of gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma by antimicrobial therapy against *Helicobacter pylori*. *H. pylori* eradication leads to a rapid resolution of chronic active gastritis. This can to some extent be accompanied by a regression of atrophic gastritis, but, it seems, not of intestinal metaplasia. Several large randomized prospective studies have reported that *H. pylori* eradication thus reduces the incidence of gastric cancer. A recent meta-analysis of seven large studies reported that *H. pylori* eradication was in the first years thereafter associated with a 35% reduction in gastric cancer incidence [Fuccio *et al.* 2009]. All of these studies were performed in areas with a high gastric cancer incidence, in particular in Asia. It thus remains unclear whether these results can be translated to other populations. We do however know that the development of gastric cancer after *H. pylori* eradication is not only an early phenomenon, but can still occur more than a decade after eradication [de Vries *et al.* 2009b]. Further studies, in particular in Western populations, are badly needed.

With respect to long-term chemoprevention, the group of drugs that has generated the most attention is the nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit the cyclooxygenase enzymes. Well-conducted animal studies, as well as epidemiologic studies in humans, have shown that the regular use of NSAIDs is clearly associated with a reduction of GI cancer risk [Funkhouser and Sharp, 1995; Giovannucci *et al.* 1995, 1994; Thun *et al.* 1991; Kune *et al.* 1988]. The protective effect is dose-dependent and is directly related to the duration of exposure [Loren *et al.* 2002; Giovannucci *et al.* 1994]. However, traditional NSAIDs are known cause renal toxicity as well as injury to the mucosa of the digestive system, resulting in renal failure, bleeding, ulceration and stricturing of the GI tract. The cyclooxigenase-2 (COX-2) selective inhibitors were considered in the search for an alternative chemopreventive agent with fewer side effects. Recent large-scale studies have shown an increased risk of cardiovascular events, raising serious concerns on the safety of

COX-2 inhibitors in chemoprevention strategies [Kerr *et al.* 2007; Bertagnolli *et al.* 2006]. Furthermore, a subset of GI cancers (20%) has low expression of COX-2, indicating that these tumors could be less responsive to COX-2 prevention.

A second category of drugs that are widely investigated for chemoprevention of upper GI cancers, both alone and in combination with NSAIDs, are proton-pump inhibitors. These studies focus in particular on the effect of proton-pump inhibitor maintenance therapy and the risk of development of esophageal adenocarcinoma in patients with Barrett's esophagus. Several cohort studies have shown that proton-pump inhibitor therapy cannot fully prevent the development of Barrett's esophagus [Kuipers, 2010], although it is unknown whether they slow the rate of development of Barrett's metaplasia. Furthermore, there are several cohort studies which report that proton-pump inhibitor therapy decreases the progression of pre-existent Barrett's mucosa to dysplasia and cancer [El-Serag *et al.* 2004; Hillman *et al.* 2004] yet this observation is not consistent throughout the complete literature [Bateman *et al.* 2003]. This implies that much further research is needed in the coming years on this very important topic.

A third category under investigation as chemopreventive agents for GI cancer are statins. In humans simvastatin and pravastatin are associated with a reduced CRC rate in patients with coronary artery disease, with a relative risk reduction of 47% after 5 years [Poynter *et al.* 2005]. Although statins have been shown to be associated with an acceptable adverse effect profile in patients with hypercholesterolemia, their long-term toxicity in patients without hyperlipidemia has yet to be assessed.

Estrogen may prevent the CRC by decreasing the production of secondary bile acids, by decreasing production of insulin-like growth factor 1, or by exerting a direct effect on the epithelium. Estrogen in combination with progesterone can induce a 37% reduction in CRC incidence in women. However, such hormonal treatment is associated with increased incidences of cardiovascular events, breast cancer, thromboembolic events and stroke [Rossouw *et al.* 2002].

Mesalamine has been studied mostly in the setting of prevention of CRC in patients with inflammatory bowel disease. While some studies show an impressive protective effect, others have failed to confirm these findings [Jess *et al.* 2007; Velayos *et al.* 2006].

Altogether, this indicates that the potential chemoprevention strategies have to be re-evaluated and effective chemoprevention remains at best at the horizon.

Imaging early cancer

For all GI cancers, the most significant prognostic factor for survival is the stage at diagnosis [Ancona *et al.* 2008; Endo and Kawano, 1997]. In the majority of patients with symptoms, the cancer has invaded into the muscularis propria or beyond. Early cancer is defined as tumor limited to the mucosa or extending into the submucosa but not invading the outer muscular wall. If diagnosed in an early stage, GI cancer is curable and has an excellent prognosis (Table 1). Since asymptomatic patients are not routinely exposed to early cancer diagnosis, these early cancer are either picked up through dedicated screening and surveillance, or during medical work-up for other reasons [Suzuki *et al.* 2006]

Despite the many enhancements in diagnostic radiology and promising developments in the field of immunochemical detection, endoscopy with histological biopsy continues to play a leading role the diagnosis of early GI cancer [Kuipers and Haringsma, 2005].

Endoscopic detection of cancer in its early stage can be difficult as most early neoplastic lesions have a normal macroscopic appearance. Precursor abnormalities and early lesions are frequently overlooked, even by the experienced endoscopist. Random biopsy protocols such as in Barrett's esophagus also frequently miss dysplastic or cancerous areas [Wani and Sharma, 2007]. Novel enhancements in endoscopic imaging techniques facilitate visualization and

Table 1. Five-year relative survival rate by stage.

TNM classification	Esophageal cancer	Gastric Cancer	Colorectal cancer
0	>95%	>90%	>95%
I	50–80%	50–80%	90–95%
II	10–40%	30–50%	70–85%
III	10–15%	10–20%	35–66%
IV	<5%	<5%	<5%

TNM, Tumor-Node-Metastases.

increase detection of early neoplastic lesions to a great extent. The leading enhancement techniques are high-resolution imaging, magnification endoscopy, spectral filtering techniques, and autofluorescence endoscopy [Ramsoekh *et al.* 2010; Adler *et al.* 2009; Wolfsen *et al.* 2008; Haringsma *et al.* 2001; Kudo *et al.* 1996]. Although still in their infancy, these imaging techniques have already started to take the place of chromoendoscopy and meticulous random biopsy protocols.

Management of precursor lesions and early cancer treatment

Surgery is still considered the standard treatment for patients with GI cancer. For many years however, endoscopic therapy has become available for certain precursor lesions and early cancer, with significant benefits and excellent outcome. Colonoscopic snare resection of stalked polyps has been employed successfully since the early 1970s [Deyhle *et al.* 1971]. Subsequently, various other techniques have been developed to routinely remove precursor lesions from the GI tract at endoscopy, including hot biopsy removal, cold snaring, piecemeal resection, and argon plasma coagulation. While protruded lesions up to 2 cm in the colorectum can be easily excised by these techniques, other nonprotruded lesion types and superficial cancers in the intestine, stomach and esophagus can be removed with more advanced endoscopic resection techniques. Although standard polypectomy can be considered a form of endoscopic resection, this terminology generally applies for 'deeper' types of resection, extending into the submucosa. The most widely applied techniques for endoscopic resection are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [Chung *et al.* 2009; Gotoda, 2008; Larghi *et al.* 2007; Gotoda *et al.* 2006].

The feasibility, safety, and results of endoscopic resection predominantly depend on operator experience [Hotta *et al.* 2010]. Recent long-term studies have shown that prognosis of complete en-bloc EMR for differentiated, nonulcerated mucosal early gastric cancers under 20 mm is comparable to surgical treatment with 10-year survival rates as high as 99% [Uedo *et al.* 2006]. Other studies have shown the cost-efficacy of such approach [Pohl *et al.* 2009]. Although some advocate endoscopic treatment of smaller undifferentiated cancers and early cancers invading the submucosa [Gotoda *et al.* 2000], generally only high-grade dysplasias and well differentiated nonulcerated GI cancers that are limited to the mucosa are candidates for endoscopic resection, as these lesions have a well-determined low risk for lymph node metastasis [Bollschweiler *et al.* 2006; Vieth and Rosch, 2006; Westerterp *et al.* 2005; Abe *et al.* 2004]. En-bloc resection is preferred over piecemeal resection, irrespective of the resection technique employed [Cao *et al.* 2009].

The risk of complications using these endoscopic minimally invasive resection techniques (i.e. bleeding, perforation, stenosis), are significant, but low in comparison with the risks of a surgical procedure [Jeon *et al.* 2010]. En-bloc resection techniques for larger lesions carry a considerably higher complication rate than EMR techniques, even in the hands of experts [Hotta *et al.* 2010].

Are we making progress?

GI cancer is amongst the most common cancers and a major cause of caner-related death around the world. The incidence, diagnostic techniques, therapeutic options have undergone major changes over the last six decades, but the prognosis generally remains poor, especially in advanced stages and in spite of aggressive adjuvant therapy and advances in surgical resection techniques. At the same time the understanding of carcinogenesis has advanced considerably leading to a marked shift towards risk stratification, prevention, early detection, and early treatment.

The results of primary prevention strategies are lagging behind the initial expectations, yet the availability of mass screening programs in high-risk populations has already substantially decreased mortality in certain cancers [Incarbone *et al.* 2002; van Sandick *et al.* 1998; Hisamichi, 1989]. It is important to note that benefit should exceed the burden of large-scale surveillance programs and such benefit remains controversial as long as documented reduction on cancer mortality is lacking [Quera *et al.* 2006].

The reason for the increased detection of early cancer is not only the success of the mass screening programs but also the awareness of physicians towards recognizing individual risks, and the attitude towards detecting early cancer in asymptomatic subjects. It may be that the paradigm shift to recognition of precancerous lesions in the GI tract is the cornerstone of progress made in preventing GI cancer and early interventions.

GI cancers, which were previously considered fatal, may now be managed at an early and curable stage.

In such approach, successful prevention of GI cancer relies upon the identification of risk factors and risk groups, availability of early detection and treatment protocols, expert centers for applying these measures to patients, and continuous evaluation of and development of procedures applied. The goal of screening and surveillance is to diagnose precursor lesions and early stage cancer and to intervene at a critical point in order to prevent progression to advanced cancer or preclude mutilating therapy. Studies have shown a survival benefit if the cancers are detected by endoscopic screening rather than when presenting with symptoms

Surgery has long been the standard treatment also for patients with early GI cancer; however there is a shift toward alternative less-invasive organ-sparing therapy. Endoscopic tools for the complete removal of early cancerous lesions have been developed with significant benefits and excellent outcome. These endoscopic techniques carry considerably lower morbidity, mortality, and long-term side effects as compared with surgical intervention. These benefits outweigh even the higher risk of local cancer recurrence. Some of these techniques such as polypectomy for the prevention of colon cancer have been employed for decades and have been proven safe in the hands of many. Given the risks and the lack of long-term outcome data for some of the newer and more aggressive endoscopic techniques, these should be restricted to experienced endoscopists in expert centers because it requires high levels of endoscopic skill and experience.

Future directions

In recent years important advances have been achieved in the adjuvant treatment of advanced cancers, where small yet firm survival benefits were demonstrated for perioperative chemotherapy and postoperative chemoradiotherapy. Even though patient prognosis for advanced disease remains very poor with median survival times rarely approaching 1 year, efforts to improve outcome of multimodality treatment for advanced disease should continue. Yet, one of the greatest challenges now facing this field is the identification of patients at risk and assessing individuals for the presence of precursor lesions with the aim of targeting only those with a survival benefit with the psychological and physical burden of regular surveillance. The use of biomarkers and simple clinical scoring systems for risk identification both have a great potential and hence provide an opportunity for less-invasive, more-effective screening and surveillance. Attempts are being made to validate these approaches in routine clinical practice.

Detection of the precancerous lesions in a high-risk population is an essential clinical goal. New optical developments are rapidly in progress. Ongoing research, teaching and training are essential to optimize detection skills. Endoscopy will continue to play a leading role in the treatment of patients with an identified precursor lesion or mucosal cancer, but minimally invasive surgical techniques can also be developed to be used as an alternative in cases referred for maximally invasive surgical resection at present. Expectations for future technology are high; however, to establish the value of various advanced diagnostic and therapeutic tools in preventing GI cancer, long-term outcomes of randomized controlled trials are required.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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